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REVIEW

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Selective serotonin reuptake inhibitors, post-treatment sexual dysfunction and persistent genital arousal disorder: A systematic review

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Abstract

Purpose: Adverse effects of selective serotonin reuptake inhibitors (SSRIs) on sexual function have been an important area of research for many years. However, the duration of SSRI-associated sexual adverse effects, and their possible persistence after treatment discontinuation, is still uncertain. The aims of the current systematic review were first to identify existing evidence of sexual dysfunction following SSRI discontinuation, and to provide an account of reported symptoms and proposed treatment options; and second, to establish whether current literature allows accurate estimates of the prevalence of such sexual dysfunction.

Methods: A systematic review was conducted on PubMed, Embase, and Google Scholar; papers with clinical data regarding patients with persistent sexual dysfunction after SSRI treatment suspension were included.

Results: Overall, two retrospective interventional studies, six observational studies and 11 case reports were judged eligible for inclusion. It was not possible to determine reliable estimates of prevalence. Similarly, a cause-effect relationship between SSRI exposure and persistent sexual impairment could not be ascertained. Nonetheless, the potential for continued sexual disturbances despite discontinuation could not be entirely ruled out.

Conclusions: There is a need to investigate a possible dose–response relationship between SSRI exposure and persistent sexual adverse effects. Treatment options for persistent dysfunctions remain limited, but novel therapeutic approaches may be required in order to address an otherwise neglected need for sexual well-being.

KEYWORDS
antidepressants, PGAD, PSSD, sexual dysfunction, SSRI

Livio Tarchi, Giuseppe Pierpaolo Merola and Ottone Baccaredda-Boy contributed equally to this study.

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Key Points

- Persisting sexual dysfunctions after SSRI exposure have been a main concern for clinicians and patients
- A systematic review with a critical appraisal of current evidence on the topic is warranted
- There was insufficient evidence to justify a limitation or an early interruption of SSRI prescriptions
- Persisting dysfunctions may be associated with a relapse in depressive or anxious symptoms
- Treatment options for persistent dysfunctions remain limited

1 | INTRODUCTION

Selective serotonin reuptake inhibitors (SSRIs) are widely used as treatments for a range of psychiatric conditions.[1,2] They are known to cause important psychological and physical sexual adverse effects during treatment, such as loss of sexual interest, emotional indifference or 'blunting', erectile dysfunction and delayed ejaculation or anorgasmia.[3] Recent reports indicate their potential to cause long-term sexual adverse effects after treatment discontinuation.[4] This phenomenon is sometimes referred to as 'post-SSRI sexual dysfunction' (PSSD),[5] and has attracted the attention of clinicians, patients' interest groups, pharmaceutical companies and pharmacovigilance centres since its description in 2006.[6]

No diagnostic standard for PSSD has been suggested, although unifying criteria have been proposed.[7] A recent review emphasised the substantial clinical heterogeneity underlying PSSD, and uncertainty over what the clinical condition might comprise.[8] Despite the paucity of robust literature, there is accumulating evidence of this concern,[9] especially in the form of case reports.[10–12] According to clinical anecdotal evidence, PSSD encompasses a broad spectrum of symptoms, but the most common accounts emphasise loss of sexual interest, pleasureless orgasms, genital dryness, and genital anaesthesia.[13] A new domain, relating to post-SSRI asexuality, has also been proposed[7]; and is described as a 'dampening of sexual interest and pleasure resulting from a prenatal or pre-teen exposure to a serotonin reuptake inhibitor'. A summary of proposed symptoms for PSSD is offered in Table 1. An aetiology is not established, although possible mechanisms underlying persistent sexual dysfunction during SSRI exposure include their effects on neurotransmitters (including serotonin, noradrenaline, and nitric oxide[12] – at both the central and autonomic level[14]), on sex-hormones (e.g., testosterone, oestrogen, prolactin[15–17]), via sensory dampening in erogenous areas,[18] and by inducing emotional blunting.[19] Various management options have been proposed for sexual dysfunctions which arise during SSRI treatment.[20] However, sexual dysfunction which persists or occurs only after SSRI discontinuation might have differing etiopathological mechanisms. For these reasons, the timing of the onset of PSSD symptoms compared to SSRI discontinuation (i.e., whether it occurs as a continuation of adverse effects first experienced during treatment, or only emerges after treatment withdrawal) is of particular interest when attempting to characterise the condition.

Sexual disturbances have more frequently been investigated in terms of hypofunction,[21] namely decreased libido, limited arousal, painful intercourse, erectile dysfunction or delayed orgasm; but this might reflect the observation that sexual 'hyperfunctioning' is generally under-reported[22] and misdiagnosed.[23,24] Sexual hyperfunction has also been described in relation to psychological or biological factors,[25] represented by an increased sexual drive, more frequent arousal, and lack of control over one's sexuality.[26] Therefore, in order to investigate the spectrum of symptoms along a continuum, literature was explored for concerns relating to sexual hyperfunctioning, not limiting the observations to hypofunction alone. In this respect, anecdotal evidence has emerged on SSRI-induced 'Persistent Genital Arousal Disorder' (PGAD).[27] As a clinical entity, PGAD has been characterised in patients who have not taken an SSRI.[28] However, reports of PGAD developing after SSRI discontinuation have also been described,[27] warranting clinical and research attention. The timing of onset of PGAD is therefore of interest to understand possible etiopathogenesis of PSSD. In a recent consensus statement, the

TABLE 1 Principal symptoms described in relation to PSSD, PGAD.

PSSD[7]	PGAD[29]
Reduction or loss of sexual desire	Persistent or recurrent, unwanted or intrusive, distressing sensations of genital arousal
Erectile dysfunction	Genito-pelvic dysesthesia (e.g., buzzing, tingling, burning, twitching, itch, pain)
Inability to orgasm or decreased sensation of pleasure during orgasm	
A change in tactile or sexual genital sensation	
Genital pain	
Reduced nipple sensitivity	
Decrease or loss of nocturnal erections	
Reduced ejaculatory force	
Flaccid glans during erection	
Decreased vaginal lubrication	

Abbreviations: PGAD, persistent genital arousal disorder; PSSD, post SSRI sexual dysfunction.

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International Society for the Study of Women's Sexual Health (ISSWSH) highlighted a definition of PGAD as being 'characterised by persistent or recurrent, unwanted or intrusive, distressing sensations of genital arousal [...] that persist for ≥3 months and may include other types of genito-pelvic dysesthesia (e.g., buzzing, burning, twitching, itch, pain)'. Furthermore, another identified criterion is the feasibility to experience PGAD symptoms in genito-pelvic regions other than the clitoris (e.g., mons pubis, vulva, vestibule, vagina, urethra, perineal region, bladder, and/or rectum). It is also noted that these sensations may be associated with the experience of uncontrollable orgasms, and/or having an excessive number of orgasms (a summary of symptoms is reported in Table 1). Finally, it underlined the potential contribution of SSRI discontinuation.[29] Patients suffering from PGAD complain principally about bursts of genital stimulation, which are described as distressing and a source of shame, leading to a decrease in quality of life.[30] No precise evaluation of the possible causative role of SSRI discontinuation on PGAD currently exists, nor is there much information on its prevalence or incidence. Current evidence suggests a higher prevalence of overall PGAD in women than in men,[31] but most literature on PGAD is primarily based on samples constituted predominantly by females. The possible mechanisms underlying PGAD are uncertain, although many potential neurological, anatomic, and biochemical factors have been considered.[32] No definite treatment has been proposed,[29] whether or not PGAD was associated with SSRI intake, reflecting the diverse presentations of the condition.[33] Theories have been proposed on the sexual adverse effects following SSRI discontinuation,[34] but given the complex nature of the phenomenon, the condition is probably multifactorial.[35] For these reasons, it is premature to establish whether PGAD can be considered as a manifestation of PSSD or a separate, wider, and only partially overlapping entity.

