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Effectiveness of 8-week TReatment with vortioxetine on depressive symptoms in major depressive disorder patients with comorbid generalized anxiety disorder in UAE (TRUE)

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Abstract

Background Major Depressive Disorder (MDD) is a leading cause of disability and results in excessive utilization of healthcare resources worldwide. The Middle East and North Africa (MENA) region shows a high prevalence of depressive disorders. Generalized Anxiety Disorder (GAD) and MDD have the highest rate of comorbidity of all mood and anxiety disorders, ranging from 40 to 98% in drug studies. Comorbid GAD results in more significant impairment in MDD and increases the severity of symptoms. Although several clinical trials supported the safety and effectiveness of vortioxetine, no data regarding these aspects has been revealed in the MENA region. This study aimed to assess the safety and efficacy of vortioxetine in patients with comorbid GAD in the United Arab Emirates (UAE).

Method In a multicenter observational study, 118 patients with confirmed anxiety and depressive disorders were evaluated over four visits (baseline visit, two weeks, four weeks, and eight weeks) using MADRS and HAM-A scales to assess depression and anxiety severity, respectively by calculating mean change and the percent using Kendall's W test.

Results A significant mean difference in MADRS score was observed, with a gradual decrease of mean MADRS total scores over the assessment weeks ($p < 0.001$) as well as in HAM-A scores, from severe to moderate-severe anxiety through the four visits ($p < 0.001$). Furthermore, only one case was reported as a serious side effect. Nausea and insomnia were the most predominant side effects reported among the studied population.

Conclusion Vortioxetine was found effective and safe among patients with MDD and comorbid GAD.

Keywords Major depressive disorder, MDD, Generalized anxiety disorder, GAD, Vortioxetine, United Arab Emirates

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Introduction

The global burden of Major Depressive Disorder (MDD) is rising, substantially burdening patients, their families, and the healthcare system. Recent statistical figures revealed that the global prevalence of depressive disorders was estimated to be 3.8%, including MDD at 2.49% [1]. It is expected that nearly 280 million people suffer from MDD worldwide. MDD is a leading cause of disability and results in excessive utilization of healthcare resources worldwide [2–4]. In line with global figures, data from the Middle East and North Africa (MENA) shows a high prevalence of depressive disorders; previous reports indicated that the prevalence of MDD in the MENA region ranges from 3 to 28.6%, according to the study population [5]. The etiology of MDD is multifactorial, and its heritability is estimated to be around 35%, affecting one out of every six adults during their lifetime [6]. Moreover, it was reported that women have a twofold higher risk of MDD than men [7]. Young age, low socioeconomic status, stress, a lack of social support, and other mental disorders, such as anxiety disorders, are associated with the development of MDD [8–10].

Generalized Anxiety Disorder (GAD) and MDD have the highest rate of comorbidity of all mood and anxiety disorders, ranging from 40 to 98% in drug studies [11–14]. According to the National Comorbidity Survey (NCS), 67% of GAD patients retrospectively report MDD, while 20% of patients with MDD retrospectively reported GAD; data also revealed a strong correlation between MDD and GAD [15].

Several researchers are looking into new substances with a rapid onset of action [16]. However, nearly one-third of MDD patients still exhibit suboptimal response or resistance to pharmacotherapy, which calls for investigating novel, effective agents.

Vortioxetine is an approved medication with multimodal antidepressant activities and a well-tolerated safety profile. According to previous clinical evidence, vortioxetine predominantly acts as a Serotonin Transporter (SERT) inhibitor while acting as an antagonist for 5-HT_3 and 5-HT_7 receptors and 5-HT_{1A} receptor agonist [17]. Animal models demonstrated that vortioxetine has pro-cognitive activities, significantly improving cognitive deficits and memory impairment [18]. In addition, the safety and effectiveness of vortioxetine are supported by several clinical trials, real-world studies, and meta-analyses assessing MDD patients. For example, the REVIDA real-world study, which recruited MDD patients from Southeast Asia, showed that the mean Patient Health Questionnaire (PHQ-9) scores significantly decreased three months after the initiation of vortioxetine. Nearly 81% of patients responded to treatment, and only 6% of patients were moderately to severely depressed at the end of treatment (compared to 76.7% at baseline) [19]. Also, the RELIEVE study assessed the effectiveness and safety of vortioxetine in routine clinical practice for treating MDD [20]. The study included 737 patients and showed significant improvement in functioning, depression severity, cognitive symptoms, and cognitive performance. Vortioxetine was well-tolerated; adverse events were observed in 21.2% of patients. The same findings were reported in the RELIEVE CHINA study [21]. The TREVIDA real-world study recruited 242 MDD patients from Taiwan and reported that vortioxetine effectively reduced depression severity, with a 6.3-point reduction in the PHQ-9 score [22]. In a recent systematic review study by the Cochrane Collaboration, MDD patients treated with vortioxetine had significantly fewer depressive symptoms [23].

