Post-SSRI Sexual Dysfunction: A Literature Review

Areeg Bala, MD, Hoang Minh Tue Nguyen, BA, and Wayne J. G. Hellstrom, MD, FACS

ABSTRACT

Introduction: Selective serotonin reuptake inhibitors (SSRIs) are a widely used class of drug. Post-SSRI sexual dysfunction (PSSD) is a condition in which patients continue to have sexual side effects after discontinuation of SSRI use. The prevalence of persistent sexual side effects after discontinuing SSRIs is unknown. The recognition and study of PSSD will increase our knowledge base of this underreported and distressing condition.

Aim: To provide coverage of the current literature on PSSD, update information on the pathophysiology of PSSD, and discuss potential management options.

Methods: Comprehensive review of literature pertaining to PSSD.

Main Outcome Measures: The symptoms, classification, pathophysiology, diagnostic considerations, and management of PSSD were reviewed.

Results: Common PSSD symptoms include genital anesthesia, pleasure-less or weak orgasm, decreased sex drive, erectile dysfunction, and premature ejaculation. Different theories have been proposed to explain the pathophysiology of PSSD: epigenetic gene expression theory, cytochrome actions, dopamine-serotonin interactions, proopiomelanocortin and melanocortin effects, serotonin neurotoxicity, downregulation of 5-hydroxytryptamine receptor 1A, and hormonal changes in the central and peripheral nervous systems. The diagnosis of PSSD is achieved by excluding all other etiologies of sexual dysfunction. Treating PSSD is challenging, and many strategies have been suggested and tried, including serotonergic antagonists and dopaminergic agonists. There is still no definitive treatment for PSSD. Low-power laser irradiation and phototherapy have shown some promising results.

Conclusion: PSSD is a debilitating condition that adversely affects quality of life. Further studies are warranted to investigate the prevalence, pathophysiology, and treatment of PSSD. **Bala A, Nguyen HMT, Hellstrom WJG. Post-SSRI Sexual Dysfunction: A Literature Review. Sex Med Rev 2018;6:29–34.**

Key Words: Post-SSRI Sexual Dysfunction; Selective Serotonin Reuptake Inhibitors

INTRODUCTION

Selective serotonin reuptake inhibitors (SSRIs) are a widely used class of drug that is prescribed for the management of different disorders, including major depression, obsessive-compulsive disorder, post-traumatic stress, generalized anxiety, and social anxiety.[1] In addition, SSRIs are used to treat pre- and postmenopausal syndromes, hot flashes, chronic pain, and chronic fatigue syndromes.[2] In the United States, one in eight people have used SSRIs in the past 10 years.[1] Occasionally, SSRIs, because of the reversible sexual side effects, are prescribed intentionally to treat cases of paraphilia and premature ejaculation.[2] Post-SSRI sexual dysfunction (PSSD) is a condition that arises after the use of SSRIs, in which patients continue to have sexual side effects after the discontinuation of SSRIs. These persistent side effects include decreased libido, genital anesthesia, erectile dysfunction, delayed ejaculation, loss of lubrication in women, and anorgasmia.[2] Bahrick[1] estimated that 1% to 10% of patients with SSRI sexual side effects will experience resolution of these side effects while still on medication, yet the remaining cohort will still exhibit these side effects as long as SSRIs are used. One post-market research study reported that 5% to 15% of patients developed impairment of sexual function after the use of SSRIs and serotonin-norepinephrine reuptake inhibitors.[3] The prevalence of persistent sexual side effects after discontinuing SSRIs is not well known.[1] With the wide use of SSRIs, psychiatrists and mental health practitioners must be well informed about the medication side effects, because these drugs affect the welfare of their patients. Sufficiently informing the patients of these potential side effects before initiating treatment and

Received June 2, 2017. Accepted July 4, 2017.

Department of Urology, Tulane University School of Medicine, New Orleans, LA, USA

http://dx.doi.org/10.1016/j.sxmr.2017.07.002

questioning for the occurrence of these effects while undergoing treatment are of clinical importance.[2] Waldinger et al[4] proposed that PSSD should be identified as a true syndrome in the literature, rather than as a side effect of SSRIs.

