

Depression and Cerebrovascular Disease: Could Vortioxetine Represent a Valid Treatment Option?

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Abstract: *Introduction:* Depression and cerebrovascular atherosclerosis often occur in comorbidity showing neuropsychological impairment and poor response to antidepressant treatment. Objective is to evaluate if new antidepressant vortioxetine may be a potential treatment option. *Mechanism of Action:* Vortioxetine has 5-HT₃, 5-HT₇ and 5-HT_{1D} antagonists, 5-HT_{1B} partial agonist and a 5-HT_{1A} agonist and serotonin transporter inhibitor property. *Efficacy and safety in Major Depressive Disorders and in cognitive impairment:* The majority of trials (one of them in older people) showed efficacy for vortioxetine against placebo and no differences against other active treatments. The Adverse Effects ranged from 15.8% more to 10.8% less than placebo. In the elderly, only nausea was found higher than placebo. Effects on arterial blood pressure and cardiac parameters including the ECG-QT segment were similar to placebo. Elderly depressive patients on vortioxetine showed improvement versus placebo and other active comparators in Auditory Verbal Learning Test and Digit Symbol Substitution Test scores. The inclusion criteria admitted cases with middle cerebrovascular disease. *Conclusion:* The mechanism of action, the efficacy on depression and safety profile and early data on cognitive impairment make Vortioxetine a strong candidate for use in depression associated with cerebrovascular disease. This information must be supported by future randomized controlled trials.

Keywords: Cerebrovascular disease, major depressive disorders, vascular depression, vortioxetine.

INTRODUCTION

Cerebrovascular atherosclerosis is a leading public health concern; atherosclerotic disease has represented up to now the leading cause of death and morbidity in developed countries and today the determinants of atherosclerosis are increasing in new developing countries. Thus, in the future they are expected to be the major causes of morbidity and mortality around the world [1] Cerebrovascular atherosclerosis determines severe acute events and it is associated with early cognitive impairment [2] Stroke is the third cause of mortality and the leading cause of long-term disability in western countries, with 800,000 events per year in the United States alone and it is rapidly increasing around the world [1, 3] We can consider that for every identified episode, about five silent, unrecognized strokes can be calculated [4].

Older age, male, family history of vascular disease, problems of blood pressure, cholesterol/high-density ratio, metabolic diseases (specifically diabetes mellitus), and tobacco addiction have been clearly identified as determinants of neuro-atherosclerosis [5]. As the risk factors are well identified, it is possible to plan and carry out proper prevention programs, but one of the factors that lower patients' compliance with therapy or prevention programs is the frequent occurrence of depressive episodes [6].

Patients suffering from chronic disease have a risk of depressive disorders two or even three times higher than the general population [7, 8]. The prevalence of depression has been found between 15-25% of patients with cardio-metabolic diseases, diabetes and stroke [9, 10] (Ali *et al.* 2006; Hadidi *et al.* 2009). A recent survey conducted by our group with a case-control methodology and the use of clinical diagnosis has found that nearly one out of four people suffering from carotid stenosis had suffered from Major Depressive Disorders during their lifetimes with a risk almost 6 times that of the control group. However, no increased risk of bipolar disorder was found in the lifetime of our cases compared to controls, although a tendency toward a higher frequency of positivity in screening for Bipolar Spectrum was shown [11].

Patients with neurovascular disease and with concomitant depression have had poorer clinical outcomes and higher mortality, as well as more risk of functional disabilities [12] The treatment of depression improves the course of coronary heart disease and improves patient compliance with various cardiac interventions as well as the prevention of acute events [6].

DEPRESSION AND CEREBROVASCULAR DISEASE

Depression and atherosclerosis are common conditions that often occur in comorbidity. Evidence shows that comorbidity may emerge because people with depression have a high risk of atherosclerosis and, vice versa, people with atherosclerosis, especially with neuro-vascular disease, are at risk of depression. These close links have led to postulating

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that the so-called vascular depression hypothesis identifying a specific subtype of depression in late life [13] appear to be characterized by the following specificities [14].

