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REVIEW ARTICLE

Vortioxetine and Cognition in Older Adults: A Mini Review

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Abstract

Aging is associated with progressive cognitive decline affecting the quality of life. Cognitive impairment may present as a symptom in various physical and psychiatric illnesses, complicating the course of the illness. Late-life depression is commonly linked to cognitive impairment and has a role in treatment response. The novel antidepressant vortioxetine acts primarily by inhibiting the serotonin transporters, 5HT3, 5HT7 and 5HT1D receptor antagonists, 5HT1A, 5HT1B receptor agonists and partial agonists, respectively. The multimodal action is responsible for its antidepressant and pro-cognitive effect. The pro-cognitive effect of vortioxetine is highlighted in few systematic reviews in comparison to other antidepressants. The published literature included studies with subjects belonging to the adult age group. Till date, one systematic review demonstrated the cognitive effect of vortioxetine in the elderly, which included three studies with a diverse study population. A total of five studies encompassing the pro-cognitive effect of vortioxetine in normal aging, late-life depression, mild cognitive impairment and Alzheimer's disease with depressive symptoms are included in the current review. A total of four studies replicated the pro-cognitive effect of vortioxetine in different dose ranges in a diverse study population in the elderly age group. One of the studies demonstrates no effect of vortioxetine on cognition in the elderly. The review directs focus to the areas needed to be further studied. Study of the long-term effect of vortioxetine on cognition, dose-response relationship, uniform study population and replication of previous study findings are needed in future context.

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Introduction

Cognitive functions like memory, language and judgment progressively decline from age 55 years onwards. Cognitive impairment is also related to various physical and psychiatric morbidities in older adults. Depressive disorder in late life is a common entity with a global prevalence of 13.3% as reported by a recent meta-analysis.[1] Depression in late life is linked with symptoms of cognitive impairment, termed as 'depressive pseudodementia' with a prevalence of 20–50%.[2-6] Executive functions, information processing speed, concentration, learning and memory are all affected in the depressed phase.[7] Antidepressant response is lower in elderly patients in the presence of cognitive impairment.[8] Presence of long-term residual symptoms and frequent relapse also complicates the treatment of depression in older adults.[6]

The currently available antidepressants have no or questionable positive effect on cognition. In adult patients, tricyclic antidepressants (TCA) have no effect on cognition, but specific serotonin (SSRI) and serotonin-norepinephrine (SNRI) reuptake inhibitors may have some pro-cognitive effect.[9] In older adults, long-term use of SSRI reduces the rate of conversion of MCI to dementia and improves cognition. In contrast, duloxetine is also reported to improve cognitive functions in older depressed adults.[10-12] It is debatable whether the cognitive improvement seen following the treatment of depressive disorders is secondary to the improvement in depressive symptomatology or a separate effect.

Vortioxetine, the new antidepressant launched recently, improves cognition in the adult depressed population.[9,13] Approved by food and drug administration (FDA) in 2013 for the treatment of adults with major depressive disorder, it is the only antidepressant to have pro-cognitive effects.[14,15] The cognitive domains improved with vortioxetine are attention, processing speed, executive function, learning and memory.[16] The pro-cognitive effects of vortioxetine is due to multimodal action on neurotransmitters rather than a mere improvement in depressive symptoms. A recent systematic review, including the adult population with MDD, reported better cognitive improvement with vortioxetine when compared to SSRI and SNRI.[9] The only review in older adults (65 years and above) published till date demonstrates the pro-cognitive effect of vortioxetine in relation to depression, dementia and age-related cognitive decline. A total of 3 studies were included and participants showed significant improvement in global and fluid cognition measures with vortioxetine treatment.[17] The present review focuses on the pro-cognitive effects of vortioxetine in older adults.

Pharmacology of Vortioxetine

Antidepressant Mechanism of Vortioxetine

Vortioxetine, with its unique mechanism of action, targets both the serotonin transporter and the receptors. It is similar to SSRI medications in binding to the serotonin transporter protein (SERT), is a 5HT1A receptor agonist, 5HT1B receptor partial agonist, and 5HT3, 5HT7 and 5HT1D receptor antagonist enhancing the antidepressant efficacy of the drug. The multimodal action of this drug together enhances the extracellular 5HT level.[18-20] Furthermore, along with increasing the 5HT neurotransmitter in different parts of the brain, it is postulated to indirectly regulate nor-epinephrine, dopamine, acetylcholine, glutamate, GABA and histamine.[15]

