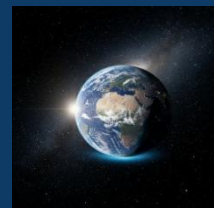




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Sexual Dysfunction Associated with Selective Serotonin Reuptake Inhibitors: Mechanisms, Clinical Manifestations, Management Strategies, and Post-SSRI Sexual Dysfunction - A Narrative Review

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Abstract

Background: Selective serotonin reuptake inhibitors (SSRIs) are first-line treatments for major depressive disorder and anxiety disorders. Sexual dysfunction is among their most common adverse effects, impairing quality of life and treatment adherence. Increasing attention has focused on post-SSRI sexual dysfunction (PSSD), in which symptoms persist after antidepressant discontinuation.

Objective: To summarize current evidence on sexual physiology, mechanisms and clinical features of antidepressant-induced sexual dysfunction (AISD) and PSSD, and available management strategies.

Methods: A narrative review of English-language literature published between 2020 and 2026 was conducted using PubMed and Google Scholar. Original studies, systematic reviews, meta-

analyses, randomized trials, observational studies, and relevant case reports were included, along with essential earlier landmark publications.

Results: SSRI-associated sexual dysfunction may affect desire, arousal, erection, ejaculation, orgasm, and sexual satisfaction. Prevalence estimates vary because of differences in study populations and assessment methods. Symptoms usually improve after dose reduction or discontinuation, but may persist as PSSD. Proposed mechanisms include serotonergic dysregulation, altered dopaminergic and neuroendocrine signaling, epigenetic changes, TRP ion channel dysfunction, neurotoxicity, and gut–brain axis disturbances, although none has been confirmed. Management includes dose reduction, switching to antidepressants with a lower risk of sexual adverse effects, pharmacological augmentation, and selected non-pharmacological interventions. No evidence-based treatment for PSSD has been established.

Conclusions: Sexual dysfunction is a major adverse effect of SSRI therapy. Routine assessment before and during treatment may facilitate recognition and management. High-quality prospective studies are needed to clarify the epidemiology, mechanisms, and optimal treatment of PSSD.

Keywords: *selective serotonin reuptake inhibitors; antidepressant - induced sexual dysfunction; post-SSRI sexual dysfunction; PSSD; depression; anxiety disorders; sexual dysfunction; adverse effects; psychopharmacology.*

1. Introduction

Selective serotonin reuptake inhibitors (SSRIs) are among the most frequently prescribed antidepressants worldwide and are currently considered first-line pharmacological treatment for major depressive disorder as well as several anxiety disorders because of their well-established efficacy, favorable tolerability, and improved safety profile compared with older classes of antidepressants. [1,2] In addition to their approved psychiatric indications, SSRIs are widely used in the treatment of obsessive-compulsive disorder, panic disorder, social anxiety disorder, post-traumatic stress disorder, and premenstrual dysphoric disorder.

[1,3]

Although SSRIs are generally well tolerated, they are associated with a broad spectrum of adverse effects. [1,30] Among these, sexual dysfunction is one of the most common and clinically relevant complications of treatment. [2,4] SSRI-induced sexual dysfunction may affect every phase of the human sexual response cycle, including sexual desire, arousal,

erection, vaginal lubrication, ejaculation, orgasm, and overall sexual satisfaction. [2,5] Because these adverse effects are often underreported unless patients are specifically questioned, their true prevalence is believed to be substantially underestimated. [1,2]

Sexual dysfunction associated with antidepressant treatment has important clinical consequences. [2,6] It may negatively affect self-esteem, intimate relationships, and overall quality of life, while also representing one of the leading causes of poor adherence and premature discontinuation of antidepressant therapy. [1,2,4] Consequently, inadequate recognition of sexual adverse effects may compromise treatment effectiveness and increase the risk of relapse or recurrence of the underlying psychiatric disorder. [1]

Interpretation of sexual symptoms in patients receiving antidepressants is further complicated by the fact that depression itself is an independent risk factor for impaired sexual functioning. [1,7] Reduced libido, diminished sexual satisfaction, anhedonia, and impaired arousal frequently occur as symptoms of depressive illness, making it difficult to distinguish disease-related dysfunction from treatment-emergent adverse effects in routine clinical practice. [2,7] Therefore, assessment of baseline sexual function before initiating antidepressant therapy is essential for appropriate diagnosis and subsequent management. [1,6]

Growing attention has recently been focused on post-SSRI sexual dysfunction (PSSD), a condition characterized by the persistence-or, in some cases, the emergence-of sexual symptoms after discontinuation of serotonergic antidepressants. [8,9] In contrast to conventional antidepressant-induced sexual dysfunction (AISD), which typically improves following dose reduction or drug withdrawal, PSSD may persist for months or even years. [8,10] Patients commonly report persistent loss of libido, genital numbness, orgasmic dysfunction, erectile or lubrication difficulties, and emotional blunting, despite discontinuation of treatment. [8,11] Although the European Medicines Agency (EMA) acknowledged persistent sexual dysfunction following SSRI and SNRI treatment in 2019, the epidemiology, biological mechanisms, and optimal management of PSSD remain incompletely understood. [8,9,12]

The aim of this narrative review is to summarize current evidence regarding the physiology of sexual function, the pathophysiological mechanisms underlying SSRI-associated sexual dysfunction, the clinical characteristics of AISD and PSSD, available therapeutic strategies, and current gaps in knowledge requiring further investigation.

