

REVIEW OF A NEW MULTIMODAL ANTIDEPRESSANT VORTIOXETINE

Oppa M^{1,2}, Cesnekova D^{1,2}, Nosalova G^{1,3}, Ondrejka I²

Comenius University in Bratislava, Jessenius Faculty of Medicine in Martin and University Hospital Martin

¹Department of Pharmacology; ²Clinic of Psychiatry, Slovakia

³Biomedical Center Martin, Jessenius Faculty of Medicine in Martin, Comenius University in Bratislava

Abstract

Vortioxetine is a novel antidepressant with two mechanisms of action – direct effect on several serotonin receptors and serotonin re-uptake inhibition. It shows antidepressant, anxiolytic and cognitive effects during the treatment of major depressive disorder (MDD). The aim of this article was to summarize the use of vortioxetine in clinical studies and assess the efficacy and tolerability. Most of the studies reported a statistically significant efficacy for vortioxetine versus placebo. In addition, vortioxetine showed efficacy in patients with an inadequate response to selective serotonin re-uptake inhibitors (SSRI) or serotonin-noradrenaline re-uptake inhibitors (SNRI) monotherapy and improved cognitive function in patients with MDD. In these studies, vortioxetine was well tolerated – most common observed adverse effect was nausea – and it was not associated with clinically important changes in laboratory test results or vital signs. Vortioxetine showed a relatively low incidence of sexual dysfunction.

Key words: vortioxetine, depression, inadequate response, cognitive function, sexual dysfunction

INTRODUCTION

Major depressive disorder (MDD) is a disease with incidence rate of 4% [1] and lifetime prevalence in the range of 8% to 12% [2]. Depression affects the life quality and it has got impact to psychological variables like hope and meaning of life [3, 4]. According to the World Health Organization in year 2020 depression will become the second leading cause of disability.

Antidepressants are nowadays the main therapeutic option in depression treatment. Despite the large number of antidepressants, there are still limitations in their efficacy and tolerability, mainly in their affection of sexual and cognitive function and induction of weight gain, which can lead to worse therapeutic adherence and treatment interruptions. For that reason, the arrival of vortioxetine as a model of antidepressant with multimodal activity and safe profile generate strong interest.

The aim of this article is to summarize the use of vortioxetine from the results of manual searching of key publications with main focus on randomized, double-blind, placebo-controlled studies of vortioxetine that involve patients with an episode of MDD by DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, 4th Edition). Principal findings are summarised and assessed in discussion.

PHARMACOLOGY OF VORTIOXETINE

Vortioxetine (1-[2-(2,4-dimethyl-phenylsulfanyl)-phenyl]-piperazine;hydrobromide, Lu AA21004) shown in Figure 1 is a novel antidepressant with multimodal activity. It has two mechanisms of action – direct effect on several serotonin receptors (5-HT₃, 5-HT₇, 5-HT_{1D} receptor antagonist, 5-HT_{1B} receptor partial agonist and 5-HT_{1A} receptor agonist) and inhibition of serotonin transporter (SERT). It does not belong to the selective serotonin re-

Address for correspondence:

Assoc. Prof. Igor Ondrejka, M.D., PhD., Clinic of Psychiatry, Jessenius Faculty of Medicine in Martin, Comenius University in Bratislava, Kollarova Str. N.2, 036 59 Martin, Slovak Republic; e-mail: ondrejka@jfmed.uniba.sk

uptake inhibitors (SSRI) because of their unimodal mechanism of action, but it is classified as a serotonin modulator and stimulator (SMS) along with vilazodone [5]. *In vivo* experimental studies have shown that vortioxetine increases extracellular concentration of serotonin in depression-related areas more than SSRIs, but it also increases the extracellular levels of noradrenaline, dopamine, acetylcholine and histamine [6].

