OXFORD

International Journal of Neuropsychopharmacology (2022) 25(12): 969–978

https://doi.org/10.1093/ijnp/pyac054
Advance Access Publication: August 19, 2022
Regular Research Article

REGULAR RESEARCH ARTICLE

Effect of Vortioxetine on Cognitive Impairment in Patients With Major Depressive Disorder: A Systematic Review and Meta-analysis of Randomized Controlled Trials

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Abstract

Background: Dementia and depression are increasingly common worldwide, and their effective control could ease the burden on economies, public health systems, and support networks. Vortioxetine is a new antidepressant with multipharmacologic actions that elevate the concentration of serotonin and modulate multiple neurotransmitter receptors in the brain. We conducted a meta-analysis to explore whether the cognitive function of patients with major depressive disorder (MDD) treated with vortioxetine would improve.

Methods: We systematically reviewed randomized controlled trials (RCTs) in the PubMed, Embase, and Cochrane databases to assess the treatment effects of vortioxetine on the cognitive function of patients with MDD. The outcome measures included the Digit Symbol Substitution Test (DSST), Perceived Deficits Questionnaire (PDQ), and Montgomery-Åsberg Depression Rating Scale (MADRS) scores. Pooled results were calculated using a fixed-effects or random-effects model according to the heterogeneity of the included trials.

Results: Six RCTs with a total of 1782 patients were included in the meta-analysis, which demonstrated that vortioxetine improved DSST, PDQ, and MADRS scores in patients with MDD. The results were consistent at the 10- and 20-mg doses. In the 20-mg group, the decrease in MADRS scores was more significant than that in the placebo group.

Conclusions: Both the 10- and 20-mg doses of vortioxetine can significantly increase DSST scores and decrease PDQ and MADRS scores in patients with MDD and cognitive dysfunction, but further studies with longer follow-up periods to assess mental function are required.

Key Words: Cognitive dysfunction, Digit Symbol Substitution Test, executive function in major depressive disorder, Perceived Deficits Questionnaire, vortioxetine

Received: December 6, 2021; **Revised:** May 26, 2022; **Accepted:** August 17, 2022July72022

Significance statement

Depression—either early or late in life— is 1 of the risk factors for developing dementia. Vortioxetine is a new antidepressant with multipharmacologic actions to elevate serotonin concentration and modulate multiple neurotransmitter receptors in the brain. This study is the first meta-analysis to evaluate the changes in cognitive function and depression in patients with major depressive disorder (MDD) treated with vortioxetine. Cognitive function improved for patients on vortioxetine 10 and 20 mg/day. Furthermore, Montgomery-Åsberg Depression Rating Scale scores improved for patients on vortioxetine 20 mg/day. These results indicated that low-dose vortioxetine could help patients with MDD recover cognitive function in spite of depressive symptoms. Whether vortioxetine has the potential to reduce the risk of developing dementia requires further longitudinal studies.

INTRODUCTION

Dementia refers to a group of symptoms related to cognitive dysfunction that includes multiple domain executive function, learning and memory, and social cognition (APA, 2013). Approximately 50 million people worldwide have dementia, and this number is expected to increase to 152 million by 2050. The global socioeconomic cost for caring for patients with dementia is expected to rise to $2.8 trillion by 2030 (Livingston et al., 2020; World Health Organization, 2021). Major depressive disorder (MDD) is also becoming increasingly prevalent. It is estimated to affect 340 million people globally and is expected to be the leading cause of disability-adjusted life-years in high-income countries by 2030 (Mathers and Loncar, 2006). Diniz et al. (2013) found a link between depression in older adults (adults aged above 65-year-old) and the risk of dementia, including both Alzheimer disease and vascular dementia. Studies have concluded that both early- and late-life depression had associations with dementia in the general population, not only in geriatrics (Kessing et al., 2009 ; Bennett and Thomas, 2014). Consequently, depression and dementia could be regarded as brain-degenerative diseases with different manifestations.

The pathophysiologic changes of cognitive impairment in MDD are related to serotonin (5-HT) depletion (Štrac et al., 2016) and hippocampus injury secondary to hypothalamic-pituitary-adrenal axis–induced glucocorticoid elevation (Byers and Yaffe, 2011). Furthermore, immune dysregulation, such as increased proinflammatory cytokines interleukin-1b, tumor necrosis factor-α, and interferons, were also noticed in depressed human and animal models (Dantzer et al., 2008; Wohleb et al., 2016). These changes increase free radicals and reduce neurotropic function, resulting in neuron loss. Hence pharmacologic reverse of cognitive function in patients with MDD might reduce the risk in these patients of developing dementia.

In 1 study, antidepressant agents were unable to modify the course of cognitive changes (Saczynski et al., 2015); another study, focused on a population of older women, concluded that the use of antidepressants, especially selective serotonin reuptake inhibitors (SSRIs) and trazodone, was associated with an increased risk of cognitive impairment 5 years later (Leng et al., 2018). Chan et al. (2019) determined that depression was associated with a higher risk of dementia, and the use of antidepressants has not been demonstrated to be a protective factor against dementia. These studies have demonstrated that antidepressants do not have significant procognitive effects.