- 1) patients with Vascular Depression have more hyperintensities at brain Magnetic Resonance Imaging (MRI);
- 2) patients with Vascular Depression and MRI hyperintensities show greater neuropsychological impairment than patients with depression with early onset;
- 3) cases with severe MRI hyperintensities show poor response to antidepressant treatment, especially when brain damage is associated with deficits in executive functioning;

Even though the condition has produced a large debate in literature there is no agreement about the diagnostic criteria of vascular depression [14]. The Alexopoulos's group emphasized the relevance of the onset of depression after age 65 accompanied by executive dysfunction impairment [15] in contrast, others have proposed as key features depression with subcortical ischemia and MRI evidence of cerebrovascular pathology [16, 17].

As this inhomogeneity has made it difficult to compare research, an attempt was made to identify the single most accurate element in defining the spectrum of disorders [18] and this showed deep white matter lesions as the better indicator. In any case, both executive function and brain alterations are closely related: in fact, Kim *et al.* [19] found a previous cerebrovascular attack as a specific determinant associated with depression and executive impairment and not with depression without a deficit of cognitive functions. Accordingly, other surveys found that subcortical hyperintensities on magnetic resonance imaging were associated with poor response to antidepressant treatment [15] but other studies have found a similar poor outcome with antidepressants in people with depression and a deficit of functional impairment [18].

The cognitive impairment of vascular depression affects verbal memory, executive functioning, visuospatial functioning, information processing, perception and attention [20].

Studies on neuroimaging have documented the localization of hyperintensities in the subcortex and the frontal area [21, 22] with concomitant pyramidal neuronal abnormalities and reduction of density [23]. A more recent study has extended the morphometric abnormalities in late-life depression to the caudate nucleus, finding a significant reduction in neuronal density both in the dorsolateral and ventromedial areas of the caudate nucleus with no changes in glial density or neuronal volume [24].

Recently, it has been suggested that the factor that may determine the genesis of both depression and cerebral vascular damage is to be found in the oxidative stress secondary to hypo-perfusion [25] In this framework Li and coll [26] have advanced two not excluding hypotheses: 1) the inflammatory one, which deals with the increased production of proinflammatory cytokines resulting from brain ischemia in cerebral areas and 2) the glutamate hypothesis, considering that stress-induced glucocorticoids via activation of the hypothalamus-pituitary-adrenal axis lead to dysfunction and can impair glutamatergic transmission. Both ways, with different

mechanisms, may influence activity in the central nervous system of neurotrophins as a brain-derived neurotrophic factor (BDNF) and vascular endothelial growth factor (VEGF). These neurotrophins attenuate apoptosis in cultured neurons, stimulate neurogenesis, increase survival and protect neuronal tissues from cell death induced by ischemia or depression [26]. Although these studies open up future prospects for therapeutics, the treatment of vascular dementia is still under debate and still represents a relevant issue.

ISSUES IN THE TREATMENT OF VASCULAR DEPRESSION

Selective serotonin reuptake inhibitors (SSRIs) are recommended as first-line antidepressant treatments for vascular dementia but only few randomized clinical trials (RCTs) with relatively small sample sizes have been carried out on the use in dementia of SSRIs [27]. On the other hand, in depression comorbid with cardiac atherosclerosis no evidence of active harm (SSRI vs placebo) was detected in two meta-analyses even when patient samples were carefully selected (for example, patients with comorbid conditions were excluded, thus making the samples far from real practice) [28, 29].

SSRIs can improve cognition in patients with stroke, this may be due to the increase in the expression of the brain-derived neurotrophic factor (BDNF) in the hippocampus [30]. However, the SSRIs may cause a higher incidence of side effects [30] not only in vascular cerebropathies, but also in other forms of atherosclerotic diseases associated with depression [31]. In fact, the use of SSRIs in depression with vascular neuropathy and other forms of atherosclerosis has been found to be associated with bleeding [32, 33] the risk of arrhythmia [34] and associated with longer-term risk of an adverse prognosis [35].