Given these uncertainties, our primary aim was to evaluate current evidence of chronic sexual dysfunction or impairment following SSRI discontinuation. As estimates of PSSD prevalence or incidence are inconclusive, our secondary aim was to estimate the prevalence for both PSSD and post-SSRI PGAD. We also aimed to provide an analytic account of onset timing, reported symptoms and potential treatments for both PSSD and post-SSRI PGAD.

2 | METHODS

The methodology of this systematic review accords with PRISMA 2020 guidelines.[36] Included articles were observational or experimental studies, either cross-sectional or longitudinal in design. Case reports and case series were included. Inclusion criteria were as follows: presence of clinical data regarding SSRI use and sexual disturbance either persisting or presenting after treatment termination. Clinical definitions of PSSD were reported, as long as both sexual dysfunction and SSRI discontinuation were present, or the term was directly mentioned, to offer an analytic account of what the entity might entail. Similar criteria were applied for the evaluation of PGAD. Exclusion criteria were as follows: the article being a systematic review, a meta-analysis, an opinion article, animal studies, or methodological or technical contributions with no analysis of clinical data. The following data were extracted from selected papers: study description, involved SSRIs, sexual symptoms reported, onset of condition in regard to SSRI treatment and additional results.

2.1 | Information sources and search strategy

We searched the electronic databases PubMed, Embase, and Google Scholar in order to select studies. The following strings were used for reviewing PSSD through Pubmed:

'(PSSD OR persistent OR suspension OR post) AND SSRI AND (sex OR sexu*)'

While on Google Scholar and Embase a more stringent search was used:

'PSSD AND SSRI AND (sex OR sexu*)'

Finally, the following string was used for post-SSRI Persistent Genital Arousal Disorder among the same databases:

'(PGAD OR "persistent genital arousal") AND SSRI'

Only papers published in English were included. The last search was run in December 2022.

2.2 | Data selection process

Four authors (O. B. B, G. P. M., L. T., and F. A.) assessed the published abstracts of potentially eligible studies independently. Eligibility assessment was performed in an unblinded standardised manner. If there were doubts concerning potential eligibility, reviewers examined the full text of the articles. The published protocol required consensus in case authors disagreed on the inclusion of a specific study. In case the opinion was not unanimous, a majority vote would have been taken between all authors: however, the authors agreed on all eligibility assessments of the studies, so no consensus vote was needed. Four authors (O. B. B., G. P. M., L. T., and F. A.) independently extracted relevant data from each included paper: study design (experimental observational, case report), population (number of subjects), incidence or prevalence of post-treatment adverse effects, reported symptoms, symptom onset, and eventual treatment.

2.3 | Risk of bias

Four authors (O. B. B., G. P. M., L. T., and F. A.) independently assessed risk of bias for individual papers using the JBI critical appraisal checklist for analytical cross-sectional observational

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studies,[37] ROBINS-I for non-randomised interventional studies,[38] RoB2 for randomised controlled trials,[39] and the JBI critical appraisal checklist for case reports.[37] Each negative answer at the JBI checklist was counted as a positive risk of bias, with the highest risk of bias being represented by 8/8. If opinions were not unanimous, a majority vote would have been taken between all authors: but all authors agreed on all the eligibility assessments of the studies, so no consensus vote was needed. Risk of bias scores are reported, in detail, in the Supplementary Materials as eContent-1.

3 | RESULTS

A total of 859 papers were found after searching: 786 were included after screening for duplicates, 571 excluded on the basis of title and abstract, and a further 196 were excluded after manuscript review and application of inclusion criteria. Consequently, 19 studies were finally selected: 2 retrospective interventional studies; 6 observational studies; and 11 case reports (see Figure 1). A detailed account of each study is provided within the Supplementary Materials.

3.1 | PSSD – Prevalence, onset and reported symptoms

Included studies mainly consisted of case-reports, case series and observational studies in the form of online anonymous surveys: as such, no accurate estimate of PSSD prevalence can be inferred, a drawback in line with previous findings.[4] The average risk of bias score was at least medium or higher, indicating that methodological limitations abounded in the included studies.

The majority of sexual dysfunction symptoms arose during SSRI treatment and did not recede after discontinuation. Most studies showed evidence of sexual dysfunction arising during SSRI intake, and not receding after interruption.

Reported adverse effects following SSRI administration and discontinuation, collectively grouped as PSSD, ranged widely and differed between males and females; and included penile anaesthesia, pleasureless orgasm, loss of libido, emotional blunting, difficulty achieving orgasm, loss of nocturnal erections, reduced seminal volume, testicular pain, reduced penis size, premature ejaculation, watery ejaculate, slow leakage of ejaculate, and reduced sense of taste and smell.[40] Most reported adverse effects overlap with adverse effects described during SSRI treatment,[41] or with general symptoms

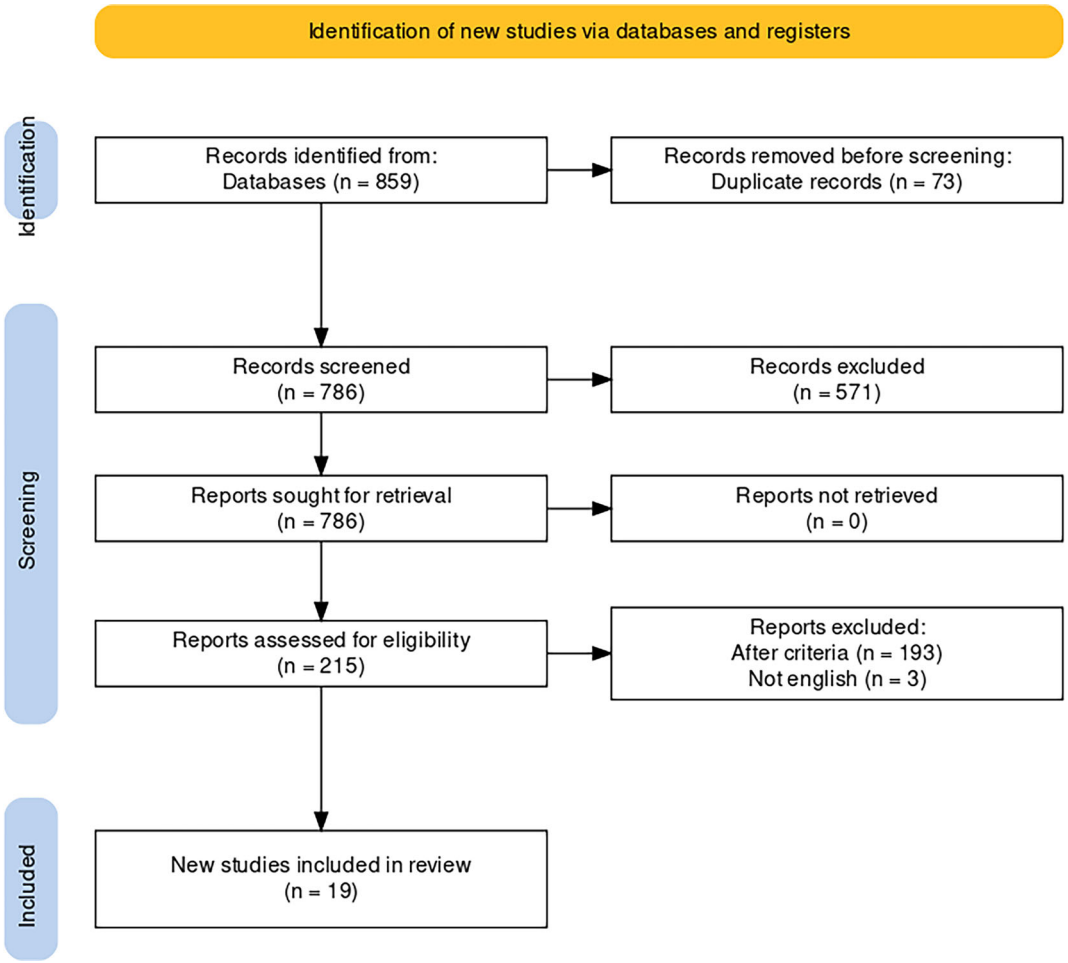

FIGURE 1 Flowchart of the inclusion and exclusion procedures.