Vortioxetine (1-[2-(2,4-dimethylphenyl-sulfanyl)-phenyl]-piperazine, Lu AA21004), which is a serotonin transporter (SERT) inhibitor and modulates the 5-HT1A receptor, is a new-generation multimodal antidepressant widely use in older patients with depression. Functional studies have demonstrated that vortioxetine acts as a SERT reuptake inhibitor; a 5-HT3, 5-HT7, and 5-HT1D receptor antagonist; a partial 5-HT1B receptor agonist; and a 5-HT1A receptor agonist (D'Agostino et al., 2015). Vortioxetine has provided evidence of improved cognitive function (Jensen et al., 2014; Wallace et al., 2014; Al-Sukhni et al., 2015; McQuaid, 2019). A study reported that vortioxetine improved cognitive function in patients with Alzheimer disease, which might be related to the modulating effect of glutamate, acetylcholine, histamine, and noradrenaline in the brain; these neurotransmitters are increased in the hippocampus by 5HT-3 blockade (D'Agostino et al., 2015). McIntyre et al. concluded that vortioxetine had a significant positive effect on psychomotor speed and delayed recall (Rosenblat et al., 2016). Vortioxetine can influence multiple cognitive domains, such as attention, orientation, executive function and concentration (Harrison et al., 2016; Bennabi et al., 2019; Cumbo et al., 2019). Among the various antidepressant agents thus far assessed, evidence for a positive, direct effect across multiple cognitive domains is strong for vortioxetine but relatively weak for other SSRI agents, serotonin-norepinephrine reuptake inhibitors, or bupropion (Jensen et al., 2014; McIntyre et al., 2015). The mechanism for improving cognitive function is hypothesized to be vortioxetine-induced elevation of serotonin levels and direct modulate the serotonin receptors (Jensen et al., 2014).

The current guidelines for depression treatment focus less on the treatment of cognitive conditions (McQuaid, 2019; Taylor et al., 2021; The National Institute for Health and Care Excellence, 2021). Additionally, the guidelines for dementia management suggest that antidepressants should not routinely be prescribed to patients to manage mild to moderate depression unless the drugs are indicated for a preexisting severe mental health problem (Butterworth, 2020; The National Institute for Health and Care Excellence, 2021). Some studies have concluded that antidepressant use may decrease the risk of developing dementia (Kessing et al., 2009; Moraros et al., 2017), but other studies have demonstrated that antidepressant use is associated with an increased risk of developing cognitive impairment and dementia (Goveas et al., 2012; Wang et al., 2016; Moraros et al., 2017; Then et al., 2017; Leng et al., 2018; Kodesh et al., 2019). Bartels et al. (2018) suggested that using SSRI to treat patients with depression for more than 4 years was associated with a delay in cognitive dysfunction. Thus, the influence of antidepressant use on cognitive function in patients with MDD remains inconclusive.

Currently, the guidelines for cognitive dysfunction in MDD treatment are still incomplete. Before 2016, some meta-analyses emphasized a change in cognitive function in patients with MDD treated with vortioxetine, but a systematic review and meta-analysis to update the management strategies for this patient population is necessary. In this study, we conducted a systematic search following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to evaluate the changes in cognitive function and depression

in patients with MDD treated with vortioxetine in randomized controlled trials (RCTs).

MATERIALS AND METHODS

This study was performed in line with the Cochrane Handbook and the PRISMA guidelines (Registration: PROSPERO CRD42021275289).

Search Strategy

The authors searched the PubMed, EMBASE, and Cochrane databases to identify RCTs comparing the efficacy and tolerability of vortioxetine in the treatment of patients with MDD. The search strategy and terms are outlined in Appendix 1. The literature search was conducted on July 15, 2021, and updated on September 12, 2021. It was limited to human participant studies, and no restrictions were imposed in terms of language or publication status. Furthermore, we manually checked the reference lists of the included studies to identify other potentially eligible studies until no additional trials could be found.

Inclusion and Exclusion Criteria

Trials meeting the following criteria were acceptable for inclusion in this meta-analysis: (1) RCT study design, (2) adult patients with a primary diagnosis of MDD, (3) patients receiving vortioxetine, and (4) trials with change-from-baseline outcome measures that included the Digit Symbol Substitution Test (DSST), Montgomery-Åsberg Depression Rating Scale (MADRS), and Perceived Deficits Questionnaire (PDQ) scores. Trials were excluded if they (1) were abstracts, reviews, letters, or case reports; (2) were a non-RCT study; (3) included patients not treated with vortioxetine; or (4) did not report the data of interest.

Data Extraction and Quality Assessment

Two authors (I.C.H. and T.S.C.) independently extracted the following data: first author, year of publication, country, number of patients in the vortioxetine and placebo groups, the administered dose of vortioxetine, duration of therapy, and changes from baseline in MADRS, DSST, and PDQ scores. A standardized Microsoft Excel file (Microsoft Corporation, Redmond, WA, USA) was used to extract the data. Any disagreements between the authors (J.C. and J.Y.S.) were resolved through discussion.

The methodological quality of each study was assessed using the Risk of Bias tool, version 2.0, introduced in the Cochrane Handbook for Systematic Reviews of Interventions, which consists of 5 domains, including bias arising from the randomization process, bias caused by deviations from the intended interventions, bias caused by missing outcome data, and bias in the selection of the reported results (Higgins et al., 2019). These domains were evaluated in all the included studies. If the 2 aforementioned authors had any disagreements during the bias assessment, all the authors met to reach a final decision. The risk-of-bias plot was generated using the robvis tool (McGuinness and Higgins, 2020).

Statistical Analysis

The changes from baseline in DSST, MADRS, and PDQ scores were treated as continuous outcomes; thus, the MADRS scores were expressed as the weighted mean difference (WMD), with 95% confidence intervals (CIs). We used the standardized mean difference (SMD) for DSST and PDQ scores. Heterogeneity among the studies was tested using the Cochrane Q χ^2 test and I^2 statistic. Studies with $I^2 > 50\%$ or $P < .1$ were considered to have heterogeneity. We used a random-effects model (DerSimonian and Laird, 1986) to pool the estimates according to the presence or absence of heterogeneity. When considerable heterogeneity was present, we performed a sensitivity analysis to explore the possible explanations for heterogeneity. We also performed a subgroup analysis based on vortioxetine dosage to establish whether different doses of vortioxetine would produce different effects compared with placebo. $P < .05$ was judged to be statistically significant, except where specified otherwise. All analyses were performed using Review Manager, version 5.4.1, software (Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen, Denmark).

