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Which Cognitive Domains are Improved by Treatment with Vortioxetine?

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Abstract

Background: These post hoc analyses evaluated vortioxetine efficacy on cognitive dysfunction in depression. Data were from a double-blind, randomized, fixed-dose, placebo-controlled, 8-week depression study in adults aged 18–65 years (n = 602) with DSM-IV–defined major depressive disorder (MDD). Subjects were randomized (1:1:1) to vortioxetine 10mg/day or 20mg/day or placebo.
Methods: Cognitive function was assessed at baseline, Week 1 (10mg/day only) and Week 8 using Digit Symbol Substitution Test (DSST) number of correct symbols, Rey Auditory Verbal Learning Test, Trail Making Test, Stroop test, Simple Reaction Time, and Choice Reaction Time tests. The cognition variables were standardized and used for constructing composite Z-scores for the cognitive domains of executive function, attention/speed of processing, and memory.
Results: At Week 1, vortioxetine 10mg/day separated from placebo for attention/speed of processing (standardized composite Z-score = 0.21; p = 0.0238) and DSST number of correct symbols (standardized effect size = 0.18; p = 0.0458) and for executive function (standardized composite Z-score = 0.20; p = 0.0274). At Week 8, vortioxetine 10mg/day and 20mg/day separated from placebo for executive function and attention/speed of processing, with standardized composite Z-scores ranging from 0.35 to 0.49 (all p < 0.01). Standardized composite Z-scores for memory were 0.31 (p = 0.0036, 10mg/day) and 0.22 (p = 0.0349, 20mg/day). Standardized effect sizes for DSST were 0.51 (p < 0.0001, 10mg/day) and 0.52 (p < 0.0001, 20mg/day). Results are limited by the post hoc nature of the analyses and the absence of an active reference in the original study.
Conclusions: Vortioxetine (10 and 20mg/day) had a multi-domain beneficial effect on cognitive performance, as evidenced by improvements in measures of executive function, attention/speed of processing, and memory. The effect on the DSST may be due to improvements in several cognitive skills.

Keywords: cognitive domains, composite Z-score, depression, vortioxetine

Introduction

Symptoms of cognitive dysfunction, such as difficulty with thinking, concentrating, or decision-making, have long been recognized as an intrinsic characteristic of major depressive disorder (MDD) and are among the most persistent symptoms both during a current major depressive episode (MDE) and in remission (Conradi et al., 2011). Evidence obtained using objective cognitive testing suggests that the foregoing observed deficits in MDD are an early feature of the disorder and of a magnitude likely to be clinically relevant (Lee et al. 2012).

In the acute phase of MDD, reduced performance on cognitive testing has been well documented (Porter et al., 2007; Hammar and Årdal, 2009; McClintock et al., 2010). The measures employed have covered key cognitive domains, including executive functioning, attention, learning, and memory. Cognitive dysfunction is present during the first episodes of depression and in recurrent depression, as well as in late-life depression (Basso and Bornstein, 1999; Lee et al., 2012; Weisenbach et al., 2012). There is also evidence to suggest that cognition in patients with recurrent

depression further deteriorates with each MDE. Furthermore, some patients show evidence of dysfunction even after remission of the MDE has been achieved (Hasselbalch et al., 2011).

Standard cognitive assessments are often those that are most clearly associated with functional outcome (Dickinson, 2008). Coding tasks, such as the Digit Symbol Substitution Test (DSST; Wechsler, 1997), reflect the coordination and speed of performance of scanning, matching, and motor operations and are sensitive to a wide variety of developmental and clinical conditions (Dickinson, 2008). Such measures are often dismissed as simple measures of processing speed. However, successful completion on measures such as the DSST is also reliant on the functional integrity of praxis, working memory, and attentional skills. The DSST has been selected as a measure of executive function for use in patients with mild cognitive impairment (Donohue et al., 2014) and was recently characterized as a timed executive function measure by the European Medicines Agency (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/10/WC500176827.pdf).

