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THE IMPACT OF VORTIOXETINE ON SEXUAL FUNCTION: A SYSTEMATIC REVIEW OF AVAILABLE CLINICAL DATA AND PHARMACOLOGICAL MECHANISMS

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ABSTRACT

Background: Sexual dysfunction is a common and often treatment-limiting side effect of antidepressants, especially SSRIs and SNRIs, impacting quality of life, adherence, and clinical outcomes in patients with major depressive disorder (MDD).
Objective: This systematic review assesses clinical and neurobiological evidence on the effects of vortioxetine—a multimodal antidepressant—on sexual function, comparing it to other antidepressants and exploring its potential to alleviate SSRI-induced sexual dysfunction.
Methods: A systematic literature search was conducted (PubMed, Embase, Web of Science, Cochrane Library) through June 2025, following PRISMA guidelines. Included studies reported on sexual outcomes in adults treated with vortioxetine, using validated tools such as ASEX or CSFQ.
Results: Vortioxetine was consistently associated with lower rates of treatment-emergent sexual dysfunction (TESD) than conventional SSRIs and SNRIs. Rates ranged from 1.1% to 16.2%, often similar to placebo and markedly lower than with paroxetine or venlafaxine. Case studies and observational data suggested vortioxetine may also improve pre-existing sexual dysfunction, including post-SSRI sexual dysfunction (PSSD), particularly in libido and orgasmic function. The most favorable outcomes were seen at doses between 5–15 mg/day.
Conclusions: Vortioxetine shows a favorable sexual tolerability profile and may reverse SSRI-induced sexual dysfunction. Its multimodal serotonergic activity likely underpins these benefits. While evidence supports its use in patients at risk for or experiencing TESD, more head-to-head trials with standardized outcome measures are needed.

KEYWORDS

Vortioxetine, Sexual Dysfunction, Orgasmic Dysfunction, 5-HT Receptor Modulation, SSRI-Induced Sexual Dysfunction, Antidepressant Side Effects

CITATION

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Introduction

Sexual dysfunction is among the most common adverse effects of antidepressant medications and represents a significant barrier to maintaining long-term pharmacotherapy in patients with major depressive disorder (MDD). These side effects negatively impact quality of life, self-esteem, and interpersonal relationships, and often lead to treatment discontinuation and depressive relapse. [1]Given the prevalence and clinical implications of this issue, there is growing interest in newer generations of antidepressants with a more favorable sexual tolerability profile.

Sexual dysfunction is one of the most frequent and distressing adverse effects associated with antidepressant treatment, particularly with selective serotonin reuptake inhibitors (SSRIs) and serotonin–norepinephrine reuptake inhibitors (SNRIs). The prevalence of antidepressant-induced sexual dysfunction (AISD) has been estimated to range from 30% to as high as 70%, depending on the population studied, the assessment method, and the specific agent prescribed. The impact of these side effects extends well beyond the sexual domain: they compromise quality of life, contribute to interpersonal strain, and represent one of the leading causes of non-adherence and premature discontinuation of pharmacological treatment in major depressive disorder (MDD). As such, sexual dysfunction is not merely a secondary concern but a central determinant of therapeutic success.

AISD typically manifests across all phases of the sexual response cycle. Patients frequently report diminished sexual desire (hypoactive sexual desire disorder), delayed orgasm or anorgasmia, and difficulties with physiological arousal, such as erectile dysfunction in men or impaired lubrication in women. While these symptoms can occur in untreated depression itself, their exacerbation or emergence under pharmacotherapy has been consistently linked to serotonergic overstimulation. Specifically, excess serotonin in brain regions

such as the spinal cord, hypothalamus, and limbic system exerts inhibitory effects on dopaminergic and noradrenergic pathways, neurotransmitter systems that are critical for sexual motivation, arousal, and orgasm.

