

PERSISTENT POST-ANTIDEPRESSANT SEXUAL DYSFUNCTION: CLINICAL INVISIBILITY AND IMPACTS ON HEALTH AND SEXUALITY

DISFUNÇÃO SEXUAL PERSISTENTE PÓS-ANTIDEPRESSIVOS: INVISIBILIDADE CLÍNICA E IMPACTOS NA SAÚDE E SEXUALIDADE

DISFUNCIÓN SEXUAL PERSISTENTE POST-ANTIDEPRESIVOS: INVISIBILIDAD CLÍNICA E IMPACTOS EN LA SALUD Y LA SEXUALIDAD

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Abstract: Post-SSRI Sexual Dysfunction (PSSD) is a persistent iatrogenic condition characterized by symptoms such as genital anesthesia, loss of libido, anorgasmia, erectile dysfunction, and lack of sexual pleasure that persist even after the discontinuation of Selective Serotonin Reuptake Inhibitors (SSRIs). Despite a growing number of reports, PSSD remains underreported, poorly understood, and absent from major diagnostic manuals. This study aims to critically review the scientific literature on PSSD, propose a diagnostic flowchart based on recognized clinical criteria, and discuss overlooked aspects of medical listening, psychosocial impacts on patients, and the urgent need to reassess current SSRI prescribing practices. The study emphasizes the need for new clinical protocols and investment in high-quality research to advance the understanding, recognition, and treatment of this syndrome.

Keywords: Post-SSRI sexual dysfunction; Antidepressants; Persistent adverse effects; Genital anesthesia; PSSD.

Resumo: A Disfunção Sexual Pós-ISRIS (PSSD) é uma condição iatrogênica persistente caracterizada por sintomas como anestesia genital, perda de libido, anorgasmia, disfunção erétil e ausência de prazer sexual, que permanecem mesmo após a suspensão dos Inibidores Seletivos da Recaptação de Serotonina (ISRIS). Apesar do número crescente de relatos, a PSSD ainda é subnotificada, pouco compreendida e ausente dos principais manuais diagnósticos internacionais. Este trabalho tem como objetivo revisar criticamente a literatura científica sobre a PSSD, propor um fluxograma diagnóstico baseado em critérios clínicos reconhecidos e discutir aspectos negligenciados da escuta médica, impactos psicossociais nos pacientes e a urgência de reavaliação dos critérios de prescrição dos ISRISs. Destaca-se a necessidade de novos protocolos clínicos e investimento em pesquisas com alto nível de evidência científica para avançar na compreensão, reconhecimento e tratamento dessa síndrome.

Palavras-chave: Disfunção sexual pós-ISRIS; Antidepressivos; Efeitos adversos persistentes; Anestesia genital. PSSD.

Resumen: La Disfunción Sexual Post-ISRIS (PSSD) es una condición iatrogénica persistente caracterizada por síntomas como anestesia genital, pérdida de la libido, anorgasmia, disfunción erétil y ausencia de placer sexual, que persisten incluso después de la suspensión de los Inibidores Selectivos de la Recaptación de Serotonina (ISRIS). A pesar del creciente número de reportes, la PSSD continúa subnotificada, poco comprendida y ausente de los principales manuales diagnósticos internacionales. Este trabajo tiene como objetivo revisar críticamente la literatura científica sobre la PSSD, proponer un diagrama de flujo diagnóstico basado en criterios clínicos reconocidos y analizar aspectos frecuentemente desatendidos en la práctica médica, los impactos psicossociales en los pacientes y la urgente necesidad de reevaluar los criterios de prescripción de los ISRIS. Se destaca la necesidad de nuevos protocolos clínicos y de inversión en investigaciones con alto nivel de evidencia científica para avanzar en la comprensión, el reconocimiento y el tratamiento de este síndrome.

Palabras clave: Disfunción sexual post-ISRIS; Antidepressivos; Efectos adversos persistentes; Anestesia genital. PSSD.



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Introduction

Selective Serotonin Reuptake Inhibitors (SSRIs) constitute a class of medications widely used in the treatment of mental disorders such as major depression, obsessive-compulsive disorder, post-traumatic stress disorder, and generalized anxiety. In addition to these indications, they also have off-label applications, such as in the treatment of premature ejaculation (Althof et al., 2014; Bala, Nguyen & Hellstrom, 2018).

According to Nardi, Silva, and Quevedo (2022), the main drugs in this class are fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram, and escitalopram. As explained by Soares (2005), although they share the same mechanism of action, these medications present structural differences and distinct pharmacokinetic and pharmacodynamic profiles, which contribute to varied adverse manifestations.

Despite their therapeutic efficacy, SSRIs are strongly associated with sexual dysfunction, the incidence of which can reach up to 73% during treatment (Zeiss et al., 2024). Furthermore, nearly 100% of users report reduced genital sensitivity within 30 minutes after drug administration (Healy, 2020). SSRI-induced sexual dysfunction can affect all phases of the sexual response, including desire, arousal, and orgasm, manifesting as erectile dysfunction, anorgasmia, and delayed ejaculation, among other symptoms (Figueiredo, Freitas & Ferreira, 2022).

In some cases, these side effects persist even after treatment discontinuation, characterizing Post-SSRI Sexual Dysfunction (PSSD) (Ben-Sheetrit et al., 2023). This set of persistent symptoms and the term PSSD were introduced into the medical literature by Bahrack (2006), and since then, the number of reports has increased significantly (Peleg et al., 2022). Subsequently, it was found that cases of PSSD had already been reported to regulatory agencies since 1991.

In 2012, Lareb (The Netherlands Pharmacovigilance Centre) issued an alert on persistent sexual dysfunction. In 2013, the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) began to mention that sexual dysfunction may endure even after the discontinuation of SSRIs. In 2019, the European Medicines Agency (EMA) officially recognized PSSD as a sexual dysfunction that can persist after discontinuing the use of SSRIs, recommending that product labels be updated to warn about this risk. Currently, the fluoxetine label in the United States also includes the possibility of long-lasting sexual dysfunction as an adverse effect (Healy, Le Noury & Mangin, 2019).

