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FEMALE SEXUAL DYSFUNCTION AND DISORDERS (T LORENZ AND R NAPPI, SECTION EDITORS)

Are There Any Sex/Gender Differences in Post-Selective Serotonin Reuptake Inhibitors (SSRI) Sexual Dysfunction (PSDD)?

Y. Reisman[1]

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Abstract

Purpose of Review Because of the sex/gender differences in the manifestation of depression, one can assume the possible existence of gender differences in post-SSRI sexual dysfunction (PSSD). This article tries to summarize the available data on sex/gender differences in PSSD and to evaluate if different approaches in diagnosis or treatment of different genders are needed.

Recent Findings Depression is a leading cause of disability worldwide. Studies observed gender differences in prevalence and clinical presentation of depression, adherence to treatment and pharmacological features of antidepressant treatment. Sexual adverse events during the use of antidepressants are well-known and occur frequently. PSSD has been recently recognized as a medical condition that can outlast discontinuation of SSRI and SNRI antidepressants. The published literature on PSDD is lacking a clear definition of PSSD and data on possible sex/gender differences are very limited. The available information shows some gender differences in frequency of the different presented symptoms, but development of validated clinical assessment instruments of all possible sexual complaints, including genital anesthesia and pleasureless orgasm, is necessary.

Summary The available scientific literature is lacking profound information about the extent, the mechanism, and possible treatment of PSSD and sex/gender differences as well. Physicians should assess sexual function prior, during, and also after treatment with antidepressants and be aware of the possibility of PSSD. Physicians should inform their patients about the possible sexual consequences of antidepressant treatment and include it, when possible, in the treatment decision-making process.

Keywords PSSD · Gender · SSRI · Sexual dysfunction

Introduction

Depression is a heterogeneous, multifaceted disorder with symptoms manifested at the physiological, psychological, and behavioral levels [1]. Depression is a leading cause of disability worldwide and is a major contributor to the overall global burden of disease [2]. Depression can manifest with reduced mood, low self-esteem, feelings of worthlessness, general fatigue, feelings of guilt, anger, absence of pleasure, disturbances in sleep, sex drive and food intake, and agitated or signs of psychomotor retardation (which include slowed speech, decreased movement, and impaired cognitive function) [1, 3, 4]. Epidemiological and clinical studies have consistently observed significant sex-specific differences among patients with depression, with women outnumbering men at about 2:1. The lifetime prevalence of major depression is 21% in women and 12% in men [2, 5, 6]. This sex difference becomes evident in adolescence [4]. A number of studies have reported clear differences in the clinical appearance and characteristics of depression in men vs. in women [6]. Below, I review several lines of research relevant to the question of possible sex/gender differences in SSRI-related sexual dysfunction: first, I review the literature on possible causes of sex/gender differences in depression and its etiology; then, I review research sexual side effects of antidepressants and the post-selective serotonin reuptake inhibitor discontinuation syndrome (PSSD); finally, I review the evidence for gender/sex differences in PSSD with recommendations for future research. Although some authors have commented on the similarities between PSSD and post-finasteride syndrome, this will not be addressed in this review as it appears only in men [7].

This article is part of the Topical Collection on *Female Sexual Dysfunction and Disorders*

✉ Y. Reisman
uro.amsterdam@gmail.com

[1] Flare-Health, W.H. Keesomlaan 12, 1183 DJ Amstelveen, The Netherlands

Gender/Sex Differences in Depression and Its Etiology

In several studies, gender differences in the role of stressful life events, marriage, parity, and educational level have been considered in the etiology of depressive illness. In women, stressful life events appear to be a risk factor for the development of depression [8]. Most neurobiological theories attribute the higher prevalence of depressive disorders in women to fluctuations in levels of reproductive hormones, mainly estrogens [9]. Changes in these reproductive hormones may directly affect the function of various neurotransmitters (e.g., serotonin, norepinephrine) and cerebral function [10].

In the treatment of depression, different antidepressants such as selective serotonin reuptake inhibitors (SSRIs), tricyclics (TCAs), and monoamine oxidase inhibitors (MAOIs) are used. The most widely prescribed antidepressants are SSRIs [2, 4]. SSRI antidepressants are also effective in treating some anxiety disorders [3]. The frequency of antidepressant use is higher among women (44.3%) than men (25.5%). Women, in comparison with men, show a significant increase in the use of these drugs with the increase in age and higher prevalence rates were found among those with a higher level of schooling and those with a larger number of chronic diseases [11].

