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Vortioxetine for cognitive dysfunction in depression: A narrative review

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ABSTRACT

Cognitive dysfunction is commonly seen in patients with major depressive disorder (MDD). It is one of the most disabling and difficult-to-treat aspects in depression. Conventional antidepressants target mostly at the alleviation of mood symptoms by altering levels of serotonin, norepinephrine and other neurotransmitters in the brain, while having less effect on the cognitive disturbances in depression. Vortioxetine, a "multi-modal" antidepressant, exerts multiple pharmacological effects by simultaneously acting at six pharmacological targets with three modes of action. It is believed to have additional efficacy for the improvement of cognitive functions in depression. In this review, we managed to identify four primary studies, two post-hoc analysis studies, one meta-analysis and three review articles on the use of vortioxetine for cognitive functions in depressive patients. In general, the current evidences for the use of vortioxetine to improve cognitive impairment are quite assuring with a satisfactory safety profile. Having the ability to augment and regulate cognitive performance in patients, it should be considered as a useful treatment option particularly in patients with major depressive disorder where cognitive impairment is present.

KEYWORDS: vortioxetine, cognitive dysfunction, depression, antidepressant.

1. INTRODUCTION

Major depressive disorder (MDD) is a growing problem globally. By the year 2020, depression is projected to be the second largest contributor to the global burden of disease, after heart disease [1]. Depression itself incurs substantial public health and economic costs; it is estimated that the annual economic burden of depression in the United States is about $43 billion with $17 billion of that resulting from lost work days [2].

More often than not, MDD is mistaken for simple feelings or unhappiness or grief brought about by the death of a loved one. Sadness and grief are normal reactions to stressful life events and often resolve without medical intervention. In fact, MDD is a disabling mental health problem that disrupts a person's mood and adversely affects his psychosocial and cognitive functioning. Studies have shown that cognitive dysfunction associated with depression plays a pivotal role in causing morbidity associated with MDD in contrast to affective symptoms alone [3]. The impairment during depression is multiplex and manifold affecting both elementary and more complex cognitive process equally [4]. The effect depression has on cognitive function determines daily function in the long term and also influences patients' degree of treatment response to psychotherapy and various other therapies [5].

Owing to the late discovery of the role of cognitive dysfunction in depression, traditional pharmacological treatment of MDD targets almost exclusively at the alleviation of mood symptoms by altering levels of serotonin, norepinephrine and other neurotransmitters in the brain, thus having less effect on the cognitive disturbances in

depression. Recently, a novel drug possessing 2 or more complementary modes of action, Brintellix™ (vortioxetine hydrobromine) was approved in the USA for the once-daily treatment of adults with MDD [6, 7].

Unlike traditional antidepressants, vortioxetine has a number of pharmacological effects that extend beyond traditional 5-HT blockade. It is a "multimodal" agent that exerts its pharmacological effects by simultaneously acting at 6 pharmacological targets with 3 modes of action, namely the inhibition of the serotonin (5HT) transporter or SERT; actions at several G-protein linked receptors (agonist actions at $5HT_{1A}$ receptors, partial agonist actions at $5HT_{1B}$ receptors, antagonist actions at $5HT_{1D}$ and $5HT_7$ receptors) and the inhibition of a ligand-gated ion channel ($5HT_3$ receptor) [8, 9].

In terms of pharmacokinetics, oral vortioxetine is absorbed slowly with an absolute bioavailability of 75% without being affected by food intake. After multiple administrations of 5-10 mg/day of vortioxetine, peak plasma concentrations of 9-33 ng/mL were reached in 7-11 hours. Being highly protein-bound (98-99%), vortioxetine is distributed extensively in peripheral tissues as evidenced by its relatively large volume of distribution. Multiple cytochrome P_{450} isozymes metabolize vortioxetine, converting it into its major, pharmacologically inactive metabolite. Liver plays a major role in metabolizing vortioxetine extensively, leaving trace amounts of unchanged parent drug in the urine. Approximately two-thirds of vortioxetine inactive metabolites are then excreted in the urine with the rest being excreted in faeces [10].

