

Antidepressant-Associated Sexual Dysfunction

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Faculty

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Faculty Disclosure

Contributing faculty, Mark Rose, BS, MA, LP, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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Division Planner/Director Disclosure

The division planner and director have disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Audience

This intermediate course is designed for psychologists involved in the care of patients who have been prescribed antidepressants.

Accreditations & Approvals



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Designations of Credit

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Disclosure Statement

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Course Objective

The purpose of this course is to provide needed information about the relationship between antidepressants and sexual dysfunction and the resultant impact on treatment efficacy and adherence so psychologists may select the best possible treatment plan.

Learning Objectives

Upon completion of this course, you should be able to:

1. Outline the demographics and etiology of antidepressant-associated sexual dysfunction.
2. Describe the approach to managing sexual side effects of antidepressant use in men.
3. Discuss potential sexual side effects of antidepressant use in women.
4. Evaluate the impact of post-treatment enduring sexual dysfunction in patients who were prescribed antidepressants.



Sections marked with this symbol include evidence-based practice recommendations. The level of evidence and/or strength of recommendation, as provided by the evidence-based source, are also included so you may determine the validity or relevance of the information. These sections may be used in conjunction with the course material for better application to your daily practice.

INTRODUCTION

Before the 1980s, reports of antidepressant-associated sexual dysfunction were rare, mainly due to under-reporting, lack of patient assessment and discussion, and the widespread assumption that persons with mental health problems were asexual and/or lacked sexual desire [1; 2]. Since then, research has established that sexual side effects are associated with all commercially available antidepressants, including tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs), and dual serotonergic/noradrenergic reuptake inhibitors (SNRIs). Among antidepressants, SSRIs/SNRIs show the highest rates of sexual dysfunction, including impaired sexual motivation, desire, arousal, and orgasm affecting men and women. Prescribers dramatically underestimate the prevalence and patient burden of sexual side effects and other adverse effects from antidepressants and other medications [3]. Comparison of spontaneous patient reporting with systematic inquiry has led to estimated sexual side effect rates that differ by $\geq 60\%$ [1; 2]. SSRIs account for most antidepressant prescriptions, and primary care providers should have a good understanding of the risk and patient impact of sexual side effects and management of this iatrogenic condition.

DEMOGRAPHICS AND ETIOLOGY OF ANTIDEPRESSANT-INDUCED SEXUAL DYSFUNCTION

In 2015–2018, 13.2% of adults 18 years of age and older used antidepressant medications in the past 30 days [4]. Antidepressants are among the most widely prescribed drugs in the United States, and SSRIs/SNRIs account for roughly 85% of these prescriptions [5; 6]. An estimated 1 in 6 American women have been prescribed antidepressants, the result of women seeking care for depression at

higher rates than men and being twice as likely to be prescribed antidepressants for the same complaint [6; 7]. Side effects largely contribute to the 31% to 60% non-adherence rate with antidepressants. Sexual side effects are the most frequent antidepressant side effect reported by primary care patients [8]. In a study involving 2,163 adults who had undergone at least eight weeks of treatment with antidepressants, 79% showed some degree of sexual dysfunction [51].

In both men and women, antidepressant-induced sexual side effects largely result from increased serotonin (5-HT) neurotransmission via reuptake blockade of serotonin transporters. Antidepressants that primarily increase dopamine and norepinephrine neurotransmission produce markedly fewer sexual side effects. SSRI/SNRI-induced sexual side effects are likely mediated by inhibitory actions on dopamine signaling in sex brain circuits and can be decreased by simultaneously increasing norepinephrine and dopamine neurotransmission but not by increasing norepinephrine alone. This provides the rationale for treatment using bupropion and other agents that simultaneously increase norepinephrine and dopamine signaling. It also suggests the theoretic basis for developing novel antidepressants that increase 5-HT and dopamine signaling. These findings are clinically relevant for patients who develop sexual side effects but also attain substantial clinical improvement or remission of depression with serotonergic agents. All reasonable options to mitigate the antidepressant-induced sexual side effect should be explored before lowering the dose or switching effective antidepressant therapies [9; 10]. Serotonergic antidepressants produce the highest rates of sexual side effects, but a multifactorial etiology is more likely than a specific neurotransmitter action. Other possible mechanisms for SSRI/SNRI-induced sexual side effects include decreased dopaminergic transmission, cholinergic and alpha-adrenergic blockade, inhibition of nitric oxide synthase 1, and prolactin elevation [11; 12].