Differences between women and men in the pharmacokinetics and/or pharmacodynamics of antidepressants treatment have been reported, although recommendations for clinical treatment at present are still identical in both sexes [9, 10]. Hormone-related changes associated with the menstrual cycle may affect antidepressant absorption and distribution. Compared with men, pre-menopausal women are more likely to respond to selective serotonin reuptake inhibitors (SSRIs) than to tricyclic antidepressants (TCAs) [12, 13]. Neuroimaging studies demonstrated elevated levels of serotonin, as well as the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA), in women compared with men, which may be related to a greater availability of the serotonin transporter in females [14, 15]. Furthermore, brain levels of serotonin and norepinephrine show greater age-related changes in females than in males. Women have been shown to possess a higher concentration of synaptic dopamine in the striatum than men do, and age decreases synaptic dopamine levels in men more than women [16].

Another gender difference has been found in adherence to antidepressant treatment, in which males aged 20 to 40 years had higher adherence than for females of the same age group. This relationship reversed later in life for those aged 50 to 70 years [17].

Sex/Gender Differences in Sexual Adverse Events of Antidepressants Use

In general, sexual dysfunction due to SSRI use is underestimated; one possible explanation is that patients and their providers are reluctant to bring up this topic [18•]. In a landmark multicenter, prospective, open-label study, 1022 patients with previously normal sexual function who were being treated with antidepressants were assessed using the Psychotropic-Related Sexual Dysfunction Questionnaire [19]. Only 20% of the patients reported their sexual dysfunction spontaneously, but rates of dysfunction as captured by the questionnaire were considerably higher. The majority of the patients stated that their distress related to sexual problems associated with antidepressant use was high. Fifty-nine percent of the patients suffered from sexual dysfunctions across all the sexual response cycles phases, with lower incidence for erectile dysfunction/decreased lubrication and higher incidence of decreased libido or disorder of orgasm and/or ejaculation. The incidence was different across different antidepressants: higher with SSRIs and lower with serotonine-2(5-HT_2) blockers like nefazodone and mirtazapine. In this study, men experienced a greater incidence of sexual dysfunction (62.4%) compared with women (56.9%), but women experienced greater intensity of decreased libido, delayed orgasm, and anorgasmia. About 80% of the patients did not show any improvement of their sexual complaints, even 6 months after initiating of treatment with SSRIs. About 40% of the patients found their sexual side effects were poorly tolerated [19]. According to another recent study published on sex/gender differences of SSRI's side effects, the percentages of adverse drug reactions were higher in women than men and were usually dose-related reactions of the most common adverse reactions. These dose-related differences in side effects were explained as differences in the pharmacokinetics of SSRIs between men and women [20].

Gender Differences in PSSD Epidemiology and Complains

The side effects of SSRIs, as reported above, are expected to disappear after discontinuation of their use. However, in 2006, the first reports of enduring sexual side effects from SSRIs appeared following with other reports of comparable cases and the designation of these effects as a post-SSRI sexual dysfunction (PSSD) [21–27]. On June 11, 2019, the European Medicines Agency (EMA) formally declared that it recognized PSSD as a medical condition that can outlast discontinuation of SSRI and SNRI antidepressants. The announcement by the European Medicines Agency came 2 weeks after the Royal College of Psychiatrists advised that it would include in its prescribing guidelines the recognition that antidepressant withdrawal can be "severe" and last for weeks or even months.

Although very recently, the European Medicines Agency recognized PSSD as a medical condition; PSSD is still not a diagnostic entity classified or defined by any formally recognized diagnostic system as DSM or ICD. As a consequence of that, the rate at which PSSD occurs is unknown and there is no

accurate estimation of the magnitude of the problem. Some authors claim that PSSD is under-diagnosed [28•]. Beside lack of definition, other factors can contribute to the low prevalence, as patients often have discomfort at raising sexual concerns with their doctor, as may medical professional feel the discomfort at inquiring about the resolution of sexual side effects once treatment has finished. On the other hand, there is still ongoing discussion on the existence of PSDD and some physicians neglect the complaints of the patients. Recently, a citizen petition to the Food and Drug administration (FDA) has been published urging the explicit warnings of sexual side effects of SSRISs and SNRIs including PSDD and Persistent Genital Arousal Disorder (PGAD) [29•]. The latest is considered a mirror image of PSDD in which the use of SSRIs or SNRIs, and often their withdrawal, has consistently been reported as one of the triggers of the condition, which can endure for years after the medication has been discontinued.

All publications concerning PSSD are case reports, possible theoretical explanations, and reviews of the available literature. As such, there is no definite evidence of possible sex/gender differences. However, in the section below, I review this research with an eye towards defining features that may be specifically related to sex/gender differences in either depression or antidepressant use experiences as outlined above.

Bolton [21] published the first case report of 26 years old male with genital anesthesia and pleasureless orgasm, following by other reports all with comparable symptoms that sometimes exist many years after discontinuation of the SSRI [22–27, 28•, 30–32]. In Table 1, all available case reports are summarized.