RESULTS

An initial database search yielded a total of 92 records; 36 were excluded because they were duplicate studies, and 19 were excluded based on a review of the abstract and title. The remaining 37 articles were subjected to a full-text evaluation, and 31 were then excluded because they did not provide the available data, used the same data in multiple publications, were not RCTs, or were unrelated to our topic. Finally, 6 RCTs that met the inclusion criteria were included in this meta-analysis. A flowchart of the search process is presented in Figure 1.

The main demographic characteristics of the trials included in this meta-analysis are presented in Table 1. The trials were published between 2014 and 2020, and the sample size ranged from 96 to 598 (a total of 1782 patients). The demographic or clinical characteristics between the vortioxetine and placebo groups were matched. The dosage of vortioxetine varied among the 6 RCTs, ranging from 10 to 20 mg/day. Because the number of included studies was under 10, we did not conduct a publication bias assessment.

We had assessed the quality of the included studies, and there are some concerns in the bias in randomization of 1 RCT (Levada and Troyan, 2019) because there was lack of blinding for the assessments and no follow-up data from a healthy control group. Another concern is that bias occurred in the selection of the reported results of 1 RCT (Smith et al., 2018): The study had included DSST data but mentioned the scores only in the supplementary data. Despite these 2 concerns, however, the studies were generally of good quality and, on average, were assessed as having a low risk of bias. The results are shown in Figure 2.

Primary Outcome: Changes From Baseline in DSST Scores (Memory Outcome)

Six RCTs reported data on DSST scores (McIntyre et al., 2014; Mahableshwarkar et al., 2015; Baune et al., 2018; Smith et al., 2018; Levada and Troyan, 2019; Inoue et al., 2020). The pooled estimates using a random-effects model indicated that vortioxetine was significantly superior to placebo with regard to the changes from baseline DSST scores (WMD, 2.44 [95% CI, 1.11-3.77; $P < .001$) (Figure 3). The test for heterogeneity was significant (heterogeneity $P < .001$, $I^2 = 76\%$); however, the heterogeneity was questionable because only 6 studies were used. We also performed a subgroup analysis based on vortioxetine dosage. The pooled results demonstrated a significant improvement in all subgroups compared with the placebo group (20 mg/

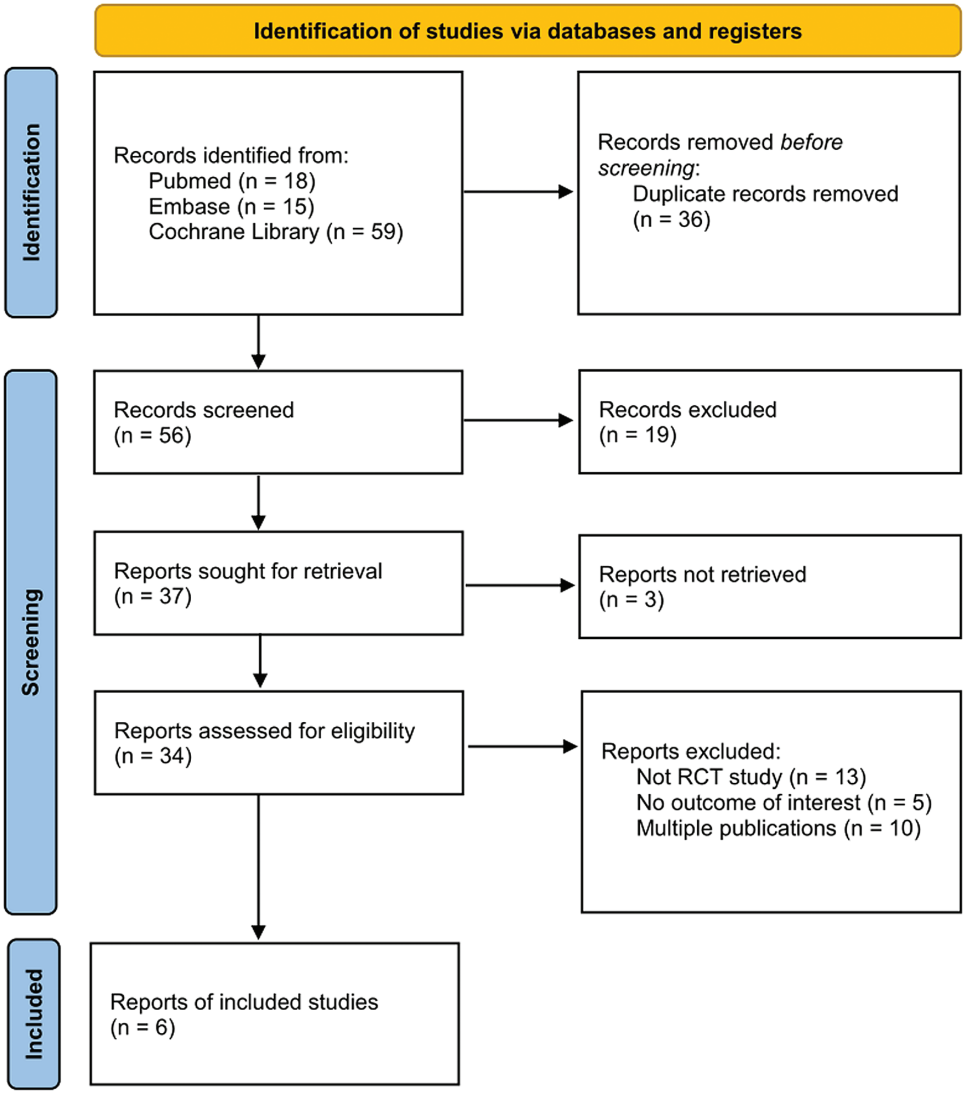

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart of the search process to identify randomized controlled trials (RCTs) for the meta-analysis.

day: WMD, 2.23 [95% CI, 0.18-4.28], $P = .003$; increasing from 10 to 20 mg/day: WMD, 1.75 [95% CI, 0.26-3.24], $P = .02$; 10 mg/day: WMD, 2.92 [95% CI, 0.25-5.58], $P = .03$) (Figure 3).

