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ORIGINAL RESEARCH

Effectiveness and Safety of Vortioxetine for Major Depressive Disorder in Real-World Clinical Practice: Results from the Single-Arm RELIEVE China Study

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Background: Major depressive disorder (MDD) affects >163 million people worldwide and is a leading cause of disability in China. Functional impairment occurs alongside cognitive symptoms, anxiety, and depression, reducing quality of life and productivity in patients with MDD.

Purpose: The multimodal antidepressant vortioxetine has demonstrated efficacy in relieving depressive and functional symptoms of MDD in randomized controlled trials (RCTs). The RELIEVE China study aimed to investigate the real-world effectiveness of vortioxetine in China.

Patients and Methods: This was an observational, prospective cohort study in patients with MDD initiating treatment with vortioxetine at physician's discretion in China. Participants were followed up for 24 weeks and assessed at 3 time points: baseline, week 8, and week 24. The primary objective was to assess the change from baseline to weeks 8 and 24 in functional impairment as measured by Sheehan Disability Scale (SDS) total score. Additional assessments included SDS subdomains, measures of depression severity, anxiety, and cognition. The safety and tolerability of vortioxetine were also examined.

Results: In total, 859 patients were included in the analysis. A consistent and significant improvement in functional impairment was observed during the study, with baseline mean SDS total score (16.7 points) decreasing by 5.42 (SE, 0.22) and 8.71 (SE, 0.226) points at week 8 and week 24, respectively ($P<0.0001$). Improvements in other functioning, cognitive, and anxiety assessments were also observed (all $P<0.0001$). A total of 74.7% of patients had responded, and 63.9% had reached remission at week 24. The tolerability profile of vortioxetine in this real-world population was consistent with the established tolerability profile for this drug.

Conclusion: This study demonstrated the short- and long-term effectiveness and tolerability of vortioxetine for patients with MDD in a real-world setting in China. These findings are consistent with the efficacy and safety profile observed during RCTs.

Keywords: China, cognition, functioning, major depressive disorder, real-world evidence, vortioxetine

Plain Language Summary

Why is the treatment of major depressive disorder (MDD) important?

MDD is a leading cause of disability worldwide and in China, where it often remains undiagnosed and undertreated. The impact of MDD on a person's ability to function in work, social life, and family life can be significant. Therefore, improvements in a patient's symptoms and ability to function throughout the day are important for increasing the chances of overall recovery.

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What question does this study answer?

Clinical trials have shown that the antidepressant vortioxetine is safe and effective for the treatment of MDD. These trials were performed in a controlled environment with a small group of similar people, and therefore may not provide clear answers for all people living with MDD. The current study helps fill this gap by evaluating vortioxetine in a large population of patients with MDD seen in routine clinical practice in China, leading to a broader understanding of how vortioxetine works in a real-world setting.

What did we find and what does it mean?

Patients treated with vortioxetine showed improvement in overall ability to function at 24 weeks compared with baseline, including functioning within work/school, social life, and family life/home responsibilities. Patients also showed improvement in depression severity, anxiety, and cognitive symptoms, such as attention, concentration, and organization. These findings are consistent with previous studies and support the real-world effectiveness of vortioxetine in people living with MDD in China.

Introduction

Major depressive disorder (MDD) is a common condition, affecting more than 163 million people worldwide,[1] and its prevalence is increasing.[2] Estimates of the lifetime prevalence of MDD in China vary, ranging from 1.8% to 6.9%.[3–5] As the second-leading cause of years lived with disability in China, MDD imposes a substantial burden on patients, impairing both functioning and quality of life.[6,7] MDD also exacts a significant societal burden through both direct and indirect costs.[8] However, the majority of patients with MDD remain undiagnosed,[9] and MDD is often undertreated.[10] A meta-analysis of 15 studies of patients with MDD in China indicated that only 19.5% of patients are treated, possibly due to patients not disclosing their symptoms to healthcare professionals and not seeking specialist mental health support to avoid stigma and discrimination associated with a diagnosis of MDD.[11] Accordingly, the National Health Commission of China released an action plan in 2020 for the prevention and control of depression to address the growing burden of depression in China.[9,12]

Patients with MDD frequently experience significant functional impairment, including reduced physical function (eg, the ability to engage in sports or perform activities of daily living), lower work productivity (eg, absenteeism), and poor psychosocial functioning (eg, the ability to recognize social cues).[13] The cognitive symptoms associated with MDD can also contribute to MDD-related social, functional, and work-related disability.[14–18] Approximately three-quarters of patients with MDD in China present with cognitive impairment, which continues for approximately one-third of patients after 6 months of treatment,[18] resulting in impaired quality of life and productivity, independent of the severity of depressive symptoms.[18–20] Therefore, both symptomatic and functional improvement during treatment of MDD are desirable for increasing patients' chances of recovery and restoration.

