Efficacy of Vortioxetine on Cognitive Functioning in Working Patients With Major Depressive Disorder

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ABSTRACT

Objective: This post hoc analysis investigates the effect of vortioxetine on cognitive functioning and depressive symptoms in working adults with major depressive disorder (MDD).

Methods: Population data from FOCUS, a double-blind, randomized, placebo-controlled study investigating the efficacy of vortioxetine versus placebo on cognitive functioning and depression in patients with MDD, were used to analyze mean change from baseline scores for the Digit Symbol Substitution Test (DSST), Trail Making Test A/B (TMT-A/B), Stroop, and Perceived Deficits Questionnaire (PDQ). FOCUS, conducted from December 2011 through May 2013, included adult patients with recurrent MDD according to *DSM-IV-TR* criteria. Change in depression severity (Montgomery-Asberg Depression Rating Scale [MADRS] total score) was analyzed using data from 3 additional short-term placebo-controlled studies (2 of which included duloxetine) and 1 relapse prevention study. Analyses were done according to patients' working status at baseline and workplace position. All analyses were made versus placebo.

Results: In FOCUS, the effect versus placebo on the DSST was 5.6 for 10 mg and 5.0 for 20 mg ($P < .001$ for both doses) in working patients; the effect was 4.0 ($P < .001$ for both doses) in total study population. The effect remained significant when adjusting for change in MADRS. In patients with "professional" positions, the effect was 9.2 for 10 mg ($P = .006$) and 9.0 for 20 mg ($P = .001$). A similar pattern of results was also observed for TMT-A/B, Stroop, PDQ, and MADRS total score. The efficacy of duloxetine was not different in working patients (MADRS).

Conclusions: The beneficial effects of vortioxetine on objective and subjective measures of cognitive functioning are greater in working patients with MDD; the observed benefits were independent of improvement in depressive symptoms.

Trial Registration: This study is a secondary analysis of data from 5 registered trials: ClinicalTrials.gov identifiers: NCT01422213, NCT00635219, NCT00735709, NCT01140906, NCT00596817

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Major depressive disorder (MDD) is associated with significant impairments in psychosocial functioning, especially work functioning.[1,2] Many studies have shown that people with MDD have increased absenteeism[3,4] and reduced work productivity[5] compared with the general population. Cognitive symptoms are common in MDD and have been shown to be present up to 94% of the time during depressive episodes and up to 44% of the time during periods of remission.[6] Evidence indicates that among adults with MDD, cognitive symptoms account for more variability in workplace performance than does total depressive symptom severity.[7] These observations support research underscoring the notion that cognitive dysfunction is a critical mediator of role impairment in MDD.[8]

Results from 2 double-blind, randomized, placebo-controlled studies demonstrated a clinical benefit of vortioxetine on cognitive functioning in adults with MDD, including objective neuropsychological tests of executive functioning, speed of processing, verbal learning, and memory.[9–11] These studies confirm and extend the results from an earlier double-blind, randomized, placebo-controlled, duloxetine-referenced study with vortioxetine in elderly (≥ 65 years) patients with MDD.[12]

The beneficial effect observed on measures of cognitive functioning with vortioxetine is of particular importance for individuals with MDD who are working and/or engaged in activities that place high demands on cognition (eg, educational pursuit). Because depression is primarily a disorder affecting people of working age,[13] it is important to understand how the effect of vortioxetine on cognitive functioning specifically affects the working population.

A replicated body of evidence indicates that individuals who are working have a greater likelihood of exhibiting improvements in depression symptom severity scores when compared with those who are not working or are not engaged in educational/volunteer activities.[14–16] Convergent evidence from "workplace depression studies" indicates that persisting impairment in workplace performance remains a significant and common problem despite improvement in mood symptoms. Results from both epidemiologic and clinical studies suggest that disturbances in cognitive functions in MDD are the principal and proximate determinants of workplace performance.[7] Consequently, interventions that are capable of targeting and improving cognitive functioning should very likely improve workplace performance/productivity. It has previously been reported that among individuals with past MDD, overall cognitive performance is more impaired in nonworking individuals than in those who are working.[17]

