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

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

Murad Atmaca

Department of Psychiatry, Firat
University School of Medicine, Elazig,
Turkey

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 effectiveness 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.

Correspondence: Murad Atmaca
Firat (Euphrates) Universitesi, Firat Tip
Merkezi, Psikiyatri Anabilim Dalı, Elazig
23119, Turkey
Tel +90 424 233 3555
Fax +90 424 238 7688
Email matmaca_p@yahoo.com

Antidepressant-Induced Sexual Dysfunction

Actual diagnostic classification systems, DSM-5,⁸ and the ICD-10⁹ 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-10⁹ 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 owing 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 be 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 and 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 contextualize 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 dose, 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 major depressive disorder who did not respond to 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–Åsberg 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-induced 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 SSRI 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 Ginkgo 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 Ginkgo 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 dose 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 weeks⁶⁶ 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.

References

- Higgins A, Nash M, Lynch AM. Antidepressant-associated sexual dysfunction: impact, effects, and treatment. *Drug Health Patient Saf.* 2010;2:141–150. doi:10.2147/DHPS.S7634
- Werner FM, Covenas R. Therapeutic effect of novel antidepressant drugs acting at specific receptors of neurotransmitters and neuropeptides. *Curr Pharm Des.* 2019;25(4):388–395. doi:10.2174/1381612825666190410165243
- Anderson IM. Selective serotonin reuptake inhibitors versus tricyclic antidepressants: a meta-analysis of efficacy and tolerability. *J Affect Disord.* 2000;58(1):19–36. doi:10.1016/S0165-0327(99)00092-0
- Preskorn SH. Comparison of the tolerability of bupropion, fluoxetine, imipramine, nefazodone, paroxetine, sertraline, and venlafaxine. *J Clin Psychiatry.* 1995;56(Suppl 6):S12–S21.
- Rosen RC, Lane RM, Menza M. Effects of SSRIs on sexual function: a critical review. *J Clin Psychopharmacol.* 1999;19(1):67–85. doi:10.1097/00004714-199902000-00013
- Dewan MJ, Anand VS. Evaluating the tolerability of the newer antidepressants. *J Nerv Ment Dis.* 1999;187(2):96–101. doi:10.1097/00005053-199902000-00005
- Goldstein BJ, Goodnick PJ. Selective serotonin reuptake inhibitors in the treatment of affective disorders—III. Tolerability, safety and pharmacoeconomics. *J Psychopharmacol.* 1998;12(Suppl 4):S55–S87. doi:10.1177/0269881198012003041
- American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders.* 5thed. Washington, DC; 2013.
- ICD-10. *Classifications of Mental and Behavioural Disorder: Clinical Descriptions and Diagnostic Guidelines.* Geneva: World Health Organisation; 1992.
- Reichenpfer U, Gartlehner G, Morgan LC, et al. Sexual dysfunction associated with second-generation antidepressants in patients with major depressive disorder: results from a systematic review with network meta-analysis. *Drug Saf.* 2014;37(1):19–31. doi:10.1007/s40264-013-0129-4
- Angst J. Sexual problems in healthy and depressed persons. *Int Clin Psychopharmacol.* 1998;13(Suppl 6):S1–S4. doi:10.1097/00004850-199807006-00001
- Balon R. SSRI-associated sexual dysfunction. *Am J Psychiatry.* 2006;163(9):1504–1509. doi:10.1176/ajp.2006.163.9.1504
- Higgins A, Barker P, Begley CM. 'Veiling sexualities': a grounded theory of mental health nurses' responses to issues of sexuality. *J Adv Nurs.* 2008;62(3):307–317. doi:10.1111/j.1365-2648.2007.04586.x
- Rothschild A. Sexual side effects of antidepressants. *J Clin Psychiatry.* 2000;61(Suppl 11):S28–S36.
- Harrison WM, Rabkin JG, Ehrhardt AA, et al. Effects of antidepressant medication on sexual function: a controlled study. *J Clin Psychopharmacol.* 1986;6(3):144–149. doi:10.1097/00004714-198606000-00004
- Kennedy SH, Eisfeld BS, Dickens SE, Bacchiocchi JR, Bagby RM. Antidepressant-induced sexual dysfunction during treatment with moclobemide, paroxetine, sertraline, and venlafaxine. *J Clin Psychiatry.* 2000;61(4):276–281. doi:10.4088/JCP.v61n0406
- Ekselius L, von Knorring L. Effect on sexual function of long-term treatment with selective serotonin reuptake inhibitors in depressed clients treated in primary care. *J Clin Psychopharmacol.* 2001;21(2):154–160. doi:10.1097/00004714-200104000-00006

