Psychiatr. Pol. 2023; 57(6): 1109–1126
PL ISSN 0033-2674 (PRINT), ISSN 2391-5854 (ONLINE)
www.psychiatriapolska.pl
DOI: https://doi.org/10.12740/PP/OnlineFirst/151570

Vortioxetine – pharmacological properties and use in mood disorders. The current state of knowledge

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Summary

Vortioxetine is an antidepressant with a unique profile of receptor activity. The pharmacodynamic spectrum of vortioxetine activity is linked to the modulation of not only serotoninergic but also noradrenergic and dopaminergic transmission. At the same time, its pharmacokinetic properties determine good tolerance and safety, which are also observed in elderly patients and those burdened with somatic comorbidity. This work aims to sum up the knowledge coming from the most recent studies assessing the efficacy of vortioxetine. The efficacy of vortioxetine in the treatment of depression was confirmed in a large number of open studies, randomized controlled studies with placebo control, and meta-analyses thereof. What is more, the latest research shows that this drug allows depressed patients to achieve not only symptomatic remission but also an improvement of anhedonia and recovery in cognitive and occupational function. Furthermore, there are studies showing that vortioxetine is efficacious in the treatment of elderly patients, as well as subjects who have experienced trauma or suffer from bipolar depression. Vortioxetine is characterized by a good tolerance profile and safety; rarely does it cause severe adverse effects.

Key words: depression, antidepressants, vortioxetine

Introduction

Nowadays, there is a wide range of antidepressants (AD) available for use, which are effective in reducing the acute symptoms in patients with depression (Major Depressive Disorder – MDD) as shown in clinical trials. Despite the diversity of these molecules, their modes of action and pharmacological properties, the efficacy of MDD treatment remains less than satisfactory. Previous studies have shown that after the first course of treatment, remission is achieved in 37% of patients and each subsequent

treatment attempt is less likely to attain it [1]. Moreover, 9-33% of patients are at risk of tachyphylaxis of the formerly effective drug and consequently the recurrence of MDD despite continuing treatment [2]. Also, the reintroduction of the same drug in the case of recurrence after completed treatment is not always successful and in 16.5% of patients a switch to another drug is required [3]. Some symptoms, such as anhedonia and cognitive functions impairment, may remain after the resolution of the acute depressive episode. The adverse effects of AD may produce further problems, i.e., emotional blunting, sexual dysfunction or insomnia. These can obstruct the achievement of functional remission or lead to discontinuation of treatment. Considering the above-mentioned issues, it is crucial to search for new, more effective and better tolerated options for the treatment of MDD.

Given that vortioxetine presents a distinct combination of pharmacologic properties it may be effective in these areas of affective symptomatology which were resistant to treatment with previous AD, and offer an opportunity of a safer, better tolerated treatment. This work aims to sum up the knowledge on vortioxetine use in affective disorders with a focus on the most recent data coming from the studies assessing the efficacy and tolerance of vortioxetine as well as the role of vortioxetine in MDD treatment.

Pharmacodynamics

In the dose range of 5-20 mg/d vortioxetine occupies from 50% to >80% of serotonin transporters (SERT). This is lower than the majority of selective serotonin reuptake inhibitors (SSRI), which used in the therapeutic dose ranges occupy >80% of SERT. In spite of this, preclinical studies show that vortioxetine produces two times higher extracellular serotonin (5HT) levels compared to SSRI. This effect is due to the activity of vortioxetine on 5HT receptors – the antagonism of 5HTD1, 5HT3 and 5HT7 as well as agonism of 5HT1A and partial agonism of 5HT1B [4]. The profile of vortioxetine affinity for the 5HT receptors is displayed in Table 1.

Table 1**. Pharmacodynamic properties of vortioxetine (based on [4])**

Receptor	Action	Ki (nM)	Pharmacological effect
SERT	Inhibition	1.6	↑ 5HT transmission
5HT3	Antagonism	3.7	↑ NA and DA transmission in prefrontal cortex ↑ DA transmission in reward system
5HT1A	Agonism	15	↑ 5HT transmission ↑ DA transmission in prefrontal cortex
5HT7	Antagonism	19	↑ 5HT transmission ↑ NA and DA transmission in prefrontal cortex

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5HT1B	Partial agonism	33	↑ 5HT transmission ↑ DA transmission in reward system
5HT1D	Antagonism	54	↑ 5HT transmission

