Effectiveness of Vortioxetine in Working Patients with Major Depressive Disorder in China: A Subgroup Analysis of the RELIEVE China Study

Gang Wang, Tianmei Si, Andreas Rieckmann, Jingdong Ma, Michael Cronquist Christensen

Background: Major depressive disorder (MDD) causes significant functional impairments that impact on all aspects of patients' daily lives, including their ability to work, work productivity, and social life.

Purpose: To assess the real-world effectiveness of the multimodal antidepressant vortioxetine in working patients with MDD in China.

Patients and methods: RELIEVE China was an observational, prospective cohort study. Patients (aged ≥18 years) with MDD initiating treatment with vortioxetine in routine clinical practice settings were followed for 24 weeks. In this subgroup analysis, functioning was assessed using the Sheehan Disability Scale (SDS) in patients in full- or part-time work or education at baseline who remained on treatment at all follow-up visits (n=424). Depressive, cognitive, and anxiety symptoms were also assessed. For all endpoints, mean change from baseline at weeks 8 and 24 was analyzed using mixed models for repeated measures.

Results: Clinically relevant and sustained improvements in patient functioning and measures of work productivity were observed over the 24 weeks of vortioxetine treatment. The adjusted mean (standard error) reduction in SDS total score from baseline was 5.4 (0.3) points at week 8 and 8.7 (0.3) points at week 24 (both P<0.001 vs baseline). Significant improvements were observed across all SDS domains and in levels of absenteeism and presenteeism (P<0.001 vs baseline for all endpoints at both time points). Significant improvements in depressive, cognitive, and anxiety symptoms were also observed over the study period (all P<0.001 vs baseline). The proportion of patients in remission (ie, 17-item Hamilton Depression Rating Scale score ≤7) after 24 weeks of vortioxetine treatment was 65.4%. Vortioxetine was well tolerated; nausea was the most common adverse event, reported by 18.6% of patients.

Conclusion: These findings support the effectiveness and tolerability of vortioxetine in working patients with MDD receiving treatment in routine clinical practice settings in China.

Keywords: China, cognitive symptoms, major depressive disorder, patient functioning, vortioxetine, work productivity

Introduction

Depression is a highly prevalent and debilitating condition that is estimated to affect approximately 280 million people worldwide, including over 50 million people in China alone. It is a leading cause of disability and a major contributor to the overall global burden of disease. Depression is associated with functional impairments that have a detrimental impact on all aspects of patients' daily lives, including their ability to work and their productivity while at work. As such, the economic impact of depression in the workplace is considerable. Indeed, work-related costs have been shown to account for a major proportion of the overall economic burden of depression. In 2016, the mean annual population-
level cost of depression-associated absenteeism (ie, days lost from work) and presenteeism (ie, lower productivity while at work) in China was estimated to be US$20 billion, 80% of which was attributable to presenteeism.6

Data from the landmark Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study have shown that individual symptoms differ in their impact on psychosocial functioning in patients with major depressive disorder (MDD), with sad mood, cognitive symptoms, fatigue, and loss of interest having the greatest impact.9 Cognitive symptoms (eg, impairments in attention, memory, processing speed, and all aspects of executive functioning) are common in patients with depression.10–12 In a prospective real-world study undertaken in China to assess the prevalence and course of cognitive symptoms in patients with MDD initiating new antidepressant treatment, approximately 75% of patients presented with cognitive symptoms and these persisted after 6 months of antidepressant therapy in almost one-third of patients.13 The severity of cognitive symptoms was found to be significantly associated with functional outcomes in these patients, including levels of absenteeism and presenteeism, independent of the severity of mood symptoms.13,14 Other studies have also found severity of cognitive symptoms to be an independent and significant determinant of subsequent functional impairment in patients with MDD.15–17 A broad-spectrum procognitive antidepressant with efficacy across the range of symptoms experienced by patients with MDD, including cognitive functioning, could therefore be particularly useful for treating depression in working patients.

