

A clinical guide to rare male sexual disorders

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Abstract

Conditions referred to as ‘male sexual dysfunctions’ usually include erectile dysfunction, ejaculatory disorders and male hypogonadism. However, some less common male sexual disorders exist, which are under-recognized and under-treated, leading to considerable morbidity, with adverse effects on individuals’ sexual health and relationships. Such conditions include post-finasteride syndrome, restless genital syndrome, post-orgasmic illness syndrome, post-selective serotonin reuptake inhibitor (SSRI) sexual dysfunction, hard–flaccid syndrome, sleep-related painful erections and post-retinoid sexual dysfunction. Information about these disorders usually originates from case–control trials or small case series; thus, the published literature is scarce. As the aetiology of these diseases has not been fully elucidated, the optimal investigational work-up and therapy are not well defined, and the available options cannot, therefore, adequately address patients’ sexual problems and implement appropriate treatment. Thus, larger-scale studies – including prospective trials and comprehensive case registries – are crucial to better understand the aetiology, prevalence and clinical characteristics of these conditions. Furthermore, collaborative efforts among researchers, health-care professionals and patient advocacy groups will be essential in order to develop evidence-based guidelines and novel therapeutic approaches that can effectively address these disorders. By advancing our understanding and refining treatment strategies, we can strive towards improving the quality of life and fostering healthier sexual relationships for individuals suffering from these rare sexual disorders.

Sections

Introduction

Post-finasteride syndrome

Restless genital syndrome

Post-orgasmic illness syndrome

Post-SSRI sexual dysfunction

Hard–flaccid syndrome

Sleep-related painful erections

Post-retinoid sexual dysfunction

Future perspectives

Conclusions

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Key points

- Rare male sexual disorders include post-finasteride syndrome, restless genital syndrome, post-orgasmic illness syndrome, post-elective serotonin reuptake inhibitor sexual dysfunction, hard-flaccid syndrome, sleep-related painful erections and post-retinoid sexual dysfunction.
- The exact mechanisms of these disorders are unclear and the conditions could involve both physical and psychological components.
- Post-finasteride syndrome symptoms can persist for months or even years after discontinuing treatment with 5 α reductase inhibitors.
- Symptoms of restless genital syndrome include unwanted and unpleasant genital sensations, often perceived as an imminent orgasm without sexual desire or stimuli, and a sense of restlessness in the genital area.
- Post-orgasmic illness syndrome presents as a combination of local (mucosal) and systemic flu-like and allergic symptoms.
- Post-selective serotonin reuptake inhibitor sexual dysfunction symptoms can occur even with a single dose of the drug and are not necessarily dose dependent.
- Hard-flaccid syndrome often occurs following penile trauma, such as excessive masturbation.
- In post-retinoid sexual dysfunction, symptoms can occur during retinoid treatment and persist after discontinuation, whereas in some patients symptoms can appear or worsen after isotretinoin is stopped.

Introduction

Men have sex not only to fulfil their sexual desire or sexual satisfaction but also to possess emotional connection and intimacy, psychological stability and physical health^{1,2}. According to the World Health Organization (WHO), sexual health is defined as “a state of physical, emotional, mental and social well-being in relation to sexuality; it is not merely the absence of disease, dysfunction or infirmity” ([WHO sexual health](#)). Indeed, sexuality forms a core part of health, and the overall well-being of all individuals should be recognized as a deeply integrated combination of mental, physical and sexual health.

Normal sexual function requires the cooperation of several psychological, neurological, vascular and endocrine mechanisms³. The limbic system, hypothalamus, autonomic and somatic nervous systems, several neurotransmitters, vascular endothelial system, muscles and sexual organs (urethra, vas deferens, seminal vesicles, prostate and penis) work together to achieve sexual function in the male. Any interruption to this integrated system from inside or outside – including drugs, substances (such as alcohol, cocaine or marijuana), hormonal disturbances and vascular pathological condition – can lead to sexual dysfunction.

The most common sexual dysfunctions in men are erectile dysfunction (ED) and premature ejaculation (PE), both of which have a prevalence up to 50% across several reports^{4–6}. Men can also experience

ejaculatory disorders – including delayed ejaculation, anejaculation, anorgasmia, retrograde ejaculation, painful ejaculation and haemospermia – and low libido^{7,8}. The rarity and unstandardized definitions of these conditions mean that their epidemiology remains unclear⁷, but all of these dysfunctions have been shown to substantially affect quality of life (QoL) of patients and their partners⁹. Thus, adequately addressing these disorders and implementing relevant therapy is of paramount importance.

However, the vast, complicated and interwoven system of male sexual function can also be affected by other, less recognized, sexual dysfunctions that are even more uncommon. Such sexual dysfunctions have been reported in the literature and include post-finasteride syndrome (PFS), restless genitalia syndrome (RGS), post-orgasmic illness syndrome (POIS), post-selective serotonin reuptake inhibitor (SSRI) syndrome (PSSD), hard-flaccid syndrome (HFS), sleep-related painful erections (SRPEs), and post-retinoid sexual dysfunction (PRSD)^{10–23}. As these disorders are often under-recognized and under-treated, patients are at risk of experiencing dismissive attitudes from professionals, unnecessary tests and misdiagnosis of a psychogenic disorder^{24,25}. Patients might then seek information about treatment from online sources and create their own chat groups to discuss their experiences^{26,27}, which can put them at risk of receiving inadequate care as poor-quality and inelaborate content can mislead patients and delay effective treatments^{28,29}. The main reasons for this need for information are the insufficiency and dispersal of data in the literature and the fact that physicians are often untrained in managing these rare and complex disorders.

In this Review, we describe the available evidence about the pathophysiology and symptoms of rare sexual male diseases from the clinical literature – including case reports, case series, observational studies and systematic reviews – in order to understand possible underlying mechanisms and improve management strategies for men with these disorders.

Post-finasteride syndrome

The 5 α reductase inhibitors (5-ARIs), specifically finasteride and dutasteride, have long been used to treat androgenetic alopecia (AGA) and benign prostatic hyperplasia (BPH) with proven efficacy and safety profile^{30–32}. Their mechanism of action is via inhibition of the conversion of testosterone into dihydrotestosterone (DHT). However, the adverse effects profile of these agents has led to debate around their use owing to the possible onset of a rare sexual dysfunction, so-called PFS, which is defined as the persistence of common adverse effects associated with 5-ARI treatment, even after the agent has been discontinued.

These agents can cause a wide range of effects – emotional, psychological, physical and sexual – all of which are collectively included in the definition of PFS. Symptoms attributed to this syndrome, including sexual effects (ED, decreased libido, chronic testicular pain and penis shrinkage), physical effects (gynaecomastia, penis shrinkage, penile curvature, testicular reduction, muscle atrophy and dry skin) and psychiatric symptoms (depression, anxiety, suicidal thoughts and insomnia), were highlighted by young patients who had been regularly using finasteride for the treatment of AGA³³. Notably, the definition of PFS extends to patients in whom the symptoms persist months or even years after treatment discontinuation³³.

The aetiology of the varied symptoms that characterize this syndrome can be explained by the wide localization of the 5-ARI enzyme in the body, including the brain, bones and muscles³⁴, which leads to the reduction of DHT in related tissues. In fact, reduced levels of

tetrahydroprogesterone, isopregnanolone and DHT and increased levels of testosterone and 17 β -oestradiol have been observed in the cerebrospinal fluid of patients with PFS after long-term 5-ARI use³⁵. In addition, reduced levels of dihydroprogesterone and increased 5 α -androstane-3 α , 17 β -diol and 17 β -oestradiol were seen in plasma from the same group of patients.

Aetiology, pathophysiology and diagnosis

5-ARIs inhibit the 5 α reductase enzyme nearly irreversibly, with high affinity and a slow rate of dissociation, resulting in long-lasting effect, regardless of the dose administered³⁶. They are rapidly absorbed after oral administration with a peak plasma concentration (C_{max}) of 9.2 μ g/l occurring 1–2 h (T_{max}) after administration of finasteride at a dose of 1 mg/day (ref. 37) and steady-state trough plasma finasteride concentrations are obtained after 3 days³⁸. Although finasteride is used to decrease prostate size for the treatment of BPH, animal studies in rats revealed changes in penile histology and architecture following the use of 5-ARIs (0.5 mg/rat/day), with a decrease in smooth muscle and an increase in collagen along with decreased expression of neuronal and endothelial nitric oxide synthase levels in the penis following treatment with dutasteride³⁹. A separate study demonstrated that rats treated with dutasteride for 12 weeks demonstrated a diminished in vivo erectile response, which did not improve following the washout period⁴⁰.

