Mental health update – update on depression with a focus on vortioxetine

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Depression, identified by the World Health Organization (WHO) in the International Classification of Diseases (ICD-11) as a complicated and multifaceted condition, affects around 280 million people globally. In sub-Saharan Africa, mental health disorders, including depression, account for nearly 10% of the total disease burden, with depressive disorders being the most frequently diagnosed. Symptoms of depression can range from feelings of worthlessness and difficulty concentrating to sleep disruptions and suicidal ideation. Among the different types of depression, major depressive disorder is the most prevalent. Extensive research has explored potential mechanisms contributing to depression, including genetic, neurochemical, and hormonal influences, such as those involving the hypothalamic-pituitary-adrenal axis. While both pharmacological and non-pharmacological treatments can effectively manage depression, antidepressants are typically the first choice. Vortioxetine, an antidepressant with multimodal activity, stands out due to its unique mechanism of action, combining serotonin transporter inhibition with direct modulation of 5-HT receptors. When left untreated, depression can result in serious physical, emotional and behavioural health concerns. This review seeks to summarise current theories on the origins of depression and treatment strategies, with a focus on the therapeutic potential of vortioxetine.

Keywords: depression, vortioxetine, antidepressant therapy, modulating 5-HT, serotonin transporter inhibitor.

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Introduction

Depression, or major depressive disorder (MDD), remains one of the leading psychiatric conditions worldwide, affecting approximately 280 million people globally according to the World Health Organization (WHO) in 2022.[1-3] Depression is a rising burden across sub-Saharan Africa and South Africa due to various socioeconomic, cultural, and healthcare-related challenges[4] and recent research showed a rising incidence, especially among at-risk groups like adolescents and those with chronic illnesses. This challenge is further exacerbated by the region's inadequate access to mental healthcare services.[5] MDD is characterised by persistent sadness, diminished interest in activities, and multiple physical and cognitive symptoms that may significantly impair day-to-day functioning.[6-8] Despite advances in treatment options, depression remains underdiagnosed and undertreated, particularly in sub-Saharan Africa, where the stigma associated with mental illness persists.[9-11]

Recent years have seen the introduction of newer antidepressants, with vortioxetine emerging as a prominent treatment option. Vortioxetine, a novel multimodal antidepressant, combines serotonergic receptor modulation with serotonin reuptake inhibition.[12] This review aims to discuss the current understanding of MDD and the role of vortioxetine in its treatment, with a focus on the South African context.

Depression: an overview

MDD is a complex, multifactorial disease influenced by genetic, environmental, and psychosocial factors.[13] The aetiology of depression is still not fully understood, but several theories, including the monoamine hypothesis, stress-related neurochemical changes, and inflammatory processes, offer insights into its pathogenesis.[13] In South Africa, the prevalence of depressive disorders has increased significantly, with approximately 9.8% of the population experiencing some form of depression in 2023. Factors such as socioeconomic disparities, unemployment, and the lingering effects of the COVID-19 pandemic have exacerbated the mental health crisis in the region.[14-15]

Pathogenesis of depression

Neurobiological theories[16-18]

The monoamine hypothesis remains one of the leading explanations for the pathophysiology of depression. It suggests that a deficiency in key neurotransmitters such as serotonin, noradrenaline, and dopamine is central to the upregulation of monoamine neuronal receptors and the onset of depressive symptoms. Additionally, dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis has been implicated in MDD, particularly in individuals exposed to chronic stress. Recent studies have also highlighted the role of inflammation in depression, with elevated levels of pro-inflammatory cytokines observed in individuals with MDD.