2. Materials and Methods

2.1 Research materials and methods

This study is a narrative literature review focusing on the impact of selective serotonin reuptake inhibitors (SSRIs) on sexual function, with particular emphasis on SSRI-induced sexual dysfunction (AISD) and post-SSRI sexual dysfunction (PSSD).

A literature search was conducted using the PubMed and Google Scholar databases. The following search terms were used individually and in various combinations: *"selective serotonin reuptake inhibitors"*, *"SSRIs"*, *"sexual dysfunction"*, *"sexual adverse effects"*, *"libido"*, *"erectile dysfunction"*, *"ejaculatory dysfunction"*, *"orgasmic dysfunction"*, *"female sexual dysfunction"*, *"post-SSRI sexual dysfunction"*, *"PSSD"*, *"pathophysiology"*, *"management"*, and *"antidepressants"*.

The literature search primarily included original research articles, systematic reviews, narrative reviews, meta-analyses, randomized and non-randomized clinical trials, observational studies, and relevant case reports published in English between 2020 and 2026. Publications were considered eligible if they addressed the epidemiology, clinical presentation, pathophysiological mechanisms, diagnosis, risk factors, or management of sexual dysfunction associated with SSRI therapy. In addition, relevant publications were identified through manual screening of the reference lists of the selected articles.

2.2 Research results

The literature search identified publications evaluating the effects of SSRIs on sexual function in patients treated for depressive and anxiety disorders. The included literature comprised systematic reviews, narrative reviews, clinical trials, observational studies, and case reports investigating the prevalence, clinical manifestations, biological mechanisms, diagnosis, and management of SSRI - induced sexual dysfunction (AISD) and post - SSRI sexual dysfunction (PSSD).

The reviewed studies differed in study design, patient characteristics, duration of antidepressant treatment, specific SSRIs investigated, and reported clinical outcomes. The principal findings of the included publications are presented and discussed in the following sections.

3. Results

3.1 Physiology of Sexual Function

Normal sexual function is a complex physiological process involving the interaction of psychological, neurobiological, hormonal, and vascular factors. [1] The classical model of the

human sexual response consists of four sequential phases: **desire, arousal, orgasm, and resolution.**

Each phase requires coordinated integration of the central and peripheral nervous systems, the endocrine system, and vascular mechanisms responsible for adequate blood flow to the genital organs. [1]

The **desire phase** is characterized by sexual motivation, erotic thoughts, and interest in sexual activity. The **arousal phase** involves physiological changes that prepare the body for sexual activity, including penile erection in men and vaginal lubrication in women. The **orgasm phase** represents the culmination of the sexual response and is characterized by coordinated activation of the central nervous system together with rhythmic contractions of the pelvic floor muscles accompanied by an intense sensation of pleasure. Finally, the **resolution phase** involves the gradual return of physiological parameters to baseline and the completion of the sexual response.

Regulation of sexual function depends on a complex interplay between excitatory and inhibitory neurotransmitters. Among the most important are **dopamine, serotonin, noradrenaline, nitric oxide (NO), and oxytocin**, each of which contributes to different aspects of sexual function. [1,13]

Among these neurotransmitters, dopamine is generally considered the principal facilitator of sexual motivation and reward, whereas serotonin predominantly exerts inhibitory effects on sexual desire, ejaculation, and orgasm. Nitric oxide plays a crucial role in penile erection and genital vasodilation, while oxytocin contributes to orgasm and pair bonding. [1,15] The physiological balance between these neurotransmitter systems is essential for normal sexual function and provides the biological basis for understanding SSRI-induced sexual dysfunction.

Table 1. Neurotransmitters and hormones involved in the regulation of sexual function

MEDIATOR	PHYSIOLOGICAL ROLE IN SEXUAL FUNCTION
dopamine	facilitates sexual desire, motivation, reward processing, and orgasm
serotonin	inhibits libido, ejaculation, and orgasm; modulates sexual behaviour
norepinephrine	enhances sexual arousal and sympathetic activation during orgasm
nitric oxide (NO)	mediates vasodilation required for penile erection and clitoral engorgement
oxytocin	promotes sexual arousal, orgasm, pair bonding, and emotional intimacy
prolactin	contributes to the post - orgasmic refractory period
testosterone	major hormonal regulator of sexual desire in both sexes
estrogens	support vaginal lubrication, genital blood flow, and sexual responsiveness

Source: author's own elaboration based on Atmaca [1].

Hormonal regulation also plays an essential role in maintaining normal sexual function.

Testosterone, estrogens, progesterone, and prolactin influence sexual desire, arousal, and reproductive physiology. [1,14] Disruption of the physiological balance between neurotransmitter systems, hormonal regulation, and vascular function may contribute to the development of sexual dysfunction. [1,2]

Because serotonin plays a central role in the regulation of sexual function, pharmacological agents that enhance serotonergic neurotransmission, particularly selective serotonin reuptake inhibitors (SSRIs), may interfere with these physiological mechanisms and contribute to the development of sexual dysfunction. [1,2,13]

3.2 Sexual Dysfunction in Depressive Disorders

Depression and anxiety disorders are independent risk factors for sexual dysfunction. Consequently, sexual dysfunction may be present before the initiation of antidepressant treatment. The prevalence of sexual dysfunction is considerably higher among patients with depression than in the general population, indicating that impaired sexual function is a common component of the clinical presentation of depressive disorders. [1,2,7]