Secondary Outcome: Changes From Baseline in PDQ Scores (Functional Outcome)

Six RCTs reported data on PDQ scores (McIntyre et al., 2014; Mahableshwarkar et al., 2015; Baune et al., 2018; Smith et al., 2018; Levada and Troyan, 2019; Inoue et al., 2020). The pooled estimates using a random-effects model demonstrated that vortioxetine was significantly superior to placebo in terms of the changes from baseline in PDQ scores (SMD, –0.40 [95% CI, –0.48 to –0.33]; $P < .001$) (Figure 4). The test for heterogeneity was nonsignificant (heterogeneity $P = .97$, $I^2 = 0\%$); however, heterogeneity was questionable because only 6 studies were used. We also performed a subgroup analysis based on vortioxetine dosage. The pooled results demonstrated a significant improvement in all subgroups compared with the placebo group (20 mg/day: SMD, –0.46 [95% CI, –0.57 to –0.34], $P \leq .001$; increasing from 10 to 20 mg/day: SMD, –0.35 [95% CI, –0.57 to –0.14], $P = .001$; 10 mg/day: SMD, –0.36 [95% CI, –0.48 to –0.25], $P < .001$) (Figure 4).

Secondary Outcome: Changes From Baseline in MADRS Scores (Depression Outcome)

Three RCTs reported data on MADRS scores (McIntyre et al., 2014; Mahableshwarkar et al., 2015; Inoue et al., 2020). The pooled estimates using a random-effects model demonstrated that vortioxetine was significantly superior to placebo in relation to the changes from baseline in MADRS scores (WMD, –4.10 [95% CI, –4.92 to –3.29]; $P < .001$) (Figure 5). The test for heterogeneity was significant (heterogeneity $P = .002$, $I^2 = 76\%$); however, the heterogeneity was questionable because only 3 studies were used. We also performed a subgroup analysis based on vortioxetine dosage. The pooled results demonstrated a significant improvement in all subgroups compared with the placebo group (20 mg/day: WMD, –5.22 [95% CI, –6.49 to –3.95], $P < .001$; increasing from 10 to 20 mg/day: WMD, –2.30 [95% CI, –4.24 to

Table 1. Demographic Information for the Six Randomized Controlled Trials

	Region	Female, %/Age	Vor/Placebo, n/N	Dosage, mg	Length, wk	Measure	Baseline DSST Score
Baune et al., 2018	Europe	67/46.2	48/48	10	8	DSST, PDQ	46.2
Inoue et al., 2020	Japan	45/40.0	329/164	10, 20	8	DSST, PDQ, MADRS	58.3
Levada et al., 2019	Ukraine	57/37.3	36/71	10	8	DSST, PDQ	57.5
Mahableshwarkar et al., 2015	United States and Europe	65/44.6	198/194	10≈20	8	DSST, PDQ, MADRS	42.9
McIntyre et al., 2014	Multiple countries[a]	66/45.7	402/196	10, 20	8	DSST, PDQ, MADRS	42.0
Smith et al., 2018	United Kingdom	55/34.9	48/48	20	2	DSST	65.6

Abbreviations: DSST, Digit Symbol Substitution Test; MADRS, Montgomery-Åsberg Depression Rating Scale; PDQ, Perceived Deficits Questionnaire; Vor, vortioxetine.
[a]Multiple countries: Australia, Canada, Finland, France, Germany, Latvia, Mexico, Serbia, Slovakia, South Africa, Ukraine, and the United States.

–0.36], $P = .02$; 10 mg/day: WMD, –3.77 [95% CI, –5.03 to –2.50], $P < .001$) (Figure 5).

DISCUSSION

This meta-analysis identified 6 placebo-controlled trials that assessed the efficacy of the application of vortioxetine in the treatment of patients with MDD, revealing that vortioxetine significantly improved cognitive function compared with placebo, as measured by DSST and PDQ scores. The psychiatric outcome measured by MADRS demonstrated a significant improvement in patients treated with vortioxetine compared with those administered the placebo. In addition, the changes in DSST, PDQ, and MADRS scores were not related to vortioxetine dosage.

The baseline DSST scores significantly improved in the vortioxetine group compared with the placebo group. This result was observed in all the included trials, except 1 (Inoue et al., 2020). In that trial, the DSST scores demonstrated no significant change in the vortioxetine or placebo groups after 8 weeks of treatment, either at 10 or 20 mg ($P = .38$ and $P = .90$, respectively). The baseline DSST scores in that trial, however, were higher than those in the other trials (58.3 vs 41.6-50.3), which may have limited the magnitude of any improvements and the statistical power to detect them because of a ceiling effect.

The meta-analysis by McIntyre et al. (2016) of 3 RCTs demonstrated that changes in DSST scores statistically favored vortioxetine compared with duloxetine and placebo ($P = .04$ and $P < .001$, respectively) after adjustments for MADRS scores, indicating that the improvement effect of vortioxetine on cognitive function was independent of disease severity. Mild MDD may, however, contribute to higher DSST baseline scores, increasing the risk of a ceiling effect. These 3 RCTs excluded participants with a MADRS score below 26 to prevent such effect.