5HT – serotonin, DA – dopamine, NA – noradrenaline, ↑ – increased

The variety of affinities for specific receptors is the reason for the dose-dependence of the treatment effect – increasing the dose initiates interactions with subsequent receptor groups resulting in higher effectiveness of the drug and potentially expanding its clinical profile. Vortioxetine is not a typical 5HT3 antagonist. Preclinical studies suggest that its activity is different form other known antagonists, i.e., ondansetron, ganisetron. It is hypothesized that in the early phase of treatment vortioxetine displays agonistic action which switches to antagonistic after a steady state is reached. This model of action would explain the nausea and vomiting which is rather common in the early phase of treatment. The later 5HT3 antagonism disinhibits noradrenergic and dopaminergic transmission in the prefrontal cortex (PFC) and dopaminergic signaling in the reward system. As a result, vortioxetine therapy is less likely to cause emotional blunting and is more effective in reducing anhedonia [5, 6]. The preclinical studies showed that 5HT1A agonism promotes faster desensitization of 5HT1A autoreceptors leading to an increased serotoninergic transmission. Additionally, it boosts dopaminergic activity in the PFC, which in the clinical context potentially translates to higher effectiveness in reducing anxiety, promoting cognition and normalizing hedonic tone as well as reducing the risk of sexual dysfunction due to SERT blockade [5]. 5HT7 antagonism and 5HT1A agonism synergistically potentiate the desensitization of 5HT1A autoreceptors and increase serotoninergic transmission. Clinically, this manifests as higher antidepressive and procognitive effectiveness [5]. 5HT1B antagonism results in serotoninergic disinhibition. As a result, increased antidepressive and antianxiety effects can be observed clinically. This mechanism might also counteract potential weight gain [5]. For now, the role of 5HT1D antagonism is unclear. While vortioxetine does not interact with acetylcholine, histamine, noradrenaline, dopamine, glutamate or GABA receptors, it nonetheless indirectly modulates the activity of these transmitters [4].

Pharmacokinetics

Vortioxetine is characterized by good bioavailability, 75% of the drug is absorbed after oral ingestion, and food has no effect on its absorption [7]. The maximum plasma concentration of the drug in blood serum is observed 7-11 hours after ingestion. Vortioxetine binds to the plasma proteins in 99%. It is mainly metabolized in the liver – 99% and only in 1% in the kidneys. The main isoenzyme which metabolizes vortioxetine is CYP2D6; the drug is also to a lesser extent metabolized by CYP3A4, CYP3A5, CYP2A6, CYP2C9 and CYP2C19 and it is glucuronized afterwards. Vortioxetine has no active metabolites which would significantly influence its clinical effect. P-glycoprotein

has a minor influence on the effect of the drug which is clinically insignificant. The half-life of vortioxetine is 59-69 hours, which translates to a decreased risk of withdrawal symptoms upon its discontinuation as well as lower risk of impaired effectiveness due to a dose omission. The drug is eliminated by the kidneys in approximately 60% and by the gastrointestinal tract in approximately 30%.

Vortioxetine has linear pharmacokinetics and therefore the treatment effects are dose-dependent. A steady-state is reached after around 12 days of regular dosing. Previous studies did not find any clinically meaningful differences in vortioxetine pharmacokinetics that would be related to sex, age or ethnicity [8]. A single study showed a 50% longer time of accumulation and elimination of vortioxetine in obese subjects, which did not significantly influence its clearance. Although it could potentially result in a delay in achieving therapeutic effects and a risk of interaction in the case of switching from vortioxetine to another drug, it does not increase the risk of excessive accumulation and toxicity of the drug [9]. No dose adjustment is needed in CYP2D6 ultrarapid metabolizers; however, it might be necessary in slow metabolizers – in individual cases selected based on tolerance of the therapy a 50% dose reduction might be needed due to increased risk of adverse drug reactions (ADR). Caution is advised upon combining the vortioxetine treatment with drugs which inhibit CYP2D6 (i.e., bupropion, amiodarone, propranolol, metoprolol, butyrophenone and phenothiazine antipsychotics, methadone, metoclopramide, quinidine) – a 50% dose reduction of vortioxetine might be needed in such cases. If vortioxetine is co-administered with inductors of cytochrome enzymes (i.e., rifampicin, barbiturates, phenytoin, carbamazepine) a dose increase might be needed. There is no need for dose adjustments if vortioxetine is combined with P-glycoprotein inhibitors [8]. The drug shows no significant interaction with ethanol. The most important pharmacokinetic properties of vortioxetine are summed up in Table 2 [10].