From 2006 to 2008, eight cases of treatment-emergent sexual dysfunction persisting after SSRI discontinuation were reported, leading to what Csoka et al[2] described as PSSD.[5–7] In 2012, the database of the Netherlands Pharmacovigilance Centre (Lareb) received 19 reports of persistent sexual dysfunction in patients who had stopped using SSRIs for 2 months to 3 years previously and had not yet regained normal sexual functioning.[8] In the reports, 13 patients were men and 6 were women. The SSRIs prescribed were paroxetine, sertraline, venlafaxine, citalopram, fluoxetine, fluvoxamine, and escitalopram.[8] Some patients reported multiple symptoms of PSSD.[8] Hogan et al[9] reported 90 cases of PSSD based on reports on RxISK.org, a portal for reporting adverse events by patients or doctors or, ideally, patients and doctors; RxISK is maintained by a group of high-profile medical experts with international renown in early detection of drug side effects and risk mitigation. Of the 90 cases, 75 were men and 15 were women.[9] Ben-Sheetrit et al[10] conducted an internet survey of sexual adverse effects in patients on antidepressants using a structured self-report questionnaire and well-defined case-definition criteria; of 532 subjects, they found 183 possible cases, including 23 high-probability cases of PSSD. Several medications have been associated with sexual dysfunction side effects after discontinuation of use. The use of finasteride and dutasteride (5α-reductase inhibitors) showed persistent erectile dysfunction in some patients treated with these drugs.[11] Sexual dysfunction was reported to persist longer than 3 months after discontinuation of the α-reductase inhibitors in male rats, which can continue for months and even years.[12] Moreover, isotretinoin was linked to anejaculation and decreased fertility.[13] Drugs that increase serotonin levels have been associated with similar sexual side effects; tricyclic antidepressants such as clomipramine, amitriptyline, imipramine, and doxepin showed the highest incidence of sexual dysfunction symptoms.[14]

However, a lack of sexual drive, decreased sexual desire, and low libido are already established symptoms of depression.[15] Mathew and Weinman[16] stated that decreased arousal was present in 40% to 50% of depressive patients, and 15% to 20% of patients reported problems with orgasm and ejaculation. These can superimpose the sexual dysfunction caused by SSRIs.

Although the PSSD literature is sparse, it continues to increase. In this communication, we aim to provide an updated review of the current literature on PSSD, possible pathogenesis, and the latest management options.

METHODS

A literature review was performed on PubMed (www.ncbi.nlm.nih.gov) using the search strings *post-SSRI sexual dysfunction* and *persistent sexual dysfunction SSRI*. We examined

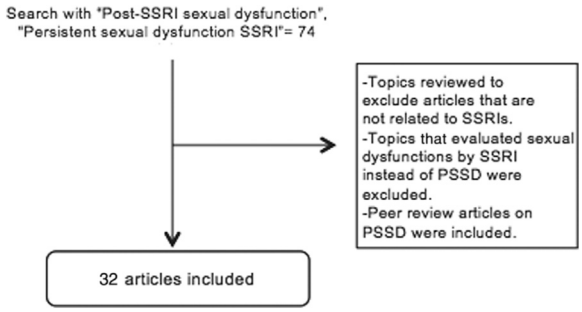

Figure 1. Literature review methodology. PSSD = sexual dysfunction after selective serotonin reuptake inhibitor use; SSRI = selective serotonin reuptake inhibitor.

74 articles and included 33 articles that were relevant to PSSD. Articles that evaluated sexual dysfunction by SSRI instead of PSSD were excluded. Based on reading the included results and examining their references, we added peer-reviewed articles on PSSD to our review (Figure 1).