Vortioxetine, a multimodal antidepressant authorized for use in patients with MDD in the United States since 2013, is approved in more than 80 countries worldwide.[21] Vortioxetine has demonstrated efficacy, safety, and an ability to improve cognitive symptoms in patients with MDD in a large clinical development program;[15,22–26] it also has a significant effect on overall patient functioning.[27] These randomized controlled trials (RCTs) have demonstrated the efficacy and safety of vortioxetine in controlled environments according to strict protocol criteria that limit patient eligibility, and thus heterogeneity and investigator discretionary treatment; however, the effectiveness of vortioxetine in real-world clinical practice remains to be determined because RCTs tend to be highly selective, homogeneous, and based on a predefined set of inclusion criteria to support regulatory approval of the drug.[28] Accordingly, the results potentially lack generalizability to the diverse patient populations encountered in clinical practice, including Asian patients.[29] Thus, observational studies are conducted to improve understanding of treatment outcomes in a real-world setting.[28]

This observational study complements the findings from RCTs by providing valuable data on the effectiveness, safety, and tolerability of vortioxetine in a real-world clinical setting. This study particularly investigates the real-world effectiveness of vortioxetine, including depressive symptom relief, cognitive symptom relief, functioning, and anxiety symptom relief, in patients with MDD in China.

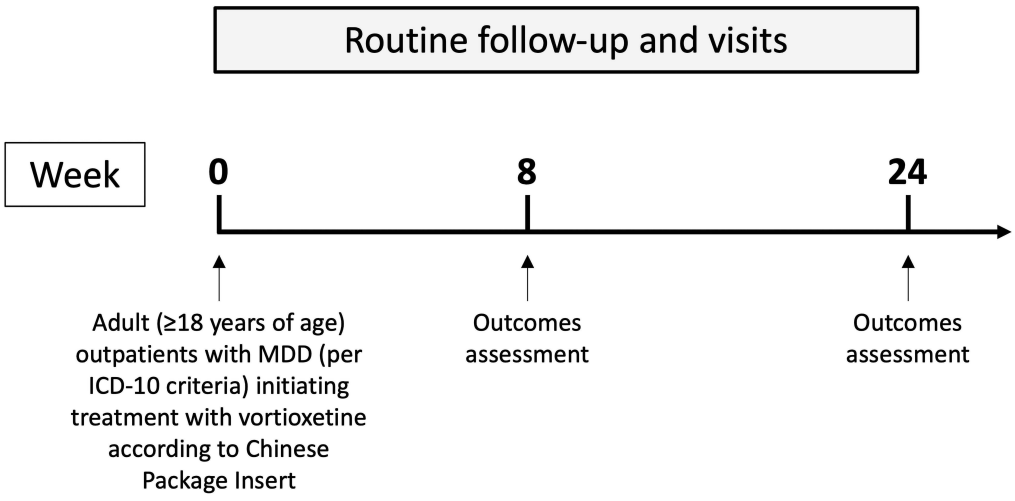
Materials and Methods

Study Design

REal-LIfe Effectiveness of VortioxEtine in Depression (RELIEVE) China was an observational, multisite, single-arm, prospective cohort study in patients with MDD initiating treatment with vortioxetine at 18 sites in China, including psychiatric hospitals and psychiatric departments of general hospitals (Supplementary Table 1). Participants were enrolled from December 2018 to March 2020, and the final visit for the last participant occurred on August 21, 2020.

Study participants were assessed at baseline, which was defined as the date vortioxetine treatment was initiated, and at weeks 8 (–1/+3 weeks) and 24 (±4 weeks) after baseline (Figure 1). Patients were followed up until the end of the study or withdrawal from the study.

Eligible patients were ≥18 years of age, had a current diagnosis of a major depressive episode (MDE) according to *International Classification of Diseases, 10th Revision* (ICD-10) criteria, and were initiating treatment with vortioxetine in an outpatient setting according to the Chinese package insert solely based on the clinical judgment of the investigator. All patients initiating vortioxetine as treatment for MDD could be included, regardless of depression severity level at baseline. Patients were excluded if they had a comorbid ICD-10 diagnosis of schizophrenia, bipolar disorder, or other



Assessment	Baseline	Month 2	Month 6
SDS	✓	✓	✓
HAM-D 17	✓	✓	✓
CGI-S	✓	✓	✓
CGI-I		✓	✓
PHQ-9	✓	✓	✓
PDQ-D	✓	✓	✓
GAD-7	✓	✓	✓
Safety	✓	✓	✓

Figure 1 Study design and assessments.

