Head-to-Head Comparison of Vortioxetine Versus Desvenlafaxine in Patients With Major Depressive Disorder With Partial Response to SSRI Therapy:

Results of the VIVRE Study

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ABSTRACT

Objective: To compare the efficacy of vortioxetine and the serotonin-norepinephrine reuptake inhibitor (SNRI) desvenlafaxine in patients with major depressive disorder (MDD) experiencing partial response to initial treatment with a selective serotonin reuptake inhibitor (SSRI).

Methods: This randomized, double-blind, active-controlled, parallel-group, 8-week study of vortioxetine (10 or 20 mg/d; n = 309) versus desvenlafaxine (50 mg/d: n = 293) was conducted from June 2020 to February 2022 in adults with a *DSM-5* diagnosis of MDD who experienced partial response to SSRI monotherapy. The primary endpoint was mean change from baseline to week 8 in Montgomery-Åsberg Depression Rating Scale (MADRS) total score. Differences between groups were analyzed using mixed models for repeated measures.

Results: Non-inferiority of vortioxetine versus desvenlafaxine was established in terms of mean change from baseline to week 8 in MADRS total score; however, a numeric advantage was observed in favor of vortioxetine (difference, −0.47 MADRS points [95% CI, −1.61 to 0.67]; *P* = .420). At week 8, significantly more vortioxetine-treated than desvenlafaxine-treated patients had achieved symptomatic and functional remission (ie, Clinical Global Impressions–Severity of Illness scale [CGI-S] score ≤ 2) (32.5% vs 24.8%, respectively; odds ratio = 1.48 [95% CI, 1.03 to 2.15]; *P* = .034). Vortioxetine-treated patients also experienced significantly greater improvements in daily and social functioning assessed by the Functioning Assessment Short Test (*P* = .009 and .045 vs desvenlafaxine, respectively) and reported significantly greater satisfaction with their medication assessed by the Quality of Life Enjoyment and Satisfaction Questionnaire (*P* = .044). Treatment-emergent adverse events (TEAEs) were reported in 46.1% and 39.6% of patients in the vortioxetine and desvenlafaxine groups, respectively; these were mostly mild or moderate in intensity (> 98% of all TEAEs in each group).

Conclusions: Compared with the SNRI desvenlafaxine, vortioxetine was associated with significantly higher rates of CGI-S remission, better daily and social functioning, and greater treatment satisfaction in patients with MDD and partial response to SSRIs. These findings support the use of vortioxetine before SNRIs in the treatment algorithm in patients with MDD.

Trial registration: ClinicalTrials.gov Identifier: NCT04448431

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Head-to-head studies of antidepressants in patients with major depressive disorder (MDD) are rare, particularly in those experiencing partial or no response to prior therapy. Selective serotonin reuptake inhibitors (SSRIs) are generally used as initial treatment in patients with MDD.[1–5] However, in approximately 50% of patients, symptoms do not improve or show only partial response to initial SSRI therapy.[6] Residual symptoms, such as emotional blunting, are associated with a more severe course of depression and poorer patient outcomes.[7–9] Partial response is also associated with decreased treatment satisfaction[10]; this can lead to non-adherence to medication,[11,12] which increases the risk of worsening symptoms and relapse.[13]

Clinical guidelines recommend switching to an agent from a different pharmacologic class in patients with suboptimal response to initial antidepressant therapy.[1–5] Serotonin-norepinephrine reuptake inhibitors (SNRIs) are typically used as second-line therapy in patients with partial response or non-response to SSRIs. However, this may not be the most appropriate option given the overlapping mechanisms of action and adverse event profiles of these drug classes.[14] Switching to an antidepressant with a mechanism of action that is more distinct from that of SSRIs may be a more appropriate strategy in partial responders.[15]

Vortioxetine is a multimodal antidepressant that mediates its effects through modulation of the activity of several serotonin (5-HT) receptor types (specifically, 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_3, and 5-HT_7 receptors) in addition to inhibition of the 5-HT transporter (the principal target of SSRIs and SNRIs).[16,17] Vortioxetine thereby modulates not only the activity of the serotoninergic system, but also that of other neurotransmitter systems relevant to the neurobiology of depression.[18,19] Vortioxetine has demonstrated efficacy across the spectrum of symptoms experienced by patients with MDD, including depressive, cognitive, and physical symptoms, as well as anxiety and functional impairment.[20–27] Vortioxetine has also been shown to improve functional and occupational outcomes in working patients with MDD.[28–30] This is particularly

Clinical Points

- Head-to-head studies of antidepressants in patients with major depressive disorder (MDD) are rare, particularly in those with inadequate response to prior therapy. This study assessed the efficacy of the multimodal antidepressant vortioxetine versus that of the serotonin-norepinephrine reuptake inhibitor desvenlafaxine in patients with MDD experiencing partial response to treatment with a selective serotonin reuptake inhibitor.
- Vortioxetine was non-inferior to desvenlafaxine in terms of reduction in depression symptom severity assessed using the Montgomery-Åsberg Depression Rating Scale.
- Vortioxetine-treated patients were significantly more likely to achieve symptomatic and functional remission and reported significantly greater improvements in daily and social functioning and significantly greater satisfaction with their medication than those who received desvenlafaxine.

relevant—and warrants further investigation—as most adult patients with MDD remain in work despite their disease and the resulting functional impairment.[31]

In previous comparative studies versus SNRIs in patients with MDD, vortioxetine demonstrated superior efficacy versus venlafaxine extended-release (XR) in terms of depressive symptom reduction[32,33] and versus duloxetine in terms of improvement on a novel dual-outcome composite measure of depressive symptoms and functional capacity.[34,35] It is therefore appropriate to investigate whether vortioxetine should be used earlier in the treatment algorithm in patients with MDD—specifically, before SNRIs in patients with partial response or no response to initial SSRI therapy.

