

# Enduring sexual dysfunction after treatment with antidepressants, $5\alpha$ -reductase inhibitors and isotretinoin: 300 cases

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## Abstract.

**OBJECTIVE:** To investigate clinical reports of post-SSRI sexual dysfunction (PSSD), post-finasteride syndrome (PFS) and enduring sexual dysfunction following isotretinoin.

**METHODS:** Data from RxISK.org, a global adverse event reporting website, have been used to establish the clinical features, demographic details and clinical trajectories of syndromes of persistent sexual difficulties following three superficially different treatment modalities.

**RESULTS:** We report on 300 cases of enduring sexual dysfunction from 37 countries following 14 different drugs comprised of serotonin reuptake inhibiting antidepressants,  $5\alpha$ -reductase inhibitors and isotretinoin. While reports of certain issues were unique to the antidepressants, such as the onset of premature ejaculation and persistent genital arousal disorder (PGAD), there was also a significant overlap in symptom profile between the drug groups, with common features including genital anaesthesia, pleasureless or weak orgasm, loss of libido and impotence. Secondary consequences included relationship breakdown and impaired quality of life.

**CONCLUSIONS:** These data point to a legacy syndrome or syndromes comprising a range of disturbances to sexual function. More detailed studies will require developments in coding systems that recognise the condition(s). Further exploration of these tardive sexual syndromes may yield greater understanding of tardive syndromes in general.

Keywords: Post-SSRI sexual dysfunction (PSSD), antidepressants, selective serotonin reuptake inhibitors (SSRIs), finasteride, isotretinoin, erectile dysfunction

## 1. Introduction

Serotonin reuptake inhibiting medications, including the selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and the serotonin reuptake inhibiting tricyclic antidepressants, as outlined in their datasheets, almost invariably affect sexual functioning and do so after a first dose. The  $5\alpha$ -reductase inhibitors, finasteride and dutasteride, according to their labels, commonly (5–9%) have acute effects on sexual functioning. Isotretinoin also has acute effects on sexual functioning [1] but the frequency of this change is unknown and is not mentioned in the medicine's label.

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The first reports of enduring sexual side effects from serotonin reuptake inhibitors appeared in 2006 with further reports and the designation of these effects as a post-SSRI sexual dysfunction (PSSD) following [2–8]. Since 2011, the US product information for Prozac (fluoxetine) has warned that “Symptoms of sexual dysfunction occasionally persist after discontinuation of fluoxetine treatment.” [9]. The fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), published in 2013, states that “In some cases, serotonin reuptake inhibitor-induced sexual dysfunction may persist after the agent is discontinued” [10].

Finasteride was licensed for male pattern baldness in 1997. The first reports of enduring sexual side effects appeared in 2011 with further reports and a designation of the condition as a post-finasteride syndrome (PFS) following [11–13]. In 2011, the US Food and Drug Administration (FDA) updated the product information for Proscar and Propecia, to warn of erectile dysfunction after stopping treatment. In 2012, this was expanded to include decreased libido that continued after discontinuation of Proscar, and libido disorders, ejaculation disorders, and orgasm disorders that continued after discontinuation of Propecia. A warning was added to both drugs describing reports of male infertility and/or poor semen quality that improved after drug discontinuation [14].

A 1994 report of ejaculatory disorder on isotretinoin noted that Roche had received more than 150 reports of male sexual dysfunction since its launch in 1983, including 32 potency disorders and two reports of ejaculatory failure [1]. Published reports of enduring sexual dysfunction after treatment date to 2014 from the present authors [7], and subsequently from Lareb, the Netherlands Pharmacovigilance Centre, who reported three patients who had either not recovered or whose symptoms had not fully resolved after stopping [15]. Health Canada has since recommended that the product information for all isotretinoin products should list erectile dysfunction as a side effect of treatment, without giving any indication of how many are affected or addressing the issue of post-treatment sexual dysfunction [16].

