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Antidepressant-Induced Female Sexual Dysfunction

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Abstract

Because 1 in 6 women in the United States takes antidepressants and a substantial proportion of patients report some disturbance of sexual function while taking these medications, it is a near certainty that the practicing clinician will need to know how to assess and manage antidepressant-related female sexual dysfunction. Adverse sexual effects can be complex because there are several potentially overlapping etiologies, including sexual dysfunction associated with the underlying mood disorder. As such, careful assessment of sexual function at the premedication visit followed by monitoring at subsequent visits is critical. Treatment of adverse sexual effects can be pharmacological (dose reduction, drug discontinuation or switching, augmentation, or using medications with lower adverse effect profiles), behavioral (exercising before sexual activity, scheduling sexual activity, vibratory stimulation, psychotherapy), complementary and integrative (acupuncture, nutraceuticals), or some combination of these modalities.

Depression is a major risk factor for sexual dysfunction, and vice versa. In one meta-analysis of over 14,000 patients, those with diagnoses of depression had a 50% to 70% risk for development of sexual dysfunction, even after adjusting for common comorbidities.[1] Relative to men, women are at increased risk for depression and anxiety, as well as increased risk of sexual dysfunction.[2] Depression may impair sexual well-being by reducing motivation for or reward from engaging in pleasurable activities, interfering with intimate relationships,[3] or increasing the risk of smoking or substance abuse.[4] Depression and its associated behavioral patterns may also contribute to other disease processes, such as metabolic syndrome, that further exacerbate female sexual dysfunction.[5]

A substantial proportion of patients will experience some disturbance of sexual function while taking antidepressants. Of note, although antidepressants are named for their effect on

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mood disorders, they are used in the clinical management of many other classes of psychological and physical problems, including (but not limited to) anxiety disorders, chronic pain, excessive weight, smoking, and menopausal hot flashes. On the basis of secondary analyses and observational studies, rates of adverse sexual effects are not thought to differ across subpopulations of antidepressant users; however, more controlled research is needed.

Three recent independent meta-analyses have examined rates of adverse sexual effects, with similar conclusions: although rates of sexual dysfunction attributable to antidepressants were approximately 40%, rates of sexual dysfunction associated with placebo were approximately 14%. [6-8] However, there was wide variability across studies, antidepressant types, and phase of sexual response: for example, only about 2% of patients taking bupropion reported arousal dysfunction compared with about 82% of patients taking citalopram. The high variability in estimates may arise from differences in assessment types and timing; typically, trials that prospectively assess sexual function over more than 6 months with a validated scale report higher rates of adverse sexual effects than trials that rely on spontaneous patient report, brief clinical assessment without a questionnaire,[6] or cross-sectional analyses.[7] Also, medications with greater effect on serotonin (eg, sertraline, citalopram, venlafaxine) are associated with significantly higher rates of treatment-emergent sexual dysfunction than medications with predominantly noradrenergic, dopaminergic, or nonmonoaminergic effects (eg, mirtazapine, bupropion).[6,7] The relative frequency of sexual dysfunction associated with several common antidepressant drugs is presented in Table 1. Notably, as depression can itself impair sexual function, some women's sexual function improves when taking antidepressants. For example, in a large clinical trial, depressed women who were untreated had a higher odds ratio of experiencing sexually related personal distress than depressed women who received antidepressants.[10]

Adverse sexual effects can be categorized according to different aspects of sexual response, such as problems with desire, arousal, orgasm, pain, and general satisfaction. Although patients who present with one of these symptoms often present with others,[6,11] there are a few notable differences across phases. The most commonly reported adverse sexual effects in women taking antidepressants are problems with sexual desire (72%) and sexual arousal (83%).[6-8,11] About 42% of women taking selective serotonin reuptake inhibitors report problems having an orgasm.[6-8,11] Data on the effect of antidepressants on sexual pain are mixed, with some studies suggesting lubrication problems leading to pain with vaginal penetration, some reporting no effect, and still others reporting improvements in vulvodynia (persistent vulvar pain) with antidepressant use.[12]

Interestingly, although men generally report higher rates of antidepressant-related adverse effects in sexual desire and orgasm, women are more likely to report sexual arousal dysfunction, particularly when taking selective serotonin reuptake inhibitors.[6] These higher rates may be due to sex differences in genital arousal processes: recent research suggests that vaginal arousal is facilitated by sympathetic nervous system activity [13] and that serotonergic medications interfere with the autonomic balance necessary to support vaginal arousal.[14] Speculatively, this same physiologic difference may partially explain why women appear to be buffered from the very high rates of antidepressant-associated orgasm dysfunction seen in

men because the suppression of sympathetically mediated orgasm reflexes may differentially affect female vs male orgasm. Another likely explanation is the higher percentage of women in the general population who report orgasm dysfunction [2]—perhaps fewer women report orgasm problems as an adverse sexual effect because they are more likely to have had orgasm problems before treatment.

