

Antidepressant-Induced Sexual Side Effects: Incidence, Assessment, Clinical Implications, and Management

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Disclosure: The authors have no relevant financial relationships to disclose.

doi: 10.3928/00485713-20170201-01

ABSTRACT

Antidepressant medications can cause numerous types of sexual dysfunction. It is important to screen for and treat antidepressant-induced sexual dysfunction, which is often under-reported and may exacerbate mood symptoms and negatively affect relationships and medication adherence. Management strategies include watchful waiting, reducing the antidepressant dose, adding a different type of antidepressant or a medication for erectile dysfunction, switching to another antidepressant, drug holidays, and timing of sexual relations with respect to antidepressant dose. [*Psychiatr Ann. 2017;47(3):154-160.*]

Sexual dysfunction (SD) is a problem among patients with depression, affecting almost

one-half of people with untreated depression.¹ Whereas 26% of non-depressed people report some sexual dysfunction, this number increases to 45% in people with untreated depression, and to 63% in medically treated patients with depression.² In addition to high levels of baseline SD in patients with depression, many antidepressant medications independently cause SD in any or all phases of the sexual response cycle, including libido, arousal, orgasm, and ejaculation.¹

TYPES OF ANTIDEPRESSANT-INDUCED SEXUAL SIDE EFFECTS

Antidepressants can cause a variety of types of sexual dysfunction. In a hallmark study by Montejo-Gonzalez et al.,³ decreased libido was seen in

40.5% to 57.6% of patients, delayed orgasm or ejaculation in 45.6% to 58.8% of patients, anorgasmia or no ejaculation in 30.9% to 48.2% of patients, and impotence in 9.5% to 34.1% of patients. These dysfunctions were most common with paroxetine and least common with fluvoxamine. In studies of citalopram, which has a high incidence of sexual side effects, 54% of patients reported decreased libido and 36% reported difficulty achieving orgasm.⁴ Among men taking citalopram, 37% had erectile dysfunction, and women were significantly more likely to report decreased libido, and have delayed orgasms or anorgasmia.³

Risk factors for decreased libido include earlier onset of illness, greater severity of depression, being married, and being male.⁴ Difficulty with orgasm is associated with younger age, earlier onset of illness, greater severity of general medical comorbidities, as well as male sex, being married, and treatment in a specialty rather than a primary care clinic.⁴

Other problems reported by patients taking antidepressants include priapism, painful ejaculation, penile anesthesia, loss of sensation in the vagina and nipples, persistent genital arousal, and non-puerperal lactation in women.⁵

PHYSIOLOGY OF ANTIDEPRESSANT-INDUCED SEXUAL SIDE EFFECTS

Normal sexual function appears to involve a wide variety of neurotransmitters, including serotonin, norepinephrine, dopamine, acetylcholine, gamma-aminobutyric acid, nitric oxide, oxytocin, and others.⁶ Sexual arousal and erections have been linked to acetylcholine in the parasympathetic system, whereas orgasm and ejaculation seem more influenced by acetylcholine and norepinephrine in the sympathetic system. Although the pathophysiology of sexual dysfunction remains unclear,

selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors have been shown to affect alpha-1 adrenergic receptors, thus causing direct inhibition of both sym-

Assessing for the sexual side effects of antidepressant medications has proven challenging.

pathetic and parasympathetic sexual function.^{3,6} These antidepressants may additionally cause inhibitory effects on dopamine by enhancing an inhibitory effect on the raphe nuclei or impairing sexual function through prolactin elevation.⁷ They may also inhibit nitrous oxide synthetase, thereby decreasing nitrous oxide availability (needed for erection).⁸

ASSESSING FOR ANTIDEPRESSANT-INDUCED SEXUAL SIDE EFFECTS

Assessing for the sexual side effects of antidepressant medications has proven challenging, probably due to the sensitive nature of the topic. For example, there is a significant increase in the incidence of SD detected when physicians asked patients directly about sexual side effects as compared to spontaneous reports from patients.³ The subjectivity of sexual experiences is also hard to quantify. The Arizona Sexual Experience Scale⁹ (ASES) has high positive and negative predictive values, internal consistency, reliability, and validity. However, this scale does not differentiate between premature and spontaneous orgasm (ie, orgasm in the absence of stimulation) as SD, which may serve as a limitation to its use. Other scales, such as the Changes in Sexual Functioning