Research on these syndromes has been hampered by the fact that coding systems, such as the Medical Dictionary for Regulatory Activities (MedDRA), do not yet recognise them, and the possibility that these conditions might happen was not known when the clinical trials of these drugs were undertaken. Regulators may have reports consistent with these effects, but in the absence of an agreed code, reports are not likely to cohere into syndromes that can be researched. While PSSD and PFS have been named in the clinical literature, post-retinoid sexual dysfunction (PRSD) has not.

## 2. Methods

RxISK.org is an independent drug safety website set up by the authors and colleagues, offering an adverse event reporting facility which began collecting data on all drugs and all adverse events in 2012. Since 2013, the site has run a number of articles about enduring sexual dysfunction following the use of SSRI/SNRIs, finasteride, and isotretinoin, and this likely encouraged reporting of these problems. RxISK offers reporters and site monitors the option to code for enduring sexual dysfunction.

The website takes reporters through a set of structured questions to establish their age, sex, country of origin, drug consumption, medical history and other relevant health information (eg. smoking, pregnancy, alcohol use) along with clinical details. This is followed by a causality assessment based on the Naranjo algorithm to help determine whether an index drug is responsible for the event. A score of 0–4 indicates that more information is required, 5–8 indicates a likely link between medication and side effect, and 9+ denotes a strong possibility of a link between medication and side effect. The Naranjo and other algorithms are not geared to scoring legacy effects, and the scores reported here are likely underestimates as a result.

Finally, reporters are asked to rate and describe the impact of the problem on various aspects of their life ie. physical, mental, work and social activities.

A total of 3033 adverse event reports were received from 17th June 2012 to 17th December 2015, and from 26th April 2016 to 21st August 2017. There is a gap in this timeline as the reporting facility was unavailable for an extended period due to website maintenance.

The database was searched for reports of post-treatment sexual dysfunction relating to serotonin reuptake inhibitors, 5 $\alpha$ -reductase inhibitors and isotretinoin. Cases were then eliminated for various reasons: unconvincing descriptions of the problem ( $n = 2$ ), duplicate entries ( $n = 5$ ), possible involvement of confounding factors ( $n = 10$ ), ambiguity ( $n = 14$ ), and those which did not offer sufficient detail to contribute to the delineation of a syndrome ( $n = 20$ ) eg. reports which simply offered loss of libido as the consequence of treatment.

Not included within this study are eight reports of enduring sexual dysfunction linked to antipsychotics and catecholamine reuptake inhibitors. These are established causes of erectile dysfunction and loss of libido but are not linked to genital anaesthesia, and it is not clear from our reports whether there is an enduring syndrome that can be attributed to the use of these agents.

### 3. Results

A breakdown of the 300 cases of post-treatment enduring sexual dysfunction reported to RxISK is shown in Table 1.

The mean causality scores were 8.9 for serotonin reuptake inhibitors, 8.8 for 5 $\alpha$ -reductase inhibitors and 8.5 for isotretinoin.

Reports were received from a total of 37 countries across six continents: Europe ( $n = 137$ ), North America ( $n = 126$ ), Oceania ( $n = 15$ ), Asia ( $n = 14$ ), South America ( $n = 6$ ) and Africa ( $n = 2$ ).

Age details were supplied by 295 subjects, ranging from 15 to 66 years (Table 2). In 16 cases, onset of the condition was reported to have occurred under the age of 18.

For 226 subjects, there were indicators as to the duration of treatment. These ranged from a single dose to over 16 years. Nineteen subjects reported being on treatment for less than two weeks with serotonin reuptake inhibitors ( $n = 15$ ), 5 $\alpha$ -reductase inhibitors ( $n = 3$ ) or isotretinoin ( $n = 1$ ).