The VIVRE study was an international, active-controlled, double-blind phase IV study undertaken to compare the efficacy of vortioxetine versus desvenlafaxine on depressive symptoms, overall functioning, and health-related quality of life in patients with MDD experiencing only partial response to initial SSRI therapy. Efficacy was also evaluated in the large subgroup of working patients participating in this study. Desvenlafaxine was chosen as the active comparator in this study as it was the most recently approved SNRI in most countries worldwide.

METHODS

Study Design and Participants

This phase IV, multicenter, randomized, double-blind, active-controlled, parallel-group study was conducted at 77 sites across 12 countries (Argentina, Belgium, Bulgaria, Czech Republic, Estonia, Latvia, Mexico, Russia, Slovakia, Spain, Sweden, and Ukraine) from June 2020 to February 2022. Due to the COVID-19 pandemic, a crisis management plan was implemented that allowed remote assessments, except for the screening, baseline, and primary outcome visits.

Participants were outpatients aged 18–65 years with a primary diagnosis of MDD (*Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition [*DSM-5*] criteria, confirmed by the Mini-International Neuropsychiatric Interview[36]), who were experiencing partial response to SSRI monotherapy (ie, escitalopram, sertraline, paroxetine, or citalopram at the approved dose for ≥ 6 weeks) and were, in the investigator's opinion, suitable candidates for switching to an alternative antidepressant. Other inclusion criteria were duration of current major depressive episode of ≥ 3 and < 12 months and baseline Montgomery-Åsberg Depression Rating Scale (MADRS) total score of ≥ 24 points (ie, moderate-to-severe depression). Exclusion criteria included any other current *DSM-5* psychiatric or Axis I disorder, treatment-resistant depression (ie, inadequate response to at least 2 antidepressants for the current depressive episode), baseline Digit Symbol Substitution Test[37] score ≥ 70, history of alcohol/substance use within the past 6 months, and clinically significant risk for suicide.

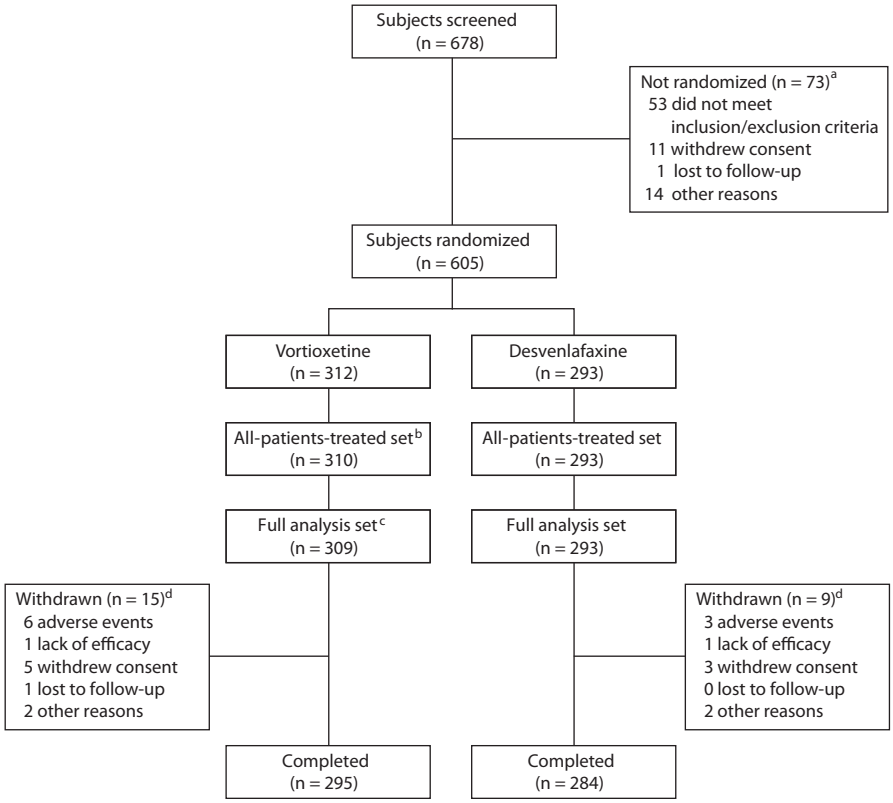
After a 2-week screening period, eligible patients were randomized (1:1) to treatment with vortioxetine (10 or 20 mg/d) or desvenlafaxine (50 mg/d) for 8 weeks, followed by a 4-week safety follow-up period. Study drugs were administered in accordance with local prescribing information. Vortioxetine was initiated at the recommended starting dose of 10 mg/d, with up-titration to 20 mg/d in all patients after 1 week. The vortioxetine dose could then be adjusted (10 or 20 mg/d) at scheduled or unscheduled visits based on investigator judgment until week 4; after week 4, no further dose adjustments were permitted. Patients in the desvenlafaxine group received the recommended dose of 50 mg/d. To maintain the blind, desvenlafaxine dose adjustment could be requested up to week 4 based on patient response and the investigator's clinical judgment. However, as highlighted in the prescribing information for desvenlafaxine, there is no evidence that doses > 50 mg/d confer any additional clinical benefit, and adverse events and withdrawals are more frequent at higher doses.[38,39] Consequently, even if desvenlafaxine dose adjustment was requested, the dosage was not changed and patients continued to receive 50 mg/d throughout the study period. Prior SSRI monotherapy was discontinued before the baseline visit, with dose-tapering if required.

The study (ClinicalTrials.gov identifier: NCT04448431) was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines and was approved by the local ethics committee at each study site. Patients provided written informed consent before participation.

Study Assessments

All assessment scales and questionnaires were administered in the local language. Severity of core depressive symptoms was assessed by MADRS total score.[40] Overall disease severity and its impact on global patient functioning was assessed using the Clinical Global Impressions–Severity of Illness scale (CGI-S) and CGI-Improvement scale (CGI-I).[41] Patient functioning was also assessed using the Functioning Assessment Short

Figure 1. Patient Disposition (CONSORT Diagram)



[a]More than one reason could be reported for a single patient.
[b]Two patients in the vortioxetine group did not receive study medication.
[c]One patient in the vortioxetine group was excluded from the full analysis set as they did not have any valid post-baseline assessment for Montgomery-Åsberg Depression Rating Scale total score.
[d]Primary reason for withdrawal.