The most frequently reported manifestations include decreased libido, erectile dysfunction, reduced sexual satisfaction, and difficulties achieving orgasm. The severity and pattern of symptoms may vary depending on the severity of depression, disease duration, and the presence of concomitant medical conditions. [2,7]

Depression is associated with dysregulation of the mesolimbic dopaminergic reward system, which contributes to anhedonia, reduced motivation, impaired reward processing, and

diminished sexual desire. These neurobiological alterations may further exacerbate sexual dysfunction independently of antidepressant treatment. [7,15]

Assessment of sexual function before initiating pharmacological treatment represents an important component of the diagnostic evaluation and facilitates appropriate interpretation of symptoms that develop during therapy. Sexual dysfunction observed after treatment initiation may be attributable to the underlying psychiatric disorder, antidepressant therapy, or a combination of both. [1,2,6]

Because depressive symptoms substantially overlap with the adverse effects of antidepressant medications, distinguishing disease-related sexual dysfunction from treatment-emergent dysfunction may be challenging in routine clinical practice. Particular attention should therefore be paid to sexual dysfunction associated with selective serotonin reuptake inhibitors (SSRIs), as it represents one of the most frequently reported adverse effects of this drug class and constitutes an important cause of impaired quality of life and premature discontinuation of antidepressant therapy. [1,2,4,6]

This overlap between disease-related and treatment-emergent sexual dysfunction represents one of the major diagnostic challenges in clinical practice and provides the rationale for distinguishing SSRI-induced sexual dysfunction from sexual dysfunction associated with the underlying psychiatric disorder. [1,2]

3.3 SSRI - Induced Sexual Dysfunction (AISD)

Sexual dysfunction occurring during antidepressant therapy is commonly referred to as **antidepressant-induced sexual dysfunction (AISD)**. [1,2] Because the present review focuses specifically on selective serotonin reuptake inhibitors (SSRIs), the term

SSRI-induced sexual dysfunction will be used throughout this review whenever referring to sexual dysfunction associated with this class of antidepressants.

It is important to distinguish **SSRI-induced sexual dysfunction (AISD)** from **post-SSRI sexual dysfunction (PSSD)**. [8,9] SSRI-induced sexual dysfunction develops during active antidepressant treatment and, in most cases, improves following dose reduction or discontinuation of the medication. [1,6] In contrast, PSSD is characterized by the persistence or, in some cases, the emergence of sexual symptoms despite discontinuation of SSRI therapy. [8-10] Owing to its distinct clinical course and incompletely understood pathophysiology, PSSD is discussed separately in a subsequent section of this review.

3.3.1 Epidemiology

Sexual dysfunction is among the most common adverse effects associated with selective serotonin reuptake inhibitors (SSRIs). [1,4,23] The reported prevalence of SSRI - induced sexual dysfunction ranges from **30% to 80%**, depending on the study population, assessment methods, and diagnostic criteria used. [1,2,4]

The true prevalence of SSRI - induced sexual dysfunction is likely to be underestimated. [2,5] Many patients do not report sexual problems spontaneously because of embarrassment or reluctance to discuss intimate concerns, while healthcare professionals do not routinely assess sexual function during follow-up visits. [1,2] Consequently, the prevalence observed in clinical practice may be lower than that reported in studies using validated questionnaires and structured assessments. [4,5,23]

Table 2. Relative risk of sexual dysfunction among SSRIs

DRUG	RELATIVE RISK OF SEXUAL DYSFUNCTION
PAROXETINE	highest
SERTRALINE	high
CITALOPRAM	high
FLUOXETINE	moderate
ESCITALOPRAM	lower
FLUVOXAMINE	lowest

Source: Author's own elaboration based on Hutters & Giraldi [16], Atmaca [1], Dagostin Ferraz et al. [4], and Zini & Turecki [5].

Among individual SSRIs, **paroxetine** has consistently been associated with the highest risk of sexual dysfunction, whereas **escitalopram** and particularly **fluvoxamine** appear to be associated with a relatively lower frequency of sexual adverse effects. [1,4,16] However, sexual dysfunction has been reported with all SSRIs, and differences between individual agents should

be interpreted cautiously because available evidence originates from studies with heterogeneous methodologies and patient populations. [4,5,32]

In addition, evidence suggests that the incidence of sexual adverse effects increases with higher SSRI doses, whereas antidepressant efficacy does not appear to improve proportionally beyond standard therapeutic doses. [17]

3.3.2 Clinical Manifestations

Sexual dysfunction associated with SSRI therapy may affect every phase of the sexual response cycle, including sexual desire, arousal, orgasm, and overall sexual satisfaction.

[2,4,5,24] The most commonly reported clinical manifestations are summarized in **Table 3**.