In addition to poor response to antidepressants, it can be considered that cardiovascular chronic diseases could be contraindicated for the use of ECT therapy [36]. The problem-solving therapy has been proposed as an alternative to antidepressant medication, but there are very few data available of studies with small patient samples [37, 38]. The employing of evidence-based psychotherapy such as Cognitive Behavior Therapy or Interpersonal Therapy, with modifications to accommodate cognitive impairments, is indicated as an add-on to antidepressants but there is a lack of randomized clinical trials showing efficacy in this specific field [39].

MECHANISM OF ACTION OF VORTIOXETINE

Vortioxetine has 5-HT₃, 5-HT₇ and 5-HT_{1D} receptor antagonists, 5-HT_{1B} receptor partial agonist and a 5-HT_{1A} receptor agonist and serotonin transporter (SERT) inhibitor property as has been demonstrated by an *in vitro* assay [40]. The *ex vivo* autoradiography assay revealed an affinity for 5-HT₃ receptors and SERT appeared to be especially high. Vortioxetine increases the extracellular concentration of serotonin (5-HT) in brain areas involved in pathophysiology of depression, such as the medial prefrontal cortex and the hippocampus. This action appears to be even stronger than the one caused by the selective reuptake inhibitors of serotonin (SSRI) [41, 42]. The blockade of 5-HT₃ receptors by vortioxetine may be involved in the powerful elevations of ex-

tracellular 5-HT and it is one of the factors distinguishing the action of this drug by SSRIs [43, 44]. In rat brain a similar elevation of the extracellular neurotransmitter was found with respect to noradrenaline (NA), dopamine (DA), acetylcholine (ACh), and histamine (HA) after vortioxetine treatment [41, 45].

Studies on drugs active on glutamatergic neurotransmission have shown new opportunities for the treatment of depressive disorders: Ketamine shows an antidepressant effect mediated through glutamate pathways [45]. It is possible to enhance glutamate transmission indirectly through the 5-HT system through the 5-HT_{1A}, 5-HT_{1B}, 5-HT₃, and 5-HT₇ receptors, in combination with 5-HT transporter inhibition. Vortioxetine can provide an example of serotonergic modulation of glutamate transmission and it may be the basis of its efficacy on depression as well on the associated cognitive dysfunction [45].

Studies on the effect of vortioxetine on synaptic transmission, long-term potentiation (LTP), and theta oscillations in the rat hippocampus and frontal cortex have indicated that vortioxetine can increase pyramidal cell output, which leads to enhanced synaptic plasticity in the hippocampus. Given the central role of the hippocampus in cognition, these findings may provide a cellular correlate to the observed pre-clinical and clinical cognition-enhancing effects of vortioxetine [46] (Dale *et al.* 2014).

Vortioxetine has a half-life of 57 hours, and it reaches stable concentrations in the plasma in <2 weeks. It binds to plasma proteins at 96% [47]. Vortioxetine is metabolized by the isoenzymes P-450 of liver CYP2D6, CYP3A4/5, CYP2C9, CYP2C19, CYP2A6, CYP2C8, and CYP2B6, but as it has linear kinetics, it does not inhibit or activate them [48] Its main metabolite is inactive [47].

EFFECT ON NEUROGENESIS AND CONSEQUENCES FOR DEPRESSION AND COGNITIVE FUNCTIONS

A deficit of neurogenesis impairing the processes of oxidation in the brain may have a role in the pathogenesis of Depressive Disorders [49-53].

In the hippocampus the effect of increasing extracellular levels of some neurotransmitters such as glutamate through metabotropic receptors can lead the up-regulation of Arc mRNA levels to stimulating synaptic plasticity with structural remodeling and functional changes [54, 55]. On studying other drugs, these effects were found associated with improvement in cognition and depressive-like behavior [56] Vortioxetine via glutamatergic system stimulation can produce these effects in conjunction with other synergistic effects such as the low-dosage blockade of 5-HT₇ receptors that improves cognition and increases mood [57, 58].