Questionnaire,¹⁰ the Brief Index of Sexual Functioning scale,¹¹ and the Sex Effects (SexFX) scale,¹² have been used. None of these scales were designed specifically to test for changes among a population of patients with depression, but could serve as potential tools for physicians to monitor sexual changes among their patients taking antidepressants.

IMPACT OF ANTIDEPRESSANT-INDUCED SEXUAL SIDE EFFECTS

Patients with antidepressant-induced sexual side effects are reported to have significantly worse quality of life, self-esteem, mood, and relationships with partners in at least one-fifth of patients sampled in a European cross-sectional survey.¹³ SD is one of the main reasons patients choose to discontinue SSRI treatment, and it can also cause poor adherence patterns among patients who choose to continue taking the medication.⁴ In one study of patients with major depressive disorder, 85% of patients rated the management of sexual dysfunction as “extremely important,” “very important,” or “important.”¹²

Qualitative studies have shown that women who face sexual side effects are likely to feel that they are “suffering in silence,”¹⁴ causing some women to use social media outlets to discuss their experiences on antidepressants with others.¹⁵

Adolescents may also be uniquely affected by antidepressant-induced sexual side effects, as adolescents have a limited understanding of their sexual baseline and may not be able to identify side effects.¹⁶

MANAGEMENT OF ANTIDEPRESSANT-INDUCED SEXUAL SIDE EFFECTS

Rule Out Other Possible Causes

Although antidepressants are known to cause sexual side effects, there are many other causes of sexual

dysfunction that must be evaluated in patients. Depressive symptoms and depressive illness are associated with impairments in sexual function, and thus physicians should ask patients to compare their sexual functioning while taking medications to their pre-medication depressive sexual functioning and not to their pre-depression baseline. Similarly, other comorbidities must be evaluated, such as alcohol use, diabetes, atherosclerosis, cardiac disease, and central and peripheral nervous system conditions.²

Wait and See

Medical treatment with antidepressants may be continued along with observation for persistence or improvement of symptoms. One study showed complete resolution of sexual dysfunction in 5.8% of patients within 6 months, whereas 81.4% of patients with sexual side effects had no improvement during this period.³ Other than complete resolution, a decrease in symptoms can be seen in some patients as tolerance to the medication is developed during the first 4 to 6 weeks.¹⁷ Other studies have noted that sexual side effects are likely to persist with medication, and that spontaneous resolution should not be expected as it is for some side effects such as dry mouth and nausea.¹⁸

Change the Time the Antidepressant Medication Is Taken

Depending on the type of medication regimen a patient may be following, changing the time a patient either takes their antidepressant medication or engages in sexual activity may help alleviate SD. Patients can plan sexual activities around times when serum drug levels are at their lowest, such as right before a dose or immediately after taking a medication.⁸ This method is more effective in patients who take medications with short half-lives, and it

has been shown to be useful in patients on sertraline and clomipramine.¹⁸

Drug Holiday

Antidepressant-induced SD is inherently a drug-induced phenomenon, and thus once patients stop using the antide-

Medical treatment with antidepressants may be continued along with observation for persistence or improvement of symptoms.

pressant they might see a complete remission of SD.³ Thus, “drug holidays” (ie, brief periods of abstinence from medication) can allow for improved sexual function. In one study, taking medication Sunday through Thursday (and skipping Friday and Saturday) allowed participants to have improved sexual functioning 50% of the time on weekends with no overall worsening of mood.¹⁹ This method is only suggested among patients who have a Hamilton Depression Rating Scale (HAM-D) score of less than 10, and patients who indicate that the degree of impairment from sexual dysfunction is so great that, if not corrected, they would choose not to continue SSRI treatment. The drug holiday method is greatly dependent on the half-life of the drug; it is more successful for patients taking sertraline and paroxetine, and not helpful for those taking fluoxetine. This technique requires patients and providers to monitor carefully for worsening depression and discontinuation syndromes.²⁰

