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One hundred and twenty cases of enduring sexual dysfunction following treatment

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Abstract.
BACKGROUND: There have been reports for over a decade linking serotonin reuptake inhibitors, finasteride and isotretinoin with enduring sexual dysfunction after treatment stops.
OBJECTIVE: To explore the clinical pictures linked to all 3 drugs.
METHODS: We have selected 120 reports to RxISK.org reporting the problem and mined these for data on age, gender, drug of use, and impact of the problem.
RESULTS: The data make it clear that the three drugs show extensive overlap in symptom profile, regardless of sex or country of origin.
CONCLUSIONS: The availability of 120 reports from over 20 countries add to the case for the validity of the syndrome. This is severe and enduring condition can result in death. An understanding of its physiology and an approach to treatment are needed.

Keywords: SSRIs, finasteride, isotretinoin, erectile dysfunction, loss of libido, genital anesthesia

1. Background

While there are long-standing reports of sexual dysfunction on isotretinoin, serotonin-reuptake inhibiting (SSRI) antidepressants and finasteride, starting from 2006 a series of descriptions of enduring sexual dysfunction following SSRIs [1–4], finasteride (Propecia) [5, 6], and isotretinoin (Accutane) [7, 8] have been published.

As of 2006, prior to the first publications, the Medicines' and Healthcare Products Regulatory Agency (MHRA) in the UK had over 200 reports of persistent sexual dysfunction linked to SSRIs but there was no warnings to this effect and little awareness of the problem more generally. If there have been this volume of reports in one country despite almost no recognition of the issue, the problem may in fact be quite common.

A number of hypotheses have been published to account for the findings [9–11].

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Those affected after SSRIs have focused on manipulations of the serotonin and dopamine systems in an effort to resolve the problems [10, 11], whereas those affected by finasteride and isotretinoin have focused more on endocrine manipulations [12]. To date neither approach has been successful.

It has been recognized that while there are some differences between the syndromes, there is considerable overlap also and this has led to more recent attempts to pool resources and efforts.

On January 27th 2014, Wikipedia took down a post on Post-SSRI Sexual Dysfunction (PSSD) that had been hosted for some years. They also removed a post on Post Finasteride Sexual Dysfunction. The justification in part was that these syndromes had not appeared in the peer reviewed literature.

This paper offers data that suggests the syndrome is real and significant.

2. Methods

The data in this article stem from people who have filed a RxISK report on RxISK.org [13].

RxISK.org is a portal for the reporting of adverse events by either patients or doctors and ideally by both combined. It was set up by three of the authors of this paper and several colleagues. It began collecting data on all drugs and all adverse events in late 2012. In early 2013 the site ran posts on its blog on the topic of enduring sexual dysfunction on SSRIs. It has since covered the topics of Post-Finasteride Syndrome and Sexual dysfunction after isotretinoin. These posts led to the reports to RxISK used to compile this article.

Reports to RxISK.org enquire systematically for the reporter's age, sex and background along with their drug consumption, medical history and country of origin. In some instances in these reports there is missing demographic data but in this paper we present all data we have rather than just the data on cases where the dataset is complete.

Using questions based on the Naranjo algorithm, RxISK takes reporters then through a causality assessment as to whether the drug has caused the problem being reported and gets them to assess the impact of the problem on their life. The RxISK system encourages detailed reporting in the belief that good quality descriptions offer the best basis for the possible detection of a physiological underpinning of the problem. It can offer no good estimates of the frequency of the problem.

3. Results

There have been 120 episodes of Post Treatment Enduring Sexual Dysfunction (PTESD) reported to RxISK. The frequency of drug involvement is laid out in Table 1.

It is worth noting that desvenlafaxine, nefazodone, fluvoxamine, duloxetine and ziprasidone are all serotonin reuptake inhibitors. There are single reports of enduring dysfunction on, buprenorphine, ondansetron, quetiapine, lithium and haloperidol. These drugs may have been co-prescribed with an SSRI at some point. Given that PTESD can happen after very brief exposure to an SSRI or related drug (3 days), or can start after the precipitating drug has been discontinued it is not unreasonable to think that some of those affected might attribute their condition to other drugs they were taking over more extended periods of time, and that this might explain the reports on drugs like buprenorphine. But in the case of the report on lithium, the reporter makes a convincing case that there were no other drugs prescribed that were likely to cause the problem.

We have had reports from 22 countries. These are laid out in Table 2.

