Medical Science

To Cite:
Krych G, Skóra M, Kazimierski B, Rusak A, Oklińska J, Jadczak K, Gniado W, Mądry D. Vortioxetine - a new antidepressant drug with multimodal action – Review of recent studies. *Medical Science* 2026; 30: e82ms3873
doi:

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Peer-Review History
Received: 29 May 2025
Reviewed & Revised: 16/June/2025 to 18/April/2026
Accepted: 25 April 2026
Published: 07 May 2026

Peer-review Method
External peer-review was done through double-blind method.

Medical Science
pISSN 2321–7359; eISSN 2321–7367

DISCOVERY SCIENTIFIC SOCIETY

Vortioxetine - a new antidepressant drug with multimodal action – Review of recent studies

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ABSTRACT

Vortioxetine is among the new antidepressant drugs. Unlike traditional antidepressants that focus on a single mechanism of action, it is a multimodal drug that improves cognitive function and has antidepressant and anti-anxiety effects. More recently, it has attracted at-tention for its ability to reduce discomfort in neuropathic pain by modulating descending inhibitory pathways in the spinal cord. Experts recognize vortioxetine as one of the most effective and best-tolerated options. The pharmacodynamic profile and clinical studies of this drug lead researchers to believe that its mechanism of action consists primarily of di-rect modulation of serotonin receptor activity (e.g., 5-HT3, 5-HT7, 5-HT1D, 5-HT1B) and selective inhibition of SERT (serotonin reuptake). Thus, this drug significantly alters the way in which two or more serotonin receptors interact.

Keywords: vortioxetine, depression, cognitive function, neuropathic pain, antidepressants

1. INTRODUCTION

In the mid-1990s, following the successful dissemination of selective serotonin reuptake inhibitors, pharmaceutical companies became interested in preclinical and clinical studies on serotonin transporter (SERT) inhibition and somatodendritic serotonin 1A (5-HT1A) au-to receptor antagonism. The results showed an earlier and significantly greater increase in non-cellular serotonin levels in the brains of rodents, resulting in higher efficacy and short-er duration of action than selective serotonin reuptake inhibitor (SSRI) drugs. Developing a drug with SERT and 5-HT1A mechanisms proved very challenging, especially in determin-ing the optimal potency ratio between the two mechanisms and the optimal activity at the 5-HT1A receptor. During drug development, researchers redirected the target profile to achieve a combination of 5-HT1A receptor agonism, SERT inhibition, and 5-HT3 receptor antagonism. They thought that 5-HT3 receptor antagonism would result in a lower rate of nausea and/or vomiting, an adverse effect of SSRIs and serotonin-norepinephrine reuptake inhibitors (SNRIs).

Vortioxetine was approved as a drug in the autumn of 2013 by the FDA and EMA for the treatment of major depression. The FDA and EMA approved

Vortioxetine as a drug in the autumn of 2013 for the treatment of major depression (Sowa-Kućma et al., 2017). Re-searchers have extensively studied the drug, and every year, there is more and more data supporting its safety and high efficacy in treating major depression (Cipriani et al., 2018).

Aim of the study

The review will provide useful information related to the drug, including its mecha-nisms of action, side effects, clinical applications, and its distinct multimodal mechanism of action. Vortioxetine has efficacy for treating major depressive disorder (MDD) and generalized anxiety disorder (GAD), as well as an increasingly recognized role in enhancing cognitive function and managing neuropathic pain.

2. REVIEW METHODS

This review follows a defined methodology to provide a complete and honest assessment of the pharmacological and clinical characteristics of vortioxetine. All literature reviewed was peer-reviewed and freely available online; major sources included PubMed, Google Scholar, and healthcare websites (e.g., hospitals, universities). Vortioxetine comprehensively searched for and excluded articles that did not have an online full text published. All con-clusions drawn from the articles examined are based on the currently available literature and scientific and clinical guidelines; thus, all of our work accurately reflects the current state of medical advancement. The screening process of the articles follows the PRISMA guidelines (Figure 1).