A phase II, blinded placebo-controlled study in 42 healthy male volunteers with no sexual or other disorders showed that administering finasteride 0.4–100 mg/day for up to 2 weeks reduced serum DHT levels from 2.02 nmol/l to 0.44 nmol/l in volunteers taking 50 mg, twice daily, which returned to pretreatment levels after 14 days⁴¹. Furthermore, slight increases in serum total testosterone and oestradiol levels (10–15%) were observed in the participants after finasteride treatment, although the oestradiol concentration remained within the normal range and the relationship between testosterone and oestradiol remained unchanged³⁷. The authors concluded that finasteride is very well tolerated, without altering the levels of other steroid hormones, and that it depresses DHT levels in healthy volunteers.

Supporting the role of 5-ARIs in sexual dysfunction, a 2016 meta-analysis focused on the clinical efficacy of 5-ARIs in a group of 5,956 patients with BPH (2,947 in the α -blocker (α -adrenergic receptor antagonist) group and 2,965 in the 5-ARI group) showed that 5-ARI therapy (dutasteride 0.5 mg or finasteride 5 mg daily) was associated with an increased risk of development of de novo ED (6.47% versus 4.71%, OR 1.42) as well as libido loss (3.37% versus 2.3%; OR 1.49)⁴².

To date, the most interesting information on this topic has come from a pharmacovigilance study published in 2015, which analysed the United States Food and Drug Administration Adverse Event Reporting System database for adverse effects in patients aged 18–45 years treated with low-dose finasteride for AGA between 1998 and 2013. The authors reported 4,910 persistent effects, 577 of which were sexual dysfunctions (11.8%). On average, sexual dysfunctions occurred 1.8 years after starting low-dose finasteride and lasted for 5.4 months after stopping treatment and included disturbances in sexual dysfunction, including ED, ejaculation disorders and orgasmic abnormalities. Interestingly, the study showed a substantial increase in persistent sexual adverse effects in 2011–2013, which was not explained by any clear hypothesis⁴³.

In an Italian survey of 79 patients who had experienced >6 months of PFS syndrome, 40.5% of patients reported ED, 16.5% difficulties in reaching orgasm and 87.3% loss of penis sensitivity, as well as reduced mental concentration (72.2%) and loss of muscle tone and/or mass (51.9%)⁴⁴. Similarly, Irwig and Kolukula³³ reported new-onset persistent

sexual dysfunctions associated with finasteride use in 71 men aged 21–46 years; overall, 94% of men reported low libido, 92% ED, 92% decreased arousal and 69% problems with orgasm. Interestingly, the mean number of reported sexual episodes per month dropped from 25.8 ± 18.0 to 8.8 ± 7.1 ($P < 0.0001$) and the total sexual dysfunction score increased before and after finasteride (from 7.4 ± 2.3 to 21.6 ± 3.4) use according to the Arizona Sexual Experience Scale ($P < 0.0001$)³³.

Furthermore, a prospective case–control study of 25 patients receiving 1 mg of finasteride for AGA and 28 control patients who did not receive 5-ARIs reported vascular abnormalities on penile Doppler ultrasound in 17 of the patients in the 5-ARI group (68%). However, these data could not be compared with controls as penile Doppler was performed only in those who had been treated with 5-ARIs⁴⁵. Even so, this study further highlights the development of possible persistent anti-androgenic sequelae even after cessation of 5-ARI therapy.

Changes in penile morphology have also been shown in animal studies. For example, in rats, both finasteride (5 mg/kg) and dutasteride (0.5 mg/kg) usage promoted penile morphological changes such as reduced sinusoidal space and smooth muscle in the corpus cavernosum on post-mortem histology compared with untreated control rats⁴⁶. Although this particular study did not assess intracavernosal pressures directly, the observed alterations in penile morphology could potentially be attributed to a decline in intracavernosal pressures. A separate study conducted in rats found that decreased intracavernosal pressure was linked to a reduction in sinusoidal space density caused by various substances (such as enalapril or sildenafil or a combination thereof)⁴⁷. However, some evidence has also suggested that some 5-ARI-related effects can also arise owing to genetic variability as well. In a small cohort of 8 patients with PFS, histological examination of tissue alteration in the skin from prepuce showed significant differences in the percentages of epithelial cells (basal cells of the epidermis) positive for nuclear androgen receptor (AR) in patients with PFS (80.66%) compared with controls (65.06%) ($P = 0.043$) and greater expression of stromal cells in PFS (40.06%) compared with controls (23.46%) ($P = 0.023$). However, the ratio of AR-positive stromal cells to serum testosterone concentrations was twofold higher in patients with PFS than in control patients ($P = 0.001$)⁴⁸, emphasizing how local variability of AR expression could be responsible for the persistent side effects of 5-ARI treatment⁴⁸.

Two polymorphisms in *AR* have been shown to be related to PFS. (CAG) rs4045402 and (GGN) rs3138869 extreme-length alleles were more frequent among patients with PFS (OR 5.88) who had AGA (OR 3.55) than patients with AGA who had not received treatment⁴⁹. In particular, the length of two trinucleotide repeats in *AR* – the polyglutamine (CAG)_n repeat and the imperfect polyglycine (GGN)_n repeat, both located in exon 1 of *AR* – might contribute to the frequency of some specific symptoms reported by patients with PFS. In this study, the onset of PFS symptoms soon after finasteride discontinuation occurred more frequently in subjects with the long (GGN) >23 repeats (28.6%) versus the medium (GGN) 23 (4.5%, OR 8.4) repeats and medium-to-short (GGN) \leq 23 (5.7%, OR 6.4) repeats haplotype. Furthermore, in patients with PFS, short (CAG)_n repeats showed a greater decrease in sexual desire and libido than medium repeats, whereas long (CAG)_n repeats were associated with worse orgasm than short repeats⁵⁰.

The faecal microbiota has also been implicated in the pathogenesis of PFS. A 2021 study demonstrated that patients with PFS had a reduction of richness and diversity of gut microbiota structure, in particular *Faecalibacterium* spp. and Ruminococcaceae UCG-005, whereas *Alloprevotella* and *Odoribacter* spp. were increased compared with

Box 1

Diagnostic criteria for PFS

Necessary:

- (1) Prior treatment with a 5 α reductase inhibitor.
- (2) Enduring sexual dysfunction after stopping treatment.

Additional:

- (3) Enduring reduction in, or loss of, sexual desire.
- (4) Enduring erectile dysfunction.
- (5) Enduring reduction in genital and orgasmic sensation.
- (6) The problem is present for ≥ 3 months after stopping treatment.

There should be:

- (7) No evidence of pre-drug sexual dysfunction that matches the current profile.
- (8) No current medical conditions that could account for the symptoms.
- (9) No current medication or substance misuse that could account for the symptoms.
- (10) No other prior medication that could account for the symptoms.

These criteria were determined by a multidisciplinary panel of experts²⁴. PFS, post-finasteride syndrome.

healthy controls⁵¹. Alterations in the steroid environment might explain faecal microbiota changes in patients receiving 5-ARIs. For example, microbial species, such as *Clostridium scindens*, mediate the conversion of glucocorticoids to androgens and can, therefore, be considered a potential target for finasteride. Furthermore, the brain–gut microbiota axis might be affected, as 5 α -reduced metabolites have been reported in plasma and cerebrospinal fluid of patients with PFS. However, this hypothesis has not been fully clarified, and further studies are required^{35,52}.

Thus, numerous controversies surround this syndrome, as studies have failed to shed light on the onset of male sexual dysfunctions in the short and long term after the suspension of 5-ARI treatment. Notably, the biological basis of the relationship between these disorders and 5-ARI therapy is not yet convincing and some patients report symptoms that cannot be adequately explained biologically, with the frequency of consultations for the conditions paralleling the respective media coverage, indicating a high degree of suggestibility^{53,54}.