The changes from baseline in PDQ scores also revealed that the performance of vortioxetine was superior to that of placebo in the self-rated cognitive dysfunction of patients. Six trials were included in the analysis of PDQ scores, all of which indicated improvements in patients treated with vortioxetine compared with those administered a placebo. Most of the trials used a 20-item questionnaire to evaluate patients' perceived deficits, and 2 trials used a 5-item questionnaire (Levada and Troyan, 2019; Inoue et al., 2020). After being adjusted for SMD, the results consistently demonstrated significant improvements in the vortioxetine group compared with the placebo group.

No difference in patients' PDQ score changes were reported for the different doses of vortioxetine. All 6 of the included RCTs demonstrated a significant reduction in PDQ scores compared with placebo after vortioxetine treatment. The effects of vortioxetine therapy did not exhibit a dose-dependent trend, and no difference in PDQ scores was seen after increasing the vortioxetine dosage from 10 to 20 mg/day (both $P < .001$). In the post hoc analysis by McIntyre et al., which evaluated the efficacy of vortioxetine on cognitive function in working patients with MDD, participants were divided into subgroups based on their working status at baseline and workplace position; a significant improvement was observed in the total study population treated with either 10 or 20 mg of vortioxetine (–4.4 and –5.7 points, respectively; both $P < .001$). In the subanalysis, however, the effect of vortioxetine treatment on the reduction of PDQ scores in working patients was –4.9 points for 10 mg ($P = .006$) and –5.7 points for 20 mg ($P < .001$); among working patients in a "professional" position, this effect was –8.3 points for 10 mg ($P = .048$) and –11.5 points for 20 mg ($P = .002$). This insight could indicate a slight association between vortioxetine dosage and

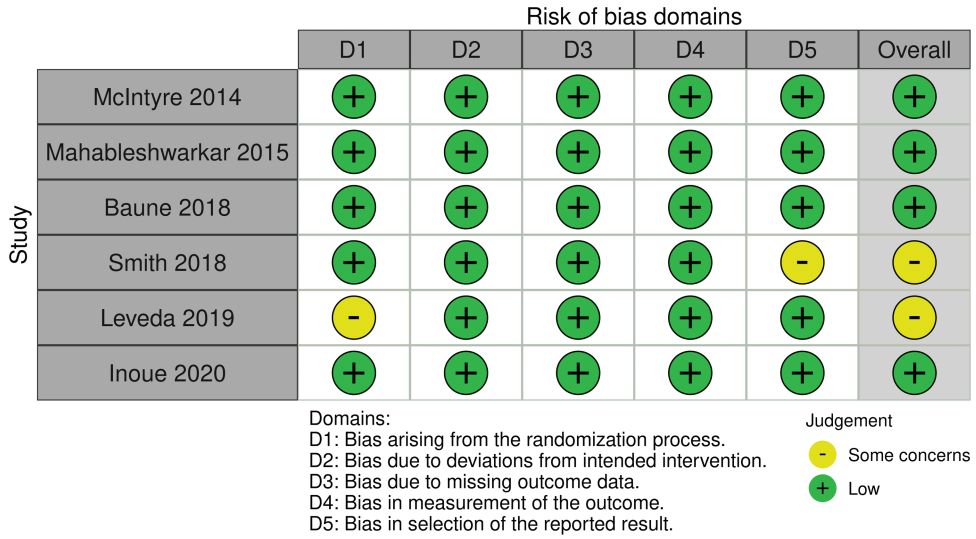

Figure 2. Risk-of-bias assessment for the randomized controlled trials.