An unfortunate clinical reality is that the onset of adverse sexual effects (across all phases) occurs within about 1 to 3 weeks of initiating a treatment regimen, whereas the antidepressant effects do not consistently appear until approximately 2 to 4 weeks after starting a medication.[15] Thus, many patients will experience detrimental sexual effects before manifestation of positive mood or symptom reduction. Helping patients navigate this critical window can considerably improve long-term treatment adherence and prevent premature discontinuation of medication. Because 1 in 6 women in the United States takes antidepressants and a substantial proportion of patients report some disturbance of sexual function while taking these medications, it is a near certainty that the practicing clinician will need to know how to assess and manage antidepressant-related female sexual dysfunction.

ASSESSMENT

When prescribing an antidepressant, sexual function must be assessed in order to maximize treatment outcomes, particularly medication adherence. One study found that 15% of women stopped taking their psychotropic medication because of adverse sexual effects. Even more striking, half of these patients never discussed their sexual health concerns with their prescriber. [16] Thus, assessment of sexual functioning before and after the prescription of an antidepressant is crucial for patient satisfaction and medication adherence.

Assessment of sexual function is needed both at initial and subsequent visits. Because nearly half of patients experiencing untreated depression also experience sexual dysfunction [17] and patients may be poor historians regarding the onset of sexual dysfunction,[18] it may be difficult to determine whether dysfunction is due to depression vs medication adverse effect without prospective assessment. Repeated measures provide important information about either decline in sexual function (due to medication adverse effects) or improvement (due to reduction in depression).

Sexual function assessment includes both a direct query of the patient and use of a validated questionnaire.[19] At most, 35% of patients spontaneously report sexual health concerns, whereas direct assessment may reveal sexual health concerns in up to 69% of patients.[1] Direct inquiry can be accomplished at baseline by simply asking during the review of systems, “Do you have any sexual health concerns?” At subsequent visits, the patient can be asked, “Have you noticed any bothersome changes in your sexual function?” It is important that the health care professional determines whether the sexual health issue is distressing or bothersome. Many women report sexual health concerns, but far fewer of these concerns actually cause personal distress. For example, 43% of women report sexual health concerns, yet only 12% report associated distress.[4] A sexual health concern warrants intervention only if it causes distress.

If the patient reports a distressing sexual health issue, the assessment should address each domain of sexual function (ie, desire, arousal, orgasm, pain). This process may be most efficiently completed with a validated screening tool. One of the most commonly utilized questionnaires is the Arizona Sexual Experience Scale, a 5-item measure designed specifically to evaluate sexual dysfunction due to psychotropic medication. It has good reliability and validity and requires approximately 5 minutes to complete.[20] However, it does not impart information about sexual pain or sexual distress.

Finally, to optimize treatment outcomes, collaboration with the patient and shared decision making is necessary. Educating patients about the potential for and prevalence of adverse sexual effects is important, as is assessing how this problem may impact their willingness to take the medication.[21] This information will inform medication choice. Patients should be advised to report any adverse sexual effects at future visits and be assured that treatment is available.

MANAGEMENT

The best clinical evidence supports starting treatment with an antidepressant that has a better adverse sexual effect profile, such as bupropion or mirtazapine, particularly in patients concerned about their sexual functioning and in those with sexual dysfunction at baseline.[17] However, this option may not be feasible in some circumstances (eg, bupropion is contraindicated in women with eating disorders [22]). Moreover, given the ubiquity of these medications, many health care professionals find themselves treating patients whose depression has already stabilized with use of an antidepressant from another prescriber.

Only 20% of prescribers discuss with their patients the management strategies for adverse sexual effects related to antidepressants.[23] Yet, there are a number of effective pharmacological and nonpharmacological treatment options for antidepressant-induced sexual dysfunction. Before discussing these options with the patient, prescribers should first ask what strategies they have already tried because the patient may already have identified a potentially effective strategy and merely needs reassurance to continue.[21] For those who have not found an effective remedy, there are a variety of management strategies available (Table 2).