Pro-cognitive Mechanism of Vortioxetine

The mechanism of the pro-cognitive action of vortioxetine is elucidated in preclinical studies. Vortioxetine increases nor-epinephrine (NE) neurotransmitters by the strong reciprocal inter-relation between 5HT and NE systems. The 5HT3 receptor antagonism and 5HT1A receptor agonism also enhance the NE release from locus ceruleus to PFC and hippocampus.[18] The role of NE is well established for attention, vigilance, learning and memory.[21] The release of dopamine in PFC is mediated by stimulation of 5HT1A receptors postsynaptically which has a role in motivation.[22] The acetylcholine (Ach) neurotransmitters in the cortex is responsible for attention and memory are either modulated directly by 5HT1A, 5HT1B and 5HT3 receptors in the cholinergic neurons or indirectly by GABA interneurons.[23] The HA release is postulated to be due to stimulation of the 5HT4 receptor as a result of overall increase in 5HT neurotransmitters. Vortioxetine enhances LTP and neuroplasticity by increasing the glutamate release which is facilitated by inhibiting GABA interneurons via 5HT3 antagonism of the drug.[24] It also has an early and steady effect on hippocampal neurogenesis as compared to other SSRIs.[15]

Search Strategy

The terms (vortioxetine or Lu AA21004) and cognition and (elder* or late life or older adult*)' were searched on Pubmed and Google Scholar. The clinical trials and randomized controlled trials, linked articles to the selected relevant citations published till the 31st of July 2022 were included. Articles with comments on cognition and study population with an age group of more than 60 years of age were included.

Table 1: Vortioxetine literature summary

Study	*Methodology*	*Population*	*Sample size*	*Vortioxetine dose (mg)*	*Comparator group*	*Cognitive tests*	*Vortioxetine effect on cognition (change of score in points)*
Katona et al. 2012	Double-blind, randomized, placebo controlled, fixed-dose active-referenced trial; 8 weeks	Age > to 65 years, with MDD	452	5	Placebo, duloxetine 60 mg/day (not as active comparator)	DSST RAVLT	DSST: 2.79; RAVLT (acquisition): 1.14 RAVLT (recall): 0.47 Vortioxetine has significant effect on processing speed, verbal learning and memory compared to placebo.
Cumbo et al. 2019	Randomized open-label, parallel group study; 12 months	AD with depressive symptoms	108	15	Escitalopram, paroxetine, bupropion, venlafaxine, and sertraline	MMSE AMs RCPMs Digit span test	MMSE: 2.91 points AMs: 3.62 points RCPMs: 3.71 points Vortioxetine has significant effect on global cognition compared to conventional antidepressants.
Lenze et al. 2020	Double-blind, randomised parallel group study; 26 weeks	Aged 65+ with age-related cognitive decline	100	10	Cognitive training and placebo	NIHTB-CB USPA	NIHTB-CB: Week 12: mean increase by 4.19 ± 1.52 points Combination of Vortioxetine with cognitive training has significant improvement in global cognition measures compared to cognitive training alone.
Sheng Neg Tan et al. 2021	Single-arm, open-label, phase II study, 6 month	MCI without depressive symptoms	110	5–10	None	MOCA DSST CDR	MoCA: 5.5 points DSST: 27.7 CDR:−0.37 points Vortioxetine has significant effect on global cognition, processing speed and progression in MCI patients
Hye Won Jeong et al. 2022	Double-blind, placebo-controlled study, 12 week	Aged 60+, AD patients with depression	100	5	Placebo	MMSE-KC Naming Word fluency Word list memory Construction Construction recall word list recognition Word list recall SVLT DS.F DS.B DSST	Vortioxetine has no significant effect on cognitive functions compared to placebo.

AD=Alzheimer's Disease, AM=Attentive Matrices, CDR=Clinical dementia rating, DSST=Digit Symbol Substitution Test, DS.F=Digit Span Forward, DS.B=Digit Span Backward, MDD=Major Depressive disorder, MMSE=Mini Mental State Examination, MMSE-KC Korean version of the Mini-Mental State Examination, MCI=Mild cognitive impairment, MOCA=Montreal cognitive assessment, NIH-TB CB=NIH Toolbox Cognition Battery fluid cognition, RAVLT=Rey Auditory Verbal Learning test, RCPM=Raven Coloured Progressive Matrices,SVLT=the Seoul Verbal Learning Test, USPA=UCSD Performance-Based Skills Assessment

The summary of the included articles is presented in a tabular form in Table 1. The search was conducted individually by two authors and data extraction from relevant articles were done.

RESULTS

A total of 5 articles were included in the review.

In Late Life Depressive Disorder

In the only study on late life depression, 5 mg of vortioxetine was superior to 60 mg of duloxetine on measures of cognition (digit symbol substitution test (DSST)[25] and rey auditory verbal learning test (RAVLT),[26] and similar to duloxetine as an antidepressant; it was superior to placebo both for improving cognition and depressive symptoms.[27] Patients on vortioxetine and duloxetine scored significantly more correct symbols as compared to placebo on DSST; the path analysis revealed 83% direct effect of vortioxetine and 26% in the duloxetine group. Similarly, on RAVLT both vortioxetine and duloxetine are superior to placebo for acquisition (71 and 65%) and delayed recall (72 and 66%), respectively for both the drugs.