Considering the unique pharmacological profile and multimodal mechanism of action vortioxetine has on multiple neurotransmitter systems, studies have been done to validate the use of vortioxetine in improving cognitive performance in patients with MDD. In this review, we aim to evaluate and summarize the evidences on the use of vortioxetine for cognition in depressive patients.

2. METHODS

To identify the studies on vortioxetine targeting cognitive dysfunction in depressed patients, we conducted a search on PubMed (year: 1950-Jan 2017) by matching the key terms: ***vortioxetine*** AND ***cognition*** OR ***cognitive***. We included review articles, controlled trials, meta-analyses, editorials, commentaries, correspondences and letters to editor published fully in peer-reviewed journals and written in English. Reference lists from the selected relevant articles were searched for additional trials or studies.

For the purpose of discussion, the methodological and sample characteristics of the included studies such as the study design, number of subjects, mean age, dosage of medication (vortioxetine), measurement tool(s) used and outcomes were extracted and tabulated according to the type of symptoms.

3. RESULTS

In total, we managed to identify one animal study on vortioxetine and 4 randomised control trials (RCTs) on the use of vortioxetine for cognitive functions. There were two additional studies on the post-hoc analyses based on the same data. A meta-analysis of three randomized controlled trials on this topic was also identified. There were another three review papers on this subject with the latest one published in 2016. One of the reviews was on preclinical evidence for the efficacy of selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs) and vortioxetine on cognitive function.

The animal study on vortioxetine by Pehrson *et al*. utilised behavioral experiments and drug exposure studies on 321 adult male rats to look into the effects of vortioxetine on scopolamine-induced cognitive impairment. For behavioral experiment, acute vortioxetine, in which the rats were randomly injected with vortioxetine, was able to reverse scopolamine-induced impairments in social and object recognition memory but not for attention. On the other hand, the drug exposure study that was conducted to establish a possible pharmacokinetics interaction between vortioxetine and scopolamine in turn displayed a modest and short-lived increase in hippocampal acetylcholine (Ach) levels for acute vortioxetine. These findings put forward that vortioxetine has some effects on

memory, which is mediated through cholinergic neurotransmission [11].

A randomized controlled trial by Theunissen *et al.* involving 24 healthy subjects studied the acute and steady-state effects of vortioxetine on actual driving and cognition. Subjects were randomly administered 10 mg vortioxetine, 30 mg mirtazapine and placebo. Primary outcome of Standard Deviation of Lateral Position and various other cognitive tests substantiate that the administration of vortioxetine did not result in cognitive or psychomotor impairment and did not impair driving after single or multiple dosing unlike mirtazepine that was shown to impair cognitive and psychomotor performance during acute treatment phase [12] (Table 1).

Majority of phase 2 and 3 RCTs on the use of vortioxetine were conducted on patients diagnosised with acute major depressive episode in the context of recurrent major depressive disorder. The first such RCT was conducted by Katona *et al*. on elderly subjects with recurrent major depressive disorder. It was a double-blind, randomized, fixed-dose, placebo-controlled, active reference (duloxetine) study that looked into the efficacy and safety of vortioxetine. It included 452 patients from 81 psychiatric, psychogeriatric and geriatric settings in seven countries. Vortioxetine was shown to be well tolerated and efficacious in the treatment of MDD among elderly patients. In terms of cognition, vortioxetine was found to be superior to placebo in speed of processing, verbal learning and memory [13]. Vortioxetine, but not duloxetine, showed an improvement compared with placebo on the digital symbol substitution test (DSST). On the Rey auditory verbal learning test (RAVLT), both vortioxetine and duloxetine showed an improvement compared with placebo. Path analysis showed that vortioxetine had an 83% direct effect on the DSST (as compared to duloxetine, 26%). On RAVLT acquisition, vortioxetine had a 71% direct effect as compared to 65% for duloxetine [13]. Table 1 summarizes the studies found in this review.

