SEXUAL MEDICINE REVIEWS REVIEWS

Post-SSRI Sexual Dysfunction (PSSD): Biological Plausibility, Symptoms, Diagnosis, and Presumed Risk Factors

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ABSTRACT

Introduction: Post-SSRI sexual-dysfunction (PSSD) is an iatrogenicsyndrome, the underlying neurobiological mechanisms of which areunclear. Symptom onset follows cessation of serotonergicantidepressants i.e. Selective Serotonin and Norepinephrine ReuptakeInhibitors (SSRI's, SNRI's), and Tricyclic antidepressants (TCA's). PSSDsymptoms include genital anesthesia, erectile dysfunction andorgasmic/ejaculatory anhedonia, and should be differentiated fromdepression-related sexual-dysfunction. Recently, accumulated data of numerous case-reports suggest additional non-sexual symptoms including, anhedonia, apathy, and blunted affect. PSSD gained official recognition after the European medical agency concluded that PSSD is a medical condition that persists after discontinuation of SSRI's and SNRI's.

Objective: To review possible underlying neurobiological mechanisms ofthis syndrome, update information on the pathophysiology, present a listof potential risk-factors and discuss potential management options forPSSD.

Methods: Extensive literature review on the main symptom-patterns ofthis disorder was undertaken using PubMed. It includes introductoryexplications of relevant neurobiology with the objective of generatinghypothesis.

Results: Precipitating factors for PSSD include previous exposure to certain drugs, genetic predisposition, psychological stress or chemical stressful reaction to antidepressants along pre-existing medical conditions affecting neuroplasticity. Different theories have been proposed to explain the pathophysiology of PSSD: epigenetic gene expression, dopamine-serotonin interactions, serotonin neurotoxicity and hormonal changes. The diagnosis of PSSD is by excluding all other etiologies of sexual-dysfunction. Treatment is challenging, and many strategies have been suggested without definitive outcomes. We offerthe contours of a future neurobiological research agenda, and propose several underlying mechanisms for the various symptoms of PSSD which could be the foundation for a future treatment algorithm.

Conclusion: There is a need for well-designed neurobiological research in this domain, as well as in the prevalence, pathophysiology, and treatment of PSSD. Practitioners should be alert to the distinctive features of PSSD. Misdiagnosing this syndrome might lead to harmful Sexual Medicine Reviews. **Peleg LC, Rabinovitch D, Lavie Y, et al. Post-SSRI Sexual Dysfunction (PSSD): Biological Plausibility, Symptoms, Diagnosis, and Presumed Risk Factors. Sex Med Rev 2021;XX:XXX–XXX**

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INTRODUCTION

Sexual Dysfunction (SD) is often without a clear cause, but may be linked to lifestyle factors such as smoking, exposure to environmental factors (eg, heavy metals), deleterious mental states (anxiety or stress), pathological conditions (i.e. major depressive disorder, hypertension, diabetes) and medication side-effects, such as those of the widely used selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs) and tricyclic antidepressants (TCAs).[1,2] Depression is strongly associated with SD as part of the core

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depressive syndrome, in which sexual function may be diminished or absent. In both sexes, decreased sexual desire in depression is the most prominent symptom, and dysfunctions of sexual arousal and orgasm may also occur. There may also be a bi-directional relationship between depression and SD.[3] However, the treatment of depression with SSRI antidepressants is itself an independent cause of SD, despite improvement of, and recovery from, the depression, as long as the treatment endures.[4–6] Over time, it emerged that SSRI-induced sexual dysfunction may persist following cessation of SSRI treatment.[7–9] This condition has been termed post-SSRI Sexual Dysfunction (PSSD). The syndrome is characterized by a wide array of symptoms that may persist for variable periods or even indefinitely. The core symptoms of PSSD are genital anesthesia, loss of pleasure derived from genital stimulation, pleasure-less or weak orgasms (anhedonic orgasm), decreased sex drive, erectile dysfunction (ED), premature ejaculation, diminished vaginal lubrication, and diminished tactile sensitivity of nipples.[10] Genital anesthesia appears to be uniquely and distinctively associated with PSSD; this phenomenon emerges in literature searches for PSSD symptoms but not in searches for SD symptoms common in depression. Furthermore, accumulated data of hundreds of case-reports which was published in recent years, suggest that there are also non-sexual symptoms including, but not limited to, anhedonia, apathy, and blunted affect.[11,12] In the year 2020 the *British Medical Journal* (BMJ) has also recognized PSSD as an important and distinct syndrome.[13] PSSD has also been described as a cause of substantial and prolonged suffering, with devastating effects on quality of life that lead to significant loss of function, culminating in suicide attempts or even successful suicides in several anecdotal cases.[14] No rational or consistent treatment has been found for this disorder. It is imperative for clinicians to be aware of non-sexual symptoms and to be able to differentiate between PSSD-associated SD and depression-related SD, as each of their symptoms can be quite distinctive with a few symptoms overlapping. We highlight these differences in this manuscript and propose a number of presumed risk factors that we have commonly encountered while reviewing cases of PSSD.