Test (FAST). This clinician-rated scale assesses functioning over the past 14 days across 6 domains: autonomy (ie, daily functioning), occupational functioning, cognitive functioning, financial issues, interpersonal relationships (ie, social functioning), and leisure time.[42] FAST total score ranges from 0 to 72 points; higher scores indicate greater impairment in functioning, with scores of 12–20, 21–40, and >40 indicating mild, moderate, and severe functional impairment, respectively.[43]

Health-related quality of life was assessed using the long form of the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q).[44] This provides a comprehensive patient-rated assessment of health-related quality of life across 10 domains: physical health, subjective feelings, work, household duties, school/course work, leisure time activities, social relationships, general activities, satisfaction with medication, and overall satisfaction and contentment. Q-LES-Q domain scores are expressed as a percentage of the maximum score possible; higher scores signify better health-related quality of life.

Safety was evaluated by the incidence of treatment-emergent adverse events (TEAEs) and using the Columbia-Suicide Severity Rating Scale.[45]

Statistical Analysis

Planned randomization was 600 patients (300 in each group); with this sample size and an expected withdrawal rate of 10%, an assumed standard deviation of 9.6 points for the change from baseline in MADRS total score at week 8 (primary study endpoint), and a priori no difference between treatments, power of at least 85% for concluding non-inferiority was expected. Efficacy was analyzed in all randomized patients who received at least one dose of study medication and had a valid baseline and at least one post-baseline assessment for MADRS total score (full analysis set). Safety was analyzed in all enrolled patients who received at least one dose of study medication (all-patients-treated set).

The primary study endpoint (ie, change from baseline to week 8 in MADRS total score) was analyzed using a mixed model for repeated measures to estimate treatment difference between vortioxetine and desvenlafaxine at week 8 and the associated 95% confidence interval (CI). The model included country and treatment (vortioxetine or desvenlafaxine) as fixed factors, baseline MADRS total score as a continuous covariate, treatment-by-week interaction, and an interaction between week and baseline MADRS total score, and an unstructured covariance matrix was

Table 1. Baseline Patient Demographics and Clinical Characteristics[a]

Variable	Vortioxetine (n = 310)	Desvenlafaxine (n = 293)
Demographic characteristics (APTS)		
Age, y	43.0 ± 12.7	43.5 ± 13.0
Female	215 (69.4)	212 (72.4)
White	284 (91.6)	272 (92.8)
Employment status		
Paid employment or self-employed	180 (58.1)	181 (61.8)
Characteristics of current MDE		
Duration of current MDE, weeks	23.7 ± 9.2	23.7 ± 9.3
No. of prior MDEs	2.5 ± 1.9	2.6 ± 2.4
Prior SSRI[b]		
Citalopram	26 (8.4)	24 (8.2)
Escitalopram	128 (41.3)	122 (41.6)
Paroxetine	46 (14.8)	46 (15.7)
Sertraline	112 (36.1)	102 (34.8)
Disease characteristics (FAS)	(n = 309)	(n = 293)
MADRS total score	30.7 ± 3.7	30.7 ± 3.9
CGI-S score	4.5 ± 0.6	4.5 ± 0.6
FAST total score	41.5 ± 12.3	41.6 ± 12.9
Q-LES-Q general activities percentage score[c]	38.8 ± 12.5	38.6 ± 13.0
Q-LES-Q satisfaction with medication percentage score[c,d]	40.4 ± 17.6	40.0 ± 17.4

[a]Data are mean ± SD or n (%).
[b]Some patients may have received more than one SSRI treatment for the current MDE.
[c]Q-LES-Q numerical scores have been converted into a percentage score by linear transformation of the scores into a scale of 0–100, in which 0 corresponds to the worst score and 100 to the best score on the numerical scale.
[d]n = 258 in the vortioxetine group and n = 231 in the desvenlafaxine group.
Abbreviations: APTS = all-patients-treated set, CGI-S = Clinical Global Impressions–Severity of Illness scale (score range, 1–7), FAS = full analysis set, FAST = Functioning Assessment Short Test (score range, 0–72), MADRS = Montgomery-Åsberg Depression Rating Scale (score range, 0–60), MDE = major depressive episode, Q-LES-Q = Quality of Life Enjoyment and Satisfaction Questionnaire, SSRI = selective serotonin reuptake inhibitor.

applied. Non-inferiority was declared if the upper bound of the 95% CI did not exceed 2.5 MADRS points. If non-inferiority was established, then superiority of vortioxetine over desvenlafaxine was investigated (2-sided test at 5% significance level).

Pre-specified secondary endpoints included changes from baseline to week 8 in CGI-S score, FAST total and domain scores, and Q-LES-Q domain scores, and the CGI-I score at week 8. Rates of symptomatic and functional remission (ie, CGI-S score ≤ 2) and response (ie, CGI-I score ≤ 2), and of MADRS response (ie, ≥ 50% reduction in MADRS total score from baseline) and MADRS remission (ie, MADRS total score ≤ 10), were also evaluated at week 8. FAST total and domain scores, and CGI-S remission and CGI-I response rates, were assessed for the overall study population and in the subgroup of working patients (ie, those in paid employment or self-employed at baseline).

Continuous secondary endpoints were analyzed using mixed models for repeated measures similar to that used for the primary endpoint or using an analysis of covariance, observed-cases model. For the analysis of CGI-I scores, respective baseline CGI-S scores were included as a covariate. The analysis of covariance model was used for endpoints with only one post-baseline assessment and as a sensitivity analysis for other endpoints. Rates of response and remission were analyzed using logistic regression. No adjustment for multiplicity was made.