Vortioxetine treatment improved the performance of elderly patients with MDD (Katona et al., 2012) and patients aged 18–65 years with MDD (McIntyre et al., 2014, Mahableshwarkar et al., 2015) on the DSST. In order to determine which domain or domains of cognition were affected, we used additional measures of specific cognitive skills in a second study (McIntyre et al., 2014). The goal of these post hoc analyses was to evaluate the efficacy after 1 and 8 weeks of vortioxetine treatment of 10 or 20 mg/day on the cognitive domains of executive function, attention/speed of processing, and memory.

Methods

Patients

A total of 602 patients with MDD, aged 18–65 years, from a double-blind, randomized, fixed-dose, placebo-controlled, depression study (NCT01422213) were randomized (1:1:1) to vortioxetine 10 mg/day, vortioxetine 20 mg/day, or placebo for 8 weeks of double-blind treatment. Patients randomized to vortioxetine 20 mg/day were up-titrated and received vortioxetine 10 mg/day during Week 1 (McIntyre et al., 2014). NCT01422213 was conducted in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki. Local research ethics committees approved the trial design, and all eligible patients provided written informed consent prior to participation.

Statistical Procedures

The following nine cognition variables were used for assessing cognitive function at baseline, Week 1, and Week 8:

1. DSST number of correct symbols,
2. Rey Auditory Verbal Learning Test (RAVLT) acquisition (equal to immediate recall for trials 1 to 3 of List A)
3. RAVLT delayed recall,
4. time to completion for the Trail Making Test (TMT) part A
5. time to completion for the TMT part B,
6. time to completion for the Stroop test congruent conditions,
7. time to completion for the Stroop test incongruent conditions,
8. Simple Reaction Time test (SRT) mean latency for correct responses, and
9. Choice Reaction Time test (CRT) mean latency for correct responses.

For the nine cognition variables, the individual patient standardized change from baseline to Week 8 was calculated as the difference between the individual change from baseline and the overall mean change from baseline. The standardization was done by dividing this difference by the overall standard deviation of the change from baseline. The same standardization approach was applied to data at Week 1. The standardized variables for the TMT part A and B, Stroop test congruent and incongruent conditions, SRT, and CRT were multiplied by -1 to ensure consistent direction of change as compared to the DSST and RAVLT measures. For each cognitive domain, a composite Z-score was calculated using equal weighting in the following way:

- Executive function: 0.5*standardized STROOP (incongruent) + 0.5*standardized TMT B
- Attention/speed of processing: 0.25*standardized STROOP (congruent) + 0.25*standardized TMT A + 0.25*standardized SRT + 0.25*standardized CRT
- Memory: 0.5*standardized RAVLT (acquisition) + 0.5*standardized RAVLT (delayed recall)
- DSST number of correct symbols was analyzed separately, because it is related to several cognitive domains.

At Week 1, the composite Z-scores and DSST number of correct symbols were analyzed using the Analysis of Covariance (ANCOVA) using the Last Observation Carried Forward approach. The model included terms for grouped site, baseline composite endpoint, and treatment group, and statistical comparisons of vortioxetine 10 mg/day and placebo were carried out. At Week 8, the composite Z-scores and DSST number of correct symbols were analyzed using the Mixed Model for Repeated Measurements with an unstructured covariance structure. The model included terms for grouped site, baseline composite endpoint, baseline composite endpoint-by-visit interaction, and treatment group-by-visit interaction. At Week 8, statistical comparisons of vortioxetine 10 mg/day and placebo as well as vortioxetine 20 mg/day and placebo were carried out. Estimated treatment differences were based on the least squares means for the treatment-by-visit interaction. The least squares means were rescaled to ensure a standard deviation of 1, to produce standardized effect sizes, and to make the results comparable between the cognitive domains as well as between the cognitive domains and DSST number of correct symbols. Furthermore, in order to investigate the potential pseudo-specificity of the cognitive effects at Week 1 and 8, we applied the ANCOVA described above with the change from baseline in Montgomery-Åsberg Depression Rating Scale (MADRS) added as an explanatory variable.

Results

The cognitive domains assessed by the different variables in this study are shown in Figure 1.