Abbreviations: CGI-I, Clinical Global Impressions–Improvement; CGI-S, Clinical Global Impressions–Severity; GAD-7, Generalized Anxiety Disorder Scale–7 items; HAM-D17, Hamilton Depression Rating Scale–17 items; ICD-10, International Classification of Diseases, 10th Revision; MDD, major depressive disorder; PDQ-D, Perceived Deficits Questionnaire–Depression; PHQ-9, Patient Health Questionnaire–9 items; SDS, Sheehan Disability Scale.

neurodegenerative disease that significantly affected cognitive functioning. Patients were also excluded if their current MDE was resistant to treatment with 2 other antidepressants or if they had attempted suicide within the last 6 months.

Study Assessments

The primary objective of this study was to assess the change from baseline to weeks 8 and 24 in overall functioning as measured by the Sheehan Disability Scale (SDS; range: 0–30; higher scores indicate greater impairment in functioning). Secondary objectives included assessment of change from baseline to weeks 8 and 24 in depression severity, cognitive symptoms, functioning subdomains, and severity of anxiety symptoms. Depression severity was assessed by the patient using the Patient Health Questionnaire–9 items (PHQ-9) and by the physician using the Hamilton Depression Rating Scale–17 items (HAM-D17), Clinical Global Impressions–Severity (CGI-S), and Clinical Global Impressions–Improvement (CGI-I), with higher scores indicating more severe symptoms. Cognitive symptoms were assessed using the Perceived Deficits Questionnaire–Depression (PDQ-D) total score, while 3 subdomains of the SDS were used to assess function in work, social life, and family life. Generalized Anxiety Disorder Scale–7 items (GAD-7) total score was used to assess anxiety symptoms. Response (≥50% decrease in HAM-D17) and remission (HAM-D17 ≤7) rates were also calculated.

Adverse events (AEs) were assessed and recorded using Medical Dictionary for Regulatory Activities (MedDRA) version 23.0. Vortioxetine doses of >10 to 20 mg were coded as a "prescribed overdose" because dosing at this level was not approved by the Chinese National Medical Products Administration until the conclusion of the study in August 2020.

Statistics

The study planned to enroll 1000 participants, assuming that information would not be available for 40% of participants at week 8 and 38% at week 24.[20] These participant numbers were expected to result in a precision of 8% and 7% for SDS assessments at weeks 8 and 24, respectively. This also allowed for the rule of 3 to be applied for safety assessments; namely, that if an AE is not observed, there is a 95% probability of the AE occurring in <0.3% of patients.[30]

All analyses, except the safety analysis, were performed on the effective analysis population, defined as all patients who had a date of prescription for initiating vortioxetine treatment and attended ≥1 post-baseline visit within the analysis time point. Descriptive statistics are presented here. The primary and secondary effectiveness analyses were performed using a mixed model for repeated measures, with an unstructured covariance matrix. The following variables were added as fixed effect covariates: analysis time point and baseline SDS total score, age at baseline, baseline depression severity using HAM-D17, vortioxetine treatment line, sex, education level, duration of current MDE at baseline, baseline psychiatric disorder, baseline somatic disorder, and site. The primary effectiveness analysis model also included an interaction term of baseline total SDS score by analysis time point.

The safety analysis population included all patients with a date of prescription for initiating vortioxetine treatment. AEs are summarized based on the safety analysis population to include the number of events and the number and percentage of patients with such events. Analyses were performed using SAS software version 9.4 or later.

Results

In total, 996 participants were included in the safety analysis population and 859 were included in the effectiveness analysis population (Supplementary Figure 1). Mean (SD) participant age was 33.1 (13.53) years (range 18–79 years), and the majority of participants were female (65.9%), single (55.3%), had a university-level education (46.4%), and were living in an urban area (86.1%) (Table 1). Approximately half (55.2%) of the participating patients were administered vortioxetine as their first line of antidepressant therapy. Comorbidities were also reported for 54.2% of patients, most commonly psychiatric comorbidities (50.4%), including anxiety disorders (38.8%) and sleep disorders (25.3%). At baseline, the mean (SD) vortioxetine dose was 9.28 (1.89) mg; 855 participants (99.65%) were receiving a dose ≤10 mg. At week 24, the mean (SD) vortioxetine dose was 11.12 (3.50) mg; of the 633 participants with available data, 120 (19.0%) were receiving a dose >10 mg.

