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ANTIDEPRESSANT-ASSOCIATED SEXUAL DYSFUNCTION (AASD) – FROM PATHOPHYSIOLOGY TO CLINICAL MANAGEMENT: A LITERATURE REVIEW

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ABSTRACT

Major Depressive Disorder (MDD) presents a global challenge, with pharmacotherapy based on SSRIs and SNRIs remaining the standard of care. Despite clinical efficacy, the tolerability of these agents is often limited by iatrogenic Antidepressant-Associated Sexual Dysfunction (AASD), a leading cause of therapeutic non-adherence and so-called "hidden non-compliance," resulting in disease relapse. This paper provides a comprehensive literature review aimed at updating knowledge on epidemiology, neurobiological mechanisms extending beyond the serotonin hypothesis, and modern management strategies for AASD, with particular emphasis on Post-SSRI Sexual Dysfunction (PSSD). Databases including PubMed, ScienceDirect, Cochrane Library, and Google Scholar were searched, focusing on studies utilizing validated psychometric tools (e.g., ASEX, PRSexDQ). The analysis reveals a significant disparity between spontaneously reported AASD rates (10–15%) and those detected via screening (70–80%). A risk hierarchy was confirmed: paroxetine and venlafaxine demonstrate the highest iatrogenic potential, attributed partly to nitric oxide synthase inhibition and dopaminergic suppression. Vortioxetine and bupropion are characterized by a neutral profile, offering a safe alternative. The review also confirms the growing clinical importance of PSSD as a persistent complication. AASD requires proactive monitoring in daily practice. Results support moving away from a "wait and see" strategy in favor of routine screening and early implementation of switching or augmentation strategies. Personalization of pharmacotherapy is crucial for maintaining patient adherence and ensuring long-term depression treatment efficacy.

KEYWORDS

Antidepressants, Sexual Dysfunction, PSSD, SSRIs, Vortioxetine, Bupropion

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Introduction

Modern psychiatry faces an unprecedented epidemiological challenge. As indicated by the latest data published in *The Lancet* by the Global Burden of Disease research group, the COVID-19 pandemic contributed to a more than 27% increase in the global prevalence of major depressive disorder (MDD), making depression one of the leading causes of disability [21]. In response to this crisis, pharmacotherapy based on serotonergic agents remains the first line of defense. However, the treatment paradigm is evolving: the goal is no longer solely the reduction of mood symptoms, but the full restoration of social and interpersonal functioning. In this context, antidepressant-associated sexual dysfunction (AASD) is emerging as one of the primary barriers to achieving full functional remission. Sexual dysfunction related to treatment is not merely a "cosmetic" defect of therapy but represents a significant clinical problem with a complex etiology. Recent studies confirm that patients experiencing sexual side effects carry a significantly higher risk of discontinuing pharmacotherapy [18]. This phenomenon leads to a vicious cycle: treatment is interrupted, depression relapses, and subsequent attempts at pharmacotherapy encounter psychological resistance from patients fearing a renewed loss of sexual function. Despite this, the problem of AASD remains marginalized. The literature points to a cognitive dissonance: while clinicians prioritize cardiovascular or metabolic safety, patients—particularly within the young adult population—consider the preservation of sexual function an equivalent priority [18]. Furthermore, the years 2020–2024 have brought concerning reports regarding Post-SSRI Sexual Dysfunction (PSSD), suggesting that in some patients, neurobiological changes may persist even after medication withdrawal. This calls into question the conventional understanding of the reversibility of adverse effects [8].

The aim of this study is a critical analysis of the available literature, focusing on three pillars: updating epidemiological data, understanding mechanisms that extend beyond the serotonergic theory, and evaluating modern therapeutic strategies. Particular emphasis is placed on differentiating depressive symptoms from treatment effects and on the role of personalized medicine in selecting medications with a sexual function-

sparing profile. Studies included in this analysis met the following criteria: (1) publication in a peer-reviewed scientific journal; (2) adult population diagnosed with MDD or anxiety disorders; (3) use of objective sexual function assessment tools (e.g., ASEX, CSFQ-14, PRSexDQ scales). Case reports (except for rare PSSD complications) and animal model studies without clinical translation were excluded.