CLINICAL PRESENTATION

Common PSSD symptoms include genital anesthesia (decrease in sensation and numbness in the genital area), pleasure-less or weak orgasm, decreased sex drive, erectile dysfunction, and premature ejaculation (Table 1). In addition, women can experience vaginal lubrication issues and nipple insensitivity.[2] Of these symptoms, the most characteristic triad consists of genital anesthesia, loss of libido, and erectile dysfunction.[9] The symptoms of PSSD can start days or weeks after beginning SSRIs and can persist after discontinuing SSRIs.[4] PSSD also can present after a single dose of an antidepressant.[2] Genital anesthesia, which is the most common symptom of PSSD, can appear within 30 minutes of the first dose of an SSRI.[9] Hogan et al[9] reported additional PSSD symptoms, including decreased penile size, smaller seminal volume, testicular atrophy and pain, and irregular menstruation for women. The symptoms of PSSD are very distressing to patients, which negatively affect their lives.[10]

Waldinger et al[4] classified PSSD into two categories based on the onset of the symptoms: (i) PSSD that is characterized by early onset, that is, sexual dysfunction occurring while SSRIs are being used and persisting after discontinuing treatments, and (ii) PSSD

Table 1. Common symptoms of sexual dysfunction after selective serotonin reuptake inhibitor use

Genital anesthesia
Decreased libido
Erectile dysfunction
Pleasure-less or weak orgasm
Premature ejaculation
Vaginal lubrication problems
Nipple insensitivity

that occurs after the discontinuation of SSRIs as an aggravation of SSRI-induced sexual side effects. In their case report, Waldinger et al also reported continued anejaculation and erectile dysfunction, despite improved penile sensitivity in their patients, suggesting the involvement of a central pathway in PSSD. Waldinger et al also reported other rare sexual side effects that might start with SSRI treatment and continue after stopping the medication; these include restless genital syndrome and persistent genital arousal disorder. Persistent genital arousal disorder is a disorder in which genital arousal persists for hours or days after the cessation of the sexual stimulation, despite the experience of at least one orgasm.[17] Leiblum and Goldmeier[17] reported several cases of persistent genital arousal disorder that was caused by antidepressant usage or withdrawal; SSRIs were found to predispose to the vast majority of cases.

PATHOPHYSIOLOGY

Uncovering the exact cause of PSSD is challenging; however, several etiologies have been proposed. Moreover, a combination of these potential theories might be operational to the pathophysiology of PSSD.

Epigenetic Change and Receptor Downregulation Theory

Csoka and Szyf[18] observed that increased binding and stimulation of 5-hydroxytryptamine receptor 1A (5HT1A) by serotonin caused downregulation of these receptors and potentiated serotonin transmission. Long-term usage of SSRIs is hypothesized to cause persistent downregulation of 5HT1A (even after discontinuation of SSRIs) by epigenetic changes in the form of increased expression of methyl binding proteins MeCP2 and MBD1. This leads to more production of HDAC2 mRNA and lowers the production of histone H3 deacetylase.[18] These epigenetic changes were observed in three areas of the brain: the frontal cortex, the dentate gyrus of the hippocampus, and the caudate-putamen. MDB1, MeCP2, and HDAC2 expression was noted to be induced by fluoxetine.[18] Popova and Amstislavskaya[19] indicated that this downregulation and desensitization of 5HT1A are involved in the regulation of sexual motivation, and thus proposed this as a theory for PSSD.

Hormonal Theories

Different hormones are proposed to play a role in PSSD in the central and peripheral nervous systems and cause neurochemical changes, including an increase in serotonin and prolactin, blockage of α_1-adrenergic receptors, a decrease in dopamine, testosterone, and oxytocin, and a decrease in nitric oxide synthesis.[2] Moreover, some neurochemical changes have been noticed in the peripheral nervous system of patients with PSSD. This is noteworthy because 95% of serotonin receptors are located outside the brain. It was postulated that SSRIs cause PSSD by affecting serotonin levels in peripheral nerves.[2] Ben-Sheetrit et al[10] postulated that serotonergic neurotoxicity also might play a role in PSSD in a similar mechanism to 3,4-methylenedioxymethamphetamine, which stimulates the release and inhibits the uptake of serotonin. 3,4-Methylenedioxymethamphetamine causes persistent sexual dysfunction long after its discontinuation, with axonal damage as the proposed mechanism.[10] Ben-Sheetrit et al[10] suggested that there might be a role for individual vulnerability to serotonin, because most patients on SSRIs do not develop PSSD. Damsa et al[20] pointed out the role of serotonin-dopamine interaction in causing PSSD. SSRIs cause inhibition of dopamine transmission in the ventral tegmental area; dopamine is essential in sexual arousal. In addition, serotonin regulates proopiomelanocortin neuron output and inhibits melanocortin MC4 receptors through 5HT2C and 5HT2A action. Not only are proopiomelanocortin and melanocortin responsible for skin coloration, they also play major roles in sexual behavior. As such, disturbances in proopiomelanocortin and melanocortin caused by SSRIs can result in persistent sexual dysfunction.[21] Furthermore, 5HT receptors play a major role in the hypothalamic-pituitary-testicular axis, and dysregulation of any of these receptors results in dysregulation of the axis, which produces lower free testosterone levels.[7]