Mahableshwarkar *et al*. conducted a double-blinded randomized controlled trial with a sample size of 602 patients with acute major depressive episode that looked into short term efficacy of vortioxetine on cognitive function. They made a comparison between the flexible doses of vortioxetine (10 mg or 20 mg) once daily and placebo. Duloxetine 60 mg once daily was also included as the active reference arm to demonstrate assay sensitivity to traditional antidepressant outcomes. During primary analysis, the difference in DSST performance score was significant between vortioxetine and placebo but not significant between placebo and duloxetine. Measurement of secondary outcomes produced statistically significant results for both vortioxetine and duloxetine in the perceived deficits questionnaire (PDQ) attention/concentration and planning/ organization subscores [14] (Table 1). Path analysis also produced evidence that the improvements in the cognitive functions of patients with depression are primarily a direct treatment effect of vortioxetine and not due to improvements in depressive symptoms.

McIntyre *et al*. conducted a double-blinded randomized controlled trial on cognitive function in recurrent moderate to severely depressed adults. A total of 602 patients were randomized to receive vortioxetine 10 mg/day, vortioxetine 20 mg/day or placebo for an 8-week period. Summary of findings was that both doses of vortioxetine were able to produce statistically significant superiority in both primary efficacy (composite cognition score comprising of DSST and RAVLT scores) and secondary efficacy (measures of executive function, attention, processing speed, learning and memory) endpoints when compared to placebo [15]. There were two post-hoc analyses conducted using the data from this study. In one of the post-hoc analyses, Harrison *et al*. concluded that vortioxetine (10 and 20 mg/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 [16]. In the other post-hoc analysis, McIntyre *et al*. found that the beneficial effects of vortioxetine on objective or subjective cognitive function were greater in the working group with MDD [17]. The post-hoc analysis of this study also supported the dissociation between improvements in cognition and improvements of depressive symptoms with the use of vortioxetine as demonstrated by the

Table 1. Summary of clinical trials that used vortioxetine for cognitive dysfunction in depression.

Author, Year, Country	Study design (No. of Subjects)	Study population	Study duration	Mean age, % Female	Medication (Placebo, Control)	Measurement	Outcome (w/ Placebo, w/Control)
Theunissen *et al*., 2013, Netherlands [12]	RCT (24)	Healthy subjects	16 days	31 (54%)	Vortioxetine 10 mg; Mirtazapine 30 mg; placebo	SDLP[a] Critical-tracking test Divided-attention task Word-learning task	Did not impair driving, cognitive or psychomotor performance after single/multiple doses.
Katona *et al*., 2012, London [13]	RCT (453)	Elderly with recurrent MDD	8 weeks	71 (67%)	Vortioxetine 5 mg; duloxetine 60 mg; placebo	DSST, RAVLT	Significant improvement in vortioxetine-treated subjects
Mahableshwarkar *et al.*, 2016, United States [14]	Double-blind RCT (602)	Major depressive episode with recurrent MDD	8 weeks	44.2 (68.2%)	Vortioxetine 10 mg q.d.; Vortioxetine 20 mg q.d.; placebo; Duloxetine (reference)	DSST[a] PDQ CGI-I score TMT A/B Stroop test GMLT DT IT One-Back Task	Significant improvement in vortioxetine group
McIntyre *et al*., 2014, United States [15]	Double-blind RCT (602)	Major depressive episode with recurrent MDD	8 weeks		Vortioxetine 10 mg/d; Vortioxetine 20 mg/d; Placebo.	DSST RAVLT TMT A/B Stroop test SRT CRT	Significant improvement in vortioxetine-treated group

Note: DSST = Digital Symbol Substitution Test (integrated cognitive functioning, including executive function, processing speed, attention, spatial perception and visual scanning); PDQ = Perceived Deficits Questionnaire; CGI-I score = Clinical Global Impressions-Severity score; RCT = Randomized Controlled Trial; TMT = Trail Making Test (A : Speed of processing; B : Executive functioning); GMLT = Groton Maze Learning Test (Visual learning and Memory); DT = Detection Task (Motor speed); IT = Identification Task; SDLP = Standard Deviation of Lateral Position; SRT = Simple Reaction Time Task; CRT = Choice Reaction Time Task; RAVLT = Rey Auditory Verbal Learning Test; Behavioural Experiments = Social Recognition Memory Task, Object Recognition Memory Task, Visual Detection Task.