At Week 1, vortioxetine 10 mg/day separated from placebo for: executive function, with a standardized composite Z-score of 0.20 (95% CI: 0.02 to 0.37; $p = 0.0274$); attention/speed of processing, with a standardized composite Z-score of 0.21 (95% CI: 0.03 to 0.38; $p = 0.0238$); and the DSST number of correct symbols, with a standardized effect size of 0.18 (95% CI: 0.004 to 0.35; $p = 0.0458$; Figure 2).

At Week 8, vortioxetine 10 mg/day and 20 mg/day separated from placebo for: (1) attention/speed of processing, with a standardized composite Z-score of 0.49 (95% CI: 0.27 to 0.70; $p < 0.0001$) for vortioxetine 10 mg/day and a standardized composite Z-score of 0.35 (95% CI: 0.14 to 0.56; $p = 0.0014$) for vortioxetine
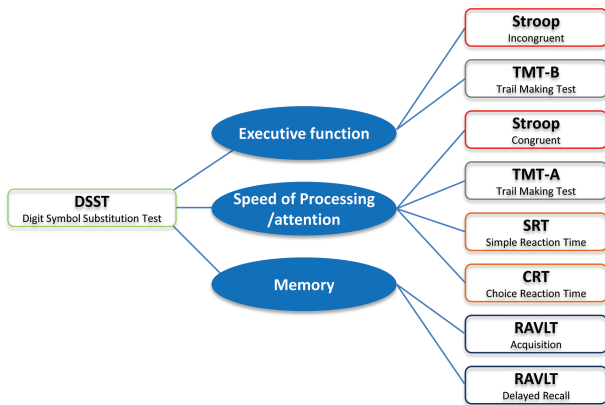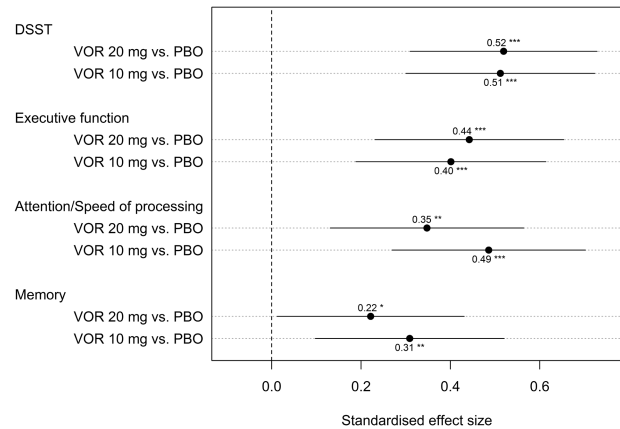
Figure 1. The cognitive domains assessed by the cognition variables. In this study, the DSST was analyzed separately and speed of processing and attention were combined (TMT A, SRT, Stroop congruent, and CRT). CRT, Choice Reaction Time test; DSST, Digit Symbol Substitution Test; RAVLT, Rey Auditory Verbal Learning Test; SRT; Simple Reaction Time test; TMT, Trail Making Test.
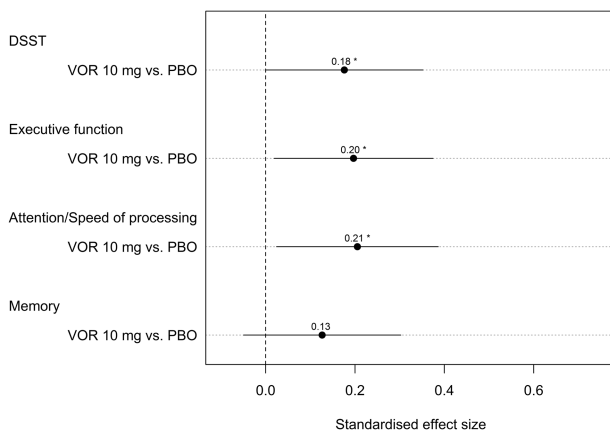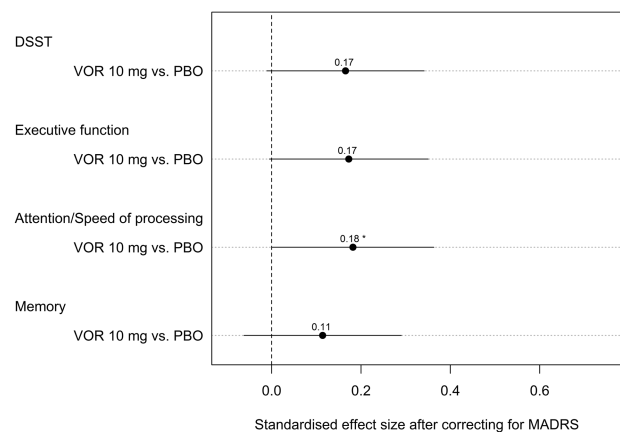