Furthermore, reports from drug control agencies are also affected by selection bias, artefact and sometimes even confusion regarding the objectivity of the symptoms reported^{55,56}. When considering these studies, one must keep in mind that voluntary reporting of these disturbances considerably distorts the scientific data as the participants were a self-selected population.

PFS is primarily associated with the use of finasteride, a medication that was approved for treating male pattern baldness in 1997. In 2011, the US product label for finasteride products Propecia and Proscar included a warning about persistent ED following the discontinuation of treatment. In 2012, the label was further updated to include persistent libido disorders, ejaculation disorders, orgasm disorders

after stopping Propecia, and decreased libido after stopping Proscar. Notably, a PFS diagnosis should not be made if prior use of isotretinoin or an SSRI is reported. Sexual dysfunction that occurs while taking finasteride but resolves after discontinuing the treatment is not considered PFS. A multidisciplinary panel of experts has established criteria for diagnosing PFS, which include the prior treatment with a 5-ARI and enduring sexual dysfunction that persists after discontinuing the treatment. Additional criteria provide further guidance for diagnosing PFS (Box 1).

Treatment of PFS

Contrasting evidence in the literature means that the treatment of PFS is still under discussion. Thus, practical recommendations must be offered before starting long-term therapy based on patients' eligibility, including appropriate informed consent and advice on adverse effects, and proposing alternatives, such as switching to topical finasteride. Treatment with 5-ARIs is contraindicated in patients with a previous history of sexual dysfunction, infertility or psychiatric disorders, which can worsen with these agents. Unfortunately, specific risk factors for PFS are not yet identified and no specific recommendations to treat this syndrome are available, owing to the combined influence of psychological effects, nocebo reactions, comorbidities and other factors.

One published case report described the use of different treatment modalities in three patients. The first patient was managed with Sabal fruit extract soft capsules, Wuling capsules, letrozole, HCG+HMG injections, and 11-ketotestosterone; the second received took tadalafil, Wu Ling capsules, Bushen Yiniao pills, zopiclone and clomiphene citrate; and the third took sildenafil, zopiclone, Wu Ling capsules and Bushen Yiniao pills⁵⁷. However, this report did not describe the patients' outcomes. In another case report, one patient was prescribed HCGu 6,000 IU/week, split into three applications of 2,000 IU/week, in conjunction with anastrozole 2 mg/week, divided into two doses of 1 mg. His symptoms gradually but steadily got better over the course of 2 months, including less penile rigidity in a flaccid state, a warmer penis, more morning erections (without any changes in the rigidity of the erections), some growth in penile girth, absence of post-ejaculatory asthenia, increased libido, increased muscular tone and strength, and better mood and self-esteem⁵⁸. The second patient was started on tadalafil 5 mg/daily. He saw part improvements in penile size and erectile function after a few weeks of tadalafil use; however, he had to stop treatment owing to adverse effects of headache and tinnitus, and was then referred for psychotherapy owing to increased sexual anxiety.

In terms of practical recommendations, the presence of previous psychiatric or sexual disorders, family history of psychiatric illnesses and the presence of previous sexual dysfunction should all be considered in patients receiving finasteride treatment who report relevant PFS symptoms. After ruling out these aspects, patients referred with PFS should be offered support for their sexual symptoms, through both psychological and pharmaceutical approaches.

Restless genital syndrome

Restless genital syndrome (ReGS) was first described by Waldinger et al. in 2009 and is a clinical syndrome combining persistent sexual arousal syndrome or persistent genital arousal disorder (PGAD) with restless leg syndrome and/or overactive bladder and/or hypersensitivity of the urethra^{10,11}. The syndrome was first described in female patients and is also known as PGAD. However, reports of men with

this syndrome are sparse in the literature^{59,60}. In 2020, an online epidemiological study consisting of two North American samples, one from Canada ($n = 1,634$; mean age 18.15 ± 1.97 years) and the other one from the USA ($n = 1,026$; mean age 46.1 ± 16.97 years) was performed by directing questions to the participants on age, gender and the 5 self-report questionnaire of PGAD developed by Leiblum and Nathan⁶¹. The prevalence of PGAD was similar, if not more, prevalent in men (1.1–4.3%) than in women (0.6–2.7%)⁶². However, the study is limited by its online format and the prevalence reported cannot be extrapolated to samples outside North America. Thus, studies from different countries with different populations are required to estimate the exact prevalence of ReGS in men worldwide.

Aetiology, pathophysiology and diagnosis of ReGS

ReGS is characterized by unwanted and unpleasant genital sensations, for example, dysaesthesias and/or paraesthesias, which are often felt as an imminent orgasm in the absence of sexual desire or stimuli and/or are often perceived as a 'restlessness' in and around the genitals¹⁶.

ReGS is highly associated in women with restless legs and complaints of overactive bladder, is aggravated by sitting and has the clinical characteristics of small-fibre sensory neuropathy of the dorsal nerve of the clitoris in women⁶³, whereas in men ReGS has the characteristics of small-fibre sensory neuropathy of the dorsal nerve of the penis⁵⁹. Although the exact pathophysiology is unknown, some vascular causes, such as pelvic vasocongestion or pelvic varices, and neurological causes, including pudendal nerve neuropathy or possible dopaminergic mechanisms, have been associated with this syndrome^{61,64,65}. Of interest, ReGS is not associated with premorbid psychiatric disorders or with previous sexual abuse⁵⁹ (Fig. 1).

In the few reported cases of ReGS in men, all the patients reported unpleasant genital sensations such as a sexual urge, worsening when sitting and increased urgency to void^{65,66} and these reported genital sensations were similar – but not identical to – sexual arousal, and did not occur in the setting of sexual thoughts or desire⁶⁰. Orgasm alleviated the arousal for only a short time, after which the symptoms would return. Sensory testing of the genital region elicited a considerable

number of points of static mechanical hyperaesthesia bilaterally of the pubic bone and above the penis in the pudendal dermatome, whereas manual examination of the inferior pubic ramus and particularly along the dorsal nerve of the penis elicited the sensations of an imminent ejaculation and sensation of restlessness at the previously mentioned trigger points⁵⁹ (Box 2). The disease can be an immense source of distress and disability for the patients and can lead to social embarrassment and isolation.⁶⁵

Treatment of ReGS

A variety of treatments have been proposed and tested for ameliorating the symptoms of ReGS. Some case studies have reported limited (electroconvulsive therapy⁶⁷, hypnotherapy⁶⁸, botulinum toxin injections⁶⁹), or substantial (pelvic floor physiotherapy⁷⁰) success in female patients. The use of psychologically based interventions – including cognitive behavioural therapy and mindfulness-based therapies – has also been recommended to treat the impact of ReGS on psychological and sexual well-being. In the cases of ReGS in men that have been reported in the literature, one patient was treated successfully with transcutaneous electrical nerve stimulation to ameliorate symptoms by around 90%⁵⁹, but transcutaneous electrical nerve stimulation had no effect at all in another patient⁵⁹.

Finally, the SSRI paroxetine (20 mg orally per day) was successfully used to treat ReGS, potentially by reducing the patient's anxiety associated with his condition⁶⁰. In another case report, diazepam (2 mg every 6 h) and pregabalin (50 mg every 6 h) in a combined therapy model relieved symptoms in a 54-year-old man who had previously failed to respond to treatment with duloxetine 30 mg (ref. 71).