Table 2. **Pharmacokinetic properties of vortioxetine**

Bioavailability: 75%
T_{max}: 7-11 hours
$T_{1/2}$: 59-69 hours
Linear pharmacokinetics
Metabolized in liver; slow CYP2D6 metabolizers might require a 50% dose reduction; P-gp does not significantly influence the treatment effect
No interaction with ethanol
T_{max} and total elimination might be extended in obese subjects

P-gp – P-glycoprotein,$T_{1/2}$ – half-life of the drug, T_{max} – time to the maximum drug concentration

Effectiveness in the treatment of depression and anxiety

Numerous previously conducted studies and their meta-analyses provided results showing that vortioxetine is more effective than placebo in the acute treatment of

depressive disorders with anxiety as well as with coexisting anxiety disorders. Results are presented in Table 3. Vortioxetine was proved to be effective in depressive disorders and depression comorbid with anxiety. Furthermore, dose-dependence of the therapeutic effect was observed. However, studies did not confirm the effectiveness of vortioxetine in generalized anxiety disorder.

Table 3. **Effectiveness of vortioxetine in the treatment of depression and anxiety disorders**

Thase et al. 2016 [11]	Meta-analysis of 11 RCT in MDD patients; 1,824 subjects in the placebo group, 3,304 subjects in the vortioxetine group	Treatment response: Placebo 36.7%; vortioxetine 5 mg 50.2%; 10 mg 48.8%; 15 mg 46.3% (no statistical significance); 20 mg 51.6% Remission: Placebo 23.8%; vortioxetine 5 mg 30.7% (no statistical significance); 10 mg 30.2%, 15 mg 28.7% (no statistical significance); 20 mg 32.3% Reduction in the MADRS score: 5 mg – 2.10; 10 mg – 2.64;15 mg – 2.26; 20 mg – 3.71 Reduction in the CGI-I score: 5 mg – 0.28; 10 mg – 0.42; 15 mg – 0.29; 20 mg – 0.50 Reduction in the CGI-S score: 5 mg – 0.29; 10 mg – 0.46; 15 mg – 0.36 (no statistical significance); 20 mg – 0.55
Cipriani et al. 2018 [12]	Network meta-analysis of 522 RCT of 21 AD; 116,477 participants	Vortioxetine was significantly more effective than placebo (OR 1.66) in achieving treatment response. It was also more effective in achieving treatment response than reboxetine and trazodone
He et al. 2018 [13]	Meta-analysis of 12 RCT in MDD patients	Reduction in the MADRS score compared to placebo: 5 mg/d – 2.38; 10 mg/d – 3.12; 20 mg/d – 4.86; 10-20 mg/d – 2.30 OR of treatment response: <5 mg/d 1.38; 5 mg/d 1.32; 10 mg/d 1.41; 20 mg/d 1.63 OR of remission: 10 mg/d 1.38; 20 mg/d 1.70
Li et al. 2016 [14]	Meta-analysis of 5 RCT; duloxetine vs. vortioxetine in MDD; 2,287 participants	OR of treatment response vortioxetine vs. duloxetine: 0.83 OR of remission vortioxetine vs. duloxetine: 0.97
Boulenger et al. 2012 [15]	RCT; vortioxetine 204 subjects, placebo 192 subjects	Risk of recurrence in the 24 weeks of maintenance treatment after achieving remission: 13% in the vortioxetine group 26% in the placebo group

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Vieta et al. 2017 [16]	A post-hoc analysis of 5 open-label studies with flexible dosing (5-20 mg/d) of vortioxetine, study duration no more than 52 weeks; 1,230 participants	Treatment response: After 8 weeks: 47.8% After 52 weeks: 75.4% Remission: After 8 weeks: 29.6% After 52 weeks: 60.7% Loss of remission between 8th and 52nd week of treatment: 18.1% Recurrence of depression: 8.0%
Qin et al. 2019 [17]	Meta-analysis of 4 RCT; patients with GAD; 1,074 in the vortioxetine group, 613 in the placebo group; doses 2.5-10 mg/d	No significant differences in achieving a treatment response or remission in vortioxetine vs. placebo group
Baldwin et al. 2016 [18]	Meta-analysis of 10 RCT; patients with MDD with anxiety; vortioxetine doses 5-20 mg/d; 1,590 subjects in the placebo group, 2,856 in the vortioxetine group	Reduction in depression severity (MADRS score) in patients with HAM-A >20: Significant difference for doses of: 5 mg/d, 10 mg/d and 20 mg/d. Treatment effect was dose-dependent. Reduction in anxiety severity (HAM-A score) in patients with HAM-A >20: Significant difference for doses of: 5 mg/d, 10 mg/d and 20 mg/d. Treatment effect was dose-dependent.