METHODS

In this paper, an extensive literature review organized around the main symptomatic patterns of Post SSRI Sexual Dysfunction (PSSD) syndrome, using PubMed. Our objective is to review, as extensively as is possible, the likely neurobiological underpinnings of this disorder. It includes introductory explications of relevant neurobiology. Our overarching objective is to generate hypotheses that may become a basis for future research. Reference is also made to publicly available clinical information gleaned from internet forums where illustrative or informative neurobiological formulations are proposed for future study.

PSSD Biological Plausibility, Development, and Occurrence

PSSD is an iatrogenic, idiosyncratic disorder, and an apparent example of the post-drug syndromes. It mainly develops following cessation of SSRIs but also other classes of antidepressant drugs.[11,15] This has been confirmed by the European Medicine Agency after reviewing the evidence, the latter being an important step towards further research into the full scope of this phenomenon.[16] Since 2006, reports of enduring sexual side effects from SSRIs usage have been accumulating, and the term "PSSD" has been retained.[11,15,16] In 2011, the US product information for Prozac (fluoxetine) has warned that symptoms of SD occasionally persist after discontinuation of fluoxetine treatment.[17] The DSM 5th edition states that in some cases, SSRI-induced sexual dysfunction may persist after the agent is discontinued.[16] PSSD can emerge after brief or long-term exposure to SSRIs and can persist for months, years, or indefinitely. It affects both genders, and currently there is no established treatment. The incidence and prevalence of this condition is not known.

Rat studies have demonstrated a permanent reduction in the sensitivity of 5HT1A receptors following the discontinuation of fluoxetine.[18,19] Moreover, studies of the chronic use of SSRIs in very young rodents resulted in a sustained reduction in sexual behavior in adulthood, with observed long-term neurological sequelae.[20] We propose that down-regulation of the pre-synaptic autoreceptors is part of the underlying mechanism of PSSD. Indeed, sustained high levels of serotonin, even after SSRI discontinuation, are chronically damaging to the serotonin transporter (SERT), as well as the 5HT1A pre-synaptic autoreceptors, and the post-synaptic 5HT1A hetero-receptors functions.[10] We have seen in clinical practice and case reports, that in some PSSD patients, clinicians treat the disorder by using buspirone or flibanserin. However, we note that the symptomatic relief from these medications may rapidly diminish over time due to pharmacological desensitization and downregulation of receptors' densities, often followed by further exacerbation of symptoms.[21] Desensitization of the post-synaptic 5HT1A receptors in several brain regions (eg, the amygdala, the hypothalamus, and the prefrontal cortex) may underlie part of the mechanisms behind PSSD occurrence.

We speculate that the 5HT1A post-synaptic receptors have significant importance in PSSD prevalence.[10] Moreover, the post-synaptic receptor has a broad and pronounced effect on sexual behavior.[22] Normally, it disinhibits excitatory dopamine (DA) and norepinephrine (NE) signaling while causes an increase in oxytocin release, which in turn causes sensitization of the limbic system to β-endorphin's effects.[23–25] The brain areas of the zona incerta and the anterior hypothalamus medial preoptic area (mPOA) are also implicated as regions which are highly related to sexual desire.[26,27] Hence, PSSD mechanisms might be related to these areas. Specifically, the incerto-hypothalamic pathway, which sends dopaminergic projections to the lateral hypothalamus, anterior hypothalamus and the mPOA of the hypothalamus, is important in sexual excitation.[28] Apart from the

epigenetic alterations leading to regulatory abnormalities of receptors, serotonergic, androgenic and dopaminergic neurotoxicity is an important facet in PSSD. Santana and colleagues showed that paroxetine treatment causes a reduction in TH immunoreactivity,[29] which serves as a suitable marker of dopamine level in neurons and fibers.