18. Montejo-Gonzales A, Llorce G, Izquierdo J, et al. SSRI – induced sexual dysfunction: fluoxetine, paroxetine, sertraline and fluvoxamine in a prospective, multicenter, and descriptive clinical study of 344 patients. *J Sex Marital Ther.* 1997;23(3):176–194. doi:10.1080/00926239708403923
19. Modell J, Katholi C, Modell J, De-Palma R. Comparative sexual side effects of bupropion, fluoxetine, paroxetine and sertraline. *Clin Pharmacol Ther.* 1997;61(4):476–487. doi:10.1016/S0009-9236(97)90198-3
20. Montejo A, Llorca G, Izquierdo J, Rico-Villademoros F. For Spanish working group for the study of psychotropic-related sexual dysfunction. incidence of sexual dysfunction associated with antidepressant agents: a prospective multicenter study of 1022 outpatients. *J Clin Psychiatry.* 2001;62(Suppl 3):S10–S21.
21. Clayton A, Pradko J, Croft H, et al. Prevalence of sexual dysfunction among newer antidepressants. *J Clin Psychiatry.* 2002;63(4):357–366. doi:10.4088/JCP.v63n0414
22. Atmaca M, Korkmaz S, Topuz M, Mermi O. Mirtazapine augmentation for selective serotonin reuptake inhibitor-induced sexual dysfunction: a retrospective investigation. *Psychiatry Investig.* 2011;8(1):55. doi:10.4306/pi.2011.8.1.55
23. Patterson WM. Fluoxetine-induced sexual dysfunction. *J Clin Psychiatry.* 1993;54:71.
24. Herman JB, Brotman AW, Pollack MH, Falk WE, Biederman J, Rosenbaum JF. Fluoxetine-induced sexual dysfunction. *J Clin Psychiatry.* 1990;51:25–27.
25. Ekselius L, von Knorring LEG. A double-blind study comparing sertraline and citalopram in patients with major depression treated in general practice [abstract]. *Eur Neuropsychopharmacol.* 1997;7(Suppl 1):S147. doi:10.1016/S0924-977X(97)88489-1
26. Baldwin DS, Thomas SC, Birtwistle J. Effects of antidepressant drugs on sexual function. *Int J Psychiatry Clin Pract.* 1997;1(1):47–58. doi:10.3109/13651509709069205
27. Bijlsma EY, Chan JS, Olivier B, et al. Sexual side effects of serotonergic antidepressants: mediated by inhibition of serotonin on central dopamine release? *Pharmacol Biochem Behav.* 2014;121:88–101. doi:10.1016/j.pbb.2013.10.004
28. Keltner NL, McAfee KM, Taylor CL. Mechanisms and treatments of SSRI-induced sexual dysfunction. *Perspect Psychiatr Care.* 2002;38(3):111–116. doi:10.1111/j.1744-6163.2002.tb00665.x
29. Veening JG, De Jong TR, Waldinger MD, Korte SM, Olivier B. The role of oxytocin in male and female reproductive behavior. *Eur J Pharmacol.* 2015;753:209–228. doi:10.1016/j.ejphar.2014.07.045
30. Pedersen CA, Boccia ML. Oxytocin maintains as well as initiates female sexual behavior: effects of a highly selective oxytocin antagonist. *Horm Behav.* 2002;41(2):170–177. doi:10.1006/hbeh.2001.1736
31. Behnia B, Heinrichs M, Bergmann W, et al. Differential effects of intranasal oxytocin on sexual experiences and partner interactions in couples. *Horm Behav.* 2014;65(3):308–318. doi:10.1016/j.yhbeh.2014.01.009
32. Bahrack A. Persistence of sexual dysfunction side effects after discontinuation of antidepressant medications: emerging evidence. *Open Psychol J.* 2008;1(1):42–50. doi:10.2174/1874350100801010042
33. Williams JW, Mulrow CD, Chiquette E, Noel PH, Aguilar C, Cornell J. A systematic review of newer pharmacotherapies for depression in adults: evidence report summary: clinical guideline, part. *Ann Intern Med.* 2000;132(9):743–756. doi:10.7326/0003-4819-132-9-200005020-00011
34. Gartlehner G, Hansen RA, Morgan LC, et al. Comparative benefits and harms of second-generation antidepressants for treating major depressive disorder: an updated meta-analysis. *Ann Intern Med.* 2011;155(11):772–785. doi:10.7326/0003-4819-155-11-201112060-00009
35. Csoka AB, Bahrack A, Mehtonen OP. Persistent sexual dysfunction after discontinuation of selective serotonin reuptake inhibitors. *J Sex Med.* 2008;5(1):227–233. doi:10.1111/j.1743-6109.2007.00630.x
