Neuropsychiatric Disease and Treatment

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REVIEW

Selective Serotonin Reuptake Inhibitor-Induced Sexual Dysfunction: Current Management Perspectives

This article was published in the following Dove Press journal:
Neuropsychiatric Disease and Treatment

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Abstract: Any type of sexual dysfunction is an important problem in half of the patients with depressive disorder. On the other hand, one to a quarter of people without any depressive disorder experience sexual dysfunction. Antidepressant agents can lead to all types of sexual side effects including arousal, libido, orgasm and ejaculation problems. Selective serotonin reuptake inhibitors (SSRIs) are a widely used class of drugs which are prescribed for the treatment of a variety of disorders, including major depressive disorder, obsessive-compulsive disorder, posttraumatic stress disorder, panic disorder, generalized anxiety disorder, and impulse control disorders. It has been reported that one in eight people have utilized one of the SSRIs in the past 10 years. Some studies reported up to 80% of SSRI-induced sexual side effects. Management of SSRI-induced sexual dysfunction seems to be complex and hard. In this paper, SSRI-induced sexual dysfunction and new perspectives in the management of this problem were reviewed.

Keywords: SSRI, sexual dysfunction, current perspectives

Introduction

Antidepressant drugs are an important choice of the treatment of depressive disorders.[1] There have been a variety of drug classes that have antidepressant properties.[1] Among them, it can be counted tricyclic antidepressants (TCAs), serotonin-norepinephrine reuptake inhibitors, heterocyclic antidepressants, norepinephrine reuptake inhibitors, serotonin modulators, dopaminergic antidepressant agents, dopamine and norepinephrine reuptake inhibitors (bupropion), selective serotonin reuptake inhibitors (SSRIs) and monoamine oxidase inhibitors.[1] Novel antidepressant medications have provided important contributions to the management of depressive disorders for a quarter-century.[2] Despite such advances in the treatment of depressive disorders, to be honest, developments in clinical effectivity among antidepressant drugs, including the newer agents and the older ones such as TCAs and monoamine oxidase inhibitors (MAOIs), have not been considerably placed in clinical investigations.[3] Probably, most important developments in the medication of depressive disorders may be unwanted effects because it is clear that compared to older antidepressants newer ones have been mentioned and emphasized in a variety of trials and reviews.[4–7] In this narrative manner review, it will be told about the SSRI-induced sexual dysfunctions, with their management.

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DovePress
http://doi.org/10.2147/NDT.S185757

Antidepressant-Induced Sexual Dysfunction

Actual diagnostic classification systems, DSM-5,[8] and the ICD-10[9] used some criteria to reveal antidepressant-induced sexual dysfunction. This definition implicates that the trouble starts after the use of a substance that has a capacity of producing sexual dysfunction. However, ICD-10[9] defines that the problem starts with the specific substance believed to be the cause of the problem. The diagnostic criteria for substance/medication-induced sexual dysfunction are available in DSM 5.[8]

Any type of sexual dysfunction is an important problem in half of the patients with depressive disorder.[10] However, just at this point, it should be mentioned that one to a quarter of people without any depressive disorder experience sexual dysfunction.[11] On the other hand, the rate of sexual dysfunction can access to 63 percent in patients with a depressive disorder who have been treated with any antidepressant medication.[11] After these data, it can be said that sexual dysfunction is already frequent in people who have not any depressive disorder but also in depressive disordered patients whereas the highest rate is owning to patients who are on antidepressant medication. Antidepressant agents can lead to all types of sexual side effects including arousal, libido, orgasm and ejaculation problems.[10] In general, on the one hand, sexual dysfunction can have considerable influences on the quality of life, couple relationships, family relationships, and self-esteem, on the other hand, it can cause compliance problems with antidepressant treatment and can lead to exacerbation of depressive symptoms. Nearly fifty years earlier, antidepressant-induced sexual dysfunction was rarely reporting the sexual side effect of available antidepressant medication.[12] The reasons for this may be a lack of questioning and evaluation, the opinion that people with psychiatric disorders would already have uninterest in sexual subjects, and the issue of underreporting.[11] Recently, the sexual side effects of antidepressant drugs have been more told. The most important reasons for this may be more questioning sexual side effects during the drug trials, actuality and popularity of the issue of quality of life, use of antidepressants in less severe situations, and probable competition in drug industry.[13] Treatment-related sexual dysfunction has been emphasized for all kinds of antidepressant agents. However, it should be accepted that it is not clear to know the real incidence of sexual side effects because of the fact that studies revealed obviously different incidence rates. In a review, it has been reported that that forty percent of patients who were ongoing antidepressant medication had any type of sexual side effect.[14] In a study, the sexual side effect rate of people who used imipramine was found to be 30%.[15] This rate was reported to be 25% to 73% for patients who were taking an SSRI.[16–19] In a study on a TCA, clomipramine, ninety-three percent of patients who were utilizing it complained anorgasmia in total or at least partial.[20] Meanwhile, a reversible MAOI, moclobemide has been linked to having the lowest incidence of sexual dysfunction, with a rate of 3.9 percent. In a larger sampled study (4534 females and 1763 males) in a out-patient setting in which patients were taking antidepressant as monotherapy, observed sexual side effects were as followings: receiving antidepressant monotherapy, reported rates of sexual dysfunction as follows: bupropion IR, with the ratio of 22 percent, bupropion SR, with the rate of 25 percent, nefazodone, with the rate of 28 percent, mirtazapine, with the rate of 36 percent and finally venlafaxine a extended-release, with the rate of 43.[21] As can be seen in these studies, almost in all antidepressant groups, sexual side effect is an important and pervasive problem even in some antidepressant studies which are known as less related to sexual side effect in clinical practice such as mirtazapine, which was used for sexual dysfunction to previous treatment as monotherapy, with SSRI for at least six weeks and appeared to be an effective and well-tolerated augmentation for sexual dysfunction caused by SSRIs.[22]