Mental illness has become a serious medical condition in the United Arab Emirates (UAE), with a reported prevalence ranging from 12.5 to 28.6%, including MDD [5]. Given this high burden of MDD, assessing the effectiveness and safety of newer therapies in this population is critical. Accordingly, this study aimed to evaluate the effectiveness as well as the safety profile of treatment with vortioxetine (10–20 mg/day) in daily clinical practice on depressive symptoms and anxiety symptoms in MDD patients with comorbid GAD in UAE.

Patients and methods

Study design and duration

This study was a national, multicenter, prospective, observational, non-interventional study to assess the effectiveness and safety of 8 weeks of vortioxetine treatment in reducing depressive and anxiety symptoms in 118 MDD patients with comorbid GAD. The study complied with recommendations of the 18th World Health Congress (Helsinki, 1964) [24] and all the laws and regulations, as well as any applicable guidelines, of the UAE where the study was conducted.

Study population

The following criteria were mandatory for all the patients recruited in this study: male or female patients aged ≥ 18 and ≤ 65 years; primary diagnosis of MDD according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) for < 12 months; current comorbid GAD diagnosed according to DSM-5 before current MDD; Montgomery–Åsberg Depression Rating Scale (MADRS) total score ≥ 22 at baseline as well as Hamilton Anxiety Rating Scale (HAM-A) score ≥ 20 at baseline. Furthermore, patients who were naïve to the vortioxetine treatment before the study initiation or taking vortioxetine as a sole decision of the treating physician were included. Moreover, patients who were receiving anxiolytic medication (benzodiazepines) in addition to vortioxetine at week one and week 2 of the study were allowed to

enter the study as per the investigator's decision. Finally, patients could read, understand, and sign an informed consent form before study inclusion. All of the following were excluded: patients with at least one contraindication to the study medication. Concurrent diagnosis or history of schizophrenia or any other psychotic disorders, bipolar disorder, dementia, or any other psychiatric comorbidities to ensure that MDD was the primary condition under investigation. Patients who received antidepressants other than vortioxetine during the study period to avoid confounding effects from multiple medications. Patients who received anxiolytic medication (benzodiazepines) in addition to vortioxetine from week 3 to week 8 of the study as this could interfere with the evaluation of vortioxetine's efficacy. Female patients who were pregnant or intended to become pregnant during the study. Patients who were participating in another clinical study and patients who were, in the investigator's opinion, unlikely to comply with the study protocol.

Data collection and validation

During the study period, the following parameters were assessed: severity of depression *[(symptoms were rated on a 7-point scale from 0 (no symptoms) to 6 (severe symptoms)]* using MADRS and severity of anxiety symptoms were rated on a 7-point scale from *[0 (no symptoms) to 6 (severe symptoms)]* using HAM-A. Data were collected at the treatment initiation (Baseline) and when the participants returned to the clinic/hospital for routine visits at approximately two weeks, four weeks, and eight weeks after the baseline visit. The following data was also revealed: demographic data, medical history, family history, concomitant medications, vital signs, and physical examination (i.e., anthropometric measures including height, weight, and Body Mass Index (BMI)). Data related to disease history, diagnosis, and vortioxetine use: this included antidepressants received, anxiolytics received, history of any previous depressive episodes, history of any prior suicide attempts, history of any prior mood disturbances, history of any last sleeping difficulties, history of any prior trouble relating to concentration, and history of weight gain or loss. Vortioxetine administration-related data: dose and frequency. Furthermore, Adverse Events (AEs) and Serious Adverse Events (SAEs) were recorded starting from the informed consent date.

Treatment

Oral Vortioxetine (10–20 mg/day) was administered for eight weeks in patients with MDD and comorbid GAD as per the investigator's decision.