36. Bet PM, Hugtenburg JG, Penninx BW, Hoogendijk WJ. Side effects of antidepressants during long-term use in a naturalistic setting. *Eur Neuropsychopharmacol.* 2013;23(11):1443–1451. doi:10.1016/j.euroneuro.2013.05.001
37. 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. doi:10.1016/j.ejphar.2014.11.031
38. Bolton JM, Sareen J, Reiss JP. Genital anesthesia persisting six years after sertraline discontinuation. *J Sex Marital Ther.* 2006;32(4):327–330. doi:10.1080/00926230600666410
39. Perlis RH, Laje G, Smoller JW, Fava M, Rush AJ, McMahon FJ. Genetic and clinical predictors of sexual dysfunction in citalopram-treated depressed patients. *Neuropsychopharmacology.* 2009;34(7):1819–1828. doi:10.1038/npp.2009.4
40. Kennedy SH, Rizvi SJ, Fulton K, Ellis J, Quilty LC, Ravindran L. The sex effects scale: pilot validation in a healthy population. *Psychopharmacol Bull.* 2010;43(3):15–25.
41. McGahuey CA, Gelenberg AJ, Laukes CA, et al. The Arizona Sexual Experience Scale (ASEX): reliability and validity. *J Sex Marital Ther.* 2000;26(1):25–40.
42. Clayton AH, McGarvey EL, Clavet GJ. The Changes in Sexual Functioning Questionnaire (CSFQ): development, reliability, and validity. *Psychopharmacol Bull.* 1997;33(4):731–745.
43. Mazer NA, Leiblum SR, Rosen RC. The Brief Index of Sexual Functioning for women (BISF-W): a new scoring algorithm and comparison of normative and surgically menopausal populations. *Menopause.* 2000;7(5):350–363. doi:10.1097/00042192-200007050-00009
44. O'Mullan C, Doherty M, Coates R, Tilley PJ. Women's experiences of coping with the sexual side effects of antidepressant medication. *Psychol Health.* 2014;29(12):1388–1406. doi:10.1080/08870446.2014.940951
45. Bahadur N. 8 Women on when antidepressants killed their sex drives. Available from: http://www.huffingtonpost.com/2015/04/15/antidepressants-decreased-my-sex-drive_n_7024738.html. Accessed February 1, 2017.
46. Rapaport L. Antidepressants have sexual side effects in teens, too. Available from: <http://www.reuters.com/article/us-antidepressants-teens-side-effects-idUSKBN0MJ24C20150323>. Accessed February 1, 2017.
47. Bala A, Nguyen HMT, Hellstrom WJ. Post-SSRI sexual dysfunction: a literature review. *Sex Med Rev.* 2018;6(1):29–34. doi:10.1016/j.sxmr.2017.07.002
48. Watson J, Davies T. ABC of mental health psycho-sexual problems. *BMJ.* 1997;315(7102):239–242. doi:10.1136/bmj.315.7102.239
49. Kennedy SH, Dickens SE, Eisfield B, Bagby M. Sexual dysfunction before antidepressant therapy in major depression. *J Affect Disord.* 1999;56(2–3):201–208. doi:10.1016/S0165-0327(99)00050-6
50. Rudkin L, Taylor M, Hawton K. Strategies for managing sexual dysfunction induced by antidepressant medication. *Cochrane Database of Systematic Reviews* 2004. Issue 4.
51. Rothschild A. Selective serotonin reuptake inhibitor-induced sexual dysfunction: efficacy of a drug holiday. *Am J Psychiatry.* 1995;152(15):1514–1516.
52. Clayton A, Warnock J, Kornstein S, Pinkerton R, Sheldon-Keller A, McGarvey E. A placebo-controlled trial of bupropion SR as an antidote for selective serotonin reuptake inhibitor-induced sexual dysfunction. *J Clin Psychiatry.* 2004;65(1):62–67. doi:10.4088/JCP.v65n0110
53. Zahiruddin A, Faridhosseini F, Zamani A, Shahini N. Comparing the efficacy of bupropion and amantadine on sexual dysfunction induced by a selective serotonin reuptake inhibitor. *Iran Red Crescent Med J.* 2015;17(12):24998. doi:10.5812/ircmj.24998
54. Ravindran A, Kennedy S, O'Donovan M, Fallu A, Camacho F, Binder C. Osmotic-release oral system methylphenidate augmentation of antidepressant monotherapy in major depressive disorder. *J Clin Psychiatry.* 2008;69(1):87–94. doi:10.4088/JCP.v69n0112
55. Evliyaoğlu Y, Yelsel K, Kobaner M, Alma E, Saygılı M. Efficacy and tolerability of tadalafil for treatment of erectile dysfunction in men taking serotonin reuptake inhibitors. *Urology.* 2011;77(5):1137–1141. doi:10.1016/j.urology.2010.12.036