Figure 2. Forest plot of composite Z-scores at Week 1 for the four cognitive domains. Values are means with the 95% confidence interval (Analysis of Covariance and Last Observation Carried Forward). *$p < 0.05$. Executive function: 0.5*standardized Stroop (incongruent) + 0.5*standardized TMT B. Attention/speed of processing: 0.25*standardized Stroop (congruent) + 0.25*standardized TMT A + 0.25*standardized SRT + 0.25*standardized CRT. Memory: 0.5*standardized RAVLT (acquisition) + 0.5*standardized RAVLT (delayed recall). CRT, Choice Reaction Time test; PBO, placebo; RAVLT, Rey Auditory Verbal Learning Test; SRT; Simple Reaction Time test; TMT, Trail Making Test; VOR, vortioxetine.

Figure 3. Forest plot of composite Z-scores at Week 8 for the four cognitive domains. Values are means with the 95% confidence interval for the Mixed Model for Repeated Measurements. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. Executive function: 0.5*standardized Stroop (incongruent) + 0.5*standardized TMT B. Attention/speed of processing: 0.25*standardized Stroop (congruent) + 0.25*standardized TMT A + 0.25*standardized SRT + 0.25*standardized CRT. Memory: 0.5*standardized RAVLT (acquisition) + 0.5*standardized RAVLT (delayed recall). CRT, Choice Reaction Time test; PBO, placebo; RAVLT, Rey Auditory Verbal Learning Test; SRT; Simple Reaction Time test; TMT, Trail Making Test; VOR, vortioxetine.
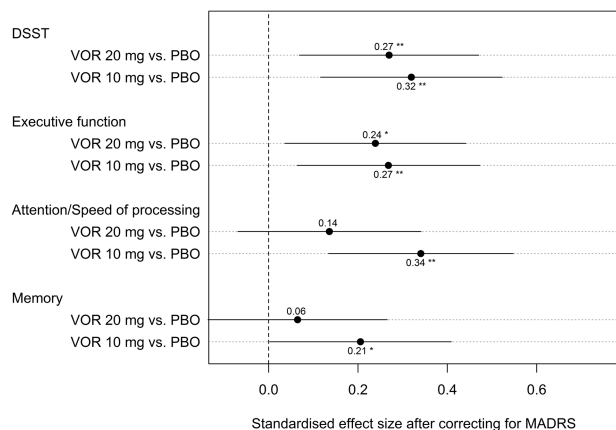

Figure 4. Forest plot of composite Z-scores at Week 1 for the four cognitive domains after correcting for MADRS score. Values are means with the 95% confidence interval (Analysis of Covariance and Last Observation Carried Forward). *$p < 0.05$. PBO, placebo; VOR, vortioxetine.

20 mg/day; (2) executive function, with a standardized composite Z-score of 0.40 (95% CI: 0.19 to 0.61; $p = 0.0003$) for vortioxetine 10 mg/day and a standardized composite Z-score of 0.44 (95% CI: 0.24 to 0.65; $p < 0.0001$) for vortioxetine 20 mg/day; (3) memory, with a standardized composite Z-score of 0.31 (95% CI: 0.10 to 0.52; $p = 0.0036$) for vortioxetine 10 mg/day and a standardized composite Z-score of 0.22 (95% CI: 0.02 to 0.43; $p = 0.0349$) for vortioxetine 20 mg/day; and (4) DSST number of correct symbols, with a standardized effect sizes of 0.51 (95% CI: 0.31 to 0.72; $p < 0.0001$) for vortioxetine 10 mg/day and 0.52 (95% CI: 0.31 to 0.72; $p < 0.0001$) for vortioxetine 20 mg/day (Figure 3).