In fact, studies have revealed that the incidence of sexual dysfunction related to a variety of antidepressant drugs may be more in clinical daily practice compared to that reported in the prescribing information.[23–25] Probably, in phase studies, report of sexual dysfunction is lower than in real situations. Because, patients and clinicians may be attributed to sexual dysfunction associated with a drug to other reasons like linking these effects to relationship problems related to psychopathology itself, rather than to the drug itself. On the other hand, in clinical trials, it is not used structured sexual dysfunction inventories, instead of this, it is utilized unstructured questions on sexual dysfunction. In addition, probably it is expected to express spontaneous reporting of sexual side effects. However, spontaneous reporting seems more difficult compared to expressing after questioning since reporting sexual side effects may be considered as shameful. It should be emphasized the notion that clinical trials may have some bias also.

As much the exact mechanism of sexual dysfunction is not well-understood, the usual sexual function seems to consist of a variety of neuromodulators, including serotonin,

dopamine, acetylcholine, gamma-aminobutyric acid, norepinephrine, nitric oxide, oxytocin, and other ones.[24] On the one hand, erectile function and sexual arousal have been related to the acetylcholine in the parasympathetic nervous system, on the other hand, the function of ejaculation and following orgasmic activity appear to associated with the norepinephrine in the sympathetic nervous system and acetylcholine.[26] Antidepressant agents can generally lead to inhibitory effects on the dopamine by increasing an inhibitory influence on the raphe nuclei or disturbing the sexual function via prolactin elevation.[27] In addition, these drugs may also cause inhibition of the nitrous oxide synthetase, thereby decreasing nitrous oxide availability to provide an erectile function.[28] Recently, the clinical importance of oxytocin in antidepressant-associated sexual dysfunction has been emphasized. It has been speculated that oxytocin might positively affect the dimensions of sexual function and marital relationships. Oxytocin is a hormone, clearly involved in human reproduction and has a critical role in human sexual arousal. In fact, it has been implicated the fact of a variety of organs like female genital organs have oxytocin receptors may lead us to consider that it has a possible preparatory role on the later and final periods of the sexual process, like ejaculation and orgasm, preparing all required muscular contraction and lubrication effects.[29] On the other hand, it has been reported that the infusion of oxytocin antagonists into cranial vertebrae has resulted in an inhibitory effect on the female sexual behavior of rats.[30] In a recent investigation, the influence of the intranasal administration of oxytocin was examined in twenty-nine healthy heterosexual couples. It has been seen that females felt more relaxed and had a greater ability to experience sexual desire.[31]

Selective Serotonin Reuptake Inhibitor-Induced Sexual Dysfunction

Selective serotonin reuptake inhibitors (SSRIs) are a widely used class of drug which is prescribed for the treatment of a variety of disorders, including major depressive disorder, obsessive-compulsive disorder, posttraumatic stress disorder, panic disorder, generalized anxiety disorder, and impulse control disorders.[32] Among antidepressant agents, due to comparable efficacy, simple titration manner, better tolerability and greater safety profile in the event of overdose use, they have substituted the older generation of antidepressant drugs.[33,34]