For this post hoc analysis, we hypothesized that the effects of vortioxetine on cognitive functioning may be more pronounced in the working population than those already reported in a full MDD population. The rationale for this hypothesis is that functional impairment from cognitive deficits in MDD would be perceived and/or have greater objective consequences in working people. We investigated the effects of vortioxetine on both objective measures (neuropsychological tests) and a subjective measure (patient-reported outcomes) of cognitive functioning according to working status and type of employment by using data from a pivotal clinical study that primarily investigated the effect of vortioxetine on cognitive functioning in adults with MDD.[9] Analyses of the effect on depressive symptoms were also conducted using data from an additional 3 short-term double-blind, randomized, placebo-controlled studies in adults with MDD that employed similar inclusion and exclusion criteria[18–20] and 1 relapse prevention study.[21]

Clinical Points

- Depression has a substantial negative impact on workplace productivity, and cognitive difficulties may play a key role. Given the relationship between cognitive dysfunction and work impairment, significant human capital gains may accrue if cognitive functioning is improved in major depressive disorder (MDD).
- Vortioxetine, which has been shown to improve cognitive functioning among patients with MDD in areas of executive functioning, speed of processing, verbal learning, and memory, has an even more pronounced cognitive effect in working adults. This improvement is shown to be independent of vortioxetine's impact on mood symptoms.
- Patients in managerial or professional positions reported the greatest improvement of cognitive function. Individuals working in these types of positions, with presumably higher demands for executive functioning, may be more resilient and have higher levels of motivation and/or internal locus of control and, thus, a greater potential for cognitive improvement during treatment with vortioxetine.

METHODS

Study Population for Investigation of Effect on Cognitive Functioning

The FOCUS study (ClinicalTrials identifier: NCT01422213)[9] was a double-blind, randomized, fixed-dose, placebo-controlled study investigating the efficacy of vortioxetine 10 and 20 mg/day versus placebo on cognitive functioning and depression in adults (N = 602) with recurrent moderate-to-severe MDD. The *study population* in the FOCUS study was defined as adults (aged 18–65 years) with a primary diagnosis of recurrent MDD according to *DSM-IV-TR* criteria, current major depressive episode (MDE) ≥ 3 months' duration (confirmed using the Mini-International Neuropsychiatric Interview),[34] and a Montgomery-Asberg Depression Rating Scale (MADRS) total score ≥ 26 at screening and at baseline visits. Patients were recruited from 79 psychiatric inpatient and outpatient settings in 12 countries (Australia, Canada, Finland, France, Germany, Latvia, Mexico, Serbia, Slovakia, South Africa, Ukraine, and the United States) from December 2011 through May 2013. The working status and type of employment were assessed at baseline according to the Health Economic Assessment (HEA) questionnaire.[22] The HEA records working status (full-time work/school; part-time work/school; unemployed; nonworking spouse, retired, or other) as well as type of job, if working (manager/administrator, professional [eg, health, teaching, legal], associate professional [eg, technical, nursing], clerical worker/secretary, skilled laborer [eg, building, electrical/factory worker], services/sales [eg, retail], and other). In this analysis, we combined the employment categories manager/administrator and professional to form a subgroup of working patients designated as "professional," as this group of working patients with MDD presumably had higher demands for executive functioning in their work capacity. All analyses were performed in the full study population (full analysis set), the working population, and the subgroup of patients within the working population identified as "professional."

Study Population for Investigation of Effect on Depressive Symptoms

In order to establish whether any additional benefit of vortioxetine in working patients with MDD would be isolated to cognitive performance or whether it was broader to also encompass an antidepressant effect, data on antidepressant response in working patients from 3 additional short-term, randomized, placebo-controlled studies[18–20] and data on the risk of relapse in 1 relapse prevention study in MDD[21] (all of which included the HEA) were also considered (ClinicalTrials identifiers: NCT00635219,[18] NCT00735709,[19] NCT01140906,[20] and NCT00596817[21]). These additional studies do not include data on cognitive end points, but provide ample data on the effect of vortioxetine on depressive symptoms in working patients with MDD. The 3 short-term studies were similar to FOCUS in terms of patient population and study duration, and, as such, allowed for a meta-analysis using data from both FOCUS and the 3 additional studies to examine change from baseline to week 8 in the MADRS total score. The relapse prevention study, even though it did not include cognitive end points, allowed for the confirmation of the maintenance of the antidepressant effect of vortioxetine in working patients with MDD.[21]