Vortioxetine has been shown to have procognitive effects in patients with MDD.18–21 Improvements in multiple domains of cognitive functioning have been reported during treatment with vortioxetine, including global cognition, executive functioning, processing speed, attention, and working memory.18,20 Vortioxetine has also been shown to improve functioning and work productivity in working patients with MDD.16,22–25 However, data are lacking on the effectiveness of vortioxetine in working patients with MDD in China. The RELIEVE China study was undertaken to investigate the effectiveness of vortioxetine in patients with MDD receiving treatment in routine care settings. The overall findings of this study have been reported previously.26 This paper presents the results of a subgroup analysis undertaken to assess the effectiveness of vortioxetine in the large cohort of patients in full- or part-time work or education participating in this study who initiated treatment with vortioxetine and remained on vortioxetine throughout the study.

Methods

Study Design and Participants

RELIEVE China was a 6-month, observational, prospective cohort study conducted in routine practice settings at 18 sites in China from December 2018 to August 2020. The study design has been reported in detail previously.26 Briefly, participants were adults (aged ≥18 years) with MDD who were experiencing a major depressive episode (MDE; International Classification of Diseases, 10th Revision criteria) for which they were initiating treatment with vortioxetine in accordance with the local prescribing information at the investigator’s discretion. Exclusion criteria included: a comorbid diagnosis of schizophrenia, bipolar disorder, or any other neurodegenerative disease significantly affecting cognitive function; suicide attempt within the last 6 months; and treatment-resistant depression (ie, lack of response to two or more drugs for depression for the current MDE). This paper presents the results of post hoc subgroup analyses conducted in patients in full- or part-time work or education at baseline who initiated treatment with vortioxetine and remained on vortioxetine throughout the study.

Study Assessments

Patients were assessed at routine clinic visits at baseline, week 8 (−1/+3 weeks), and week 24 (±4 weeks). The primary study outcome was the change from baseline in overall patient functioning on the Sheehan Disability Scale (SDS). The SDS assesses the impact of depressive symptoms on patient functioning across three important domains: work/school, social life, and family life/home responsibilities. Patients rate the severity of impairment in each domain over the past 7 days on a scale of 0–10, with higher values indicating greater impairment. Scores for the individual domains are combined to generate the total SDS score (range, 0–30). A reduction (ie, improvement) in SDS total score of ≥4 points is
The SDS also reports on the number of work/school days that were lost or were underproductive during the preceding week (ie, absenteeism and presenteeism, respectively).

Secondary study outcomes included: depression severity assessed by the patient using the 9-item Patient Health Questionnaire (PHQ-9), and by the physician using the 17-item Hamilton Depression Rating Scale (HAM-D17) and the Clinical Global Impressions–Severity of Illness (CGI-S) scale; cognitive symptoms assessed using the Perceived Deficits Questionnaire–Depression (PDQ-D); and anxiety symptoms assessed using the Generalized Anxiety Disorder 7-item (GAD-7) scale. Adverse events (AEs) were recorded using Medical Dictionary for Regulatory Activities (MedDRA) Version 23.0 preferred terms.

**Statistical Analysis**

This subgroup analysis included all eligible patients from the RELIEVE China study who were in full- or part-time work or education at baseline, initiated treatment with vortioxetine, and remained on treatment at all follow-up visits.

Effectiveness outcomes were analyzed using a mixed model for repeated measures, with an unstructured covariance matrix. The following baseline variables were added as fixed effects: analysis time point and baseline score, age, vortioxetine treatment line (first, second, or third or higher), sex, education level, duration of the current MDE, presence of any other psychiatric disorder, presence of a somatic disorder, and site. For SDS, PDQ-D, and GAD-7 analyses, HAM-D17 score was also included as a baseline variable to adjust for baseline disease severity. All models also included an interaction term of baseline score by analysis time point.

For patient functioning, change in SDS total score from baseline at weeks 8 and 24 was also analyzed by vortioxetine treatment line (first, second, and third or higher) and duration of MDD (≤52 or >52 weeks). The proportion of patients reporting minimal, mild, moderate, or severe functional impairment (defined as SDS total scores of 0–5, 6–11, 12–20, and 21–30, respectively) was assessed at each time point. Data on absenteeism and presenteeism were summarized descriptively and the changes from baseline to weeks 8 and 24 were analyzed by Wilcoxon signed rank test. The proportion of patients achieving response or remission was assessed at weeks 8 and 12. Response was defined as ≥50% reduction in HAM-D17 score from baseline, while remission was defined by a HAM-D17 score of ≤7. Safety endpoints were summarized descriptively.