Sample size calculation

The primary objective of this study was to assess the effectiveness of 8 weeks of treatment with vortioxetine on depressive symptoms in patients with MDD and comorbid GAD by calculating the change from baseline through 8 weeks of follow-up in MADRS total score. The pooled mean (±SD) reductions from baseline in MADRS total score after vortioxetine treatment from 12 clinical trials through a meta-analysis model were 15.8 (±0.83). Accordingly, in the precision-based calculation, when the sample size is 92, a two-sided 95% confidence interval for the difference in paired means will extend 0.17 points on the MADRS total score from the observed mean, assuming that the standard deviation is known to be 0.83. The confidence interval is based on the significant sample Z test statistic. To account for an expected dropout rate of 10%, 100 patients were appropriate. The sample size was calculated using nQuery Advisor 6.01.

Statistical analysis methods

Data analysis was performed using SPSS software (version 22.0). A descriptive statistical analysis was conducted to determine the demographic and clinical characteristics, safety results, and baseline findings of MADRS and HAM-A. Categorical variables were reported as counts and percentages (%); meanwhile, continuous variables were reported as mean and standard deviation (SD). The mean change from baseline and at 2, 4, and 8 weeks in MADRS total score and the percent reduction in MADRS total score after 2, 4, and 8 weeks of treatment were calculated using Kendall's W test. The Kendall's W test was used to assess the effect size of changes over time, given its suitability for non-parametric data and repeated measures. The comparison was considered statistically significant at a P value < 0.5.

Results

All 118 enrolled patients were eligible and included in our safety analysis. Out of the 118 patients, 24 patients (20.3%) discontinued the study due to the following causes: 17 patients (14.4%) were lost to follow-up, six patients (5.2%) had AEs, one patient (16.7%) had a SAE, and one patient (0.85%) had withdrawn participation consent. Accordingly, 94 patients completed the study and entered our efficacy analysis (Fig. 1).

Baseline data

Demographic characteristics

The mean age±SD of the patients was 35.8±10.1 years. The majority of included patients were female (59.3%). Around 28% of the patients were Caucasian, while 21.1% were Black. Less than half of the included patients were single, 49 (41.5%), while married and divorced patients were 63 (53.4%) and 6 (5.1%), respectively. Most of the included patients had a college degree. Seventy-eight patients (66.1%) had never smoked; 81 patients (68.6%) had full-time jobs, and 30 patients (25.4%) were not