56. Fava M, Nurnberg H, Seidman S, et al. Efficacy and safety of sildenafil in men with serotonergic antidepressant-associated erectile dysfunction. *J Clin Psychiatry*. 2006;67(2):240–246. doi:10.4088/JCP.v67n0210
57. Worthington J, Simon N, Korbly N, Perlis R, Pollack M. Ropinirole for antidepressant-induced sexual dysfunction. *Int Clin Psychopharmacol*. 2002;17(6):307–310. doi:10.1097/00004850-200211000-00006
58. Cohen AJ, Bartlik B. Ginkgo biloba for antidepressant-induced sexual dysfunction. *J Marital Sex Ther*. 1998;24(2):139–143. doi:10.1080/00926239808404927
59. Kang BJ, Lee SJ, Kim MD, Cho MJ. A placebo-controlled, double-blind trial of ginkgo biloba for antidepressant-induced sexual dysfunction. *Hum Psychopharmacol*. 2002;17(6):279–284. doi:10.1002/hup.409
60. Michelson D, Kociban K, Tamura R, Morrison M. Mirtazapine, yohimbine or olanzapine augmentation therapy for serotonin reuptake-associated female sexual dysfunction: a randomized, placebo-controlled trial. *J Psychiatric Res*. 2002;36(3):147–152. doi:10.1016/S0022-3956(01)00060-7
61. Aizenberg D, Zemishlany Z, Weizman A. Cyproheptadine treatment of sexual dysfunction induced by serotonin reuptake inhibitors. *Clin Neuropharmacol*. 1995;18(4):320–324. doi:10.1097/00002826-199508000-00003
62. Decastro RM. Reversal of MAOI-induced anorgasmia with cyproheptadine. *Am J Psychiatry*. 1985;142(6):783.
63. Lorenz T, Meston C. Exercise improves sexual function in women taking antidepressants: results from a randomized crossover trial. *Depress Anxiety*. 2013;31(3):188–195. doi:10.1002/da.22208
64. Stanton AM, Handy AB, Meston CM. The Effects of Exercise on Sexual Function in Women. *Sex Med Rev*. 2018;6(4):548–557. doi:10.1016/j.sxmr.2018.02.004
65. Najafidoulatabad S, Mohebbi Z, Nooryan K. Yoga effects on physical activity and sexual satisfaction among the Iranian women with multiple sclerosis: a randomized controlled trial. *Afr J Tradit Complement Altern Med*. 2014;11(5):78–82. doi:10.4314/ajtcam.v11i5.13
66. 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(1):54–60. doi:10.1002/hup.2282
67. Farnia V, Hojatitabar S, Shakeri J, et al. Adjuvant Rosa Damascena has a small effect on SSRI-induced sexual dysfunction in female patients suffering from major depressive disorder. *Pharmacopsychiatry*. 2015a;48(4–5):156–163. doi:10.1055/s-0035-1554712
68. Farnia V, Shirzadifar M, Shakeri J, et al. Rosa damascena oil improves SSRI-induced sexual dysfunction in male patients suffering from major depressive disorders: results from a double-blind, randomized, and placebo-controlled clinical trial. *Neuropsychiatr Dis Treat*. 2015b;11:625–635.