The clinical relevance of AISD has prompted increasing attention to the pharmacological mechanisms underlying these adverse effects. SSRIs, by strongly and selectively inhibiting the serotonin transporter (SERT), are highly effective in enhancing serotonergic tone but lack modulatory actions on other receptor systems. This pharmacological profile explains both their therapeutic efficacy and their high burden of sexual side effects. SNRIs, such as venlafaxine and duloxetine, add noradrenergic reuptake inhibition but continue to produce TESD in a large proportion of patients. By contrast, antidepressants with multimodal or mixed mechanisms—such as bupropion, agomelatine, and vortioxetine—have been investigated for their ability to treat depression while minimizing disruption of sexual functioning.

Vortioxetine, introduced in the past decade, is a novel antidepressant with a distinct multimodal mechanism of action. It not only inhibits SERT but also modulates several serotonin receptor subtypes, including antagonism at 5-HT_3, 5-HT_7, and 5-HT_1D receptors, partial agonism at 5-HT_1B receptors, and full agonism at 5-HT_1A receptors. This receptor profile is thought to restore balance between serotonergic, dopaminergic, and noradrenergic activity, thereby preserving functions typically impaired by SSRIs. Beyond mood improvement, vortioxetine has been associated with cognitive benefits and a comparatively benign tolerability profile, particularly in relation to sexual function.

Emerging evidence suggests that vortioxetine may be associated with substantially lower rates of treatment-emergent sexual dysfunction (TESD) compared with SSRIs and SNRIs. Several randomized controlled trials have reported incidence rates of TESD in vortioxetine-treated patients that are close to placebo levels, while observational and switch studies indicate that vortioxetine may even improve pre-existing dysfunction, particularly in patients transitioning from SSRIs. Importantly, improvements have been noted across multiple domains, including libido, orgasmic function, and overall sexual satisfaction. Case reports further highlight its potential in alleviating post-SSRI sexual dysfunction (PSSD), a rare but highly distressing condition characterized by persistent sexual dysfunction after discontinuation of SSRIs.

Despite these encouraging findings, gaps remain. Many clinical trials did not prioritize sexual function as a primary endpoint, and validated assessment tools such as the Arizona Sexual Experiences Scale (ASEX) or the Changes in Sexual Functioning Questionnaire (CSFQ) were inconsistently employed. The influence of sex, age, comorbidities, and dose on vortioxetine's sexual tolerability is incompletely understood, and long-term data are still scarce. Moreover, while vortioxetine appears advantageous, it is not entirely free of sexual side effects; rare cases of dysfunction have been reported even at therapeutic doses[2].

Given these considerations, a systematic review synthesizing both clinical trial and real-world evidence is warranted. By integrating data from randomized controlled studies, open-label trials, cohort studies, and case reports, the present work aims to provide a comprehensive assessment of vortioxetine's impact on sexual function. Particular emphasis is placed on comparing vortioxetine with other antidepressants, evaluating its role in patients with SSRI-induced dysfunction, and exploring the neurobiological mechanisms that may account for its distinctive profile. The findings are intended to guide clinical decision-making and inform individualized treatment strategies for patients in whom sexual health is a critical component of overall recovery from depression.

Vortioxetine is an antidepressant with a unique multimodal mechanism of action, combining serotonin transporter (SERT) inhibition with activity at multiple serotonin receptors (5-HT3, 5-HT7, and 5-HT1D antagonism; 5-HT1B partial agonism; and 5-HT1A agonism)[3]. This pharmacodynamic profile provides not only antidepressant efficacy but also potential benefits in cognitive function, sleep regulation, and the mitigation of sexual side effects commonly seen with serotonergic agents[4].

Data from randomized clinical trials indicate that the incidence of sexual dysfunction during vortioxetine treatment (1.6–1.8%) is comparable to or only slightly higher than placebo (1.0%) and significantly lower than with traditional selective serotonin reuptake inhibitors such as venlafaxine or duloxetine[5]. Moreover, real-world evidence (RWE) studies suggest improvements in sexual functioning, particularly in patients previously treated with SSRIs, as confirmed by clinical narrative analyses and patient-reported outcome measures[6].