Safety endpoints were summarized using descriptive statistics. All analyses were performed using SAS statistical software (version 9.4; SAS Institute Inc.; Cary, North Carolina).

RESULTS

Study Population

Of the 678 patients screened, 603 were randomized and received at least one dose of study medication (310 and 293 in the vortioxetine and desvenlafaxine groups, respectively) (Figure 1). Patient disposition by country is shown in Supplementary Table 1.

Treatment groups were well matched in terms of baseline demographic and clinical characteristics (Table 1 and Supplementary Table 2). Mean age was 43.3 years, 70.8% of participants were female, and most (92.2%) were White. Escitalopram and sertraline were the most frequently used prior SSRIs (received by 41.5% and 35.5% of patients, respectively). Concomitant antidepressants were used during the study by 3 patients in the vortioxetine group (sertraline [n = 2] and escitalopram [n = 1]) and 2 patients in the desvenlafaxine group (sertraline and vortioxetine [both n = 1]). Benzodiazepines were continued or started after the first dose of study medication by 41 patients (13.2%) and 34 patients (11.6%) in the two groups, respectively.

Mean MADRS total score at baseline was 30.7, indicating a population with moderate-to-severe depression. Mean baseline CGI-S and FAST scores were 4.5 and 41.5, respectively, indicating moderate-to-severe illness and severely impaired patient functioning. Patients reported poor health-related quality of life at baseline (mean Q-LES-Q domain scores ranging from 28.7% to 42.6%) and low satisfaction with prior SSRI therapy (mean Q-LES-Q satisfaction with medication score, 40.3%) (Supplementary Table 2).

Table 2. Primary and Secondary Efficacy Outcomes in the VIVRE Study[a]

Outcome	Vortioxetine (n = 309)	Desvenlafaxine (n = 293)	Treatment Difference (95% CI)	*P* Value
Depressive symptoms[b]				
MADRS total score	−13.6 (0.5)	−13.1 (0.5)	−0.47 (−1.61 to 0.67)	.420
Overall disease severity[b]				
CGI-I score[c]	2.3 (0.1)	2.4 (0.1)	−0.09 (−0.24 to 0.05)	.196
CGI-S score	−1.5 (0.1)	−1.4 (0.1)	−0.13 (−0.28 to 0.02)	.084
Functioning[d]				
FAST total score	−15.8 (0.9)	−14.2 (0.9)	−1.64 (−3.47 to 0.19)	.079
FAST autonomy score	−2.5 (0.2)	−2.1 (0.2)	−0.47 (−0.82 to −0.12)	**.009**
FAST interpersonal relationships score	−3.8 (0.4)	−3.2 (0.4)	−0.55 (−1.09 to −0.01)	**.045**
Health-related quality of life[e]				
Q-LES-Q general activities score	18.0 (1.6)	17.1 (1.6)	0.87 (−1.49 to 3.22)	.470
Q-LES-Q satisfaction with medication score	27.5 (1.7)	23.8 (1.7)	3.65 (0.10 to 7.20)	**.044**

[a]Mean (standard error) change from baseline to week 8 shown unless otherwise indicated. Significant treatment differences (*P* values) are shown in bold.
[b]Full analysis set, mixed model for repeated measures. Negative treatment difference represents advantage for vortioxetine.
[c]For CGI-I score, value at week 8 is shown.
[d]ANCOVA, OC: negative treatment difference represents advantage for vortioxetine.
[e]ANCOVA, OC: positive treatment difference represents advantage for vortioxetine.
Abbreviations: ANCOVA, OC = analysis of covariance, observed cases; CGI-I = Clinical Global Impressions–Improvement scale; CGI-S = Clinical Global Impressions–Severity of Illness scale; FAST = Functioning Assessment Short Test; MADRS = Montgomery-Åsberg Depression Rating Scale; Q-LES-Q = Quality of Life Enjoyment and Satisfaction Questionnaire.

Dosing

Vortioxetine dose was increased to 20 mg/d after 1 week of treatment in all but 1 patient (99.7%). Of the 309 patients in whom vortioxetine dose was increased, 275 (89.0%) received vortioxetine 20 mg/d from week 1 to week 8. Vortioxetine dose was reduced to 10 mg/d between weeks 1 and 4 in 30 patients (9.7%); further dose information was unavailable for the remaining 4 patients (1.3%). Dose reduction was requested for 7.0% of patients in the desvenlafaxine group; however, dose remained unchanged in these patients.

Efficacy

Comparable effect was observed in terms of depressive symptom reduction from baseline to week 8 (ie, mean change in MADRS total score at week 8, the primary endpoint) for vortioxetine and desvenlafaxine (Table 2), with a numeric difference in favor of vortioxetine of −0.47 points (95% CI, −1.61 to 0.67; $P = .420$). Significantly more vortioxetine-treated patients achieved symptomatic and functional remission (ie, CGI-S score ≤ 2) (32.5% vs 24.8% in the desvenlafaxine group; odds ratio [OR] = 1.48 [95% CI, 1.03 to 2.15]; $P = .034$). The proportions of patients achieving response assessed by CGI-I and MADRS criteria and remission assessed by MADRS criteria were similar in the two groups (Supplementary Table 3).

Improvement in functioning assessed by the FAST was seen in both groups over the 8 weeks of treatment (Figure 2A), with numerically greater improvement in FAST total score and significantly greater improvements in FAST autonomy (daily functioning) and interpersonal relationships (social functioning) domain scores in vortioxetine-treated patients (pre-specified comparisons; $P = .009$ and .045 vs desvenlafaxine, respectively). In terms of health-related quality of life assessed by the Q-LES-Q, mean improvements from baseline were generally numerically greater in vortioxetine-treated patients across all Q-LES-Q domains (Figure 2B). There was a significant difference in favor of vortioxetine in mean change in the Q-LES-Q satisfaction with medication domain score from baseline to week 8 (pre-specified comparison, 27.5% vs 23.8% in the desvenlafaxine group; $P = .044$).