Waldinger et al[4] postulated that PSSD is linked to transient receptor potential ion channel transduction, which is responsible for skin sensitivity to temperature, touch, taste, and smell. Disturbances to these transient receptor potentials could manifest as PSSD.

ANIMAL STUDIES

A few animal studies have been conducted to determine the long-term effect of SSRIs on sexual function. In their research on rats, Raap et al[22] found that treatment with fluoxetine resulted in persistent desensitization of 5HT1A, even after discontinuation of the drug. Sukoff-Rizzo et al[23] noted that 5HT1A antagonists treated and prevented the sexual dysfunction in rats that had been administered fluoxetine. Further studies suggested that administering SSRIs in young rats resulted in persistent sexual side effects into adulthood.[24,25] Gouvêa et al[26] administered fluoxetine in pregnant mice and observed an impairment of sexual motivation in the adult offspring of these pregnant mice. A systematic review of animal studies documented evidence of persistent sexual behavioral changes in rats that had been exposed to SSRIs at a young age.[27]

DIAGNOSIS

Almost all patients who have used SSRIs develop some type of sexual side effect.[18] The exact prevalence of PSSD is undetermined owing to a paucity of studies. Ben-Sheetrit et al[10] cautioned that PSSD could be challenging to diagnose. For example, a patient visits a doctor for a mental illness, where the patient is prescribed an SSRI. The patient might experience a

sexual side effect(s) with administration of the SSRI. The patient discontinues the medication because of these effects, but the sexual dysfunction could persist, which leads to another visit to the doctor. At this point, there will be confusion as to whether the persistent sexual dysfunction is caused by the mental illness or the SSRI. If the patient resumes the SSRI, the drug will be blamed for the sexual side effects. Either way, confirming a PSSD diagnosis is problematic.[10] Reisman[28] also suggested that the overlapping between PSSD symptoms and the actual mental illness symptoms renders the diagnosis of PSSD to be slightly challenging. PSSD is diagnosed by reviewing all elements of a patient's clinical presentation, such as history of drug use, onset of symptoms, and premorbid conditions. Furthermore, excluding other possible causes of sexual dysfunction helps in diagnosing PSSD. Some authorities have used genital anesthesia as an indicator of the severity of sexual dysfunction caused by SSRIs in PSSD.[10] According to Higgins et al,[29] a full detailed evaluation is the first step in evaluating PSSD to ensure that the sexual side effects are indeed an outcome of SSRI use. This evaluation ranges from physical assessment to a formal sexual health inquiry. In general, the clinician should exclude confounding elements such as age, smoking, alcohol, and substance abuse, because they are recognized to cause sexual dysfunction symptoms. Similarly, the physicians must consider other diseases that can affect sexual functions, such as diabetes, hypertension, and depression.[29]