Clinical Assessments

Cognitive functioning was assessed using the following objective neuropsychological tests: Digit Symbol Substitution Test (DSST: executive functioning, speed of processing, attention), Rey Auditory Verbal Learning Test (RAVLT: learning, memory), Trail Making Test A/B (TMT-A: speed of processing; TMT-B: executive functioning), Stroop test (congruent and incongruent: executive functioning), simple reaction time task (SRT: speed of processing), and the choice reaction time task (CRT: attention), supplemented by a

Table 1. Demographics and Baseline Clinical Characteristics of Populations From McIntyre et al[9] (FOCUS study), Baldwin et al,[18] Henigsberg et al,[19] and Boulenger et al[20] (FAS)

	All Patients		Working Patients		
Variable	Mean ± SD	N	Mean ± SD	N	%
Age, y	45.9 ± 12.7	2,206	42.6 ± 11.0	1,254	56.8
Median length of current MDE, wk	20	2,202	20	1,253	56.9
Previous MDEs, no.	2.0 ± 2.0	2,206	1.8 ± 1.7	1,254	56.8
Assessment scores					
MADRS total score	31.5 ± 3.8	2,206	31.3 ± 3.6	1,254	56.8
CGI-S score	4.74 ± 0.69	2,205	4.74 ± 0.71	1,253	56.8
HARS total score	21.5 ± 6.8	1,620	21.1 ± 6.5	927	57.2
SDS total score	20.0 ± 5.8	1,216	19.8 ± 5.8	875	72.0

Abbreviations: CGI-S = Clinical Global Impressions–Severity, FAS = full analysis set, HARS = Hamilton Anxiety Rating Scale, MADRS = Montgomery-Asberg Depression Rating Scale, MDE = major depressive episode, SD = standard deviation, SDS = Sheehan Disability Scale.

subjective measure of cognitive functioning, the patient-reported Perceived Deficits Questionnaire (PDQ). Depressive symptoms were assessed by MADRS in all studies. For all assessments, the results are reported as absolute values. In addition, the standardized effect sizes are also reported for all neuropsychological tests to allow for comparisons of the magnitude of the effect sizes across end points and studies.

Statistical Analysis

For data from the FOCUS study, the changes from baseline in DSST, TMT-A/B, Stroop, RAVLT, SRT, CRT, and PDQ after 8 weeks of treatment were analyzed using analysis of covariance (ANCOVA) and last observation carried forward (LOCF), with treatment and pooled center as fixed factors and baseline score as covariate. The change from baseline in DSST was also analyzed, adjusting for change from baseline in MADRS total score to control for any improvement in cognitive functioning driven by improvement in mood. For the analysis of the antidepressant effect, the changes from baseline in MADRS total score were analyzed using a mixed model for repeated measurements (MMRM). A standard random effects meta-analysis for antidepressant response was carried out using the MADRS results from FOCUS and each of the short-term placebo-controlled trials. The relapse prevention study was considered separately for risk of relapse using a Cox proportional hazard model. All analyses were made versus placebo.

RESULTS

Baseline Characteristics

A total of 2,206 patients were included in the full analysis set from the 4 short-term clinical studies,[18–21] excluding patients treated with nontherapeutic doses of vortioxetine (1 and 2.5 mg). The relapse prevention study included 396 patients randomized after open-label treatment. In the short-term studies,[18–20] 57% (n = 1,254) of the patients indicated that they were working (full-/part-time) or pursuing an educational degree at baseline. In the relapse prevention study,[21] 59% (n = 234) reported at baseline that they were working. There were no substantial differences in baseline characteristics between the working population and the total study population in the 4 short-term studies of acute MDD (Table 1). In the total study population, 66% were women compared to 63% within the working population. In terms of cognitive functioning, there were no substantial differences in baseline performance scores between the 3 treatment arms (placebo, 10-mg vortioxetine, and 20-mg vortioxetine) across the neuropsychological tests used in the FOCUS study (Table 2). No significant difference was observed in withdrawal rates due to lack of efficacy between working patients and the total study population (results not shown). The patients were recruited in a total of 32 countries, primarily in Europe (66%). Among countries contributing at least 30 patients, there was a consistent proportion (approximately 60%) of working patients across the countries.