Table 1 Baseline Characteristics of the Efficacy Analysis Population of the RELIEVE China Study

Characteristics	N=859
Age, years, mean (SD)	33.1 (13.53)
Range	18–79
>65 years, n (%)	17 (2.0)
Sex, male, n (%)	293 (34.1)
Marital status, n (%)	
Single	475 (55.3)
Married/living together	360 (41.9)
Divorced/separated	20 (2.3)
Widowed	2 (0.2)
Unknown	2 (0.2)
Living area, n (%)	
Urban	740 (86.1)
Educational level, n (%)	
No degree or diploma	3 (0.3)
Elementary school	28 (3.3)
Middle school	111 (12.9)
High school	108 (12.6)
Junior college	116 (13.5)
University	399 (46.4)
Postgraduate school or above	94 (10.9)
Years since first MDD diagnosis, mean (SD)	2.03 (4.06)
Duration of current MDE, weeks (SD)	44.01 (84.89)
Prior MDEs, n (SD)	1.7 (11.04)[a]
Participants with ≥1 relevant comorbidity at baseline, n (%)	466 (54.2)
Participants with ≥1 psychiatric comorbidity at baseline, n (%)[b]	433 (50.4)
Anxiety disorder	333 (38.8)
Sleep disorders	217 (25.3)
Vortioxetine treatment line, n (%)	
First	474 (55.2)
Second	290 (33.8)
Third+	95 (11.1)
Baseline assessments, mean (SD)	
SDS total score	16.7 (6.93)
PHQ-9 total score	16.1 (5.94)
CGI-S score	4.3 (0.90)
HAM-D17 score	19.3 (5.82)
PDQ-D score	36.5 (17.34)
GAD-7 total score	12.1 (5.23)
SDS work/school dimension score	5.9 (2.69)
SDS social life dimension score	5.6 (2.57)
SDS family life/home responsibilities dimension score	5.3 (2.72)

Notes: [a]n=852. [b]Psychiatric comorbidities with a prevalence >5%.

Abbreviations: CGI-S, Clinical Global Impressions–Severity; GAD-7, Generalized Anxiety Disorder Scale–7 items; HAM-D17, Hamilton Depression Rating Scale–17 items; MDD, major depressive disorder; MDE, major depressive episode; PQD-D, Perceived Deficits Questionnaire–Depression; PHQ-9, Patient Health Questionnaire–9 items; SDS, Sheehan Disability Scale.

Functioning

Mean SDS total score decreased from 16.7 points at baseline by 5.42 (95% CI, 4.99–5.85) and 8.71 (95% CI, 8.27–9.15) points at weeks 8 and 24 of vortioxetine therapy, respectively ($P<0.0001$ at both time points) (Figure 2). Improvements were also observed for all SDS subscores ($P<0.0001$ for all) (Figure 2).

At baseline, approximately 75% of patients were categorized as having moderate or marked functional impairment (SDS total score of 12–30), but within 8 weeks of initiating vortioxetine treatment, approximately half (54.6%) reported only mild (SDS total score of 6–11) or minimal (SDS total score of 0–5) functional impairment (Figure 3). Further

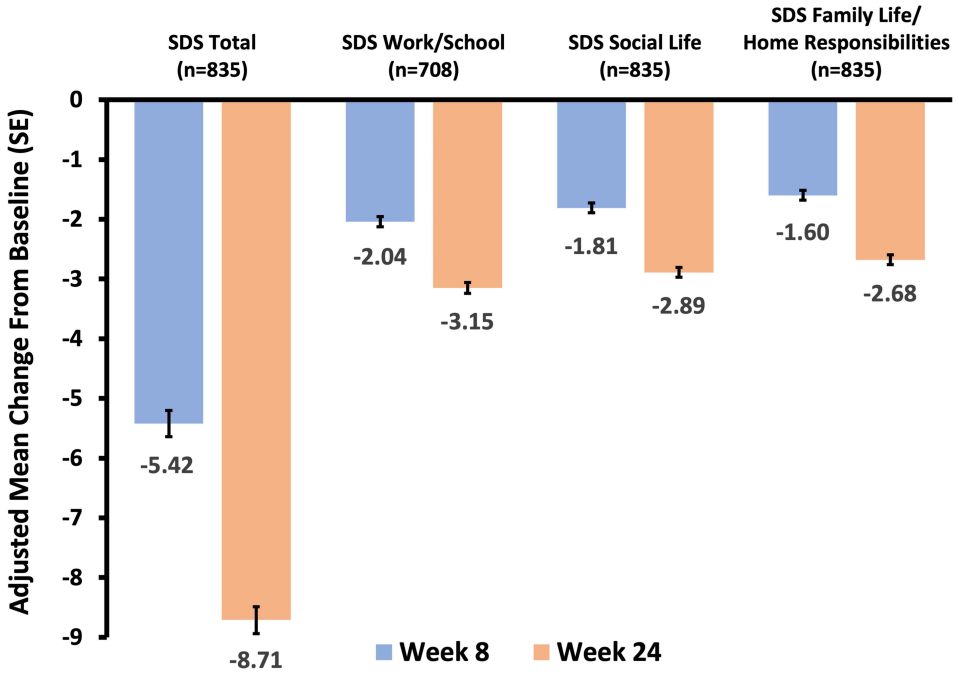


Figure 2 Change in adjusted mean scores from baseline to weeks 8 and 24 for SDS total score and SDS subscores (MMRM analysis).
Notes: Mean (SD) baseline scores: SDS (n=859), 16.7 (6.93); SDS Work/School (n=755), 5.9 (2.69); SDS Social Life (n=859), 5.6 (2.57); SDS Family Life/Home Responsibilities (n=859), 5.3 (2.72). All statistical comparisons were significant vs baseline with $P<0.0001$.
Abbreviations: MMRM, mixed-model repeated measures; SDS, Sheehan Disability Scale.

