Baseline Cognition is Not Associated with Depression Outcomes with Vortioxetine for Major Depressive Disorder: Findings from Placebo-Controlled Trials

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1. Introduction

- Cognitive dysfunction is observed in 30-60% of those with MDD
- Individuals with cognitive dysfunction are less likely to respond to antidepressants
- Vortioxetine is an approved antidepressant with comparable efficacy to other antidepressants
- Unlike other antidepressants, vortioxetine has demonstrated pro-cognitive effects
- Because vortioxetine improves cognition in MDD, baseline cognitive function may moderate the relationship between treatment and change in depression outcomes

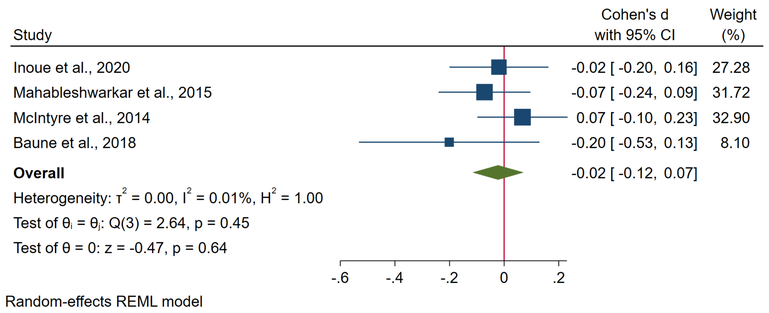
2. Study Design

- Data were analyzed from four placebo-controlled trials that measured cognitive performance at baseline
  - NCT01422213 (N = 590)
  - NCT01564862 (N = 587)
  - NCT02389816 (N = 484)
  - NCT02279966 (N = 151)
- All subjects were ≤ 65, met criteria for MDD and had a Montgomery-Asberg Depression Rating Scale (MADRS) of ≥ 26 at baseline
- Altogether, 1,812 subjects were included in analyses
- The Digit Symbol Substitution Test (DSST) was the primary cognitive measure used as vortioxetine has been shown to improve DSST performance; secondary analyses examined whether other cognitive domains moderated treatment outcomes in vortioxetine

3. Data Analysis

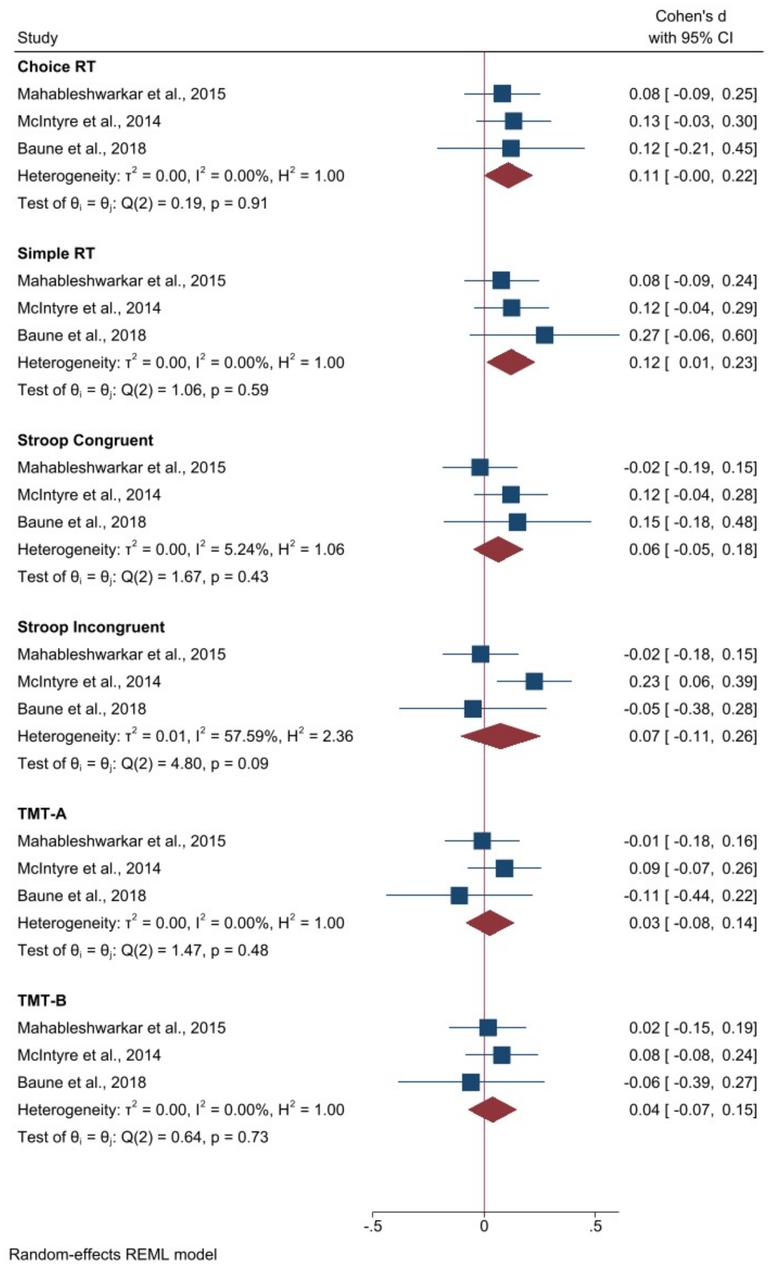
- Mixed Models for Repeated Measures (MMRM) tested whether the relationship between baseline cognitive function and change on the MADRS differed between vortioxetine and placebo (or active comparator)
- Baseline cognitive function was treated as a continuous variable
- Effect sizes (Cohen's d) of the differences between slopes were extracted from each study
- Results were pooled with a random-effects model

4. Primary Analysis (DSST)



Effect sizes are based on the contrast in slopes between vortioxetine and placebo of the relationship between baseline DSST scores and MADRS change at week 8. Positive values favor vortioxetine.

5. Secondary Analyses (Other Cognitive Tests)



Effect sizes are based on the contrast in slopes between vortioxetine and placebo of the relationship between baseline cognitive scores and MADRS change at week 8. Positive values favor vortioxetine.

6. Single Study Exploratory Analyses

- Several studies had different cognitive measures or an active comparator arm; False Discovery Rates (FDR) were applied within study to control for Type I error
- One study (NCT01422213) administered the Rey Auditory Verbal Learning Test; learning and recall measures did not moderate treatment outcomes (d ≤ 0.16, P ≥ 0.055)
- One study (NCT01564862) administered the Groton Maze Learning Test and One-Back; neither test moderated treatment outcomes (d ≤ 0.07, P ≥ 0.398)
- One study had duloxetine (NCT01564862) as an active comparator, while another had paroxetine (NCT02279966); there was no difference in slopes between vortioxetine and active comparators (d ≤ 0.43, FDR-adjusted P > 0.05)

7. Conclusions

- These findings suggest that baseline cognition does not moderate antidepressant treatment outcomes for vortioxetine
- In addition to prior work, these findings suggest that baseline cognitive function does not mediate nor moderate depression outcomes in vortioxetine
- Vortioxetine does not appear to behave differently than other antidepressants in improving depression outcomes despite its pro-cognitive effects
- Antidepressants with novel mechanisms of action (i.e., those that enhance synaptic plasticity or promote neurogenesis) may moderate depression outcomes in patients with cognitive deficits

8. Acknowledgments

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