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associated with depression,[42,43] with the exception of nipple[40] and genital anaesthesia.[6,10,12,13,44–46]

3.2 | Post-SSRI PGAD – Prevalence, onset and reported symptoms

Persistent genital arousal disorder was reported in 6 of 19 selected studies.[27,40,47–49] It was not possible to derive a precise estimate of the incidence or prevalence of PGAD from included studies. Estimates were based on case reports and online surveys and were mainly focused on female samples. When considering the time of onset, studies with larger sample sizes did not include adequate accounts of the timing of symptom onset in relation to SSRI treatment. Case reports had a balanced distribution of symptom presentation, before and after treatment discontinuation, with the latter being slightly more frequent.[27,49]

Some common features of PGAD have been identified and include physiological symptoms of persistent sexual arousal (lasting hours to days), in the absence of any form of sexual desire. Symptoms generally did not subside after the experience of sexual climax.[47] In some cases, genital sensations were not just reported as undesired, but also as distressing and unpleasant, being defined in more than one case as vaginal dysesthesia and/or allodynia.[50]

4 | DISCUSSION

This review summarises current literature on PSSDs, including the recent attempts to better characterise the clinical syndrome and its varying manifestations. Despite accumulating evidence, it was not possible to make a reliable estimate of the incidence or prevalence of the condition. This emphasises the need for a standardised approach in handling and reporting suspected PSSD or post-SSRI cases. To allow a better characterisation of PSSD or post-SSRI PGAD, a qualitative description of the symptomatology represents a useful starting point, as it typically involves a more comprehensive consideration of the subject. Both in case reports and observational studies, men and women anecdotally reported sexual under-function after SSRI interruption: however, only women were described as exhibiting PGAD after SSRI discontinuation, and only in case reports.

4.1 | PSSD – Presumptive mechanisms of action

Nearly every SSRI currently marketed in Western Europe and Northern America has been associated with reports of PSSD, with the sole exception of dapoxetine, which is mainly targeted at sexual functioning rather than mood regulation, unlike other SSRIs.[57] Selected studies often explored adverse effects of other serotonergic drugs, such as SNRIs (venlafaxine, desvenlafaxine, duloxetine) and TCAs (clomipramine), which are therefore briefly mentioned in Tables 2, 3, and 4. Data on these classes is currently limited, although a citizen petition suggests they might be less likely to induce PSSD compared to SSRIs.[5]

Potential aetiological mechanisms include 'serotonergic neurotoxicity' of SSRIs.[13] A plausible neurobiological explanation could be increased serotonergic tone induced by SSRIs, and secondary dopaminergic inhibition of sexual function. A prominent role could also be played by neuroactive steroids (e.g., testosterone), which are possibly involved in another phenomenon which shares several features with PSSD, namely 'post-finasteride syndrome'.[58] Animal studies[59] suggest evidence of 5HT-$_{1A}$ receptor activation by SSRI; and PSSD-like symptoms induced in rats exposed to fluoxetine,[60] which persisted after a 20-day washout period.[61] Interestingly, 5HT-$_{1A}$ antagonists seemed to alleviate symptoms in the animal model,[60] and preliminary evidence has shown amelioration following the administration of vortioxetine,[51] a known 5HT-$_{1A}$ inhibitor.[62] The activation of postsynaptic serotonin 5HT-$_{2A}$ receptors has also been implicated in sexual disturbances during SSRI treatment, but its potential role in PSSD is not clarified.[63,64] Oxytocin release dysfunction has been further shown to mediate PSSD symptoms in animal models[65]: oxytocin involvement seems to be relevant to post-SSRI symptomatology, as it was observed to be chronically reduced after prolonged administration of SSRI in rats.[66,67] Maternal exposure to SSRI was also associated with lower levels of oxytocin in the offspring.[68] Oxytocin infusion in rats was shown to ameliorate PSSD symptoms, at least in males.[69]

The clinical features of the condition suggest an associated cognitive mechanism in parallel with neurobiological factors. Several considerations have been offered about the interplay between SSRIs, depressive symptoms, and their impact on overall functioning. First, after an extended period of SSRI treatment, and due to experienced sexual functioning impairment, a patient might develop negative conditioning towards sexual activity[70]: accordingly, SSRIs would not directly cause PSSD, but the experienced sexual impairment could induce worsening of anxiety, anticipatory or consummatory, negative expectations and automatic thoughts regarding sex through classical conditioning mechanisms.[70] Second, a reduction in libido or sexual satisfaction has also been associated with SSRI, which could further reinforce conditioning,[71] as well as exacerbate potential stressors within an intimate interpersonal relationship.

Selective serotonin reuptake inhibitors are among first line treatments for depressive and anxiety disorders, whose features can include loss of libido and sexual dysfunctions.[72] These symptoms may overlap with PSSD, thus warranting attention on the putative causal role of SSRIs discontinuation. SSRI interruption could expose an underlying residual depressive symptomatology or a worsening of the clinical condition, hindering interpretation of potential causal relationships.[73,74] However, among sexual adverse effects reported in relation to PSSD, nipple and genital anaesthesia do not seem fully explained by a relapse in depressive or anxious symptoms. Nonetheless, these sexual disturbances might epitomise the diagnostic criteria of acquired Male Hypoactive Sexual Desire Disorder (HSDD) or Female Sexual Interest/Arousal Disorder (SIAD), which the DSM-5-TR describes as associated with depressive or anxious symptomatology.[75] In favour

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TABLE 2 Results, interventional studies.

References	SSRI involved	Description	Sexual symptoms reported	Symptoms onset (average)	Additional results
De Luca 2022[51]	Citalopram, Paroxetine, Sertraline, Fluoxetine, Escitalopram	Retrospective interventional study, without control. 13 male patients treated: 5 with Vortioxetine 2 with Vortioxetine and nutraceuticals 1 with Bupropion 1 with Bupropion, Tadalafil and nutraceuticals 1 with Bupropion and nutraceuticals 1 with Tadalafil 1 with nutraceuticals only 1 with mechanical stimulation (Vibra-Plus)	An enduring change in somatic (tactile) or erogenous (sexual) genital sensation after (SSRI) treatment stops. Enduring reduction in or loss of sexual desire. Enduring erectile dysfunction Enduring inability to orgasm or decreased sensation of pleasure during orgasm.	From 2 to 4 weeks after starting treatment (8 patients) From 2 to 4 weeks after discontinuation (5 patients)	Amelioration of sexual functioning (assessed by International Index of Erectile Function 15) after 12 months.
Reisman 2021[44]	Fluoxetine, Sertraline, Escitalopram, Venlafaxine[a], Amitriptyline[b]	Retrospective interventional study, without control. 12 male patients. Biopsychosocial intervention, with L-Arginine and L-Carninitine supplementation. Phosophodiesterase inhibitors and Buspirone according to patient needs.	11 with loss of libido 9 with reduced sexual activities 9 with pleasureless orgasm 9 with loss of morning erections 8 with genital numbness 6 with erectile dysfunction 6 with 'disconnection between genitals and brain' 5 with emotional blunting 5 with reduced orgasmic intensity 4 with difficulty to achieve orgasm 1 with reduced power of ejaculation	3 patients with pleasureless orgasm after discontinuation 3 patients with genital numbness after discontinuation The rest of symptoms (majority) during treatment	Improvement at follow-up visit (6 months)

[a]Included although a serotonin-noradrenaline reuptake inhibitor.
[b]Included even if not an SSRI.