Table 3. Most common clinical manifestations of SSRI-induced sexual dysfunction

MANIFESTATION	TYPICAL CLINICAL PRESENTATION
decreased libido	reduced or absent sexual desire
erectile dysfunction	difficulty achieving or maintaining an erection
delayed ejaculation	delayed or absent ejaculation
orgasmic dysfunction	delayed, weak or absent orgasm
female sexual dysfunction	reduced sexual arousal, impaired vaginal lubrication and anorgasmia

Source: Author's own elaboration based on Rothmore [2], Atmaca [1], Zini & Turecki [5] and Dagostin Ferraz et al. [4]

Symptoms may occur individually or coexist in the same patient, affecting multiple phases of the sexual response simultaneously. [1,2]

Clinical manifestations usually develop within **days to weeks** after initiation of SSRI therapy. [1,6] Their severity is variable and may differ according to the specific SSRI prescribed, the administered dose, and individual patient susceptibility. [1,4,17]

Delayed orgasm and delayed ejaculation are generally considered the most characteristic manifestations of SSRI-induced sexual dysfunction, reflecting the inhibitory effects of enhanced serotonergic neurotransmission on orgasmic function. [1,5,24]

3.3.3 Risk Factors

Several factors have been associated with an increased risk of developing sexual dysfunction during SSRI therapy. The most important include **higher antidepressant doses, longer treatment duration, older age, male sex, pre-existing sexual dysfunction, greater severity of depression, and the presence of concomitant medical conditions**. [1,4,5]

These factors should be considered during treatment planning and follow-up, as they may help identify patients at increased risk of developing antidepressant-induced sexual dysfunction. [1,6]

3.3.4 Impact on Quality of Life and Treatment Adherence

Sexual dysfunction associated with SSRI therapy may substantially impair patients' quality of life, negatively affect intimate relationships, reduce self-esteem, and adversely influence psychological well-being. [1,2,4,6] In some patients, these symptoms may contribute to increased rumination, feelings of guilt, and emotional distress. [2,6,7]

Consequently, sexual adverse effects represent one of the leading causes of poor treatment adherence, premature discontinuation of antidepressant therapy, and an increased risk of relapse or recurrence of depressive and anxiety disorders. [2-6] In addition, persistent sexual dysfunction may negatively influence patients' confidence in treatment and weaken the therapeutic relationship between patients and healthcare professionals. [6,11]

Table 4. Comparison of the clinical features of antidepressant-induced sexual dysfunction (AISD) and post-SSRI sexual dysfunction (PSSD)

FEATURE	AISD	PSSD
onset	during treatment	during or after treatment
duration	usually reversible	persistent
improves after discontinuation	usually yes	no
genital numbness	rare	typical
evidence - based treatment	available options	none established
main symptoms	libido, orgasm, ED	libido, genital numbness, anhedonia, ED

Source: Author's own elaboration based on references [1,6,8-11].

3.4 Proposed Pathophysiological Mechanisms Underlying PSSD

3.4.1 Persistent Serotonergic Dysregulation

The primary mechanism of action of selective serotonin reuptake inhibitors (SSRIs) is inhibition of the serotonin transporter (SERT), resulting in increased serotonin concentrations within the synaptic cleft. [1,10] During the early phase of treatment, activation of presynaptic **5-HT1A** and **5-HT1B autoreceptors** transiently reduces serotonergic neuronal activity. With continued treatment, these autoreceptors gradually undergo desensitization, leading to sustained enhancement of serotonergic neurotransmission. [1]

Enhanced serotonergic activity inhibits dopaminergic pathways and suppresses physiological mechanisms involved in erection, vaginal lubrication, ejaculation, and orgasm thereby explaining the development of sexual dysfunction during SSRI therapy. [1,2,13] However, it remains unclear why these alterations persist in only a subset of patients after discontinuation of therapy, suggesting that mechanisms beyond the acute pharmacological effects of SSRIs may contribute to the development of PSSD. [8-11]

3.4.2 Neurochemical and Hormonal Imbalance

In addition to serotonergic dysregulation, alterations involving other neurotransmitter systems and hormonal pathways have been proposed to contribute to SSRI-associated sexual dysfunction. [1,10]

Increased serotonergic activity suppresses dopaminergic neurotransmission, which plays a central role in sexual motivation, reward processing, and libido. [1,13] Furthermore, reduced nitric oxide (NO) activity has been proposed to contribute to erectile dysfunction through impaired vasodilation and reduced genital blood flow. [1,2]

Other proposed mechanisms include disturbances in oxytocin signaling, elevated prolactin concentrations, and dysregulation of the hypothalamic-pituitary-gonadal axis, potentially resulting in reduced testosterone levels and impaired sexual function. [1,10,12]

Although these mechanisms provide plausible explanations for antidepressant-induced sexual dysfunction (AISD), they do not adequately explain the persistence of symptoms after discontinuation of SSRI therapy and therefore cannot fully account for the development of PSSD. [8-10]

3.4.3 TRP Ion Channels

One proposed hypothesis suggests that dysfunction of **transient receptor potential (TRP) ion channels** may contribute to the development of PSSD. [18,31] These channels play an

important role in sensory signal transmission; therefore, their dysfunction has been proposed as a potential explanation for one of the hallmark symptoms of PSSD-**genital numbness**.

To date, however, this hypothesis has not been confirmed by robust experimental or clinical evidence and requires further investigation. [9,18,31]

3.4.4 Neurotoxicity

Another proposed mechanism involves the potential neurotoxic effects of prolonged serotonergic overstimulation. It has been hypothesized that chronic exposure to elevated serotonin concentrations may induce structural and functional alterations within serotonergic neurons. This hypothesis is partly based on comparisons with

3,4-methylenedioxymethamphetamine (MDMA), which is known to produce serotonergic neurotoxicity. Nevertheless, there is currently no convincing evidence demonstrating that a similar mechanism occurs in patients receiving SSRIs. Consequently, this hypothesis remains speculative and requires further experimental validation. [9]

3.4.5 Epigenetic Mechanisms

Epigenetic alterations represent one of the most frequently discussed hypotheses regarding the persistence of PSSD symptoms. [9]

Long-term SSRI exposure has been proposed to induce persistent changes in gene expression through epigenetic mechanisms, including **DNA methylation** and **chromatin remodeling**.