Table 1  
Treatments linked to enduring sexual dysfunction

Drug	Male	Female	Total (%)
Isotretinoin	49	5	54 (18.0)
Escitalopram	30	12	42 (14.0)
Citalopram	29	12	41 (13.7)
Paroxetine	36	4	40 (13.3)
Sertraline	22	10	32 (10.7)
Fluoxetine	24	7	31 (10.3)
Finasteride	24	0	24 (8.0)
Venlafaxine	16	3	19 (6.3)
Duloxetine	8	2	10 (3.3)
Fluvoxamine	2	0	2 (0.7)
Vortioxetine	2	0	2 (0.7)
Clomipramine	1	0	1 (0.3)
Desvenlafaxine	1	0	1 (0.3)
Dutasteride	1	0	1 (0.3)

Table 2  
Age of subjects

	SRIs		Isotretinoin		5 $\alpha$ -RIs
	Female <i>n</i> = 49	Male <i>n</i> = 170	Female <i>n</i> = 5	Male <i>n</i> = 47	Male <i>n</i> = 24
Minimum age	15	16	23	15	17
Maximum age	54	66	34	44	61
Mean age	30.1	32.0	26.4	23.2	30.0

SRIs = serotonin reuptake inhibitors, 5 $\alpha$ -RIs = 5 $\alpha$ -reductase inhibitors.

Table 3a  
Symptom profile and frequency (male)

Symptom	SRIs (%)	Isotretinoin (%)	5 $\alpha$ -RIs (%)	Total (%)
Erectile dysfunction	147 (86.0)	46 (93.9)	23 (92.0)	216 (88.2)
Loss of libido	135 (78.9)	35 (71.4)	23 (92.0)	193 (78.8)
Genital anaesthesia	84 (49.1)	18 (36.7)	11 (44.0)	113 (46.1)
Pleasureless or weak orgasm	73 (42.7)	4 (8.2)	3 (12.0)	80 (32.7)
Difficulty achieving orgasm	56 (32.7)	3 (6.1)	2 (8.0)	61 (24.9)
Emotional blunting	35 (20.5)	5 (10.2)	6 (24.0)	46 (18.8)
Loss of nocturnal erections	22 (12.9)	10 (20.4)	4 (16.0)	36 (14.7)
Reduced seminal volume	23 (13.5)	5 (10.2)	5 (20.0)	33 (13.5)
Penile or testicular pain	12 (7.0)	3 (6.1)	5 (20.0)	20 (8.2)
Reduced penis size	11 (6.4)	2 (4.1)	7 (28.0)	20 (8.2)
Premature ejaculation	17 (9.9)	0	0	17 (6.9)
Decreased testosterone	8 (4.7)	4 (8.2)	4 (16.0)	16 (6.5)
Watery ejaculate	4 (2.3)	3 (6.1)	8 (32.0)	15 (6.1)
Testicular atrophy	3 (1.8)	0	8 (32.0)	11 (4.5)
Other skin numbness	6 (3.5)	1 (2.0)	2 (8.0)	9 (3.7)
Soft glans	4 (2.3)	1 (2.0)	0	5 (2.0)
Reduced sense of smell	3 (1.8)	0	1 (4.0)	4 (1.6)
Reduced sense of taste	2 (1.2)	0	2 (8.0)	4 (1.6)
Penile curvature	2 (1.2)	0	0	2 (0.8)
PGAD	2 (1.2)	0	0	2 (0.8)
Reduced nipple sensitivity	1 (0.6)	0	0	1 (0.4)

SRIs = serotonin reuptake inhibitors, 5 $\alpha$ -RIs = 5 $\alpha$ -reductase inhibitors, PGAD = persistent genital arousal disorder.

Tables 3a and 3b break down the individually reported features by gender.

Seventeen subjects within the serotonin reuptake inhibitor group reported developing premature ejaculation. There is a previous case report in the literature in which the subject developed premature ejaculation 4-5 days after discontinuing citalopram, which persisted for several weeks, resolved after citalopram was reintroduced, and reappeared on further discontinuation [17].

Six cases of persistent genital arousal disorder (PGAD) were reported. This syndrome involves a relentless sense of arousal and discomfort in the genitals, but without any accompanying feeling of desire. These reports related to serotonin reuptake inhibitors which have previously been implicated as one of the causes of PGAD [18–20].