In order to investigate the potential pseudo-specificity of the cognitive effects, the analyses were corrected for change in depression severity using the change from baseline in MADRS as a mediator. In the corrected analysis, vortioxetine 10 mg/day separated from placebo for attention/speed of processing (standardized composite Z-score = 0.18; $p = 0.0448$; Figure 4).

At Week 8, vortioxetine 10 mg/day separated from placebo for executive function, attention/speed of processing, memory, and DSST after correcting for change in depression severity with standardized Z-scores ranging from 0.21 to 0.34 (all $p < 0.05$). Vortioxetine 20 mg/day separated from placebo for executive function with a standardized Z-score of 0.24 ($p = 0.019$) and DSST with a standardized Z-score of 0.27 ($p = 0.007$; Figure 5).

Discussion

The data reported in this analysis show that cognitive deficits in patients with MDD can be treated with the use of pharmacological interventions such as vortioxetine. Previous studies of vortioxetine (Katona et al., 2012; Mahableshwarkar et al., 2015) have shown improvement on the DSST. However, successful performance on this test requires the functional integrity of a variety of cognitive domains. Hence impairment or improvement may be due to changes in attention, working memory, praxis,

Figure 5. Forest plot of composite Z-scores at Week 8 for the four cognitive domains after correcting for MADRS score. Values are means with the 95% confidence interval for the Mixed Model for Repeated Measurements. *$p < 0.05$, **$p < 0.01$. PBO, placebo; VOR, vortioxetine.

or executive function. Our intention in extending the number and variety of tasks in this study (FOCUS, McIntyre et al., 2014) was to determine which cognitive domains were improved by treatment. The results of this study indicate that there is no evidence of specific target engagement with any particular cognitive domain. Instead, treatment appears to benefit performance on a variety of cognitive domains.

There are caveats to attach to the foregoing comments and observations. It is important to point out that whilst individual cognitive tests are often labeled measures of specific domains, in reality they index multiple cognitive skills. For example, the RAVLT is conspicuously a measure of episodic verbal memory, but it is evident that some contribution from working memory, executive skills, and language are required for normal performance. Similarly, the DSST is often described as solely a measure of psychomotor speed, though this description does not capture the comprehensiveness of the DSST.

A further issue for consideration is the importance of the selected measures with respect to functional impact. Whilst functional measures, such as the University of California, San Diego (UCSD) Performance-Based Skills Assessment, were not a feature of the FOCUS study (McIntyre et al., 2014), the effect of vortioxetine on this measure has been reported in the CONNECT study (Mahableshwarkar et al., 2015). The CONNECT study also yielded positive treatment effects on the DSST, though with a marginally smaller effect size than was seen in the FOCUS study. Statistical significance on cognitive testing has been shown in the data presented in this study, but a key related issue is whether these statistically significant effects are realized as making clinically significant differences in overall and/or domain-specific psychosocial function. A possibly useful context in which to consider this issue is with respect to the efficacy of drugs that have received marketing approval in other indications. For example, acetylcholinesterase inhibitors that are indicated for use in mild-to-moderate Alzheimer's disease yield a median standardized effect size of 0.28 (range: 0.01 to 0.31) when high doses are used (Rockwood, 2004). If one accepts a similar benchmark for improving cognition in patients with MDD, the results reported here would represent a clinically relevant effect. In the context of our understanding of the fundamental deficits seen in patients with MDD, it is worth noting that in a recent review article, Millan et al. (2012) highlighted processing speed as being "a core, severe and virtually universal

characteristic of the disorder" (p. 144). Note also that both DSM-5 and International Classification of Diseases, 10th version (ICD-10) make reference to the presence of psychomotor retardation. It is our view that psychomotor or processing speed do not constitute an independent cognitive domain and that these constructs are instead best thought of as outcome measures. We suggest that deficits even on tasks such as the SRT, traditionally viewed as relatively pure measures of psychomotor speed, are best explained with reference to deficits in other cognitive domains such as attention, working memory, and aspects of executive function. It is our contention that just as successful DSST performance requires the functional integrity of attention, working memory, praxis, etc., so too does performance on "simple" measures such as the SRT. It has previously been argued (Harrison et al., 1995) that performance on reaction time tasks "usually requires a complex arrangement of attentional, perceptual, and motor operations that include preparatory activities, stimulus processing, use of working memory for retrieval of stimulus-response mappings and generation of predictions, and decision making" (p. 506).