Persistent regulation of serotonin receptor expression, particularly that of the

5-HT1A receptor, has also been suggested. [9,18]

Such changes could theoretically persist after drug discontinuation and provide a potential explanation for the prolonged sexual symptoms observed in PSSD. However, direct evidence supporting this hypothesis remains limited, and further studies are required to establish its clinical relevance. [9,19]

3.4.6 Other Hypotheses

Several additional hypotheses have been proposed to explain the pathogenesis of PSSD. These include disturbances of glutamatergic neurotransmission, persistent structural and functional alterations within the central nervous system, and mechanisms resembling persistent adverse neurological effects observed following exposure to antipsychotic medications, including extrapyramidal syndromes. [10,18]

More recently, increasing attention has been directed toward the potential role of the **gut-brain axis** and alterations in the intestinal microbiota. Emerging evidence suggests that the gut

microbiome participates in the regulation of serotonergic neurotransmission, immune function, neuroendocrine signaling, and neuroinflammatory processes. [20] Based on these observations, it has been hypothesized that disturbances within the gut-brain axis may also contribute to the development of PSSD. However, direct evidence supporting this hypothesis remains lacking. [10,20]

Potential biological similarities between PSSD and other persistent drug-induced syndromes, particularly **post-finasteride syndrome (PFS)**, have also been proposed, suggesting that these conditions may share partially overlapping pathophysiological mechanisms. [19]

Despite the growing number of proposed hypotheses, **none of the currently available mechanisms has been conclusively confirmed**. Further basic and clinical research is required to clarify the pathophysiology of PSSD and facilitate the development of effective therapeutic strategies. [10,11]

3.5.1 Definition

Post-SSRI sexual dysfunction (PSSD) is an iatrogenic clinical syndrome characterized by the persistence or, in some cases, the emergence of sexual dysfunction following discontinuation of selective serotonin reuptake inhibitor (SSRI) therapy. Unlike conventional **SSRI-induced sexual dysfunction (AISD)**, symptoms of PSSD persist after drug discontinuation and may continue for months or even years. [8-10]

The most commonly reported symptoms include decreased libido, erectile dysfunction, delayed or pleasureless orgasm, and reduced or complete loss of genital sensation (genital numbness). [8-11]

Awareness of PSSD has increased considerably in recent years. [3,10] In 2019, the European Medicines Agency (EMA) officially acknowledged that sexual dysfunction may persist following treatment with SSRIs and serotonin-norepinephrine reuptake inhibitors (SNRIs). Subsequently, persistent sexual dysfunction following SSRI/SNRI treatment was recognized within the Medical Dictionary for Regulatory Activities (MedDRA). [2,10] Nevertheless, PSSD remains underrecognized by both clinicians and patients, and its pathophysiology has not yet been fully elucidated. [2,10]

3.5.2 Epidemiology

The true prevalence of PSSD remains unknown. This is largely attributable to the absence of prospective studies, inconsistent diagnostic criteria used in earlier publications, and probable underreporting of cases. Current evidence is derived primarily from case reports, case series, observational studies, and pharmacovigilance databases. [2,4,6,8]

Although the true prevalence of PSSD remains uncertain, **the first available cohort study** suggests that the risk of persistent sexual dysfunction following serotonergic antidepressant treatment may be low but clinically relevant. The authors estimated the risk of PSSD to be approximately **1 case per 216 treated patients (0.46%)**. However, these findings were obtained exclusively in a selected male population and therefore cannot be directly generalized to the overall population. [2,21]

Assessment of the epidemiology of PSSD is further complicated by patients' reluctance to report sexual symptoms, difficulties distinguishing persistent adverse effects from manifestations of the underlying psychiatric disorder, and the lack of routine baseline assessment of sexual function before initiating antidepressant treatment. [2,3,6] **Cases persisting for more than 20 years after SSRI discontinuation have been reported**, although the true magnitude of this phenomenon remains unknown. [4,6]

3.5.3 Clinical Presentation

The clinical presentation of PSSD is heterogeneous and includes both sexual and non-sexual symptoms. The hallmark feature of the syndrome is the persistence of symptoms despite complete discontinuation of the antidepressant and remission of the underlying psychiatric disorder. [5,6,8,22]

Table 5. Main clinical manifestations of post-SSRI sexual dysfunction (PSSD)

CATEGORY	CLINICAL MANIFESTATION	TYPICAL PRESENTATION
SEXUAL SYMPTOMS	loss of libido genital numbness erectile dysfunction delayed ejaculation orgasmic dysfunction female sexual dysfunction	persistent reduction or absence of sexual desire reduced or complete loss of genital sensation persistent difficulty obtaining or maintaining an erection delayed or absent ejaculation delayed, weak, or pleasureless orgasm reduced arousal, impaired lubrication, and anorgasmia
NON - SEXUAL SYMPTOMS	emotional blunting anhedonia apathy cognitive impairment	reduced emotional responsiveness and affective flattening reduced ability to experience pleasure loss of motivation and initiative difficulties with attention, concentration, or memory (reported in a subset of patients)

Source: Author's own elaboration based on Peleg et al., Chinchilla Alfaro et al., Xie et al., and Healy et al. [5,6,8,22].