Desire Dysfunction

Pharmacological Strategies.—Augmentation strategies consist of adding another drug to counteract the adverse sexual effects related to the initial antidepressant treatment. In a randomized, double-blind, placebo-controlled trial involving 42 patients (37 women and 5 men) with antidepressant-induced sexual dysfunction, sustained-release bupropion at 150 mg twice daily resulted in a statistically significant increase in self-reported desire and frequency of sexual activity at 4 weeks compared with placebo.[35] A recent Cochrane review concluded that bupropion in higher doses may be an effective augmentation strategy for women.[33] A 12-week course of transdermal testosterone (300-μg patch) has been found to significantly increase the number of sexually satisfying events over placebo in a double-blind, randomized, placebo-controlled trial involving 34 premenopausal and 10

postmenopausal women.[36] Currently, however, no testosterone products have been approved by the US Food and Drug Administration for use in women.

Behavioral Strategies.—A small but well-controlled trial found that for women with severe adverse sexual effects, simply attempting sexual activity 3 times a week was sufficient to significantly improve sexual function, particularly sexual desire.[24]

Other Strategies.—In one uncontrolled investigational case study, acupuncture was found to improve sexual desire. After undergoing 12 consecutive weeks of a traditional Chinese medicine acupuncture protocol, women reported significant improvement in sexual desire and vaginal lubrication compared with baseline.[27]

Arousal Dysfunction

Pharmacological Strategies.—Although there is some evidence of effectiveness of phosphodiesterase type 5 inhibitors in managing adverse arousal effects in men,[33] they have not proven effective in improving arousal in women[37].

Behavioral Strategies.—There is ample evidence that exercise reduces symptoms of depression and can improve sexual wellbeing in unmedicated depressed patients.[38] Thus, it is not surprising that exercise may ameliorate antidepressant adverse sexual effects. Moreover, female sexual arousal may be disrupted by antidepressants via interference with sympathetic contributions to vaginal arousal. As such, exercise, which is a potent stimulator of the sympathetic nervous system, may improve genital arousal in women if conducted immediately before sexual activity.[14] A small but well-controlled randomized clinical trial found that 30 minutes of cardiovascular and strength-training exercise before sexual activity significantly improved sexual functioning in women taking serotonergic antidepressants, above and beyond the effects of exercise at other times.[24] The authors recommended a prescription of 30 minutes of moderately intense exercise 3 times a week, scheduled immediately before sexual activity for maximal benefit, to reduce adverse sexual effects.

Other Strategies.—In one randomized, doubleblind, placebo-controlled study, saffron (*Crocus sativus* L), 30 mg daily, was used to treat sexual dysfunction induced by fluoxetine. It improved women's sexual arousal and vaginal lubrication compared with the placebo group after 4 weeks.[29]

Orgasm Dysfunction

Pharmacological Strategies.—One small randomized, double-blind, placebo-controlled trial reported improvement in orgasm functioning in women with antidepressant-associated adverse sexual effects treated with the phosphodiesterase type 5 inhibitor sildenafil.[37]

Behavioral Strategies.—For women experiencing arousal and orgasm adverse effects, more intense stimulation with the use of a vibrator may help counter decreased tactile sensitivity related to an antidepressant.[26]

It is worth considering whether other factors may have changed concurrent with antidepressant treatment that may also contribute to orgasm dysfunction. For example,

women with a history of depression more often prefer solitary sexual activity over partnered sexual activity, particularly while depressed.[39] As women recover from depression, they may transition from one form of sexual stimulation that is likely to lead to orgasm (self-stimulation) to another less likely to be orgasmic (ie, partnered sexual activity).[40] In the absence of careful assessment, these changes may be misinterpreted as antidepressant-associated orgasm dysfunction.

Other Strategies.—Maca root (*Lepidium meyenii*) has been found to improve orgasmic function for women with antidepressant-induced arousal and orgasm dysfunction. In a double-blind, placebo-controlled trial,[28] postmenopausal women taking 3.0 g/d of maca root for 12 weeks reported significant improvement in sexual function compared with the placebo group, particularly in orgasmic function.

Improvement Across Domains of Sexual Function

Pharmacological Strategies.—Switching to an antidepressant with fewer adverse sexual effects is a therapeutic option, although there is a lack of randomized, controlled clinical trial data to support this theory.[33] In one study, switching to vortioxetine, an antidepressant with a multimodal mechanism of action, was associated with significant improvements in sexual function scores compared with switching to escitalopram, while maintaining antidepressant efficacy.[34]

Simply waiting for sexual symptoms to improve can be an effective strategy. One study suggested that adverse effects will remit in 6 months in approximately 80% of patients,[15] but others note that adverse effects remit in 6 months for only about 10% of patients.[41] A small subset of patients (3%-5%) may continue to experience these effects even after discontinuing the medication. The strongest predictors of postdiscontinuation adverse sexual effects are female sex, depressive symptoms (suggesting incomplete remission), and decreased genital sensitivity.[42] Because it may take several months for symptoms related to sexual dysfunction to improve with watchful waiting, this may not be a practical solution for some, and medication nonadherence is a potential concern.