Methodology

This paper is a narrative literature review based on a systematic search of the PubMed, ScienceDirect, Cochrane Library, and Google Scholar databases, covering publications released between 2000 and 2025. The search strategy utilized terms such as: "antidepressant-associated sexual dysfunction" (AASD), "PSSD", "SSRI side effects", "quality of life", and "pharmacological management," combined using Boolean operators (AND/OR). Priority was given to high-quality evidence (Level of Evidence I–II), including randomized controlled trials (RCTs), meta-analyses, and systematic reviews. The final analysis included only full-text articles in English that utilized validated psychometric tools (such as ASEX, CSFQ-14, and PRSexDQ), ensuring the objectivity and reliability of the gathered data.

Results

Discrepancy in Epidemiological Data

Literature analysis reveals a fundamental discrepancy between data obtained through routine clinical interviews and the results of targeted screening. In observational studies based on spontaneous reporting, the incidence of AASD is estimated at 2% to 15% [22]. This result is falsely low, stemming from communication barriers and a lack of patient awareness.In contrast to these data are the findings of studies utilizing structured questionnaires. Classic research [17] and more recent analyses cited in clinical guidelines [18] indicate that the actual incidence of sexual dysfunction during SSRI therapy reaches 50–70%, and in the case of certain substances, even 80%. Studies employing sensitive tools, such as the PRSexDQ or ASEX questionnaires, confirm that this problem is pervasive rather than marginal.

Gender and Demographic Differences

The symptom profile exhibits sexual dimorphism. Women more frequently report desire disorders (hypoactive sexual desire disorder) and anorgasmia, while erectile dysfunction and delayed ejaculation predominate in men [7]. Notably, although age is a natural risk factor for sexual dysfunction, research indicates that among young adults (aged 18–40), AASD is the strongest predictor of treatment discontinuation, leading to the dangerous phenomenon of "hidden non-compliance" [2].

Risk Stratification of Antidepressants

Based on a review of comparative studies, antidepressants were categorized according to their iatrogenic potential in the sexual sphere (Table 1).

High-Risk Group (SSRIs and SNRIs)

Selective Serotonin Reuptake Inhibitors (SSRIs) and Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs) carry the highest risk, estimated at 60–80% [2].

- **Paroxetine:** Associated with the most severe adverse effect profile due to potent inhibition of the serotonin transporter (SERT), as well as additional anticholinergic activity and inhibition of nitric oxide synthase (NOS), which directly impairs the erectile mechanism [26].
- **Venlafaxine and Duloxetine:** Exhibit risk levels similar to SSRIs, often dose-dependent (the noradrenergic effect typically emerges only at higher doses, which may slightly mitigate the profile compared to pure SSRIs).

Favorable Profile Group (Sparing Agents)

There is strong evidence that medications with non-serotonergic or multimodal mechanisms do not negatively impact sexual function, serving as first-line alternatives for sexually active patients.

- **Bupropion:** As a Norepinephrine-Dopamine Reuptake Inhibitor (NDRI), multiple studies show an incidence of dysfunction at placebo levels [25]. Its dopaminergic mechanism may even improve libido in patients with anhedonia, making it a drug of choice for switching or augmentation strategies [3].
- **Vortioxetine:** Distinguished by its unique multimodal profile. Head-to-head studies comparing vortioxetine with escitalopram showed a statistically significant advantage for vortioxetine in terms of preserving desire and arousal. This is attributed not only to SERT blockade but primarily to antagonism of 5-HT3 and 5-HT7 receptors and agonism of 5-HT1A, which bypasses the effect of sexual "blunting" [11], [18].

Table 1. Classification of antidepressants by AASD risk
(Author's own compilation based on analyzed literature)

Risk Category	Medications (INN)	Estimated Incidence*	Dominant Mechanism
High Risk	Paroxetine, Venlafaxine, Clomipramine	60% – 80%	Potent, non-selective inhibition of the serotonin transporter (SERT). Specifically for paroxetine: anticholinergic activity and inhibition of nitric oxide synthase (NOS).
Moderate/High Risk	Sertraline, Citalopram, Escitalopram, Duloxetine	50% – 70%	Non-specific stimulation of postsynaptic 5-HT2A and 5-HT2C receptors, leading to dopamine suppression in the reward system and inhibition of sexual reflexes.
Low Risk	Vortioxetine, Mirtazapine, Trazodone	10% – 25%	Receptor modulation: 5-HT3 and 5-HT7 antagonism (vortioxetine); 5-HT2A and 5-HT2C blockade (mirtazapine, trazodone). Bypassing the dopamine inhibition pathway.
Neutral/Favorable Profile	Bupropion, Agomelatine, Moclobemide	< 10% (placebo level)	Non-serotonergic mechanism. Bupropion: pro-dopaminergic activity (NDRI). Agomelatine: resynchronization of circadian rhythms and 5-HT2C antagonism.