LIKELIHOOD OF SEXUAL SIDE EFFECTS WITH SPECIFIC ANTIDEPRESSANTS ^a		
Agent	Percent of Male Patients Affected	Percent of Female Patients Affected
Desire Dysfunction		
Citalopram	84.11%	70.78%
Fluoxetine	86.18%	74.39%
Paroxetine	73.65%	72.89%
Sertraline	84.15%	71.92%
Venlafaxine	80.62%	72.00%
Arousal Dysfunction		
Paroxetine	64.51%	83.96%
Sertraline	67.05%	82.00%
Venlafaxine	75.00%	77.71%
Orgasm Dysfunction		
Citalopram	74.05%	39.47%
Fluoxetine	77.23%	40.36%
Paroxetine	80.23%	44.84%
Sertraline	71.64%	44.22%
Venlafaxine	82.14%	44.85%
^a These figures are based on data that did not record the duration of, or distress from, sexual side effects.		
Source: [15]		Table 1

The association between major depressive disorder and sexual dysfunction is bidirectional. Estimated prevalence rates of antidepressant-induced sexual side effects are very high for several antidepressants, but estimation of true prevalence is complicated by the high prevalence of sexual dysfunction in all patients with mood disorders and by the under-reporting of sexual side effects. Baseline sexual functioning should be assessed with validated rating scales at the same time depression is evaluated [10; 13].

As discussed, the prevalence of sexual side effects in antidepressant use is highest for SSRIs and venlafaxine. TCAs and MAOIs have moderate rates of sexual side effects, and low rates are noted with bupropion, trazodone, nefazodone, mirtazapine, agomelatine, and vilazodone. Perhaps the lowest rate is associated with moclobemide, a reversible MAOI [1; 14]. Women often require considerably more time to climax than men, which can make SSRI-induced delayed orgasm unwanted in women but a desired effect in men. A meta-analysis of sexual side effect rates with SSRIs and venlafaxine reported that orgasm and desire dysfunction are more common in men, while arousal dysfunction is more common in women (*Table 1*) [15].



The American Psychiatric Association recommends that men and women who are taking antidepressants be asked whether sexual side effects are occurring with these medications.

(http://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/mdd.pdf. Last accessed October 27, 2022.)

Strength of Recommendation: I (Recommended with substantial clinical confidence)

MANAGEMENT

As noted, switching medications to an antidepressant with fewer sexual side effects has been considered highly undesirable and should be avoided, if possible, in patients showing an otherwise positive therapeutic response. However, it may be an option of select patients. A 2019 study analyzed the effects of switching agents on participants with well-treated depressive symptoms but SSRI-associated sexual dysfunction. The patients were directly switched from an SSRI (citalopram, paroxetine, or sertraline) to vortioxetine or escitalopram [50]. Both groups maintained antidepressant efficacy after eight weeks, but patients switched to vortioxetine experienced greater improvements in treatment-emergent sexual dysfunction. The authors concluded that vortioxetine was a safe and effective option for adults with SSRI-induced sexual dysfunction [50].

If low sexual response or libido is a known problem prior to the initiation of antidepressant therapy, selection of an effective agent with the lowest rate of sexual side effects is recommended. Another strategy is antidepressant dose reduction, on the basis of a dose-response relationship in sexual side effects. Although common as a first-line approach and suggested by the American Psychiatric Association, this may precipitate symptomatic relapse and should be avoided in most patients with serious depression [16; 17; 18]. Taking a drug holiday by stopping the antidepressant for a few days has also been suggested [19]. This may be feasible with fluoxetine, owing to its long half-life, but it is not advised with other antidepressants, as patients can experience discontinuation symptoms, disruption of therapeutic effect, and worsening of depression symptoms [18].

Adding medications with mechanisms that offset the SSRI/SNRI side effects is a valid approach. 5-HT receptor antagonists or agonists or dopamine agonists are most commonly used for this purpose. Several trials have found favorable response with the 5-HT₂ and 5-HT₃ receptor antagonist mir-

tazapine, which broadly improves sexual side effects but can cause weight gain; the 5-HT_{2A} antagonist cyproheptadine, which alleviates SSRI-induced orgasm disruption but can cause sedation; the 5-HT_{1A} agonist buspirone; and the norepinephrine and dopamine agonist bupropion, which has the greatest evidence support and most extensive use for this indication [20; 21; 22; 23; 24].