AD – antidepressant, CGI-I – Clinical Global Impressions Scale – Improvement, CGI-S – Clinical Global Impressions Scale – Severity, GAD – generalized anxiety disorder, HAM-A – Hamilton Anxiety Rating Scale, MADRS – Montgomery-Asberg Depression Rating Scale, MDD – major depressive disorder, OR – odds ratio, RCT – randomized controlled trial

Anhedonia and emotional blunting

Vortioxetine's pharmacodynamic profile suggests that this drug is effective in reducing anhedonia and emotional blunting. In recent years, clinical studies were performed in order to verify this assumption. An open-label trial was performed to assess the efficacy of vortioxetine in the acute treatment of depressive symptoms measured with Montgomery-Asberg Depression Rating Scale – MADRS, including anhedonia, as well as anhedonia symptoms measured with Snaith-Hamilton Pleasure Scale – SHAPS. It was observed that treatment with vortioxetine resulted not only in a reduction of MADRS score but also a significant decrease in the level of anhedonia as well as an improvement in functioning and quality of life. Moreover, it was noted that the improvement of overall depression symptoms, general functioning and quality of life was mediated by anhedonia [19]. Another work assessed the effectiveness of vortioxetine in decreasing the severity of emotional blunting in patients with moderate

or severe depression who only partially responded to treatment with SSRI or SNRI (serotonin and noradrenaline reuptake inhibitors). The level of emotional blunting was measured with the appropriate MADRS items and the Oxford Depression Questionnaire (ODQ). Furthermore, the level of energy and motivation was assessed with the Motivation and Energy Inventory (MEI). Subjects were treated with vortioxetine in a mean dose of 15.3 mg/d. From the first week on, a significant reduction in ODQ and MADRS scores (both overall and the item measuring anhedonia) as well as improvement in cognitive functioning were noted, which increased with time. Following the 8th week of treatment, 50.8% of patients denied experiencing emotional blunting. After 4 weeks of vortioxetine pharmacotherapy a significant increase in motivation and energy was reported. Vortioxetine treatment resulted in a significant improvement in patients' functioning, especially in the occupational / educational area. Mediation analyses showed that the main factor mediating the functional improvement was the decrease of emotional blunting (64.3%). The reduction of depression symptoms was significantly less important and mediated 36.6% of the functional improvement [20].

The influence of vortioxetine treatment on cognitive functions

Impaired cognitive functioning, particularly in the aspects of attention and executive functioning, is one of the main symptoms which persists after the acute depressive episode. It is a significant mediator of social functioning improvement or remission [21]. A network meta-analysis of 12 RCT which assessed cognitive functioning with the Digit Symbol Substitution Test (DSST) showed that vortioxetine, duloxetine, desipramine and sertraline were superior to placebo in improving the cognitive functioning. Other drugs (citalopram, escitalopram, fluoxetine, phenelzine, nortriptyline) negatively influenced the cognitive functioning. However, the results were statistically significant only in the case of vortioxetine [22]. McIntyre et al. [23] published a meta-analysis comparing vortioxetine in the dose of 5-10 mg/d, duloxetine in the dose of 60 mg/d and placebo. The results showed that vortioxetine in both doses was significantly superior to placebo; no such difference was shown for the comparison of duloxetine vs. placebo. The procognitive effect was independent of the antidepressive effect [23].

In recent years, a long-term open-label trial AtWoRC assessed the relationship between reported impairment of cognitive functioning and productivity of work in patients with MDD treated with vortioxetine. Cognitive functions were measured with DSST and self-report questionnaire Perceived Deficits Questionnaire (PDQ), and the productivity of work was measured with a self-report scale – the Work Limitations Questionnaire (WLQ). Moreover, the severity of affective symptoms was assessed with Quick Depression Symptomatology Inventory – Self Report (QIDS-SR), general functioning with the 12-level WHO scale and Sheehan Disability Scale (SDS), the level of anxiety with Generalized Anxiety Disorder-7 (GAD7), and the overall clinical impression with the Clinical Global Impression scale (CGI) including Improvement (Clinical Global Impression scale – Improvement, CGI-I) and Severity (Clinical Global