69. Farnia V, Tatari F, Alikhani M, et al. Rosa Damascena oil improved sexual function and testosterone in male patients with opium use disorder under methadone maintenance therapy-results from a double-blind, randomized, placebo-controlled clinical trial. *Drug Alcohol Depend*. 2017a;176:117–125. doi:10.1016/j.drugalcdep.2017.02.008
70. Farnia V, Tatari F, Alikhani M, et al. Rosa Damascena oil improved methadone-related sexual dysfunction in females with opioid use disorder under methadone maintenance therapy - results from a double-blind, randomized, and placebo-controlled trial. *J Psychiatric Res*. 2017b;95:260–268. doi:10.1016/j.jpsychires.2017.08.011
71. Jahangard L, Sadeghi A, Ahmadpanah M, et al. Influence of adjuvant omega-3-polyunsaturated fatty acids on depression, sleep, and emotion regulation among outpatients with major depressive disorders - Results from a double-blind, randomized and placebo-controlled clinical trial. *J Psychiatric Res*. 2018;107:48–56. doi:10.1016/j.jpsychires.2018.09.016
72. Jahangard L, Tayebi M, Haghighi M, et al. Does rTMS on brain areas of mirror neurons lead to higher improvements on symptom severity and empathy compared to the rTMS standard procedure? - Results from a double-blind interventional study in individuals with major depressive disorders. *J Affective Disord*. 2019;257:527–535. doi:10.1016/j.jad.2019.07.019
73. Salehi I, Hosseini SM, Haghighi M, et al. Electroconvulsive therapy (ECT) and aerobic exercise training (AET) increased plasma BDNF and ameliorated depressive symptoms in patients suffering from major depressive disorder. *Journal of Psychiatric Research*. 2017;176:1–8. doi:10.1016/j.jpsychires.2016.01.012
74. Braillon A. The “pharmaceuticalisation” of life. *BMJ*. 2019;365:1972. doi:10.1136/bmj.11972
75. Hengartner MP, Plöderl M. Statistically significant antidepressant-placebo differences on subjective symptom-rating scales do not prove that the drugs work: effect size and method bias matter! *Front Psychiatry*. 2018;9:517. doi:10.3389/fpsyt.2018.00517
76. Braillon A, Lexchin J, Noble JH, et al. Challenging the promotion of antidepressants for nonsevere depression. *Acta Psychiatr Scand*. 2019;139:294–295. doi:10.1111/aps.13010

Neuropsychiatric Disease and Treatment

Dovepress

Publish your work in this journal

Neuropsychiatric Disease and Treatment is an international, peer-reviewed journal of clinical therapeutics and pharmacology focusing on concise rapid reporting of clinical or pre-clinical studies on a range of neuropsychiatric and neurological disorders. This journal is indexed on PubMed Central, the ‘PsycINFO’ database and CAS, and

is the official journal of The International Neuropsychiatric Association (INA). The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <https://www.dovepress.com/neuropsychiatric-disease-and-treatment-journal>