Despite these promising findings, the impact of vortioxetine on sexual function remains underexplored, especially in the context of long-term use, sex differences, and psychiatric comorbidities. This systematic review aims to synthesize and evaluate the available clinical and pharmacological data on the sexual effects of vortioxetine, drawing on findings from both controlled trials and real-world clinical practice, and to explore the neurobiological mechanisms underlying its observed effects.

Search Strategy

A systematic literature search was conducted following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines to identify relevant studies evaluating the impact of vortioxetine on sexual function. We searched PubMed, Embase, Web of Science, and the Cochrane Library from database inception to June 2025 using combinations of the following keywords: "vortioxetine," "sexual dysfunction," "sexual function," "antidepressants," "SSRI-induced sexual dysfunction," and "pharmacology." Boolean operators (AND/OR) were applied to optimize the search. The search was supplemented by manually screening the reference lists of key articles and reviews.

Eligibility Criteria

Studies were included if they met the following criteria:

- Published in English.
- Human studies involving adults (≥18 years).
- Clinical trials (randomized controlled trials [RCTs], open-label studies, or observational studies) evaluating the effects of vortioxetine on sexual function.
- Studies comparing vortioxetine to placebo or other antidepressants, or assessing its impact on SSRI-induced sexual dysfunction.
- Reports providing original data on sexual function outcomes, including validated measures such as the Arizona Sexual Experiences Scale (ASEX), Changes in Sexual Functioning Questionnaire (CSFQ), or patient-reported outcomes.

Results

Clinical investigations into vortioxetine's effects on sexual function reveal a nuanced picture, shaped by dose, treatment duration, population characteristics, and assessment methods. Across multiple studies, vortioxetine consistently demonstrated a more favorable sexual side effect profile compared to conventional antidepressants, particularly SSRIs and SNRIs.

A long-term open-label extension study by Baldwin et al. (2012) involving 535 patients with MDD found that only six patients (1.1%) reported treatment-emergent adverse events related to sexual dysfunction, including decreased libido, erectile dysfunction, and abnormal orgasm. Importantly, none of these patients discontinued treatment due to these effects, suggesting a generally tolerable profile for vortioxetine over extended use.[7]

In contrast, a case report by Dönmezler et al. (2021) highlighted the potential for dose-dependent sexual side effects. A 38-year-old female patient reported decreased libido after self-initiating vortioxetine at 20 mg/day. Following a structured dose reduction to 10 mg/day and implementation of sensate focus exercises, her sexual functioning improved notably. This case underscores the possibility of sexual dysfunction at higher doses, even with vortioxetine, and suggests clinical utility in dose adjustment as a mitigation strategy[8].

Comparative data further illustrate vortioxetine's relative advantage. Clayton et al. (2014) reviewed sexual dysfunction incidence across antidepressants, noting that SSRIs such as sertraline, paroxetine, and fluoxetine frequently induce SD in 58–73% of users, primarily via serotonin-mediated suppression of sexual desire and orgasm. In contrast, agents like bupropion and vortioxetine exhibit lower SD incidence, likely due to their multimodal mechanisms that include dopaminergic and noradrenergic activity, and partial 5-HT1A agonism, which may support sexual function[9].

Jacobsen et al. (2015), cited by Dönmezler et al., also found that switching patients from SSRIs to vortioxetine alleviated SSRI-induced sexual dysfunction in some cases, with symptom improvement particularly in orgasmic function[10]. These effects likely stem from vortioxetine's 5-HT3 antagonism, which may reduce serotonin-induced inhibition of sexual reflexes.

Collectively, these findings suggest that while vortioxetine is not entirely devoid of sexual side effects, its risk is lower than that associated with standard SSRIs and SNRIs. Moreover, dose management and patient-specific approaches—such as combining pharmacological and behavioral interventions—may further optimize outcomes in patients experiencing treatment-emergent sexual dysfunction.

Further support for vortioxetine's favorable sexual tolerability comes from large-scale pooled analyses and real-world data. A pooled analysis of randomized controlled trials (RCTs) by Baldwin et al. (2016) examined treatment-emergent sexual dysfunction (TESD) in patients with major depressive disorder (MDD) or generalized anxiety disorder (GAD) treated with vortioxetine. The incidence of TESD in treatment-naive patients receiving vortioxetine was 16.2%, versus 34.3% for duloxetine and 35.1% for escitalopram.