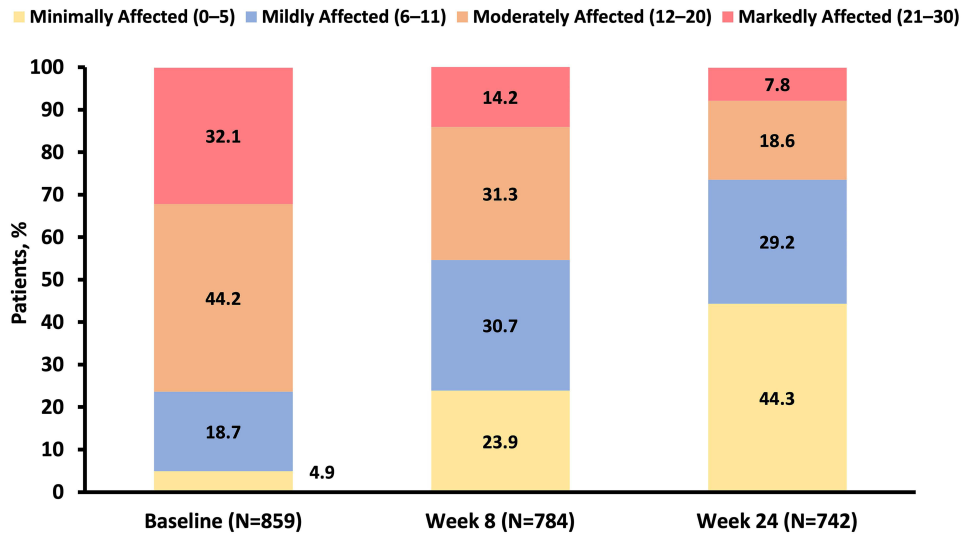


Figure 3 Classification of functional impairment category at baseline, week 8, and week 24.

improvement was observed by the end of the study, with the majority (73.5%) of patients reporting mild or minimal functional impairment. Similar improvements in the proportion of patients who were mildly to minimally affected were also observed across the SDS dimensions of work/school, social life, and family life/home responsibilities (Supplementary Figure 2).

Depression Severity

A decrease in the severity of depression symptoms was observed in the period after initiating vortioxetine treatment. A 5.40-point (95% CI, 5.03–5.77) reduction and 8.15-point (95% CI, 7.76–8.54) reduction occurred in adjusted mean total PHQ-9 score from baseline (16.1 points) at weeks 8 and 24, respectively (P<0.0001 at both time points) (Figure 4A). At baseline, 533 (62.0%) patients were categorized as having moderately severe or severe depression (PHQ-9 score of 15–27), but the majority (67.7%) of patients reported none (PHQ-9 score of 0–4) or mild (PHQ-9 score of 5–9) depression by the end of the study (Supplementary Figure 3A).

Mean HAM-D17 scores were reduced from a baseline of 19.3 points by 8.72 (95% CI, 8.33–9.12) and 12.04 (95% CI, 11.60–12.49) points at weeks 8 and 24, respectively (P<0.0001 at both time points) (Figure 4B). The proportion of patients with moderate or severe depression according to the HAM-D17 scale (score of 15–52) was also reduced from 69.6% at baseline to 18.6% and 9.5% at weeks 8 and 24, respectively (Supplementary Figure 3B).

CGI-S score was also improved, with mean scores reduced by 1.33 (95% CI, 1.26–1.41) and 2.08 (95% CI, 2.00–2.16) points at weeks 8 and 24 from a baseline of 4.3 points (Figure 4C), and the proportion of patients with a CGI-S score of 1–3 (normal to mildly ill) increased from 17.9% at baseline to 70.8% and 88.0% at weeks 8 and 24, respectively