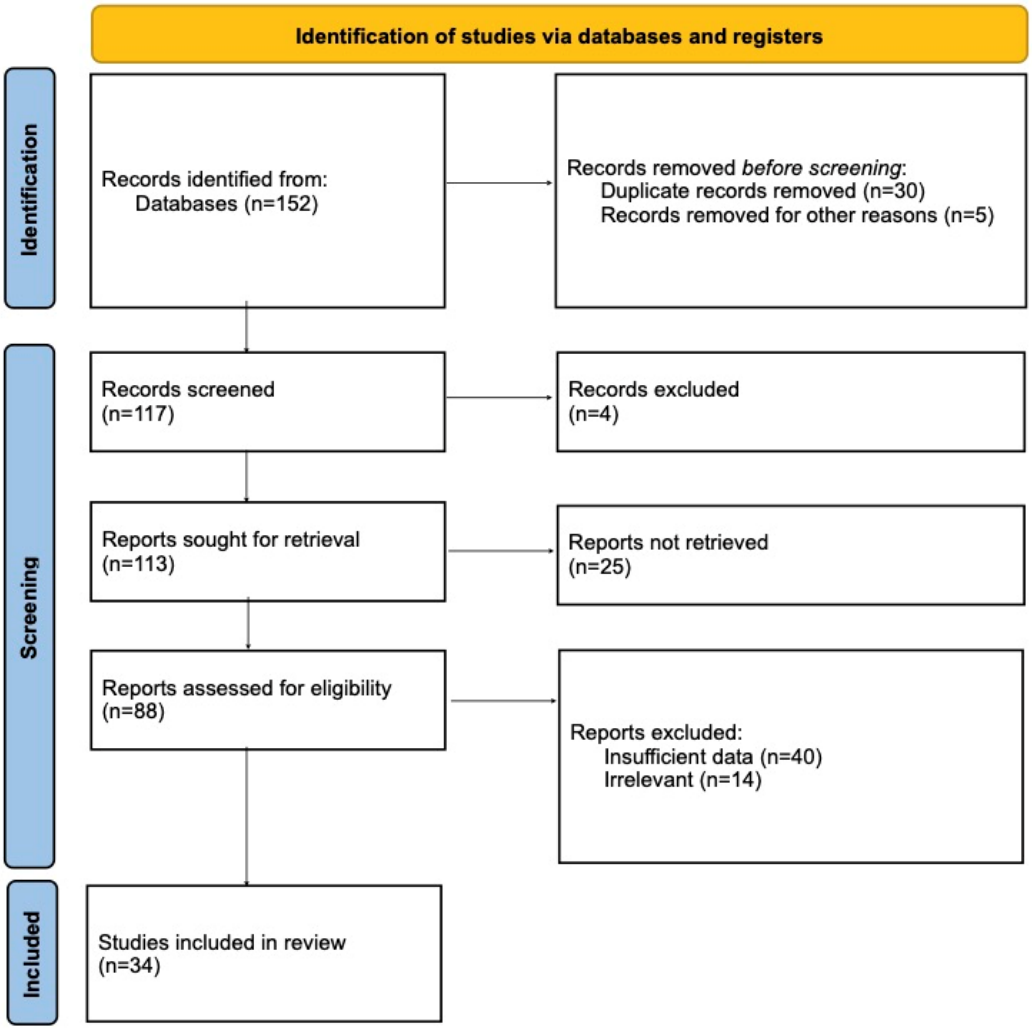

Figure 1. PRISMA CONSORT chart

3. RESULTS & DISCUSSION

Structure and mechanism of action

Vortioxetine is a drug that is chemically named 1-[2-(2,4-dimethyl-phenylsulfanyl)-phenyl] piperazine. The molecular weight is 298.45 g/mol. We can describe the drug's mechanism of action as multimodal, as it has multiple mechanisms: SERT inhibition and direct modulation of various serotonin receptors, including 5-HT1A receptor agonism, 5-HT1B receptor partial agonism, and 5-HT3, 5-HT1D, and 5-HT7 receptor antagonism. Ther-apeutic doses (5-20 mg/day) used in humans correspond to 50-80% SERT occupancy. Pre-clinical studies have shown that it affects the activity of multiple systems, including 5-HT, norepinephrine, histamine, dopamine, glutamate, acetylcholine, and GABA (Sowa-Kućma et al., 2017). In scientific studies using progesterone withdrawal and tryptophan depletion, the mechanisms of action of vortioxetine beyond SERT inhibition are important for explain-ing the drug's antidepressant effect (Li et al., 2013; Hlavacova et al., 2018).