Importantly, TESD rates in vortioxetine-treated patients were comparable to placebo (14.9%), particularly at doses ≤15 mg/day[11].

Similarly, real-world evidence from the French cohort of the RELIEVE study (Etain et al., 2022) highlighted that 6 months of vortioxetine treatment led to a significant improvement in overall functioning, with sexual function contributing positively to patient-reported quality-of-life outcomes[12]. While the study did not focus exclusively on sexual dysfunction, improvements in interpersonal relationships and vitality indirectly suggest a reduction in sexual side effects, particularly in contrast with prior SSRI/SNRI treatment.

Montejo et al. (2019) provided additional insight into the clinical management of TESD. Their review emphasized that the most frequent sexual side effects across antidepressants include decreased libido, anorgasmia, and delayed ejaculation, especially among SSRIs like paroxetine, which demonstrates the highest incidence of TESD (up to 70%)[13]. By contrast, vortioxetine, thanks to its multimodal serotonin modulation and limited impact on dopaminergic and noradrenergic systems, shows a considerably lower risk profile. Their recommendations strongly advocate for vortioxetine as a first-line alternative in sexually active patients concerned with TESD.

These findings align with conclusions from Jing & Straw-Wilson (2016), who reviewed pharmacological strategies to mitigate SSRI-induced sexual dysfunction. Vortioxetine was highlighted as a promising alternative due to its low observed rates of anorgasmia and libido reduction in controlled trials[14].

Taken together, both controlled and real-world studies reinforce the consistent finding that vortioxetine is associated with significantly fewer sexual side effects than traditional SSRIs and SNRIs. The risk of TESD with vortioxetine appears dose-dependent, with higher rates at 20 mg, but remains markedly lower than that of most other agents in its class. This evidence positions vortioxetine as a valuable therapeutic option in MDD treatment, particularly for patients who prioritize sexual function or have previously experienced SSRI-induced TESD[15].

A pivotal retrospective cohort study by De Luca et al. (2022) explored the efficacy of vortioxetine in 13 male patients diagnosed with PSSD following SSRI use. Over 12 months, patients treated with vortioxetine (10–20 mg/day) showed significant improvement in International Index of Erectile Function (IIEF-15) scores (mean increase from 7.3 to 17.7; $p = 0.003$), with therapeutic success ranging from 33.3% to 60% in terms of restoring sexual function[16]. Notably, these improvements were especially marked in domains such as orgasmic function and libido. Importantly, no major side effects were reported, and adjunct use of nutraceuticals further supported recovery in some individuals.

Mechanistically, Alvarez et al. (2014) detailed the pharmacological profile of vortioxetine, emphasizing its multimodal action: inhibition of the serotonin transporter (SERT) and modulation of various 5-HT receptors, including antagonism at 5-HT_3 and 5-HT_7 and agonism at 5-HT_1A. This receptor profile allows vortioxetine to increase extracellular levels of serotonin, dopamine, and norepinephrine, particularly in brain regions such as the medial prefrontal cortex and hippocampus[17]. This neurochemical footprint likely contributes to its low incidence of sexual dysfunction and its potential to reverse SSRI-induced impairments.

In contrast, Abler et al. (2011) used fMRI in a placebo-controlled crossover study to examine the neural correlates of SSRI-induced sexual dysfunction. Compared to bupropion and placebo, paroxetine was associated with reduced activation in the anterior cingulate cortex (ACC), ventral striatum, and midbrain—areas implicated in sexual arousal and reward processing. Meanwhile, bupropion enhanced activation in similar regions, confirming the serotonergic contribution to SD and underscoring the advantage of agents like vortioxetine that preserve dopaminergic tone[18].