Table 2. Baseline Scores of Neuropsychological Tests and the PDQ From the FOCUS Study[9] by Population (FAS, Mean Scores)

Neuropsychological Test	Placebo	Vortioxetine 10 mg	Vortioxetine 20 mg
DSST			
Total	42.5	42.0	41.6
Working	44.8	44.2	44.1
Professionals	46.4	45.9	43.2
RAVLT (acquisition)			
All	22.2	22.4	22.6
Working	23.0	23.0	23.6
Professionals	22.9	21.5	23.7
RAVLT (delayed recall)			
All	5.7	5.8	6.0
Working	6.2	6.4	6.5
Professionals	5.9	6.3	6.7
TMT-A			
All	48.7	46.4	46.2
Working	47.7	44.0	41.8
Professionals	47.8	39.9	45.2
TMT-B			
All	104.8	101.7	103.1
Working	101.1	97.6	96.7
Professionals	104.6	87.1	102.7
SRT			
All	2.6	2.6	2.6
Working	2.6	2.6	2.6
Professionals	2.7	2.7	2.7
CRT			
All	2.8	2.8	2.8
Working	2.8	2.8	2.8
Professionals	2.8	2.8	2.8
Stroop (congruent)			
All	49.9	49.4	49.7
Working	49.1	49.5	46.3
Professionals	51.0	46.3	54.1
Stroop (incongruent)			
All	85.6	84.9	83.3
Working	82.9	84.2	78.2
Professionals	90.1	77.3	93.5
PDQ			
All	39.8	41.5	41.0
Working	40.0	40.9	39.5
Professionals	41.6	40.1	40.9

Abbreviations: CRT = choice reaction time task, DSST = Digit Symbol Substitution Test, FAS = full analysis set, PDQ = Perceived Deficits Questionnaire, RAVLT = Rey Auditory Verbal Learning Test, SD = standard deviation, SRT = simple reaction time task, TMT-A = Trail Making Test-speed of processing, TMT-B = Trail Making Test-executive functioning.

Table 3. Efficacy, Change From Baseline to Week 8, Difference to Placebo (mean ± SE [effect size] and SES ± SE) According to Working Status and Type of Employment in the FOCUS Study[9] (FAS, ANCOVA, LOCF)