In fact, pre-clinical studies in mice found that vortioxetine significantly increases cell proliferation, cell survival and maturation of immature granule cells in the subgranular zone of the dentate gyrus of the hippocampus after 21 days of treatment. Vortioxetine accelerates the maturation of immature neurons as it increases the dendritic length and the quantity of dendrite intersections. These effects were observed at low levels of 5-HT transporter occupancy, thus with a

mechanism of action alternative to 5-HT reuptake inhibition [59].

EFFICACY OF VORTIOXETINE IN MAJOR DEPRESSIVE DISORDERS

Twelve short-term (6-12 weeks) randomized clinical trials were found in the meta-analysis by [60] and the review by [47]. Ten cited papers are exactly the same ones cited in the previous two papers [61-70].

Each study cited two different papers but each of them seem apparently to come from the same trial of the corresponding paper cited in the other study [71-74].

Six RCTs compared Vortioxetine with an active control other than placebo (Venlafaxine extended-release, Duloxetine); one was with Agomelatine without a placebo arm and five compared Vortioxetine with placebo. Even though the diagnosis of MDD was carried out according to DSM-IV-TR criteria, the studies showed different inclusion criteria: severity of MDD measured with the Montgomery-Åsberg Depression Rating Scale (MADRS) was 22, 26 or 30. Exclusion criteria included treatment-resistant depression or comorbid with psychiatric or physical conditions. The doses of active drug varied 1, 2.5, 5, 10, 15 and 20 mg/d, once daily [60]. The primary outcome measures were the mean change from baseline in total scores on the Hamilton Rating Scale for Depression (HAM-D) or in the MADRS, as defined in each study. All the trials made the intention-to-treat analysis with the last observation carried forward (LOCF) but including all patients who fulfilled at least one assessment after randomization.

Eight studies comparing vortioxetine to placebo showed positive results for vortioxetine, and four studies showed no significant differences against placebo [47].

As regards primary end-point overall efficacy, the eleven studies show vortioxetine efficacy against placebo with an SMD of -0.217 (95% CI -0.313 to -0.122) in a pooled sample of 4947 patients (vortioxetine, n = 3276 v. placebo, n = 1671), [60].

Comparing the secondary end-point, Vortioxetine shows an OR of 1.652 (95% CI 1.321-2.067) for response and an OR of 1.399 (95% CI 1.104-1.773) for remission against placebo [60].

The majority of positive studies achieved positive results in the arms with 5-20 mg/day only in two positive studies: vortioxetine was superior to placebo only in the dose arms of 20 mg/day (Alvarez *et al.* 2014).

Improvement with vortioxetine appeared after approximately 2 weeks of treatment, with the maximum response at the fourth week [47]. Only the trial by McIntyre [71] showed improvement at the first week but only in the arm with 20 mg/day.

The efficacy of Vortioxetine versus other antidepressants was provided by a sample of 2843 (vortioxetine, n = 1847) patients drawn from the seven cited studies. It showed for the primary analysis a SMD of 0.081 (95% CI -0.062 to 0.223) and revealed no difference between the treatment groups.

The percentage of patients in each trial who completed the full study ranged from 74% to 90%.

As regards the issue addressed in this paper, the trial by Katona *et al.* [69] is of specific interest as it concerns patients aged 65 and over, the age group with the highest risk of cerebrovascular diseases. It was an 8-week three arm randomized clinical trial comparing placebo, duloxetine 60 mg and vortioxetine 5 mg. Both active comparisons were found superior to placebo at week 8 as concerns the primary efficacy outcome: with a decrease in the HAMD score (last observation carried forward). The interesting findings concerning cognitive performance and adverse effect will be discussed in the dedicated paragraphs.

Another interesting trial is the 12-week one by Häggström *et al.* [72] who recruited non-responding or inadequately responding patients to SSRI or SNRI monotherapy. The patients were randomized to receive agomelatine (25-50 mg/day) or vortioxetine (10–20 mg/day). At the end of the trial patients had improved significantly in both groups (16.5 points MADRS in vortioxetine; 14.4 points in agomelatine on the average). However, both in therapeutic response and remissions vortioxetine was found better than agomelatine.