Researchers highlight the significant role of glutamatergic signaling and neuroplasticity in the pathophysiology of depression and the effectiveness of antidepressants (Du Jardin et al., 2016). In postmortem studies, lower neuronal density and size, as well as reduced glial cell and dendrite abundance, were observed in the frontal cortex and hippocampus of patients with major depressive disorder (Rajkowska et al., 1999). A detailed review and exploration of the mechanisms of action suggest that 5-HT3 receptor blockade is one of the most im-portant properties of vortioxetine for improving cognitive function, as observed in clinical trials (Bennabi et al., 2019).

The modulating effects of neurotransmitters, i.e., dopamine, norepinephrine, histamine, or acetylcholine, in the medial prefrontal cortex, and the enhancement of neurogenesis and, most importantly, neurotrophic processes in the hippocampus are considered additional mechanisms contributing to the procognitive effects of vortioxetine. Studies have shown that vortioxetine causes spectral changes in quantitative electroencephalography (qEEG) that differ from those of SNRIs and SSRIs. In particular, the effect of vortioxetine, in con-trast to escitalopram and duloxetine, on increases in cortical frequency ranges was high-lighted, which may play a significant role in improving cognition (Leiser et al., 2014). The potent 5-HT3 antagonism prompted the testing of vortioxetine in animal models of neuro-pathic pain. Studies have shown that 5-HT3 receptors are actively involved in the patho-physiology of neuropathic pain (Ossipov et al., 2010). In addition, vortioxetine has shown immunomodulatory effects, including antioxidant and anti-inflammatory, which may result in clinical benefits (Talmon et al., 2018). Moreover, vortioxetine has better anti-inflammatory effects than other antidepressants (Tomaz et al., 2020).

Thus, vortioxetine has multiple mechanisms of action that regulate different neuro-transmitters. Vortioxetine not only offers patients the advantages of an antidepressant but also enhances cognition, alleviates pain, and reduces inflammation (Talmon et al., 2018; Salagre et al., 2018).

Pharmacokinetics

Vortioxetine is a slowly absorbed drug that peaks after about 8 hours. Consumption of a meal does not affect the absorption process. The drug's pharmacokinetics are linear. The half-life is 2.75 days, and the steady state (the state in which the rate and amount of drug entering the body equals the rate and amount of drug leaving) is about 2 weeks. It is a drug that binds strongly to proteins. It has the potential to interact with other drugs that also bind to proteins. Vortioxetine undergoes hepatic metabolism primarily via cytochrome P450 isozymes, primarily CYP2D6, with CYP3A4/5 also contributing. For this reason, one must be careful and mindful of drug interactions with CYP 2D6 inhibitors (i.e., fluoxetine, paroxetine, quinidine, and bupropion) and CYP 3A4/5 inducers (i.e., carbamazepine), among others. There are also possible interactions with serotonergic drugs (risk of serotonin syndrome) and drugs that increase bleeding (i.e., aspirin, warfarin). Vortioxetine is a drug with no active metabolites (Keks et al., 2015)

Pharmacodynamics

Clinical studies in rats have shown that vortioxetine's potency at serotonin receptors is not uniform. The order of action on different 5-HT receptor elements in the ranking is as follows: 5-HT3 > SERT > 5-HT1B > 5-HT1A ≈ 5-HT7. An electroencephalographic (EEG) study showed that vortioxetine, compared with escitalopram and duloxetine, selectively in-creased frontal cortex impulsivity and oscillatory activity. Researchers did not observe these effects with the tested SSRI and SNRI group drugs. They believe that cortical activa-tion results from the agonism of 5-HT1A receptors and the antagonism of 5-HT3 and 5-HT7 receptors. Such effects help improve cognitive function in depressed patients (Gonda et al., 2019).