Genetic and environmental factors

Literature suggests that approximately 40% of the risk for developing depression is linked to genetic factors, while the remaining 60% is influenced by personal environmental conditions.[19] The risk for developing MDD can predominantly be attributed to the following genetic factors, with specific polymorphisms in the serotonin transporter gene (SLC6A4) linked to increased vulnerability to depression.[19-21] Environmental

Table I: Pharmacological treatment modalities (Adapted from Maldonado-García, et al.)[1]

Category	Mechanism of action	Examples
Selective serotonin reuptake inhibitors (SSRIs)	Increase serotonin levels in the brain by blocking its reuptake, enhancing serotonin activity in the synaptic cleft.	Citalopram, escitalopram, paroxetine, sertraline, fluoxetine, fluvoxamine
Serotonin-noradrenaline reuptake inhibitors (SNRIs)	Prevent the reabsorption of serotonin and noradrenaline in the synapses, boosting receptor stimulation.	Venlafaxine, desvenlafaxine, duloxetine, milnacipran, levomilnacipran
Atypical antidepressants	This group acts through various mechanisms, including: - Bupropion inhibits dopamine and noradrenaline reuptake. - Mirtazapine blocks alpha-2 adrenergic receptors and enhances noradrenaline release and antagonises postsynaptic 5HT2 and 5HT3 receptors. - Agomelatine activates melatonin receptors, particularly MT1 and MT2, and promotes the release of dopamine and norepinephrine.	Bupropion, mirtazapine, agomelatine
Serotonin modulators	Act on different serotonin pathways: - Trazodone and Nefazodone act on serotonin receptors, reducing serotonin reuptake and blocking additional receptors. - Vortioxetine modulates various serotonin receptors and the serotonin transporter.	Nefazodone, trazodone, vilazodone, vortioxetine
Tricyclic antidepressants (TCAs)	Reduce noradrenaline and serotonin reuptake at the presynaptic terminals.	Amitriptyline, clomipramine, doxepin, imipramine, trimipramine, desipramine, nortriptyline, protriptyline, maprotiline, amoxapine
Monoamine oxidase inhibitors (MAOIs)	Block monoamine oxidase enzymes, which break down serotonin, noradrenaline and dopamine.	Moclobemide, tranylcypromine, isocarboxazid, phenelzine

stressors, including early childhood trauma and chronic illnesses, further increase the likelihood of developing MDD.[21]

Vortioxetine: a multimodal antidepressant: mechanism of action[22–25]

Vortioxetine, first approved by the Food and Drug Administration (FDA) in 2013, represents a significant advance in the treatment of depression due to its unique mechanism of action. Unlike traditional selective serotonin reuptake inhibitors (SSRIs), vortioxetine exhibits a distinctive pharmacological profile and multimodal mechanism of action both reuptake inhibition and receptor activity modulation at various serotonergic receptors.

Notably, vortioxetine is the only antidepressant that directly modulates 5-HT activity, acting as a full agonist at 5-HT1A, a partial agonist at 5-HT1B, and an antagonist at 5-HT1D, 5-HT3, and 5-HT7 receptors. Refer to Figure 1 for a description of the mechanism of action of vortioxetine.

The potency ranking of vortioxetine is as follows: 5-HT3 > SERT > 5-HT1B > 5-HT1A = 5-HT7. Vortioxetine has a strong affinity for the serotonin transporter (SERT), and its inhibition increases serotonin levels in the synaptic cleft.

At therapeutic doses, vortioxetine inhibits minimal SERT activity (50%), which may elucidate its lower incidence of sexual side effects compared to other SERT inhibitors, such as SSRIs and SNRIs, which typically exhibit near-complete SERT inhibition at similar doses.

Vortioxetine's multimodal mechanism allows it to enhance neurotransmission in both serotonergic and non-serotonergic pathways, potentially improving cognitive function in addition to alleviating depressive symptoms.[12] This makes vortioxetine particularly suitable for patients who experience cognitive impairments as part of their depressive symptomatology.[26]

Thus, vortioxetine's multimodal activity allows it to exert effects beyond traditional serotonin reuptake inhibition. By modulating various serotonin receptors, it has the potential to not only treat mood-related symptoms of depression but also address cognitive dysfunction and anxiety. Its unique receptor profile allows it to manage a broad spectrum of depressive symptoms while possibly reducing typical side effects like sexual dysfunction and sedation, often seen with other antidepressants.