Vortioxetine shows good bioavailability after oral administration (75%) with a t_{\max} of 7–8 hours and $t_{1/2}$ of 57 hours and it also shows a stable plasma concentrations in <2 weeks. Rate of binding to plasma proteins was 96%. Vortioxetine is extensively metabolized, primarily by oxidation and subsequent glucuronic acid conjugation. The P450 enzymes responsible for the metabolism include CYP2D6, CYP3A4/5, CYP2C9, CYP2C19, CYP2A6, CYP2C8, and CYP2B6 [7]. Vortioxetine shows no significant inhibition or induction of P450 enzymes, and is thus less prone to drug interactions, although dosage adjustment may be required when co-administered with bupropion (CYP2D6 inhibitor), or rifampicin (CYP inducer) [8].

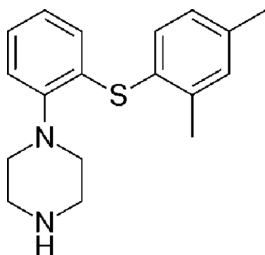


Fig. 1. Chemical structure of vortioxetine.

EFFICACY OF VORTIOXETINE

Efficacy of vortioxetine has been studied in 12 short-term (6, 8 or 12 weeks) clinical trials [9–20]. Eight of them were positive (seven for vortioxetine versus placebo, one for vortioxetine versus agomelatine as active comparator), three showed no significant differences versus placebo and one study failed because neither vortioxetine nor the duloxetine as active comparator were superior to placebo [9]. Six of the positive short-term studies showed positive results in the dosages 5–20 mg/day, but in two other positive studies vortioxetine was superior to placebo only in the highest dosage 20 mg/day. Patients typically respond to vortioxetine after two weeks of treatment, with the maximum response near the fourth week [1]. Outcomes are summarized in Table 1.

Vortioxetine showed statistically significant improvement versus placebo in the Rey Auditory Verbal Learning Test (RAVLT) and the Digit Symbol Substitution Test (DSST), which are cognitive neuropsychological tests of executive function, attention, speed of processing, verbal learning and memory in elderly patients with MDD [10]. In other short-term study with non-elderly adults with MDD, vortioxetine also showed significant difference versus placebo on the composite cognition score measured by DSST and RAVLT. Analyses indicated that the effect on cognitive performance was largely a direct treatment effect and not solely due to improvements in depressive symptoms [11]. Another study with MDD patients with an inadequate response to SSRI/SNRI monotherapy showed that vortioxetine was statistically superior to agomelatine as an active comparator in primary efficacy outcome [12].

Due to the character of the depression, long-term studies are necessary to demonstrate the effects of treatment over time and ability to prevent relapses. Two long-term efficacy studies of vortioxetine have been performed. The first one showed significant difference in time to relapse compared to placebo, with relapse rates of 13% for vortioxetine versus 26% for the placebo group [21]. The second study was an extension of a short-term study [9]. At the end of the treatment period, the mean MADRS (Montgomery and Asberg Depression Rating Scale) total score had improved by 8 points and the remission rate was 83% versus 42% in the lead-in study [22].

Table 1. Vortioxetine efficacy short-term randomized double-blind clinical studies in MDD patients.