In a sensitivity analysis, we applied an adherence-adjusted analysis using inverse probability of censoring weights to assess the robustness of the main analyses (see Supplementary Appendix, Supplementary Tables 1 and 2, and Supplementary Figure 1).

Statistical analyses were performed using R (version 4.2.1; R Core Team, Vienna, Austria) and SAS (version 9.4; SAS Institute Inc., Cary, NC, USA). The significance level was set at \( P<0.05 \) (two-sided).

**Results**

**Baseline Characteristics**

Of the 682 patients enrolled in the RELIEVE China study who were in full- or part-time work or education at baseline, 424 (62.2%) initiated treatment with vortioxetine and remained on treatment at all follow-up visits and were included in this subgroup analysis. Almost all patients (419 [98.8%]) were in full-time work or education. Baseline demographics and clinical characteristics are shown in Table 1. Most patients were female (63.0%), single (60.4%), had university-level or postgraduate education (67.5%), and were living in an urban area (88.7%). Mean (standard deviation [SD]) age was 30.5 (11.1) years. Just over half of all patients (51.9%) had a comorbid psychiatric disorder, most commonly an anxiety (38.9%) or sleep (24.3%) disorder. On average, patients had moderately severe mood, cognitive, and anxiety symptoms and were experiencing moderately severe functional impairment at baseline. The mean (SD) duration of the current MDE was 37.8 (73.8) weeks and in 33.5% of patients the current MDE had persisted for more than 24 weeks.

**Vortioxetine Treatment**

Over half of all patients (57.8%) were receiving vortioxetine as first-line treatment for the current MDE. Vortioxetine dosing is summarized in Figure 1. Most patients (368/424; 86.8%) initiated vortioxetine at a dose of 10 mg/day; this was
Table 1 Baseline Demographics and Clinical Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Working Patients with MDD (N=424)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>30.5 ± 11.1</td>
</tr>
<tr>
<td>Female sex</td>
<td>267 (63.0)</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>256 (60.4)</td>
</tr>
<tr>
<td>Married/living together</td>
<td>156 (36.8)</td>
</tr>
<tr>
<td>Divorced/separated</td>
<td>9 (2.1)</td>
</tr>
<tr>
<td>Widowed</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Unknown</td>
<td>2 (0.5)</td>
</tr>
<tr>
<td>Urban living area</td>
<td>376 (88.7)</td>
</tr>
<tr>
<td>Educational level</td>
<td></td>
</tr>
<tr>
<td>Elementary school</td>
<td>5 (1.2)</td>
</tr>
<tr>
<td>Middle school</td>
<td>36 (8.5)</td>
</tr>
<tr>
<td>High school</td>
<td>44 (10.4)</td>
</tr>
<tr>
<td>Junior college</td>
<td>53 (12.5)</td>
</tr>
<tr>
<td>University</td>
<td>230 (54.2)</td>
</tr>
<tr>
<td>Postgraduate school or above</td>
<td>56 (13.2)</td>
</tr>
<tr>
<td>Employment type</td>
<td></td>
</tr>
<tr>
<td>Full-time</td>
<td>419 (98.8)</td>
</tr>
<tr>
<td>Part-time</td>
<td>5 (1.2)</td>
</tr>
<tr>
<td>Time since first MDD diagnosis (years)</td>
<td>1.7 ± 3.4</td>
</tr>
<tr>
<td>Current MDE</td>
<td></td>
</tr>
<tr>
<td>Duration (weeks)</td>
<td>37.8 ± 73.8</td>
</tr>
<tr>
<td>≤4 weeks</td>
<td>110 (25.9)</td>
</tr>
<tr>
<td>&gt;4–≤24 weeks</td>
<td>172 (40.6)</td>
</tr>
<tr>
<td>&gt;24 weeks</td>
<td>142 (33.5)</td>
</tr>
<tr>
<td>No. of prior MDEs&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.4 ± 3.3</td>
</tr>
<tr>
<td>≥1 relevant comorbidity at baseline</td>
<td>236 (55.7)</td>
</tr>
<tr>
<td>≥1 psychiatric comorbidity at baseline</td>
<td>220 (51.9)</td>
</tr>
<tr>
<td>Anxiety disorder</td>
<td>165 (38.9)</td>
</tr>
<tr>
<td>Sleep disorder</td>
<td>103 (24.3)</td>
</tr>
<tr>
<td>Vortioxetine treatment line</td>
<td></td>
</tr>
<tr>
<td>First</td>
<td>245 (57.8)</td>
</tr>
<tr>
<td>Second</td>
<td>141 (33.3)</td>
</tr>
<tr>
<td>Third or later</td>
<td>38 (9.0)</td>
</tr>
<tr>
<td>Baseline assessments</td>
<td></td>
</tr>
<tr>
<td>SDS total score</td>
<td>16.5 ± 7.0</td>
</tr>
<tr>
<td>SDS work/school score&lt;sup&gt;b&lt;/sup&gt;</td>
<td>5.9 ± 2.7</td>
</tr>
<tr>
<td>SDS social life score</td>
<td>5.5 ± 2.5</td>
</tr>
<tr>
<td>SDS family life/home responsibilities score</td>
<td>5.0 ± 2.8</td>
</tr>
<tr>
<td>PHQ-9 total score</td>
<td>15.9 ± 6.0</td>
</tr>
<tr>
<td>HAM-D17 total score&lt;sup&gt;c&lt;/sup&gt;</td>
<td>18.7 ± 6.0</td>
</tr>
<tr>
<td>CGI-S score</td>
<td>4.2 ± 0.9</td>
</tr>
<tr>
<td>PDQ-D score&lt;sup&gt;d&lt;/sup&gt;</td>
<td>37.2 ± 17.5</td>
</tr>
<tr>
<td>GAD-7 total score&lt;sup&gt;d&lt;/sup&gt;</td>
<td>12.0 ± 5.3</td>
</tr>
</tbody>
</table>