Symptoms

It is important to differentiate between depression-related SD symptoms and those of PSSD. Among all symptoms of SD, some seem to be more associated with PSSD rather than with depression.[10,15,16,30] In the absence of a depressive syndrome, PSSD-related symptoms are as follows:

Genital Anesthesia & Decreased Tactile Sensitivity of Nipples. Diminution of genital sensation is a common symptom of PSSD[15] and appears to be unique to it. The cause may be altered spinal nerve conductance (personal communication: Dr. Erwin Goldstein MD). Reduced tactile sensitivity in the genital and nipples of a female subject were reported by Csoka and Shipko among other symptoms which appeared few days into the treatment with fluoxetine.[7,9] Symptoms partially resolved after drug cessation. Spinal pain fibers which carry serotonergic and noradrenergic receptors may have an altered function in this setting.[31] Alternatively, this may be an expression of a small fiber neuropathy (SFN).[16] Transient receptor potential ion channels (TRP) may also be involved.[32] Disruption of the organization of thalamocortical sensory neural circuits was found in rodents after exposure to SSRIs during brain development leading to persistent changes into adulthood. This highlights the possible role of the thalamus in this disorder.[33]

Absent or Diminished Sexual Desire. We propose that in PSSD patients, the psychological component of sexual desire is not directly affected and probably is not an underlying part of PSSD's biological plausibility. A sporadic resurgence of sexual interest during random periods of remission or in response to successful treatment has been noted.[34] Despite this, the physiological component, which includes the subjective pleasant sensation of sexual arousal, is absent. Thus, in PSSD, even under normal psychological conditions, there is an inability to experience sexual desire and normal sexual sensation of excitation and arousal.[16,19,30] This physiological PSSD-related deficit raises a question of possible dopaminergic deactivation of the pleasure centers of the hypothalamus, the ventral tegmental area (VTA), and the nucleus accumbens (NAc).

The probable starting point in the neurobiology of normal sexual desire involves androgen and estrogen receptor signaling in the hypothalamus, which eventually results in dopaminergic activation of the mPOA. This in turn increases dopamine at the VTA, and the latter projects into the NAc. Interruptions of this process in PSSD are related to the elevated levels of serotonin in the limbic system as well as the PFC which has a significant top-down control over the limbic system.[35]

Erectile Dysfunction & Diminished Vaginal Lubrication. PSSD patients report a reduction or loss of nocturnal erections. This form of erection is triggered within the pons of the brainstem.[36] Other affected erection types in PSSD include psychogenic erections and, in more severe cases, we may find loss of reflexogenic erections which are mediated via a spinal reflex.[36,37] Loss of erection could be explained by reduced oxytocin in several brain regions such as the paraventricular nucleus of the hypothalamus. Administration of oxytocin into male rat brains has been found to potentiate penile erections.[40] D2 receptor activation in this brain region increases oxytocin release and thus increases the extra-cellular levels of dopamine at the NAc.[41] The mPOA of the hypothalamus and ventromedial oxytocin administration leads to lordosis in female rats.[38,39] Moreover, systemic oxytocin administration in male rats, chronically treated with fluoxetine, enabled ejaculation.[40,41]

Oxytocin stimulates the penile erection when injected into several brain regions which control penile erection, through modulation of oxytocinergic and dopaminergic mesolimbic neurons.[42] Androgen receptor (AR) inactivation in mice led to reduction in hypothalamic neural nitric oxide synthase (nNOS), indicating the regulatory sexual function of this neurotransmitter.[43] Furthermore, activation of the pre and post-synaptic 5HT1A receptors was found to be correlated with inhibitory effect on erectile function.[44] All of these factors are speculated to be involved in this symptom and might be related to epigenetic alteration of androgen receptor (AR) and estrogen receptor (ER) densities due to influence of SSRIs on the epigenome.[45]