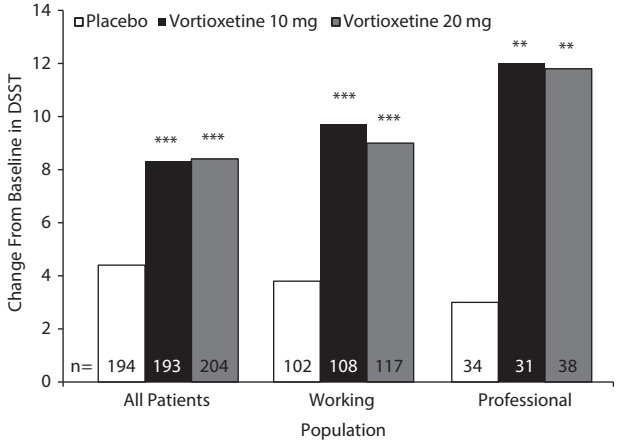
	All Patients				Working Patients				"Professionals"			
	Vortioxetine 10 mg (n = 193)		Vortioxetine 20 mg (n = 204)		Vortioxetine 10 mg (n = 108)		Vortioxetine 20 mg (n = 117)		Vortioxetine 10 mg (n = 31)		Vortioxetine 20 mg (n = 38)	
Assessment	Δ Placebo	*P*	Δ Placebo	*P*	Δ Placebo	*P*	Δ Placebo	*P*	Δ Placebo	*P*	Δ Placebo	*P*
Neuropsychological tests (objective)												
DSST (number of correct symbols)												
ES	3.96 ± 0.84	< .001	4.01 ± 0.83	< .001	5.62 ± 1.28	< .001	5.01 ± 1.22	< .001	9.18 ± 3.22	.006	9.02 ± 2.68	.001
SES	0.48 ± 0.10		0.48 ± 0.10		0.61 ± 0.14		0.56 ± 0.14		0.71 ± 0.25		0.79 ± 0.24	
RAVLT (acquisition)												
ES	1.15 ± 0.46	.012	0.63 ± 0.45	.163	1.23 ± 0.71	.083	0.25 ± 0.67	.710	2.32 ± 1.53	.137	1.42 ± 1.27	.270
SES	0.26 ± 0.10		0.14 ± 0.10		0.24 ± 0.14		0.05 ± 0.14		0.37 ± 0.25		0.26 ± 0.24	
RAVLT (delayed recall)												
ES	0.71 ± 0.23	.002	0.62 ± 0.22	.006	0.78 ± 0.34	.021	0.65 ± 0.32	.042	0.89 ± 0.65	.174	0.56 ± 0.53	.299
SES	0.32 ± 0.10		0.28 ± 0.10		0.32 ± 0.14		0.28 ± 0.14		0.34 ± 0.25		0.25 ± 0.24	
TMT-A, s												
ES	−3.60 ± 1.29	.006	−3.68 ± 1.28	.004	−4.19 ± 1.64	.011	−4.33 ± 1.57	.006	−10.65 ± 4.03	.011	−8.75 ± 3.32	.011
SES	0.28 ± 0.10		0.29 ± 0.10		0.35 ± 0.14		0.37 ± 0.14		0.66 ± 0.25		0.62 ± 0.24	
TMT-B, s												
ES	−7.46 ± 2.71	.006	−8.21 ± 2.67	.002	−11.30 ± 3.69	.002	−7.82 ± 3.51	.027	−15.77 ± 7.34	.036	−13.67 ± 6.08	.029
SES	0.28 ± 0.10		0.31 ± 0.10		0.42 ± 0.14		0.30 ± 0.14		0.53 ± 0.25		0.53 ± 0.24	
SRT, $\log_{10}$ ms												
ES	−0.05 ± 0.01	< .001	−0.03 ± 0.01	.020	−0.05 ± 0.02	.003	−0.01 ± 0.02	.388	−0.10 ± 0.04	.021	−0.04 ± 0.03	.267
SES	0.42 ± 0.10		0.24 ± 0.10		0.42 ± 0.14		0.12 ± 0.14		0.59 ± 0.25		0.27 ± 0.24	
CRT, $\log_{10}$ ms												
ES	−0.03 ± 0.01	< .001	−0.01 ± 0.01	.312	−0.03 ± 0.01	.012	0.00 ± 0.01	.867	−0.05 ± 0.03	.110	0.01 ± 0.02	.571
SES	0.36 ± 0.10		0.10 ± 0.10		0.35 ± 0.14		0.02 ± 0.14		0.41 ± 0.25		0.13 ± 0.24	
STROOP (congruent), s												
ES	−3.87 ± 1.24	.002	−4.01 ± 1.22	.001	−4.12 ± 1.66	.014	−4.84 ± 1.58	.002	−7.74 ± 4.24	.073	−8.99 ± 3.51	.013
SES	0.32 ± 0.10		0.33 ± 0.10		0.34 ± 0.14		0.41 ± 0.14		0.45 ± 0.25		0.61 ± 0.24	
STROOP (incongruent), s												
ES	−6.47 ± 2.01	.001	−6.05 ± 1.98	.002	−8.69 ± 2.99	.004	−6.60 ± 2.84	.021	−16.85 ± 6.20	.009	−18.30 ± 5.19	< .001
SES	0.33 ± 0.10		0.31 ± 0.10		0.40 ± 0.14		0.32 ± 0.14		0.68 ± 0.25		0.83 ± 0.24	
Patient-reported outcomes (subjective)												
PDQ total score												
ES	−4.40 ± 1.19	< .001	−5.68 ± 1.18	< .001	−4.86 ± 1.77	.006	−5.73 ± 1.70	< .001	−8.28 ± 4.09	.048	−11.50 ± 3.44	.002
SES	0.39 ± 0.10		0.50 ± 0.10		0.39 ± 0.14		0.47 ± 0.14		0.51 ± 0.25		0.82 ± 0.25	

Abbreviations: ANCOVA = analysis of covariance, CRT = choice reaction time task, DSST = Digit Symbol Substitution Test, ES = effect size, FAS = full analysis set, LOCF = last observation carried forward, MADRS = Montgomery-Asberg Depression Rating Scale, PDQ = Perceived Deficits Questionnaire, RAVLT = Rey Auditory Verbal Learning Test, SE = standard error, SES = standardized effect size, SRT = simple reaction time task, TMT-A = Trail Making Test-speed of processing, TMT-B = Trail Making Test-executive functioning.