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TABLE 3 Results, observational studies.

References	SSRI involved	Description	Sexual symptoms reported	Symptoms onset (average)	Additional results
Alfaro 2021[52]		86 reports of PSSD submitted to the Netherlands Pharmacovigilance Center of Lareb between 1992 and 2021	53 reports of loss of libido 23 of erectile dysfunction 5 with anorgasmia	Not reported	Longest duration of illness reported was 23 years. SSRI may cause PSSD (no control).
Dannon 2004[53]	Paroxetine	72 patients who discontinued paroxetine after 1 year maintenance therapy were assessed regarding panic disorder and persistence of sexual adverse effects after treatment discontinuation	Unspecified sexual impairment	The sexual adverse effects onset generally date back to the initiation/maintenance phase of treatment	Secondary outcome was assessing the sexual adverse effects: sexual dysfunction was mainly reported and assessed before the discontinuation of the paroxetine therapy; the prevalence of sexual advsere effects did not differ between patients who completed 12 months of paroxetine treatment (29%) and patients who received paroxetine for more than 12 months (33%; df 1, $\chi^2 = 0.56$, $p > 0.05$)
Healy 2018[5] Hogan 2014[54] (Same as Healy 2018 [less complete version of the same data, 120 accounts])	Escitalopram Citalopram Paroxetine Fluoxetine Sertraline Fluvoxamine Venlafaxine[a] Duloxetine[a] Vortioxetine Clomipramine[a] Desvenlafaxine[a]	221 accounts collected through a website focused on informing about PSSD	Most frequent among males: loss of libido, genital anaesthesia, difficulty achieving orgasm, emotional blunting, loss of nocturnal erections, reduced seminal volume. Penile or testicular pain. Reduced penis size, premature ejaculation. Reduced testosterone. Watery ejaculate. Testicular atrophy. Other skin numbness. Soft glans, reduced sense of smell. Reduced sense of taste, penile curvature, PGAD, reduced nipple sensitivity. Most frequent among females: loss of libido, genital anaesthesia, difficulty achieving orgasm, emotional blunting, pleasureless or weak orgasm, vaginal dryness/pain, other skin numbness. Reduced nipple sensitivity. PGAD. Reduced sense of taste.	Not reported	SSRI may cause PSSD (no controls)

(Continues)

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TABLE 3 (Continued)

References	SSRI involved	Description	Sexual symptoms reported	Symptoms onset (average)	Additional results
Patacchini 2021[55]	Any SSRI included	135 subjects (115 males) recruited through an online survey. Subjects self-reported PSSD (the sample might thus be biased)	Outcome measured through Arizona Sexual Experiences Scale, Hospital Anxiety and Depression Scale, World Health Organisation Wellbeing Index	17 subjects experienced symptoms after discontinuation	Prevalence of 12.6% overall; no gender-specific prevalence reported
Sheetrit 2015[13]	Escitalopram Citalopram Paroxetine Fluoxetine Sertraline Venlafaxine[a] Desvenlafaxine[a]	23 patients from independent website; strict inclusion criteria were applied	Genital anaesthesia, pleasureless orgasm, mean ASEX scale score 21.6	Not reported	SSRI may cause PSSD (no controls)

[a]Not classified as an SSRI, but mechanism of action involves serotonin reuptake inhibition.

of an interplay between PSSD and a relapse in depressive or anxious symptoms, an interventional study[51] has shown a significant amelioration of the condition—defined in the inclusion criteria as 'an enduring change in somatic (tactile) or erogenous (sexual) genital sensation after (SSRI) treatment stops'—following administration of vortioxetine.

4.2 | PSSD – Proposed therapeutic approaches

Pathophysiological understanding of PSSD may be enhanced by knowledge of ameliorating factors. Vortioxetine, bupropion, tadalafil, and nutraceuticals have been reported as being employed for PSSD.[51] Cognitive-behavioural therapy has also been proposed as a warranted intervention for PSSD.[4] No specific guidelines for PSSD treatment are currently available.[4] Low power laser irradiation appeared beneficial in a single PSSD case report[12]; the dietary supplement 'EDOVIS' was also reported to apparently improve PSSD symptoms in a case report.[11] Failed therapeutic attempts were described with sequential bupropion, cabergoline and selegiline in one case.[6] Sildenafil and supplemental testosterone did not reverse symptoms in one report.[9] Preliminary evidence has also been gathered on animal models, as previously mentioned; in fact, oxytocin infusions in rats were shown to ameliorate PSSD symptoms.[69] In summary, current evidence is not sufficient to suggest a single approach in order to address sexual adverse effects in the general population.[69,70] This lack of sufficient evidence emphasises the need to develop and evaluate novel treatments for sexual hypofunctions.[76]

4.3 | Post-SSRI PGAD – Presumptive mechanisms of action

The aetiology of PGAD is not established. Several theories have been proposed[77] and some risk factors have been suggested, including hormonal influences, pudendal nerve neuropathy, and Tarlov cysts.[48] Research focused on psychological factors underlines the importance of anxiety and obsessive-compulsive disorder in pathogenesis.[78] SSRIs are hypothesised to cause receptor desensitisation,[66] at a local genital level or central level,[18] and that discontinuation exacerbates dysfunction as receptors remain desensitised for a longer period while circulating monoamines fall to pre-treatment levels.[8] SSRI discontinuation has been theorised to induce PGAD through the influence of atrial natriuretic peptide (ANP),[32] which may explain the higher prevalence of sexual dysfunctions in women with cardiovascular disease.[33] Increased blood levels of ANP have been observed in association of SSRI treatment.[79] Furthermore, ANP has been shown to cause vasodilation.[80]

4.4 | Post-SSRI PGAD – Proposed therapeutic approaches

Several attempts at treatment of post-SSRI PGAD have been reported, with variable outcomes. A case report of pharmacological

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TABLE 4 Results, case reports.