Breastfeeding

The level of vortioxetine in breast milk, based on scientific studies, is low. The study evaluated vortioxetine levels in breastfeeding mothers and drug concentrations in milk at 5 time points within 24 hours (Marshall et al., 2021). In another scientific study, re-searchers observed infants whose mothers were breastfeeding and taking vortioxetine. None of the mothers reported unusual behavior in the infant (Monfort et al., 2021). In conclusion, vortioxetine is a drug that appears in breast milk in low concentrations and is relatively safe. If the mother requires the drug, then it should not be discontinued, or breastfeeding should be interrupted. Since there are not many clinical data available, caregivers should approach breastfeeding with caution and carefully observe the infant and their development.

Side Effects

Common side effects include nausea, dizziness, constipation, drowsiness, and dry mouth. Of the far rarer side effects, we can distinguish mood disorders, suicidal thoughts, serotonin syndrome, increased risk of bleeding, or hypersensitivity reactions. Hypersensi-tivity reactions to the drug include rash, eosinophilia, and fever. Elevated liver enzymes may occur during treatment with vortioxetine, although this occurs in less than 1% of cases. Elevations in liver enzymes are self-limiting and do not require a change in dose or treat-ment. Starting at 10 mg/day, increasing to 20 mg/day based on the patient's efficacy and tolerability. Lower doses, i.e., 5 mg once daily, can be used when adverse effects of the drug are present. Side effects of the drug can also include sexual dysfunction (ejaculatory and erectile dysfunction, abnormal orgasm, or decreased libido).

Gender matters in this case, as during treatment, it is men who have a higher risk of experiencing side effects in the form of sexual disorders. Interestingly, this type of disorder was reported more frequently with the 2.5 mg dose compared to the 5 mg dose (Faquih et al., 2019). Vortioxetine does not affect blood pressure or cardiovascular risk (Calvi et al., 2021). Moreover, the risk of QT interval prolongation during therapy is minimal (Kahl et al., 2022). Vortioxetine can cause hyperprolactinemia and galactorrhea in some patients. Interestingly, vortioxetine is a safe drug and well-tolerated after alcohol consumption. Pa-tients with liver dysfunction can receive it without restriction.

Depression

Depression is one of the most common and debilitating conditions worldwide. Many episodes of depression go unrecognized. Women are 3 times more likely to suffer from de-pression than men. Relapses characterize major depression, and their risk is higher after an-other relapse. The median onset of depression is 25 years, and an initial episode as well as a relapse can occur at any age. Patients with depression have a high level of functional disa-bility, greater than those with hypertension, diabetes, or coronary artery disease. Most pa-tients come to the doctor with somatic symptoms, i.e., unexplained pain, gastrointestinal symptoms, or headache. Many complain of extreme fatigue. Few initially mention the axial symptoms of depression, i.e., sadness, depression, or lack of motivation (Rakel, 1999).

The effectiveness of vortioxetine in treating depression has been confirmed in both short-term (6-8 weeks) and long-term (up to 52 weeks) studies. It has broad positive effects on physical, emotional, and cognitive symptoms (De Diego-Adeliño et al., 2022). Many studies have confirmed the effectiveness of drugs in treating major depression. Moreover, increasing doses of vortioxetine (5-20mg/day) have been associated with greater efficacy (Thase et al., 2016). Vortioxetine in depression has shown high efficacy in treating anhe-donia, defined as an impaired ability to experience pleasure. The drug's efficacy has been associated with improvements in functioning and overall quality of life (Cao et al., 2019). Placebo-controlled studies have sought to determine the effect of vorioxetine in alleviating somatic symptoms associated with depression, i.e., headaches, muscle tension, sleep dis-turbances, appetite, or sexual dysfunction. These symptoms are often present in a depressive episode, including chronic symptoms, and often co-occur with anxiety disorders. Vortiox-etine effectively relieves most somatic symptoms, even in individuals with high levels of anxiety. Vortioxetine doesn't increase the risk of suicide in adults with major depression (De Diego-Adeliño et al., 2022).