[a]: Primary Outcome Measurement

improved cognitive function in the subgroup of patients who were non-responders and non-remitters.

McIntyre published a report on the meta-analysis of three randomized controlled trials. The three studies were similarly designed. All studies were randomized, double-blind and placebo-controlled trials conducted for 8 weeks in patients with MDD. In all three trials, change in cognitive function was assessed using the DSST score. In two of the source studies, duloxetine 60 mg/day was used as an active reference for assay sensitivity. The results showed that after adjustment for underlying depressive symptoms, vortioxetine had significant DSST improvement compared to placebo in all the three trials and both duloxetine-referenced trials. Whereas, duloxetine showed no significant DSST improvement compared to placebo. The authors concluded that vortioxetine, but not duloxetine, significantly improved cognition, independent of depressive symptoms [18].

A review article by Pehrson *et al*. summarizes the preclinical data on the effects of antidepressants, including SSRI, SNRI and vortioxetine on cognition. Data of behavioral tests of cognition such as cognitive flexibility, attention and memory; cognition-relevant mechanistic assays such as electroencephalography, *in vivo* microdialysis, *in vivo* or *in vitro* electro-physiology, and molecular assays related to neurogenesis or synaptics prouting were included in the review [19]. Preclinical studies evaluated in this review article by Pehrson *et al*. showed that just blocking the reuptake of serotonin or norepinephrine was insufficient to reinstate memory deficits due to serotonin depletion [20, 21]. In normal animals, SSRI and SNRI have been shown to have either no effect or impaired the attention [22, 23]. Both vortioxetine and duloxetine have been shown to increase vigilance in rats but their effects on brain rhythms were different [24, 25]. Vortioxetine dosing at serotonin transporter occupancy levels as low as 60% has been shown to reverse the deficit in reversal learning due to serotonin depletion [26], and acute vortioxetine treatment improved memory performance at doses that are clinically relevant [27]. Vortioxetine reversed stress-induced impairment of hippocampal long term potentiation, that correlates with learning and memory, as compared to SSRIs or SNRIs that have variable effects on the hippocampal long term potentiation [28-31]. Vortioxetine also increases the firing rate of pyramidal neurons in medial prefrontal cortex that may result in the cognition enhancement effects observed with the use of this medication [32]. The authors concluded that vortioxetine may have advantages over SSRI or SNRI in terms of its effects on cognitive function. However, the use of antidepressant doses was outside the therapeutically- relevant range in those preclinical studies. There was also lack of data on target engagement or exposure and there was a tendency to investigate acute rather than long-term antidepressant effect. The authors suggested the use of biologically relevant depression models and appropriate antidepressant doses in future preclinical studies, with techniques focused on measuring target occupancy or brain exposure. It is important to develop direct links between the mechanistic effects of antidepressants and their effects on cognitive function. Quantitative electroencephalography was recommended to create this link [19].

There were two other review articles on this topic. The review article by Frampton focused on vortioxetine effects on cognition and general functioning in adults with MDD. Frampton concluded that across three large, placebo-controlled studies in adults with recurrent MDD, short-term treatment with vortioxetine almost always resulted in statistically significant and clinically meaningful improvements in various domains of cognitive functions namely the executive function, processing speed, attention, learning and memory on two objective measures, the DSST and RAVLT. These cognitive improvements were shown to be more pronounced in working patients with major depressive disorder especially in the subgroup identified as “professional” (e.g. manager/administrator positions). The review article also mentioned that vortioxetine demonstrated significant improvement in subjective measure of cognitive function which was more pronounced in the “professionals” subgroup of patients with MDD

based on the perceived deficits questionnaire (PDQ) [33].