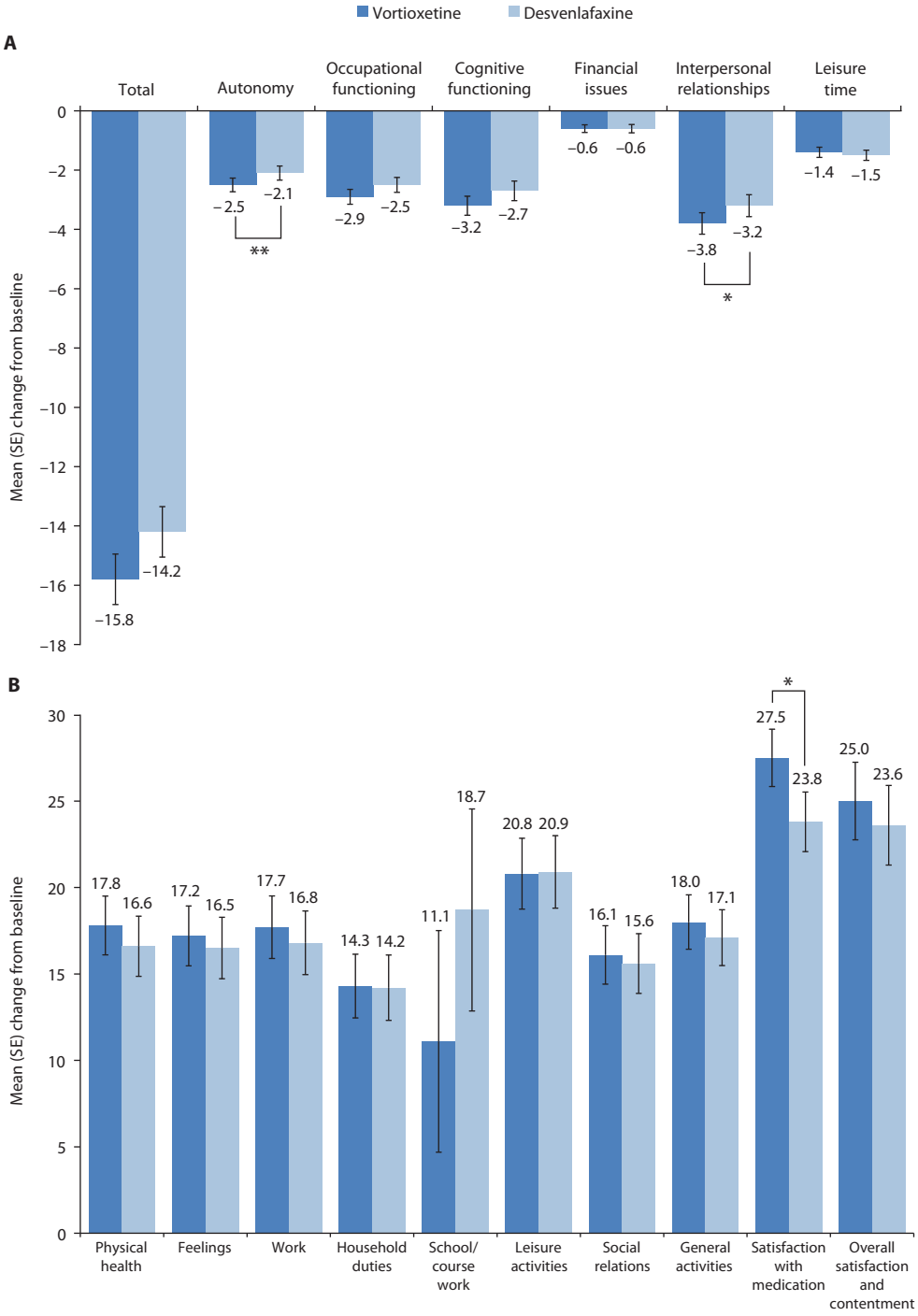
Working Patients Subgroup

Overall, 361 patients were in paid employment or self-employed at baseline (ie, 59.9% of the all-patients-treated set, evenly distributed between treatment groups). In working patients, mean FAST total score at baseline was 40.0 in the vortioxetine group and 40.3 in the desvenlafaxine group, indicating severe functional impairment (Supplementary Table 4). A significantly greater change from baseline to week 8 in FAST total score was seen in vortioxetine-treated patients (−16.6 vs −14.1 points in desvenlafaxine-treated patients; difference, −2.52 [95% CI, −4.88 to −0.15]; $P = .037$). Significantly greater improvements in daily and social functioning were also seen with vortioxetine ($P = .012$ and .046 vs desvenlafaxine for the autonomy and interpersonal relationship domains, respectively) (Supplementary Figure 1). At week 8, the proportion of working patients achieving symptomatic and functional remission (ie, CGI-S score ≤ 2) was 36.2% (63/174) with vortioxetine versus 25.1% (44/175) with desvenlafaxine (OR = 1.72 [95% CI, 1.08 to 2.75; $P = .023$).

Safety

During the 8-week treatment period, TEAEs were reported in 46.1% of patients in the vortioxetine group and 39.6% of those in the desvenlafaxine group (Table 3). TEAEs were mostly mild or moderate (> 98% of all TEAEs in each group). In both groups, the most common TEAEs were nausea, headache, and dizziness. The incidence of nausea

Figure 2. Change From Baseline to Week 8 for (A) FAST Total and Domain Scores[a] and (B) Q-LES-Q Percentage Scale Scores[b] (Analysis of Covariance, Observed Cases)



[a]For FAST scores, reduction represents improvement.
[b]For Q-LES-Q scores, increase represents improvement.
*$P < .05$. **$P < .01$.
Abbreviations: FAST = Functioning Assessment Short Test, Q-LES-Q = Quality of Life Enjoyment and Satisfaction Questionnaire, SE = standard error.