Reducing the dose or discontinuing the antidepressant is feasible only if the mood disorder is well controlled because this action may lead to recurrence of symptoms.[31] A drug holiday (eg, temporarily discontinuing the drug on weekends) is not recommended because it may induce withdrawal symptoms related to discontinuation, particularly with shorter-acting antidepressants. Additionally, this practice may lead to medication nonadherence and relapse in patients who fail to restart the medication.[32]

Behavioral Strategies.—As noted previously, scheduling sexual activity may itself be an intervention for adverse sexual effects, particularly if the patient is able to engage in sexual activity at a time when adverse effects will be minimized (eg, in the morning before taking the daily antidepressant dose).[25]

Other Strategies.—A double-blind, placebo-controlled study of citronellol of *Rosa damascena* oil [30] reported significant improvements in overall sexual function and reduced sexual pain compared with placebo.

Certain genetic polymorphisms related to inefficient serotonin transport (eg, *5-HTTLPR*) are associated with significantly higher risk of adverse sexual effects.[43] Women with vulnerable polymorphisms are at significantly increased risk of adverse sexual effects if they take hormonal contraceptives,[44] suggesting that switching to a low-dose or nonhormonal contraceptive method may improve sexual function in a subset of female antidepressant users. However, this recommendation is speculative and further research is needed to examine the efficacy of this strategy.

Finally, for women receiving long-term antidepressant therapy in whom other treatment strategies have not been helpful, acceptance of current sexual function may be a useful therapeutic option. Women who have accepted their sexual function "as is" have utilized the following coping strategies: (1) emphasizing the benefits of the antidepressant over the consequences, (2) attending to the positives in their relationship with their partner and to emotional vs physical satisfaction, and (3) changing sexual expectations.[21]

CONCLUSION

Treatment with antidepressant medications can cause difficulty with sexual function in the domains of sexual desire, arousal, and orgasm. Rates of sexual dysfunction with antidepressant use are very high, particularly during the adjustment phase. Medications with the greatest serotonin effect are associated with the highest rates of sexual dysfunction. Determining the cause of the sexual dysfunction (underlying mood disorder vs medication-induced vs other contributing factors, eg, relationship concerns, chronic medical conditions) can be challenging for the clinician. Assessment of sexual functioning is important, not only at the initial visit but also at subsequent visits and can be accomplished with direct inquiry. Treatment options for antidepressant-associated sexual dysfunction include pharmacological strategies such as drug discontinuation or dose reduction but may not be feasible; drug holidays may cause discontinuation symptoms and may lead to nonadherence and relapse. Augmentation, switching to medications with fewer adverse sexual effects, or starting a medication with a better adverse effect profile a priori may be preferable strategies. Behavioral strategies include exercise, scheduling sexual activity, vibratory stimulation, and psychotherapy. Complementary and integrative treatments require additional study but include acupuncture, maca root, saffron, or *R demascena* oil.

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Learning Objectives: On completion of this article, you should be able to (1) list the antidepressants most likely to cause sexual dysfunction; (2) describe how and when to assess for antidepressant-induced sexual dysfunction; and (3) evaluate the interventions available for antidepressant-induced sexual dysfunction.

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TABLE 1.

Relative Frequency of Sexual Dysfunction by Drug[a]

Drug	Sexual desire	Sexual arousal	Orgasm
Bupropion	+	+	+
Citalopram	+++	+++	+++
Fluoxetine	+++	++	+++
Fluvoxamine	+++	++	+++
Mirtazapine	++	++	++
Nefazodone[b]	+	+	+
Paroxetine	+++	+++	+++
Sertraline	+++	+++	+++
Venlafaxine	+++	+++	+++
Vilazodone	+	+	+

[a] + = <10% frequency or <5% relative to placebo; ++ = 10%-25% frequency; +++ = >25% frequency.

[b] Not available in the United States.

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TABLE 2.

Treatment Strategies for Antidepressant-Induced Sexual Dysfunction

Treatment type	Specific therapy	References
Behavioral	Exercise	14,24
	Scheduling sexual activity	24,25
	Vibratory stimulation	26
	Psychotherapy	21
Complementary and integrative	Acupuncture	27
	Maca root *(Lepidium meyenii)*	28
	Saffron *(Crocus sativus* L)	29
	Rosa damascena oil	30
Pharmacological	Dose reduction or discontinuation of antidepressant	31,32
	Watchful waiting	15
	Drug holiday	32
	Switching antidepressants	33,34
	Adjunctive treatment (eg, phosphodiesterase type 5 inhibitor, bupropion, testosterone)	35-37