Author	Duration	FAS (n)	Placebo	Active com-parator	Primary analysis	P-value	Results
Alvarez et al., 2012 ^[13]	6 weeks	426	Yes	VLF	MADRS	p<0.0001 (VOR vs. PBO), p<0.0001 (VEN vs. PBO)	Positive ¹
Baldwin et al., 2012 ^[9]	8 weeks	755	Yes	DLX	MADRS	NS (VOR vs. PBO), NS (DLX vs. PBO)	Failed ²
Boulenger et al., 2014 ^[14]	8 weeks	604	Yes	DLX	MADRS-24	p<0.0001 (VOR 15 + 20 mg vs. PBO), p<0.0001 (DLX vs. PBO)	Positive ¹
Häggström et al., 2013 ^[12]	12 weeks	493	No	AGO	MADRS-24	p<0.001 (VOR vs. AGO)	Positive ¹
Henisberg et al., 2012 ^[15]	8 weeks	556	Yes	No	HAMD-24	p<0.001 (VOR 10 mg vs. PCB)	Positive ¹
Jacobsen et al., 2013 ^[16]	8 weeks	385	Yes	No	MADRS	p=0.002 (VOR vs. PBO)	Positive ¹
Jain et al., 2013 ^[17]	6 weeks	578	Yes	No	HAMD-24	NS (VOR vs. PBO)	Failed/negative ⁴
Katona et al., 2012 ^[10]	8 weeks	448	Yes	DLX	HAMD-24	p=0.0011 (VOR vs. PBO), p=0.0001 (DLX vs. PBO)	Positive ¹
Mahableshwarkar et al., 2013a ^[18]	8 weeks	434	Yes	No	MADRS	NS (VOR vs. PBO)	Failed/negative ⁴
Mahableshwarkar et al., 2013b ^[19]	8 weeks	597	Yes	DLX	HAMD-24	NS (VOR vs. PBO), p<0.005 (DLX v. PBO)	Negative ³
Mahableshwarkar et al., 2013c ^[20]	8 weeks	591	Yes	DLX	MADRS	p=0.023 (VOR vs. PBO) p<0.001 (DLX vs.PBO)	Positive ¹
McIntyre et al., 2014 ^[11]	8 weeks	591	Yes	No	MADRS	p<0.001 (VOR vs. PBO)	Positive ¹

FAS: full analysis set, NS: non-significant, PBO: placebo, VOR: vortioxetine, VLF: venlafaxine, DLX: duloxetine, AGO: agomelatine.
¹Positive: The primary efficacy analysis was statistically significant. ²Failed: In the primary efficacy analysis, vortioxetine did not separate from placebo, nor did the active comparator. ³Negative: Vortioxetine did not but the active comparator did separate from placebo on the primary efficacy analysis. ⁴Failed/negative: Vortioxetine did not separate from placebo on the primary efficacy analysis, and no active reference was included in the study.

TOLERABILITY OF VORTIOXETINE

The safety data from the short-term as well as long-term clinical studies showed that the vortioxetine treatment is well tolerated. The incidence of adverse events was close to placebo level with the highest incidence of nausea mainly reported during the first weeks of dosing. Nausea was most often transient, with a median duration of 10 to 16 days. Clinical studies with vortioxetine have also shown that the incidence of sleep-related TEAEs (treatment emergent adverse events) like insomnia, hyposomnia or dyssomnia was ranged from 2.0 to 5.1% for vortioxetine compared to 4.4% for placebo [23]. The studies also reported that the percentage of patients who develop sexual dysfunction is lower than for other antidepressants with serotonergic activity. Rates of sexual dysfunction were low with vortioxetine in both short-term and long-term studies. The incidence of treatment-emergent sexual dysfunction in patients treated with vortioxetine ranged from 1.6 to 2.6% versus 4.5% with duloxetine. The review of vortioxetine conducted by the European Medicines Agency reported that the incidence of serious adverse events was generally low (<3%) [24].

DISCUSSION

Vortioxetine represents a new therapeutic option for the treatment of depression acutely and for relapse prevention. As a drug interacting with multiple receptors, it is associated with antidepressant, anxiolytic and cognitive effects during the treatment of MDD. Studies shown that vortioxetine was efficacious and well tolerated. Most of the studies reported a statistically significant efficacy for vortioxetine versus placebo. The effect of vortioxetine in patients with an inadequate response to SSRI or SNRI monotherapy can be explained by different mechanism of action. In addition, vortioxetine is associated with improved cognitive function in patients with MDD that is independent of improvement in depressive symptoms. The results from the long-term studies support the efficacy of vortioxetine in decreasing the risk of recurrence of depressive episodes after remission is achieved.