Clinical Outcomes

In the FOCUS study,[9] the difference versus placebo in the DSST for number of correct symbols was 5.6 for 10 mg ($P < .001$) and 5.0 for 20 mg ($P < .001$) in working patients, while the difference versus placebo in the total population was 4.0 for 10 mg ($P < .001$) and 4.0 for 20 mg ($P < .001$) of vortioxetine (Table 3; Figure 1). The effect in the working population was not mediated by a greater change in overall depressive symptom severity. The effect on the DSST after adjusting for change from baseline in MADRS total score was 3.8 for 10 mg ($P = .002$) and 2.8 for 20 mg ($P = .021$) in working patients and 2.6 for 10 mg ($P = .002$) and 2.2 for 20 mg ($P = .007$) in the total study population. For "professional" working patients, the effect on the DSST versus placebo was 9.2 and 9.0 for 10 mg ($P = .006$) and 20 mg ($P = .001$), respectively. For both the population of working patients and the subpopulation of "professional" working patients, a statistically significant improvement versus placebo was also observed on TMT-A (10 and 20 mg), TMT-B (10 and 20 mg), SRT (10 mg), and Stroop (congruent/incongruent; 10 and 20 mg) (Table 3). A significant improvement was also

Figure 1. Change From Baseline to Week 8 in DSST According to Working Status and Type of Employment in the FOCUS Study[9] (FAS, ANCOVA, LOCF)



**$P < .01$ vs placebo.
***$P < .001$ vs placebo.
Abbreviations: ANCOVA = analysis of covariance, DSST = Digit Symbol Substitution Test, FAS = full analysis set, LOCF = last observation carried forward.

Table 4. Meta-Analyses of the Change From Baseline to Week 8 in MADRS Total Score Difference to Placebo According to Working Status From Baldwin et al,[18] Henigsberg et al,[19] Boulenger et al,[20] and McIntyre et al (FOCUS study)[9] (FAS, MMRM)

	All Patients				Working Patients				"Professionals"			
Study	N	Δ Placebo	SE	*P*	N	Δ Placebo	SE	*P*	N	Δ Placebo	SE	*P*
Baldwin et al[18]												
Placebo	123	…	…	…	78	…	…	…	19	…	…	…
Vortioxetine 5 mg	122	−2.51	1.06	.018	73	−2.95	1.33	.028	22	−3.73	2.42	.127
Vortioxetine 10 mg	119	−2.65	1.08	.014	73	−5.25	1.35	<.001	19	−4.45	2.54	.084
Duloxetine	112	−3.00	1.08	.006	65	−2.77	1.38	.045	18	−4.18	2.56	.106
Henigsberg et al[19]												
Placebo	128	…	…	…	74	…	…	…	33	…	…	…
Vortioxetine 5 mg	129	−4.18	1.00	<.001	76	−4.63	1.33	<.001	23	−5.50	2.24	.016
Vortioxetine 10 mg	122	−4.75	1.01	<.001	66	−5.81	1.38	<.001	19	−5.25	2.33	.027
Boulenger et al[20]												
Placebo	130	…	…	…	80	…	…	…	26	…	…	…
Vortioxetine 15 mg	118	−5.53	1.09	<.001	67	−7.06	1.44	<.001	22	−6.74	2.76	.017
Vortioxetine 20 mg	125	−7.09	1.08	<.001	81	−7.27	1.39	<.001	25	−6.90	2.64	.011
Duloxetine	131	−9.45	1.07	<.001	75	−9.28	1.43	<.001	25	−9.04	2.69	.001
McIntyre et al (FOCUS)[9]												
Placebo	162	…	…	…	87	…	…	…	28	…	…	…
Vortioxetine 10 mg	172	−4.63	0.89	<.001	98	−5.74	1.22	<.001	29	−9.55	1.97	<.001
Vortioxetine 20 mg	181	−6.58	0.88	<.001	102	−7.28	1.21	<.001	35	−12.0	1.82	<.001
Meta-analysis												
Placebo	543	…	…	…	319	…	…	…	106	…	…	…
Vortioxetine 5 mg	251	−3.39	0.83	<.001	149	−3.79	0.94	<.001	45	−4.68	1.64	.004
Vortioxetine 10 mg	413	−4.09	0.65	<.001	237	−5.61	0.76	<.001	67	−6.70	1.66	<.001
Vortioxetine 15 mg	118	−5.53	1.09	<.001	67	−7.06	1.44	<.001	22	−6.74	2.76	.015
Vortioxetine 20 mg	306	−6.79	0.68	<.001	183	−7.27	0.91	<.001	60	−9.81	2.52	<.001
Duloxetine	243	−6.23	3.22	.053	140	−6.01	3.25	.065	43	−6.54	2.43	.007