Decrease the Dose

Decreasing the dose may also improve SD. In a small cohort of 30 pa-

tients, 23 patients reported that their SD improved “to some extent” or “quite a lot” when their fluoxetine dose was decreased by 50%.²¹ The theory behind this model is the concept of a flat-dose response curve, in that a patient who responds to a certain dose is not likely to respond more to a greater dose, and may respond just as well to a lesser dose.³ However, not all authors agree with this approach, and instead propose that dosage decrease may lower side effects for the patients but may not be sufficient for treating their depression.¹⁸ As cautioned with the drug holiday approach, lowering the amount of antidepressant taken each day may cause withdrawal reactions (particularly in people taking paroxetine, sertraline, and venlafaxine extended release, which are cleared from the body quickly) or an increase in depressive symptoms.

Switch to or Add Mirtazapine

Evidence for treatment of antidepressant-induced SD with mirtazapine is mixed. Multiple small studies demonstrate improvement of antidepressant-induced SD with mirtazapine therapy,^{22,23} but these studies lack placebo controls. One study of 25 patients reported improved desire, arousal, and orgasm during treatment with mirtazapine monotherapy (flexible dosing, maximum dose of 45 mg/day).²⁴ HAM-D scores also dropped significantly. In this study, 16 patients dropped out of the study or were lost to follow-up. Some patients dropped out due to drowsiness or other adverse events, emphasizing the importance of determining which side effects are a priority to the patient.²⁴

In contrast with the smaller studies, a randomized, double-blind, placebo-controlled study of mirtazapine (15 mg/day), yohimbine (5.4 mg/day), and olanzapine (2.5 mg/day) found no improvement in sexual function with treatment compared to placebo.²⁵ There

was an increase in sexual function in all groups, including placebo, when compared with baseline. As with other studies of mirtazapine, a significant number of patients discontinued mirtazapine due to somnolence. Further studies should clarify whether mirtazapine mitigates antidepressant-induced SD independently of depression scores and placebo effects.

Switch to or Add Bupropion

A randomized, blinded placebo-controlled trial²⁶ found no improvement in sexual function on any parameter included in the ASES or Brief Index of Sexual Functioning. In this study, 41 patients received bupropion augmentation (150 mg/day) of their current SSRI. In another study of bupropion (150 mg twice daily) versus placebo, treated patients experienced a significant increase in desire by week 4.²⁷ However, patients experienced no improvement in orgasm, arousal, or global sexual function. The authors reported a correlation between testosterone levels and frequency of sexual activity. This correlation suggests that testosterone levels may be a confounding factor in studies of treatment for SD.

In support of bupropion augmentation, a group in Iran demonstrated mitigation of SSRI-induced SD in a cohort of 20 people.²⁸ In this blinded trial of bupropion (200 mg/day) versus amantadine (200 mg/day), the bupropion group reported more improvement in desire, arousal, and pleasure. A double-blind, randomized, placebo-controlled study that was published in favor of bupropion augmentation was later retracted.²⁹

Future studies should investigate dose amounts (150 mg/day vs 200 mg/day), dose timing (morning vs before intercourse), and the formulation (sustained- vs immediate-release). Despite the lack of evidence showing reversal, recent studies continue to

show that bupropion induces fewer sexual side effects than other antidepressants.³⁰ Therefore, bupropion is an important choice for patients in whom sexual dysfunction must be prevented, but it should not be expected to reverse iatrogenic dysfunction.