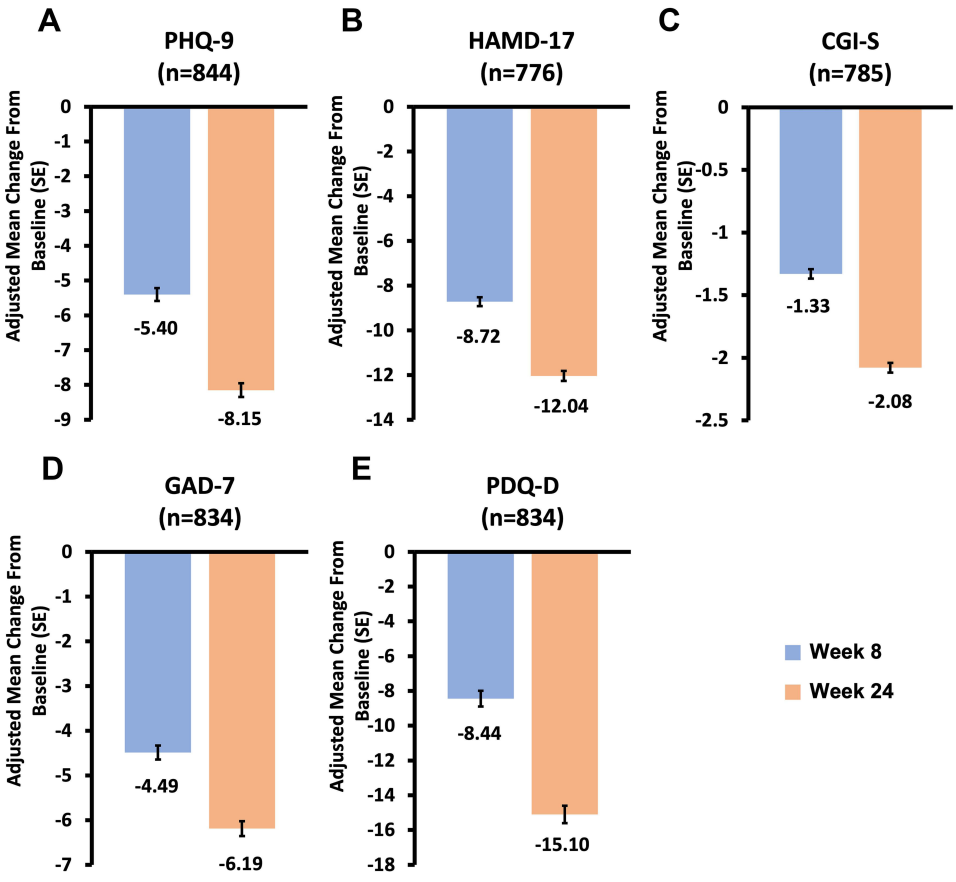


Figure 4 Change in adjusted mean scores from baseline to weeks 8 and 24 for (**A**) PHQ-9, (**B**) HAM-D17, (**C**) CGI-S, (**D**) GAD-7, and (**E**) PDQ-D (MMRM analysis).
Notes: Mean (SD) baseline scores: PHQ-9 (n=859), 16.1 (5.94); HAM-D17 (n=852), 19.3 (5.82); CGI-S (n=859), 4.3 (0.90); GAD-7 (n=857): 12.1 (5.23); PDQ-D (n=856): 36.5 (17.34). All statistical comparisons were significant vs baseline with P<0.0001.
Abbreviations: CGI-S, Clinical Global Impressions–Severity; GAD-7, Generalized Anxiety Disorder Scale–7 items; HAM-D17, Hamilton Depression Rating Scale–17 items; MMRM, mixed-model repeated measures; PDQ-D, Perceived Deficits Questionnaire–Depression; PHQ-9, Patient Health Questionnaire–9 items.

(Supplementary Figure 3C). Mean CGI-I was 2.48 points (95% CI, 2.41–2.54) at week 8 and 1.99 points (95% CI, 1.91–2.07) at week 24 (Supplementary Figure 3D).

Anxiety Symptoms

The severity of anxiety symptoms was reduced after initiating treatment with vortioxetine. Mean baseline GAD-7 score (12.1 points) was reduced by 4.49 (95% CI, 4.19–4.80) and 6.19 (95% CI, 5.87–6.52) points at weeks 8 and 24, respectively ($P<0.0001$ at both time points) (Figure 4D), and the proportion of patients with moderate or severe anxiety according to the GAD-7 scale (score of 10–21) was reduced from 67.3% at baseline to 31.0% and 20.7% at weeks 8 and 24, respectively (Supplementary Figure 4).

Cognitive Symptoms

Symptoms of cognitive dysfunction, assessed using mean PDQ-D score, were reduced by 8.44 (95% CI, 7.55–9.33) and 15.10 (95% CI, 14.11–16.10) points at weeks 8 and 24, respectively, from a baseline of 36.5 points ($P<0.0001$ at both time points) (Figure 4E). The proportion of patients with a PDQ-D score ≥36 decreased from approximately half (50.8%) at baseline to 31.9% and 19.4% at weeks 8 and 24, respectively (Supplementary Figure 5).