Impression scale – Severity, CGI-S) subscales. The data were analyzed separately for patients who started treatment in the current MDD episode with vortioxetine and those who first started taking a different medication (for 6 weeks) and later switched to vortioxetine due to lack of effectiveness. The observation of the first 12 weeks indicated that treatment with vortioxetine resulted in a significant decrease in the severity of depression and anxiety as subjectively reported by the patients and objectively measured by the level of cognitive function impairment as well as an improvement in general functioning and work productivity. Additionally, the percentage of patients reporting work absence due to depression decreased from the initial 57% to 22%. The improvement of general cognitive functioning was significantly associated with an increase in work productivity [24]. The analysis after 52 weeks showed a further improvement in the affective and anxiety symptoms, cognitive and general functioning of subjects as well as an even greater decrease in work absence to the level of 9%. It was also noted that the level of cognitive impairment measured during the 12th and 26th week of treatment was a predictor of the level of general functioning assessed with SDS on subsequent visits, and this association remained significant after correction for the severity of depression [25].

Another study compared the effectiveness of vortioxetine (10-20 mg/d) and escitalopram (10-20 mg/d) in reducing the impairment of cognitive and general functioning. The cognitive performance assessed with Rey Auditory Verbal Learning Test (RAVLT) was significantly improved only in the verbal memory domain. The treatment with vortioxetine vs. escitalopram prompted a greater improvement in patients' functioning evaluated with SDS. The improvement in cognitive functioning and depressed mood (assessed with MADRS items) were predictors of functional improvement [26]. In the study conducted by Park et al. [27], 81 subjects received vortioxetine 10-20 mg/d for 8 weeks, the dosing was flexible and depended on tolerance and treatment response. The cognitive performance was measured with THINC-it, a mobile application comprising a battery of cognitive tests, and the evaluations took place before the onset of treatment, after 2 weeks and after 8 weeks. The improvement of cognitive functioning after 2 weeks of therapy was a predictor of decrease in the severity of depression and remission [27].

Patients with trauma history

The research in MDD patients indicates that childhood trauma is not only a predictor of depression in adulthood but it is also associated with cognitive deficits, impaired hedonic tone and decreased motivation compared to subjects with no history of trauma. Early life trauma is a negative predictor of treatment response to SSRI or SNRI in adults with MDD and it is a risk factor for MDD recurrence as well as persistent, treatment-resistant depressive symptoms [28]. A meta-analysis of studies including MDD patients treated with vortioxetine 5-20 mg/d, with no trauma history and those who experienced trauma in the first 3 years of life of or in the 3 years prior to the study, showed that vortioxetine was superior to placebo in reducing the level of depression

evaluated by MADRS, CGI-S, CGI-I, anxiety measured with HAM-A, improving general functioning assessed with SDS and the quality of life associated with mental health. These effects were present in both groups of patients who reported trauma in the early life and in 3 years prior to the study. The 20 mg/d dose was effective in all of the above-mentioned symptom dimensions. Vortioxetine 10 mg/d and 20 mg/d effectively decreased the level of depression in all groups of patients, including those with no trauma history. In the group with trauma history, the effectiveness in decreasing depressive symptoms, achieving treatment response, remission, reducing anxiety and improving the functioning was observed if vortioxetine was used in higher doses. This once more highlights the dose-dependence of treatment effects of vortioxetine and suggests that patients with trauma history should receive higher vortioxetine doses.

Moreover, data were analyzed from a double-blind trial that compared the effectiveness vortioxetine (5 or 10 mg/d) vs. placebo in preventing MDD recurrence. It was observed that the patients burdened with either childhood or recent trauma treated with vortioxetine at either dose were less likely to relapse than subjects receiving placebo [29].