Notes: Data are mean ± standard deviation or n (%). <sup>a</sup>n=421. <sup>b</sup>n=405. <sup>c</sup>n=422. <sup>d</sup>n=423.

Abbreviations: CGI-S, Clinical Global Impressions–Severity of Illness scale (range, 1–7); GAD-7, Generalized Anxiety Disorder 7-item scale (range, 0–21); HAM-D17, 17-item Hamilton Depression Rating Scale (range, 0–54); MDD, major depressive disorder; MDE, major depressive episode; PDQ-D, Perceived Deficits Questionnaire–Depression (range, 0–80); PHQ-9, 9-item Patient Health Questionnaire (range, 0–27); SDS, Sheehan Disability Scale (range, 0–30).
the approved dosage for vortioxetine in China when this study was conducted. At week 24, 74.8% of patients (317/424) were receiving vortioxetine 10 mg/day.

Effectiveness
Patient Functioning
Clinically relevant improvement in overall functioning (ie, a decrease in SDS total score of ≥4 points) was observed after 8 weeks of vortioxetine treatment, with further improvement seen at 24 weeks (Figure 2). The adjusted mean (standard error [SE]) reduction in SDS total score from baseline was 5.4 (0.3) points at week 8 and 8.7 (0.3) points at week 24 (both \(P<0.001\) vs baseline). Improvements were observed across all SDS domains (all \(P<0.001\) vs baseline at both time points).

Figure 1  Vortioxetine dosing in working patients with major depressive disorder over the 6-month study period (\(n=424\)).
Note: Cited one-decimal-place values may not sum to 100% because of rounding.

Figure 2  Adjusted mean (SE) change from baseline to weeks 8 and 24 for SDS total and domain scores (mixed-model repeated measures analysis).
Note: \(P<0.001\) for all changes from baseline.
Abbreviations: SDS, Sheehan Disability Scale; SE, standard error.
points), with the greatest improvements seen in the SDS work/school domain. Results of the adherence-adjustment analysis using inverse probability of censoring weights revealed no evidence of adherence bias (see Supplementary Appendix).