Dopamine has a role in promoting male sexual behaviour in rats and other mammals. This effect is partially mediated by its action in the medial preoptic area (mPOA) of the brain. The mPOA is believed to be involved in directing the male's motivation towards sexually relevant stimuli, coordinating the necessary genital reflexes for achieving erection and ejaculation, and enhancing the specific motor patterns associated with male copulation⁷². Several studies have proposed using pramipexole, a dopamine D3-selective receptor agonist typically used

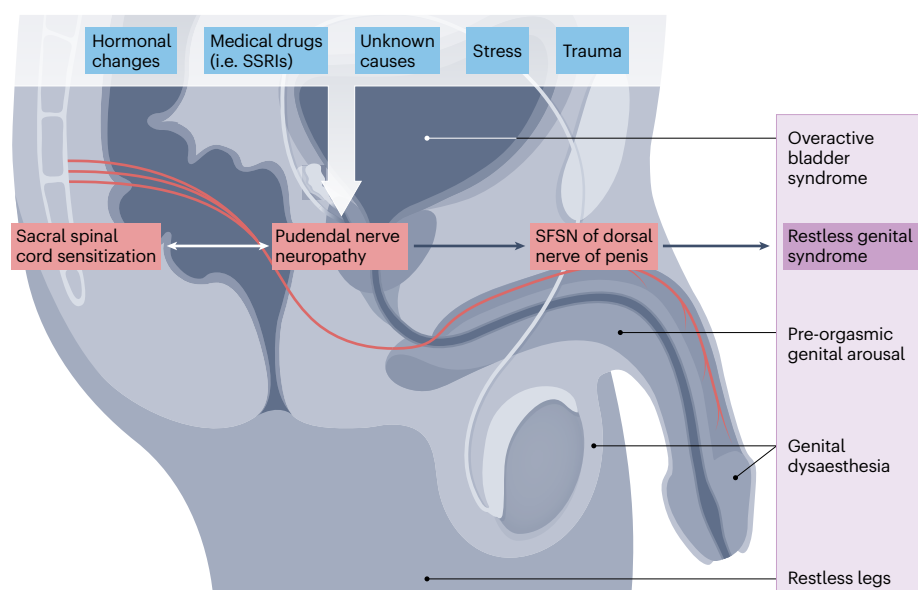


Fig. 1 | Restless genital syndrome has the characteristics of small-fibre sensory neuropathy of the dorsal nerve of the penis, possibly triggered by hormonal changes, drugs, stress, trauma and other unknown contributors. Symptoms include pre-orgasmic genital arousal, dysaesthesia and overactive-bladder-like symptoms, as well as symptoms similar to restless leg syndrome. SFSN, small-fibre sensory neuropathy; SSRI, selective serotonin reuptake inhibitor.

Box 2

Diagnostic criteria for ReGS

Necessary:

- (1) Persistent unwelcome sensations of genital arousal or irritability.
- (2) Genital arousal is painful or altered in quality rather than pleasurable.
- (3) Sexual activity provides limited or no resolution.
- (4) The abnormal sensations can be triggered by non-sexual stimuli.

Additional:

- (5) Spontaneous unwelcome and unpleasant orgasmic events.
- (6) The condition is highly distressing and ego-dystonic.
- (7) Management strategies, such as access to ice packs, are necessary.
- (8) A history of efforts to have the problem treated is common.
- (9) The problem is continuous (although episodic exacerbations and/or remissions may occur).
- (10) If linked to a selective serotonin reuptake inhibitor, the problem starts after discontinuation of the drug.
- (11) The problem is present for ≥ 3 months after stopping treatment.

These criteria are mostly for women and were determined by a multidisciplinary panel of experts²⁴. ReGS, restless genital syndrome.

to treat Parkinson disease and restless leg syndrome, in the treatment of ReGS in women^{73,74}. Typically, pramipexole would be expected to increase genital blood flow, given the role of dopamine in the mPOA. However, chronic use of pramipexole decreases phasic dopamine release (up to 40%), resulting in reduced genital blood flow, which might ameliorate the symptoms of ReGS^{74,75}. One case report has described successful treatment of a 45-year-old man diagnosed with ReGS using pramipexole, with an initial dosage of pramipexole 0.25 mg to be taken at night. After 1 week, the dosage was increased to 0.5 mg taken at night⁶⁶.

Further systematic medical research is needed in a large, well-designed cohort of males with ReGS in order to elucidate the key characteristics of its symptomatology, potential risk factors and treatment. However, identifying patients willing to participate in such research could be difficult, owing to the rarity of the disease and its poor acknowledgement by clinicians.

Post-orgasmic illness syndrome

POIS is an extremely rare disorder associated with flu-like or allergy-like symptoms – including extreme fatigue, nasal congestion, weakness and muscle pain, sweating, fever, irritability or mood disturbances, and poor concentration⁷⁶ – that emerge and progress within seconds, minutes or hours after ejaculation and usually last for 2–7 days. POIS was first reported in 2002 by Waldinger and Schweitzer, who presented two cases⁷⁶. The exact prevalence of POIS is unknown owing to the paucity of studies in the literature⁷⁷; but it has been recognized as a rare disorder by the National Institutes of Health Office of Rare Disease Research ([NIH GARD postorgasmic illness syndrome](#)). However, POIS is believed to be under-reported and underdiagnosed owing to the self-reported nature of the disease and the fact that the condition is

not recognized by many urologists^{78,79}. Waldinger et al.⁸⁰ classified POIS into two major types: primary (lifelong) POIS and secondary POIS starting from late adulthood.

Aetiology, pathophysiology and diagnosis of POIS

Although the underlying mechanism of POIS is not clear, some hypotheses have been proposed, including immunological phenomena^{80–82}, hypersensitivity and disordered cytokines^{80,83}, neuroendocrine response⁸⁴, transient deregulation of the autonomic nervous system⁸⁵ and opioid-like withdrawal⁷⁹ (Fig. 2).

According to Waldinger and colleagues, who proposed the immunological hypothesis of POIS⁸¹, an immunological reaction occurs against specific protein fractions of seminal plasma. The mechanism was confirmed using the skin-prick test (SPT), which was conducted with intracutaneous inoculation of autologous semen, with skin reactions observed 15 min after injection⁸¹. Waldinger et al. also hypothesized that the mucosal epithelium of the urinary tract might show hyperactive immune responses to the seminal fluid, which might be explained by the close contact of seminal peptides and T lymphocytes⁸⁰. By contrast, in a separate study, Jiang and colleagues could not detect semen-specific IgE to autologous semen, although the patient had a positive SPT⁷⁹. Thus, they postulated that IgE-mediated immunological reactions might not sufficiently explain the aetiology of POIS. Instead, they suggested that chemical imbalances in the brain were the basis of POIS, and that psychological factors serve as risk factors. In particular, they hypothesized that POIS might be related to opioid withdrawal, as orgasm triggers the consumption of large amounts of endogenous opioids, which might result in symptoms mimicking opioid withdrawal. An alternative hypothesis was suggested by Ashby and Goldmeier⁸⁴, who proposed that POIS was associated with a disordered cytokine or neuroendocrine response. According to this hypothesis, the release of catecholamines and neurotransmitter substances such as dopamine, noradrenaline, melanocortins, oxytocin, opioids, endocannabinoids and serotonin might contribute to arousal during orgasm. Additionally, orgasm can result in changes to the innate immune system, including changes in the number of leukocytes and natural killer cells in peripheral blood⁸⁶. Thus, a disordered or exaggerated cytokine and/or neuroendocrine response could drive the symptoms of POIS.

POIS presents as a combination of local and systemic flu-like and allergic symptoms, mostly occurring seconds to hours after ejaculation^{80,81}. Local symptoms are observed as mucosal manifestations, such as nasal congestion or itching eyes⁸¹, whereas systemic symptoms include fatigue, headache, concentration difficulties, muscle tension, fever and mood changes⁸¹. Diagnostic criteria for POIS – based on symptom type, onset and duration – were suggested by Waldinger and colleagues in 2016 and were further expanded by Strashny and colleagues, who suggested adding enquiries about pain and QoL in 2019 (ref. 87) (Box 3).

Treatment of POIS

On the basis of the proposed immunological or allergic aetiology of POIS, hyposensitization treatment using autologous semen was performed in two patients whose SPTs with autologous semen were positive⁸¹. According to the hyposensitization therapy protocol, increased concentrations of intracutaneous injections of autologous semen (from initial semen dilutions of 1/40,000 and 1/20,000 in gradually increasing titres) were applied. Symptoms improved after 15 and 31 months of injections in these two men. This procedure should be

considered in well-equipped centres, but the risk of anaphylaxis and systemic reactions must be taken into account⁸¹.

Another case report describes the treatment of a Korean man diagnosed with POIS, in whom the presence of semen-specific IgE was detected by IgE immunoblotting and enzyme-linked immunosorbent assay, and who was treated with intralymphatic immunotherapy. This approach further supports the immunological and allergic hypothesis, as the alleviation of POIS-related symptoms in this patient indicates a possible association of POIS with type 1 hypersensitivity reactions⁸².