References	SSRI involved	Description	Sexual symptoms reported	Symptoms onset (average)	Additional results
Bolton 2006[45]	Sertraline	Genital anaesthesia and decreased libido persisting 6 years after sertraline discontinuation in a 26-year old male	Genital anaesthesia: decreased libido, delayed orgasm, anorgasmia, decreased genital tactile sensation	The sexual adverse effect onset dates back to the initiation of treatment (Onset during treatment)	Based on the provided evidence, there is a possible correlation between sertraline and persistent sexual dysfunction after treatment discontinuation in absence of urological disease
Calabrò 2019[11]	Citalopram	Single male, 23 years old, concurrent treatment with mirtazapine	Loss of libido, erectile dysfunction, anejaculation	During (immediately after administration)	Dietary supplement 'EDOVIS' seemed to be effective
Csoka 2006[6]	Citalopram, Fluoxetine, Sertraline	2 male and 1 female patient, aged mid-late 20 s	Anorgasmia, ED, reduced libido, decreased genital tactile sensation (citalopram), reduced libido, decreased genital and nipple tactile sensation, anorgasmia, reduced libido (fluoxetine), loss of libido, partial anorgasmia, reduced ejaculate volume, and genital numbness (sertraline)	The sexual adverse effects onset date back to the initiation of treatment (Onset during treatment)	SSRI administration held a strong chronological correlation with the sexual dysfunction reported by these 3 patients, as the symptomatology emerged shortly after their initiation (and persisted long after their discontinuation). A direct causality between SSRIs and sexual disturbances may exist, according to this anecdotal information
Csoka 2008[10]	Case 1: Fluoxetine Case 2: Citalopram Case 3: Paroxetine, Sertraline, Venlafaxine	3 CRs of male patients affected by sexual dysfunction following SSRIs administration	Case 1 and 2: Pleasureless orgasm, genital anaesthesia, difficulty maintaining and achieving erection Case 3: weak erection, continuous, slow leakage of seminal fluid during sexual activity but prior to ejaculation, significantly decreased genital sensitivity, and anorgasmia	During treatment, persistent thereafter	Symptoms appeared during treatment and were thereafter irreversible
Curran 2019[23]	Not disclosed	16-year old adolescent woman with concurrent bupropion treatment. Significant comorbidities and risk factors (depression; history of childhood sexual abuse; morbid obesity; dysmenorrhea)	Unwanted genital arousal, Spontaneous orgasms that interfere with social functioning, in absence of sexual desire. Additional trigger by movement or vibration.	Symptoms occurred at time of implant insertion (Etonogestrel rod) and concurrent SSRI interruption. Symptoms worsened after implant removal.	
de Magalhães 2015[47]	Citalopram	57-year old woman. Concurrent worsening of depression and PGAD. Concurrent anxiety related to physical sensations	Feelings of palpitations in the chest, which migrated distally to produce sensations of abdominal fluttering and of movement/ palpitations in vagina and	Symptoms occurred after the interruption of the medication with antidepressant.	As far as the researchers knew, this was the first case of likely association between citalopram and PGAD.

(Continues)

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TABLE 4 (Continued)

References	SSRI involved	Description	Sexual symptoms reported	Symptoms onset (average)	Additional results
			rectum. Uncontrollable sexual arousal		
Eibye 2014[48]	Paroxetine	31-year old woman, referred to the outpatient psychiatric department for depression, anxiety, somatic concerns, dependent personality disorder. History of familiarity for mood disorders, violence, adverse childhood experiences. Low compliance to treatments (paroxetine, sertraline, citalopram, fluoxetine, duloxetine, venlafaxine, mianserin, amitriptyline, nortriptyline, pregabalin, gabapentin, chlorprothixene, quetiapine and benzodiazepines).	Six symptoms of PGAD, as described by Goldmeier et al.[56] No further information on symptoms. Presence of Tarlov cyst, excluded as cause of PGAD.	Symptoms subjectively recalled after cessation of paroxetine.	Amelioration after reintroduction of paroxetine in treatment. Worsening upon introduction of agomelatine. Electroconvulsive therapy ameliorated the condition but did not achieve full remission.
Korda 2009[49]	Paroxetine	Middle-aged woman, age at onset not disclosed. Precise age not disclosed. Concurrent bipolar disorder.	Anorgasmia, unwanted genital arousal, Genital pulsing, tingling, engorgement, pressure, swelling, lubrication, not related to sexual desire, excitement, thoughts, or fantasies. Vaginal pain either throbbing, sharp or burning.	After abrupt discontinuation of paroxetine (duration not reported)	Increased severity by heat, exercise, driving, horseback riding. Decreased severity by cooling, topical anaesthetics, oral analgesics
Leiblum 2008[27]	Case 1: Venlafaxine and Escitalopram Case 2: Venlafaxine Case 3: Fluoxetine Case 4: Venlafaxine, as drug was reduced to 35 mg Case 5: Sertraline	5 women undergoing an interview. Subjective recall of PGAD as a result of antidepressants usage or withdrawal.	Increased libido, decreased capacity to reach orgasm. Unwanted genital arousal. Vibration or movement worsened sensations. Spontaneous orgasms that did not, or only partially relieve arousal.	Case 1: during and after discontinuation Case 2: after discontinuations for about 2 years Case 3: during and after discontinuation Case 4: anorgasmia during treatment, PGAD due to drug dose lowering until probable wash out after 2–4 weeks after discontinuation Case 5: after treatment discontinuation	SSRI anecdotally presented by patients as correlated to PGAD Amelioration after reintroduction of SSRI
Patacchini 2020[46]	Sertraline	21-year old male who underwent treatment with sertraline for 2 years. The drug was discontinued, and several symptoms emerged on	Premature ejaculation, physical impotence, absence of libido and sexual pleasure, tactile, and temperature anaesthesia in the genital area, emotional flattening	After gradual discontinuation of sertraline (duration not reported)	Case report of potential PSSD

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TABLE 4 (Continued)

References	SSRI involved	Description	Sexual symptoms reported	Symptoms onset (average)	Additional results
		discontinuation and lasted for 4 years. Treatment of these symptoms was only partially successful	and hedonic sphere, detachment, and alienation, reduced creative capacity/abstraction/ imagination, memory problems and attention deficits		
Waldinger 2015[12]	Paroxetine	Single male patient undergoing irradiation treatment	Penile anaesthesia	During (immediately after administration)	Low power laser irradiation may be effective in treating PSSD

therapy with duloxetine or pregabalin notes a reduction in symptoms within 2 weeks and complete resolution within 4 months.[81] Transcutaneous electrical nerve stimulation was also described, with beneficial results within a few hours[82]; at 2-month follow-up a large reduction (>90%) in spontaneous orgasms was reported. In one report, clitoridectomy was undertaken, but with only partial resolution of PGAD symptoms.[50] In another report,[48] an amelioration of symptoms was reported after the reintroduction of paroxetine in treatment. Electroconvulsive therapy ameliorated the condition in the same patient but did not result in full remission.[48] Agomelatine worsened the persistent and unwanted genital arousal.[48] Leuprolide held promising results in the management of PGAD, with one report suggesting that improvement achieved might be long-lasting, up to more than 1 year.[83]

4.5 | Clinical relevance and future perspectives

There are limited data concerning the onset timing and overall prevalence of these conditions in the current literature. With regard to PSSD, most studies show evidence of sexual dysfunction symptoms arising during SSRI treatment and not receding after interruption. For PGAD, studies with larger sample sizes do not report the time of onset of PGAD in relation to SSRI treatment, and case reports indicate a balanced distribution of symptom presentation before and after treatment discontinuation, with a slight prevalence of the latter.[27,49] Little is known about the prevalence of PSSD and more recent reviews have focused mainly on potential pathological mechanisms rather than characterising the condition and estimating its prevalence.[4]

Another consideration pertains to the potential long-term persistence of PSSD and post-SSRI PGAD. Much of the literature derives from case reports (some of which followed the patient for up to 2 years – References 12,45,46,84), small case series, and cross-sectional observational studies, and limited longitudinal data are available regarding the duration of PSSDs. The longest duration of illness reported was 23 years.[52] Longitudinal investigations are clearly needed. However, the findings of the current review support the European Medical Agency caution on SSRIs, namely the potential for continued sexual disturbances despite SSRI discontinuation.[85] Nonetheless, reports of amelioration after reintroduction of SSRIs have also been presented, signalling an interplay between depressive or anxious symptoms and sexual disturbances experienced after discontinuation.[48] The findings of our systematic review suggest considering PSSD and post-SSRI PGAD as potentially linked but distinct entities, though differing in treatment some aspects of pathogenesis and treatment approaches. Moreover, the scientific literature currently offers no data on post-SSRI PGAD in males, whereas PSSD has been described in both sexes. As further consideration, PSSD has been more frequently associated with hypofunction in males, whereas post-SSRI PGAD has been described as a sexual hyperfunction in females. In conclusion, we caution against routine early SSRI discontinuation, as the benefit–risk balance also needs to consider global quality of life, the impact on general functioning, overall reduction in