**Data refer to studies utilizing structured diagnostic tools (e.g., PRSexDQ, ASEX).*

Discussion

The comprehensive literature analysis conducted in this study allows for the formulation of fundamental conclusions that redefine the role of sexual dysfunction in modern psychopharmacotherapy. The gathered evidence clearly indicates that Antidepressant-Associated Sexual Dysfunction (AASD) is no longer treated as a secondary, "cosmetic" defect of treatment; instead, it has risen to the rank of a key clinical challenge determining long-term prognosis in major depressive disorder (MDD) [16], [18]. Below is a detailed analysis of the conclusions categorized by epidemiological, neurobiological, pharmacological, and clinical domains.

Epidemiology and "Hidden Non-Compliance"

The first and most striking conclusion from the review is the drastic disproportion between the perception of clinicians and the actual experience of patients. As large-scale cross-sectional studies demonstrate, up to 70% of patients treated with selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) experience clinically significant adverse sexual symptoms [2], [18]. This phenomenon makes AASD—alongside weight gain—the most common cause of treatment non-adherence.

Particularly significant in this context is research [18] that sheds light on systemic errors in psychiatric diagnostics. The authors demonstrated that routine, spontaneous reporting is a highly inefficient tool, detecting only the "tip of the iceberg" of patients' sexual problems. The use of structured diagnostic tools, such as the Psychotropic-Related Sexual Dysfunction Questionnaire (PRSexDQ), revealed the presence of dysfunction in the vast majority of respondents who did not report these complaints during casual conversation. The clinical implications of this finding are critical. Undetected AASD leads to "hidden non-compliance," where the patient, unwilling to confront the physician with an embarrassing problem, independently reduces the drug dose or completely discontinues therapy [17]. This leads to depressive relapses that the physician misinterprets as treatment resistance, often escalating drug doses (and thus intensifying the dysfunction) instead of changing the pharmacological profile of the therapy. The conclusion is unambiguous: active monitoring of the sexual sphere using scales (e.g., ASEX, CSFQ-14) must become a standard of care rather than an optional addition [2], [18].

Neurobiological Mechanisms: More Than Just Serotonin

In the light of current knowledge, a simplified model explaining AASD solely by the stimulation of 5-HT2 serotonin receptors is insufficient. More recent neurobiological analyses emphasize the crucial role of the disturbed balance between the serotonergic and dopaminergic systems. Chronically elevating serotonin levels in the nucleus accumbens and other structures of the mesolimbic pathway leads to a secondary inhibition of dopamine release through the stimulation of 5-HT2C receptors [23]. Clinically, this manifests not only as a decrease in libido but as a broader spectrum of symptoms, including sexual anhedonia (lack of pleasure despite orgasm), apathy, and emotional blunting. Patients often describe this state as "being behind glass" or a loss of the ability to feel intense emotions, which negatively affects partner relationships and overall quality of life [6], [14].

The peripheral mechanism is equally important [26]. It has been shown that certain antidepressants (particularly paroxetine) inhibit nitric oxide synthase (NOS) activity. Nitric oxide is a key mediator of vasodilation necessary for erection in men and physiological lubrication and genital engorgement in women. Understanding this mechanism is crucial for selecting targeted treatment—it explains why phosphodiesterase type 5 (PDE-5) inhibitors, which enhance the NO pathway, are effective in symptomatic treatment.

Evidence-Based Pharmacotherapy

The literature review allows for the creation of an evidence-based medicine (EBM) hierarchy of antidepressants regarding their impact on sexual function. The literature is exceptionally consistent in this regard [22], [19]. Paroxetine and venlafaxine remain at the pole of highest iatrogenic risk [22]. Due to potent serotonin transporter (SERT) blockade and (in the case of paroxetine) anticholinergic activity, these drugs should be avoided as first-line treatments in sexually active patients unless specific clinical indications exist.