Depression in the elderly

The analysis of five open-label studies published by Vieta et al. [16] on the efficacy of vortioxetine, which was described in Table 3, showed similar rates of treatment response and remission in groups of subjects aged less than and more than 55 years [16]. In the meta-analysis by Krause et al. [30] vortioxetine was one of the few substances (together with quetiapine, duloxetine, imipramine and agomelatine) that significantly differed from placebo in achieving treatment response in MDD treatment in the geriatric population. Also, vortioxetine was significantly more effective in attaining treatment response than nortriptyline, fluoxetine and tianeptine. Regarding the levels of remission, vortioxetine was significantly superior to venlafaxine, fluoxetine and trazodone; its superiority over other comparators apart from quetiapine, duloxetine, dothiepin, mirtazapine, agomelatine and paroxetine did not reach statistical significance. It was also more effective than placebo in reducing the severity of depression [30]. Vortioxetine treatment was also assessed in participants with mild cognitive impairment as evaluated with Mini Mental State Exam (MMSE; score 18-24) and depression measured with Geriatric Depression Scale (GDS; score >5). The severity of depression (HAM-D), Cornell Scale for Depression in Dementia [CSDD]) and level of cognitive functioning (MMSE, Raven Coloured Progressive Matrices [RCPM], Digit Span, Attentive Matrices) were assessed upon the study entrance and in the following year of an open-label observation. Patients were randomly assigned to the group treated with vortioxetine (15 mg/d) or other AD (venlafaxine, bupropion, escitalopram, sertraline, paroxetine). A significantly higher improvement in cognitive functions (MMSE, RCPM) and decrease in the severity of depression (both scales) was noted after one year in patients treated with vortioxetine compared to those taking other AD [31].

Depression in the course of bipolar affective disorder (BD)

A recently published open-label trial conducted in 60 patients with BD showed that augmentation of normothymic treatment (i.e., lamotrigine, quetiapine, olanzapine, valproate) with vortioxetine 10-20 mg/d resulted in treatment response in 73% (after the mean time of 3.88 ± 1.71 weeks) and remission of depression in 52% (after the mean time of 8.97 ± 4.05 weeks) of subjects. No relationship between the effectiveness of vortioxetine and its dose, BD type (I, II, rapid cycling), clinical stage, history of psychosis, symptomatology of depression and the type of mood stabilizer was observed. A phase switch during treatment was noted in 11.7% of participants. These results are comparable to the risk observed in SSRI treatment (10-15%). Studies of vortioxetine effectiveness on larger groups of BD subjects are currently lacking [32].

Adverse drug reactions and safety of vortioxetine

Vortioxetine's unique pharmacodynamic profile also translates to its good tolerance and safety. Numerous studies indicate that the risk of discontinuation due to ADR is low and suggest that the tolerance of vortioxetine is one of the highest among AD. It is worth noting that in the meta-analysis by Citrome et al. [33], the number needed to harm (NNH) for vortioxetine treatment was 42.7, which was the highest among all studied AD. The most common ADR of treatment with vortioxetine are nausea and vomiting. These are in most cases transient and occur in the first 2 weeks of treatment; only 2% of patients report that these ADR persist later in the treatment. Nausea and vomiting are most often mild or moderate. Their prevalence is higher in women and increases with the dose of the drug [33].

Table 4 displays the results of studies assessing the risk of discontinuation due to adverse effects comparing vortioxetine to other AD.

Table 4. **Risk of discontinuation of therapy due to adverse effects of vortioxetine and other AD**

Citrome 2014 [33]	Systematic review	Risk of discontinuation due to ADR (NNH): Vortioxetine 10mg/d: 40; 15 mg/d: 24; 20 mg/d: 21 Venlafaxine XL 225 mg/d: 10 Duloxetine 60 mg/d: 20
Citrome 2016 [34]	Meta-analysis	Risk of discontinuation due to ADR (NNH): Vortioxetine: 42.7; Escitalopram: 30.7; Vilazodone: 26.1; Duloxetine: 24.5; Levomilnacipran: 18.2; Venlafaxine: 7.8; Sertraline: 6.5
Pae et al. 2015 [35]	Meta-analysis	Risk of discontinuation (OR) of treatment with vortioxetine compared with: Placebo: 1.530; SNRI and agomelatine: 0.753

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Kennedy et al. 2018 [36]	Meta-analysis	Risk of discontinuation of treatment with vortioxetine (10-20 mg/d) vs. agomelatine (25-50 mg/d): no statistically significant difference
Llorca et al. 2014 [37]	Meta-analysis	Risk of discontinuation (OR) compared with placebo: Agomelatine 0.89; Vortioxetine 1.58; Duloxetine 2.10; Escitalopram 2.36; Vilazodone 2.47; Desvenlafaxine 2.89; Venlafaxine 3.39; Sertraline 5.25
Cipriani et al. 20198 [12]	Network meta-analysis	Direct comparisons of tolerance defined as the risk of discontinuation (OR) showed that vortioxetine was statistically significantly superior over: Clomipramine 2.20; Duloxetine 1.99; Fluvoxamine 1.78; Reboxetine 2.32; and Venlafaxine 1.69. Comparisons with other drugs included in this meta-analysis (Agomelatine, Amitriptyline, Bupropion, Citalopram, Escitalopram, Fluoxetine, Sertraline, Paroxetine, Milnacipran, Nefazodone, Mirtazapine, Trazodone) also indicated the superiority of Vortioxetine but did not reach statistical significance.