Response and Remission Status

At week 8, 49.2% of patients were considered to have responded to treatment with vortioxetine, and 35.8% were in remission. By week 24, the proportion of patients in response and remission increased to 74.7% and 63.9%, respectively (Figure 5).

Safety

Overall, 634 treatment-related AEs were reported by 419 (42.1%) patients (Table 2). The most common treatment-related AE was nausea (18.3% of patients), with all other treatment-related AEs occurring in <5% of patients. The proportion of patients with prescribed overdose of vortioxetine was 21.9% (>10 mg, the maximum indicated dose of vortioxetine in China during the study period). No treatment-related AEs resulting from a drug interaction were reported. Treatment was discontinued following a treatment-related AE in 22 (2.2%) patients, most commonly due to nausea (0.7%), vomiting (0.4%), and constipation (0.2%).

Serious AEs (SAEs) were reported in 42 patients (48 events), including 15 patients with depression (1.5%; 16 events), 4 patients with intentional overdose (0.4%; 4 events), and 3 patients with a suicide attempt (0.3%; 3 events). The 3 suicide attempts occurred on days 49, 82, and 86 after the first study dose, respectively. All 3 patients recovered without hospitalization and continued in the study. Only 5 (0.5%) SAEs were considered possibly or probably related to

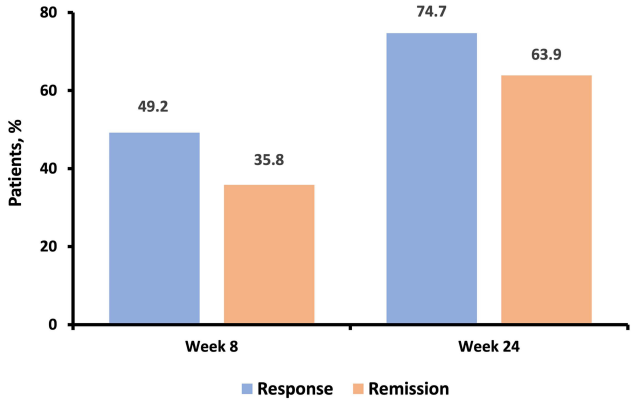


Figure 5 Response and remission rates at weeks 8 and 24.
Notes: Response and remission status definitions were based on physician-rated assessments at week 8 or week 24, respectively, as follows: for remission, HAM-D17 total score ≤7 points; for response, a reduction of 50% or more of the HAM-D17 total score.
Abbreviation: HAM-D17, Hamilton Depression Rating Scale–17 items.

Table 2 Treatment-Related AEs Reported During the RELIEVE China Study

	Safety Analysis Population (N=996)
	Patients, n (%)
Treatment-related AEs	419 (42.1)
Treatment-related SAEs	42 (4.2)
Treatment-related AEs leading to discontinuation	22 (2.2)
Deaths, n (%)	0 (0.0)
Treatment-related AEs in ≥1.0% of patients	
Prescribed overdose[a]	218 (21.9)
Nausea	182 (18.3)
Dizziness	32 (3.2)
Vomiting	31 (3.1)
Pruritus	24 (2.4)
Headache	13 (1.3)
Decreased appetite	11 (1.1)
Somnolence	10 (1.0)

Notes: [a]Vortioxetine doses of >10 to 20 mg administered prior to August 2020 were coded as a "prescribed overdose" because dosing at this level had not been approved by the Chinese National Medical Products Administration at that time.
Abbreviations: AE, adverse event; SAE, serious adverse event.

treatment, including 3 cases of depression (0.3%; 3 events) and 1 event each of discomfort and suicide attempt (0.1% of patients). No deaths were reported during the study period.

Discussion

Patients with MDD in this study had improved overall function and ameliorated cognitive symptoms, in addition to reduced symptoms of depression and anxiety, after initiating vortioxetine treatment in a real-world setting. Vortioxetine also appeared to be well tolerated, and a low proportion of patients discontinued treatment because of treatment-related AEs. No new safety concerns were identified.

The functional and cognitive improvements observed in the RELIEVE China study are consistent with observations of the efficacy of vortioxetine in RCTs,[15,22–26,31] as well as with a similar study observing real-world patients with MDD in North America and Europe after they initiated treatment with vortioxetine.[32] For example, vortioxetine 10 mg was associated with a 7.59-point reduction in total SDS score after 8 weeks when starting from a baseline of 18.9 points in an earlier randomized controlled trial in Asia compared with a 5.42-point reduction from a baseline of 16.7 points in the current study.[31] In addition, the 8.44-point reduction in PDQ score observed among patients treated with vortioxetine in the RELIEVE China study at week 8 (baseline, 36.5 points) is also similar to the 12.2- to 13.5-point reduction reported in an earlier meta-analysis of patients with MDD administered vortioxetine 10–20 mg in clinical trials (baseline, 41.1–41.4 points).[22] In particular, the higher baseline scores for patients participating in clinical trials may account for the greater magnitude of reductions within 8 weeks, while the longer follow-up in this study demonstrated that functional improvements continued to accrue between 8 and 24 weeks. However, the current study population observed was younger than the population found to have an MDE or depressive symptoms when screening >500,000 Chinese people (33 vs 51 years).[10]