A number of other therapeutic approaches have been tested in case studies. Treatment with antihistamines, prednisone, benzodiazepines and SSRIs have not been shown to be effective at managing the somatic symptoms of POIS, despite improving mood, especially with SSRIs⁸³. By contrast, a case report showed that treatment with the NSAID diclofenac 75 mg improved symptoms up to 80% and doubled (from 2 to 4 times) the sexual intercourse frequency of the patient per month⁸⁴. Nevertheless, NSAID therapy has not successfully improved the POIS-related symptoms in other patients, suggesting the need for further elucidation of the pathophysiology and management of this disorder⁸³. In a 2021 report, it was found that silodosin, a highly selective $\alpha 1A$ -blocker that causes anejaculation, was an effective treatment for POIS in 8 of 14 patients (57%)⁸⁸. However, for now, POIS remains a challenge for clinicians, with no clear diagnosis or treatment.

Post-SSRI sexual dysfunction

SSRIs are prescribed to manage a wide variety of mental health concerns such as depression, post-traumatic stress disorder, obsessive-compulsive disorder, generalized and social anxiety, chronic pain, chronic fatigue and post-menopausal syndromes⁸⁹. In addition, SSRIs have been used as off-label treatments for PE and paraphilia^{79,90}. Almost all patients who take SSRIs report a degree of genital sensory change (reduced sensitivity, numbness) within 30 min of administration and experience some forms of sexual side effects while on medication⁹¹. The sexual dysfunction is expected to resolve upon drug termination; however, some patients experience persistent sexual effects including decreased libido, ED, delayed ejaculation, genital anaesthesia, vaginal dryness, nipple insensitivity and anorgasmia after discontinuation of SSRIs^{92,93}. In men, a decrease in sensation and numbness in the genital area, decreased sexual drive, pleasureless orgasm or anorgasmia, ED and PE are common symptoms of PSSD^{89,92–94}.

PSSD was first reported in 2006 as a case report ($n = 3$) and subsequently became recognized as a unique disorder^{18,95,96}. In 2019, The European Medicines Agency recommended an update on SSRI and serotonin and noradrenaline reuptake inhibitor (SNRI) product labels to include information about persistent sexual disorders after discontinuing the medication⁹⁷. No dose–response correlation has been shown, as only one dose of the drug can result in PSSD^{94,98}.

Aetiology, pathophysiology and diagnosis of PSSD

SSRIs work by blocking the reuptake of serotonin (5-HT) by the serotonin transporter, leading to an increase in the amount of 5-HT in the synaptic space⁹⁹. Although the exact process is not fully understood, serotonin is widely believed to have a dampening effect on sexual function, whereas dopamine enhances it¹⁰⁰.

The specific impact of serotonin on sexual function could be due to its interaction with different subtypes of 5-HT receptors – stimulation of 5-HT_{2A} receptors has been linked to negative effects on sexual function such as libido loss, ED and orgasmic abnormalities^{101–103}. The stimulation of 5-HT pathways in the raphe nuclei, which run down the

spine and into the brain, is believed to have a detrimental effect on the three stages of sexual activity: interest and desire, physiological arousal and orgasm^{101–103}. This theory is supported by studies showing that the stimulation of 5-HT₂ and 5-HT₃ receptors decreases sexual function in rodents¹⁰⁴. In humans, SSRIs, which increase 5-HT signalling, are commonly associated with adverse sexual effects, whereas drugs with 5-HT_{2A} antagonist activity (such as mirtazapine and nefazodone) have a low likelihood of causing sexual effects¹⁰⁵. The extent and type of sexual side effects experienced vary greatly among patients using SSRIs, suggesting that genetic factors might also have a role in an individual's reaction to a particular SSRI treatment¹⁰⁶.

Several theories have been proposed for the pathogenesis of PSSD, including biochemical and neurochemical changes and epigenetic gene expression alterations. Although none of them has been proven to be the exact underlying mechanism, a combination of those theories might be involved in the pathophysiology of this syndrome^{13,89}. Understanding the exact pathophysiology of the disorder is hindered by a lack of awareness in clinicians. For example, a study by Healy et al.²⁵ included 62 patients from 23 countries who reported PSSD to an adverse event reporting website (RxISK) and analysed clinicians' attitudes towards patients (as reported by the patients). Many study

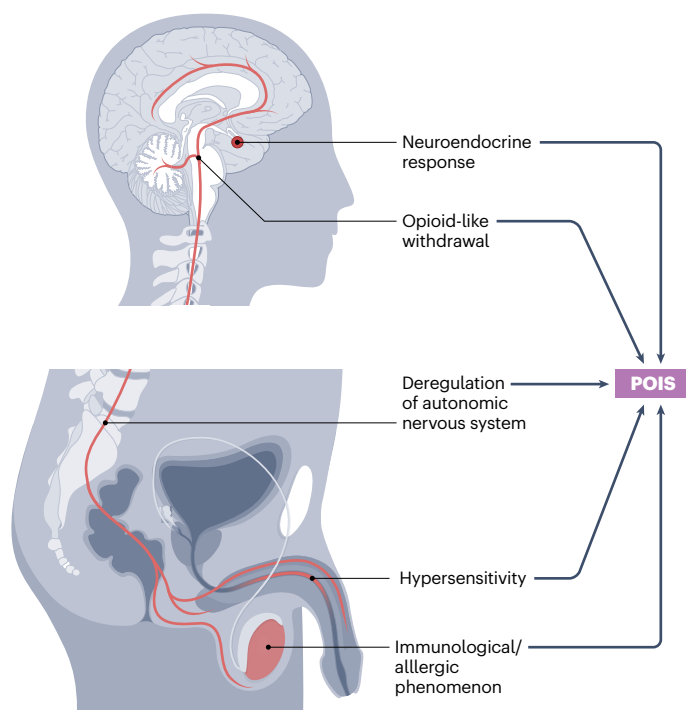


Fig. 2 | The hypothetical pathophysiology of post-orgasmic illness syndrome in men. Several hypotheses have been proposed for the pathophysiology of post-orgasmic illness syndrome (POIS). First, an immunological and/or allergic phenomenon, whereby a possible immunological reaction occurs against a substance in the seminal fluid. Second, hypersensitivity, whereby the mucosal epithelium lining the urinary tract launches a hyperactive immune response to the seminal fluid. Third, the syndrome may be caused by opioid-like withdrawal, as orgasm triggers the consumption of large amounts of endogenous opioids, reducing their circulating levels. Finally, a neuroendocrine response and deregulation of the autonomic nervous system might underlie POIS, in which the released catecholamines and neurotransmitter substances contribute to excessive arousal during orgasm.

Box 3

Diagnostic criteria for POIS^{12,80,87}

Five preliminary criteria

Criterion 1. One or more of the following symptoms: sensation of a flu-like state, extreme fatigue or exhaustion, weakness of musculature, experiences of feverishness or perspiration, mood disturbances and/or irritability, memory difficulties, concentration problems, incoherent speech, congestion of nose or watery nose, itching eyes.

Criterion 2. All symptoms occur immediately (seconds), soon (minutes), or within a few hours after ejaculation initiated by coitus, and/or masturbation, and/or spontaneously (e.g. during sleep).

Criterion 3. Symptoms occur always or nearly always, e.g. after >90% of ejaculation events.

Criterion 4. Most of these symptoms last for ~2–7 days.

Criterion 5. The symptoms disappear spontaneously.

Seven clusters of criterion 1

Cluster 1 (general cluster). Extreme fatigue, exhaustion, palpitations, problems finding words, incoherent speech, dysarthria,

concentration difficulties, quickly irritated, cannot stand noise, photophobia, depressed mood.

Cluster 2 (flu-like cluster). Feverish, extreme warmth, perspiration, shivery, ill with flu, feeling sick, feeling cold.

Cluster 3 (head cluster). Headache, foggy feeling in the head, heavy feeling in the head.

Cluster 4 (eyes cluster). Burning, red eyes, blurred vision, watery, irritating, itching eyes, painful eyes.

Cluster 5 (nose cluster). Nasal congestion, watery, runny nose, sneezing.

Cluster 6 (throat cluster). Dirty taste in mouth, dry mouth, sore throat, tickling cough, hoarse voice.