Among these manifestations, **genital numbness is widely regarded as one of the hallmark clinical features of PSSD** and is only rarely observed in conventional SSRI-induced sexual dysfunction. In some patients, sexual symptoms coexist with non-sexual manifestations such as anhedonia, apathy, emotional blunting, and cognitive impairment. [5,6,8]

3.5.4 Diagnostic Criteria

The diagnosis of PSSD is based primarily on a detailed clinical history and exclusion of alternative causes of sexual dysfunction. At present, no specific laboratory biomarkers or

imaging studies are available to confirm the diagnosis; therefore, PSSD remains a **clinical diagnosis**. [5,6,22]

To facilitate consistent recognition of PSSD, proposed diagnostic criteria have been published and are summarized in **Table 6**.

Table 6. Proposed diagnostic criteria for post-SSRI sexual dysfunction (PSSD)

CRITERION	DESCRIPTION
previous normal sexual function	no clinically significant sexual dysfunction before SSRI/SNRI treatment
exposure to SSRI/SNRI	current or previous treatment with a serotonergic antidepressant
symptom onset	development of sexual dysfunction during treatment or shortly after discontinuation
persistence of symptoms	symptoms persist despite discontinuation of SSRI/SNRI
exclusion of alternative causes	no psychiatric, endocrine, neurological, or other medical condition explaining the symptoms

Source: Author's own elaboration based on Healy et al., Peleg et al., and Xie et al. [5,6,22].

The proposed diagnostic criteria aim to standardize the recognition of PSSD in both clinical practice and research settings. Their application may facilitate appropriate patient identification and improve comparability across future clinical studies. [22]

3.5.5 Differential Diagnosis

The diagnosis of PSSD requires careful exclusion of alternative causes of sexual dysfunction. Particular attention should be paid to differentiating PSSD from sexual dysfunction associated with depressive disorders, anxiety disorders, endocrine abnormalities, neurological diseases, and other medical conditions. [5,6,22]

Table 7. Differential diagnosis of post-SSRI sexual dysfunction (PSSD)

CONDITION	DISTINGUISHING FEATURES
depression	sexual dysfunction precedes treatment and improves with remission
anxiety disorders	symptoms fluctuate with anxiety severity
diabetes mellitus	peripheral neuropathy and vascular complications
endocrine disorders	hormonal abnormalities, including hypogonadism and hyperprolactinaemia
neurological disorders	sensory deficits unrelated to SSRI exposure
drug - induced sexual dysfunction	associated with medications other than SSRIs

Source: Author's own elaboration based on Peleg et al., Xie et al., and Healy et al. [5,6,22].

Exclusion of sexual dysfunction related to other medications, endocrine disorders, and neurological diseases is essential before establishing the diagnosis of PSSD. [5,6,22]

3.5.6 Current Evidence

Despite the growing number of publications, PSSD remains a poorly understood clinical entity. Most currently available evidence originates from case reports, case series, and observational studies, whereas well-designed prospective and randomized clinical studies are virtually absent. [10,12] Consequently, the true prevalence of PSSD remains uncertain, and no validated biomarkers are currently available to establish the diagnosis. [8,9,10,12]

Current evidence supports the concept that PSSD represents a genuine clinical condition. However, most proposed pathophysiological mechanisms remain hypothetical, and no treatment with proven efficacy is currently available. [8,9,11,12] Further basic, translational, and clinical research is required to improve our understanding of the epidemiology and pathophysiology of PSSD and to facilitate the development of effective therapeutic strategies. [9,12,19]

3.6 Management

3.6.1 Prevention

Antidepressant - induced sexual dysfunction (AISD) is one of the most common adverse effects associated with selective serotonin reuptake inhibitors (SSRIs) and represents a frequent cause of poor treatment adherence and premature discontinuation of antidepressant therapy. [1,2,4-6] Because discontinuation of antidepressant treatment may increase the risk of relapse or

recurrence of depressive and anxiety disorders, management of AISD should aim to alleviate sexual symptoms while maintaining adequate control of the underlying psychiatric condition. [1,2,6]

Current management strategies include preventive measures, dose reduction, switching to an antidepressant with a more favorable sexual side-effect profile, pharmacological augmentation, and selected non-pharmacological interventions. Despite the growing number of available therapeutic approaches, no single strategy has consistently demonstrated efficacy across all patient populations. Consequently, management should be individualized according to symptom severity, psychiatric stability, comorbidities, and patient preferences. [1,5,6]

3.6.2 Dose Reduction

Dose reduction is widely regarded as the first therapeutic option in patients with mild to moderate AISD whose psychiatric symptoms remain well controlled. [1,5,6] Because the occurrence and severity of sexual dysfunction are often dose-dependent, reducing the SSRI dose may improve libido, sexual arousal, orgasmic function, or ejaculation in selected patients. [1,5,17]

However, dose reduction should be undertaken cautiously, as decreased antidepressant exposure may increase the risk of relapse or recurrence of depressive symptoms. Therefore, this strategy should be individualized and considered only after careful assessment of the balance between psychiatric stability and the severity of sexual adverse effects. [1,5,6]