Table 3. Summary of TEAEs Reported During the 8-Week Active Treatment Period (All-Patients-Treated Set)[a]

Variable	Vortioxetine (n = 310)	Desvenlafaxine (n = 293)
Patient-years of exposure	46	44
Patients with TEAEs	143 (46.1)	116 (39.6)
Patients with serious adverse events, n	0	1 (0.3)
Patients with TEAEs leading to withdrawal	6 (1.9)	3 (1.0)
No. of deaths	0	0
TEAEs with incidence of ≥ 2% in either group		
Nausea	62 (20.0)	27 (9.2)
Headache	30 (9.7)	25 (8.5)
Dizziness	16 (5.2)	16 (5.5)
Pruritus	8 (2.6)	1 (0.3)
Somnolence	7 (2.3)	14 (4.8)
Nasopharyngitis	6 (1.9)	8 (2.7)
Dry mouth	4 (1.3)	8 (2.7)

[a]Data are n (%) unless otherwise stated.
Abbreviation: TEAE = treatment-emergent adverse event.

was higher in vortioxetine-treated patients (20.0% vs 9.2% for desvenlafaxine). The incidence of other TEAEs was generally similar between groups.

One serious adverse event was reported (severe vomiting lasting for 3 days in 1 patient in the desvenlafaxine group, considered unrelated to treatment). The incidence of TEAEs leading to withdrawal from the study was low (1.9% and 1.0% in the vortioxetine and desvenlafaxine groups, respectively). The majority (≥ 97%) of patients in both groups did not experience suicidal ideation or behavior during the treatment period.

DISCUSSION

VIVRE is the first head-to-head study of vortioxetine versus an SNRI in patients with MDD experiencing partial response to SSRI monotherapy; published data are notably lacking concerning the comparative efficacy of antidepressants in this patient population. VIVRE assessed treatment effects across the spectrum of symptoms experienced by patients with MDD and, as such, provides clinically relevant information about the role of vortioxetine versus SNRIs in this setting.

The results support earlier use of vortioxetine in the treatment algorithm in patients with MDD failing to respond to initial SSRI therapy, prior to an SNRI. Comparable efficacy was observed for vortioxetine and desvenlafaxine in terms of improvement in depressive symptoms as assessed by change in MADRS total score over the 8 weeks of treatment. However, significantly more patients treated with vortioxetine achieved symptomatic and functional remission assessed using the version of the CGI-S that measures depression severity and its impact on global patient functioning.[41] Vortioxetine-treated patients also experienced significantly greater improvements in daily and social functioning assessed using the FAST than those who received desvenlafaxine. These findings are clinically important, as improvements in global, daily, and social functioning are positively linked to maintaining antidepressant response and preventing relapse in patients with MDD.[13,46,47]

Vortioxetine-treated patients also reported significantly greater satisfaction with their medication as assessed using the Q-LES-Q than those who received desvenlafaxine. Satisfaction with antidepressant medication combines patient perceptions of treatment efficacy and tolerability and has been shown to directly correlate with treatment adherence in patients with MDD.[11,12] Non-adherence to antidepressant therapy remains a major challenge in clinical practice, being associated with suboptimal clinical outcomes.[13] In a network meta-analysis of head-to-head studies in patients with MDD,[48] vortioxetine was found to offer the best balance of efficacy and acceptability among the 21 antidepressants included.

The VIVRE study findings add to the growing body of evidence supporting significantly greater efficacy of vortioxetine versus SNRIs on clinically relevant outcomes for patients with MDD. In the SOLUTION study,[32] significantly greater reduction in depressive symptoms as assessed by MADRS total score was seen in patients who received vortioxetine 10 mg/d versus those who received venlafaxine XR 150 mg/d. Significantly more vortioxetine- than venlafaxine-treated patients also achieved treatment success, defined by the dual outcome of ≥ 50% reduction in MADRS total score from baseline and no TEAEs during the 8-week treatment period.[33]

The significantly greater effect of vortioxetine versus desvenlafaxine on daily functioning replicates earlier findings versus another SNRI, duloxetine. In the CONNECT study,[34,35] which objectively measured improvement in patient functioning using the University of California San Diego Performance-based Skills Assessment (UPSA), significantly greater improvement in UPSA composite score was seen with vortioxetine compared with duloxetine. Vortioxetine, but not duloxetine, also demonstrated a robust effect versus placebo on a novel dual-outcome composite measure of depressive symptoms and functional capacity (defined as a change from baseline of ≥ 50% for MADRS total score and ≥ 7 points on the UPSA) in that study.[35]

MDD is known to be one of the major causes of absenteeism and presenteeism in the workplace.[49] Patients with MDD experience significant impairments in their ability to function at work, particularly in terms of planning and executing tasks.[50] Over half (60%) of all patients were in paid employment at baseline in the VIVRE study. Working patients treated with vortioxetine experienced significantly greater improvements in overall functioning and domains of autonomy (ie, activities of daily life) and interpersonal relationships (ie, social life) than those who received desvenlafaxine and were more likely to achieve symptomatic and functional remission assessed using the CGI-S. Remission has been shown to be significantly associated with improved work performance and productivity in patients with MDD.[51] Our findings are consistent with those of previous studies showing significant improvements in functional and occupational outcomes in working patients with MDD treated with vortioxetine.[28–30]

The superior benefits of vortioxetine versus desvenlafaxine are most likely due to its multimodal mechanism of action. Vortioxetine is a 5-HT_3, 5-HT_7, and 5-HT_{1D} receptor antagonist, a 5-HT_{1B} receptor partial agonist, and a 5-HT_{1A} receptor agonist as well as an inhibitor of the 5-HT transporter.[16,52,53] Vortioxetine therefore not only inhibits 5-HT reuptake, but also directly and indirectly modulates the downstream release of other neurotransmitters relevant to the neurobiology of depression through its effects on specific 5-HT receptors, including norepinephrine, dopamine, acetylcholine, histamine, γ-aminobutyric acid, and glutamate.[18,19] For example, norepinephrine has been implicated in the regulation of motivation and energy,[54] while dopamine appears important for motivation and reward processing.[55,56] The observed improvements in global, daily, and social functioning seen in vortioxetine-treated patients in this study may therefore reflect improvements in motivation, energy, and reward processing arising from modulation of these neurotransmitter systems.