In Alzheimer's Disease Patients with Depressive Symptoms

E Cumbo *et al.* (2019) studied the effect of vortioxetine in cognition in comparison to commonly used antidepressants in patients of Alzheimer's disease with depressive symptoms.[28] Patients were randomized in the ratio 1:2 into a vortioxetine group (5–15 mg/day) and a control group receiving escitalopram, paroxetine, bupropion, venlafaxine, and sertraline. Compared to baseline on MMSE,[29] attentive matrices (AM) and raven colored progressive matrices (RCPM) the vortioxetine group demonstrated significant improvement. In the control group change from baseline scores were not significant. The MMSE, AM, RCPM scores in the vortioxetine group were higher than in the control group with a *p-value* 0.05.

Hye Won Jeong *et al.* (2022) studied the effect of Vortioxetine on depression and cognition in patients with Alzheimer's disease (AD).[30] A total of 51 and 49 subjects in the vortioxetine and placebo group, respectively, were followed up at weeks 4, 8 and 12. In terms of depressive symptom score and several cognitive domain assessment scores, the groups are found to be comparable. A possible limitation of this study is the exclusion of patients with MMSE score <24. The cognitive effect is studied on depressive patients with normal cognition despite cognitive impairment being a common symptom of elderly depression.

In Normal Aging

Lenze *et al.* (2020), in a randomised controlled parallel group clinical trial studied the augmenting effect of vortioxetine in comparison to placebo in patients receiving computerised cognitive training (scientific brain training pro) in age related cognitive decline.[31] A total of 100 subjects were randomized into vortioxetine and placebo groups and were assessed at week 4, 12, 26 using NIH toolbox battery fluid cognition for primary outcome measures.[32] Combined vortioxetine and cognitive training group at week 12 showed significant improvement compared to only the cognitive training group in NIH toolbox battery fluid cognition. Functional cognition assessed using the UCSD performance-based skills assessment (UPSA) at week 26 found the groups to be comparable.

In Mild Cognitive Impairment Patients

A study by Sheng Neg Tan *et al.* (2021) investigated the cognitive effects of vortioxetine in MCI patients.[33] The mean MOCA score, DSST score and global CDR scores of patients receiving vortioxetine (5–10 mg/day) significantly improved from baseline at all time points.[34,35] The global CDR score means improved to a cognitively normal range by the end of the study. Impression of change based on clinician interviews along with assessment revealed improvement in 89.6% of patients by the end of 6 months.

Discussion

Among the studies included in the review, four studies delineated the pro-cognitive effect of vortioxetine in a diverse group of elderly populations ranging from normal cognition to dementia

patients. In the study by Katona *et al.* in 2012; the vortioxetine group showed a significant increase in DSST score to duloxetine. DSST is used to assess processing speed, but it is also quite sensitive for any alteration in multiple cognitive domains. Both vortioxetine and duloxetine showed significant improvement in RAVLT acquisition and delayed recall scores, indicating its effect on verbal learning and memory. Path analysis of vortioxetine revealed a significant direct effect on the DSST, RAVLT acquisition, RAVLT delayed recall scores. This finding indicates the cognitive benefit is independent of the antidepressant effect. In the study by E Cumbo *et al.* 2019 vortioxetine significantly improved the MMSE, AM and RCPM total scores indicating its effect on global cognition, attention, executive functions, short-term memory, recall and also reasoning ability (non-verbal). The study was conducted in Alzheimer's disease patients with depressive symptoms, which implicates the cognitive effect of vortioxetine in the true cognitively impaired population. Lenze *et al.* 2020 revealed the additive pro-cognitive effect of vortioxetine in cognitive training for improving fluid cognition in age-related cognitive impairment patients, which is the ability to take decisions quickly, solve problems and adapt to new situations. In the study, Sheng Neg Tan *et al.* highlighted disease severity improving property of vortioxetine in MCI patients along with improvement in global cognition and DSST score. In the study by Hye Won Jeong *et al.* 2022 the cognitive effect of vortioxetine is refuted as compared to other studies. The subjects included in this study had more severe cognitive impairment, highlighting that vortioxetine did not have any cognitive effect in moderate to severely impaired patients.

Sample sizes varied in the studies ranging from 452 to 100 and significant attrition in the study population was seen in the studies. A specific population group is studied in a controlled condition in the studies. The generalisability of the findings of these studies is limited. In the aforementioned studies, no real specific comparator drug is taken in the control group with the exception of one study including commonly used antidepressants. The dose of vortioxetine showing pro-cognitive effect ranges from 5 to 20 mg/day, highlighting any dose of vortioxetine can have a significant effect. The dose-response relationship for the pro-cognitive effect needs to be further evaluated. The duration of follow-up of the patients in these studies ranges from 8 week to 12 months, highlighting the acute and maintenance effect of vortioxetine in cognition. Studies with a long-term follow-up are required to assess the steady effect of vortioxetine on cognition.

Conclusion

The foregoing review highlights the positive cognitive effect of vortioxetine in elderly patients. In addition, it directs focus to the lacunae in the studies in terms of the study population, sample size, severity of cognitive impairment, control group, drug dose, and follow-up duration. Replicating the findings and taking care of the research gap may provide valuable insight and pave the way to new research in this area.

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