3.6.3 Switching Antidepressants

When dose reduction is ineffective or clinically inappropriate, switching to an antidepressant with a more favorable sexual tolerability profile represents an important therapeutic option. Antidepressants with predominantly dopaminergic or multimodal mechanisms of action generally demonstrate a lower incidence of treatment-emergent sexual dysfunction than SSRIs. [1,4-6]

Among the available alternatives, bupropion has consistently been associated with the lowest risk of sexual dysfunction and is frequently recommended when preservation or restoration of sexual function is a therapeutic priority. [1,5,6] Vortioxetine has also demonstrated favorable sexual tolerability and may improve sexual functioning in selected patients following a switch from SSRI therapy. [5,6] Other antidepressants, including mirtazapine and agomelatine, appear to be associated with lower rates of sexual adverse effects than SSRIs, although comparative evidence remains limited. [1,5,6]

The decision to switch antidepressants should always consider previous treatment response, psychiatric history, relapse risk, comorbid conditions, and patient preferences. [1,5,6]

3.6.4 Pharmacological Treatment

Several pharmacological augmentation strategies have been investigated for the management of AISD; however, the overall quality of available evidence remains limited. [5,6]

Among currently available therapeutic options, bupropion has the strongest evidence supporting its efficacy. [5,6,25] Recent systematic reviews and meta-analyses of randomized controlled trials indicate that bupropion sustained-release (150 mg twice daily) significantly improves sexual desire, arousal, and orgasmic function in women with AISD compared with placebo. Nevertheless, the overall certainty of the evidence remains low because of the limited number of high-quality studies. [25]

Buspirone has also been proposed as an adjunctive treatment, particularly in patients presenting with delayed ejaculation or orgasmic dysfunction. Although several case reports and small clinical studies suggest potential benefit, robust evidence from randomized controlled trials remains lacking, and its routine use cannot currently be recommended. [26]

In patients with erectile dysfunction, phosphodiesterase type 5 (PDE-5) inhibitors [5,6], particularly sildenafil, have demonstrated efficacy in improving erectile function while allowing continuation of antidepressant therapy. Their benefits appear to be greatest in men with predominant erectile dysfunction rather than generalized sexual dysfunction.

Other pharmacological interventions, including testosterone supplementation, ephedrine, and several investigational compounds, have been evaluated in small clinical studies. [5,6,25] However, current evidence remains insufficient to support their routine clinical use.

3.6.5 Non - pharmacological Treatment

Several non-pharmacological and complementary approaches have also been investigated as potential management strategies for AISD. [5,6]

One proposed strategy is the use of drug holidays, consisting of temporary interruption of short half - life SSRIs before anticipated sexual activity. [28,29] Recent randomized clinical trials demonstrated improvements in several domains of sexual function in both men and women receiving SSRIs other than fluoxetine, without significant deterioration of psychiatric symptoms during short-term follow-up. [28,29] Nevertheless, this approach should be considered only in carefully selected patients because interruption of antidepressant therapy may increase the risk of withdrawal symptoms or psychiatric relapse. [5,6,28,29]

Growing interest has also focused on nutraceuticals. A recent systematic review of randomized controlled trials suggests that high-dose maca root, saffron, and S-adenosyl-L-methionine (SAME) may improve selected aspects of sexual function, whereas current evidence does not support the efficacy of *Ginkgo biloba* or yohimbine. *Rosa damascena* has demonstrated potential benefits, particularly in men, although the available evidence remains limited. [27]

Psychosexual counseling, lifestyle modification, and regular physical activity may further contribute to improved sexual well-being and relationship satisfaction. However, high-quality evidence supporting the effectiveness of these interventions specifically for ASD remains limited. [5,6]

4. Discussion

Selective serotonin reuptake inhibitors (SSRIs) remain the first-line pharmacological treatment for major depressive disorder and most anxiety disorders because of their well-established efficacy and favorable safety profile compared with older classes of antidepressants. [1-3] Nevertheless, sexual dysfunction remains one of their most common and clinically significant adverse effects. [1,2,4,5] The present review demonstrates that sexual dysfunction frequently occurs during SSRI therapy and may affect multiple domains of sexual function, including sexual desire, arousal, orgasm, ejaculation, and overall sexual satisfaction. [2,4,5] Importantly, these adverse effects substantially impair patients' quality of life and represent one of the leading causes of poor treatment adherence and premature discontinuation of antidepressant therapy. [1,4-6]

One of the principal clinical challenges highlighted by the reviewed literature is the difficulty in distinguishing sexual dysfunction attributable to the underlying psychiatric disorder from treatment-emergent adverse effects. Depression itself is independently associated with reduced libido, impaired sexual arousal, anhedonia, diminished self-esteem, and interpersonal difficulties, all of which may compromise sexual functioning before pharmacological treatment is initiated. [1,2,7,15] Consequently, failure to assess baseline sexual function may result in underrecognition or misclassification of treatment-emergent sexual adverse effects. These findings emphasize the importance of routine assessment of sexual function both before initiating antidepressant therapy and during subsequent follow-up visits. [1,2,6]

The available evidence also suggests considerable heterogeneity among individual SSRIs with respect to their propensity to induce sexual dysfunction. [4,5,16] Although all SSRIs may adversely affect sexual functioning, **paroxetine** has consistently been associated with the

highest risk, whereas **fluvoxamine** and **escitalopram** appear to be associated with a relatively lower frequency of sexual adverse effects. [4,5,16] Furthermore, higher SSRI doses are associated with an increased incidence of adverse effects without substantial improvement in antidepressant efficacy, supporting current recommendations to prescribe the lowest effective dose whenever clinically appropriate. [17]