Conversely, drugs with novel mechanisms occupy a well-established "safe" pole:

- **Vortioxetine:** Thanks to its unique multimodal profile—encompassing not only serotonin transporter inhibition but primarily 5-HT3 receptor antagonism and 5-HT1A agonism—this drug shows a significant advantage over classic SSRIs. In head-to-head studies, vortioxetine was observed to have a significantly lower impact on desire and orgasm compared to escitalopram [11], [18].
- **Bupropion:** As a norepinephrine-dopamine reuptake inhibitor (NDRI), this drug bypasses serotonergic pathways, maintaining its status as the "gold standard" in sexual function-sparing therapies [25]. Its pro-dopaminergic mechanism may even improve libido in patients with a dominant anhedonia component.

The conclusion drawn from this hierarchy is the necessity of treatment personalization. Initiating therapy with neutral-profile drugs (vortioxetine, bupropion) in young and sexually active patients should be considered the standard of care to prevent AASD [13], [18].

Post-SSRI Sexual Dysfunction (PSSD)

Special, alarming attention in the literature of the last five years has been devoted to Post-SSRI Sexual Dysfunction (PSSD). Studies [20] and [8] document cases of patients suffering from persistent genital anesthesia, anhedonia, and lack of libido despite complete discontinuation of pharmacotherapy and elimination of the drug from the body. While the etiology of PSSD remains unclear, research hypotheses are evolving toward permanent neuroplastic changes. They suggest that the phenomenon may be rooted in epigenetic changes (e.g., DNA methylation) leading to permanent desensitization of 5-HT1A receptors or changes in the expression of androgen receptors in the hypothalamus [1], [5].

Official recognition of PSSD by the European Medicines Agency (EMA) represents a turning point, forcing clinicians to change their approach to informed consent [4], [20]. There is an ethical and legal imperative to inform patients about this rare but potentially irreversible risk before initiating SSRI treatment. PSSD currently represents an area of unmet medical need, requiring intensified basic research into mechanisms for reversing neuroadaptation.

Management Algorithms

Based on the conducted systematic review, an effective AASD management algorithm can be formulated. In the event of bothersome symptoms, a "wait and see" strategy is rarely effective, as tolerance to sexual side effects seldom develops [17], [2]. The most effective, evidence-based strategy is **"switching"** to a drug with a different mechanism of action (e.g., from sertraline to vortioxetine or bupropion) [13], [18]. This allows for the elimination of the causative factor while maintaining control over depressive symptoms. An alternative is the **augmentation** strategy. Adding bupropion to an SSRI (in doses of 150–300 mg) can counteract dopaminergic suppression, restoring drive and libido, as confirmed by research [3]. For symptomatic treatment in men, adding PDE-5 inhibitors (sildenafil, tadalafil) is highly effective in combating erectile dysfunction [26]. Unfortunately, for women, evidence for the efficacy of PDE-5 inhibitors is limited

and inconclusive, indicating a gap in pharmacological options for female sexual dysfunction. Simultaneously, the literature dictates caution regarding **"drug holidays."** As indicated by [24], periodic discontinuation of drugs with a short half-life (e.g., paroxetine, venlafaxine) is associated with a high risk of discontinuation syndrome (dizziness, paresthesia, irritability) and serum concentration instability, which may lead to a relapse of affective symptoms and worsened patient cooperation.

In summary, sexual dysfunction represents an inherent part of the risk associated with depression pharmacotherapy; however, modern medicine offers tools for effective management. The key to success lies in moving away from a paternalistic treatment model toward a partnership where the patient's quality of life—including sexual satisfaction—is treated with the same gravity as the remission of mood symptoms [10], [13].

Conclusions

The conducted systematic literature analysis allows for the formulation of fundamental conclusions regarding the role of sexual dysfunction in modern psychopharmacotherapy. The gathered evidence unequivocally indicates that antidepressant-associated sexual dysfunction (AASD) is no longer treated as a secondary, "cosmetic" defect of treatment, but has risen to the rank of a key clinical challenge determining long-term prognosis in major depressive disorder (MDD). Detailed conclusions are presented below across four primary clinical domains.

Epidemiological Analysis and the "Diagnostic Gap"

Epidemiological analysis reveals a drastic disproportion between clinicians' perceptions and the actual experiences of patients. As demonstrated by recent cross-sectional studies, including the key work [18], the prevalence of sexual disorders in the population treated with SSRIs and SNRIs is dramatically underestimated in routine practice. While this issue is reported by only 2–15% of patients during spontaneous clinical interviews, the application of structured diagnostic tools (such as the PRSexDQ questionnaire) reveals that it affects the majority of patients—reaching up to 70–80% in specific subgroups. This "diagnostic gap" carries serious therapeutic consequences. Patients, feeling shame or viewing sexual dysfunction as an inevitable price of treatment, rarely initiate conversation on the subject. This leads to a phenomenon defined in the literature as "hidden non-compliance." Patients, unable to accept iatrogenic sexual anhedonia or erectile dysfunction, independently reduce dosages or discontinue therapy entirely without informing their physician. The clinician, interpreting the relapse of depressive symptoms as treatment failure, paradoxically increases the dose of the offending drug, closing a "vicious cycle" of therapeutic failure. In light of available scientific evidence [18], it must be recognized that the failure to actively monitor the sexual sphere constitutes a clinical error that directly threatens the stability of remission.