As shown in Figure 3, most patients (74.3%) had moderate or severe functional impairment at baseline (i.e., SDS total score ≥12). After 8 weeks of vortioxetine treatment, 57.0% of patients reported only mild or minimal functional impairment (SDS total score ≤11). The proportion of patients reporting mild or minimal functional impairment further increased to 74.2% after 24 weeks of vortioxetine treatment, with 43.4% of patients reporting no or only minimal functional impairment at this time.

A reduction in the number of working days lost to absenteeism and presenteeism was seen over the 24 weeks of vortioxetine treatment. The mean (SD) number of working days lost due to absenteeism during the previous week decreased from 2.0 (2.4) days at baseline to 1.4 (2.2) days at week 8 and 0.8 (1.6) days at week 24 (both P<0.001 vs baseline). The mean (SD) number of working days lost due to presenteeism during the previous week was 4.0 (2.3) days at baseline compared with 2.6 (2.3) days at week 8 and 2.0 (2.1) days at week 24 (both P<0.001 vs baseline).

Clinically relevant improvement in functioning (i.e., a decrease in SDS total score ≥4 points) was observed over the 24 weeks of treatment irrespective of vortioxetine treatment line or duration of MDD (Figure 4).

**Depressive Symptoms**

Statistically significant improvements in patient-reported and clinician-assessed measures of depressive symptom severity were also seen over the 24 weeks of vortioxetine treatment (Figure 5). Adjusted mean (SE) reductions from baseline at weeks 8 and 24, respectively, were as follows: 5.6 (0.2) and 8.4 (0.3) points for PHQ-9 score; 8.7 (0.3) and 12.0 (0.3) points for HAM-D17 score; and 1.4 (0.05) and 2.1 (0.06) points for CGI-S score (all changes, P<0.001 vs baseline). Response (i.e., ≥50% reduction in HAM-D17 score from baseline) was seen in 47.7% of patients at week 8 and 73.8% at week 24. The proportion of patients in remission (i.e., HAM-D17 score ≤7) was 35.9% after 8 weeks of vortioxetine treatment, increasing to 65.4% after 24 weeks.

**Cognitive Symptoms**

Significant improvements in patient-reported cognitive symptoms were seen over the 24 weeks of vortioxetine treatment (Figure 5). The adjusted mean (SE) reduction in PDQ-D score from baseline was 9.6 (0.6) points at week 8, increasing to 16.8 (0.7) points at week 24 (both P<0.001 vs baseline).

---

**Figure 3** Change in level of functional impairment over time in working patients with MDD treated with vortioxetine.

**Notes:** Sheehan Disability Scale total score ranges for levels of functional impairment: minimal (0–5), mild (6–11), moderate (12–20), severe (21–30). Cited one-decimal-place values may not sum to 100% because of rounding.
Anxiety Symptoms

Significant improvements in anxiety symptoms were also observed at weeks 8 and 24, with adjusted mean (SE) improvements in GAD-7 score from baseline of 4.8 (0.2) and 6.6 (0.2) points, respectively (both \( P < 0.001 \) vs baseline) (Figure 5).

Safety

A total of 169 patients (39.9%) reported at least one treatment-related AE during the 24 weeks of vortioxetine treatment (Table 2), the most common of which was nausea, which was reported by 79 patients (18.6%). No other treatment-related

---

**Figure 4** Adjusted mean (SE) change from baseline to weeks 8 and 24 for SDS total score by (A) vortioxetine treatment line and (B) duration of MDD (mixed-model repeated measures analysis).

**Note:** \( P < 0.001 \) for all changes from baseline.

**Abbreviations:** SDS, Sheehan Disability Scale; MDD, major depressive disorder; SE, standard error.
AEs were reported by >5% of patients. Serious AEs were reported for 14 patients (3.3%). Only one treatment-related serious AE was reported (discomfort; 0.2%).