MANAGEMENT AND PREVENTION

There is still no definitive treatment for PSSD. The treatments described in the literature were meant for sexual dysfunction induced by SSRI. Although there is no actual treatment for PSSD, Waldinger et al[4] reported the effect of low-power laser irradiation, or phototherapy, directed toward the scrotal skin and the shaft of the penis in a male patient with PSSD and penile anesthesia. Low-power laser irradiation improved the function of transient receptor potentials, which is proposed as one of the PSSD etiologies. In this patient, penile sensitivity improved by 40%. Nonetheless, despite the partial relief of penile anesthesia and penile temperature sensitivity, low-power laser irradiation failed to alleviate anejaculation and erectile dysfunction symptoms of PSSD in the same patient.[4] Hogan et al[9] suggested that focusing on serotonergic and dopaminergic systems by adding 5HT1 agonists and 5HT2 and 5HT3 antagonists could accomplish the management of PSSD. The drugs used were buspirone, trazodone, and mirtazapine, respectively. The latter two drugs can induce priapism and increase libido in normal people, but has little to no effect in patients with PSSD. For the dopamine agonists, pramipexole and cabergoline have been tried for treatment of PSSD, with little benefit reported.[9] However, a 5HT1A antagonist has been tested in rats and documented a 70% improvement in penile erection that had been impaired by fluoxetine use.[23] Montejo et al[7] reported on a Spanish case-control study that evaluated a switch from SSRIs to a dopaminergic antidepressant (amineptine) in patients with sexual dysfunction and observed that 55% of these patients using SSRIs had persistent sexual dysfunction 6 months after treatment cessation, whereas only 4% of patients who had switched to amineptine had these complaints at 6 months. Patients also tried sildenafil, vardenafil, and other phosphodiesterase type 5 inhibitors and testosterone, but no improvement was documented.[9] An additional treatment option might be for patients to switch to bupropion or nefazodone, antidepressants that are not known to cause any sexual adverse effects.[29] Bupropion does not have serotonergic activity and, hence, does not affect sexual function in patients. In a placebo-controlled comparison study of bupropion and sertraline treatment in patients, it was noted that sexual dysfunction symptoms were present in sertraline-treated patients; however, sexual desire and orgasm dysfunction were reported much less in patients with bupropion. Overall, the patients treated with bupropion reported satisfaction with their sexual function.[30] Adjunct therapy with bupropion demonstrated promising results in treating SSRI-related sexual dysfunction.[29] Another double-blinded study conducted by Clayton et al[31] with bupropion added as an adjunct drug to SSRI-induced sexual dysfunction showed that bupropion was a successful antidote. Patients treated with bupropion documented a recovery from their sexual dysfunction in desire and frequency of sexual activity. This highlights the difficulty of managing patients with PSSD and the importance of PSSD prevention.

Cognitive-behavioral therapy also has been used by psychiatrists to help patients reach a better understanding of their condition and cope better with their situation. Cognitive-behavioral therapy is useful for dealing with the negative thoughts that develop in many patients, such as sexual inadequacy and low self-esteem.[29] Partners need to be involved in this approach, because they are collaterally affected by PSSD. Sex therapy and couples counseling should aim to educate the partners that the sexual dysfunction is a side effect of the medication and not a lack of interest. In addition, such behavioral therapies can provide emotional and psychological support for patients and partners.[29]

These encouraging results suggest more research into the management of PSSD could provide further breakthroughs. With that in mind, it is crucial that all mental health practitioners counsel their patients about PSSD before initiating treatment.[4] Clinicians need to record baselines in these patients and perform regular follow-ups for sexual function before, during, and after SSRI administration.[10] Kashani et al[32] anecdotally reported that saffron exhibited some benefit in improving sexual arousal and lubrication and might improve the sexual side effects created by SSRI use. Physicians need to instruct patients to report any loss of taste or smell, skin sensitivity, or genital numbness, so that the physician can titrate the SSRI dose or discontinue or change the medication. Whether a dose reduction

will avert the possibility of PSSD is uncertain.[5] The patient's informed consent and the right to choose SSRIs as a treatment option should be required before starting SSRIs.[10]

CONCLUSION

PSSD is a persistent sexual dysfunction that occurs after discontinuation of SSRI use. Commonly reported symptoms include genital anesthesia, erectile dysfunction, pleasure-less orgasm, decreased sex drive, decrease or absence of erection, premature ejaculation, vaginal lubrication issues, and nipple insensitivity in women. PSSD can result in patient non-compliance to SSRIs.[7] Different theories have been proposed to explain the pathophysiology of PSSD: epigenetic gene expression, cytochrome actions, dopamine-serotonin interactions, proopio-melanocortin and melanocortin effects, serotonin neurotoxicity, downregulation of 5HT1A, and hormonal changes in the central and peripheral nervous systems. Diagnosing PSSD is challenging and should be done by reviewing the patient's drug history, onset of symptoms, and the patient's sexual condition before starting such a medication. Furthermore, excluding other comorbid diseases and conditions that can cause PSSD is mandatory.