Vaginal lubrication problems have been documented in PSSD.[10] This may simply be a consequence of diminished libido, but given the normal variability of the female sexual response,[46] the link with PSSD is unclear. Vaginal lubrication is dependent upon the synthesis of nitric oxide (NO), and the enzymatic function of NO synthesis is amplified by estrogen.[47,48] Vasoactive intestinal peptide (VIP) has been shown to play a role as well.[49] It is unknown as to whether SSRIs affect VIP, but there are indications that in animal models, SSRIs may inhibit NO production in males.[50] There are no studies examining the effect of SSRIs on vaginal mucosal NO. This nevertheless raises intriguing questions as to the possibility of direct SSRI effects on vaginal lubrication, and *ipsi facto*, the possible role of PSSD pathophysiology within this domain.

Flaccid Penile Glans. In male PSSD sufferers, the penile shaft can be rigid during erection, yet the glans of the penis remains flaccid.[16] This symptom may arise from hypo-activation of the dopaminergic and oxytocinergic pathways.[41] The glans of the penis, in particular, receives its blood supply from the deep dorsal artery.[51] Perhaps this points to a selective arterial malfunction relative to pelvic floor dysfunction which usually accompanies PSSD.

Anorgasmia, Premature Ejaculation, and Ejaculatory Anhedonia. Anorgasmia and ejaculatory anhedonia are the

most frequent symptoms of PSSD.[16,30,52] PSSD-mediated dysfunction commonly results in weakened or pleasure-less orgasms, or complete orgasmic anhedonia. Abnormally low release of oxytocin and β-endorphin are key neuro-endocrinological features of these symptoms, mediated through poor post-synaptic 5HT1A signaling. In some patients, premature ejaculation (PE) may occur resulting in truncated and unsatisfying orgasm. The frequency of PE in PSSD patients is unknown. In discussion with PSSD-sufferers, we have learned that PSSD-mediated PE results in a short, muted and low intensity orgasms.

It is important to note that although this manuscript emphasizes SD symptoms of PSSD, it is our clinical impression that there is also a degree of non-specific emotional malfunctioning in most of PSSD patients. This includes anhedonia, apathy, and blunted affect. These symptoms also seem to occur in high proportions of patients during SSRI-induced sexual dysfunction. PSSD-related emotional changes need to be distinguished from secondary depression as a reaction to the chronic distress of the disorder. No systematic studies have been done to date in this domain.[50] SSRIs were shown to reduce DA neurotransmission in the VTA[53] and DA neurotransmission is highly associated with the hedonic response.[54] Patton, et al. found that diminished post-synaptic reactivity towards phasic DA firing led to a loss of consummatory reward cue.[35] As such, anhedonia could be thought of as a dysfunction in dopamine and β-endorphin reward pathways.[55,57]

Furthermore Lorraine and colleagues have shown that the levels of serotonin at the anterior lateral hypothalamus were increased after ejaculation. Consequently, a decrease in DA levels at the nucleus accumbens (NAc) was observed, which correlates with reduced sexual desire due to satiety.[56]

We argue that dual dysfunction of those neurotransmitter systems stands at the center of the syndrome. Therefore, we propose that high serotonin is central in the mechanisms of both PSSD and anhedonia. Animal models of anhedonia correlated this condition with disrupted mu opioid receptors signaling,[59] thus suggesting the involvement of the opioid system in PSSD.

We also note that excessive anxiety or conversely, a complete loss of the anxiety response, can also be features in many anecdotal reports from PSSD sufferers.

Diagnosis & Treatment of PSSD

Multiple factors have to be considered in order to diagnose PSSD, such as medication history, the time of onset relating to SSRI treatment and cessation and, most importantly, excluding depression-related symptoms of sexual dysfunction in case of reemergence of depressive illness.[15,16,30] It is important for clinicians to take into consideration non-sexual symptoms of PSSD,[11] including but not limited to, apathy and blunted affect.