Another review article by Al-Sukhni *et al.* summarized the pharmacodynamic and pharmacokinetic properties of vortioxetine. It has been found that vortioxetine exhibited lower serotonin transporter occupancy rates than SSRIs and SNRIs but brings significant clinical effects indicating that vortioxetine has additional mechanisms that are involved in its antidepressant and domain-specific effects on cognition. The review also gave a brief overview of the efficacy of vortioxetine in the case of cognition in depressed patients. The authors concluded that vortioxetine is the first antidepressant agent to demonstrate meaningful clinical efficacy in improving cognition in adults with MDD, independent of improvement in depressive symptoms [34].

DISCUSSION

Although the functional disability in patients with major depressive disorder is thought to be primarily caused by mood disorder, cognitive inefficiency and impairment are increasingly appearing to be a harbinger of subsequent crippling in daily living even for patients who have achieved remission [35]. Amongst the common symptoms reported for patients with cognitive impairments include slowed thoughts, poor concentration, distractibility and reduced capacity to process information. They also display diminished attention to self-care and to their environment, whereas transient cognitive impairment, especially involving attention, concentration, and memory storage and retrieval, are demonstrable through neuropsychological testing [36-38].

Moreover depression is primarily a disorder affecting people of working age, and hence treatment of major depressive disorder should aim not only to alleviate mood symptoms but to encompass the aspect of cognitive functioning as well. Vortioxetine may therefore prove to be a useful tool to breathe a new life into the existing treatment of depression [12, 13, 14, 15, 18]. This review found positive results with regard to vortioxetine, that is improvement of cognitive dysfunction in patients with major depressive disorder.

Vortioxetine is a “multimodal” agent that acts at 6 pharmacological targets with three modes of action. Vortioxetine inhibits the serotonin transporter or SERT; acts at several G-protein linked receptors (agonist actions at 5HT1A receptors, partial agonist actions at 5HT1B receptors, antagonist actions at 5HT1D and 5HT7 receptors) and inhibits ligand-gated ion channel (the 5HT3 receptor) [8, 9]. 5HT neurons terminate upon glutaminergic pyramidal neurons directly and GABAergic inhibitory interneurons indirectly, resulting in an array of excitatory and inhibitory actions of the neuronal network of the prefrontal cortex. The prefrontal cortex and hippocampus are hypothesized to be the sites of critical nodes responsible for various cognitive functions such as learning, working memory, attention, and behavioral flexibility [39-44]. Vortioxetine enhances firing of pyramidal neurons, presumably due to its antagonism of 5HT3 receptors, as this removes the 5HT-mediated inhibition from a population of GABA interneurons, thus disinhibiting pyramidal neurons [45, 46]. In addition, 5HT1A agonism by vortioxetine inhibits both the major subpopulations of GABA interneurons, further disinhibiting pyramidal neurons. Another vortioxetine’s precognitive action mediated by its 5HT3 antagonist properties is enhanced release of both norepinephrine (NE) and ACh. The release of 5HT, NE, and ACh by vortioxetine could theoretically improve the efficiency of information processing by facilitating long-term potentiation, synaptic plasticity, and enhanced pyramidal neuron activity leading to improvement of cognitive symptoms in major depressive disorder [45, 47-50]. The other pro-cognitive activity of vortioxetine is *via* the action on 5HT1A and 5HT1B. GABA release is inhibited by 5HT1A input to these GABAergic interneurons. When vortioxetine stimulates 5HT1A receptors, this could potentially disinhibit the release of ACh, NE, and dopamine (DA) from their nerve terminals in the prefrontal cortex [51-56]. Lastly, blockade of postsynaptic 5HT1B heteroreceptors on presynaptic nerve terminals could theoretically be another mechanism whereby ACh, NE,

DA, and histamine (HA) release is enhanced by vortioxetine [50, 57].