The main symptoms of PSSD include genital anesthesia, loss of libido, erectile dysfunction, and muted orgasms, with the most characteristic triad being genital anesthesia, loss of libido, and erectile dysfunction. In some cases, PSSD can emerge after a single dose of an SSRI, causing profound suffering and impact on the patients' quality of life (Bala, Nguyen & Hellstrom, 2018). The lack of an effective treatment, diagnostic difficulties, and lack of awareness of the condition among healthcare professionals exacerbate the suffering of patients, who frequently face emotional difficulties, social isolation, and a lack of adequate support (Stinson, 2013).

Given the relevance of this condition and the scarcity of scientific literature on the subject in Brazil, this pioneering article aims to analyze, through an integrative literature review, the impacts of Post-SSRI Sexual Dysfunction (PSSD). The focus will be on highlighting the most relevant aspects of the condition, exploring its pathophysiological mechanisms, diagnostic criteria, risk factors, and clinical management strategies. The goal is to assist healthcare professionals in recognizing PSSD and providing adequate support to affected patients. Furthermore, it aims to foster knowledge about the condition and encourage new research, contributing to the updating of psychiatric and pharmacological practices in the country.

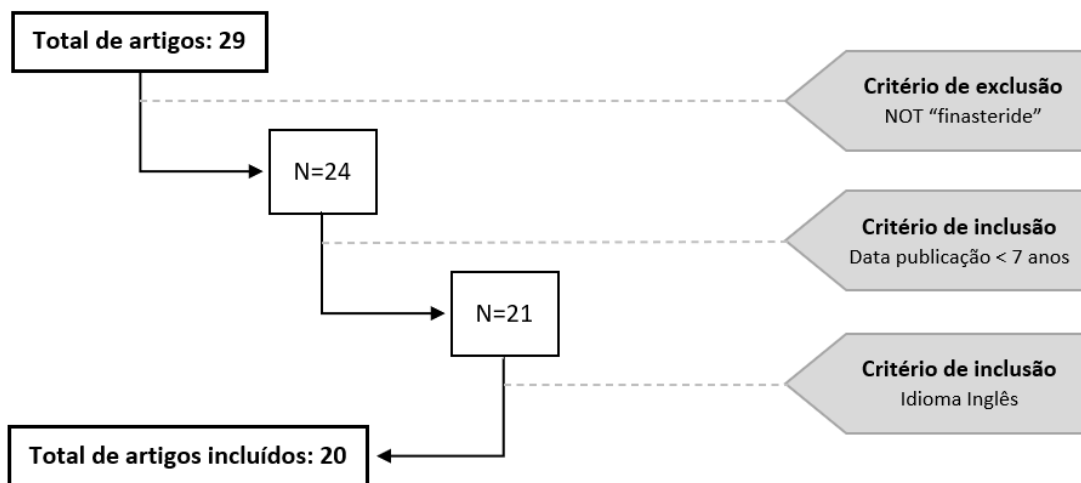
Methodology

The methodology used for this study was an integrative literature review, using the electronic database PubMed/MEDLINE (US National Library of Medicine). The descriptors used were "Post-SSRI Sexual Dysfunction" and "finasteride", using the Boolean operator "NOT" to exclude articles that mentioned "finasteride". The literature was selected considering the following inclusion criteria: full-text literature available electronically, in English, published within the last 7 years (2018-2025).

The search in the databases resulted in a total of 29 articles. Excluding articles containing the descriptor

“finasteride” resulted in 24 articles, of which 21 were published in the last seven years. Among these, 1 was not published in English. Finally, the remaining 20 articles were used in this study, as presented in Figure 1.

Figure 1 - Flowchart of results obtained in the review of bibliographic references from PUBMED



Source: Vitor Salles Coelho dos Reis (2025).

Results

The studies included in this review indicate that post-SSRI sexual dysfunction (PSSD) persists in a significant proportion of patients, even after the discontinuation of the medication.

Among the most frequently described symptoms, reduced libido was cited in 90% of the articles, followed by anorgasmia and muted orgasm (70%), decreased genital sensitivity (65%), and erectile dysfunction or insufficient lubrication (60%). These findings reinforce the clinical consistency of PSSD, showing a recurrent symptomatic pattern.

From a physiological standpoint, several studies suggest potential mechanisms involved in the development of PSSD. The most cited hypotheses include the desensitization of serotonergic receptors, alterations in the hypothalamic-pituitary-gonadal axis, and modifications in dopaminergic neurotransmission. These alterations may contribute to the maintenance of symptoms, even after the drug has been eliminated from the body.

The psychosocial impact of PSSD was widely addressed, being cited in 55% of the analyzed articles. The studies indicate that patients experienced significant psychological distress associated with decreased self-esteem, impairment in romantic relationships, and worsening of depressive and anxiety symptoms resulting from persistent sexual dysfunction.

Table 1 - Characterization of the articles according to year of publication and main conclusions

No.	Article Title	Author and Year	Main Results
1	Post-SSRI Sexual Dysfunction: A Literature Review	Bala, Nguyen, and Hellstrom (2018)	Literature review describing SSRI-induced sexual dysfunction, focusing on the persistence of symptoms after discontinuation. It discusses the scarcity of clinical data and the lack of recognition of PSSD.
2	Post-SSRI Sexual Dysfunction: Preclinical to Clinical. Is It Fact or Fiction?	Coskuner et al. (2018)	Review discussing clinical and preclinical evidence regarding persistent sexual symptoms after SSRI use. It does not conclude that PSSD is an established condition but recognizes the need for further studies on the condition.