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suicidality[86,87] and the fact that switching antidepressant therapy could reduce sexual dysfunctions.[88]

Our review has identified a high risk of bias in most included reports, so warranting caution in generalising from these reports to wider clinical practice. The current evidence on PSSD suffers from uncertain inclusion criteria in the sampling processes, and in not adequately controlling for potential confounding factors such as psychopathology and comorbidities. Online surveys tend to not include a detailed description of the demographic and clinical characteristics of enrolled participants and are at risk of selection bias in recruiting participants, in favour of a higher prevalence of the disorder. Moreover, online surveys cannot accurately discriminate if sexual complaints concur with relational stressors, or whether sexual dysfunctions encompass a single partner, multiple partners, intercourse, or self-stimulation. A high-quality observational longitudinal study, with sufficient statistical power, and supported by clinical diagnostic interviews, is needed before definitive accounts of the condition can be provided.

4.6 | Limitations

This systematic review was performed through an inclusive string search, and over three different databases. The authors detected some discrepancies in comparison to previous reviews, even after accounting for the recency of the publications.[4,54,74,89] We limited our current review to articles in English, for which the full text was available.

5 | CONCLUSIONS

The seeming heterogeneity of PSSD as a condition emphasises the need for further detailed characterisation. The prevalence of PSSD or post-SSRI PGAD cannot be reliably derived from current reports, partly due to heterogeneity and methodological limitations in previous investigations. With regard to PSSD, most studies show evidence of sexual dysfunction symptoms arising during SSRI treatment and not receding after interruption. For post-SSRI PGAD, only reports of women were described, and only in case reports. Therefore, limited evidence supports symptom presentation after treatment discontinuation, but with contrasting evidence of similar accounts during treatment, and not receding after interruption. We advocate further studies to address patients' concerns, especially in the form of longitudinal observational studies. Sequential use of specific questionnaires and checklists would aid in estimating the prevalence of both PSSD and PGAD, with the additional benefit of accounting for potential mediating effects of either residual or worsening symptoms upon treatment discontinuation. There is a need to investigate the possible dose–response relationship between SSRI exposure and persistent sexual adverse effects. Treatment options for these conditions remain limited, but novel therapeutic approaches may be needed in order to address an otherwise neglected need for sexual well-being in large populations of patients.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The database of the studies, with the extracted data items, can be shared upon reasonable request to the corresponding author.

ETHICS STATEMENT

The authors state that no ethical approval was needed.

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REFERENCES

1. Pizarro M, Fontenelle LF, Paravidino DC, Yücel M, Miguel EC, de Menezes GB. An updated review of antidepressants with marked serotonergic effects in obsessive-compulsive disorder. *Expert Opin Pharmacother*. 2014;15(10):1391-1401.
2. Jakobsen JC, Katakam KK, Schou A, et al. Erratum to: Selective serotonin reuptake inhibitors versus placebo in patients with major depressive disorder. A systematic review with meta-analysis and Trial Sequential Analysis. *BMC Psychiatry*. 2017;17(1):162.
3. Atmaca M. Selective serotonin reuptake inhibitor-induced sexual dysfunction: current management perspectives. *Neuropsychiatr Dis Treat*. 2020;16:1043-1050.
4. Bala A, Nguyen HMT, Hellstrom WJG. Post-SSRI sexual dysfunction: a literature review. *Sex Med Rev*. 2018;6(1):29-34.
5. Healy D. Citizen petition: sexual side effects of SSRIs and SNRIs. *Int J Risk Saf Med*. 2018;29(3–4):135-147.
6. Csoka AB, Shipko S. Persistent sexual side effects after SSRI discontinuation. *Psychother Psychosom*. 2006;75(3):187-188.
7. Healy D, Bahrick A, Bak M, et al. Diagnostic criteria for enduring sexual dysfunction after treatment with antidepressants, finasteride and isotretinoin. *Int J Risk Saf Med*. 2022;33(1):65-76.
8. Peleg LC, Rabinovitch D, Lavie Y, et al. Post-SSRI sexual dysfunction (PSSD): biological plausibility, symptoms, diagnosis, and presumed risk factors. *Sex Med Rev*. 2022;10(1):91-98.

10991557, 2023, 10, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5653 by Universita Di Firenze Sistema, Wiley Online Library on [04/09/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