ADR – adverse drug reaction, NNH – number needed to harm, OR – odds ratio

Compared to other AD, vortioxetine also shows superior tolerability regarding the risk of sexual dysfunctions (Treatment Emergent Sexual Dysfunction, TESD). Vortioxetine treatment is not linked to significant risk of TESD in doses of less than 15 mg/d; however, in higher doses these ADR might be more common. Switching to vortioxetine might result in improvement of sexual functions in patients reporting TESD due to SSRI treatment. A summary of studies of TESD is presented in Table 5.

Table 5. **Risk of sexual dysfunction (TESD) due to treatment with vortioxetine and other AD**

Baldwin et al. 2016 [38]	Analysis of RCT and open-label studies	Prevalence of TESD: Placebo 1% of subjects; Vortioxetine 5 mg/d: 1.6% 10 mg/d: 1.8%, 15 mg/d: 1.6%. 20 mg/d: 1.8%; Venlafaxine 22 5mg/d: 12.4%; Duloxetine 60 mg/d: 4.5%. ADR were considered significant if their occurrence exceeded 5% or was over 2 times higher than the prevalence of ADR in placebo group
Jacobsen et al. 2015 [39]	RCT	Normalization of sexual functions assessed with the CSFQ-14 after 8 weeks of therapy: vortioxetine 52.1% vs. escitalopram 44.2% Improvement of sexual functions (CSFQ-14 score increase of ≥3 points): vortioxetine 74.7% vs. escitalopram 62.6% Superiority of vortioxetine over escitalopram in 4 of 5 subscales (pleasure, desire/frequency, arousal/ erection and orgasm).

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Jacobsen et al. 2016 [40]	Analysis of 8 RCT	TESD evaluated with ASEX > 19 (score >=5 in one subscale or score >=4 in three subscales) Vortioxetine: 5 mg/d (similar to placebo); 10-20 mg/d (no significant difference vs. placebo), noticeable dose-dependence of TESD risk Duloxetine: 60 mg/d significantly higher risk compared to placebo or vortioxetine 5-10 mg/d
Jacobsen et al. 2019 [41]	RCT	TESD evaluated with CSFQ-14 (after 5 weeks): Vortioxetine 10 mg/d vs. placebo: no differences Paroxetine 20 mg/d vs. placebo: significant superiority of placebo Paroxetine 20 mg/d vs. vortioxetine 10 mg/d: significant superiority of vortioxetine (no statistically significant difference in the group taking vortioxetine 20 mg/d)

ADR – adverse drug reaction, ASEX – Arizona Sexual Experiences Scale, CSFQ-14 – Changes in Sexual Functioning Questionnaire Short Form, RCT – randomized controlled trial, TESD – treatment emergent sexual dysfunction

Vortioxetine was also compared to other AD regarding other ADR. One study assessed the prevalence of complaints of somnolence due to AD in the US Food and Drug Administration Adverse Event Reporting System (FAERS) reported between 2004-2019. The results indicated that vortioxetine, aside from levominlacipran, was linked to the lowest relative odds ratio (ROR) of drug-related somnolence, which equaled 1.3 (this study included 30 AD of different groups i.e., tricyclic AD, monoamine oxidase inhibitors, SSRI, SNRI, bupropion and others) [42]. In an analysis of hyponatremia reports due to AD in the FAERS base between 2004-2018, the ROR of hyponatremia due to vortioxetine was 1.72. The risk of hyponatremia due to vortioxetine was lower than the risk due to treatment with all SSRI, duloxetine, venlafaxine, mirtazapine, clomipramine and moclobemide. Amitriptyline, desvenlafaxine, vilazodone, trazodone and bupropion were characterized by lower ROR of hyponatremia than the one observed for vortioxetine [43].

Furthermore, vortioxetine is linked to a lower risk of hemorrhagic complications compared to SSRI and SNRI, perhaps due to the fact that vortioxetine is less potent in reducing the reuptake of serotonin. In spite of this, a case of urinary tract bleeding and a case of nosebleed that occurred during the combined treatment with vortioxetine and warfarin were reported, potentially due to the competition of vortioxetine and warfarin in binding to plasma proteins and the resulting higher free plasma warfarin levels [44].