Table 3b  
Symptom profile and frequency (female)

Symptom	SRI (%)	Isotretinoin (%)	Total (%)
Loss of libido	36 (72.0)	5 (100.0)	41 (74.5)
Genital anaesthesia	30 (60.0)	3 (60.0)	33 (60.0)
Difficulty achieving orgasm	30 (60.0)	2 (40.0)	32 (58.2)
Emotional blunting	14 (28.0)	0	14 (25.5)
Pleasureless or weak orgasm	13 (26.0)	0	13 (23.6)
Vaginal dryness/pain	9 (18.0)	3 (60.0)	12 (21.8)
Other skin numbness	5 (10.0)	1 (20.0)	6 (10.9)
Reduced nipple sensitivity	5 (10.0)	0	5 (9.1)
PGAD	4 (8.0)	0	4 (7.3)
Reduced sense of taste	1 (2.0)	0	1 (1.8)

SRI = serotonin reuptake inhibitors, PGAD = persistent genital arousal disorder.

Sixteen reporters sent details of decreased testosterone. PSSD and PFS can sometimes result in borderline testosterone; this may be a consequence of the condition rather than the cause. Testosterone treatment has not been reported to benefit these syndromes.

Five subjects reported the glans penis remaining flaccid when the shaft was erect. Four related to serotonin reuptake inhibitors and one to isotretinoin.

There were two reports involving SSRIs describing an onset of penile curvature. This problem is not associated with SSRIs. It is difficult to know whether it is treatment-linked or incidental.

Six subjects reported a reduction of nipple sensitivity. A further 15 subjects described reduced sensation across other parts of the body, in some cases involving most or all of the body. A previous paper in the literature described a male subject who developed severe tactile insensitivity of his chest and abdomen in addition to penile numbness after using citalopram; and a female subject who experienced a reduction of genital and nipple sensitivity on fluoxetine which only partially resolved after discontinuation of the drug [3].

In many instances the sexual dysfunction only appeared or became significantly worse when treatment was stopped. There were 41 (18.6%) reports for serotonin reuptake inhibitors, 9 (16.7%) for isotretinoin, and 7 (28.0%) for 5 $\alpha$ -reductase inhibitors. Three subjects on SSRIs reported an increasing loss of sexual function as the dose was tapered. For all three drug groups there were reports of profound dysfunction appearing within days of stopping. This has similarities to antipsychotic-induced tardive dyskinesia which can appear on treatment and remain afterwards, or only appear when the drug is stopped.

Finasteride and isotretinoin are usually stopped abruptly whereas antidepressants are often tapered over weeks or months due to a withdrawal syndrome. At present, it appears that PSSD is equally likely following abrupt or gradual discontinuation of an SSRI or SNRI.

There were consistent reports that the condition made it difficult or impossible to engage in normal romantic relationships, with 25 reporting that the condition had led to the breakup of a relationship, including nine marriages. Ninety subjects reported that their work had been affected, including 12 who had lost jobs.

Seventeen subjects reported having the syndrome for at least 10 years since stopping treatment with isotretinoin ( $n = 8$ ), serotonin reuptake inhibitors ( $n = 8$ ) or finasteride ( $n = 1$ ). Of these, five subjects reported that it had been over 20 years since stopping isotretinoin ( $n = 4$ ) or fluoxetine ( $n = 1$ ).

Subjects also reported fatigue (9%), muscle weakness (3%), and cognitive problems including brain fog (19%) and memory impairment (11%). These were worse on finasteride. The cognitive symptoms

appear to be a meta-cognitive problem in that testing rarely reveals deficits on what are tests of higher order cognitive function. Other drugs such as statins are linked to comparable difficulties.

#### **4. Discussion**

The ability of serotonin reuptake inhibitors to reduce genital sensation is well known. Almost everyone who takes one will experience some degree of genital numbing, often within 30 minutes of taking the first dose. None of the many patients with PSSD who have contacted us directly has not had genital anaesthesia, yet not everyone has reported it in this series.