9. Reisman Y. Sexual consequences of post-SSRI syndrome. *Sex Med Rev*. 2017;5(4):429-433.
10. Csoka AB, Csoka A, Bahrick A, Mehtonen OP. Persistent sexual dysfunction after discontinuation of selective serotonin reuptake inhibitors. *J Sex Med*. 2008;5(1):227-233.
11. Calabrò RS, De Luca R, Manuli A, Portaro S, Naro A, Quattrini F. Towards improving post-SSRI sexual dysfunction by using nutriceuticals: lessons from a case study. *J Sex Marital Ther*. 2019;45(6):562-565.
12. Waldinger MD, van Coevorden RS, Schweitzer DH, Georgiadis J. Penile anesthesia in post SSRI sexual dysfunction (PSSD) responds to low-power laser irradiation: a case study and hypothesis about the role of transient receptor potential (TRP) ion channels. *Eur J Pharmacol*. 2015;15(753):263-268.
13. Ben-Sheetrit J, Aizenberg D, Csoka AB, Weizman A, Hermesh H. Post-SSRI sexual dysfunction: clinical characterization and preliminary assessment of contributory factors and dose-response relationship. *J Clin Psychopharmacol*. 2015;35(3):273-278.
14. Ahrold TK, Meston CM. Effects of SNS activation on SSRI-induced sexual side effects differ by SSRI. *J Sex Marital Ther*. 2009;35(4):311-319.
15. Kim S, Park YM. Serum prolactin and macroprolactin levels among outpatients with major depressive disorder following the administration of selective serotonin-reuptake inhibitors: a cross-sectional pilot study. *PLoS One*. 2013;8(12):e82749.
16. Lupu D, Pop A, Cherfan J, Kiss B, Loghin F. In vitro modulation of estrogen receptor activity by norfluoxetine. *Clujul Med*. 2015;88(3):386-390.
17. van Rooij K, Poels S, Worst P, et al. Efficacy of testosterone combined with a PDE5 inhibitor and testosterone combined with a serotonin (1A) receptor agonist in women with SSRI-induced sexual dysfunction. A preliminary study. *Eur J Pharmacol*. 2015;15(753):246-251.
18. Corona G, Ricca V, Bandini E, et al. Selective serotonin reuptake inhibitor-induced sexual dysfunction. *J Sex Med*. 2009;6(5):1259-1269.
19. Opbroek A, Delgado PL, Laukes C, et al. Emotional blunting associated with SSRI-induced sexual dysfunction. Do SSRIs inhibit emotional responses? *Int J Neuropsychopharmacol*. 2002;5(2):147-151.
20. Jing E, Straw-Wilson K. Sexual dysfunction in selective serotonin reuptake inhibitors (SSRIs) and potential solutions: a narrative literature review. *Ment Health Clin*. 2016;6(4):191-196.
21. McCabe MP, Sharlip ID, Lewis R, et al. Incidence and prevalence of sexual dysfunction in women and men: a consensus statement from the fourth international consultation on sexual medicine 2015. *J Sex Med*. 2016;13(2):144-152.
22. Dhuffar M, Griffiths M. Understanding the role of shame and its consequences in female hypersexual behaviours: a pilot study. *J Behav Addict*. 2014;3(4):231-237.
23. Curran KA. Case report: persistent genital arousal disorder in an adolescent woman. *J Pediatr Adolesc Gynecol*. 2019;32(2):186-188.
24. Millman AL, Rebullar K, Millman RD, Krakowsky Y. Female sexual dysfunction – awareness and education among resident physicians. *Urology*. 2021;150:175-179.
25. Asiff M, Sidi H, Masiran R, et al. Hypersexuality as a neuropsychiatric disorder: the neurobiology and treatment options. *Curr Drug Targets*. 2018;19(12):1391-1401.
26. Carvalho J, Štulhofer A, Vieira AL, Jurin T. Hypersexuality and high sexual desire: exploring the structure of problematic sexuality. *J Sex Med*. 2015;12(6):1356-1367.
27. Leiblum SR, Goldmeier D. Persistent genital arousal disorder in women: case reports of association with anti-depressant usage and withdrawal. *J Sex Marital Ther*. 2008;34(2):150-159.
28. Pease ER, Ziegelmann M, Vencill JA, Kok SN, Collins CS, Betcher HK. Persistent genital arousal disorder (PGAD): a clinical review and case series in support of multidisciplinary management. *Sex Med Rev*. 2022;10(1):53-70.
29. Goldstein I, Komisaruk BR, Pukall CF, et al. International Society for the Study of Women's Sexual Health (ISSWSH) review of epidemiology and pathophysiology, and a consensus nomenclature and process of care for the management of persistent genital arousal disorder/genito-pelvic dysesthesia (PGAD/GPD). *J Sex Med*. 2021;18(4):665-697.
30. Faubion SS, Rullo JE. Sexual dysfunction in women: a practical approach. *Am Fam Physician*. 2015;92(4):281-288.
31. Jackowich RA, Pukall CF. Prevalence of persistent genital arousal disorder in 2 North American samples. *J Sex Med*. 2020;17(12):2408-2416.
32. Goldmeier D, Bell C, Richardson D. Withdrawal of selective serotonin reuptake inhibitors (SSRIs) may cause increased atrial natriuretic peptide (ANP) and persistent sexual arousal in women? *J Sex Med*. 2006;3(2):376.
33. Bell C, Richardson D, Goldmeier D, Crowley T, Kocsis A, Hill S. Persistent sexual arousal in a woman with associated cardiac defects and raised atrial natriuretic peptide. *Int J STD AIDS*. 2007;18(2):130-131.
34. Kruger THC. Can pharmacotherapy help persistent genital arousal disorder? *Expert Opin Pharmacother*. 2018;19(15):1705-1709.
35. Facelle TM, Sadeghi-Nejad H, Goldmeier D. Persistent genital arousal disorder: characterization, etiology, and management. *J Sex Med*. 2013;10(2):439-450.
36. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;29(372):n71.
37. Munn Z, Barker TH, Moola S, et al. Methodological quality of case series studies: an introduction to the JBI critical appraisal tool. *JBI Evid Synth*. 2020;18(10):2127-2133.
38. Sterne JA, Hernán MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ*. 2016;12(355):i4919.
39. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*. 2019;28(366):l4898.
40. Healy D, Le Noury J, Mangin D. Enduring sexual dysfunction after treatment with antidepressants, 5α-reductase inhibitors and isotretinoin: 300 cases. *Int J Risk Saf Med*. 2018;29(3–4):125-134.
41. Rosen RC, Lane RM, Menza M. Effects of SSRIs on sexual function: a critical review. *J Clin Psychopharmacol*. 1999;19(1):67-85.
42. West SL, Vinikoor LC, Zolnoun D. A systematic review of the literature on female sexual dysfunction prevalence and predictors. *Annu Rev Sex Res*. 2004;15:40-172.
43. Thakurdesai A, Sawant N. A prospective study on sexual dysfunctions in depressed males and the response to treatment. *Indian J Psychiatry*. 2018;60(4):472-477.
44. Reisman Y, Jannini TB, Jannini EA. Post-selective serotonin reuptake inhibitor sexual dysfunctions (PSSD): clinical experience with a multimodal approach. *J Mens Health*. 2022;18(8):165.
45. Bolton JM, Sareen J, Reiss JP. Genital anaesthesia persisting six years after sertraline discontinuation. *J Sex Marital Ther*. 2006;32(4):327-330.
46. Patacchini A, Cosci F. A paradigmatic case of postselective serotonin reuptake inhibitors sexual dysfunction or withdrawal after discontinuation of selective serotonin reuptake inhibitors? *J Clin Psychopharmacol*. 2020;40(1):93-95.
47. de Magalhães FJC, Kumar MT. Persistent genital arousal disorder following selective serotonin reuptake inhibitor cessation. *J Clin Psychopharmacol*. 2015;35(3):352-354.
48. Eibye S, Jensen HM. Persistent genital arousal disorder: confluent patient history of agitated depression, paroxetine cessation, and a tarlov cyst. *Case Rep Psychiatry*. 2014;2014:529052.
49. Korda JB, Pfaus JG, Kellner CH, Goldstein I. Persistent genital arousal disorder (PGAD): case report of long-term symptomatic management with electroconvulsive therapy. *J Sex Med*. 2009;6(10):2901-2909.
50. Jackowich RA, Pink L, Gordon A, Pukall CF. Persistent genital arousal disorder: a review of its conceptualizations, potential origins, impact, and treatment. *Sex Med Rev*. 2016;4(4):329-342.