3	Towards Improving Post-SSRI Sexual Dysfunction by Using Nutraceuticals: Lessons from a Case Study	Calabrò et al. (2019)	Case study of a PSSD patient who showed partial improvement after using a nutraceutical. After 4 weeks of treatment, improvement in some symptoms was observed. It recognizes the limitation of generalizing from a single case.
4	Post-SSRI sexual dysfunction: Patient experiences of engagement with healthcare professionals	Healy, Le Noury, and Mangin (2019)	Qualitative study with 62 patient reports collected via a public call on the RxISK.org website. It shows that many patients face disbelief, medical attribution of symptoms to mental health, and a lack of clinical knowledge about PSSD when seeking help.
5	Post-SSRI sexual dysfunction & other enduring sexual dysfunctions	Healy (2020)	Editorial discussing PSSD and other drug-induced persistent sexual dysfunctions. It advocates for its recognition, highlights its underreporting, and proposes that the condition must be treated seriously in research and clinical practice.
6	Post-SSRI sexual dysfunction	Reisman (2020)	Describes the persistent sexual adverse effects of PSSD. It discusses the impact on quality of life, the lack of medical recognition, and the need for a more precise diagnosis. It suggests that the duration of post-treatment symptoms can vary.
7	Post-SSRI Sexual Dysfunction: A Bioelectric Mechanism?	Healy, LaPalme, and Levin (2020)	Proposes that PSSD could be explained by bioelectric dysfunction of ion channels, affecting nerve conduction in genital regions. It suggests that SSRIs may alter the electrical balance of the peripheral nervous system, contributing to symptoms. It raises the possibility that drugs restoring ionic balance could offer therapeutic benefits.
8	Antidepressant-induced sexual dysfunction	Rothmore (2020)	Narrative review describing the high prevalence of sexual dysfunction associated with antidepressant use. It highlights the importance of sexual anamnesis before starting treatment and continuous reassessment during use. Strategies for management are discussed.
9	Exposure to serotonin selective reuptake inhibitors or serotonin noradrenaline reuptake inhibitors and sexual dysfunction: Results from an online survey	Patacchini and Cosci (2021)	Online survey with 135 participants revealed that the use of SSRIs and SNRIs is frequently associated with persistent sexual dysfunction. It concludes that in many cases, PSSD follows a more malignant course than the initial psychiatric illness that required SSRI/SNRI treatment.
10	Effects of paroxetine treatment and its withdrawal on neurosteroidogenesis	Giatti et al. (2021)	Preclinical study with male mice showed that paroxetine treatment significantly alters neurosteroid levels in the central and peripheral nervous systems. After drug withdrawal, some alterations persisted.
11	Characterizing post-SSRI sexual dysfunction and its im-	Studt et al. (2021)	Study evaluating 239 responses from an online survey administered to individuals with PSSD. It concludes that the condition causes an extremely negative impact on

	pact on quality of life through an international online survey		quality of life and suggests the need for greater clinical recognition and in-depth research.
12	Post-SSRI Sexual Dysfunction (PSSD): Biological Plausibility, Symptoms, Diagnosis, and Presumed Risk Factors	Peleg et al. (2022)	Narrative review describing the biological plausibility of PSSD based on clinical data and mechanistic hypotheses. It suggests that ongoing sexual dysfunction after SSRIs may reflect complex neuroendocrine alterations. It highlights risk factors and proposes preliminary diagnostic criteria.
13	Persistent sexual dysfunction after SSRI withdrawal: a scoping review and presentation of 86 cases from the Netherlands	Chinchilla Alfaro, Van Hunsel, and Ekhart (2022)	Scoping review based on data from the Dutch pharmacovigilance database identified 86 cases of PSSD. The mean persistence time was 19 months, with cases lasting up to 13 years. The authors highlight the need for greater awareness.
14	Cutting the First Turf to Heal Post-SSRI Sexual Dysfunction: A Male Retrospective Cohort Study	De Luca et al. (2022)	Retrospective study with 13 men diagnosed with PSSD treated with nutraceuticals and other neuroprotective compounds. After 3 months, 9 patients reported partial or significant improvement in genital sensitivity and erectile function.
15	The pathophysiology of Post SSRI Sexual Dysfunction - Lessons from a case study	Klaas et al. (2023)	Detailed case study of a patient who underwent extensive physiological, neurological, and psychological evaluation. It proposes that PSSD may involve specific neurophysiological dysfunction independent of emotional factors. It highlights the importance of developing objective diagnostic protocols.
16	Estimating the risk of irreversible post-SSRI sexual dysfunction (PSSD) due to serotonergic antidepressants	Ben-Sheetrit et al. (2023)	Retrospective study based on a questionnaire administered to 82 participants who reported symptoms compatible with PSSD. It concludes that although rare, the risk of irreversible PSSD is real and measurable.
17	A clinical review of antidepressants, their sexual side-effects, post-SSRI sexual dysfunction, and serotonin syndrome	Marks (2023)	Review contextualizing PSSD within the spectrum of drug-induced sexual adverse effects. It discusses common neurobiological mechanisms between sexual dysfunctions during use and those that persist after discontinuation.
18	Post-SSRI sexual dysfunction: barriers to quantifying incidence and prevalence	Healy and Man- gin (2024)	Editorial discussing the main obstacles to determining the prevalence of PSSD. It highlights the absence of diagnostic codes, low reporting in pharmacovigilance systems, and the bias of attributing symptoms to the original psychiatric condition.
19	Frequency of self-reported persistent post-treatment genital hypoesthesia among past antidepressant users: a cross-sectional survey of sexual and gender minority youth in Canada and the US	Pirani et al. (2024)	Cross-sectional study with 343 LGBTQIA+ youth who were former antidepressant users evaluated the frequency of persistent genital hypoesthesia after the end of treatment. 25% reported symptoms compatible with PSSD, which was more common with SSRI use and in treatments initi-

ated before age 18. They recommend including persistent adverse effect information on labels.

Source: Prepared by the authors (2025).

Clinical Presentation

Klaas *et al.* (2023) suggest two potential classifications for PSSD: PSSD-I, whose side effects emerge during SSRI treatment and remain after discontinuation, and PSSD-II, whose symptoms appear only after the discontinuation of the drug treatment. Despite this distinction, the pathophysiological mechanisms justifying it are not yet understood (Klaas *et al.*, 2023). Calabrò *et al.* (2019) point out that the duration of antidepressant use leading to the development of PSSD has been estimated to range between 4 days and 2.5 years. The duration of the syndrome can vary from a few days or months to cases where the condition persists indefinitely (Peleg *et al.*, 2022).

The most frequently reported symptoms of PSSD include: genital anesthesia, muted or pleasureless orgasms (anedonic orgasm), decreased libido, inability to feel sexual attraction through visual or tactile stimuli or thoughts related to a sexual partner, erectile dysfunction, decreased or absent nocturnal erections, premature ejaculation, decreased vaginal lubrication, flaccidity of the glans penis, and reduced tactile sensitivity of the nipples (Patacchini & Cosci, 2021; Peleg *et al.*, 2022; Reisman, 2020; Studt *et al.*, 2021). Among these symptoms, the most characteristic triad is composed of genital anesthesia, decreased libido, and erectile dysfunction (Bala, Nguyen & Hellstrom, 2018). According to Chinchilla Alfaro, Van Hunsel, and Ekhart (2022), the most distinctive symptom of PSSD is genital anesthesia, a finding that has not been reported by patients presenting with sexual dysfunction due to other psychological conditions. Furthermore, it has been described that the genital anesthesia effect caused by SSRIs resembles the effect of applying lidocaine to the genital region (Healy, LaPalme & Levin, 2020). Other less frequent clinical manifestations have also been reported, such as reduced penile size, reduced seminal volume, testicular atrophy or pain, and irregular menstrual cycles (Bala, Nguyen & Hellstrom, 2018).