Hogan et al. [26] mentioned in their publications that 90% of the patients had high to extreme severity intolerance of the symptoms. Notably, they did not find any differences between males and females in severity scores of the complaints.

Ben-Sheetrit [31] conducted a causality assessment according to defined criteria, classifying 23 of 183 probable cases as having high probability of PSSD (that is, having sexual dysfunction attributable to discontinuation of SSRIs). Of these, 4 were females with mean age of 36 years; 3 (75%) of these women had signs of genital anesthesia. Additionally, there were 19 males with mean age of 32 years, of whom 16 (84%) had genital anesthesia [31]. Genital anesthesia was a predictor of worse sexual dysfunction and correlated significantly with sexual dysfunction severity according to scores on a validated clinical survey of sexual functioning ($r = 0.56$; $p = 0.001$), while depression scale score was only weakly correlated with current sexual dysfunction severity ($r = 0.32$; $p = 0.01$). Their conclusion was that genital anesthesia probably causes or worsens sexual dysfunction. The decreased sensation is likely to lead to decreased pleasure, which can result in erectile dysfunction or decreased lubrication, and the latter may have negative influence on libido and arousal by means of negative feedback. Pleasureless orgasm (not as genital anesthesia) was an independent predictor of both depression severity and case probability.

Stinson [32] reported on different aspects of PSSD in a small group of males and females. The report included 5 females with PSSD, with a mean age of 33.6. All females reported loss of libido, 2 had evidence of genital anesthesia, 1 reported anorgasmia, and 1 reported pleasureless orgasm.

Table 1 Published PSSD case reports

Author	No. of cases	Gender	Age**	Duration of SSRIs use	Duration of symptoms after discontinuation of SSRIs
Bolton [21]	1	1♂	26	5 months	6 years
Csoka [22]	3	2♂ 1♀	27 (24–30)	3–35 days	7 months–3 years
Kauffman [24]	1	1♂	32	Few days	1 year
Csoka [30]	3	3♂	33 (18–44)	3 days–2years	4–11 years
Ekhart [25]	19	13♂ 6♀	30 (20–59)	9 days–10years	2 months–2 years
Stinson [32]	9	4♂ 5♀	34.7 (22–59)	4 months–1 year	2 months–3.9 years
Hogan [26]	90	75♂ 15♀	31 (15–65)	3 days–15 years	Up to 18 years
Waldinger [27]	1	1♂	43	1 week	2 years
Ben-Sheetrit [31]	183	143♂ 40♀	36 ± 11.4	1 day–15 years	1 month–19 years
Healy [28•]	229*	170♂ 49♀	31 (15–66)	1 day–16 years	Up to 20 years

*only post-SSRI patients are counted, **mean ± SD or median (range)

Additionally, there were 4 males with an average age of 36; all of whom reported erectile dysfunction, 2 with genital anesthesia, and 2 with pleasureless orgasm or anorgasmia.

In one of the largest studies to date on PSSD, Healy et al. [28•] collected 300 cases of sexual dysfunction after treatment with antidepressants, 5α-reductase inhibitors, and isotretinoin; of these, 229 were after the treatment with SSRIs. The authors conducted causality assessment according to the Naranjo algorithm [33] to help determine whether an index drug was responsible for the event. Score of 5–8 indicates a likely link between medication and side effect; 9+ denotes a strong possibility of a link between medication and side effect. The average score of these 229 cases was 8.9.

There were consistent reports from patients that the condition made it difficult or impossible to engage in normal romantic relationships, with 25 reporting that the condition had led to relationships breakup. Ninety subjects reported that their work had been affected, including 12 who had lost jobs [28•].

Seventeen cases have been reported with complaint about premature ejaculation on citalopram, mainly after withdrawal. This seems surprising as antidepressant are known for prolongation of the intravaginal ejaculatory latency time (IELT), but this phenomenon is in accordance with an earlier report in which citalopram induced premature ejaculation [34]. Six cases have been reported with complaints resembling persistent genital arousal disorder (PGAD), of whom 4 were females and 2 were males. In the literature, PGAD is predominantly reported in females [35–37].

So far, the Healy study [28•] is the only report in which detailed information about the complaints in the different gender groups are given. The 49 females had an average age of 30 years (range, 15–54) and the 170 males of 32 years (range, 16–66). In Tables 2 and 3, the symptoms of both gender groups were given according to the frequency of complains. Loss of libido was the most commonly reported symptom in female subjects, and the second most reported feature in male subjects. Against a background of genital anesthesia and pleasureless orgasm, it is not surprising that a loss of libido and/or development of sexual dysfunction may be a secondary effect, but it should be noted that this can occur on acute treatment with SSRIs and SNRIs as well. Ten females reported reduced sensitivity of the nipples and 7 males reported reduced sensitivity or numbness in different skin region. Reduced taste was also one of the complaints patients mentioned.