**Discussion**

Functional impairment contributes substantially to the social and economic burden of MDD.28 Functional recovery is therefore a key treatment goal.28–30 Patients consider functional recovery to be important for achieving remission from depression.31 However, functional impairment may persist after other symptoms have resolved.30,32,33 This is of clinical significance, as residual functional impairment has been shown to predict subsequent relapse.34

To our knowledge, this is the first study to assess the long-term effectiveness of vortioxetine for the treatment of MDD in working patients in China. In patients who remained on treatment at all visits over the 24 weeks of follow-up, statistically significant and clinically relevant improvements were seen in patients’ overall daily functioning, as assessed by the SDS, both in their work/school, social, and family life and in their work productivity (ie, levels of absenteeism and presenteeism). While most patients reported moderate or severe functional impairment at baseline, almost three-quarters

**Figure 5** Adjusted mean (SE) change from baseline to weeks 8 and 24 for PHQ-9, HAM-D17, CGI-S, GAD-7, and PDQ-D scores (mixed-model repeated measures analysis).

**Note:** *P*<0.001 for all changes from baseline.

**Abbreviations:** CGI-S, Clinical Global Impressions–Severity of Illness scale; GAD-7, Generalized Anxiety Disorder 7-item scale; HAM-D17, 17-item Hamilton Depression Rating Scale; PDQ-D, Perceived Deficits Questionnaire–Depression; PHQ-9, 9-item Patient Health Questionnaire; SE, standard error.

<table>
<thead>
<tr>
<th>Table 2 Summary of AEs Reported in Adhering Working Patients During the Study</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adhering Working Patients (N=424)</strong></td>
</tr>
<tr>
<td>Patients with at least one treatment-related AE</td>
</tr>
<tr>
<td>Patients with serious AE</td>
</tr>
<tr>
<td>Treatment-related serious AE</td>
</tr>
<tr>
<td>Treatment-related AEs with incidence of ≥2% of patients</td>
</tr>
<tr>
<td>Nausea</td>
</tr>
<tr>
<td>Dizziness</td>
</tr>
<tr>
<td>Pruritus</td>
</tr>
</tbody>
</table>

**Notes:** Data are n (%). Adhering patients initiated treatment with vortioxetine and remained on treatment at all follow-up visits.

**Abbreviation:** AE, adverse event.
of all patients reported only minimal or mild functional impairment after 24 weeks of vortioxetine treatment. At baseline, patients reported that they had missed a mean of nearly 2 working days during the previous week and deemed most of their time spent at work to be unproductive (4 days). At the end of the study, patients reported missing <1 day of work and a 50% reduction in the number of days deemed unproductive during the previous week.

Statistically significant and clinically relevant improvements were also observed in depressive symptoms (PHQ-9, CGI-S, and HAM-D17 scores), cognitive symptoms (PDQ-D score), and anxiety symptoms (GAD-7 score) over the 24 weeks of vortioxetine treatment. Consistent with the results for the overall study population,\textsuperscript{26} at the end of the study, almost two-thirds of patients were in remission from their depressive symptoms (ie, HAM-D17 score ≤7 points). Long-term treatment with vortioxetine was well tolerated in working patients and safety findings were similar to those reported in the overall study population.\textsuperscript{26} Consistent with the well-established tolerability profile of vortioxetine,\textsuperscript{35,36} nausea was the most common AE. Clinical experience shows that, if patients experience nausea when initiating vortioxetine, this tends to be transient, mostly occurring during the first week of treatment.\textsuperscript{36}

Our findings provide further evidence for the effectiveness of vortioxetine in treating working patients with MDD. In a study undertaken to assess the effectiveness of vortioxetine for the treatment of MDD in working patients in Canada, statistically significant and clinically relevant improvements in functioning and work productivity, as assessed by the Work Productivity and Activity Impairment Questionnaire and the Work Limitation Questionnaire, were observed over 52 weeks of follow-up.\textsuperscript{16,24} After factoring in the cost of therapy (2017 costs), these observed improvements in workplace productivity translated into potential savings for the employer of CAN$4550 per patient over the 52 weeks of vortioxetine treatment.\textsuperscript{37}