The main study limitation is the relatively short duration of follow-up (8 weeks), as patients with MDD generally require long-term treatment. However, long-term functional benefits have previously been demonstrated in working patients with MDD treated with vortioxetine for up to 1 year, including those with partial response to prior antidepressant therapy.[29,30] The ability to request dose adjustment in the desvenlafaxine group without an increase actually being implemented may have introduced expectation bias, potentially impacting treatment outcomes.[57]

In conclusion, the VIVRE study demonstrates that vortioxetine confers superior clinical benefits versus SNRI treatment in patients with MDD with only partial response to SSRI monotherapy, including a greater likelihood of achieving symptomatic and functional remission, better daily and social functioning, and greater treatment satisfaction. Our findings support earlier use of vortioxetine in the treatment algorithm in patients with MDD.

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Supplementary Material

Article Title: Head-To-Head Comparison of Vortioxetine Versus Desvenlafaxine in Patients With Major Depressive Disorder With Partial Response to SSRI Therapy: Results of the VIVRE Study

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SUPPLEMENTARY MATERIALS

Supplementary Table 1. Patient Disposition by Country (All-Patients-Treated Set)

Country	Vortioxetine (n = 310)	Desvenlafaxine (n = 293)
Argentina	68	64
Belgium	1	0
Bulgaria	15	17
Czech Republic	37	36
Estonia	10	10
Latvia	6	4
Mexico	14	13
Russia	76	73
Slovakia	28	25
Spain	3	5
Sweden	9	6
Ukraine	43	40

Supplementary Table 2. Baseline FAST Total and Domain Scores and Q-LES-Q Long-Form Domain Scores (Full Analysis Set)

	Vortioxetine (n = 309)	Desvenlafaxine (n = 293)
FAST total and domain scores		
Total score[a]	41.5 ± 12.3	41.6 ± 12.9
Autonomy[b]	5.7 ± 2.7	5.7 ± 2.8
Occupational functioning[a]	9.4 ± 4.2	9.2 ± 4.1
Cognitive functioning	9.5 ± 2.8	9.6 ± 3.0
Financial issues	2.2 ± 1.7	2.3 ± 1.8
Interpersonal relationships	10.2 ± 3.5	10.3 ± 3.7
Leisure time	4.4 ± 1.4	4.4 ± 1.6
Q-LES-Q domain scores (%)[c]		
Physical health	35.9 ± 11.9	35.9 ± 13.2
Feelings	38.6 ± 14.7	38.7 ± 14.4
Work[d]	43.1 ± 24.7	42.0 ± 23.3
Household duties[e]	42.7 ± 19.9	42.3 ± 19.4
School/course work[f]	32.2 ± 23.5	25.5 ± 26.3
Leisure activities	32.8 ± 22.6	30.5 ± 21.5
Social relations	39.8 ± 17.1	38.5 ± 16.9
General activities	38.8 ± 12.5	38.6 ± 13.0
Satisfaction with medication[g]	40.4 ± 17.6	40.0 ± 17.4
Overall satisfaction and contentment	29.9 ± 18.0	30.1 ± 17.5

Data are mean ± standard deviation.
[a]n = 305 in the vortioxetine group and n = 291 in the desvenlafaxine group.
[b]n = 308 in the vortioxetine group and n = 292 in the desvenlafaxine group.
[c]Q-LES-Q numeric scores have been converted into a percentage score by linear transformation of the scores into a scale of 0–100, where 0 corresponds to the worst score and 100 to the best score on the numeric scale.
[d]n = 219 in the vortioxetine group and n = 210 in the desvenlafaxine group.
[e]n = 297 in the vortioxetine group and n = 284 in the desvenlafaxine group.
[f]n = 53 in the vortioxetine group and n = 59 in the desvenlafaxine group.
[g]n = 258 in the vortioxetine group and n = 231 in the desvenlafaxine group.
Abbreviations: FAST = Functioning Assessment Short Test (score range, 0–72), Q-LES-Q = Quality of Life Enjoyment and Satisfaction Questionnaire.

Supplementary Table 3. Rates of CGI and MADRS Response and Remission at Week 8 (Full Analysis Set, Observed Cases)

Outcome	Vortioxetine (n = 295)	Desvenlafaxine (n = 286)	Odds ratio (95% CI)	*P* Value
Response				
CGI-I (score ≤ 2)	194 (65.8)	174 (60.8)	1.24 (0.88 to 1.74)	.217
MADRS (≥ 50% reduction from baseline)	128 (43.4)	105 (36.7)	1.32 (0.95 to 1.85)	.100
Remission				
CGI-S (score ≤ 2)	96 (32.5)	71 (24.8)	1.48 (1.03 to 2.15)	**.034**
MADRS (score ≤ 10)	53 (18.0)	58 (20.3)	0.86 (0.57 to 1.31)	.485

Data are n (%), unless otherwise indicated. Significant treatment differences (*P* values) are shown in bold.
Abbreviations: CGI-I = Clinical Global Impressions–Improvement scale, CGI-S = Clinical Global Impressions–Severity of Illness scale, MADRS = Montgomery-Åsberg Depression Rating Scale.