There is no definitive treatment for PSSD; however, there are some proposed management options. Lowering SSRI dosage could decrease the sexual side effects but weaken the drug's initial treatment strategy. Adjunct therapy such as adding sildenafil and bupropion did not show statistical benefit. Cognitive-behavioral therapy might help with PSSD. Buspirone, trazodone, donepezil, ketamine, metformin, and mirtazapine have been tested as PSSD treatments, with varying degrees of success. Clinicians and mental health practitioners need to counsel their patients about PSSD. All patients need to be educated about the possibility of persistent impairment of sexual dysfunction with SSRI usage. There are still many unknowns about PSSD. It is important to investigate PSSD further to elucidate its pathogenesis and to discover effective treatments for PSSD.

Corresponding Author: Wayne J. G. Hellstrom, MD, FACS, Department of Urology, Tulane University School of Medicine, New Orleans, LA, USA; E-mail: whellst@tulane.edu

Conflicts of Interest: The authors report no conflicts of interest.

Funding: None.

STATEMENT OF AUTHORSHIP

Category 1

(a) **Conception and Design**
Areeg Bala; Wayne J. G. Hellstrom
(b) **Acquisition of Data**
Areeg Bala; Hoang Minh Tue Nguyen
(c) **Analysis and Interpretation of Data**
Areeg Bala; Hoang Minh Tue Nguyen

Category 2

(a) **Drafting the Article**
Areeg Bala
(b) **Revising It for Intellectual Content**
Hoang Minh Tue Nguyen; Wayne J. G. Hellstrom

Category 3

(a) **Final Approval of the Completed Article**
Areeg Bala; Hoang Minh Tue Nguyen; Wayne J. G. Hellstrom

REFERENCES

1. Bahrick A. Persistence of sexual dysfunction side effects after discontinuation of antidepressant medications: emerging evidence. **Open Psychol J 2008;1:42-50.**
2. Csoka AB, Bahrick A, Mehtonen OP. Persistent sexual dysfunction after discontinuation of selective serotonin reuptake inhibitors. **J Sex Med 2008;1:227-233.**
3. Bahrick AS. Post SSRI sexual dysfunction. **Am Soc Adv Pharmacother Tablet 2006;7:2-3.**
4. Waldinger MD, van Coevorden RS, Schweitzer DH, et al. Penile anesthesia in post SSRI sexual dysfunction (PSSD) responds to low-power laser irradiation: a case study and hypothesis about the role of transient receptor potential (TRP) ion channels. **Eur J Pharmacol 2015;753:263-268.**
5. Bolton JM, Sareen J, Reiss JP. Genital anesthesia persisting six years after sertraline discontinuation. **J Sex Marital Ther 2006;32:327-330.**
6. Kauffman RP, Murdock A. Prolonged post-treatment genital anesthesia and sexual dysfunction following discontinuation of citalopram and the atypical antidepressant nefazodone. **Open Womens Health J 2007;1:1-3.**
7. Montejo AL, Llorca G, Izquierdo JA, et al. Sexual dysfunction with antidepressive agents. Effect of the change to amineptine in patients with sexual dysfunction secondary to SSRI. **Actas Esp Psiquiatr 1999;27:23-34.**
8. Ekhart GC, van Puijenbroek EP. Does sexual dysfunction persist upon discontinuation of selective serotonin reuptake inhibitors? **Tijdschr Psychiatrie 2014;56:336-340.**
9. Hogan C, Le Nourya J, Healya D, et al. One hundred and twenty cases of enduring sexual dysfunction following treatment. **Int J Risk Saf Med 2014;26:109-116.**
10. Ben-Sheetrit J, Aizenberg D, Csoka AB, et al. Post-SSRI sexual dysfunction: clinical characterization and preliminary assessment of contributory factors and dose-response relationship. **J Clin Psychopharmacol 2015;35:273-278.**
11. Kiguradze T, Temps WH, Yarnold PR. Persistent erectile dysfunction in men exposed to the 5α-reductase inhibitors, finasteride, or dutasteride. **PeerJ 2017;5:e3020.**
12. Irwig MS. Persistent sexual side effects of finasteride: could they be permanent? **J Sex Med 2012;9:2927-2932.**
13. Coleman R, MacDonald D. Effects of isotretinoin on male reproductive system. **Lancet 1994;344:198.**
14. Shankar GS. Serotonin and sexual dysfunction. **J Autacoids Horm 2015;5:e129.**