Clinical efficacy and safety

First approved by the FDA in 2013, vortioxetine has been available for over a decade in more than 83 countries globally. Vortioxetine

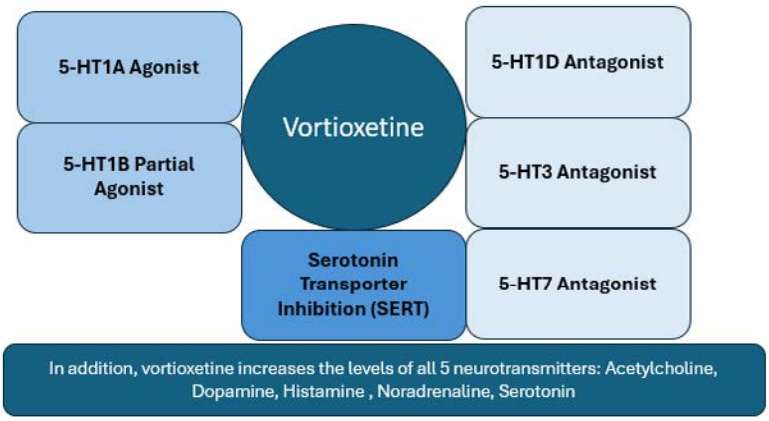

Figure 1: Multimodal mechanism of action of vortioxetine

is supported by evidence from clinical trials involving over 7 000 patients. Several meta-analyses have demonstrated its efficacy in reducing depressive symptoms in MDD.[26]

In a Cochrane review, Koesters et al. (2017) analysed data from 15 studies involving 7 746 participants, including seven trials comparing vortioxetine with a placebo and eight comparing it to SNRIs.[27] Vortioxetine showed higher effectiveness than placebo in terms of response rates (Mantel-Haenszel risk ratio [RR]: 1.35, 95% confidence interval [CI]: 1.22–1.49; 14 studies with 6 220 participants), remission rates (RR: 1.32, 95% CI: 1.15–1.53; 14 studies, 6 220 participants), and reduction in depressive symptoms (mean difference [MD]: -2.94, 95% CI: -4.07 to -1.80; 14 studies, 5 566 participants) as measured by the Montgomery-Asberg Depression Rating Scale (MADRS). Rates of treatment discontinuation showed no significant difference between vortioxetine and placebo (RR: 1.05, 95% CI: 0.93–1.19; 14 studies, 6 220 participants). Additionally, some evidence from eight studies indicated minimal clinically meaningful differences in response or remission rates when comparing vortioxetine to SNRIs.

According to Koesters et al. (2017), there was no significant difference between trials comparing vortioxetine to duloxetine or venlafaxine ($p = 0.09$), but total dropout rates were significantly lower for vortioxetine compared to venlafaxine (RR 0.70, 95% CI 0.52 to 0.93; $p = 0.02$; 2 studies, 767 participants).[27] There was no statistically significant difference between vortioxetine and duloxetine for total dropouts (RR 0.96, 95% CI 0.76–1.21; $p = 0.74$; 6 studies, 2 392 participants).[26]

According to De Diego-Adeliño et al. (2021), switching to vortioxetine as a treatment yielded notable improvements in effectiveness, daily functioning, and quality of life when compared to agomelatine.[28] Comparative analyses further indicated that vortioxetine may achieve higher remission rates and experience fewer discontinuations due to adverse effects than other antidepressants, including bupropion, citalopram, sertraline, or venlafaxine.

Findings from this extensive real-world study by Mattingly et al. (2022), which included 737 patients treated with vortioxetine for 24 weeks, highlight its effectiveness and tolerability in managing MDD within a large, diverse patient group representative of everyday clinical practice.[29] Patients with MDD who received vortioxetine showed clinically meaningful improvements in overall functioning, depressive and cognitive symptoms, performance, and health-related quality of life over the six-month treatment period. In this study, the authors reported that the most substantial benefits were observed when vortioxetine was used as a first-line therapy.