Some patients have described PSSD as a sort of “disconnection” between the brain and the genitalia (De Luca *et al.*, 2022). Data from numerous case reports suggest the presence of non-sexual symptoms occurring in parallel with sexual symptoms. Many patients report increased anxiety, greater emotional reactivity, anhedonia, apathy, reduced capacity to express emotions, difficulty concentrating, and memory problems (Peleg *et al.*, 2022; Patacchini & Cosci, 2021). Through an international survey, Studt *et al.* (2021) estimated that approximately 70% of the analyzed patients manifested at least one non-sexual symptom.

Moreover, the duration, frequency, and intensity of PSSD vary among patients and may increase or decrease over time (Chinchilla Alfaro, Van Hunsel & Ekhart, 2022). It is also possible that, over time, the presentation of symptoms changes, or that a partial or total relapse of the condition or of specific symptoms occurs (De Luca *et al.*, 2022).

In this context, some individuals may erroneously attribute the condition to other causes, especially if they experienced an improvement in sexual function after discontinuing the antidepressant. For example, some patients regain the ability to achieve orgasm after experiencing anorgasmia during drug use; however, even with this recovery, the orgasm is frequently perceived as less intense than before. Since these individuals are no longer using the medication, it is common for changes like this to be attributed to aging, considering that a large proportion of patients remain on SSRIs for many years after the start of treatment (Healy & Mangin, 2024).

Risk Factors

Regarding the risk factors associated with PSSD, there is still a scarcity of epidemiological data (Chinchilla Alfaro, Van Hunsel & Ekhart, 2022). However, it is widely accepted that the syndrome can affect individuals of any ethnicity, sex, or age group.

The condition has already been associated with the use of various antidepressants, such as selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and even some tricyclic antidepressants (Chinchilla Alfaro, Van Hunsel & Ekhart, 2022; Peleg et al., 2022). Patacchini and Cosci (2021) observed that when comparing patients with severe sexual dysfunction to those with moderate or mild forms, no significant differences were identified regarding demographic variables, type of medication used, or treatment duration.

Peleg et al. (2022) further suggest other hypotheses as risk factors: genetic predisposition, especially less efficient variants of the MTHFR gene (C677T and A1298C); prolonged mental stress before, during, or after SSRI use; using antidepressants for the first time without PSSD sequelae—it is believed to be possible that the first exposure to antidepressants may increase the risk of developing PSSD during subsequent use of these medications; pre-existing disorders related to glutamate metabolism, such as bipolar disorder, epilepsy, and autism spectrum disorder (ASD); use of psychoactive substances in parallel with antidepressant use, such as MDMA (ecstasy), methamphetamine, cocaine, and methylphenidate; and prior exposure to isotretinoin or 5-alpha-reductase inhibitors (e.g., finasteride, dutasteride, and saw palmetto).

Diagnosis

PSSD can be difficult to diagnose, lacking established criteria by recognized systems such as the DSM or ICD. This requires a meticulous clinical evaluation that considers the history of antidepressant use, as well as the chronology of symptoms in relation to the initiation and discontinuation of treatment. It is essential to ensure that the persistent symptoms are not related to the recurrence of the depressive disorder, given that sexual dysfunction is also a common symptom of this disorder (Chinchilla Alfaro, Van Hunsel & Ekhart, 2022; Peleg et al., 2022). Marks (2023) reinforces that it is important to evaluate pre-morbid sexual function and activity, determining the presence and severity of any sexual dysfunction before initiating medication use. This helps to understand whether the sexual dysfunction is a symptom of the mental illness or a side effect of the treatment.

The exclusion of other potential causes of sexual dysfunction is indispensable when considering a diagnosis of PSSD. Generally, the physician must exclude confounding elements such as age, smoking, alcohol consumption, and substance abuse, as they are recognized causes of sexual dysfunction symptoms (Bala, Nguyen & Hellstrom, 2018). Ben-Sheetrit et al. (2023) utilized several exclusion criteria when selecting patients for their study, including: medical comorbidities—cardiovascular, cerebrovascular, neurological, metabolic, and endocrine; severe respiratory diseases; rheumatological, severe dermatological, chronic or severe infectious, severe orthopedic, gastrointestinal, hepatic, genitourinary, and oncological conditions, and post-transplant status—which were associated with sexual dysfunction or could plausibly lead to it based on clinical considerations; a history of other psychiatric comorbidities related to sexual dysfunction (for example: schizophrenia, bipolar disorder, autism, intellectual disability, dementias, post-traumatic stress disorder, dissociative disorders, personality disorders, somatoform disorders, or gender dysphoria); and the use of medications associated with sexual dysfunction during the study period, as well as a history of substance abuse—such as alcohol, cannabis, tobacco, or other drugs that can trigger sexual symptoms.

De Luca et al. (2022) also suggest performing a complete sexual hormone profile, including laboratory measurements of testosterone, LH, FSH, prolactin, and estrogens. These authors base their diagnosis on criteria already proposed in the literature, including as essential elements: prior treatment with a selective serotonin reuptake inhibitor (SSRI) and a persistent change in somatic (tactile) or erogenous (sexual) genital sensation after treatment discontinuation. Additional criteria include: persistent reduction or loss of sexual desire; prolonged erectile dysfunction (in men); persistent inability to achieve orgasm or diminished orgasmic pleasure; and symptoms present for at least one month after drug discontinuation. For the diagnosis, there must be no: evidence of prior sexual dysfunction compatible with the current presentation; medical condition that can explain the symptoms; or use of medications or substances that can justify the symptoms.

Although some cases of PSSD may be simpler to diagnose in clinical practice when all details of the medical history and clinical presentation are available, there are several factors that obscure the visibility of

PSSD in a broader population. This represents a significant challenge for epidemiologists and an informational gap of great importance for patients and healthcare professionals (Healy & Mangin, 2024).