The following data can shed light on its use in a wide range: It has been reported that one in eight people have utilized one of the SSRIs in the past 10 years.[35] Nowadays, available SSRIs in use are sertraline, paroxetine, fluvoxamine, fluoxetine, citalopram, and escitalopram. The most important side effects of the SSRIs are gastrointestinal side effects, sleep disorders particularly insomnia, and headache.[36] The most frequent gastrointestinal side effects are diarrhea, stomach ache, and gastric distress. Beyond these side effects, the sexual side effect is the other one which is obviously frequent and negatively affects the compliance of the treatment and can even lead to drug withdrawal.[37,38] It has been shown that sexual side effects are one of the main reasons for patients preferring to withdraw SSRI treatment, and it can also lead to poor adherence patterns among patients who prefer to maintain to take the treatment.[39] In an investigation on examining patients with major depressive disorder, eighty-five percent of patients scored the management of sexual dysfunction as "extremely important," "very important," or "important.[40] In fact, SSRIs may negatively influence all dimensions of the sexual response cycle, leading to a decrease in libido, the disturbing situation of arousal, erectile dysfunction and, absent or retarded orgasm. On the other hand, these side effects result in considerable interpersonal troubles.[41–43] It seems that the rate of sexual side effects is so high, but, the exact prevalence rate is not known exactly. Some studies reported up to 80% of SSRI-induced sexual side effects.[43] The experience of sexual side effects varies between males and females beyond adolescents. The investigations have revealed that female antidepressant users who had sexual side effects related to antidepressants particularly seem more likely not to report ad remain in a silent situation compared to male subjects.[44] They seem more prone to share their experiences in social media platforms in an interactive manner.[45] As for the adolescents, they may have sexual side effects via SSRI use but it should be noted that they seem to know little understanding of their sexual situation before SSRI use and could not context their experience of side effects.[46] Post-SSRI sexual side effect is a condition that is seen within two months after receiving a drug and does not exist at the beginning of treatment. Important feature of this condition is that sexual dysfunction persists after the discontinuation of SSRIs.[47] That condition may influence all dimensions of sexual activity like sexual desire, erectile function, arousal phase and, orgasm.[35] However, the exact prevalence of this type of persistent sexual dysfunction after discontinuation of SSRIs has not been well known.[32] Post-SSRI sexual dysfunction also can occur after only one dose of the drug.[33]

Management of SSRI-induced sexual dysfunction seems to be complex and hard. In fact, Balon summarized the management of antidepressant-induced sexual dysfunction so well: "Given the scarcity of evidence-based treatments the management of sexual dysfunction is still an art rather than a science".[12] The first thing to take into consideration when managing SSRI-induced sexual dysfunction is to evaluate other causes of sexual dysfunction. For example, the comorbid organic situation such as prostate infection or diabetes mellitus may lead to sexual side effects in patients taking SSRI treatment. So, the first step of effective treatment of SSRI-induced sexual side effects is a detailed evaluation to sure that the reported sexual event is indeed a result of the treatment itself. For this, first of all, to eliminate confounding things for sexual dysfunction such as age or alcohol/substance use is important. Second, excluding a comorbid physical condition, such as adverse effects of agents utilized to treat a variety of medical diseases like hypertension, diabetes mellitus, or cardiac diseases which might lead to sexual dysfunction.[48] On the other hand, medical illnesses themselves can contribute to sexual dysfunction, for example, atherosclerotic conditions, cardiac illnesses, central and peripheral nervous system diseases, diabetes mellitus, and alcohol abuse.[49] In addition, it is also important to exclude ongoing, or residual symptoms of the depressive disorder. In this context, Kennedy et al reported a group of individuals who had a major depressive disorder, over 40% of males and 50% of females reported reduced sexual interest before antidepressant drug use.[49] Actually, it is easy to assess a part of the clinical presentation of depressive disorder as SSRI-induced sexual dysfunction.

Management of SSRI-Induced Sexual Dysfunction

There have been a variety of pharmacological and non-pharmacological methods to manage SSRI-induced sexual dysfunction. First of all, SSRI use should be short term as soon as possible.[20] However, it is required to accept that this claim does not mirror reality, real psychiatry clinical practice. It should be emphasized to the patients that all pharmacological agents have an adaptation period to habituate their unwanted effects. For this reason, the first step of the management of SSRI-induced sexual dysfunction seems to be the "wait and observe" approach. For example, Montejo et al reported that ten percent of patients who took antidepressant agents including SSRIs experienced reversible sexual side effects.[20] But, an important part of patients who use SSRI or other antidepressant drugs may not respond to this type of approach at all. For this reason, this method may not be available for all patients. Often, patients' ongoing SSRI treatment use over the optimum dosage of medication. On the other hand, SSRI-induced sexual dysfunction may be related to dose-dependent. In these circumstances, it can be considered to reduce the dosage of SSRI used from the current level to minimum effective döşe, with attention to the patient's mental health situation. Like for other side effects SSRIs, another method to cope with sexual dysfunction is to switch to another class antidepressant agent. This approach can provide to maintain antidepressant efficacy whereas SSRI-induced sexual dysfunction is relieved. It was found that switching from sertraline to nefazodone considerably reduced drug-related sexual dysfunction, without any worsening of clinical presentation.[50]