Vortioxetine's safety profile is favourable, showing a lower incidence of common antidepressant-related adverse effects, such as sexual dysfunction compared to traditional SSRIs.[30]

A recent study by Huang et al. (2022) reported improved cognitive performance in patients with MDD.[26] Thus, vortioxetine's favourable tolerability partnered with a lower risk of withdrawal symptoms make vortioxetine a viable long-term treatment option, particularly for patients requiring cognitive support alongside mood stabilisation.[28]

Vortioxetine in the South African context

In South Africa, access to mental healthcare is limited, particularly in rural and underserved areas.[31] Vortioxetine, while available, is often not the first-line treatment due to its higher cost compared to generic SSRIs. However, for patients who do not respond adequately to SSRIs or experience intolerable side effects, vortioxetine offers a valuable alternative.

The **South African Society of Psychiatrists** (**SASOP) guidelines** recommend the use of both pharmacotherapy and psychotherapy for MDD, with first-line treatment typically involving SSRIs.[32] Vortioxetine is increasingly used in patients who do not respond well to SSRIs or SNRIs and may be considered for individuals with cognitive symptoms of MDD.

The **South African Depression and Anxiety Group (SADAG)** plays an advocacy role in ensuring broader access to newer antidepressants and proper treatment across both urban and rural healthcare settings.[33]

Key Information for pharmacists from the approved South African Package Insert[12]

Scheduling: Schedule 5.

Pharmacological class: Vortioxetine is classified as a serotonin modulator and stimulator (SMS) antidepressant.

Indications: Vortioxetine is indicated for the treatment of major depressive disorder and to reduce the risk of relapse.

Formulation: Vortioxetine is available in 5 mg, 10 mg, 15 mg, and 20 mg film-coated tablets, each containing vortioxetine hydrobromide.

Dosing: The typical initial dosage of vortioxetine is 10 mg once daily, which can be taken with or without food. Based on how the patient responds and tolerates the medication, the dosage can be increased to 20 mg. The dose can also be adjusted according to the patient's needs, with a maximum of 20 mg per day or reduced to as low as 5 mg daily if necessary. For older adults or patients prone to side effects, it is advised to start at 5 mg daily. There is limited information available on the use of doses higher than 10 mg per day in elderly individuals. After symptom relief, continuing treatment for at least six months is recommended to maintain the antidepressant effect. No dosage modification is required for patients with renal or hepatic impairments.

Elimination: Vortioxetine has a relatively long half-life of 66 hours, allowing for once daily dosing.

Drug interactions

Pharmacists should be aware of the following important interactions when dispensing vortioxetine:

CYP450 enzyme interactions: Vortioxetine is primarily broken down by the CYP2D6 enzyme. Care must be taken when administering it alongside potent inducers of CYP3A4, such as rifampicin, carbamazepine, or phenytoin, as these can diminish vortioxetine's effectiveness. Conversely, strong CYP2D6 inhibitors, such as bupropion, quinidine, fluoxetine, and paroxetine, can elevate vortioxetine levels in the bloodstream, potentially requiring a reduction in the vortioxetine dose.

Serotonin syndrome: Concurrent use of vortioxetine with other serotonergic medications — such as triptans, SSRIs, SNRIs, opioids, or St. John's Wort — heightens the risk of developing serotonin syndrome, a severe and potentially fatal condition. Vigilant monitoring is essential when vortioxetine is combined with any serotonergic agent.

Monoamine oxidase inhibitors (MAOIs): Vortioxetine is contraindicated with MAOIs due to the risk of serotonin syndrome. A gap of at least 14 days is required between discontinuing an MAOI and starting vortioxetine. Similarly, vortioxetine must be stopped for at least 14 days before beginning an MAOI. The antibiotic, linezolid, a weak MAOI, should also be avoided in patients taking vortioxetine, and if combined, close monitoring for serotonin syndrome is necessary.