One may speculate that perhaps women report more often about loss of genital sensation and anorgasmia, while more loss of libido and arousal problems appear in men. Other complains like pleasureless orgasm is more or less parity across sexes.

None of the reports, except Stinson, gave information about the sexual orientation of the patients. In the Stinson, 2 of the males were gay and 1 female was bisexual [32].

Table 2 Most apparent symptoms of 170 male cases (a) and 49 female cases (b) with PSSD according to frequency of complains. Based on Healy et al [28•]

Symptom	%
a. 170 male patients	
Erectile dysfunction	86
Loss of libido	79
Genital anesthesia	49
Pleasureless orgasm	43
Difficulty in achieving orgasm	33
Emotional blunting	20
Loss of nocturnal erections	13
Reduced ejaculation volume	13
Premature ejaculation	10
b. 49 female patients	
Loss of libido	72
Genital anesthesia	60
Difficulty achieving orgasm	60
Emotional blunting	28
Pleasureless orgasm	26
Vaginal dryness	18
Other skin numbness	10
Reduced nipple sensitivity	10

Discussion

Although the number of not-industry supported studies and publications on sexual side effect of antidepressant is increasing, we still have limited knowledge on the magnitude of the problem, the mechanism of action, and the risk factors. In clinical practice, many patients are not informed about the possibility of these sexual side effects and the subject often remains unspoken [38]. Gender differences are, to some extent, known in the prevalence of depression in different age groups and phase of life, the clinical presentation, and pharmacological features of different SSRIs. Still we have limited information on gender differences with respect to treatment recommendation, treatment adherence, and risk factors for the development of adverse events. The situation is even worse in the case that sexual side effects continue to exist even after therapy with SSRIs ceases, as in the case of PSSD.

As for today, there is no clear, evidence-based definition of PSSD, the rate at which the condition occurs is unknown, the possible mechanism is not understood, and persons at risk are not identified. Many patients have usually discomfort to discuss sexual complaints or bother with their physicians, while health care providers have discomfort to inquire about sexual complaints, and the subject is often remained unspoken. Whenever matching PSSD complaints are mentioned, they are often assigned to manifestation of the underlying depression because of the limited knowledge and awareness of the possible existence of PSSD. The patient is often remaining alone and needs to deal not only with the symptoms but also with the lack of recognition, support, and understanding.

As for today, we have limited information about possible gender differences in the prevalence of PSSD, the prevalent symptoms, the duration of the dysfunctions, and any relationship with specific SSRIs.

In comparison with men, depression appears more often in females and the use of antidepressants is higher among women (10), while according to the larger multicentral study (26), more males complain about sexual side effects of antidepressant use. As far as we know, PSSD show the same patron with higher prevalence among men. One can speculate that according to the data from brain imaging study, women have higher concentration of synaptic dopamine in the striatum than men do (15), reducing the prevalence of sexual side effects and PSSD among women.

From the only detailed publication about PSSD symptoms appearance in different genders [28•], the most apparent complaint in males is concerning the arousal phase of the sexual response cycle, erectile dysfunction. While the equivalent in female loss of lubrication/dry vagina is less apparent in females, loss of libido, which is a more subjective experience, is the most commonly reported symptom in female subjects and the second most reported feature in male subjects. Possible explanation is the lack of awareness of many females for their objective arousal signs [39] which is markedly underreported, and females are more aware about the subjective feeling of desire. Many males often unrecognized that their erectile dysfunction can be caused by the loss of libido. It is not a surprise that when there are desire and/or arousal problems and genital anesthesia in both genders, they almost equally suffer from orgasmic problems.

Physicians and all healthcare providers should be able to discuss basic sexual function with their patients, certainly when prescribed medication or intervention has possible negative influence on patient's sexuality. Therefore, basic education on sexual health of all healthcare professionals is requisite [40]. Review about PSSD advised that patients should be warned about PSSD when using antidepressants [41, 42].

There is a need for systemic information about sexual functioning at baselines (pre-medication) during follow-up and after cessation of treatment with antidepressant. The sexual functioning inquiry needs to include symptoms of genital numbness or orgasmic anhedonia. Development of objective, validated questionnaires which will include information about genital anesthesia and pleasureless orgasm is necessary.

Conclusion

Sexual side effects are frequently present as a consequence of antidepressant treatment and sometimes continue to exist after discontinuation of treatment. This may have major implications on the informed consent and choice of therapy for patients with depressive or anxiety disorders. Physicians should assess sexual function prior, during, and also after treatment with antidepressants and be aware of the possibility of PSSD.

Extensive, systemic research is warranted on the magnitude of PSSD, possible mechanism, possible gender differences, and identification of patients at risk.

Compliance with Ethical Standards

Conflict of Interest The author declares that there are no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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