Generalized anxiety disorder

Generalized anxiety disorder (GAD) impairs a patient's daily functioning. People with Generalized Anxiety Disorder (GAD) experience worse psychosocial functioning than individuals who have recently suffered a heart attack or congestive heart failure. Their im-paired functioning resembles that of someone experiencing a major depressive episode. Those with GAD frequently exhibit somatic symptoms of anxiety, including sleep disturb-ances, irritability, restlessness, muscle tension, and fatigue. Additionally, they often experi-ence cognitive dysfunction, characterized by deteriorating attention and reduced concentra-tion. Such patients often worry that they or a loved one will become ill, have an accident, or die. In randomized clinical trials, vortioxetine is well tolerated and highly effective in the

treatment of GAD. Clinicians should exercise caution in practice because the number of studies is limited. Well-designed studies comparing the efficacy of vortioxetine to other antidepressants are still lacking (Pae et al., 2015).

Cognitive disorders

Cognitive impairment in depression isn't just in one area; it's a broad spectrum (im-pacting executive function, memory, and processing speed), especially in geriatric popula-tions. These deficits do not always resolve alongside mood improvements and can linger as residual symptoms even once a patient enters remission. (Lee et al., 2012). In a meta-analysis, vortioxetine was the drug that produced the greatest improvement in the digital symbol substitution test, which is a neurocognitive test that integrates multiple domains affected in depressed patients. Vortioxetine proved to be the only antidepressant drug that significantly induced changes in this test. Vortioxetine showed cognitive-enhancing effects in both older and younger subjects. The greater the baseline functional dysfunction, the greater the improvement with the treatment. Interestingly, the improvement in cognitive function was independent of the antidepressant effect (Baune et al., 2018).

Data on the drug's efficacy in Alzheimer's disease are sparse, but it appears to show greater efficacy in improving neuropsychiatric symptoms compared to placebo with cognitive training or other antidepressants (Cumbo et al., 2019). Underlying the positive effects pro-duced by vortioxetine are 5-HT3 or 5-HT7 antagonism, or 5-HT1A and 5-HT1B agonism, effects on other neurotransmitter systems, or hippocampal neuroplasticity. Direct effects on frontal-limbic networks have also been generally demonstrated (Bennabi et al., 2019).

Table 1. Summary of Vortioxetine.

Category	Key Details & Findings
Drug Classification	Multimodal antidepressant.
Mechanism of Action	**SERT Inhibition:** Selective serotonin reuptake inhibition. **Receptor Modulation:** 5-HT1A (agonist), 5-HT1B (partial agonist), 5-HT3, 5-HT1D, and 5-HT7 (antagonist).
Primary Indications	Major Depressive Disorder (MDD) and Generalized Anxiety Disorder (GAD).
Secondary Benefits	**Cognitive Function:** Improves executive function, memory, and processing speed (independent of mood improvement). **Neuropathic Pain:** Modulates descending inhibitory pathways in the spinal cord. **Anti-inflammatory:** Shows antioxidant and immunomodulatory effects.
Pharmacokinetics	**Absorption:** Peak ~8 hours (not affected by food). **Half-life:** 2.75 days (steady state reached in ~2 weeks). **Metabolism:** Hepatic via CYP2D6 (primary) and CYP3A4/5.
Common Side Effects	Nausea (most common), dizziness, constipation, dry mouth, and drowsiness.
Safety Highlights	Low risk of QT interval prolongation; well-tolerated with alcohol; safe for patients with liver dysfunction; minimal suicidal risk in adults.
Sexual Dysfunction	Risk of ejaculatory/erectile dysfunction and decreased libido; higher risk in men.
Special Populations	**Elderly:** First-line choice due to cognitive benefits and safety profile. **Breastfeeding:** Found in low concentrations in breast milk; generally considered safe but requires infant observation.