Treatment

Currently, there is no established treatment for PSSD. Patients are treated based on their characteristics, needs, expectations, and according to limited data from existing case reports and series (De Luca *et al.*, 2022). In an attempt to find a treatment that works, patients have resorted to a wide range of medications acting on various dopamine and serotonin receptors, as well as phosphodiesterase inhibitors and other drugs (Healy, LaPalme & Levin, 2020).

It is observed, both in clinical practice and in case reports, that some patients with PSSD are treated with buspirone or flibanserin. However, it is noted that the symptomatic relief promoted by these medications can diminish rapidly over time due to pharmacological desensitization and down-regulation of receptor density, frequently followed by a worsening of symptoms (Peleg *et al.*, 2022). Therapeutic alternatives focused on the serotonergic and dopaminergic systems have been suggested, utilizing 5-HT₁ agonists and 5-HT₂ and 5-HT₃ receptor antagonists, such as buspirone, trazodone, and mirtazapine. Although the latter two drugs can induce priapism and increased libido in healthy individuals, they have shown little or no efficacy in PSSD patients. Dopaminergic agonists such as pramipexole and cabergoline have also been tested, but the reported benefits were minimal. Trials using low-level laser phototherapy were performed on a patient with penile anesthesia; this intervention resulted in a 40% improvement in penile sensitivity, but it was not effective for anejaculation and erectile dysfunction symptoms in the same patient (Bala, Nguyen & Hellstrom, 2018). Calabrò *et al.* (2019) verified the improvement of a patient who used a nutraceutical (EDOVIS) containing L-citrulline, Tribulus terrestris, Andean maca, damiana, muira puama, and folic acid. They attributed the improvement in sexual function to the dietary supplement's action on the balance between the serotonergic/nitroxiidergic systems and neurosteroids, since the symptoms ceased only after treatment with EDOVIS, while other more common medications proved ineffective. Healy and Mangin (2024) state that it is important to point out that PDE5 inhibitors are not a treatment for PSSD, since they have no direct effect on the loss of pleasure sensation. De Luca *et al.* (2022) conducted a retrospective cohort study that tested the therapeutic success of some patients who used vortioxetine, bupropion, tadalafil, and pelvic muscle vibration therapy (Vibra-Plus). The results show some improvement with the use of practically all methods, highlighting vortioxetine and Vibra-Plus, which achieved the highest therapeutic success rates. However, the small sample size and the retrospective design of the study limit the generalizability of the data.

Most therapeutic approaches adopted so far have focused largely on reversing acute sexual effects rather than acting on the mechanism responsible for the persistent effects. This is similar to research efforts on tardive dyskinesia, which, for four decades, focused on the dopaminergic system without achieving a solution. Thus, a second challenge consists of precisely identifying a mechanism that may underlie persistent effects such as those witnessed in PSSD (Healy, LaPalme & Levin, 2020).

Pathophysiology

During the use of SSRIs, various changes are observed, such as: elevation of serotonin (5-HT) levels, reduction of dopamine, blockade of cholinergic and α 1-adrenergic receptors, inhibition of nitric oxide (NO) synthesis, elevation of prolactin levels, and reduction of testosterone and oxytocin levels. It is unknown, however, whether these changes normalize upon therapy discontinuation (Coskuner *et al.*, 2018).

The pathogenesis of PSSD remains unknown (Giatti *et al.*, 2021), despite several proposed etiologies, and it is possible that a combination of these theories is directly involved in the pathophysiology of this condition (Bala, Nguyen & Hellstrom, 2018). In light of this, Chinchilla Alfaro, Van Hunsel, and Ekhart (2022) report that hypotheses found in the literature include endocrine and neurochemical imbalances, neurotoxicity, ion channel alterations, and epigenetic modifications. Some authors even suggest that PSSD may result from mechanisms similar to the extrapyramidal effects reported by some SSRI users, with the difference lying

in the affected brain region (Healy, 2020).

According to Klaas et al. (2023), prolonged use of SSRIs is capable of desensitizing and dysregulating pre-synaptic 5-HT_{1A} autoreceptors, weakening the inhibition of serotonin release and elevating synaptic levels of this neurotransmitter. In this vein, Peleg et al. (2022) propose that sustained elevated levels of serotonin, even after treatment cessation, are chronically damaging to the serotonin transporter (SERT), as well as to presynaptic 5-HT_{1A} autoreceptors and postsynaptic 5-HT_{1A} receptors. It is also believed that this dysregulation negatively affects sexual motivation and that the effect of SSRIs on serotonin levels in peripheral nerves causes axonal damage (serotonergic neurotoxicity), similarly to 3,4-methylenedioxymethamphetamine (ecstasy), a substance likewise associated with sexual dysfunction after discontinuation (Rothmore, 2020).

Giatti et al. (2021) and Peleg et al. (2022) point to the possibility that the deficit in physiological sexual desire related to PSSD raises the question of a potential dopaminergic deactivation of the pleasure centers of the hypothalamus, the ventral tegmental area (VTA), and the nucleus accumbens (NAc). The neurobiological trigger of physiological sexual desire likely involves androgen and estrogen receptor signaling in the hypothalamus, which eventually results in dopaminergic activation of the medial preoptic area of the hypothalamus (mPOA), the central region responsible for controlling erections.

Along with this, Chinchilla Alfaro, Van Hunsel, and Ekhart (2022) add that serotonergic receptors are involved in the negative feedback regulation of the hypothalamic-pituitary-testicular (HPT) axis, such that dysregulation additionally promotes a reduction in testosterone and, therefore, an imbalance in the sexual response cycle. There are also reports of reduced plasma levels of luteinizing and follicle-stimulating hormones (LH and FSH, respectively) in SSRI users with associated sexual dysfunction when compared to asymptomatic patients also undergoing treatment with this medication.

Further, there is no consensus on how the sensory alterations caused by SSRIs arise. Lidocaine, which also causes genital numbness, seems to do so through an action on late sodium currents; curiously, serotonin reuptake inhibitor medications also exhibit effects on these ion currents (Healy, 2020; Reisman, 2020). Healy, LaPalme, and Levin (2020), through experimental assays involving intact planarians and fluoxetine, demonstrated that planarians whose bioelectric circuits were briefly modulated by small pharmacological molecules presented permanent alterations in the bioelectric patterns of their tissues, as well as in cellular and tissue functions, even long after the withdrawal of the original medications. Apparently, this process occurs over several months and seems to have a permanent effect despite the rapid turnover of all its somatic cells within a few weeks. Therefore, it is suggested that exposure to SSRIs is capable of modifying the bioelectric properties of neural and non-neural cells, resulting in persistent modifications of electrophysiology and cellular signaling.