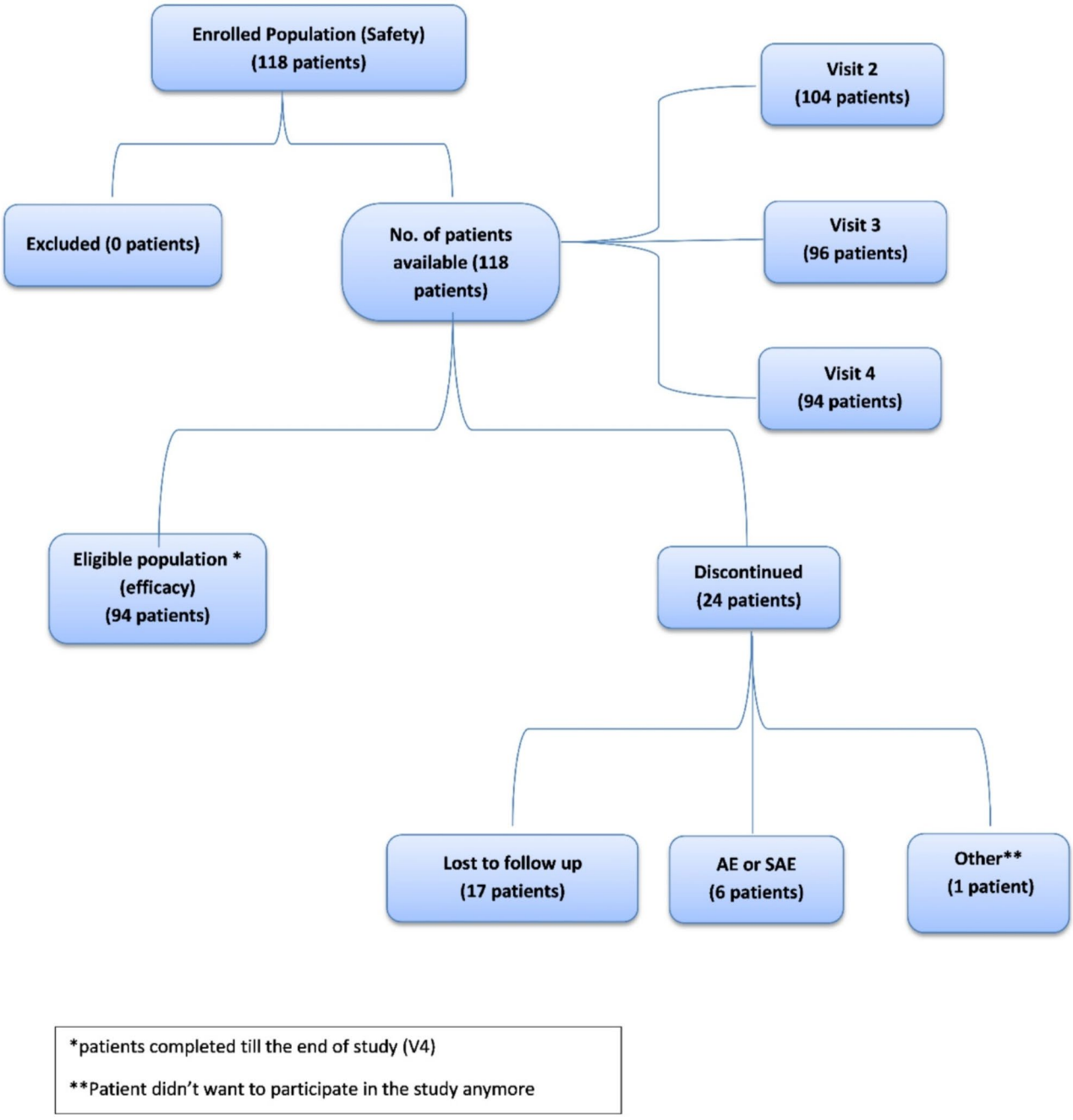

Fig. 1 CONSORT diagram for the included/enrolled patients

employed. Among the 30 non-employed patients, 29 (96.7%) revealed that MDD or GAD did not cause work-related disability, while only one case (3.3%) revealed such a problem. Regarding patients' residence area, 113 patients (95.8%) were from urban areas, and the rest were from suburban areas. Other socio-demographic data are presented in (Suppl. 1). The complete data of patients' medical history are presented in (Suppl. 2).

Clinical history characteristics

Antidepressants such as Norepinephrine Reuptake Inhibitors (NRIs) and Serotonin Modulator and Stimulators (SMSs) were taken by one patient each (0.8%). In contrast, Selective Serotonin Reuptake Inhibitors (SSRIs) were taken by 18 patients (15.3%), and 96 patients (81.4%) had other antidepressants. Among the 96 cases who received other antidepressants, 93 (96.9%) did not receive any antidepressant previously. Anxiolytics, including benzodiazepines, were used by 14 patients

(11.9%). Furthermore, upon investigation, 33 (28%) of patients had previous depressive episodes. Moreover, suicidality (thoughts or attempts) was reported in 16 patients (13.6%), and four patients (25%) had attempted suicide once. Among 118 cases, 107 (90.7%) experienced mood disturbances, 98 (83.1%) had trouble sleeping, 103 (87.3%) had concentration problems, weight gain was reported in 28 (23.7%) patients, and weight loss was detected in 20 (16.9%) patients. Regarding family history, 26 patients (22%) reported a positive history of MDD, and 21 patients (17.8%) reported a positive history of GAD, while a family history of other psychiatric disorders was reported in 17 patients (14.4%).

Most of the included patients (90.4%) received 10 mg oral vortioxetine at the baseline visit. More data about the administration of vortioxetine is presented in (Suppl. 3).

Description of vortioxetine administration-related data during the study period

The MADRS total scores at weeks 2, 3, and 4 were 21.9±7.8, 17.3±7.5, and 14±7.5, respectively. A significant reduction in MADRS total scores was reported in all visits, with a mean difference of 6.7, 11.3, and 14.6, respectively (Fig. 2). While the mean±SD HAM-A at weeks 2, 4, and 8 were 20.9±8.3, 17.3±7.5, and 13.3±7.14, respectively. A significant reduction in HAM-A was reported in all visits, with a mean difference of 5.2, 10.1, and 12.9 at visits 2, 3, and 4, respectively (Fig. 3).

Furthermore, HAM-A were 30.3±8.8 and 27.6±8.5, respectively. According to the MADRS and HAM-A assessments, most of the included patients were moderately depressed (71.2%), while 52.5% had mild to moderate anxiety at baseline visits (Tables 1 and 2).