The most commonly observed adverse effect was nausea. Vortioxetine was not associated with clinically important changes in laboratory test results or vital signs [24]. It appears that vortioxetine have no effect on weight, which can lead to better therapeutic adherence than other antidepressants in which the association with weight gain has been established. Sexual dysfunction is known to be a potential symptom of depression, as well as a potential adverse event associated with certain drugs. Relatively low incidence of sexual dysfunction can be the advantage of vortioxetine opposite the other antidepressants with serotonergic activity. But the mechanism of this remains to be studied in more details in the future studies.

REFERENCES

1. Alvarez E, Perez V, Artigas F. Pharmacology and clinical potential of vortioxetine in the treatment of major depressive disorder. *Neuropsychiatric Disease and Treatment*. 2014; 10: 1297-1307.
2. Andrade L, Caraveo-Anduaga JJ, Berglund P et al. The epidemiology of major depressive episodes: results from the International Consortium of Psychiatric Epidemiology (ICPE) Surveys. *Int J Methods Psychiatr Res*. 2003; 12 (3): 165.
3. Farsky I, Smetanka A, Dubinska S. Spirituality of patients with selected psychiatric disorders. *Osetrovatelstvi a Porodni Asistence*. 2012; 3 (3): 433-441.
4. Halama P, Ondrejka I, Ziakova K, Farsky I. Existential and spiritual correlates of mental health in normal population and psychiatric patients. *Ceskoslovenska psychologie*. 2010; 54 (1): 42-57.
5. Santarsieri D, Schwartz TL. Antidepressant efficacy and side-effect burden: a quick guide for clinicians. *Drugs Context*. 2015; 4: 212290. Published October 8, 2015. Accessed June 30, 2016.
6. Mørk A, Pehrson A, Brennum LT et al. Pharmacological effects of Lu AA21004: a novel multimodal compound for the treatment of major depressive disorder. *J Pharmacol Exp. Ther*. 2012; 340 (3): 666-675.
7. Hvenegaard MG, Bang-Andersen B, Pedersen H, Jørgensen M, Püschl A, Dalgaard L. Identification of the cytochrome P450 and other enzymes involved in the in vitro oxidative metabolism of a novel antidepressant, Lu AA21004. *Drug Metab Dispos*. 2012; 40 (7): 1357-1365.