In addition, it is hypothesized that prolonged use of SSRIs causes a persistent down-regulation of 5-HT_{1A} receptors (even after drug discontinuation) through epigenetic changes, in the form of increased expression of MeCP2 and MBD1 (Klaas et al., 2023). Subsequently, these changes promote an increase in the production of HDAC2 mRNA and, simultaneously, a reduction in the production of histone deacetylase (HDAC) H3. This process of epigenetic modification was observed in three brain areas: the frontal cortex, the dentate gyrus of the hippocampus, and the putamen. Therefore, it is believed that the down-regulation and desensitization of 5-HT_{1A} receptors are involved in the regulation of sexual motivation, thus proposing a new theory for PSSD (Bala, Nguyen & Hellstrom, 2018).

Finally, it is suggested that PSSD may be related to genetic polymorphisms in genes linked to the glutamatergic system of patients with depression or to structural alterations in brain regions involved in the sexual response. It was observed that the use of paroxetine for the treatment of obsessive-compulsive disorder (OCD) caused a significant reduction in the volume of the left amygdala in adolescent patients (Chinchilla Alfaro, Van Hunsel & Ekhart, 2022). That is, different studies indicate that SSRIs, by acting on the functioning of the glutamatergic system in different brain areas, are capable of causing imbalances in neuroplasticity. Thus, it is speculated that the ability of these medications to profoundly alter the neuroplastic profile may explain, in part, the nature of the permanent symptoms of PSSD (Peleg et al., 2022).

Impact

It is a fact that the persistent sexual symptoms caused by PSSD can be extremely distressing for the individuals who experience them (Marks, 2023). In a survey conducted by Studt et al. (2021), 59% of patients responded that the condition had an extremely negative effect on their quality of life, while another 23% stated that the impact was very negative. In written responses, individuals with PSSD reported receiving new diagnoses of depression, anxiety, and PTSD as a result of their condition. There were also reports of suicide attempts, current suicidal ideation, and acquaintances who suffered from these persistent changes and ended their own lives. A worrying theme in the written responses is the unprecedented willingness of patients to experiment with potentially harmful and illicit substances to treat PSSD symptoms. One man reported spending over 80 thousand dollars and traveling through several countries in a frustrated attempt to obtain symptom relief. Such accounts illustrate the level of suffering and desperation faced by individuals with PSSD.

The damage caused goes beyond sexual consequences. The emotional impact affects identity and behavior and provokes a negative self-perception. Furthermore, it is important to emphasize that PSSD is not a visible disability, and most of the time, patients feel misunderstood. Romantic relationships are also affected by the condition. For some patients, the condition led to the end of their marriage; for others, whose self-esteem was shattered, remaining alone seemed like a better solution than facing multiple rejections until finding a new partner. Finally, in the social sphere, there are reports of patients who lost their jobs due to PSSD. One of the first barriers faced by patients is the lack of credibility and the underestimation of the condition by healthcare professionals (Chinchilla Alfaro, Van Hunsel & Ekhart, 2022).

The lack of knowledge about PSSD among healthcare professionals was mentioned as a factor contributing to feelings of anger, frustration, and hopelessness. Most patients with PSSD were not even advised about the possibility of developing sexual dysfunction symptoms during the use of an SSRI. Others reported negative experiences with healthcare professionals who had never heard of PSSD or who dismissed the sexual dysfunction symptoms after SSRI withdrawal (Studt et al., 2021). Normally, this manifestation ends up being interpreted by physicians as a sign of depression relapse, ignoring the potential impact of SSRI use, which can even contribute to the onset of a new depressive episode (Chinchilla Alfaro, Van Hunsel & Ekhart, 2022). In this context, it becomes imperative for professionals to be attentive to non-sexual symptoms and to be able to differentiate the sexual dysfunction associated with PSSD from that related to depression, given that the symptoms of each condition can be quite distinct, with only a few overlapping symptoms (Peleg et al., 2022). Marks (2023) mentions that physicians need to do more to ensure that patients are informed about potential adverse effects before starting antidepressant use. By doing so, they can simultaneously offer hope and potentially improve treatment adherence by informing patients that PSSD is rare and that sexual dysfunction during SSRI use can be managed by switching medications, reducing the dose, using PDE5 inhibitors, or psychosexual therapy. He further adds that omitting this information can be viewed as a violation of medical ethics.

The current priority must be to increase awareness of the condition among patients and healthcare professionals. Professionals need to be aware of the intense suffering experienced by patients with PSSD, provide information about sexual function, and record it chronologically before prescription, during regular follow-ups, and after the discontinuation of SSRI use. It is also necessary to develop objective and validated questionnaires that include information about genital anesthesia and pleasureless orgasm (Chinchilla Alfaro, Van Hunsel & Ekhart, 2022). The concept that an essential pharmacological treatment can lead to long-term adverse effects after its discontinuation must be considered in clinical practice. PSSD is currently a new and important example of this (Peleg et al., 2022).

Discussion

Despite advances in the clinical characterization of PSSD, its diagnosis still represents a significant challenge for healthcare professionals, especially due to the absence of criteria formally recognized by classification systems such as the DSM or ICD (Chinchilla Alfaro, Van Hunsel & Ekhart, 2022). This gap contributes to

the underreporting of the condition, delays in initiating therapeutic interventions, and the recurrent invalidation of patient complaints in the clinical setting.

Given this situation, a diagnostic flowchart based on a critical review of the current literature and its most cited criteria was proposed in this study. The tool aims to guide clinical reasoning through a systematic outline, promoting greater diagnostic certainty and the exclusion of potential concurrent causes of sexual dysfunction.