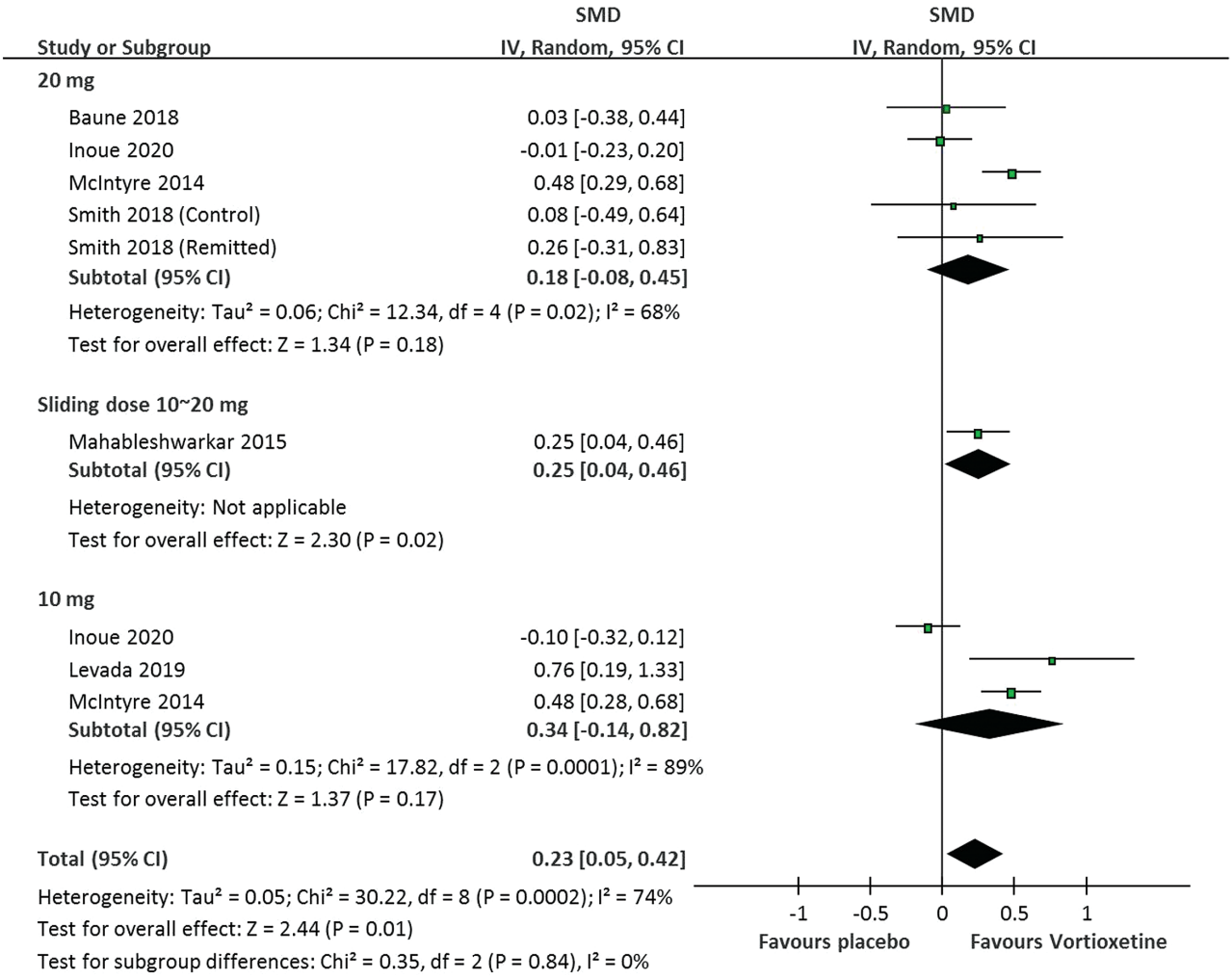

Figure 3. Change in Digital Symbol Substitution Test scores from baseline. CI, confidence interval; SMD, standardized mean difference.

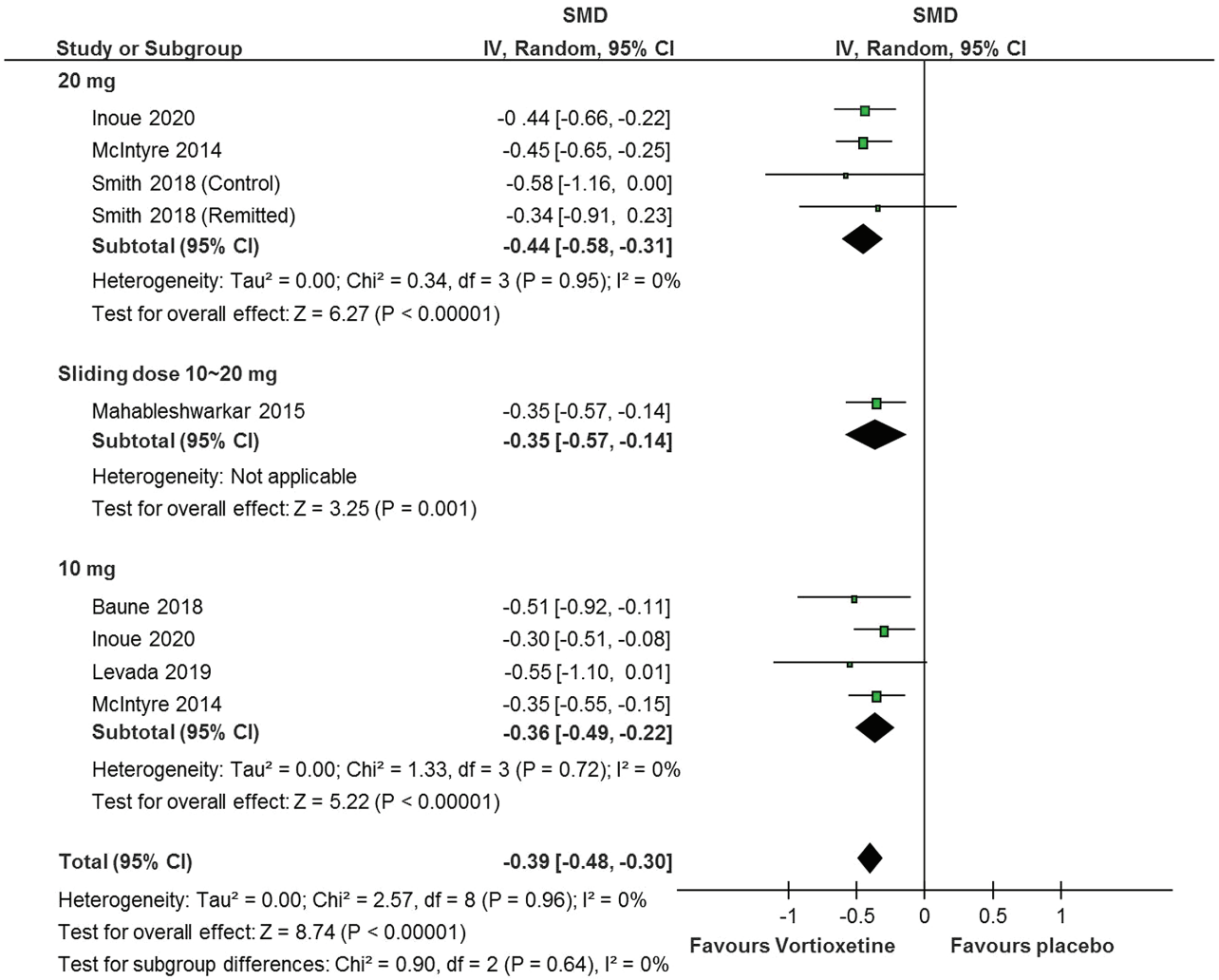

Figure 4. Change in Perceived Deficits Questionnaire scores from baseline. CI, confidence interval; SMD, standardized mean difference.

its efficacy on self-rated cognitive deficits and employment position (McIntyre et al., 2017).