Abbreviations: FAS = full analysis set, MADRS = Montgomery-Asberg Depression Rating Scale, MMRM = mixed model for repeated measures, SE = standard error.

observed in CRT for working patients treated with 10 mg of vortioxetine. In subjective reporting of cognitive functioning assessed using the PDQ, the effect in working patients was −4.9 points for 10 mg ($P = .006$) and −5.7 for 20 mg ($P < .001$), while the effect in the total study population was −4.4 points for 10 mg ($P < .001$) and −5.7 for 20 mg ($P < .001$). The effect versus placebo among working patients in a "professional" position was −8.3 points for 10 mg ($P = .048$) and −11.5 for 20 mg ($P = .002$).

In regard to treatment effect on depressive symptom severity, in the FOCUS study, the difference versus placebo in change from baseline in MADRS total score was −5.7 for 10 mg ($P < .001$) and −7.3 for 20 mg ($P < .001$) in the working population, while in the total study population, the effect was −4.6 for 10 mg ($P < .001$) and −6.6 for 20 mg ($P < .001$) (Table 4). For "professional" working patients, the change was −9.6 points for 10 mg ($P < .001$) and −12.0 for 20 mg ($P < .001$). The meta-analysis of all the short-term placebo-controlled studies supports this observation—the change in MADRS total score versus placebo for vortioxetine ranged from −3.39 to −6.79 (all *P* values < .001) in the total population, while in the overall working population, the range was −3.79 to −7.27 (all *P* values < .001) and among "professionals," −4.68 to −9.81 (all *P* values ≤ .015) (larger effect with higher dose; Table 4). For duloxetine, the change in MADRS total score versus placebo was −6.23 ($P = .053$) in the total population, −6.01 ($P = .065$) in the working population, and −6.54 ($P = .007$) among "professionals."

In the relapse prevention study, working patients randomized to placebo were statistically significantly more likely to relapse than those randomized to vortioxetine (hazard ratio of 2.3; full analysis set, Cox model) (95% confidence interval [CI], 1.26–4.04; $P = .006$), while the hazard ratio for the total study population was 2.0 (95% CI, 1.26–3.21; $P = .004$).

DISCUSSION

This analysis provides the first assessment of the effects of vortioxetine on cognitive functioning in working patients with MDD. In fact, it represents the most comprehensive assessment to date of the effect of any antidepressant in a working MDD population. Compared with previously reported results for vortioxetine in adult and elderly patients with MDD (working and nonworking)[9,10,12] and in accordance with our hypothesis, we observed a more pronounced effect on cognitive functioning in working patients with MDD. Significant and substantial differences were observed in the performance on objective neuropsychological tests as well as in patient-reported cognitive functioning. Furthermore, the superior effect observed on measures of cognitive functioning was even more pronounced in patients with a "professional" (ie, manager/administrator or professional [eg, health, teaching, legal]) type of position.

The clinical relevance of the effect of vortioxetine on neuropsychological tests has previously been reported in reference to the magnitude of the standardized effect size.[9] In depressed individuals with MDD, the standardized effect size of the deficits observed is typically 0.2 to 0.6 below a matched, normative sample, depending on the cognitive

domain.[23–25] In the FOCUS study,[9] the standardized effect sizes for the DSST were 0.56 (10 mg) and 0.61 (20 mg) in the working MDD population compared to 0.48 (10 and 20 mg) in total study population. Hence, the magnitude of improvement in the DSST in working patients with MDD with vortioxetine treatment compared to placebo is as large as the baseline deficits found in individuals with MDD versus the normative population.