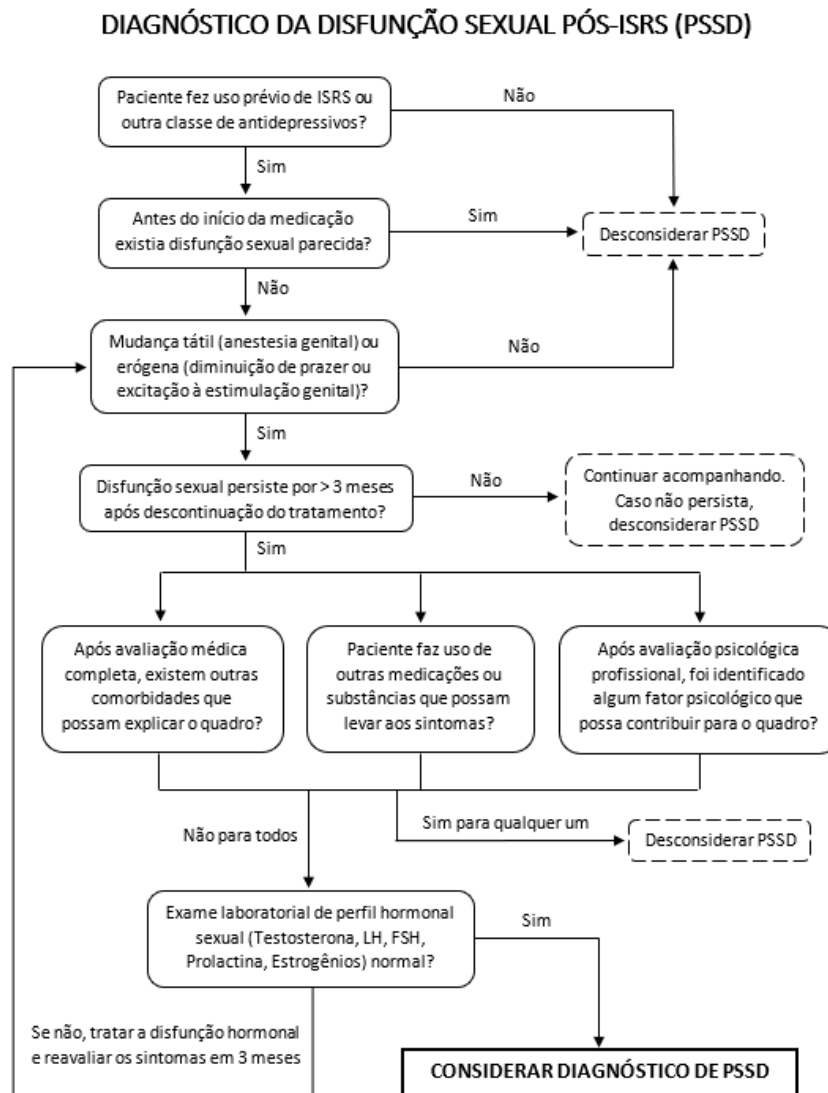
The flowchart begins with the verification of prior use of SSRIs or other classes of antidepressants and, from there, guides the investigation into the onset, type, and persistence of symptoms, with an emphasis on the presence of tactile and erogenous changes, considered hallmark characteristics of the syndrome. The structure of the algorithm also includes complementary clinical evaluations, such as hormone tests, the exclusion of medical comorbidities, and a formal psychological evaluation. The objective is to ensure that a diagnosis of PSSD is only considered after all plausible differential hypotheses have been ruled out. See Figure 2.

It is important to emphasize that this proposal does not replace official diagnostic criteria, but it presents itself as a relevant contribution to clinical practice, as it offers a clear and structured tool to support professionals in dealing with a complex, multifactorial, and often neglected condition.

The large proportions that this condition has been reaching are indisputable. In recent years, several major international and national media outlets have published articles on PSSD, such as: The New York Times – “After Antidepressants, a Loss of Sexuality” (Ghorayshi, 2023), The Guardian – “‘It feels like we’ve been lobotomised’: the possible sexual consequences of SSRIs” (Cox, 2024), G1 – “O risco de anestesia genital depois de interromper o uso de antidepressivos” (Tavares, 2024), Brasil em Folhas – “Disfunção sexual pós-antidepressivos gera preocupação em pacientes e especialistas” (Oliveira, 2024), and New York Post – “Gen Zers say antidepressants have ruined their sex lives: ‘I’m dead inside’” (Schlott, 2025).

With the increasing visibility of the topic, several websites dedicated to supporting PSSD patients and promoting new research on the syndrome have emerged. Some examples include: rxisk.org (which offers a \$100,000 USD prize to whoever finds a cure), sidefxhub.com, pssdnetwork.org, pssdforum.org, pssdcanada.ca, pssd-uk.org, survivingantidepressants.org, and antidepressantrisks.org.

Figure 2 - Proposed flowchart for the clinical diagnosis of PSSD

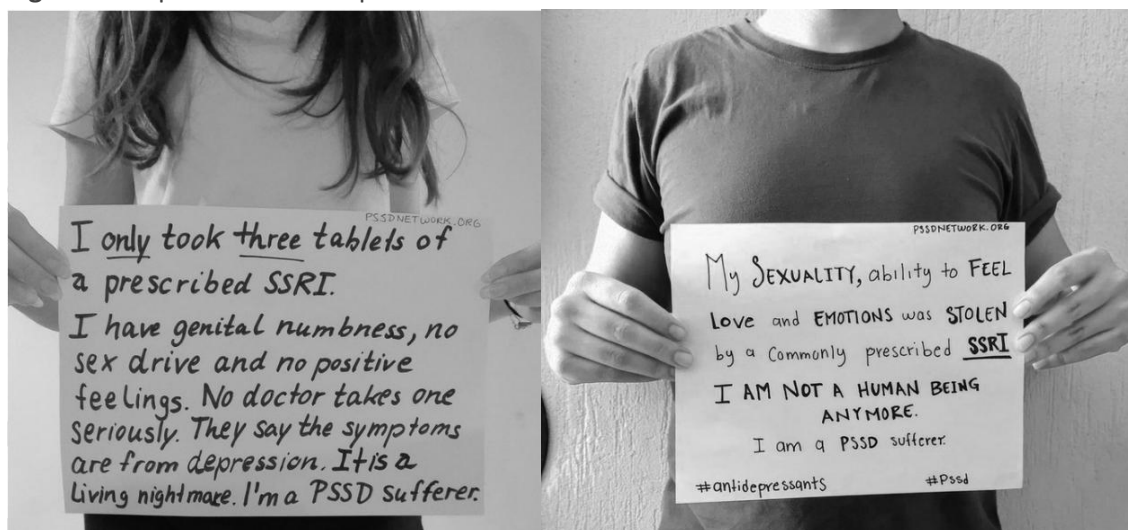


Note: This flowchart is based on the integration of observational evidence, case reports, and unofficial guidelines; it is not yet recognized by formal classification systems such as the DSM or ICD.