Another method is the drug holidays. It should be accepted that drug holiday is a high-risk management alternative in which SSRI treatment is discontinued on the day of or prior to, expected sexual relationship. In daily clinical practice, this method can be beneficial in partial. But, according to our practical observation, it requires more than one day, probably two days at least. There have been reports which have implicated that there has been no beneficial potential to do drug holiday. However, in an investigation performed by of Rothschild, it was instructed patients not to take their SSRIs for three days and it was found that patients who were receiving sertraline and paroxetine but fluoxetine group noted a considerable improvement in their sexual functioning, such as increased libido and feeling of satisfaction, without any clinical worsening in their clinical presentation of depression including increased scores of HAM-D.[51] Meantime, it has been suggested that drug holidays might disturb therapeutic efficiency and cause withdrawal syndrome. Therefore, when it is decided to use drug holidays, it should be taken into consideration SSRIs' half-life. For example, one of SSRIs, fluoxetine has a longer half-life, for this reason, it requires a longer period of drug holidays, leading to exacerbation of depressive symptoms. On the other hand, because of the fact that sertraline and paroxetine have a shorter half-life compared to that of fluoxetine, it might have better results in regard to exacerbation of depressive symptoms beyond the improvement of sexual side effects. At this point, it should be mentioned about the risk for the mechanization of scheduling sexual interaction. In addition, this can lead to performance

anxiety for sexual activity, with the requirement for concluding sexual activity in a current period.

Adjunct treatment is a strategy used in a variety of psychiatric disorders for enhancing the efficacy of the current medication. On the other hand, it is utilized to decrease the side effect profile when augmenting to ongoing treatment. In this context, the augmentation approach is another strategy to relieve SSRI-induced sexual dysfunction. In their study in which double-blind design was used, Clayton et al reported that bupropion augmentation to SSRI might be an effective strategy for SSRI-induced sexual dysfunction, showing that patients taking bupropion augmentation had a considerably greater improvement in libido and frequency of engaging in sexual activity compared to those who were taking placebo as adjunct therapy.[52] In another small sampled case series, it was found that bupropion 75 mg q.d. can be so beneficial for SSRI induced sexual dysfunction. For bupropion, another support came from Iran. In that study, compared to amantadine augmentation of 200 mg per day, bupropion of the same dose per day was found to lead to more improvement in desire, arousal, and pleasure in patients with SSRI-induced sexual dysfunction.[53] Stimulant agents may be also another choice for augmentation strategy in SSRI-induced sexual dysfunction. Ravindran et al reported that patients with majör depressive disorder who did not respond a variety of antidepressant agents including SSRIs did not also respond to osmotic controlled-release oral delivery system methylphenidate of 18 to 54 mg per day, without any considerable change in the Montgomery–Asberg Depression Rating Scale scores, but exhibited better sexual function scores on SEX-FX (function) scale compared to placebo augmentation.[54] On the other hand, phosphodiesterase (PDE) inhibitors showed positive results in various clinical trials on patients with SSRI-induced sexual dysfunction. Tadalafil with the dose of 10 to 20 mg per day was found to be efficacious in patients who had SSRI-induced sexual dysfunction, with an improvement in erectile function, orgasm, and sexual satisfaction.[55] Sildenafil of 25 to 100 mg was reported to be efficacious in male patients who experienced SSRI-induce sexual dysfunction and to lead to improved sexual function and satisfaction.[56] In a study aiming to investigate changes in sexual dysfunction in patients under mirtazapine augmented SSRT treatment, we determined that the addition of 15 to 45 mg mirtazapine to ongoing SSRI medication was considerably effective to decrease sexual dysfunction, as detected by Arizona Sexual Experience Scale (ASEX).[20] Only in a unique study, it was examined the effects of the dopamine agonist, ropinirole on antidepressant agents including SSRIs associated sexual dysfunction, with the dose of 0.25 to 4 mg per day.[57] The authors revealed that the mean ASEX score after ropinirole augmentation was significantly decreased from the baseline and provided an improvement in multiple aspects of sexual function over 50 percent of patients. Herbal treatments have been also used to reduce antidepressant including SSRIs related to sexual dysfunction. Probably, the most important ones are Gingko Biloba and yohimbine. In an open-label investigation, Ginkgo Biloba was reported to have beneficial effects in managing antidepressants including SSRIs induced sexual dysfunction, providing its effects on all four phases of the sexual response cycle: desire, excitement, orgasm, and resolution.[58] Interestingly, the investigators found more successful for female patients compared to male ones in that study. Nevertheless, the opposite results were also obtained. Another study did not report any beneficial effects of Gingko Biloba to extract on none of the sexual activity phases in a double-blind placebo-controlled study while the placebo showed satisfaction in orgasmic function.[59] Yohimbine, a tree bark extract conventionally utilized as an aphrodisiac, was considered as an alternative to be helpful for relieving SSRI-induced sexual dysfunction but was found not to have beneficial effects on sexual function.[60] An investigation found cyproheptadine adjunctive treatment, with the doıse of 4 to 12 mg before sexual intercourse to be effective in patients who were receiving SSRIs for their obsessive-compulsive disorder.[61] A case presentation reported a patient who had monoamine oxidase inhibitor-induced anorgasmia and responded to cyproheptadine.[62]