After vortioxetine administration, the mild MADRS class significantly increased, while the moderate and severe classes showed notable reductions from baseline to weeks 2, 4, and 8 ($P<0.001$). Similarly, anxiety severity, measured by HAM-A scores, decreased significantly throughout the study. At baseline, 60.6% of patients had mild to moderate anxiety, while 19.1% had moderate to severe and 20.2% had very severe anxiety. By week 8, 80.9% of patients had mild anxiety ($P<0.001$). Detailed results are shown in Tables 3 and 4.

Patients who completed all follow-up visits (94 patients) received their medication as prescribed with no treatment discontinuation. However, a dose modification was reported in four patients (4.3%), either due to clinical improvement in one patient (25%) or expected future improvement in three patients (75%).

Safety results

Finally, the assessment of the safety of vortioxetine in this study demonstrated the following: around 14% experienced various adverse events, including nausea (37.5%),

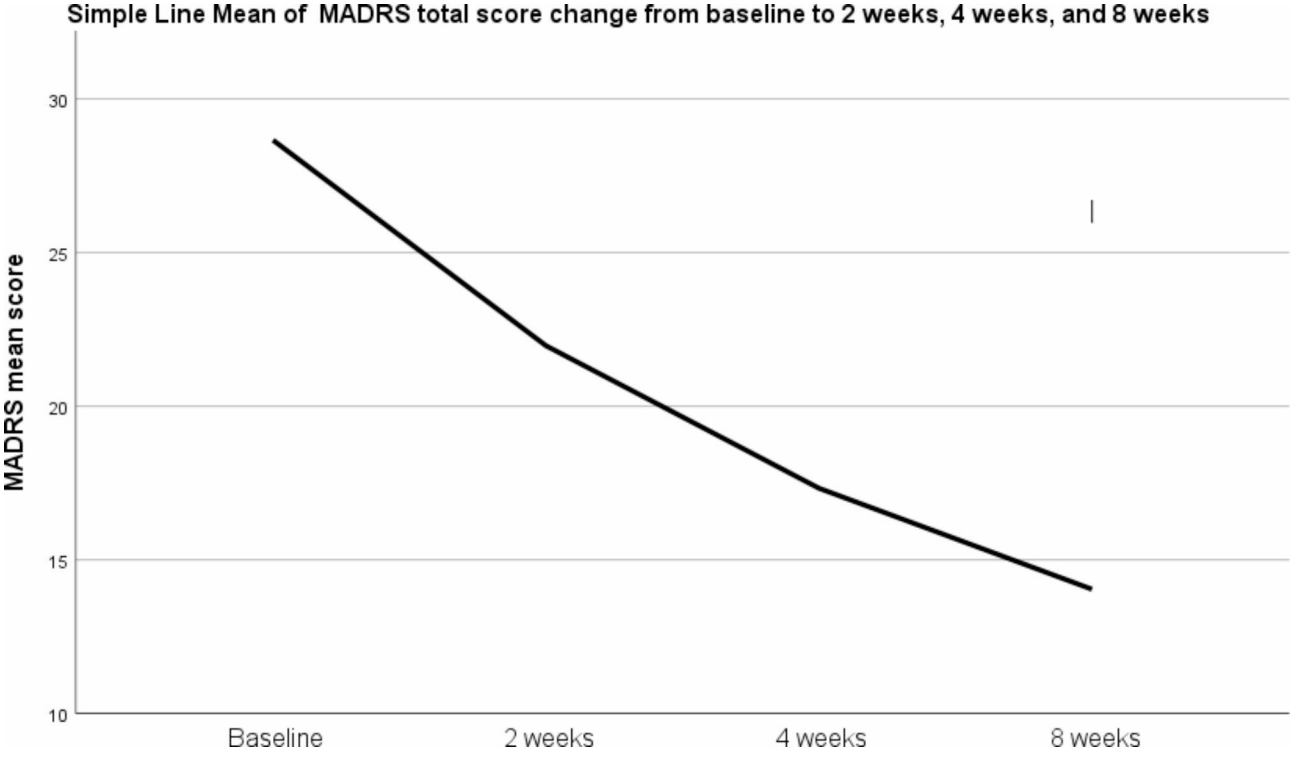

Fig. 2 Change in mean MADRS scores from baseline to 2, 4, and 8 weeks

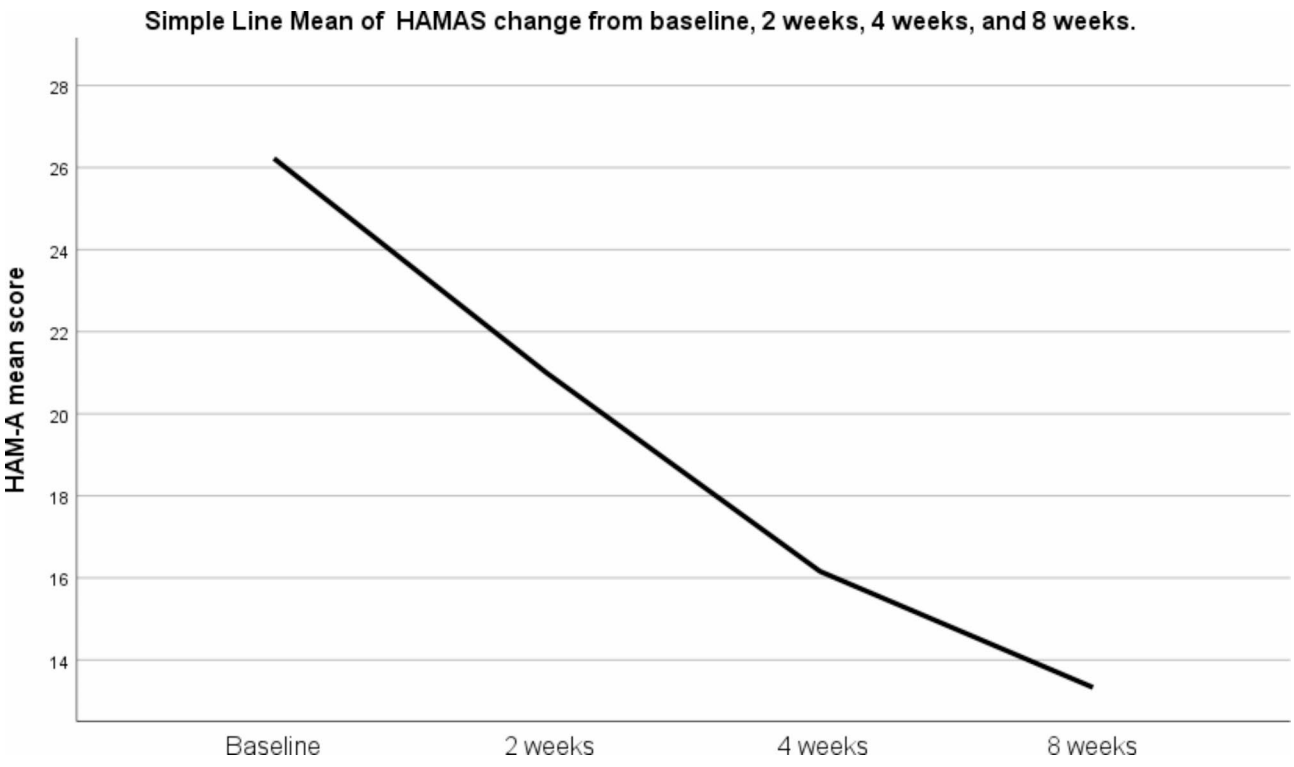

Fig. 3 Change in mean of HAM-A from baseline after 2, 4, and 8 weeks