Source: Vitor Salles Coelho dos Reis (2025).

The website pssdnetwork.org created a highly impactful awareness campaign in which patients with the condition publish their photos holding signs that share the impact the disease has had on their lives. As an example, we present the accounts of two anonymous young individuals suffering from PSSD: One young person states: "I only took three tablets of a prescribed SSRI. I have genital numbness, no sex drive and no positive feelings. No doctor takes me seriously. They say the symptoms are from depression. It is a living nightmare. I'm a PSSD Sufferer." The other wrote: "My sexuality, ability to feel love, and emotions were stolen by a commonly prescribed SSRI. I am not a human being anymore. I am a PSSD sufferer." See Figure 3.

Figure 3 - Reports from PSSD patients



Source: Adapted from the PSSD Network website. Available at: <https://www.pssdnetwork.org>. Accessed on: June 9, 2025.

In light of this growing social mobilization and the evident suffering in patient narratives, it becomes urgent to rethink the ways in which the medical field has approached persistent antidepressant-induced adverse effects. Despite the progress in recognition of the condition by the media and the patient community, many healthcare professionals continue to minimize or deny the possibility that PSSD represents a real and distinct iatrogenic phenomenon from depression.

Many patients report negative clinical experiences, including the dismissal of their accounts, refusal to acknowledge published literature, and the automatic attribution of symptoms to a relapse of the depressive condition. This pattern not only compromises proper diagnosis but also exacerbates the psychological suffering of those affected (Healy, Le Noury & Mangin, 2019). As Stinson (2013) shows, many PSSD patients had already overcome their depressive episode or did not present concurrent mood symptoms, remaining exclusively with sexual symptoms after discontinuing the SSRI. Such data reiterate that PSSD is not a trivial complaint but a potentially devastating condition that compromises fundamental aspects of human identity, affectivity, and sexuality.

In this scenario, and given the consolidation of evidence regarding PSSD and its severe impacts, we must, more than ever, reevaluate current prescription criteria for antidepressants, especially in mild or sub-clinical cases of mood or anxiety disorders. It is recommended that medications be used at the lowest possible dose capable of achieving the desired therapeutic effect, minimizing excessive and prolonged exposure to biochemical changes that contribute to the onset of persistent conditions. Since we do not yet have an established treatment or full comprehension of the condition's pathophysiology, prevention becomes fundamental. Specialists recommend the immediate discontinuation of the medication as soon as genital anesthesia emerges (Ben-Sheetrit et al., 2023).

It is observed in clinical practice that most patients who enter a psychiatric office end up leaving with an SSRI prescription. This class of medications, because they exhibit good efficacy and being considered safe for a long time, became established as the first therapeutic choice for various disorders such as depression, anxiety, bulimia, and premenstrual dysphoric disorder. However, emerging data point to a need for greater caution. For example, would it be appropriate to prescribe an SSRI to a 22-year-old individual with mild anxiety, being aware of the risk—even if rare—of permanent loss of sexual function? In this case, do the benefits outweigh the risks? The objective of this discussion is not to discredit the use of SSRIs, but rather to problematize their indiscriminate prescription, often without due consideration of the risk/benefit ratio in light of new scientific evidence.

It is equally important to recognize the methodological limitations of the present study, which, as a narrative rather than a systematic review, implies a greater susceptibility to selection and interpretation biases. The inclusion of sources was influenced by availability, perceived clinical relevance, and recent visibility,

without the comprehensiveness guaranteed by formal systematic review protocols. Furthermore, most of the available literature on PSSD consists of case reports, small series, and unofficial documents, limiting the strength of the conclusions and preventing more robust quantitative analyses. The existence of temporal and language restrictions may have excluded relevant publications in other languages or periods. The absence of primary data collection reinforces that the findings described here should be interpreted as critical syntheses of the existing literature rather than definitive evidence.

Final Considerations

Post-SSRI Sexual Dysfunction (PSSD) constitutes a syndrome that is still underreported and insufficiently understood, characterized by symptoms such as genital anesthesia, loss or reduction of libido, anorgasmia, erectile dysfunction, and an absence of sexual pleasure, which persist even after the discontinuation of the antidepressant. These symptoms significantly affect the quality of life, identity, and romantic bonds of affected patients.

Despite the increase in clinical reports and the growing mobilization of patient and researcher communities, the scientific literature remains marked by substantial gaps. Data regarding prevalence, incidence, time of onset, clinical evolution, risk factors, comorbidities, and demographic characteristics remain scarce. This absence compromises the formal recognition of the syndrome in international classification systems, such as the DSM and ICD, and reinforces institutional neglect regarding the condition.

Given this scenario, this study aimed to systematize current knowledge on PSSD, propose a practical diagnostic flowchart to assist in identifying the condition, and critically reflect on medical listening, the clinical recognition of the syndrome, its psychosocial impacts, and current SSRI prescription criteria.

As a narrative review, this study presents inherent limitations to its design, such as the absence of a systematized search protocol, which reduces exhaustiveness and may introduce selection bias regarding the included sources. Furthermore, the existing literature is mostly composed of case reports, small series, and unofficial documents, restricting the strength of the conclusions and preventing robust epidemiological estimates. Language and temporal limitations may also have occurred in the selection of publications, reinforcing that the presented results should be interpreted as a critical synthesis of current production rather than conclusive evidence.

For PSSD to be properly understood, diagnosed, and treated, the development of robust studies with a high level of scientific evidence is imperative. This includes multicenter longitudinal controlled studies with large and global samples. These studies are fundamental to precisely estimating the prevalence of the syndrome, identifying clinical, genetic, hormonal, or environmental risk factors, understanding its pathophysiological mechanisms, and, above all, developing effective therapeutic interventions that restore sexual function and quality of life for patients.

Further, the urgent need for clinical protocols to evaluate sexual function before, during, and after antidepressant use is highlighted, as well as the strengthening of active pharmacovigilance strategies. The clinical recognition of PSSD, combined with qualified and empathetic listening, represents not only a technical-scientific advance but an ethical imperative that reinforces the principles of patient autonomy and informed consent.

We conclude, therefore, that PSSD must be treated as a real condition with disabling potential that demands greater investments in scientific research. It is hoped that the information gathered here will contribute to expanding knowledge about this syndrome and serve as a basis for future research, so that in the near future, patients will no longer be rendered invisible and can finally receive dignified care backed by solid scientific knowledge and clinical sensitivity.

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