15. Balon R. SSRI-associated sexual dysfunction. **Am J Psychiatry 2006;163:1504-1509.**
16. Mathew RJ, Weinman ML. Sexual dysfunctions in depression. **Arch Sex Behav 1982;11:323-328.**
17. Leiblum SR, Goldmeier D. Persistent genital arousal disorder in women: case reports of association with anti-depressant usage and withdrawal. **J Sex Marital Ther 2008;34:150-159.**
18. Csoka AB, Szyf M. Epigenetic side-effects of common pharmaceuticals: a potential new field in medicine and pharmacology. **Med Hypotheses 2009;73:770-780.**
19. Popova NK, Amstislavskaya TG. Involvement of the 5-HT(1A) and 5-HT(1B) serotonergic receptor subtypes in sexual arousal in male mice. **Psychoneuroendocrinology 2002;27:609-618.**
20. Damsa C, Bumb A, Bianchi-Demicheli F, et al. Dopamine-dependent side effects of selective serotonin reuptake inhibitors: a clinical review. **J Clin Psychiatry 2004;65:1064-1068.**
21. Van der Ploeg LH, Martin WJ, Howard AD, et al. A role for the melanocortin 4 receptor in sexual function. **Proc Natl Acad Sci U S A 2002;99:11381-11386.**
22. Raap DK, Garcia F, Muma NA, et al. Sustained desensitization of hypothalamic 5-hydroxytryptamine1A receptors after discontinuation of fluoxetine: inhibited neuroendocrine responses to 8-hydroxy-2-(dipropylamino)tetralin in the absence of changes in Gi/o/z proteins. **J Pharmacol Exp Ther 1999;288:561-567.**
23. Sukoff Rizzo SJ, Pulicicchio C, Malberg JE, et al. 5-HT1A receptor antagonism reverses and prevents fluoxetine-induced sexual dysfunction in rats. **Int J Neuropsychopharmacol 2009;12:1045-1053.**
24. de Jong TR, Snaphaan LJ, Pattij T, et al. Effects of chronic treatment with fluvoxamine and paroxetine during adolescence on serotonin-related behavior in adult male rats. **Eur Neuropsychopharmacol 2005;16:39-48.**
25. Maciag D, Simpson KL, Coppinger D, et al. Neonatal antidepressant exposure has lasting effects on behavior and serotonin circuitry. **Neuropsychopharmacology 2005;31:47-57.**
26. Gouvêa TS, Morimoto HK, de Faria MJ, et al. Maternal exposure to the antidepressant fluoxetine impairs sexual motivation in adult male mice. **Pharmacol Biochem Behav 2008;90:416-419.**
27. Simonsen AL, Danborg PB, Gøtzsche PC. Persistent sexual dysfunction after early exposure to SSRIs: systematic review of animal studies. **Int J Risk Saf Med 2016;28:1-12.**
28. Reisman Y. Sexual consequences of post-SSRI syndrome. **Sex Med Rev 2017;5:429-433.**
29. Higgins A, Nash M, Lynch AM. Antidepressant-associated sexual dysfunction: impact, effects, and treatment. **Drug Healthc Patient Saf 2010;2:141-150.**
30. Coleman CC, Cunningham LA, Foster VJ. Sexual dysfunction associated with the treatment of depression: a placebo-controlled comparison of bupropion sustained release and sertraline treatment. **Ann Clin Psychiatry 1999;11:205-215.**
31. Clayton A, Warnock J, Kornstein S, et al. A placebo-controlled trial of bupropion SR as an antidote for selective serotonin reuptake inhibitor-induced sexual dysfunction. **J Clin Psychiatry 2004;65:62-67.**
32. Kashani L, Raisi F, Saroukhani S, et al. Saffron for treatment of fluoxetine-induced sexual dysfunction in women: randomized double-blind placebo-controlled study. **Hum Psychopharmacol 2013;28:54-60.**