Revision of First-Line Treatment Standards

The literature review necessitates a revision of first-line treatment standards for depression, particularly in sexually active patients. The current paradigm, which automatically positions classic SSRIs (such as paroxetine or escitalopram) as the gold standard, is challenged by data regarding their tolerability profile. Head-to-head comparative studies, including randomized clinical trials cited by [18] and [11], provide strong evidence for a clear hierarchy of sexual safety among antidepressants.

Vortioxetine—due to its unique multimodal mechanism (including 5-HT3 receptor antagonism and 5-HT1A agonism)—and bupropion—acting via norepinephrine and dopamine reuptake inhibition—exhibit the most favorable safety profiles. Unlike pure SERT inhibitors, these drugs do not cause "emotional blunting" or libido suppression. Research [11] demonstrated that switching from an SSRI to vortioxetine resulted in a statistically significant improvement in sexual function while maintaining antidepressant efficacy. The conclusion is unambiguous: in patients for whom preserving sexual function is a priority, initiating treatment with high-risk drugs (e.g., paroxetine, venlafaxine) without specific clinical indications is sub-optimal practice. Sparing agents (bupropion, vortioxetine, as well as mirtazapine) should be considered as first-line treatments, representing a significant shift in decision-making algorithms.

Post-SSRI Sexual Dysfunction (PSSD)

One of the most concerning findings in the literature of the last five years is the confirmation of the existence of Post-SSRI Sexual Dysfunction (PSSD). Work [8] sheds new light on the long-term safety of pharmacotherapy, challenging the dogma of the full reversibility of adverse effects after drug elimination from the system.

PSSD appears as a real iatrogenic phenomenon with a still unclear etiology, potentially involving permanent epigenetic changes (e.g., silencing of receptor expression in the hypothalamus) or neuroplastic remodeling of dopaminergic pathways [5]. Symptoms such as persistent genital anesthesia, pleasureless

orgasm, and loss of libido can persist for years, devastating patients' quality of life. The findings from [8] impose a new ethical and legal obligation on physicians: the necessity of obtaining informed consent that includes the risk (albeit rare) of permanent complications. PSSD requires further intensive research into neuroplasticity mechanisms to develop effective therapeutic strategies, as medicine currently lacks a causal treatment for this syndrome.

Modern Standards: Monitoring and Personalization

In light of the presented data, it is essential to implement new standards of clinical management. First, the routine use of sexual function assessment scales (such as the Arizona Sexual Experience Scale—ASEX [15] or the Changes in Sexual Functioning Questionnaire—CSFQ-14 [12]) must become a standard component of every psychiatric visit, analogous to monitoring weight or blood pressure. Only active screening for symptoms allows for early intervention (switching or augmentation) and prevents the discontinuation of therapy [13], [18]. The future of depression treatment lies in personalization that extends beyond simple drug selection based on symptoms. Research emphasizes the importance of individual factors in maintaining treatment continuity. The key to optimization is the inclusion of pharmacogenetics [16]. Polymorphisms of the *CYP2D6* gene can drastically alter the metabolism of many antidepressants. Patients who are "poor metabolizers" are exposed to significantly higher blood concentrations of the drug at standard dosages, which translates directly into increased severity of adverse effects, including sexual dysfunction, as confirmed by CPIC consortium guidelines [9]. Implementing pharmacogenetic testing into clinical practice would allow for precise dose adjustment and the avoidance of medications that a patient cannot effectively metabolize. Personalization of therapy—understood as the integration of genetic profiling, patient preferences, and the drug's receptor profile—represents the only path toward improving recovery rates and the quality of life for patients with depression.

In summary, sexual dysfunction is not an inevitable cost of treating depression, but rather an avoidable complication. Shifting from a reactive to a proactive approach, based on sound pharmacological knowledge and open communication with the patient, is essential for modern psychiatry.

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