Another important observation emerging from the present review is the increasing recognition of **post-SSRI sexual dysfunction (PSSD)** as a distinct clinical entity. Unlike conventional antidepressant-induced sexual dysfunction, PSSD may persist long after discontinuation of treatment and may be accompanied by genital numbness, emotional blunting, anhedonia, and cognitive impairment. [8-12] Although regulatory agencies such as the **European Medicines Agency (EMA)** now acknowledge the possibility of persistent sexual dysfunction following SSRI treatment, the true prevalence of PSSD remains uncertain because the available evidence is derived primarily from case reports, pharmacovigilance databases, retrospective studies, and only limited observational cohorts. [9,10,12] Consequently, both underdiagnosis and underreporting are likely to contribute to the current uncertainty regarding its epidemiology. [12]

The pathophysiology of PSSD remains poorly understood. [8,9,12] Persistent serotonergic dysregulation, alterations in dopaminergic neurotransmission, neuroendocrine imbalance, TRP ion channel dysfunction, epigenetic modifications, neurotoxicity, and disturbances of the gut-brain axis have all been proposed as potential mechanisms. [8,9,18-20] However, none has been conclusively confirmed. [8,9,12] Recent experimental studies investigating serotonergic receptor regulation and receptor-trafficking proteins, such as Yif1B, suggest that persistent alterations in serotonergic signaling may contribute to long-lasting symptoms, although translational evidence in humans remains limited. Likewise, hypotheses involving epigenetic regulation and neuroplasticity are biologically plausible but currently rely predominantly on preclinical rather than clinical evidence. [18,19]

Current therapeutic options for SSRI-induced sexual dysfunction remain limited. [5,6] The principal management strategies include dose reduction, switching to antidepressants with a more favorable sexual tolerability profile, and pharmacological augmentation. [1,5,6] Among available interventions, **bupropion** currently has the strongest evidence supporting its efficacy, whereas **buspirone**, **phosphodiesterase type 5 inhibitors**, and selected **nutraceuticals** have demonstrated promising but less consistent results. [25-27] Recent randomized clinical trials investigating **drug holidays** have also suggested potential benefits in carefully selected patients

receiving short half-life SSRIs, although this strategy cannot be universally recommended because of the potential risk of withdrawal symptoms or relapse of psychiatric illness. [28,29] In contrast, **no evidence-based treatment has yet been established for PSSD**, highlighting one of the most important unmet clinical needs in contemporary psychopharmacology. [9,12] Several limitations of the current literature should be acknowledged. Existing studies differ substantially with respect to patient populations, diagnostic criteria, assessment tools, treatment duration, antidepressant exposure, and follow-up periods, limiting direct comparison of study findings. [4,5,9-12] Furthermore, many investigations rely predominantly on patient-reported outcomes rather than standardized clinical assessments, while prospective longitudinal studies remain scarce. [10,12] Funding by the pharmaceutical industry, reported in several studies, also raises concerns regarding potential publication bias, particularly with respect to the tolerability profiles of antidepressants. [5,6] Finally, despite increasing recognition of PSSD, large epidemiological studies employing standardized diagnostic criteria are still lacking. [9,12,22] Future research should focus on establishing universally accepted diagnostic criteria for PSSD, identifying reliable biological markers, clarifying the underlying pathophysiological mechanisms, and developing evidence-based therapeutic strategies. In particular, well-designed prospective longitudinal studies are needed to determine the incidence, natural history, and risk factors of persistent sexual dysfunction following antidepressant exposure. Greater emphasis should also be placed on routine assessment of sexual function in psychiatric practice to facilitate early recognition, improve patient counseling, and optimize long - term treatment outcomes.

5. Conclusions

Sexual dysfunction is one of the most common adverse effects associated with selective serotonin reuptake inhibitors (SSRIs) and may affect multiple domains of sexual function in both men and women. These complications substantially impair quality of life, negatively influence intimate relationships, and frequently contribute to poor treatment adherence and premature discontinuation of antidepressant therapy.

Although antidepressant-induced sexual dysfunction is generally reversible following dose reduction or discontinuation of treatment, a subset of patients may develop persistent symptoms consistent with **post-SSRI sexual dysfunction (PSSD)**. Despite increasing recognition of this condition among clinicians and regulatory agencies, its epidemiology, underlying biological mechanisms, and optimal management remain insufficiently understood.

Current evidence supports several management strategies for SSRI-induced sexual dysfunction, including dose reduction, switching to antidepressants with a more favorable sexual tolerability profile, pharmacological augmentation, and selected non-pharmacological interventions. However, **no evidence-based treatment has yet been established for PSSD**, highlighting an important unmet clinical need.

Routine assessment of sexual function before initiating antidepressant therapy and during follow - up should become an integral component of clinical practice. Increasing clinicians' awareness, improving patient education, and encouraging open discussion of sexual adverse effects may facilitate earlier recognition of these complications, improve treatment adherence, and optimize long-term clinical outcomes.

Further high-quality prospective studies are needed to clarify the mechanisms underlying persistent sexual dysfunction, establish standardized diagnostic criteria for PSSD, identify reliable biomarkers, and develop effective evidence-based therapeutic strategies.

Disclosure

Author Contributions

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