Table 1 Baseline Montgomery-Asberg Depression Rating Scale (MADRS) scores

Variable	Mean	SD
Baseline Montgomery-Asberg Depression Rating Scale (MADRS) Scores	30.3	8.8
MADRS Interpretation	Count	%
Normal or absent	0	0
Mild	0	0
Moderate	84	71.2
Severe	34	28.8
Total	118	100

Table 2 Baseline Hamilton anxiety rating scale (HAM-A) scores

Variable	Mean	SD
Hamilton anxiety rating scale (HAM-A) Scores	27.6	8.5
Interpretation	**Count**	**%**
Mild	0	0
Mild to Moderate	62	52.5
Moderate to Severe	24	20.3
Very Severe Anxiety	32	27.1
Total	118	100

insomnia (12.5%), while headache, somnolence, and blurred vision each had 8.3%. Only one patient (0.8%) had a serious adverse event; he had a history of chronic kidney disease and was admitted to the hospital and diagnosed with hematuria (Table 5).

Discussion

MDD and GAD frequently manifest together, and individuals experiencing comorbid GAD represent one of the largest patient groups within the overall population with MDD [25, 26]. When comorbid, MDD and GAD are associated with more severe symptoms, greater impairment in functioning and health-related quality of life (HRQoL), and greater risk of suicidal ideation than seen in patients with either condition alone [27].