One long-term efficacy randomized double-blind controlled multicenter clinical trial was designed to assess prevention of relapses with duloxetine [75]. The 639 patients recruited were treated with open-label flexible doses of vortioxetine for 12-weeks (5-10 mg/day); the dose was then fixed. Remitted patients were randomized to placebo or vortioxetine and then followed for at least 24 weeks. The mean relapse rate was higher in the placebo group (26% against 13%, $P=0.0035$) [75].

VORTIOXETINE TOLERABILITY

Most AEs found in the aforementioned trial were nausea, vomiting, constipation and headaches. The AEs caused by vortioxetine were higher than those by placebo only at the highest (20 mg/day) dose, ranging from 15.8% more than placebo [75] to 10.8% less than placebo [63].

In the trial on elderly patients, the only adverse event in which the incidence was found higher with vortioxetine than placebo was nausea (21.8% vs 8.3%). Duloxetine had a higher incidence than placebo of nausea, constipation, hyperhidrosis and somnolence.

Sexual dysfunctions reported by vortioxetine users were similar to those of people assuming placebo [47].

The trend of AE-related withdrawals, considering all the aforementioned trials at 10 mg or more, was greater in the vortioxetine arms versus placebo and lower than the active comparator [47].

The AE-related withdrawal rates in the trial on older people by Katona *et al.* [69] were 2.8% for placebo, 5.8% for vortioxetine and 9.9% for duloxetine [69].

A crucial point concerning the potential use of the drug on cerebrovascular disease is that vortioxetine was found similar to placebo in its impact on vital signs such as arterial blood pressure and heart rate, as well as on cardiac parameters – including the QT segments at ECG.

COGNITIVE FUNCTIONS AND USE OF VORTIOXETINE

Vortioxetine has been shown to improve cognitive performance in several preclinical rat models [46] and it is supposed that vortioxetine's effects on recognition and spatial working memory assessed in the Y-maze spontaneous alternation test performance may involve 5-HT_{1A} receptor agonism, whereas the effects on recognition and spatial working memory assessed in the object recognition test performance may involve 5-HT₃ receptor antagonism and 5-HT_{1A} receptor agonism [76].

Taking into account these pre-clinical findings, the study by Katona *et al.* (2012) on the treatment of depression in old age is of great relevance. This survey offers data on the assessment of cognitive function with baseline end of the study comparison for verbal learning, memory, and processing speed measured by means of the Rey Auditory Verbal Learning Test (RAVLT) and the digit symbol substitution test (DSST). The inclusion criteria admitted patients with a mini-mental state (MMSE) score of at least 24 points, thus eliminating cases with severe neurodegenerative disease or severe cerebrovascular disease, but not cases with middle cerebrovascular disease. Patients on vortioxetine showed significantly greater improvement versus placebo and versus the other active comparators in both DSST and RAVLT scores.

A trial carried out by Theunissen *et al.* [77] measured the effect of vortioxetine at a dose of 20/mg per day, placebo and mirtazapine on driving and some related cognitive functions in healthy subjects. Vortioxetine assumption was not associated with impairment of driving and in cognitive function throughout the trial (16 days); in contrast, mirtazapine was not at the beginning owing to sedation.

CONCLUSION

The mechanism of action, the efficacy on depression and safety profile and early data on cognitive impairment make Vortioxetine a strong candidate for use in depression associated with cerebrovascular disease. This information must be supported by future randomized controlled trials

CONFLICT OF INTEREST

Prof Mauro Giovanni Carta has received grants from the European Commission, European Social Fund, AIFA (Agenzia Italiana del Farmaco), Fondazione Banco di Sardegna and the Sardinia Region. Prof Carta is advisor for the Economic and Social Committee of the European Union. Dr Andrea Norcini-Pala didn't receive funds or grants by drug companies. Dr Maria Francesca Moro received grants from Fondazione Banco di Sardegna.

ACKNOWLEDGEMENTS

Declared none.

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Received: December 18, 2014

Revised: January 08, 2015

Accepted: January 12, 2015

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