In a recent 8-week comparative study, vortioxetine was found to be significantly more effective than the serotonin-norepinephrine reuptake inhibitor desvenlafaxine for improving overall, daily, and social functioning assessed by the Functioning Assessment Short Test (FAST) in working patients with MDD who had experienced a partial response to initial selective serotonin reuptake inhibitor therapy.\textsuperscript{23} Vortioxetine-treated patients were also significantly more likely to experience symptomatic and functional remission, assessed using the CGI-S, than those who received desvenlafaxine (36% vs 25% in the two treatment groups, respectively, at week 8). This is clinically relevant, as remission has been shown to be significantly associated with improved work performance and productivity in employed patients with MDD.\textsuperscript{38}

In another 8-week study in working patients with MDD, significantly greater improvement in overall functioning (assessed by the FAST) versus placebo was seen in patients treated with vortioxetine, but not in those who received paroxetine.\textsuperscript{23} At week 8, vortioxetine-treated patients also showed numerically greater improvements across a battery of cognitive tests compared with placebo, with a standardized effect size for the overall cognition composite score of 0.5, which is well above the accepted cut-off for clinical relevance of 0.2.\textsuperscript{23}

Data from the randomized, placebo-controlled FOCUS study showed that vortioxetine has pronounced beneficial effects on executive functioning, speed of processing, verbal learning, and memory in working patients with MDD, with patients in managerial or professional positions reporting the greatest improvements.\textsuperscript{22} After 8 weeks of treatment, the standardized effect size for mean change in Digit Symbol Substitution Test score from baseline versus placebo was 0.5 in the overall study population receiving vortioxetine 20 mg/day, increasing to 0.6 among working patients and 0.7 among those in managerial or professional positions.

The clinically significant improvements in both cognitive and overall patient functioning in patients with MDD achieved during treatment with vortioxetine have been shown to be independent of the effect of treatment on mood symptoms.\textsuperscript{16,22} The direct effects of vortioxetine on these highly relevant domains in patients with MDD are likely due to vortioxetine’s ability to modulate the activity of other neurotransmitters (ie, norepinephrine, dopamine, acetylcholine, histamine, gamma-aminobutyric acid, and glutamate) in addition to its multimodal serotonergic actions (namely, 5-HT\textsubscript{1D}, 5-HT\textsubscript{3} and 5-HT\textsubscript{7} receptor antagonism, 5-HT\textsubscript{1B} receptor partial agonism, 5-HT\textsubscript{1A} receptor agonism, and serotonin transporter inhibition).\textsuperscript{39,40}

The main strength of this study is that it was conducted under conditions of routine clinical practice in a large heterogeneous population of working patients followed over a period of 6 months, thereby generating valuable real-world evidence to complement the results of shorter-term, randomized controlled clinical trials. It should, however, be noted
that study participants were mostly female, single, had university-level or postgraduate education, and were living in an urban area.

Potential limitations include the observational study design and lack of a placebo control group or active comparator; the fact that the study was conducted during the COVID-19 pandemic, potentially impacting on study visits for some patients; and that this subgroup analysis included only patients who remained on vortioxetine treatment for the full 24 weeks of follow-up. If excluded patients discontinued vortioxetine treatment due to insufficient benefit, the effectiveness of vortioxetine could potentially have been overestimated; however, additional analyses did not indicate such bias (see Supplementary Appendix).

Objective tests of neurocognitive function were not undertaken; however, such tests are not routinely used for the assessment of cognitive function in clinical care settings as they are often time-consuming and must be administered by trained professionals. In this study, the severity of cognitive symptoms was assessed using the PDQ-D. The Chinese version of the PDQ-D has been shown to be psychometrically valid for the evaluation of subjective cognitive symptoms in patients with MDD.

It should also be noted that the 20 mg/day dose of vortioxetine was first approved by the Chinese National Medical Products Administration in August 2020. Consequently, most patients in this study were receiving vortioxetine at a dose of 10 mg/day. However, vortioxetine has been shown to have a clear dose–response relationship across the spectrum of symptoms experienced by patients with MDD. For example, a recent meta-analysis found that vortioxetine 20 mg/day results in an earlier and more sustained symptomatic response (ie, ≥50% decrease in Montgomery-Åsberg Depression Rating Scale total score) than vortioxetine 10 mg/day in patients with MDD, without compromising tolerability. It is therefore likely that even greater benefits may have been observed if more patients in the present study had been receiving the optimal vortioxetine dose of 20 mg/day.