Taken together, the clinical efficacy of vortioxetine in both SSRI-naïve and SSRI-experienced patients—alongside neuroimaging and mechanistic evidence—positions it as a promising agent for managing antidepressant-induced sexual dysfunction. Its multimodal receptor activity appears to counteract the serotonergic suppression typical of SSRIs, while maintaining antidepressant efficacy and cognitive benefits.

Several observational and open-label studies have provided further insight into vortioxetine's sexual tolerability in naturalistic settings. In one prospective cohort, patients with MDD who had discontinued SSRIs due to sexual side effects were directly switched to vortioxetine. After 12 weeks, improvements were noted not only in depressive symptoms but also in specific aspects of sexual functioning such as orgasmic latency and overall satisfaction, as measured by the CSFQ. Importantly, these changes occurred without loss of antidepressant efficacy, underscoring vortioxetine's dual benefit in mood stabilization and sexual health[19].

Another strand of evidence comes from subgroup analyses focusing on age. Younger adults (<40 years) reported lower rates of treatment-emergent sexual dysfunction compared to older cohorts, suggesting that

baseline vulnerability to TESD may interact with both age and medication choice. While the sample sizes were limited, this trend highlights the importance of tailoring antidepressant therapy across the lifespan[20].

Finally, evidence from switch studies demonstrates that vortioxetine may provide symptomatic relief even in treatment-resistant populations. Patients with high psychiatric comorbidity—including anxiety disorders and somatoform conditions—experienced reductions in both self-reported and clinician-rated sexual dysfunction after switching, despite long histories of poor tolerability with other antidepressants. These findings add real-world relevance to the clinical trial data.

Discussion

This systematic review provides a comprehensive evaluation of the available clinical data on the effects of vortioxetine on sexual function in individuals with major depressive disorder (MDD). The findings indicate that vortioxetine consistently exhibits a more favorable sexual side effect profile compared to traditional serotonergic antidepressants, including SSRIs and SNRIs.

A growing body of evidence from both controlled trials and real-world studies supports the notion that vortioxetine is associated with lower rates of treatment-emergent sexual dysfunction (TESD). Montejo et al. demonstrated in a 3-month prospective study that switching to vortioxetine significantly reduced TESD, with the SALSEX total score dropping from 10.32 to 3.78 ($p < 0.001$). Improvements were evident across key domains including libido, orgasm, and arousal, with 83.8% of patients reporting clinical benefit, and 43.2% describing it as "greatly improved". Furthermore, real-world data show that switching to vortioxetine often enables patients to continue antidepressant therapy that they would otherwise abandon due to sexual side effects. This is critical because TESD is a major contributor to poor adherence and relapse in MDD. According to Montejo et al., over 83% of patients maintained vortioxetine treatment post-switch, and many showed parallel improvements in depressive symptoms, emphasizing its dual efficacy[21].

The favorable profile of vortioxetine may be attributed to its unique multimodal mechanism of action. Unlike pure SSRIs, vortioxetine acts as a serotonin transporter inhibitor while also modulating multiple serotonin receptor subtypes, including antagonism at 5-HT_3 and 5-HT_7, partial agonism at 5-HT_1B, and agonism at 5-HT_1A receptors[22]. These properties likely mitigate serotonergic inhibition of sexual function, while enhancing dopaminergic and noradrenergic neurotransmission—systems crucial to sexual desire and arousal.

Notably, a case report by Sutar et al. provided rare documentation of vortioxetine's efficacy in improving erectile dysfunction (ED) that preceded depressive symptoms. The patient, previously unresponsive to sertraline, mirtazapine, and phosphodiesterase inhibitors, exhibited significant sexual function restoration following treatment with vortioxetine. Improvement in Arizona Sexual Experience Scale (ASEX) scores was rapid and substantial—from 26 at baseline to 5 after just two weeks.The efficacy of vortioxetine in improving pre-existing sexual dysfunction—rather than merely avoiding TESD—has significant clinical implications. It challenges the assumption that antidepressant-induced sexual dysfunction is inevitable or only reversible upon discontinuation. Moreover, this effect appears dose-sensitive; while most improvements are observed at standard doses (10–15 mg/day), some evidence suggests an increase in TESD rates at higher doses (20 mg/day), warranting careful dose titration based on individual tolerability[23].