In preclinical quantitative electroencephalography studies, vortioxetine increased vigilance which was measured during the waking state. Vortioxetine at a dose corresponding to 80% serotonin transporter occupancy increased delta, theta and gamma power significantly [24, 25]. Furthermore, vortioxetine increased hippocampal output [47], pyramidal neuron firing and frontal cortical gamma oscillatory power in rats, which indicated that the cellular framework for activating cortical neurons and eliciting gamma is engaged.

Acute administration of vortioxetine was shown to counteract the serotonin depletion-induced deficit in reversal learning, and improve memory performance in a fear conditioning task as well as in a novel objection recognition test. Electrophysiological study showed that vortioxetine increased the firing rate of pyramidal neurons in the medial prefrontal cortex. In the hippocampus, exposure to stress has been shown to impair long-term potentiation, a model of synaptic plasticity that correlates with learning and memory. Study showed that acute treatment with vortioxetine can reverse the serotonin-induced inhibition of Cornu Ammonis area 1 (CA1) pyramidal cells and enhance theta-burst long-term potentiation in hippocampal slices [47]. Neurogenesis has been linked with hippocampal-dependent memory formation in tasks such as fear conditioning and spatial memory [58-62].

Chronic treatment with vortioxetine induces neurogenesis in normal animals and can restore impaired neurogenesis in stress paradigms, possibly leading to enhanced plasticity and cognitive function. Study showed that chronic vortioxetine (5 mg/kg p.o.) in mice elevated the number of doublecortin-positive cells, prolonged the survival of bromodeoxyuridine-positive cells in the dentate gyrus, and increased dendritic branching at a dose of 20 mg/kg, p.o. [63].

In general, preliminary results demonstrated that vortioxetine at clinically relevant doses enhanced neurogenesis and plasticity-promoting effects. The effect vortioxetine have in behavioral tests of cognition and in potentially cognition-relevant mechanistic assays suggests that it may have advantages over existing antidepressants in terms of its effect on cognitive function.

Study of vortioxetine on healthy subjects showed that it did not impair cognitive and psychomotor performance unlike other antidepressants [12] and the results of other studies conducted on vortioxetine for cognitive enhancing effects in MDD patients were quite promising. Post-hoc analyses of vortioxetine efficacy on cognitive performance point towards beneficial effects particularly in measures of executive function, attention or speed of processing, and memory. As evidenced by digital symbol substitution test (DSST) from majority of studies, dosages of 5 mg-20 mg/day seem to produce a consistent and statistically significant improvement regardless of depressive symptoms [16].

Multiple papers have hypothesized that the efficacy of vortioxetine across disparate domains of cognitive functioning is mediated by its multimodal action [12, 13, 14, 15, 18]. In areas of cognitive executive functioning, speed of processing, verbal learning and memory, vortioxetine has an even more pronounced effect in working class, managers and professionals. This could be due to the fact that patients in these positions have higher demands for executive functioning, more resilient and have higher levels of motivation thus having more room for cognitive improvement during the period of treatment. Given the direct relationship between cognitive dysfunction and work impairment, it is safe to assume that human capital gains may be benefited from a societal perspective if cognitive functioning is improved in MDD [17].

CONCLUSION

In conclusion, the current evidence for the use of vortioxetine to improve cognitive impairment is quite assuring despite majority of supporting studies have been limited by small sample sizes, absence of placebo controls, lack of links between pre-clinical and clinical results, and an inability to differentiate between direct and indirect effects. As a novel, multimodal antidepressant, vortioxetine proves itself to be generally efficacious with an overall safety profile similar to that of existing first-line antidepressants. Having the ability

to augment and regulate cognitive performance in patients, it should be considered as a useful treatment option particularly in patients with MDD where cognitive impairment is apparent.

CONFLICT OF INTEREST STATEMENT

None.

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