Our study revealed significant improvements in both depression and anxiety symptoms among vortioxetine-treated patients, as evidenced by a significant change in MADRS total scores for depression and HAMA-A scores for anxiety. Our findings align with previous research. A meta-analysis of 7,269 patients demonstrated a significant improvement in MADRS scores for vortioxetine in treating depression, anxiety, and cognitive deficits [3]. Similar meta-analyses have also highlighted the broad efficacy of vortioxetine across various symptom domains in MDD [28–30]. Furthermore, in a comparative clinical trial involving 21 antidepressants, vortioxetine emerged as superior in treating MDD [31].

In the realm of non-interventional studies, Inoue et al. demonstrated the dose-dependent efficacy of vortioxetine in 338 Japanese patients aged 20–75 with recurrent MDD and/or concurrent moderate to severe depression. This was substantiated by a significant difference in the HAM-D anxiety/somatization factor scores between

Table 3 Change between MADRS classes from baseline to 2, 4, and 8 weeks

MADRS class	V1 (baseline)		V2 (2 weeks)		V3 (4 weeks)		V4 (8 weeks)	
	Count	%	Count	%	Count	%	Count	%
Normal or Absent	0	0	1	1.1	5	5.3	15	16.0
Mild	0	0	31	33	63	67	63	67
Moderate	73	77.7	56	59.6	24	25.5	14	14.9
Severe	21	22.3	6	6.4	2	2.1	2	2.1
Total	94	100.0	94	100.0	94	100.0	94	100.0
P-value*	*P*-value < 0.001							

* Kendall's W

Table 4 Change between HAMA-A classes from baseline to 2, 4, and 8 weeks

HAM-A Class	V1 (baseline)		V2 (2 weeks)		V3 (4 weeks)		V4 (8 weeks)	
	Count	%	Count	%	Count	%	Count	%
Mild severity	0	0	24	25.5	65	69.1	76	80.9
Mild to moderate	57	60.6	50	53.2	19	20.2	13	13.8
Moderate to severe	18	19.1	9	9.6	7	7.4	3	3.2
Very severe	19	20.2	11	11.7	3.2	3.2	2	2.1
Total	94	100	94	100	94	100	94	100
P*-value	*P*-value < 0.001							

* Kendall's W

Table 5 Adverse events associated with vortioxetine

Patients Experienced AEs	Count	%
Yes	16	13.5
No	102	86.5
Total	118	100
Patients who experienced serious AEs		
Yes	1	0.8
No	117	99.2
Total	118	100
AE Intensity		
Mild	17	70.8
Moderate	4	16.7
Severe	3	12.5
Total	24	100
AE Diagnosis*		
Adjustment disorder with mixed disturbances of emotion and conduct	1	4.2
Constipation	1	4.2
Dryness	1	4.2
Headache	2	8.3
Insomnia	3	12.5
Moodiness	1	4.2
Nausea	9	37.5
Nightmares	1	4.2
Palpitations	1	4.2
Somnolence	2	8.3
Vision Blurred	2	8.3
Total	24	100

* Subjects may have more than one adverse event

patients treated with vortioxetine at 10 mg or 20 mg and those receiving a placebo [32]. In a study with 100 patients suffering from severe MDD and comorbid GAD, vortioxetine was effective over eight weeks, whether used as the primary treatment or as a switch from another antidepressant. The trial showed significant improvements in depression and anxiety symptoms, functioning, and quality of life. 52% of patients had positive responses, and 31% achieved remission after eight weeks of therapy without unexpected side effects [33].

Furthermore, vortioxetine exhibited significant efficacy in patients with GAD, particularly when assessing the HAM-A total score [34]. The RELIEVE Study also emphasized the effectiveness and tolerability of vortioxetine in 737 MDD patients with comorbid anxiety and GAD, with improvements detected in various assessments, including the Patient Health Questionnaire-9 (PHQ-9), 5-item Perceived Deficits Questionnaire-Depression (PDQ-D-5), and the Digit Symbol Substitution Test (DSST) scores [20]. Highlighting these findings underscores the effectiveness of vortioxetine in patients with comorbid MDD and GAD, aligning with our study's outcomes.