Exercise has been also considered to be helpful increase arousal by increasing the sympathetic nervous system. In association with this, female patients with antidepressant-related sexual dysfunction including SSRIs were made an erotic movie watched for 5 or 15 minutes after exercise, or without exercise.[63] It was found that genital arousal was increased in females who do exercise but not in those who did not do any exercise by using vaginal photoplethysmograph method, without any influence on self-reported arousal perceptions. The beneficial effects of physical exercise on sexual dysfunction were also reported in some other studies.[64,65]

Another herbal compound, saffron, a spice obtained by the flower of *Crocus sativus* plant comparatively placebo was also tried in patients who were taking the fluoxetine of 15 mg twice daily and developed sexual dysfunction for four weeks[66] and was found that compared to placebo augmentation the saffron group showed a better improvement in a variety of dimensions of sexuality such as arousal, lubrication, and pain, without any difference between side effect and safety profiles of saffron plant and placebo. In addition, recently, it has been reported that Rosa damascena oil had an improvement effect on sexual function in patients under SSRI treatment, methadone treatment for opium use disorder.[67–70] Psychosocial approaches particularly cognitive-behavioral therapy (CBT) may be utilized in an

antidepressant-induced sexual dysfunction. Whereas the CBT is widely used in a variety of psychiatric disorders, the limited number of investigations has been in antidepressant-associated sexual dysfunction. I personally use the CBT in sexual dysfunction including SSRI-induced sexual dysfunction. In fact, it should be accepted that the CBT approach to sexual dysfunction does not seem to be effective when it is used alone. But, it looks like to have beneficial effects on negative feelings that may have a considerable negative influence on self-esteem and self-image of patients who had SSRI-induced sexual dysfunction. It can improve belief errors which can negatively affect sexual activity.

Conclusions

Antidepressant drugs are compounds which are widely used in a variety of psychiatric disorders in the World especially in the treatment of depression, if required, with adjuvant methods such as neuromodulation, physical activity, or psychotherapy, and adjuvant supplements like omega-3-polyunsaturated fatty acids[71–73] although some studies questioned the requirement of antidepressant drugs in a variety of situations.[74–76] SSRIs are probably the first choice when it is considered to use any antidepressant agent. Now, although there is strong evidence that SSRIs are well tolerated and effective, they have various sexual side effects both in female and male patients, with a wide spectrum from loss of sexual desire to delayed orgasm troubles. These side effects can unfortunately, affect patients' compliance with the treatment and lead to cessation of treatments.

SSRI-induced sexual dysfunction should be well screened and managed because it is often ignored, not questioned and might affect treatment prognosis badly, causing problems of medication adherence. If they can be managed better, this can enhance therapeutic alliance and increase compliance with the treatment. There are important treatment alternatives for SSRI-induced sexual dysfunction including drug choices from switching to treatment to adjunctive agents, herbal remedy methods, and psychotherapeutic approaches particularly CBT. Meanwhile, when trying to overcome sexual dysfunction related to SSRI use, it should be careful not to disturb the current treatment response. However, it should be taken into consideration that some of these management alternatives do not have enough evidence level, solely supported by case reports or case series. For this reason, it should be examined in future studies with a larger sample.

Acknowledgment

I would like to thank Asli Kazgan, M.D., for her technical support.

Disclosure

The author reports no conflicts of interest in this work.

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