This numbing is comparable to the effect of local anaesthetics such as lidocaine, and underpins the use of both SSRIs and local anaesthetics in the management of premature ejaculation. Two studies have captured this effect on neurophysiological testing. One study looked at the effectiveness of clomipramine as a possible treatment for premature ejaculation [21]. The study found that the drug increased ejaculatory latency, and increased penile sensory threshold from 24.4V before treatment to 30.2V (24%) at the end of 30 days. A second study involving fluoxetine found an increase in penile sensory threshold from 4.9 mA pre-treatment to 6.1 mA (24%) after one month [22].

This effect can endure after treatment stops. One of the authors had a patient that developed persistent genital numbness after citalopram, who resorted to scraping her vulva with a hard bristled hairbrush in an attempt to induce some stimulation, but without success. Waldinger et al reported on a subject with penile anaesthesia following paroxetine use, whose penis was insensitive to the effect of Tiger Balm [8].

In cases of enduring dysfunction, finasteride and isotretinoin appear to induce genital effects comparable to those found with serotonin reuptake inhibitors. However, finasteride and isotretinoin do not routinely cause acute onset genital anaesthesia that patients we have questioned are aware of. In this series, the numbness sometimes developed while on finasteride or isotretinoin, and occasionally appears to have done so shortly after commencement, but more often this feature became apparent during later treatment or after stopping the drug.

Pleasureless or weak orgasm is also common to the three treatment groups. This is experienced as a reduction or loss of pleasurable feeling, so that orgasm becomes a set of rhythmic muscle contractions with little accompanying sensation. These muscle contractions can also be weaker than normal, and may be noticed in male subjects as reduced ejaculatory force.

Against a background of genital anaesthesia and pleasureless orgasm, a loss of libido and development of dysfunction is not surprising and may reflect secondary effects, although loss of libido is the most commonly reported symptom here in female subjects, and the second most reported feature in male subjects. This loss occurs on acute treatment with SSRIs and SNRIs, but develops after anaesthesia.

A study which examined the electronic records of patients who were prescribed finasteride found that out of 4284 men aged between 16 to 42 years old without any prior sexual dysfunction, 34 (0.8%) had persistent erectile dysfunction with a median duration of 1534 days (4.2 years) after discontinuation of the drug [23]. It also found that young men with more than 205 days of finasteride exposure had a 4.9-fold higher risk of persistent erectile dysfunction than men with shorter exposure.

In terms of serotonin reuptake inhibitors, the rate at which PSSD occurs is unknown. Several factors might contribute to an under-diagnosis of the condition. These include patient discomfort at raising sexual concerns with their doctor, as may medical discomfort at enquiring about the resolution of sexual side effects once treatment has finished. While neither genital anaesthesia nor pleasureless orgasm are features of depression or anxiety [4], and patients typically have normal functioning prior to starting an antidepressant, physicians appear to default to attributing problems a patient has after treatment to manifestations of an underlying nervous diathesis.

It isn't known how many people fully regain their original genital sensation, libido and other domains of sexual functioning after using a serotonin reuptake inhibitor. Studies which have included six month follow-up after discontinuation of the drug have found evidence of enduring changes to sexual function [24–26]. Bahrack [4] highlighted the results of a study in which 55% of subjects still had sexual dysfunction six months after switching from an SSRI to amineptine, compared to 4% who were treated solely with amineptine, a drug with no action on the serotonin system [27].

The fact that symptoms can sometimes only appear when the drug is stopped or subjects only recognise they have an enduring problem at that point undoubtedly adds to the difficulty in recognising a link.

The physiological mechanisms underpinning genital anaesthesia and enduring dysfunction as seen in these reports are yet to be understood. It remains unclear whether the problem is neurological or endocrinological, or whether genital anaesthesia arises centrally or peripherally.