In sum, the cumulative evidence underscores vortioxetine's advantageous profile in preserving or restoring sexual function, without compromising antidepressant efficacy. It should be considered a first-line therapeutic alternative in sexually active patients or in those with a history of TESD. Further research, particularly placebo-controlled trials focused on sexual function as a primary outcome, would be valuable in confirming these findings across broader populations.

While vortioxetine appears advantageous in minimizing treatment-emergent sexual dysfunction (TESD), several considerations further contextualize its clinical utility. A comparative clinical study by Nakajima et al. specifically addressed direct switching from other antidepressants in patients with well-controlled depression who developed TESD. Patients switched to vortioxetine experienced significantly less deterioration in mood (as measured by QIDS-J) and global functioning (GAF) compared to those switched to escitalopram, suggesting vortioxetine may offer superior maintenance of antidepressant response while mitigating sexual side effects.

Moreover, economic modeling highlights an important dimension of tolerability. A 2022 systematic review and network meta-analysis by Kearns et al. found that although trazodone ranked best overall in safety and cost minimization, vortioxetine consistently exhibited one of the lowest risks of sexual dysfunction among modern antidepressants (OR 1.41, CrI 0.79–2.57), significantly outperforming agents like venlafaxine or

sertraline[24]. However, vortioxetine treatment incurred the highest total healthcare costs in eight of nine European countries evaluated, primarily due to higher acquisition cost, not adverse event management—a finding with implications for formulary decisions in public health settings.

A broader systematic review by Citrome (2013) confirmed vortioxetine's favorable safety-to-benefit ratio. Across several pivotal trials, the number needed to treat (NNT) for response was 7 (95% CI 6–9), while the number needed to harm (NNH) for discontinuation due to any adverse event was 36 (95% CI 24–70)[25]. These results underscore the drug's tolerability, especially when juxtaposed with the high prevalence of TESD reported for SSRIs, where rates up to 70% have been documented.

Despite these promising findings, heterogeneity in trial designs, duration, and outcome assessments must be acknowledged. Few studies used validated scales such as ASEX or CSFQ as primary outcomes, and definitions of sexual dysfunction varied. Furthermore, direct head-to-head trials comparing vortioxetine to SSRIs or bupropion with sexual function as a primary endpoint remain limited, representing a gap in current evidence.

Another limitation relates to dose dependency. Several studies indicated that TESD risk may increase with vortioxetine doses exceeding 15 mg/day, particularly among patients with prior SSRI-induced dysfunction. While dose reduction was effective in some cases. This strategy is not universally applicable, especially when higher doses are needed for adequate antidepressant response.

An additional clinical perspective highlights the need for individualized treatment approaches in patients experiencing antidepressant-induced sexual dysfunction. The review by Baldwin et al. (2018) noted that while vortioxetine is generally associated with a lower incidence of treatment-emergent sexual dysfunction compared to SSRIs and SNRIs, clinicians should remain vigilant for persistent or treatment-resistant sexual side effects in some patients. Moreover, the authors emphasized that patient-centered strategies—such as dose adjustments, switching to agents like bupropion, or incorporating non-pharmacological therapies (e.g., mindfulness, exercise, or even testosterone therapy)—may enhance sexual recovery, especially among women with complex sexual response profiles or comorbid anxiety disorders[26].

The overall tolerability profile of vortioxetine plays a key role in treatment continuity, which indirectly influences patient outcomes related to sexual functioning. According to Thase et al. (2015), vortioxetine was associated with low rates of treatment-emergent adverse events, with nausea being the most commonly reported side effect, and generally mild in intensity. Importantly, discontinuation rates due to adverse effects were consistently low across short- and long-term trials, suggesting that vortioxetine is well tolerated in real-world use. This tolerability is especially relevant in the context of sexual dysfunction, as adverse effects are a leading cause of non-adherence in antidepressant therapy. The ability to maintain treatment without debilitating side effects increases the likelihood of full symptomatic remission, which can further enhance sexual health through indirect pathways—improved mood, energy, and relational functioning. Thus, even in the absence of focused sexual function outcomes, evidence from tolerability studies reinforces the broader conclusion that vortioxetine may offer advantages in both adherence and overall quality of life, making it a viable choice for patients who prioritize sexual side effect profiles when selecting an antidepressant[27].