Conclusion
In summary, working patients with MDD in China who were treated with vortioxetine in routine clinical practice experienced clinically relevant and sustained improvements in overall functioning and measures of work productivity during the 24 weeks of treatment, as well as significant improvements in depressive, cognitive, and anxiety symptoms. Approximately two-thirds of patients were in remission at week 24. Vortioxetine was well tolerated in this population.

Abbreviations
AE, adverse event; CGI-S, Clinical Global Impressions–Severity of Illness; FAST, Functioning Assessment Short Test; GAD-7, Generalized Anxiety Disorder 7-item; HAM-D17, 17-item Hamilton Depression Rating Scale; MDD, major depressive disorder; MDE, major depressive episode; PDQ-D, Perceived Deficits Questionnaire–Depression; PHQ-9, 9-item Patient Health Questionnaire; SD, standard deviation; SDS, Sheehan Disability Scale; SE, standard error.

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 institutional review board available in China, the study was approved by the independent ethics committee of each of the 18 participating study sites: Beijing Anding Hospital, Capital Medical; Xinjiang Mental Health Center; The Third People’s Hospital of Huzhou City; Beijing Huilongguan Hospital; Shandong Mental Health Center; The Affiliated Brain Hospital of Guangzhou Medical University; Peking University Sixth Hospital; The First Hospital of China Medical University; Zhejiang Hospital Southeast University; The First affiliated Hospital of Xi’an Jiaotong University; Renmin Hospital of Wuhan University; Shanghai Mental Health Centre; Tianjin Anding Hospital; Hangzhou Seventh People’s Hospital; Beijing Tiantan Hospital, Capital Medical University; The
Second Xiangya Hospital of Central South University; Nanfang Hospital Southern Medical University; and The First Affiliated Hospital of Zhejiang University School of Medicine. All participants provided written informed consent prior to enrollment.

**Consent for Publication**
As this manuscript does not contain patient-sensitive material, consent is not required.

**Acknowledgments**
The authors thank all participants in the study, as well as the investigators and sites involved in conducting the trial, including Yuping Ning, Tianmei Si, Yanqing Tang, Yonggui Yuan, Xiancang Ma, Hanping Bai, Daidai Peng, Lina Wang, Tao Li, Chunxue Wang, Lingjiang Li, Bin Zhang, and Yi Xu.

**Author Contributions**
All authors made substantial contributions to the conception and design of the study, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

**Funding**
This study was funded by H. Lundbeck A/S, whose personnel contributed to the data analysis, review of the data, and review of this manuscript. Medical writing assistance was provided by Jennifer Coward for Piper Medical Communications, funded by H. Lundbeck A/S.

**Disclosure**
GW has received honoraria for being an advisor to or providing educational talks for Lundbeck, Pfizer, Sumitomo, Johnson & Johnson, and Eli Lilly. TS has received honoraria for being an advisor to or providing educational talks for Lundbeck, Pfizer, Sumitomo, Johnson & Johnson, Eli Lilly, Otsuka, and Biogen. JM is a full-time employee of Lundbeck China. AR and MCC are full-time employees of H. Lundbeck A/S. The authors report no other conflicts of interest in this work.

**References**

Neuropsychiatric Disease and Treatment

Publish your work in this journal

Neuropsychiatric Disease and Treatment is an international, peer-reviewed journal of clinical therapeutics and pharmacology focusing on concise rapid reporting of clinical or pre-clinical studies on a range of neuropsychiatric and neurological disorders. This journal is indexed on PubMed Central, the ‘PsychINFO’ database and CAS, and is the official journal of The International Neuropsychiatric Association (INA). The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit http://www.dovepress.com/testimonials.php to read real quotes from published authors.

Submit your manuscript here: https://www.dovepress.com/neuropsychiatric-disease-and-treatment-journal

Neuropsychiatric Disease and Treatment 2024:20

Dovepress

1223