Cluster 7 (muscle cluster). Muscle tension in the back or neck, muscle weakness, painful muscles, heavy legs, stiff muscles.

In addition to the preliminary diagnostic criteria, Strashny et al.⁸⁷ reported that patients should also be asked about symptom severity in four domains: physical pain, interference of symptoms with social activities or relationships, work or school, and daily activities such as walking, eating, dressing and hygiene. POIS, post-orgasmic illness syndrome.

participants reported that their clinicians had limited awareness or knowledge about PSSD, and felt that they were not being listened to and/or received unsympathetic or inappropriate responses, emphasizing how a lack of information might be a barrier to elucidating the exact pathophysiology of the disorder.

Animal studies support this hypothesis and suggest that early exposure to an SSRI has substantial and long-lasting effects on sexual behaviour¹⁰⁷. In a systematic review of 14 animal studies evaluating the effect of SSRI use on sexual behaviour after treatment, rats exposed to SSRIs in early life demonstrated a higher risk of no mounting behaviour (RR 0.73; 95% CI 0.62–0.86), no intromission behaviour (RR 0.74; 95% CI 0.60–0.92) and no ejaculation behaviour (RR 0.49; 95% CI 0.24–1.00), compared with rats treated with placebo¹⁰⁷. However, the included studies were limited by lack of randomization (only 4 studies used a randomization method), having no conflicts of interest section ($n = 9$), and lacking reporting of the number of excluded animals ($n = 10$).

Making the diagnosis of PSSD is often challenging (Box 4) – it is usually misdiagnosed as a psychological issue rather than being related to the use of SSRIs, as depression itself also can cause sexual dysfunction and decreased arousal, most likely through direct or indirect effects on neurotransmitters such as serotonin, dopamine and norepinephrine^{108,109}. When a patient experiences sexual side effects while on medication, they might stop taking their SSRI; however, these effects can be persistent, leading to confusion about whether the persistent sexual dysfunction is caused by the SSRI per se or by an underlying psychological disease⁸⁹. A 2021 online survey study analysed

135 self-declared PSSD patients and showed that 118 subjects experienced symptoms both during and after the administration of SSRI and/or SNRI medications. Additionally, 17 participants only experienced symptoms after the administration of these medications, suggesting an iatrogenic effect of SSRI and/or SNRI medications¹¹⁰. Although most patients with PSSD had symptoms during and after SSRI/SNRI administration, 17 patients (12%) reported symptoms beginning only after discontinuing the medication¹¹⁰. The diagnosis mainly relies on taking a comprehensive history of medication, onset and profile of symptoms and eliminating other possible causes¹³.

Treatment of PSSD

Treating PSSD is also challenging. Many strategies have been proposed, including serotonergic antagonists and dopaminergic agonists, as well as laser irradiation and phototherapy of the penis^{92,111}. A case-control study, evaluating the effect of amineptine on sexual function in 111 patients demonstrated that switching SSRIs to a dopaminergic antidepressant (amineptine) in patients with sexual dysfunction decreased the occurrence rate of PSSD after 6 months of discontinuing SSRIs compared with those who switched to paroxetine treatment (55% versus 4%)¹¹². Moreover, no improvement was observed in patients with PSSD who were prescribed phosphodiesterase-5 inhibitors (PDE5is) and testosterone⁹². Some patients with PSSD have reported some degree of spontaneous recovery with time ranging from a few days to decades, suggesting that these symptoms do not arise from permanent damage¹¹³.

In a 2022 report, therapy with vortioxetine – an SSRI and serotonin receptor modulator – led to a substantial improvement in all International Index of Erectile Function-5 (IIEF-5) areas from baseline to 12-month follow-up ($P = 0.05$) in the majority of patients (10 out of 12 patients). In addition, a single patient who was treated with pelvic muscle vibration experienced quite favourable outcomes, with their IIEF-15 score increasing by 10 points to 25 (ref. 114).

Nevertheless, all of these treatment strategies remain anecdotal and no definitive treatment exists. PSSD is underdiagnosed and can be debilitating and distressing for patients, significantly decreasing their QoL – pleasureless orgasm in particular was found to be an independent predictor for the development of both depression and anxiety⁹⁴. Thus, a multidisciplinary approach – including specialists in urology, psychology and endocrinology – is required to manage patients with the possible diagnosis of PSSD. Additionally, patients should be well informed about the possible side effects of SSRIs and their sexual function should be assessed before initiating the treatment, while on medication, and after discontinuation¹¹⁵.

Hard-flaccid syndrome

HFS was first introduced in a case report in 2019 (ref. 14) and is a rare sexual dysfunction in which the penis remains flaccid, despite being physically stimulated to become erect¹⁴ (Box 5). A qualitative analysis of this syndrome was subsequently published in 2020, and included analysis of an internet forum discussion between patients reporting relevant symptoms²⁶.

Aetiology, pathophysiology and diagnosis of HFS

The aetiology of HFS is not completely understood. One hypothesis suggests that the onset of this chronic, painful condition might be due to a minor trauma, which triggers inflammation resulting in neuropathic pain and muscle spasms¹⁴. These muscle spasms might increase the intracavernosal pressure during the flaccid phase and inhibit optimal (Grade IV) erection during the rigid phase, resulting in a 'hard-flaccid' penis. This neuropathy, as well as penile hypoxia, might also explain the reported symptoms of coldness and numbness in the penile shaft and glans, whereas muscle spasms might be responsible for chronic prostatitis/chronic pelvic pain syndrome-like voiding symptoms that patients can experience. Furthermore, anxiety and depression caused by HFS might worsen pelvic muscle spasms and further worsen the patient's symptoms¹⁴. This vicious circle between emotional stress and HFS symptoms results in a chronic pain disorder that can require a multidisciplinary treatment approach (Fig. 3).

Men presenting with possible HFS describe a semi-rigid penis in the flaccid state and a semi-erect penis during the rigid phase²⁶. Penile sensory changes (numbness or coldness in the glans), softness in the glans and ED are also frequently reported (Box 5). Pelvic pain, lower urinary tract symptoms and painful ejaculation can also accompany HFS, making differentiation from chronic prostatitis/chronic pelvic pain syndrome difficult¹¹⁶. Psychological symptoms such as anxiety and depression are also widespread among men with HFS, which worsen the symptoms of this newly recognized condition²⁶.

Treatment of HFS

HFS treatment has not yet been clearly established, but lifestyle changes, cognitive-behavioural therapies and pelvic floor relaxation exercises might alleviate the symptoms based on anecdotal reports from Internet forums²⁶. In a 2022 case report, a 16-year-old male patient's symptoms (semi-rigid penis in the flaccid state, ED, penile

sensory changes of numbness and coldness and incomplete voiding), which emerged after masturbation, were relieved after specialized pelvic floor physiotherapy¹¹⁷. However, the details of the physiotherapy were not described in the text. Analgesics can be helpful in pain management, whereas antidepressants might be needed to treat HFS-related anxiety and depression²⁶. PDE5Is and low-intensity shock wave therapy might be beneficial in increasing the blood supply to the penis and restoring erectile function along with relief in penile coldness and/or numbness¹⁴. However, more clinical data are needed to clarify the exact pathophysiological pathways involved in HFS and to provide effective therapeutic approaches¹¹⁸.

Sleep-related painful erections

SRPEs describe a type of parasomnia with recurrent painful erections that are typically experienced during rapid eye movement sleep episodes^{23,119}. These painful erections occur instead of normal painless nocturnal erections with varying frequency and wake the patient from his sleep, which naturally results in sleep deprivation with associated daytime fatigue and irritability. These patients have normal and painless erections related to sexual activity, and their SRPEs typically last ~15 min and seldom >1 h (ref. 120). In most cases, no acknowledged initiating factors are known, but various connections to stress, sexual activity and intake of food and/or alcohol before bedtime have been noted^{120,121}, and no predisposing conditions have yet been established. Symptoms are typically alleviated by physical activity and/or urination^{120,122} and tend to occur frequently, sometimes several times each night. Although almost certainly under-reported, SRPEs are considered rare, with only ~100 cases described in the literature^{123,124}. Thus, the condition is not well investigated and its aetiology, pathophysiology and management

Box 4

Diagnostic criteria for PSSD

Necessary:

- (1) Prior treatment with a serotonin reuptake inhibitor
- (2) An enduring change in somatic (tactile) or erogenous (sexual) genital sensation after treatment stops

Additional:

- (3) Enduring reduction or loss of sexual desire
- (4) Enduring erectile dysfunction
- (5) Enduring inability to orgasm or decreased sensation of pleasure during orgasm
- (6) The problem is present for ≥ 3 months after stopping treatment

There should be:

- (7) No evidence of pre-drug sexual dysfunction that matches the current profile
- (8) No current medical conditions that could account for the symptoms
- (9) No current medication or substance misuse that could account for the symptoms

These criteria were determined by a multidisciplinary panel of experts²⁴. PSSD, post-SSRI sexual dysfunction.