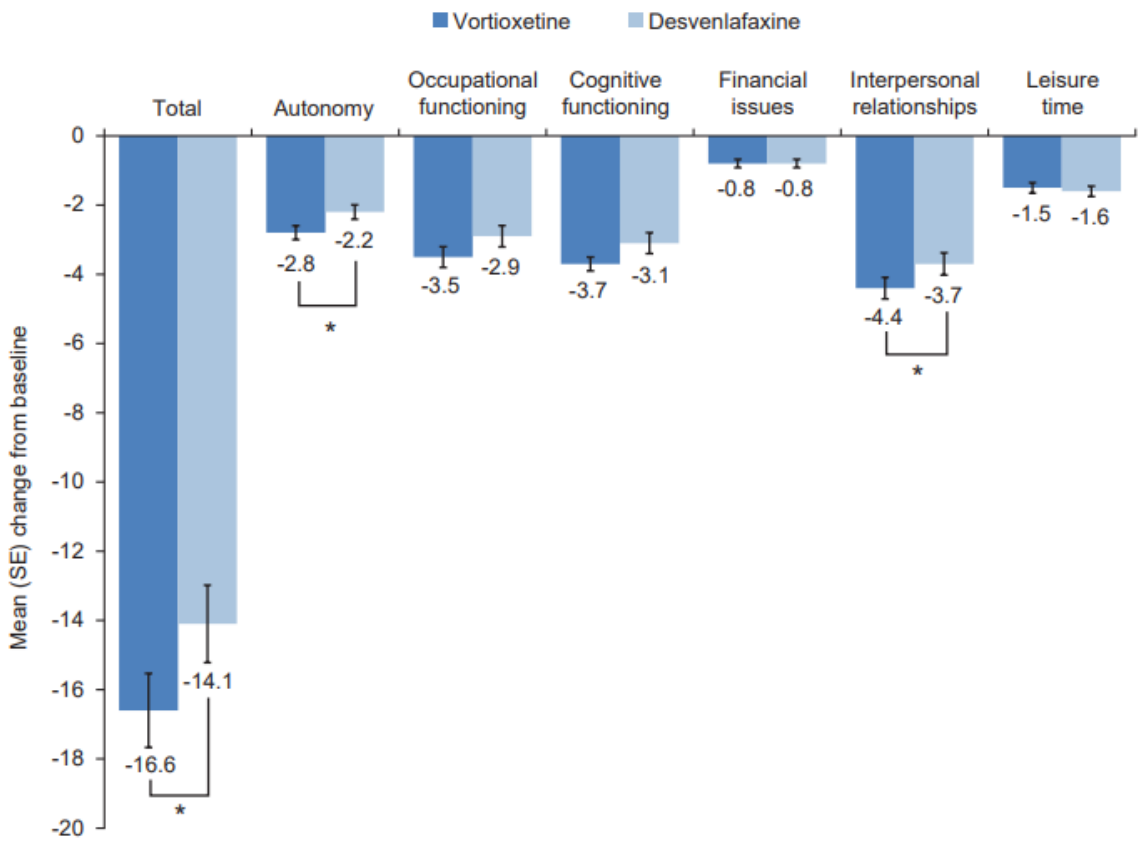
Supplementary Table 4. Baseline Patient Demographics and Clinical Characteristics for the Working Population

	Vortioxetine	Desvenlafaxine
Demographic characteristics (APTS)	**(n = 180)**	**(n = 181)**
Age, y	42.7 ± 11.0	43.4 ± 11.5
Female	122 (67.8)	124 (68.5)
White	163 (90.6)	167 (92.3)
Disease characteristics (FAS)	**(n = 179)**	**(n = 181)**
MADRS total score	30.5 ± 3.7	30.6 ± 3.9
CGI-S score	4.5 ± 0.6	4.5 ± 0.6
FAST total score	40.0 ± 12.3	40.3 ± 12.1
Autonomy[a]	5.5 ± 2.6	5.4 ± 2.7
Occupational functioning	8.6 ± 3.8	8.7 ± 3.6
Cognitive functioning	9.5 ± 2.9	9.5 ± 2.9
Financial issues	2.1 ± 1.7	2.2 ± 1.9
Interpersonal relationships	9.9 ± 3.7	10.1 ± 3.6
Leisure time	4.4 ± 1.4	4.4 ± 1.5
Q-LES-Q domain scores (%)[b]		
Physical health	36.4 ± 12.1	36.2 ± 13.0
Feelings	39.7 ± 15.0	41.0 ± 14.2
Work[c]	48.3 ± 20.1	46.8 ± 20.6
Household duties[d]	44.0 ± 20.2	44.7 ± 18.0
School/course work[e]	38.3 ± 25.0	30.5 ± 29.0
Leisure activities	33.1 ± 23.9	31.7 ± 22.4
Social relations	40.6 ± 17.7	40.3 ± 16.8
General activities	39.9 ± 13.1	40.7 ± 12.8
Satisfaction with medication[f]	39.8 ± 17.6	41.1 ± 17.2
Overall satisfaction and contentment	30.9 ± 18.0	32.7 ± 18.5

Data are mean ± standard deviation or n (%).
[a]n = 178 in the vortioxetine group and n = 180 in the desvenlafaxine group.
[b]Q-LES-Q numeric scores have been converted into a percentage score by linear transformation of the scores into a scale of 0–100, where 0 corresponds to the worst score and 100 to the best score on the numeric scale.
[c]n = 174 in both groups.
[d]n = 173 in the vortioxetine group and n = 175 in the desvenlafaxine group.
[e]n = 20 in the vortioxetine group and n = 29 in the desvenlafaxine group.
[f]n = 150 in the vortioxetine group and n = 141 in the desvenlafaxine group.

Abbreviations: APTS = all-patients-treated set, CGI-S = Clinical Global Impressions–Severity of Illness scale (score range, 1–7), FAS = full analysis set, FAST = Functioning Assessment Short Test (score range, 0–72), MADRS = Montgomery-Åsberg Depression Rating Scale (score range, 0–60), Q-LES-Q = Quality of Life Enjoyment and Satisfaction Questionnaire.

Supplementary Figure 1. Change from Baseline to Week 8 for FAST Total and Domain Scores[a] in Working Patients (Analysis of Covariance, Observed Cases)



[a]For FAST scores, reduction represents improvement.
*$P < .05$
Abbreviations: FAST = Functioning Assessment Short Test, SE = standard error.

Appendix 1. VIVRE Study Principal Investigators

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Hector Lamaison	Instituto de Neurociencias San Agustin SA, La Plata
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