Presumed Risk Factors of PSSD Genetic Predisposition

PSSD is certainly a rare syndrome and does not appear in most individuals treated with SSRIs, SNRIs or other classes of antidepressants. This appears to be an idiosyncratic drug reaction with varying levels of severity.[15] We believe that genetic predisposition and vulnerability is extremely relevant to epigenetic processes that underlie this syndrome. The central question here, to which genetics is probably the answer, is why and how SSRI-discontinuation causes PSSD in some but not all patients?

Chemical Stressors. Etiologically, SSRIs, and SNRIs represent serious chemical stress for those who later develop PSSD. In fact, initial worsening of depressive pathology which may lead to suicidal ideation and attempts has been reviewed in the literature, leading to SSRIs carrying a black box warning of such risks.[17]

SSRIs and SNRIs can alter neurochemical states, triggering manic or mixed episodes in the susceptible.[58,59]

Psychological Stressors. Prolonged mental stress may be a significant factor before, during and often after SSRI intake, affecting behavioral and cognitive performance and central neurochemical state. Many PSSD patients report a history of anxiety and increased emotional reactivity. Studies show that acute stress causes an increase in cortisol release, partly through the action of the post-synaptic 5HT1A receptors.[60] It has been demonstrated that this stress elicits a threefold rise in tryptophan hydroxylase (TPH) mRNA levels in the raphe nuclei (RN), accompanied by a corresponding rise in TPH-enzyme levels, which results in greater serotonin synthesis from l-tryptophan and an increase in serotonin levels within the RN.[60] It has also been demonstrated that stress-induced cortisol release causes an increase in glutamate release, which in turn alters neuronal plasticity, thus maintaining evoked neurological changes.[37,61] Altogether, stress or external cortisol, cause down-regulation of the pre-synaptic 5HT1A receptors, desensitization of the post-synaptic 5HT1A receptors, increases in TPH mRNA and protein levels and increases in glutamate release. Thus, in PSSD-susceptible individuals, stress may trigger maladaptive neuronal processes resulting in permanent maladaptive neurological changes. Using PTSD as a model, it often takes a single event (here, even the first tablet) to create permanent alterations where in both syndromes high cortisol stands at the center.

Previous Exposure to Finasteride & Isotretinoin. Finasteride is a 5-alpha reductase inhibitor, an FDA-approved drug for Benign Prostate Hyperplasia (BPH) and Androgenetic Alopecia (AGA). Isotretinoin (Roaccutane) is an FDA approved drug for acne. Post-discontinuation syndromes have been described for both medications and include sexual and emotional symptoms.[62] Previous use of those drugs may increase the probability of PSSD being triggered by SSRI use. We may assume that insufficient epigenetic and persistent steroid and neuro-steroid receptors alterations were consequent to exposure to these drugs and SSRIs consolidate these changes.

First-Time Use of Antidepressants Without PSSD Sequelae. We believe that it is possible that first exposure to antidepressants may increase the risk for PSSD development in subsequent use of these drugs, inasmuch as SSRIs may alter epigenetic expression. This could be understood as sub-threshold epigenetic modifications and/or neurotoxic damage, insufficient to cause PSSD "first time around" in such cases.

Maladaptive Neuroplastic Changes. Long-term potentiation and long-term depression (LTP/LTD) can be elicited by N-methyl-d-aspartate (NMDA)-type glutamate receptors, typically by the coincident activity of pre- and post-synaptic neurons.[63]

Glutamate indeed activates NMDA receptors at the limbic system, mainly the hippocampus, and, depending on intrinsic pathway signaling, can either trigger LTP or LTD.[63,64] As mentioned earlier in the manuscript, SSRIs and SNRIs may trigger manic or mixed episodes upon intake, albeit rarely so, even in unipolar depression. Upon clinical practice and reviewing hundreds of PSSD case reports, it is our impression that a significant portion of patients who developed PSSD did report on a prior manic or hypomanic episode either upon SSRI/SNRI intake or upon discontinuation. This observation can only be evaluated in epidemiological studies. Thus, having a condition of abnormal glutamate metabolism, such as bipolar disorder, epilepsy or autism spectrum disorders before treatment with an SSRI may be a presumed risk factor for PSSD development.