Table 1
Drugs reported to RxISK linked to PTESD

Drug	Frequency (%)
Citalopram	18 (15.5)
Paroxetine	18 (15.5)
Escitalopram	15 (12.9)
Sertraline	14 (12.1)
Fluoxetine	13 (11.2)
Venlafaxine	9 (7.8)
Isotretinoin	7 (6.0)
Finasteride	6 (5.2)
Duloxetine	2 (1.7)
Buprenorphine	1 (0.9)
Lamotrigine	1 (0.9)
Olanzapine	1 (0.9)
Ondansetron	1 (0.9)
Quetiapine	1 (0.9)
Ziprasidone	1 (0.9)
Desvenlafaxine	1 (0.9)
Fluvoxamine	1 (0.9)
Nefazodone	1 (0.9)
Lithium	1 (0.9)
Haloperidol	1 (1.7)

The mean age of the 94 subjects for whom we have ages was 30.9 years with a range from 15 to 65 years. Of these 15 were female and 79 were male. The age data on the remaining 26 was incomplete.

Of the 7 isotretinoin cases and 6 finasteride cases, all were male. For the 90 serotonin reuptake inhibitors, 15 were female and 75 male. The other drugs split evenly between men and women.

In the case of 70 subjects we have indicators as to the length of treatment prior to the syndrome developing or the syndrome being noticed. These ranged from as short as three days to 15 years. One of the common features not caught in Table 4 below is that fact that in many instances the problem only emerges after stopping treatment. This appears true of all three drugs.

The profile of symptoms was as follows:

Finasteride, isotretinoin and SSRIs had very similar symptom profiles – See Table 6.

The consequences of PTESD have been severe. There are well documented cases of individuals who have committed suicide in the face of persistent dysfunction. The patient ratings of impact severity are laid out below in Table 6.

The longest case we have in the series has had PSSD for 18 years since a relatively brief exposure to fluoxetine at the age of 18.

4. Discussion

These data argue for the occurrence of an enduring sexual dysfunction that follows on treatment with drugs that inhibit serotonin reuptake, as well as with finasteride and isotretinoin. There appears

Table 2
Country of origin of the reports

Country	Frequency of PTESD
United States	40 (34.5)
United Kingdom	20 (17.2)
Australia	5 (4.3)
Poland	4 (3.4)
Brazil	3 (2.6)
Germany	3 (2.6)
Hungary	2 (1.7)
India	2 (1.7)
Netherlands	2 (1.7)
Belgium	1 (0.9)
Canada	1 (0.9)
China	1 (0.9)
Denmark	1 (0.9)
Ireland	1 (0.9)
Italy	1 (0.9)
Mexico	1 (0.9)
New Zealand	1 (0.9)
Norway	1 (0.9)
Slovakia	1 (0.9)
South Africa	1 (0.9)
Sweden	1 (0.9)
Switzerland	1 (0.9)

Table 3
PTESD by gender and age

Gender	*N*	Minimum age	Maximium age	Mean age	Days treated
Female	15	15	65	32.7	1476 ($n=6$)
Male	79	16	60	31.0	605 ($n=59$)
Combined	94	15	65	30.9	703 ($n=70$)

Table 4
Duration of exposure prior to the development of PTESD

Min number days treated ($n=70$)	Max number days treated ($n=70$)	Mean number of days treated
3	5840	703

to be a common syndrome involving erectile dysfunction in men, loss of lubrication in women, genital anaesthesia, lack of orgasm and loss of libido.

There are some differences between the symptoms reported that appear to stem primarily from the fact that close to 20% of the SSRI group are female while the finasteride and isotretinoin groups are male.

Table 5
Symptom profile from all reporters of PTESD

Side effect	Frequency (%)
Loss of libido	86 (75.4)
Erectile dysfunction	74 (64.9)
Orgasm difficulties	62 (54.4)
Genital anesthesia	35 (30.7)
Ejaculation problems	17 (14.9)
Vaginal dryness/pain	14 (12.3)
Reduced seminal volume	11 (9.6)
Memory impairment	10 (8.8)
Anxiety	9 (7.9)
Sexual fantasies altered	8 (7.0)
Drug withdrawal	8 (7.0)
Depression	8 (7.0)
Reduced size penis	8 (7.0)
Impaired concentration	7 (6.1)
Muscle weakness	7 (6.1)
Testicular atrophy/pain	6 (5.3)
Heterosexuality	5 (4.4)
Fatigue	5 (4.4)
Brain fog	4 (3.5)
Decreased testosterone	2 (1.8)
Sexual deviation	2 (1.8)
Irregular menstruation	2 (1.8)

Table 6
Comparative profiles of finasteride, isotretinoin & SSRIs

Symptom	Finasteride frequency (%)	Isotretinoin frequency (%)	SSRI frequency (%)
Loss of libido	6 (100)	6 (85.7)	63 (76.8)
Genital anaesthesia	3 (50)	3 (42.9)	23 (28)
Orgasm difficulty	1 (16.7)	1 (14.3)	50 (61)
Ejaculation problems	1 (16.7)	1 (14.3)	13 (48.1)
Erectile dysfunction	4 (66.7)	7 (100)	42 (77.8)
Testicular atrophy/pain	2 (33.3)	0	2 (3.7)
Reduced size penis	4 (66.7)	0	3 (5.6)
Reduced seminal volume	0	0	7(13)
Muscle weakness	4 (66.7)	0	2 (2.4)
Memory impairment	3 (50)	1 (14.30)	3 (3.7)
Irregular menstruation	0	0	2 (15.4)
Vaginal dryness/pain	0	0	10 (66.7)
Sexual fantasies altered	0	0	7 (8.5)
Decreased testosterone	0	0	2 (3.7)
Emotional blunting	0	2 (28.6)	8 (9.8)