Box 5

Symptoms of HFS^{26,118}

Penis

Feels constantly hard when in a flaccid state
During masturbation, a slight ache at the base of the penis
Noticeable superficial veins
Bubble around the glans (very rare)
Scar tissue (very rare)

Erections

No morning erections
Often feel hollow or empty but also more rigid than usual
Glans is often soft, sometimes cold or numb
Difficult to maintain erections
Best in lying on back position, worst in stood upright

Libido

Generally low

Pain

Penile and/or perineal (occasionally)

Urination

Painful urination
Weak stream (rare)

Ejaculation

Painful (or slightly painful) ejaculation

Examinations and tests

Normal physical examinations, sometimes mild curvature
Generally normal hormone levels and other blood tests
Normal penile Doppler ultrasonography (no Peyronie's disease, no fibrosis)
Normal MRI and other imaging modalities

HFS, hard-flaccid syndrome.

are subjects of debate. However, in all reported cases, the issue has arisen in adulthood, typically after the age of 20 years, with previously normal nocturnal erections.

Aetiology, pathophysiology and diagnosis of SRPEs

Unsurprisingly, SRPEs have been compared with stuttering priapism episodes¹²⁴, and penile ischaemia has been suggested as a cause of the pain²³. No study has ever included penile gas analysis during an episode of SRPE to test this hypothesis conclusively; however, the two conditions do differ in several aspects. First, episodes of priapism last longer – by definition, at least 4 h – and only the corpora cavernosa are rigid in cases of priapism, whereas the corpus spongiosum is also engorged in SRPEs. Additionally, sleep studies have suggested that erections tend to become painful almost immediately in SRPEs and only a fraction of patients show prolonged erections, meaning that ischaemia does not

have time to develop as a cause of the pain¹²⁰. Another distinguishing factor between the two conditions is that erotic erections do not become compromised in SRPEs, even after several years of suffering from the condition, whereas the erectile tissue is known to be damaged over time in cases with recurrent ischaemic priapism episodes.

Another possible cause of SRPEs is hypertonicity and/or spasm of the pelvic floor muscles, including the ischiocavernosus and bulbospongiosus, with subsequent referred pain to the penis¹²⁰. This theory is, in part, based on the finding that many patients describe their pain radiating to adjacent areas, including the groin and perineum. In addition, some studies have shown increased muscle tone in the pelvic floor on either physical examination or electromyography during REM cycles in men with SRPE^{120,122,125,126}.

A third intriguing possibility is that SRPEs are caused by dysfunctional autonomic regulation. A 1996 study in 10 patients with SRPE showed reduced cardiac vagal activity during sleep, indicating nocturnal β -adrenergic hyperactivity, compared with 25 control patients without SRPE¹²⁷. Other proposed aetiologies for SRPEs include sleep apnoea with resulting neural disturbances, neurovascular compression of the basal forebrain¹²⁸, incomplete spinal cord lesions¹²⁹ and marital issues as well as anxiety^{120,130}. However, these theories are mainly based on case reports and might represent coincidental findings rather than actual associations.

Polysomnographic tests have universally shown sleep fragmentation and decreased sleep efficiency in patients with SRPEs¹²³. Such tests can be undertaken, if possible, with the addition of nocturnal penile tumescence monitoring to confirm the diagnosis. However, as the results of such tests have no immediate effect on management, the investigation is not considered mandatory. Aside from these effects on sleep, no other universal physical findings have been described. Hormone levels, including testosterone, follicle-stimulating hormone, luteinizing hormone and oestradiol, have been normal in the vast majority of examined patients^{120,124}. No significant underlying pathological condition has been noted on pelvic or abdominal CT or on MRI scans of the penis. In addition to stuttering from priapism, the main differentials include phimosis and Peyronie's disease, which can be assessed by taking a full patient history combined with a physical examination.

Thus, the main goals are to evaluate the pelvic floor and genitals and determine the effects of the condition on the patient's QoL. The clinician should ask about daytime drowsiness and how this might affect work and relationships. Patients should also be asked about any influence on their sexual function and should be screened for depression and anxiety. Physicians should attempt to offer supportive measures based on the answers, and the patients' subjective experience should serve as a guide as to the level of side effects that might be acceptable with treatment.

Treatment of SRPEs

A multitude of drugs have been used in patients with SRPEs, targeting the suggested pathophysiological mechanisms by reducing erections, relaxing the pelvic floor muscles, manipulating peripheral or central nervous activity, and improving sleep. Many of the different treatments evaluated were found to be ineffective in managing SRPE^{120,122,124,131}. Only a few treatments showed some effectiveness, but their efficacy was limited to a few weeks or months. The most studied and most promising of these is baclofen, a muscle relaxant that works by stimulating GABAB receptors at the spinal level^{120,122,124,132,133}. Baclofen treatment has been described in a total of 27 patients, and is typically given at bedtime,

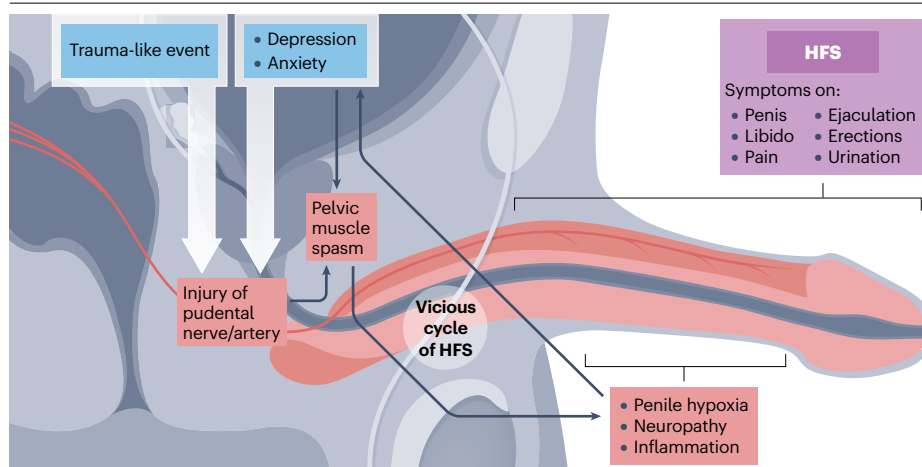


Fig. 3 | Potential pathophysiology of hard-flaccid syndrome. A trauma-like event, for example, sustained during masturbation or sexual intercourse, might harm the pudendal nerve and/or artery at the level of the radix penis, which could trigger penile hypoxia, inflammation and neuropathy. Neuropathy and penile hypoxia can result in symptoms of coldness and numbness in the penile shaft and glans, whereas muscle spasms might be responsible for chronic prostatitis/chronic pelvic pain syndrome-like voiding symptoms. Furthermore, emotional stress arising from hard-flaccid syndrome (HFS) might worsen the pelvic muscle spasms and further deteriorate the patient's symptoms in a vicious cycle.

either starting at 10 mg or 30 mg with gradual adjustments as needed, based on the effect. Complete response was reported in 7 of the men whose experience with baclofen has been described, another 17 experienced partial responses and only 3 patients reported no effect at all¹²¹. However, baclofen use was somewhat limited by associated adverse effects, including headaches and drowsiness, and symptoms of SRPEs tended to return after discontinuation. Another study demonstrated that baclofen administration (10 to 75 mg) in 14 patients suffering from SRPE achieved complete remission of symptoms within a few weeks in 11 patients. Out of the remaining 3 patients, 2 noticed a slight improvement in their symptoms, whereas only 1 patient reported no effect at all from the treatment¹²⁰.