Neuropathic pain

Neuropathic pain has a very high prevalence worldwide, and its treatment is still not satisfactory to an adequate degree, probably due to the elaborate pathomechanism of the pain, which is still not fully understood (Alles and Smith, 2018; McWilliams and Walsh, 2017). Patients with this condition mainly complain of burning sensations and pain elicited by non-painful stimuli (i.e., light touch) (Colloca et al., 2017). Chronic neuropathic pain is a complex phenomenon with both emotional and perceptual components. It often co-occurs with depression, anxiety, and sleep disorders (Yalcin et al., 2014). For this reason, special attention should be paid not only to analgesic treatment but also to the treatment of poten-tially comorbid conditions and psychiatric disorders (Colloca et al., 2017).

Clinicians place special emphasis on using antidepressants for neuropathic pain, such as specifically tricyclic antidepressants (TCAs), selective serotonin-norepinephrine reuptake inhibitors (SNRIs), and selective serotonin reuptake inhibitors (SSRIs). These drugs act as neuromodulators in the central nervous system and are effective simultaneously in relieving pain and controlling anxiety, depression, and sleep quality (Attal et al., 2010). Vortioxetine, classified as an "other antidepressant," effectively treats neuropathic pain. Evidence sug-gests that pain inhibition requires the involvement of multiple endogenous neurotransmit-ters, including opioids, cannabinoids, and serotonin. In the case of serotonin, special atten-tion must be paid to the induction of analgesia via activation of 5-HT7 receptors and hyper-algesia via activation of 5-HT3 receptors (Nicholson and Verma, 2004).

Researchers have demonstrated that vortioxetine effectively treats pain hypersensitivity and mood disorders through its multimodal action in both experimental and clinical studies. During the drug's action, there is inhibition of SERT, antagonism of serotonin 5-HT3, 5-HT1D, and 5-HT7 receptors, and agonism of 5-HT1A and 5-HT1B receptors. In the clinical trials performed, vortioxetine has shown efficacy in treating patients with chronic facial pain. Moreover, compared with other antidepressants, higher clinical response and remis-sion rates, as well as better acceptability, tolerability, and safety, were observed. Given the new findings, it is worth considering vorioxetine as a drug for neuropathic pain, especially with the co-occurrence of cognitive impairment and depression (Adamo et al., 2021). A summary of this review is provided in Table 1.

4. CONCLUSION

Vortioxetine is a new drug mainly used for the treatment of depression, especially one of high severity. It shows additional cognitive-enhancing effects, so it is one of the first-line medications indicated for older people with depression. Side effects are rare, making it a safe choice, especially for older people burdened with other diseases. Its mechanism of ac-tion is unique - it modulates and stimulates serotonin transmission. More and more studies are emerging to confirm its efficacy as a neuropathic pain treatment by modulating the de-scending inhibitory pathways in the spinal cord and generalized anxiety disorder. Random-ized controlled trials are still necessary to establish the drug's efficacy for the indication and to examine its safety profile.

Acknowledgments

We thank all participants who contributed to the studies included in this systematic review. We also acknowledge the support of our institution and colleagues who guided manuscript preparation.

Authors' Contributions

Conceptualization, supervision, and project administration: Michał Skóra, Gabriela Krych.
Methodology: Klaudia Jadczak, Bartłomiej Kazimierski, Weronika Gniado
Software, validation, formal analysis, investigation, resources, writing original draft prepa-ration: Weronika Gniado, Aleksandra Rusak, Dawid Mądry.
Writing, review editing, and visualization: Michał Skóra, Gabriela Krych.
All authors have read and agreed with the published version of the manuscript.

Informed consent

Not applicable.

Ethical approval

Not applicable. This article does not contain any studies with human participants or animals performed by any of the authors.

Funding

This research did not receive any external funding like specific grant from funding agencies in the public, commercial, or nonprofit sectors.

Conflict of interest

The authors declare that they have no conflicts of interest, competing financial interests or personal relationships that could have influenced the work reported in this paper.

Data and materials availability

All data associated with this study will be available based on the reasonable request to corresponding author.

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