The collective evidence suggests that vortioxetine occupies a distinctive position among modern antidepressants. Unlike SSRIs, which predominantly amplify serotonergic tone and thereby suppress sexual function, vortioxetine's multimodal receptor activity appears to balance neurotransmitter systems in a way that preserves or enhances sexual response. This pharmacological nuance places vortioxetine closer to agents like bupropion or agomelatine, which are often considered when sexual side effects are a primary clinical concern[28].

Another important point relates to functional outcomes. Preservation of sexual function has downstream effects on quality of life, treatment adherence, and relational stability. Patients who maintain sexual health during antidepressant therapy are more likely to sustain treatment long enough to achieve remission, reducing the risk of relapse. This functional benefit distinguishes vortioxetine not only as a pharmacological agent but as a driver of holistic recovery[29].

Nonetheless, important limitations remain. Most RCTs considered sexual dysfunction as a secondary or exploratory endpoint, and standardized tools like ASEX or CSFQ were inconsistently applied. Case reports highlight individual variability, with rare instances of significant dysfunction even at low doses. Furthermore, economic analyses suggest vortioxetine's acquisition cost may limit its widespread adoption, particularly in resource-constrained settings. These challenges underscore the need for pragmatic trials that assess both sexual outcomes and cost-effectiveness in routine practice.

Taken together, vortioxetine emerges as a clinically valuable option for patients with MDD in whom sexual health is a treatment priority. By offering a balance between efficacy, tolerability, and functional outcomes, vortioxetine helps bridge the gap between symptomatic remission and meaningful quality of life improvements.

In conclusion, the available literature positions vortioxetine as a promising antidepressant for patients at risk of or suffering from sexual dysfunction. Its multimodal serotonergic action appears to preserve sexual function better than conventional SSRIs and SNRIs, and it may even reverse SSRI-induced persistent dysfunction in some cases. Nevertheless, individual variability, economic considerations, and the need for further targeted trials must be taken into account when positioning vortioxetine within therapeutic algorithms for MDD.

Conclusions

Sexual dysfunction remains a critical and often under-recognized barrier to effective and sustained antidepressant therapy. This systematic review demonstrates that vortioxetine, owing to its distinct multimodal mechanism of action, offers a clinically meaningful advantage over conventional serotonergic antidepressants in terms of sexual tolerability. Across randomized clinical trials, pooled analyses, real-world studies, and case reports, vortioxetine consistently showed lower rates of treatment-emergent sexual dysfunction (TESD), and in some cases, even improvements in pre-existing sexual impairments—particularly those induced by prior SSRI treatment.

The sexual safety profile of vortioxetine appears dose-sensitive, with optimal outcomes generally observed at 5–15 mg/day. Its receptor profile, particularly 5-HT1A agonism and 5-HT3 antagonism, likely contributes to preservation of sexual function by modulating serotonergic inhibition and enhancing dopaminergic and noradrenergic activity. In both male and female patients, vortioxetine demonstrated favorable outcomes across all phases of sexual response—desire, arousal, and orgasm—making it a valuable therapeutic option for sexually active individuals with MDD or those with prior antidepressant-induced sexual side effects.

Despite its promise, further independent, long-term, head-to-head trials are warranted, especially those employing standardized sexual function scales and focusing on patient subgroups (e.g., age, gender, comorbidities). Additionally, economic factors and individual response variability should be considered in clinical decision-making.

In summary, vortioxetine emerges as an evidence-based, patient-centered alternative for the treatment of major depressive disorder in individuals for whom preservation or restoration of sexual function is a treatment priority.

Authors' Contributions Statement

All authors have read and agreed with the published version of the manuscript.

All authors have reviewed and agreed to the publication of the final version of the manuscript.

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