The National Health Commission of China's action plan to implement a screening program to improve the diagnosis of MDD in China will no doubt identify a significant proportion of the population who are currently undiagnosed and may benefit from vortioxetine therapy.[9] Importantly, despite approximately 80% of Chinese people with an MDE reporting loss of interest, insomnia, tiredness, and difficulty concentrating, <10% of individuals are receiving specific medications for their symptoms.[10]

Given the high proportion of patients in China diagnosed with MDD and presenting with cognitive impairment, which often continues in patients after receiving antidepressant therapy,[18] vortioxetine offers an important treatment option to address these symptoms. Cognitive and functional symptoms in MDD are also inherently linked, so any improvement in cognitive and functional impairment associated with vortioxetine may be expected to improve quality of life and productivity among Chinese patients with MDD.[19,20,33]

Vortioxetine was well tolerated, and the safety profile in this real-world study population of Chinese patients with MDD was consistent with the known profile of observations from clinical trials and other real-world studies of vortioxetine.[31,32,34] Nausea was the most common treatment-related AE, but this has previously been reported as generally occurring within the first few weeks of initiating treatment and tends to be transient in nature.[34]

The relatively high proportion of patients (>20%) prescribed an overdose of vortioxetine in this study, which accounted for approximately one-third of treatment-related AEs, can be explained by marketing authorization for a 20-mg dose of vortioxetine approved by the Chinese National Medical Products Administration in August 2020, when the study was already underway. Therefore, any prescribed dosage of >10 mg to 20 mg of vortioxetine has been coded as a prescribed overdose in the context of this study, even though this dosing regimen was approved in many jurisdictions outside China. However, the interim results of this study[35] demonstrated safety of the higher dose, and the need for higher dosing to achieve adequate effectiveness in some patients, directly supporting the need for an expanded label for vortioxetine in China.

While the mechanisms of action of many herbal medicines used in traditional Chinese medicine (TCM) have not been fully characterized, they are hypothesized to involve some pathways also targeted by antidepressants.[19] Therefore, the absence of drug-drug interaction–related AEs is important in a real-world population of patients in China, where TCM has historically been used to treat depression, and many patients use herbal medicine, vitamins, and other health products to manage MDD.[10,19]

This study has several strengths, including a large sample size and long-term follow-up over 6 months. A wealth of naturalistic information was also derived from both physician- and patient-reported information on the current MDE, as well as functional outcomes. However, this study was limited by its observational nature, the lack of a comparator arm, and patients being enrolled both prior to and during the COVID-19 pandemic, which may have affected treatment and visit patterns. The lack of a comparator arm also means that the relative effectiveness of vortioxetine versus other treatment options could not be assessed.

Conclusions

This study supports the short- and long-term effectiveness of vortioxetine in patients with MDD in a real-world setting in China and was consistent with the efficacy and safety profile of vortioxetine observed during RCTs. Particularly, patients treated with vortioxetine demonstrated reduced functional impairment as assessed by SDS score, which was associated with a high remission rate, and depression severity decreased after initiating treatment. Cognitive symptoms and anxiety symptoms also improved. Vortioxetine was well tolerated in this large population of patients with MDD, with no new safety concerns observed compared with prior RCTs. These findings support the effectiveness of vortioxetine in the treatment of patients with MDD in China in a real-world setting.

Data Sharing Statement

The authors confirm that the data supporting the findings of this study are available within the article. The authors may be contacted for further data sharing.

Ethics Approval and Informed Consent

The study was conducted in accordance with Good Clinical Practice guidelines, the principles of the Declaration of Helsinki, and local laws; as there was no central IRB available in China, the study was approved by the independent ethics committee of each participating study site. All participants provided written informed consent prior to enrollment.

Consent for Publication

This manuscript does not contain patient-sensitive material; therefore, no consent is needed.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

GW has received honoraria for being an advisor to or providing educational talks for Lundbeck, Pfizer, Sumitomo, Johnson & Johnson, and Eli Lilly. JM is a full-time employee of Lundbeck China. EHR and LHH are full-time employees of H. Lundbeck A/S. HR and KS were employees of H. Lundbeck A/S at the time of the study. ZW, LB, XX, and PG report costs for conducting clinical study from Lundbeck, during the conduct of the study. The authors report no other conflicts of interest in this work.

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