Although a ubiquitous concept in considerations of cognitive deficits in MDD, psychomotor speed conceived as a cognitive domain seems to us unhelpful. We suggest that poor performance on tests typically labeled as measures of simply psychomotor or processing speed might better be considered and explained as deficits in the various processing stages of task performance. Harrison et al. (1995) have previously argued that: "If there is a case to be made for the application of RT [reaction time] measures, it must surely lie in the century and a half of experimental exploration of the variables that influence RT, together with attempts at a functional interpretation of the outcomes of these manipulations. This apparatus has hardly yet been brought to bear on the investigation of information processing defects in Parkinson's disease and their anatomical and pharmacological substrates" (p. 506). We suggest the same circumstances currently prevail with respect to our understanding of psychomotor speed deficits in patients with MDD.

Two recent reviews of cognitive dysfunction in MDD conclude that cognitive symptoms are present in patients with MDD, have a substantial impact on the outcome of the illness, persist as residual symptoms in remitted patients, and are not adequately treated by current therapies. Both conclude that the domains that are impaired are psychomotor speed, attention, memory, and executive functioning (Papakostas, 2014; Trivedi and Greer, 2014). Moreover, deficits in cognitive function may be a more robust predictor of workplace function in adults with MDD than total depressive symptom severity.

Current treatments for MDD help resolve mood symptoms in many patients but leave others with residual symptomatology, including cognitive symptoms (Conradi et al., 2011). While antidepressants may potentially treat cognitive dysfunction to some degree in patients with MDD, the small sample size, methodological constraints, and the absence of replication of these studies limit the generalizability of the results (Biringer et al., 2009; McIntyre et al., 2013; Baune and Renger, 2014). A further consideration is that the presence and extent of cognitive impairment may vary substantially between individual patients, with some patients exhibiting no or only modest deficits. In such a cohort the opportunities for rescuing cognition would clearly be more limited. Future analysis of data from vortioxetine trial data might helpfully address this issue, as well as other possible factors that might impact response to treatment. The methodological constraints include the lack of an active control and comparisons only assessing treatment effect compared to baseline.

The results of the present study are limited by the post hoc nature of the analyses and the absence of an active reference in the original study (McIntyre et al. 2014). Whilst not *per se* a limitation of the reported study, there are important cautions to be highlighted with respect to the cognitive domains reported. We have selected specific cognitive tests based on a traditional understanding of the domains under investigation. However, the selected tests are by no means the only possible indices of these domains and we might reasonably have selected other, well-known measures of attention, executive function, and episodic memory. For example, in the latter case we could reasonably have selected other examples of auditory verbal learning tests, such as the Hopkins or California. On this theme, it is our contention that cognitive test selection should not be dogmatic, but instead based on two firm principles. First, cognitive measures should meet best practice guidance for test selection, such as those set out by Ferris et al. (1997) and by Harrison (2016). Second, that the selected tests should successfully index the relevant cognitive domains. A perceived virtue of the employment of a fixed assessment is that this makes it possible to compare performance across studies. We recognize the appeal of such an approach, but would suggest that this instead be achieved by employing effect size as a common vocabulary for comparing studies, treatments, cohorts, etc.

In conclusion, vortioxetine (10 and 20 mg/day) significantly improves cognitive performance in patients with MDD across several domains, including executive function, attention/ speed of processing, and memory, confirming previous results in elderly patients with MDD (Katona et al., 2012). The positive effect on the DSST appears to be due to improvements in a number of cognitive skills in this large placebo-controlled randomized study, with a statistically significant improvement in objectively-measured cognitive performance in adult patients with recurrent MDD, in which the primary outcome measure evaluated multi-domains of cognitive function. Improvement in cognitive performance in patients with MDD was also found even after correcting for change in depression severity.

Acknowledgements

Statement Of Interest

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