Serotonin and its receptors are known to modulate glutamate release in various brain regions to modify glutamate-mediated effects.[65] SSRIs and SNRIs have been repeatedly shown to interfere with glutamate system function, starting with modulation of NMDA, AMPA and metabotropic glutamate receptors.[66,67] NMDA receptors activity leads to neuroplastic alterations, which happen faster and persist longer in case of long-term potentiation and depression (LTP/LTD). Antidepressants reduce glutamate release and synaptic transmission; in particular, it was found that antidepressants prevent the acute stress-induced enhancement of glutamate release.[66] Furthermore, antidepressant treatment can block or reverse the spine synapse alterations caused by stress via increasing BDNF and TrkB receptor activation.[68,69] The deletion of 5HT1A and 5HT1B receptors decreased the expression of genes involved in long-term potentiation and adult neurogenesis and reduced hippocampal neuron survival.[71]

Several studies have also provided evidence that chronic treatment with SSRIs modify the endocannabinoid system and alter the balance of neuroplasticity through modulating this pathway. SSRI treatment increases anandamide (AEA) and 2-arachidonoylglycerol (2-AG) within several brain structures, such as the hippocampus and the striatum.[70] The SSRI fluoxetine increases the expression and promotes a facilitation of CB1 receptor mediated signaling in limbic areas such as the prefrontal cortex.[72,73] Conversely, citalopram reduced CB1 mediated neurotransmission in the hippocampus and hypothalamus.[74]

Therefore, we speculate that the ability of SSRIs to profoundly alter the neuroplasticity profile is the basis for the permanent nature of PSSD we often witnessed in anecdotal cases.

MTHFR Gene Variants (C677T and A1298C). The methylation cycle is profoundly affected by MTHFR gene variants and can lead to psychiatric disorders, including major depressive disorder.[77–79] In our clinical practice, we have repeatedly noticed the expression of less efficient MTHFR variants in PSSD patients (C677T and A1298C). MTHFR mutations can lead to high plasma level of homocysteine. Furthermore, elevated level of homocysteine can activate the NMDA glutamate receptors triggering maladaptive neuroplasticity and can even lead to neuronal death.[75,76] As we pointed out earlier, maladaptive neuroplasticity might be an important risk factor in PSSD.

Substance Abuse & Combination With Antidepressants. Another important risk factor may be substances which alter mood, behavior or state of consciousness. Many patients of PSSD have reported to have engaged in high or prolonged sessions of MDMA (Ecstasy), methamphetamine, cocaine, methylphenidate or combinations of such; often while still being under the effect of an antidepressant. We speculate that substance abuse, especially when combined and mixed with SSRIs, might have a pre-conditioning effect on neural pathways involving neuroplasticity and neurotoxicity, possibly increasing the risk of triggering PSSD.

CONCLUSION

In this manuscript, we review post-SSRI sexual dysfunction (PSSD) in terms of its biological plausibility, occurrence, symptoms, and presumed risk factors. We propose that pre-existing factors and previous drug use are implicated in triggering of PSSD and its persistent nature. Upon cessation of SSRI therapy, depressive illness may re-emerge, therefore it is of importance to note the difference between depression-related sexual dysfunction and PSSD-associated sexual dysfunction, as highlighted in this manuscript, when attempting to diagnose PSSD. There is a paucity of data on the frequency, incidence, prevalence, onset, course and outcomes, comorbidity, demographics and risk factors of this syndrome, arising from the discontinuation of such a ubiquitous class of medications (SSRIs). Some of the hypotheses raised here, may have an impact on the understanding of the long-term effects and pharmacological mechanisms of medications affecting the central nervous system (CNS). The concept, that essential pharmacological treatment may lead to long term post-continuation adverse effects, should be taken into clinical consideration. PSSD is now a new, important example of that. As it is slowly gaining its recognition as a prevalent syndrome, improved knowledge may offer new insights into the prevention and treatment of this condition. General epidemiological studies in the domain of PSSD might be especially revealing and useful.

We present this information hoping it may be useful for aiding future research into possible risk factors, causes and for potential treatments of this syndrome.

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