For reducing depressive symptoms, vortioxetine therapy demonstrated a slight dose-dependent trend in MADRS scores, with improvements in depression-related outcomes increasing as vortioxetine doses increased from 10 to 20 mg/day (Δ–3.77 and Δ–5.22, respectively) but not in patients on 10 mg/day of vortioxetine in the first week or on flexible doses of 10 to 20 mg of vortioxetine a day (Δ–2.30; $P = .02$). This finding could be because only 1 trial included a sliding dosage subgroup (Mahableshwarkar et al., 2015). The meta-analysis of vortioxetine by Thase et al. (2016) demonstrated a general dose-dependent trend in improvements in MADRS scores. Notably, the dose relationship was observed at 5 and 10 mg/day and again at 20 mg/day (Δ–2.27, Δ–3.57, and Δ–4.57, respectively; $P < .01$) but was not significant at 15 mg/day (Δ–2.60; $P = .105$), although this subgroup was the smallest and had substantially wider confidence intervals than the other subgroups.

In the trials included in the present meta-analysis, vortioxetine demonstrated significant effects on depressive symptoms during an 8-week treatment period (McIntyre et al., 2014; Mahableshwarkar et al., 2015; Inoue et al., 2020). In terms of reducing cognitive impairment, vortioxetine exhibited an improved antidepressant effect compared with placebo. To compare vortioxetine with other antidepressants, 1 RCT used duloxetine as an active reference, revealing that the performance of both vortioxetine and duloxetine was superior to that of placebo in terms of PDQ and MADRS scores, but only vortioxetine significantly improved DSST scores. This study also indicated that vortioxetine's cognitive benefits were primarily a direct treatment effect rather than the result of the alleviation of depressive symptoms (Mahableshwarkar et al., 2015). Another RCT directly compared vortioxetine with escitalopram in relation to cognition and depressive symptoms; although the results were not statistically significant, numerical improvements across DSST, PDQ, and MADRS scores generally favored vortioxetine (Vieta et al., 2018). Overall, the studies supported vortioxetine as the first antidepressant drug to demonstrate proven efficacy in improving the cognitive symptoms of depression (Perini et al., 2019).

Regarding dosage, for treating cognitive dysfunction, no significant difference was demonstrated between 10 and 20 mg of vortioxetine per day. If we try to exclude the result of the trial by Inoue et al. from the meta-analysis because of relatively high baseline DSST scores, however, the meta-analysis of the remaining 5 articles demonstrated that a 10-mg dose of vortioxetine was associated with a significant improvement in DSST scores (z score = 5.44; $P < .001$), but a 20-mg dose was not

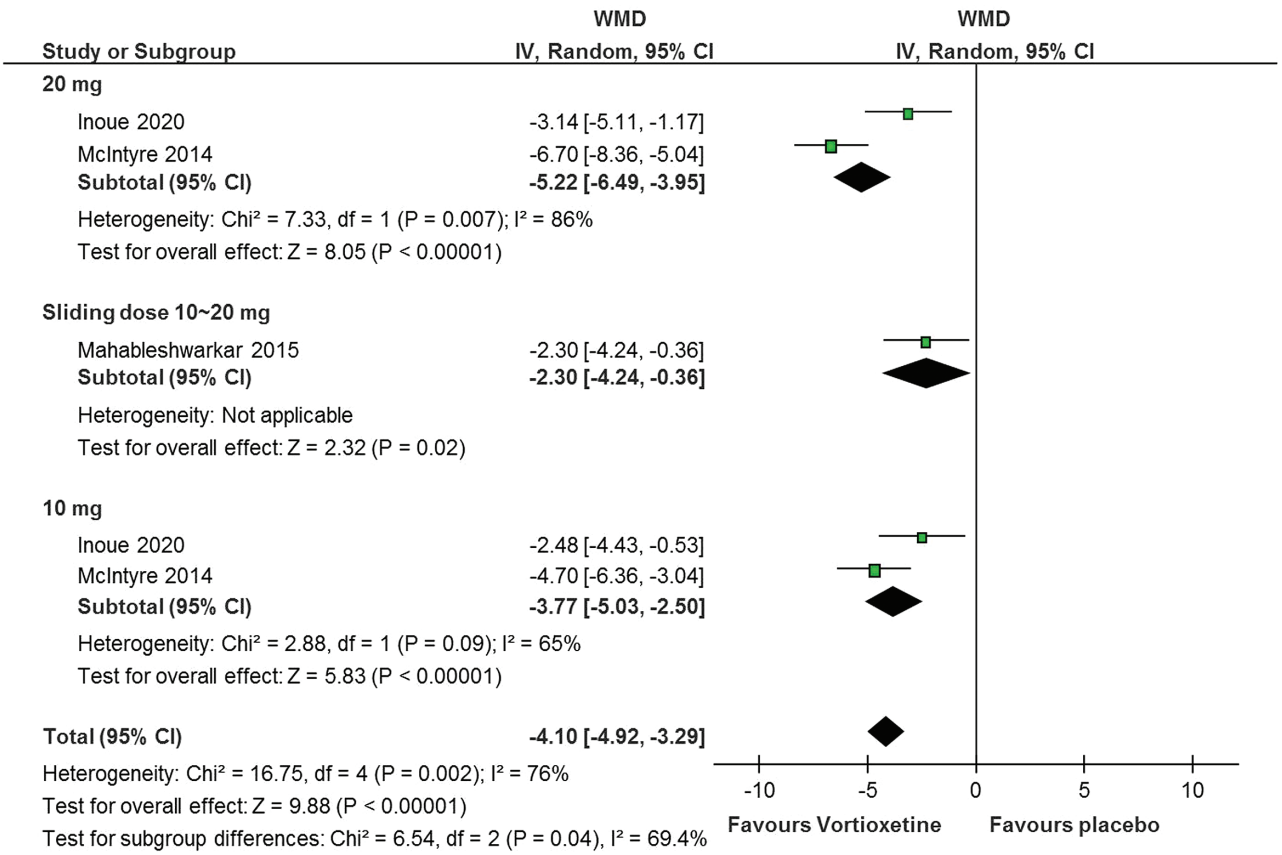

Figure 5. Change in Montgomery-Åsberg Depression Rating Scale scores from baseline. CI, confidence interval; WMD, weighted mean difference.