Little data are available regarding the risk of seizures during vortioxetine treatment. There are no reports of seizures due to vortioxetine in the preregistration clinical trials or post-marketing studies [45]. Concerning the safety of vortioxetine in patients with epilepsy, a case series of nine patients, of whom seven had partial seizures with secondary generalization and two had tonic-clonic seizures were presented. In the

described subjects, three were diagnosed with BD and six with a mood disorder due to known physiological condition Additional somatic comorbidities included: insulin-independent diabetes mellitus, hypertension, ischemic heart disease, chronic obstructive pulmonary disease, dyslipidemia, migraine and nephrolithiasis. Vortioxetine was used in 10-20 mg/d administered to address the clinical presentation of depression, comorbidities, ineffectiveness of prior treatment or in order to minimize the risk of drug interactions due to polytherapy. The observation time lasted from 2 to 48 months. All patients achieved remission of depression and the treatment was well tolerated. Seizures were noted in two patients; however, it was evaluated that their occurrence was not associated with AD but rather with inadequate anticonvulsive treatment [46].

Vortioxetine treatment is not associated with a significant risk of cardiologic complications. An analysis of VigiBase, a database of reported ADR, assessing the risk of QTc prolongation showed that vortioxetine use was not linked to an increase in QTc prolongation reports [47]. Currently, there is no evidence suggesting that vortioxetine is related to nephrotoxicity or hepatotoxicity, and no dose adjustments are needed in patients with impaired kidney or liver function [48]. Vortioxetine does not cause significant weight gain; moreover, vortioxetine treatment is safe in diabetes. In a RCT conducted by Tovilla-Zárate et al. [49], vortioxetine showed good safety in subjects with type 2 diabetes, and after 8 weeks participants receiving this drug achieved an improvement in metabolic parameters (glycated hemoglobin, waist circumference, fasting glucose, triglyceride levels).

No data are available regarding the risk of glaucoma exacerbation or cataract development due to vortioxetine use. The existing literature shows no risk of increased Parkinson's Disease symptoms [50]. Vortioxetine is safe in the geriatric population. In the meta-analysis by Krause et al. [30], the only ADR which showed statistically significant risk in the elderly was nausea (RR 2.52).

Furthermore, the discontinuation of vortioxetine is related to low risk of ADR. In a retrospective study which included 263 patients who stopped vortioxetine treatment, the antidepressant discontinuation syndrome was observed in 8 (3%) of subjects. The median time to the onset of discontinuation symptoms was 3 days and the median duration was 7 days. All affected patients reported mood swings, 75% irritability, 75% sudden worsening of mood, 37.5% nervousness and agitation. Among other less common discontinuation symptoms headaches, tearfulness, impaired concentration, sleep disorders, tremor, vertigo, abdominal pain, hypersensitivity to stimuli, anergy, apathy, weakness and amotivation were noted. All affected subjects reported that their discontinuation symptoms caused significant discomfort and impairment of functioning. An increased risk of discontinuation syndrome was associated with accidental drug withdrawal, discontinuation without prior medical advice and longer duration of vortioxetine treatment (median duration of treatment was 272 days in patients with discontinuation syndrome vs. 74 in subjects without discontinuation syndrome). The risk of discontinuation syndrome was not linked to age, sex, way of drug discontinuation (sudden vs. gradual), dose or psychiatric comorbidity. It is worth noting that

the occurrence of ADR due to vortioxetine withdrawal is significantly lower than in other formerly assessed ADs – paroxetine 35-66%, venlafaxine 23-78%, duloxetine 6-55%, milnacipran 13-30% [51].

Summary

Vortioxetine was proved effective in the treatment of MDD as well as in the management of depression with anxiety, depression in patients with trauma history, depression in the elderly and bipolar depression. The effect of vortioxetine treatment is dose-dependent. Vortioxetine positively impacts the level of cognitive functioning and hedonic tone and therefore significantly increases the chances of achieving functional remission. It is characterized by a favorable tolerance profile compared to the majority of currently available AD. The most common ADR due to vortioxetine treatment are nausea and vomiting, which are usually transient. Vortioxetine use is linked to a low risk of sexual dysfunction, which is more likely to appear if high doses of the drug are used. It is safe in patients with various comorbidities as well as in the elderly. Treatment with vortioxetine is not related to a significant risk of drug-to-drug interactions. Vortioxetine is an effective and safe treatment choice in many patient groups.

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