A host of putative mechanisms may moderate and/or mediate the findings in this study. For example, it is well established that behavioral activation is an effective antidepressant treatment strategy.[26] It is not known, however, if behavioral activation improves performance on neuropsychological measures.[27] Notwithstanding, ongoing participation in the workforce can be conceptualized as a form of behavioral activation; thus, for MDD patients during vortioxetine treatment, staying at work may have additive beneficial effects compared with being out of work. In addition, ongoing participation in the workforce provides social and interpersonal support that also could serve as a moderating effect.[28]

It is hypothesized that the efficacy of vortioxetine across disparate domains of cognitive functioning is mediated by its multimodal action, for example, interactive effects on the monoaminergic and glutamatergic systems.[29] The observation that the antidepressant efficacy of duloxetine, as measured by MADRS, was not different in working patients may be a consequence of the fact that duloxetine has a more narrow beneficial effect on cognitive domains (ie, learning and memory) than does vortioxetine, consequently resulting in less opportunity for the potentiating effects of interpersonal and behavioral activation from being in the workplace setting. For example, perceived inattention has been shown to impair work performance,[7] and vortioxetine showed significant effects on tests (DSST, TMT-A, SRT, CRT) assessing attention and processing speed. It could therefore be speculated that there is a synergistic effect between the actions of vortioxetine on multiple cognitive domains and the behavioral activation effects of the working environment.

An additional conceptual framework may implicate cognitive reserve and/or resiliency. Resilience has been operationalized to include multiple biological, psychological, and temperamental aspects that broadly refer to positive adaptation. It is hypothesized that in adults with mood disorders, a functional abnormality exists within and between circuits and networks that subserve cognitive processing, emotion control, and reward dependence.[30] It may be conjectured that individuals who are more resilient may have differences in the functional connectivity of pertinent neural circuits as evidenced by greater affect control.[31] A robust literature in psychology also has implicated, defined, operationalized, and measured dimensions of motivation (both internal and external), as well as perceived locus of control.[32] In our working population, individuals with "professional" types of positions exhibited greater improvements on several cognitive measures compared to what was observed in the overall population, especially measures assessing executive functioning (DSST, Stroop, and TMT-B). It could be that individuals working in these types of positions, with presumably higher demands for executive functioning, are more resilient and have higher levels of motivation and/or internal locus of control and, thus, have a greater potential for cognitive improvement during treatment with vortioxetine. These hypotheses can be tested in future studies using measures of motivation or locus of control.

The results reported here are important from a patient perspective as well as in a societal context. A survey conducted by the European Depression Association indicated that 1 in 10 working people have taken time off from work because of a depressive disorder (mean absence of 35.9 days during previous depressive episode), yet only about one-third were willing to tell their employer that depression was the reason for their absence.[33] For working patients with MDD, having access to an effective means of treating the cognitive symptoms of depression may address an important barrier in employee–employer relations. Given the relationship between cognitive dysfunction and work impairment, it is clear that significant human capital gains may be accrued from a societal perspective if cognitive functioning is improved in MDD.

There are some limitations to this research. All analyses have been conducted post hoc, preventing any conclusive statements on the unique effect of vortioxetine in the working population. Nevertheless, the analysis is based on a large sample of individuals (approximately 60% of total study population), and consistent effects were observed on all end points and across studies. In addition, a direct statistical comparison between working and nonworking patients with MDD in terms of effects on cognitive functioning could also be of scientific interest. However, this study was not designed to address this comparison between the 2 subgroups. Furthermore, working patients with MDD are likely to differ from nonworking patients not only by their work status, but also by their educational achievement, family history, support of family and friends, personal motivation, and a number of other personal characteristics that can influence employment. Some of these personal characteristics may be very difficult to measure and thereby hard to capture in a clinical study. The present study should be considered hypothesis generating, and a more definitive study should consider a direct comparison of the 2 subgroups. Finally, our research is limited by the general limitations associated with randomized clinical trials in MDD, such as short treatment duration or that study participants are not necessarily representative of patients with MDD seen in usual clinical practice.

To our knowledge, this is the first report to evaluate the effect of a pharmacologic intervention on measures of cognitive functioning in adults with MDD as a function of working status. When compared to previous reports on patients with MDD (working or nonworking), our study observed a more pronounced effect among working individuals treated with vortioxetine. The synergistic effects of vortioxetine on cognitive functioning in working adults

with MDD have conceptual (ie, putative mechanisms of action) and practical implications insofar as this finding provides an additional rationale for recommending evaluation, measurement, and specific targeting of cognitive functioning in the treatment of adults with MDD.

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