Table 7
Patient rated estimate of severity

Patient rated severity of PTESD ($n = 114$)	Frequency (%)
Extreme	44 (38.6)
Missing data	31 (27.2)
High	27 (23.7)
Medium	7 (6.1)
Mild	5 (4.4)

But in addition there are features that are specific to each drug, such as testicular atrophy and muscle weakness on finasteride that may stem either from the anti-androgen effect of this drug, and emotional blunting on SSRIs on the one hand or popular portrayals of what these syndrome must entail based on hypotheses regarding its cause – such as an anti-androgen effect.

There is therefore likely to be some mixture of symptoms arising from an underlying physiological dysfunction and some arising from other sources. This makes it difficult to say for certain that the syndromes following all three drug groups are identical. There is however a degree of commonality that may be based in common physiological changes.

Efforts to manage post SSRI Sexual Dysfunction (PSSD) have focussed on manipulating the serotonergic and dopaminergic systems [10, 11], but to little avail. These have included 5HT-1 agonists like buspirone, as well as 5HT 2 and 5HT-3 antagonists like trazodone and mirtazapine. These latter two drugs can induce priapism and increased libido respectively in normal people but have little effect in PSSD.

Affected subjects also report trying dopamine agonists such as pramipexole and cabergoline along with buproprion, dexamphetamine and other stimulants but to no avail. In addition patients have tried sildenafil, vardenafil and related drugs as well as testosterone but with little benefit.

These failures in part have perhaps contributed to proposals that the enduring difficulties are tied to epigenetic changes [9], but such proposals have not led to any treatment leads so far.

In contrast, the profile of finasteride has pointed to a possible androgen deficiency leading to androgen receptor hypersensitivity [12]. However at present there are no reports that testosterone or other related replacement therapies have made any difference.

It is possible that there are common mechanisms linking the two syndromes. There is little doubt that drugs active on the serotonergic system can have endocrine effects and that either these or other changes lead to a reduction in sperm numbers and functionality as well as ovarian shrinkage [13–16]. These changes would seem likely to underpin the loss of libido linked to longer term use of SSRIs. However in some instances, PSSD can be present after the first few doses of an SSRI, and genital anaesthesia which is such a marked feature of PSSD, can be present from 30 minutes after the first dose of treatment.

In terms of a possible endocrine mechanism, however, GnRH analogues like leuporelin and goserelin are at present being given to women for a range of conditions and to men for prostate cancer. They can induce impotence in men, but do not appear to produce the triad of anaesthesia, loss of libido and loss of function enduring after treatment stops that is characteristic of this syndrome.

If the problems are not mediated by a common endocrine effect, the converse possibility is that finasteride and isotretinoin have effects on the serotonin system. This possibility is certainly true for isotretinoin [17], but an action on the serotonin system has not been reported for finasteride to date.

Enduring sexual dysfunction after treatment is one of the most debilitating conditions imaginable. Finding a treatment is a key goal. Evidence for a therapeutic benefit will hopefully also offer some solid

leads as to the nature of the core condition and what might be done to avoid it happening in the first instance.

In terms of treatment options, in addition to the ones already tried by members of the PSSD and PFS communities, a number of healthy volunteers linked to RxISK have taken ketamine, donepezil and metformin in an effort to explore the possibility of restoring genital sensation but at present no one has found a benefit from any of these.

This legacy phenomenon is worth taking seriously for several reasons. It is of interest because in many instances, somewhat like tardive dyskinesia, the problem only emerges when treatment is stopped, which helps broaden out our understandings of how side effects happen. Aside from this, as with tardive dyskinesia, there are some reports that in some people it can be managed by increasing the dose of the agent that has caused it –although intuitively given the example of tardive dyskinesia this does not seem a good long-term strategy. Finally as with tardive dyskinesia it helps recalibrate out ideas of how long a treatment related effect can endure.

The physiological mechanisms that underpin legacy effects like this of treatment need to pinpointed and if discovered widely reported as there are likely a number of other legacy effects of a range of different drugs that would be accepted and perhaps remedied if physicians were unable to dismiss the phenomena as physiologically impossible.

In summary, the number of cases reported here offer enough evidence to warrant an exploration of the physiological underpinnings of enduring post treatment sexual dysfunction. It is only when these are elucidated that we will be able to decide for certain if there is a common syndrome here and where its boundaries lie.

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