Add Phosphodiesterase Inhibitors

Multiple, randomized placebo-controlled studies of phosphodiesterase (PDE) inhibitors demonstrate an improvement in antidepressant-induced SD. In two studies of tadalafil (10 or 20 mg prior to intercourse), men reported more successful intercourse, erections, and orgasms, and greater satisfaction.^{31,32} In studies of sildenafil (25-100 mg), both men and women reported improved sexual function and satisfaction.³³⁻³⁵ In one study,³³ women who improved also had higher baseline testosterone and thyroxine levels. This finding, in corroboration with similar findings in a study of bupropion, emphasizes the potentially confounding (or synergistic) effect of testosterone in studies of sexual function.^{27,33}

Together, these studies support the use of PDE inhibitors for antidepressant-induced SD in both men and women. In all of these studies, the mean age of the population was younger than age 60 years. There is a need for studies of PDE inhibitors in older adults with antidepressant-induced SD.

Other Pharmacotherapies

Amantadine. In an investigation of amantadine augmentation for clomipramine-induced SD, the sexual behavior of rats was recorded after treatment with amantadine plus one of three doses of clomipramine.³⁶ Results demonstrated reduced sexual function despite amantadine augmentation. Histological analysis demonstrated testicular damage and low tes-

tosterone. This study in rats does not support use of amantadine to mitigate antidepressant-induced SD in people.

Buspirone. Two studies suggest a strong placebo effect with buspirone for SSRI-induced SD. In 47 patients receiving buspirone (20-60 mg/day, mean 48.5 mg/day), there was no statistically significant difference between placebo and treatment on sexual function.³⁷ In another study, women were randomized to buspirone (20 mg/day), amantadine (50 mg/day), or placebo.³⁸ All groups, including placebo, reported the same sexual functionality and satisfaction, resulting in significant improvement from baseline.

Stimulants. In a study of stimulants for antidepressant-induced SD, patients with major depressive disorder who had failed multiple treatments received augmentation with osmotic controlled-release oral delivery system methylphenidate (18-54 mg/day).³⁹ Treatment had no significant effect on the Montgomery-Asberg Depression Rating Scale scores. Despite the lack of effect on mood, sexually active patients treated with methylphenidate had higher sexual function scores on SEX-FX (function) scale compared with placebo at the end of the study. Because baseline sexual function of sexually active patients was not reported, it is unclear whether sexual function can truly be compared between groups.

Ropinirole. One group explored the potential for dopamine agonist treatment of antidepressant-induced SD with ropinirole (0.25-4 mg/day).⁴⁰ Mean ASES score after ropinirole treatment was decreased from baseline, indicating an improvement in multiple aspects of sexual function. Seven of 13 patients in the study had clinically significant improvement, indicating that “responders” may benefit from ropinirole augmentation.

This study is limited by lack of a placebo control.

Vilazodone. Vilazodone has SSRI activity and partial agonist activity at the 5-HT_{1A} receptor.⁴¹ Two placebo-controlled studies and one long-term tolerability and safety trial found no SD associated with this compound.⁴²⁻⁴⁴ As in other studies, both the treated and placebo groups experienced increased sexual function with no difference between the groups, suggesting a placebo effect on sexual function.

Triple reuptake inhibitors. Cases of improvement of SD with combinations of drugs that work on different receptors (such as SSRIs plus dopamine agonists) support the theory that an antidepressant targeting multiple receptors might have fewer sexual side effects. Multiple compounds that inhibit transporters of dopamine, serotonin, and norepinephrine, called triple reuptake inhibitors, are currently being explored. For example, the serotonin-norepinephrine-dopamine reuptake inhibitor DOV 216,303 was tested in rats for its effects on depression and sexual function.⁴⁵ In rats, DOV 216,303 decreased depression and caused no sexual dysfunction, suggesting that DOV 216,303 might be an alternative antidepressant without sexual side effects. Triple reuptake inhibitors are promising therapies with low risk of sexual side effects, but their potential to reverse iatrogenic SD has not yet been reported.

Cyproheptadine. One study reported reversal of SD with cyproheptadine therapy (4-12 mg prior to sexual activity) in patients taking SSRIs for obsessive-compulsive disorder.⁴⁶ Of the seven patients, two patients experienced transient improvement of SD, and three patients experienced lasting improvement. Multiple case reports of individual patients experiencing

improvement with cyproheptadine support these results.⁴⁷ No larger placebo-controlled studies demonstrate reversal of SSRI-induced SD with cyproheptadine.