In this study, the recommended initial vortioxetine dose in adult patients with MDD is 10 mg once daily. According to each patient's response, the dosage of vortioxetine was either increased to a maximum of 20 mg/day or decreased to a minimum of 5 mg/day [35]. Initial optimization of antidepressant dosing is done to achieve the maximum treatment outcomes. Sub-therapeutic dosing has contributed to early withdrawal from

antidepressant treatment in patients with MDD [36]. In addition, a dose-response relationship has been observed for improvements in both depressive symptoms and overall functioning, with the highest effect seen at a vortioxetine dosage of 20 mg/day [3, 37, 38]. Similarly, 4.3% in our study had dose modification, where 3 cases had to increase the dose to 20 mg daily to reach optimum vortioxetine efficacy. Similar results were revealed by Zheng et al. using a 10 mg daily dose of vortioxetine, where significant differences in response rates were exhibited [39].

In the RELIEVE study, adverse events were detected in 21.2% of patients [particularly nausea (8.2%)] [20]. Zheng et al. reported that 10 mg/day vortioxetine was associated with nausea (OR=4.18, 95% CI=3.21–5.44, $P<0.00001$) and constipation (OR=1.88, 95% CI=1.14 to 3.09, $P=0.01$) [39]. An article detailing the safety and tolerability of vortioxetine (at doses of 5-20 mg/day) found that the most common side effects were nausea (20.9–31.2%) and vomiting (2.9–6.5%). Higher doses were associated with insomnia (2.0-5.1%) and sexual dysfunction (1.6–1.8%) [40]. These above studies align with our study results, where 14% of 118 patients experienced side effects of mild to moderate severity (particularly insomnia and nausea), and around 92% spontaneously recovered.

In the Cipriani et al. study, vortioxetine along with agomelatine, citalopram, escitalopram, fluoxetine, and sertraline demonstrated superior tolerability compared to other antidepressants (range of ORs 0.43–0.77) [31]. For antidepressant drugs, the risk of suicidality is addressed in the product label [41]. In this study, no increased risk for suicide-related events was detected, which comes in line with the clinical trial data for vortioxetine [42].For strengths and limitations, the study effectively evaluated the impact of vortioxetine on both depression and anxiety symptoms, as well as overall quality of life, using robust methodology, including validated scales like MADRS, HADS, and CLCI. Additionally, its focus on real-world data from Gulf countries provides valuable insights into treatment outcomes in this specific population. However, the short-term follow-up limits the ability to assess the long-term efficacy of vortioxetine, and the lack of a control group makes direct comparisons with other treatments or placebos difficult. The high dropout rate may limit the generalizability of our findings to routine clinical practice, where patients with comorbidities or those experiencing adverse effects may be more likely to discontinue treatment.

Conclusion

Our study confirms the efficacy of vortioxetine in improving depression, anxiety symptoms, and quality of life in patients with comorbid MDD and GAD, aligning with previous research. The use of real-world data from the Gulf region adds valuable insights into its clinical application. However, the lack of a control group and short follow-up period limit the study's scope. Further long-term and comparative research is needed to solidify these findings. Nonetheless, vortioxetine remains an effective and well-tolerated treatment option for this patient population.

Abbreviations

AEs	Adverse Events
BMI	Body Mass Index
DSM-5	Diagnostic and Statistical Manual of Mental Disorder
DSST	Digit Symbol Substitution Test
GAD	Generalized Anxiety Disorder
HAM-A	Hamilton Anxiety Rating Scale
MADRS	Montgomery–Åsberg Depression Rating Scale
MDD	Major Depressive Disorder
MENA	Middle East and North Africa
NCS	National Comorbidity Survey
NRIs	Norepinephrine Reuptake Inhibitors
PDQ-D-5	Perceived Deficits Questionnaire-Depression
PHQ-9	Patient Health Questionnaire
SAEs	Serious Adverse Events
SERT	Serotonin Transporter
SMSs	Serotonin Modulator and Stimulators
SSRIs	Serotonin Reuptake Inhibitors
UAE	United Arab Emirates

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12991-024-00526-w.

Supplementary Material 1

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Author contributions

A. All authors provided critical feedback and helped shape the research, analysis and manuscript. All authors read and approved the final manuscript.

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Data availability

Data are available upon request from the corresponding author.

Declarations

Ethics approval and consent to participate

The protocol complied with the recommendations of the 18th World Health Congress (Helsinki, 1964) and all applicable amendments. The protocol also adhered to the laws and regulations and any relevant guidelines of the UAE where the study was conducted. The IRB approval documents are provided as supporting files to this manuscript.

Patient consent

Written informed consent was obtained before the initiation of the study at the screening/baseline visit, and patients were screened to fulfill the eligibility criteria. The occurrence of AEs and SAEs starting from the informed consent date was also recorded.

Competing interests
The authors declare no competing interests.

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