Finally, experience with PDE5Is, pseudoephedrine and beta-blockers, which have all shown effects in some patients and offer a milder side effect profile, is limited^{15,120,124}. In one study, daily tadalafil 5 mg once a day was associated with full remission of SRPEs in 2 out of 4 patients¹²⁰, pseudoephedrine (dose not reported) was associated with a partial response in 6 of 19 patients¹²⁴ and the beta-blocker propranolol (20 mg given at night) significantly reduced the number of SRPEs in 1 patient over a period of 5 weeks¹⁵.

In addition to pharmacological treatment, one study has reported full symptom remission after pelvic-floor-muscle relaxing exercises in 3 of 5 patients¹²⁰. Finally, one 2021 study reported invasive treatment in men with refractory SRPEs, whereby 2 patients received penile implants and another 2 underwent cavernosal artery embolization¹²⁴, but symptoms remained unchanged in all 4 patients.

Based on the available knowledge, management of SPRE should be pragmatic and introduce management strategies beginning with the least invasive possible option until a resolution is reached. Thus, any initiating events – such as sexual activity and intake of food/alcohol before bedtime – should be sought and eliminated in the first instance. These initiating events can also include stress and other psychological concerns, for which patients should be offered psychological support if appropriate. Subsequently, patients should be offered pelvic physiotherapy to relax pelvic floor muscles before any medications are introduced. As a first-line option in the treatment of SRPE, baclofen is preferred, but it can be preceded by drugs with a less severe side effect profile, such as PDE5Is, pseudoephedrine and beta-blockers, despite limited evidence supporting their effectiveness. If these attempts fail, any subsequent treatment attempts remain purely experimental and surgical treatment is strongly discouraged.

Post-retinoid sexual dysfunction

Isotretinoin is an orally administered systemic retinoid that is primarily used to treat severe acne that is resistant to other forms of treatment¹³⁴. Sexual dysfunction was first reported as a side effect of etretinate, a now-discontinued retinoid derivative, in the late 1980s^{20,21} and, only a decade later, sexual dysfunction was linked to the use of isotretinoin, which remains in clinical use²². A 2018 study of 49 males (mean age 23.2 years; range 15–44 years), reported that isotretinoin caused sexual dysfunction, including ED (93.9%), loss of libido (71.4%), genital hyposthenia (36.7%) and loss of nocturnal erections (20.4%)¹³⁵. Case reports of ED and anejaculation have also been published^{22,136,137}. Most symptoms seem to be noticed during retinoid treatment and can persist after discontinuation, whereas some symptoms appear or worsen only after isotretinoin is stopped¹³⁵. In August 2017, sexual dysfunction was formally recognized as a side effect of isotretinoin and the European Medicines Agency stated that “the product information should be updated to include ‘sexual dysfunction including ED and decreased libido’ as an undesirable effect with an unknown frequency”¹³⁸. The proportion of patients who have persistent symptoms after isotretinoin withdrawal is, as yet, unclear.

Aetiology, pathophysiology and diagnosis of PRSD

Animal studies have demonstrated the effect of retinoids on the male reproductive system. A single administration of retinol (10,000 IU (3 mg) in 0.1 ml, subcutaneously, during the first day after birth) to neonatal rats was shown to significantly decrease their sexual activity as adults¹³⁹. Specifically, in the treated group, the number of single

Glossary

Bushen Yiniao

An ancient Chinese herbal medicine made of 15 different medical herbs used for clinical anti-ageing¹⁴⁷.

Sabal fruit

A small palm tree native to south-eastern USA. The medicinal part is the ripe, dried berry¹⁴⁵.

Wu Ling

A traditional Chinese medicine consisting of a rare type of fungus used in traditional Chinese medicine for the treatment of major depressive disorders¹⁴⁶.

Box 6

Diagnostic criteria for PRSD²⁴

Necessary:

- Prior treatment with isotretinoin
- Enduring sexual dysfunction after stopping treatment
- No evidence of pre-drug sexual dysfunction that matches the current profile
- No current medical conditions that could account for the symptoms
- No current medication or substance misuse that could account for the symptoms
- No other prior medication that could account for the symptoms

Additional:

- Enduring reduction or loss of sexual desire
- Enduring erectile dysfunction
- Enduring reduction in genital and orgasmic sensation
- The problem is present for ≥ 3 months after stopping treatment

These criteria are mostly for women and were determined by a multidisciplinary panel of experts²⁴. PRSD, post-retinoid sexual dysfunction.

ejaculations was found to be significantly higher ($P < 0.02$) compared with the control group. However, in the control group, multiple ejaculations occurred in a higher number of rats, although this difference was not statistically significant ($P > 0.05$). No significant difference was observed between the two groups regarding mounting and intromission. However, the time taken for the first ejaculation was significantly longer ($P < 0.01$) in the treated group compared with the control group¹³⁹. Testicular atrophy with spermatogenic arrest has also been observed in rats treated with the retinoids vitamin A, tretinoin and isotretinoin¹⁴⁰. Reduced total testosterone has been suggested as one of the pathophysiological mechanisms for isotretinoin-related sexual dysfunction, but the evidence is limited and unclear. During treatment, total testosterone can decrease in a dose-dependent manner¹⁴¹, but seems to return to normal at least 6 months after treatment withdrawal¹⁴². Serotonergic effects have also been suggested as a possible pathophysiological mechanism, but studies have shown that isotretinoin increases the expression of 5-HT1A receptor and serotonin reuptake transporter protein in vitro¹⁴³; thus, retinoids might decrease serotonin availability at synapses. In a small pilot study in humans, no significant change in circulating serotonin levels was seen during or after isotretinoin use¹⁴⁴. Thus, the link between PRSD and serotonergic neurotransmission seems, so far, to be anecdotal at best.

Diagnosis of PRSD is based on medical and sexual history. Patients reporting a history of treatment with isotretinoin and enduring sexual dysfunction after treatment discontinuation in the absence of pre-treatment sexual dysfunction or another current condition that could account for the symptoms should make the clinician suspect PRSD. A multidisciplinary panel of experts has proposed a set of ten criteria that should be fulfilled in order to establish the diagnosis of PRSD²⁴, but these criteria are not evidence-based (Box 6).

Treatment of PRSD

As no therapy is yet known to be effective for PRSD, treatment should be aimed at improving patients' acceptance and coping mechanisms, and use a symptom-directed treatment approach (that is, if a patient reports ED as a PRSD symptom, the recommended treatments for ED should be begun). A worldwide support group is available ([Propecia help](#)), which can help patients to cope with PRSD.

Future perspectives

Recognition and acknowledgement are needed to appreciate that rare sexual diseases can arise not only from psychological causes but also organic aetiologies. Clinicians must not ignore these scarce and often debilitating conditions; on the contrary, they are obligated to pursue the possible pathophysiological mechanisms and develop more effective management strategies. In addition, clinicians have a duty of care to inform patients about the potential sexual side effects of 5ARIs and SSRIs before prescribing them. When possible, topical treatments should be used before systematic administration. Furthermore, investigating the presence of poor baseline sexual function before treatments are initiated might prevent worsening of the symptoms.

Patients with rare sexual male disorders should be encouraged to participate in clinical trials. Owing to the rarity of these syndromes, multinational, multicentre organizations can be helpful in shaping understanding of these disorders. Without a deeper understanding of their causes and management, patients with rare sexual diseases could be continued to be stereotyped and stigmatized by clinicians, which leads not only to dissatisfied patients but also to a barrier to understanding the underlying mechanisms of the conditions. Increasing awareness – in clinicians and patients – is key.

Conclusions

Rare sexual disorders are under-recognized and undertreated and can cause a great deal of physiological and psychiatric morbidities in affected patients. Such disorders can be the result of medication for an unrelated problem, such as PRSD, which arises after treatment with isotretinoin, an acne treatment, or PFS. Others can arise seemingly idiopathically, such as SRPEs, which have no known causative factors but might be related to lifestyle, or HFS.

In order to address the sexual dysfunctions described by these patients and implement appropriate treatments, physicians must become more familiar with the existence of these disorders and actively seek to investigate them in patients in whom they form part of the differential diagnosis.

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Author contributions

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