Nefazodone. A single-blind comparison of nefazodone (400 mg/day) versus sertraline (100 mg/day) for patients who previously experienced

Exercise is hypothesized to increase arousal by increasing sympathetic nervous system activity.

sertraline-induced SD found a lower incidence of sexual dysfunction in the nefazodone group.⁴⁸ At week 1, SD reemerged in 55% (18/33) of sertraline patients compared with only 18% (7/39) of nefazodone patients. By the end of the study, at week 8, SD had reemerged in 76% (25/33) of sertraline patients and 26% (10/39) of nefazodone patients. Almost every patient in both groups reported adverse events.

Plant-Based Therapies

Natural remedies recognized anecdotally for their enhancement of sexual function have been tested in placebo-controlled studies for antidepressant-induced SD.

Saffron. In a study from Iran, 34 women taking fluoxetine received saffron (15 mg twice daily), a spice derived from the flower of *Crocus sativus*, or placebo for 4 weeks.⁴⁹ The saffron group reported improvement in arousal, lubrication, and pain. The side effect and safety profile was similar between saffron and placebo, which the authors highlight as a benefit of saffron compared to cyprohep-

tadine or yohimbine (which may exacerbate mood symptoms).

Ginkgo. The first report supporting supplementation with ginkgo (60mg to 120mg twice daily) for antidepressant-induced SD was not placebo-controlled.⁵⁰ The study included 30 women and 30 men and demonstrated greater improvement in women. In a subsequent randomized, placebo-controlled, double-blind trial, 37 patients diagnosed with either depressive disorder or anxiety disorder received ginkgo (titrated up to 240 mg daily).⁵¹ Both the treatment and placebo groups reported increased sexual function from baseline, with no significant difference between the two groups. These results suggest a strong placebo effect with ginkgo.

Maca. One double-blind, randomized trial compared 1.5 g/day and 3 g/day of maca (*Lepidium meyenii*, a plant native to the Peruvian Andes) for SSRI-induced SD in 17 women and 3 men.⁵² Mean sexual function scores increased for both the high-dose and low-dose groups, but only the increase in the high-dose group was statistically significant. The authors tout maca as a safe and cheaper alternative for patients who cannot use PDE inhibitors or sildenafil. Although these results seem promising, increase in function may be related to a decrease in HAM-D score in the high-dose group, possibly with no relation to maca use.

Yohimbine. Yohimbine is a tree bark extract traditionally used as an aphrodisiac.⁵³ A placebo-controlled trial of yohimbine found no improvement in sexual function with treatment compared with placebo, suggesting a placebo effect on sexual function.²⁵

Exercise

Exercise is hypothesized to increase arousal by increasing sym-

pathetic nervous system activity. In one study, 47 women with antidepressant-related SD watched an erotic film 5 or 15 minutes after exercising, or after no exercise.^{54,55} Vaginal photoplethysmograph measured greater genital arousal in women who exercised than in those who did not, and the increase in arousal was greater 5 minutes after exercise than 15 minutes after exercise. However, there was no significant effect on self-reported feelings of arousal. A second study by the same authors found that exercise completed immediately before sexual activity may also improve antidepressant-induced SD.⁵⁴

CONCLUSION

In patients treated with antidepressants, it is important to screen for and treat antidepressant-induced SD, which is often under-reported and may exacerbate mood symptoms and negatively affect relationships and medication adherence. A wide range of remedies, from herbal supplements to pharmacotherapies to exercise, has been reported. Some remedies, such as PDE inhibitors, are supported by large, randomized placebo-controlled studies. Some remedies are supported only by case reports and warrant larger studies. With all remedies, there appears to be a significant placebo effect on sexual dysfunction. This placebo effect may be useful clinically, but should be heeded in the design of future studies. Also, as with all remedies, it is crucial for physicians and patients to analyze the risks and benefits of switching treatments with the primary goal of ameliorating this side effect. Although SD should not be minimized, some treatments are associated with other side effects that may be even less favorable. Overall, there are many possibilities for treatment of antidepressant-induced SD, allowing the physician and patient to determine the best option.

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