Medications that lower the seizure threshold: Antidepressants with serotonergic properties, including vortioxetine, can reduce the seizure threshold. Caution is advised when vortioxetine is used together with medications that can also lower the seizure threshold, such as tricyclic antidepressants, SSRIs, SNRIs, antipsychotics (phenothiazines, thioxanthones, butyrophenones), mefloquine, bupropion, or tramadol.

These considerations are crucial to ensure the safe dispensing of vortioxetine and the prevention of adverse interactions.

Use in pregnancy and lactation

Safety and efficacy in pregnant women have not been established, therefore the package insert recommends against the use of vortioxetine during pregnancy due to potential neonatal risks and complications.

Women are advised not to breastfeed while on vortioxetine due to the lack of safety data and potential excretion in breast milk.

Special populations

The focus on patient populations, such as the elderly and those with renal or hepatic impairment, is crucial for pharmacists to consider.

The safety and efficacy of vortioxetine in children and adolescents aged less than 18 years have not been established.

Elderly: Exposure to vortioxetine is up to 27% higher in elderly patients, necessitating caution, due to the increased risk of side-effects in this population group.

Renal and hepatic impairment: No dose adjustment is needed in patients with renal or hepatic impairment.

Contraindications

Vortioxetine is contraindicated in individuals with known hypersensitivity to vortioxetine.

Special warnings and precautions for use

Haemorrhage: Vortioxetine may lead to irregular bleeding manifestations, including ecchymosis, purpura, and other bleeding events, such as those affecting the gastrointestinal or gynaecological systems. Patients should be monitored carefully if they are on anticoagulants or medications that impact platelet function (e.g. atypical antipsychotics, phenothiazines, many tricyclic antidepressants, nonsteroidal anti-inflammatory drugs [NSAIDs], or aspirin) and if they have known bleeding tendencies or disorders.

Hyponatremia: Hyponatremia, likely resulting from inappropriate antidiuretic hormone secretion (SIADH), has been observed with antidepressants that act on serotonin (SSRIs/SNRIs). Caution is advised in patients who are at higher risk, including the elderly, those with liver cirrhosis, or those on other medications known to induce hyponatremia. If symptomatic hyponatremia occurs, discontinuing vortioxetine should be considered, and suitable medical treatment should be provided.

Side effects

Vortioxetine is generally well-tolerated, with a side effect profile comparable to other antidepressants.

The most frequent adverse effect is nausea, occurring in approximately 20% of patients, particularly within the first two weeks of treatment, which tends to be transient. Other common adverse effects include vomiting, constipation, dizziness, and headache.

Unlike many SSRIs and SNRIs, vortioxetine has a lower incidence of sexual dysfunction. This factor might contribute to better adherence and treatment outcomes.

There is an emphasis on the increased risk of suicidal thoughts, especially in individuals under the age of 25.

There is a possible risk of developing hyponatremia (low sodium levels), particularly in elderly patients, those with liver cirrhosis, or individuals taking other medications, such as diuretics, which can also contribute to hyponatremia.

Reporting any suspected adverse reactions after a medicine has been authorised is crucial as it enables ongoing assessment of the medication's benefit/risk profile. Healthcare professionals are encouraged to report any suspected adverse events to the South

African Health Products Regulatory Authority (SAHPRA) using the '6.04 Adverse Drug Reactions Form', which is available online in the publications section of SAHPRA's website at https://www.sahpra.org.za/Publications/Index/8.

The most recent 2024 vortioxetine approved South African package insert provides further details, which complement the previously extracted information, ensuring that pharmacists have a comprehensive understanding of vortioxetine's usage, safety, and necessary precautions.

Conclusion

Depression remains a major public health challenge in South Africa, with significant social and economic repercussions. Vortioxetine offers a promising treatment option for individuals with MDD, particularly those with cognitive impairments or who do not respond well to first-line SSRIs. Continued research and clinical trials will be essential in further understanding the full therapeutic potential of vortioxetine and ensuring its accessibility to all South Africans in need of effective mental health treatment.

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Conflict of interest

The author declarer that there are no conflicts of interest.

Ethical approval

Ethical approval was not required.

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