8. Chen G, Lee R, Højer AM, Buchbjerg JK, Serenko M, Zhao Z. Pharmacokinetic drug interactions involving vortioxetine (Lu AA21004), a multimodal antidepressant. *Clin Drug Investig*. 2013; 33: 727-736.
9. Baldwin DS, Loft H, Dragheim M. A randomised, double-blind, placebo controlled, duloxetine-referenced, fixed-dose study of three dosages of Lu AA21004 in acute treatment of major depressive disorder (MDD). *Eur Neuropsychopharmacol*. 2012; 22 (7): 482-491.
10. Katona C, Hansen T, Olsen CK. A randomized, double-blind, placebo-controlled, duloxetine-referenced, fixed-dose study comparing the efficacy and safety of Lu AA21004 in elderly patients with major depressive disorder. *Int Clin Psychopharmacol*. 2012; 27 (4): 215-223.
11. McIntyre RS, Lophaven S, Olsen CK. A randomized, double-blind, placebo-controlled study of vortioxetine on cognitive function in depressed adults. *International Journal of Neuropsychopharmacology*. 2014; 17 (10): 1557-67.
12. Häggström L, Nielsen RZ, Poulsen L, Danchenko N. A randomised, double blind, active controlled study of vortioxetine (10–20 mg/day) versus agomelatine (25–50 mg/day) in adults with Major Depressive Disorder with inadequate response to antidepressant treatment. Poster presented at: 26th Congress of the European College of Neuropsychopharmacology (ECNP); October 5-9, 2013; Barcelona, Spain.
13. Alvarez E, Perez V, Dragheim M, Loft H, Artigas F. A double-blind, randomized, placebo-controlled, active reference study of Lu AA21004 in patients with major depressive disorder. *Int J Neuropsychopharmacol*. 2012; 15 (5): 589-600.
14. Boulenger JP, Loft H, Olsen CK. Efficacy and safety of vortioxetine (Lu AA21004), 15 and 20 mg/day: a randomized, double-blind, placebo-controlled, duloxetine-referenced study in the acute treatment of adult patients with major depressive disorder. *Int Clin Psychopharmacol*. 2014; 29 (3): 138-149.
15. Henisberg N, Mahableshwarkar AR, Jacobsen P, Chen Y, Thase ME. A randomized, double-blind, placebo-controlled 8-week trial of the efficacy and tolerability of multiple doses of Lu AA21004 in adults with major depressive disorder. *J Clin Psychiatry*. 2012; 73 (7): 953-959.
16. Jacobsen PL, Mahableshwarkar AR, Serenko M, Chan S, Trivedi MH. A randomized, double-blind, placebo-controlled study of the efficacy and safety of vortioxetine 10 mg and 20 mg in adults with Major Depressive Disorder. Poster presented at: American Psychiatry Association Annual Meeting; May 18-22, 2013; San Francisco, USA.
17. Jain R, Mahableshwarkar AR, Jacobsen PL, Chen Y, Thase ME. A randomized, double-blind, placebo-controlled 6-wk trial of the efficacy and tolerability of 5 mg vortioxetine in adults with major depressive disorder. *Int J Neuropsychopharmacol*. 2013; 16 (2): 313-321.
18. Mahableshwarkar AR, Jacobsen PL, Serenko M, Chen Y, Trivedi MH. A randomized, double blind, parallel, placebo-controlled, fixed-dose study comparing the efficacy and safety of 2 doses of vortioxetine (Lu AA21004) in acute treatment of adults with major depressive disorder. Poster presented at: American Psychiatry Association Annual Meeting; May 18-22, 2013; San Francisco, USA.
19. Mahableshwarkar AR, Jacobsen PL, Chen Y. A randomized, double-blind trial of 2.5 mg and 5 mg vortioxetine (Lu AA21004) versus placebo for 8 weeks in adults with major depressive disorder. *Curr Med Res Opin*. 2013; 29 (3): 217-226.
20. Mahableshwarkar AR, Jacobsen P, Serenko M, Chcen Y, Trivedi MH. A duloxetine-referenced fixed dose study comparing efficacy and safety of 2 vortioxetine doses in the acute treatment of adult patients with MDD. Poster presented at: 166th Annual Meeting of the American Psychiatric Association (APA); May 18-22, 2013; San Francisco, USA.
21. Boulenger JP, Loft H, Florea I. A randomized clinical study of Lu AA21004 in the prevention of relapse in patients with major depressive disorder. *J Psychopharmacol*. 2012; 26 (11): 1408-1416.
22. Baldwin DS, Hansen T, Florea I. Vortioxetine (Lu AA21004) in the long-term open-label treatment of major depressive disorder. *Curr Med Res Opin*. 2012; 28 (10): 1717-1724.
23. Baldwin DS, Serenko M, Palo W, Lophaven S, Matz J. The safety and tolerability of vortioxetine (Lu AA21004) in the treatment of adults with major depressive disorder (MDD): a pooled analysis. *Int J Psychiatry Clin Pract*. 2013; 17 (Suppl. 2): 16-17.
24. Sanchez C, Asin KE, Artigas F. Vortioxetine, a novel antidepressant with multimodal activity: Review of preclinical and clinical data. *Pharmacology & Therapeutics*. 2015; 145: 43-57.

Acknowledgement:

This work was supported by grants UK/90/2016 and UK 75/2016, and by the projects „Biomedical Center Martin“, ITMS code 262202220187, the project is co-financed from EU sources.

Received: April,26,2016

Accepted: June,27,2016