(z score = 1.93; $P = .05$). Multiple cognitive domains, such as executive function, working memory, attention, and motor speed, are assessed in the DSST (Jaeger, 2018). In the post hoc analysis by Harrison et al. (2016), which evaluated vortioxetine efficacy on cognitive dysfunction in patients with MDD, participants were randomly administered 10 or 20 mg of vortioxetine per day or placebo. Both 10 and 20 mg of vortioxetine (z score = 0.52 and 0.52, respectively; $P < .001$) demonstrated a multidomain beneficial effect on cognitive performance, with changes from baseline in DSST scores established independently of vortioxetine dosage. None of the trials reported that patients treated with 20 mg of vortioxetine per day had improved DSST scores compared with those administered 10 mg/day.

Ultimately, most of these clinical trials demonstrated the positive effect of vortioxetine on the cognitive function of patients with MDD, with no difference in dosage. Based on those trials, at an initial dose of 10 mg vortioxetine, patients' cognitive function improved first; furthermore, depressive symptoms improved at the 20-mg dose afterwards.

The common side effects of vortioxetine include headache, diarrhea, nausea and vomiting, insomnia, and dizziness. Two of the trials failed to mention safety issues or side effects (Baune et al., 2018; Smith et al., 2018). Among these common side effects, the most common reasons for discontinuing vortioxetine were nausea and headache, although the numbers were small (1.9% and 1.0%, respectively) (McIntyre et al., 2014). According to the literature, vortioxetine results in fewer adverse events than duloxetine. In the study by Mahableshwarkar et al., the rate of discontinuing vortioxetine treatment because of adverse events was similar to the rate of discontinuing placebo. The study duration of the RCTs was mostly 8 weeks (McIntyre et al., 2014; Mahableshwarkar et al., 2015; Baune et al., 2018; Levada and Troyan, 2019; Inoue et al., 2020), although 1 study had a duration of just 2 weeks (Smith et al., 2018). In 2 studies on the long-term use of vortioxetine (Jacobsen et al., 2015; Baldwin et al., 2016), the adverse events reported were the same as those in the short-term clinical trials, with no significant changes in patient body weight, vital signs, or laboratory data after 52-week trials. No studies with a duration of vortioxetine use longer than 52 weeks are currently available, however.

According to the studies, the use of vortioxetine for 2 weeks resulted in improvements in PDQ scores. For the other outcome measures (DSST and MADRS), however, no data existed on using vortioxetine for only 2 weeks. These RCTs all used a vortioxetine dosage frequency of once a day.

The trials included in this meta-analysis, which studied patients with MDD aged 33.8 to 46.15 years, demonstrated that vortioxetine was an effective and well-tolerated antidepressant, with the added benefit of improving cognition and functioning in young adults. Cognition and functioning play a crucial role in social and work situations as well as in overall quality of life. Chokka et al. investigated the association between cognitive symptoms and workplace productivity in working patients (mean age, 40.8 years) with MDD who received vortioxetine in a simulated real-life setting. At 12 weeks, improvements in PDQ ($r = 0.634$; $P < .001$) and DSST ($r = -0.244$; $P = .003$) scores were significantly associated with improvements in workplace productivity (Chokka et al., 2019b), and this association continued until week 52 (Chokka et al., 2019a). These findings demonstrate the long-term benefits of vortioxetine treatment in working patients with MDD and

emphasize the strong association between cognitive symptoms and functioning in a real-world setting. To date, vortioxetine treatment is the most efficient treatment for improving cognitive function and could be a particularly helpful therapeutic intervention in daily life for the working patient population.

This meta-analysis had 3 limitations that should be considered when interpreting the results. First, our study was based on only 6 RCTs, and some of the pooled estimates were based on a limited number of trials and a modest sample size. This limitation could lead to an underpowered estimation of the treatment effect. Second, because of the limited number of included studies, the pooled results in the subgroup analysis could be underpowered. Third, most of the included studies, except for that by Inoue et al., had restricted patients' DSST scores at baseline; patients were not included if their DSST score was higher than 70. In the study by Inoue et al. (2020), the baseline DSST score was higher; therefore, the ceiling effect was a concern.

CONCLUSION

Vortioxetine dosages of both 10 and 20 mg/day demonstrated improvements in the treatment of depressive and cognitive symptoms based on the results of this meta-analysis. In light of the potential bias and confounding of the included studies in this meta-analysis, well-conducted, large-scale RCTs are necessary to verify these findings. Accordingly, 10 mg/day vortioxetine could benefit patients with MDD who also experience cognitive dysfunction. A longitudinal study for vortioxetine use in a real-world setting is still necessary to clarify whether the cognitive improvement can lower the risks of dementia in patients with MDD.

Acknowledgments

I.C.H., T.S.C., C.C., and J.Y.S. had full access to all the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. Editorial and medical writing support was provided by Melanie Tankard and Nicholas Doenges of Wallace Academic Editing, funded by Research Promotion Center, Office of Research and Development, Taipei Medical University.

Funding

This work was supported by Wan Fang Hospital, Taipei Medical University (Grant No. 110TMU-WFH-13).

Statement of Interest

All authors report no biomedical financial interests or potential conflicts of interest.

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