Rodents given fluoxetine were found to have sustained desensitisation of 5-HT<sub>1A</sub> receptors after removal of the drug [28]. In another study, a 5-HT<sub>1A</sub> antagonist was shown to reverse and prevent sexual dysfunction in rodents that were being administered with fluoxetine [29]. However, PSSD sufferers through online support forums have tried and reported on the effects of all combinations of medicines acting on serotonin and dopamine systems, and medicines known to enhance function such as sildenafil, but without benefit. The problem is again similar to tardive dyskinesia in this respect, in that counter manipulations of systems on which triggering agents work do not seem to remedy the problem.

With regard to peripheral effects, amitriptyline, a potent serotonin reuptake inhibitor can cause degeneration of peripheral nerve fibres [30]. In PFS patients, those with severe erectile dysfunction, as opposed to mild-moderate, were found to have evidence of peripheral neuropathy of the pudendal nerve [31]. Immunohistochemical evaluation of androgen receptor in human foreskin has revealed differences between PFS patients and healthy controls who had never taken finasteride [32].

In the Tiger Balm case mentioned earlier, the patient reportedly gained a small degree of sensation after undergoing treatment with low-power laser irradiation, though this improvement did not extend to any aspects of sexual responsiveness. It was hypothesised that SSRIs may induce disturbances of transient receptor potential (TRP) ion channels [8]. The serotonin reuptake inhibiting antidepressants all have effects on sodium currents and other ion channels, raising the possibility that enduring effects arise from this source rather than at conventional receptor sites.

In PFS patients, abnormalities have been reported in the cerebrospinal fluid and plasma levels of neuroactive steroids [31]. Persistent changes to neuroactive steroids have also been seen in the brains of rodents after withdrawal of finasteride [33]. Similar studies have not been carried out for serotonin reuptake inhibitors, but these drugs have certainly been found to have effects on sex steroids [34]. Serotonin reuptake inhibitors have also been found to produce a range of effects that would typically be associated with the endocrine system, including hormone imbalance, breast enlargement, and reproductive issues including reduced sperm numbers and functionality [35, 36].

Finally, there has been a preliminary report of abnormal function in brain areas linked to sexual arousal in fMRI scans of PFS patients viewing erotic stimuli [37].

It is difficult to know which of these physiological, endocrine or central neurological features are primary and which secondary. In terms of investigating tardive sexual syndromes further, these conditions need coding and classifying so that they register in databases and in trials. A revision of causality algorithms to accommodate legacy effects is also needed as algorithms like the Naranjo algorithm work well for problems that occur on acute exposure to treatment or after treatment has been stopped, but not for problems that may arise on treatment and continue thereafter.

A next step will involve a systematic approach to patient groups with structured sets of symptoms to establish whether there is a single syndrome here. The problems linked to PFS and PSSD have stimulated the formation of vigorous online communities. Within the PFS community there has been a focus on neurosteroids and this may underpin perceptions of testicular and penile atrophy on finasteride, which are reported to a lesser extent on serotonin reuptake inhibitors and isotretinoin. Factors such as this may obscure common features of syndromes triggered by differing agents. Structured interviews would appear the best way to explore this further.

There is a need to explore prior treatment histories in more detail. A number of antibiotics related to tetracycline for instance can cause acute sexual dysfunction and might contribute to the clinical picture seen here, but few of our reporters will have known about this or thought to report it.

Exploring these tardive sexual syndromes in turn might help to explain the physiological basis for tardive syndromes in general, and point to other syndromes at present unrecognised. Conversely, prior research on tardive dyskinesia might usefully be brought to bear on the syndromes reported here.

In addition to clinical need and research opportunities, these syndromes raise philosophical questions. The most common initial clinical and research response is to think about brain function. It is equally possible the problems arise peripherally, consistent with the James–Lange theory of the emotions which sees affective states arising from the periphery and more of our cognitive functioning as stemming from the body than is ordinarily supposed.

Fascinating as these possibilities are, clinically the priorities are to raise awareness of these issues among patients and professionals, and to find treatments for a debilitating set of conditions that can have a profound impact on quality of life.

### **Conflict of interest**

All three authors are linked to RxISK.org. None have any consultancy or other links to groups with an interest in these results.

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