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51. De Luca R, Bonanno M, Manuli A, Calabrò RS. Cutting the first turf to heal post-SSRI sexual dysfunction: a male retrospective cohort study. *Medicines*. 2022;9(9):45.
52. Chinchilla Alfaro K, van Hunsel F, Ekhart C. Persistent sexual dysfunction after SSRI withdrawal: a scoping review and presentation of 86 cases from The Netherlands. *Expert Opin Drug Saf*. 2022;21(4):553-561.
53. Dannon PN, Iancu I, Cohen A, Lowengrub K, Grunhaus L, Kotler M. Three year naturalistic outcome study of panic disorder patients treated with paroxetine. *BMC Psychiatry*. 2004;11(4):16.
54. Hogan C, Le Noury J, Healy D, Mangin D. One hundred and twenty cases of enduring sexual dysfunction following treatment. *Int J Risk Saf Med*. 2014;26(2):109-116.
55. Patacchini A, Cosci F. Exposure to serotonin selective reuptake inhibitors or serotonin noradrenaline reuptake inhibitors and sexual dysfunction: results from an online survey. *Int J Risk Saf Med*. 2021;32(3):229-242.
56. Goldmeier D, Mears A, Hiller J, Crowley T, BASHH Special Interest Group for Sexual Dysfunction. Persistent genital arousal disorder: a review of the literature and recommendations for management. *Int J STD AIDS*. 2009;20(6):373-377.
57. Pryor JL, Althof SE, Steidle C, et al. Efficacy and tolerability of dapoxetine in treatment of premature ejaculation: an integrated analysis of two double-blind, randomised controlled trials. *Lancet*. 2006;368(9539):929-937.
58. Giatti S, Diviccaro S, Panzica G, Melcangi RC. Post-finasteride syndrome and post-SSRI sexual dysfunction: two sides of the same coin? *Endocrine*. 2018;61(2):180-193.
59. Sukoff Rizzo SJ, Pulicicchio C, Malberg JE, et al. 5-HT(1A) receptor antagonism reverses and prevents fluoxetine-induced sexual dysfunction in rats. *Int J Neuropsychopharmacol*. 2009;12(8):1045-1053.
60. Popova NK, Amstislavskaya TG. Involvement of the 5-HT(1A) and 5-HT(1B) serotonergic receptor subtypes in sexual arousal in male mice. *Psychoneuroendocrinology*. 2002;27(5):609-618.
61. de Jong TR, Snaphaan LJAE, Pattij T, et al. Effects of chronic treatment with fluvoxamine and paroxetine during adolescence on serotonin-related behavior in adult male rats. *Eur Neuropsychopharmacol*. 2006;16(1):39-48.
62. du Jardin KG, Jensen JB, Sanchez C, Pehrson AL. Vortioxetine dose-dependently reverses 5-HT depletion-induced deficits in spatial working and object recognition memory: a potential role for 5-HT1A receptor agonism and 5-HT3 receptor antagonism. *Eur Neuropsychopharmacol*. 2014;24(1):160-171.
63. Winter J, Curtis K, Hu B, Clayton AH. Sexual dysfunction with major depressive disorder and antidepressant treatments: impact, assessment, and management. *Expert Opin Drug Saf*. 2022;21(7):913-930.
64. Stahl SM. *Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications*. 5th ed. Cambridge University Press; 2021:644.
65. de Jong TR, Veening JG, Olivier B, Waldinger MD. Oxytocin involvement in SSRI-induced delayed ejaculation: a review of animal studies. *J Sex Med*. 2007;4(1):14-28.
66. Raap DK, Garcia F, Muma NA, Wolf WA, Battaglia G, van de Kar LD. Sustained desensitization of hypothalamic 5-Hydroxytryptamine1A receptors after discontinuation of fluoxetine: inhibited neuroendocrine responses to 8-hydroxy-2-(Dipropylamino)Tetralin in the absence of changes in Gi/o/z proteins. *J Pharmacol Exp Ther*. 1999;288(2):561-567.
67. Svirsky N, Levy S, Avitsur R. Prenatal exposure to selective serotonin reuptake inhibitors (SSRI) increases aggression and modulates maternal behavior in offspring mice. *Dev Psychobiol*. 2016;58(1):71-82.
68. Gouvêa TS, Morimoto HK, de Faria MJSS, Moreira EG, Gerardin DCC. Maternal exposure to the antidepressant fluoxetine impairs sexual motivation in adult male mice. *Pharmacol Biochem Behav*. 2008;90(3):416-419.
69. Cantor JM, Binik YM, Pfaus JG. Chronic fluoxetine inhibits sexual behavior in the male rat: reversal with oxytocin. *Psychopharmacology (Berl)*. 1999;144(4):355-362.
70. Brom M, Both S, Laan E, Everaerd W, Spinhoven P. The role of conditioning, learning and dopamine in sexual behavior: a narrative review of animal and human studies. *Neurosci Biobehav Rev*. 2014;38:38-59.
71. Jannini EA, Screponi E, Carosa E, et al. Lack of sexual activity from erectile dysfunction is associated with a reversible reduction in serum testosterone. *Int J Androl*. 1999;22(6):385-392.
72. Kennedy SH, Rizvi S. Sexual dysfunction, depression, and the impact of antidepressants. *J Clin Psychopharmacol*. 2009;29(2):157-164.
73. Baldwin DS, Cooper JA, Huusom AKT, Hindmarch I. A double-blind, randomized, parallel-group, flexible-dose study to evaluate the tolerability, efficacy and effects of treatment discontinuation with escitalopram and paroxetine in patients with major depressive disorder. *Int Clin Psychopharmacol*. 2006;21(3):159-169.
74. Montejo AL, Llorca G, Izquierdo JA, et al. Disfunción sexual con antidepresivos. Efecto del cambio a amineptino en pacientes con disfunción sexual secundaria a ISRS [Sexual dysfunction with antidepressive agents. Effect of the change to amineptine in patients with sexual dysfunction secondary to SSRI]. Actas Esp Psiquiatr. 1999;27(1):23–34. (Spanish).
75. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders: Fifth Edition Text Revision DSM-5-TR™*. American Psychiatric Association Publishing; 2022.
76. Baldwin DS, Palazzo MC, Masdrakis VG. Reduced treatment-emergent sexual dysfunction as a potential target in the development of new antidepressants. *Depress Res Treat*. 2013;2013:256841.
77. Kapuśniak N, Piegza M. Persistent genital arousal disorder – the present knowledge. *Psychiatr Pol*. 2021;19:1-17.
78. Leiblum SR, Chivers ML. Normal and persistent genital arousal in women: new perspectives. *J Sex Marital Ther*. 2007;33(4):357-373.
79. Cao C, Han JH, Kim SZ, Cho KW, Kim SH. Diverse regulation of atrial natriuretic peptide secretion by serotonin receptor subtypes. *Cardiovasc Res*. 2003;59(2):360-368.
80. Curry FRE. Atrial natriuretic peptide: an essential physiological regulator of transvascular fluid, protein transport, and plasma volume. *J Clin Invest*. 2005;115(6):1458-1461.
81. Philippsohn S, Kruger THC. Persistent genital arousal disorder: successful treatment with duloxetine and pregabalin in two cases. *J Sex Med*. 2012;9(1):213-217.
82. Waldinger MD, de Lint GJ, Venema PL, van Gils APG, Schweitzer DH. Successful transcutaneous electrical nerve stimulation in two women with restless genital syndrome: the role of adelta- and C-nerve fibers. *J Sex Med*. 2010;7(3):1190-1199.
83. Deka K, Dua N, Kakoty M, Ahmed R. Persistent genital arousal disorder: successful treatment with leuprolide (antiandrogen). *Indian J Psychiatry*. 2015;57(3):326-328.
84. Ekhart GC, van Puijenbroek EP. Does sexual dysfunction persist upon discontinuation of selective serotonin reuptake inhibitors? *Tijdschr Voor Psychiatr*. 2014;56(5):336-340.
85. European Medical Agency. Serotonin and noradrenaline reuptake inhibitors (SNRI); Selective serotonin reuptake inhibitors (SSRI) – Persistent sexual dysfunction after drug withdrawal. 2019 May. [cited 2022 Aug 3]. Report No: EMA/PRAC/265212/2019. Available from: https://www.ema.europa.eu/en/documents/prac-recommendation/prac-recommendations-signals-adopted-13-16-may-2019-prac-meeting_en.pdf
86. Hofmann SG, Curtiss J, Carpenter JK, Kind S. Effect of treatments for depression on quality of life: a meta-analysis. *Cogn Behav Ther*. 2017;46(4):265-286.
87. Geddes JR, Carney SM, Davies C, et al. Relapse prevention with antidepressant drug treatment in depressive disorders: a systematic review. *Lancet Lond Engl*. 2003;361(9358):653-661.

10991557, 2023, 10, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5653 by Universita Di Firenze Sistema, Wiley Online Library on [04/09/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

88. Jacobsen PL, Mahableshwarkar AR, Chen Y, Chrones L, Clayton AH. Effect of vortioxetine vs. escitalopram on sexual functioning in adults with well-treated major depressive disorder experiencing SSRI-induced sexual dysfunction. *J Sex Med*. 2015;12(10):2036-2048.
89. Balon R. SSRI-associated sexual dysfunction. *Am J Psychiatry*. 2006; 163(9):1504-1509. quiz 1664.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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