MALE SEXUAL DYSFUNCTION

The incidence of male sexual dysfunction is much higher with SSRIs/SNRIs and much lower with antidepressants with primary adrenergic or dopaminergic mechanism. Ejaculatory delay is highly prevalent with serotonergic antidepressants. However, as noted, this can be a desired instead of adverse effect in men with premature ejaculation. In fact, the SSRI dapoxetine has become first-line therapy in the treatment of premature ejaculation [25; 26]. Certain antidepressants, particularly trazodone, may rarely cause priapism (prolonged and painful erection) [46].

Trazodone

The antidepressant trazodone inhibits central nervous system 5-HT uptake and increases central dopamine transmission without peripheral norepinephrine reuptake inhibition. While efficacy in erectile dysfunction has been inconsistent in controlled trials, trazodone may be effective in treating SSRI-induced sexual dysfunction [27; 28].

S-Adenosyl-L-methionine

Men with SSRI/SNRI-induced sexual dysfunction were randomized to daily S-adenosyl-L-methionine (SAME) or placebo for six weeks, while maintaining their SSRI/SNRI. Controlling for baseline sexual dysfunction severity and depression improvement from baseline, significantly greater reduction in arousal and erectile dysfunction was found with SAME versus placebo. SAME is used for mild-to-moderate depression, and the authors state improvements in male sexual dysfunction were likely independent of an antidepressant effect [29].

FEMALE SEXUAL DYSFUNCTION

Up to 96% of women taking antidepressants report at least one sexual side effect, with 20% to 50% qualifying as a distinct clinical problem [30; 31]. Antidepressants can prominently affect female sexual functioning and cause decreased libido, problems with arousal, and anorgasmia at prevalence rates as high as 80% [32].

Drugs that increase 5-HT negatively impact female sexual behavior, while decreases in 5-HT apparently facilitate sexual behavior facilitation. In particular, 5-HT_{1A} receptor agonists inhibit sexual behavior, while 5-HT₂ or 5-HT₃ receptors may exert a positive influence. There is substantial evidence to support a role for 5-HT in the modulation of female consummatory sexual experience, but studies on the role of 5-HT in other elements of female sexuality, such as desire, motivation, and sexual appetite, are much fewer [33].

Exercise

Exercise may improve antidepressant-related genital arousal problems. Because exercise increases genital arousal in healthy women most likely by increasing sympathetic nervous system (SNS) activity, a clinical trial measured the impact of exercise on genital arousal in 47 women taking antidepressants (68% SSRIs) and reporting antidepressant-related sexual arousal problems. Measures of genital and SNS arousal while watching an erotic film were compared when preceded by no exercise or 20 minutes of exercise 5 or 15 minutes before the film. Exercise prior to sexual stimuli was associated with increased genital arousal in both groups. Women reporting more severe sexual dysfunction had greater increases in genital arousal post-exercise. For women taking SSRIs, genital arousal was linked to SNS activity [34].

Bupropion

Adding bupropion 300 mg/day to a current SSRI regimen seems to improve sexual function in women experiencing sexual side effects [35]. Treatment of SSRI-induced female sexual dysfunction with adjunctive bupropion 300 mg/day for 12 weeks was studied in 218 women (25 to 45 years of age). Compared to placebo, the bupropion group showed greater improvement in mean total Female Sexual Function Index (FSFI) score (17.2 vs. 25.9) and in all FSFI domain scales. The bupropion group showed greatest increase from baseline in FSFI scores for desire (86.4%) and lubrication (69.2%) domains [36].

Testosterone

A randomized controlled trial evaluated transdermal testosterone therapy 300 mcg/day in 44 women (35 to 55 years of age) with SSRI/SNRI-emergent libido loss [37]. After 12 weeks, the increase in frequency of satisfactory sexual events and reduction in sexual distress were significantly greater with transdermal testosterone than placebo. No women withdrew because of androgenic adverse events. No improvement was found on the primary measure of sexual function, possibly from poor sensitivity in the study's measuring instrument. The researchers concluded that transdermal testosterone therapy benefits some women with SSRI/SNRI-associated libido loss [37].

Interesting results were found in a comparison of premenopausal women with major depressive disorder and a premenopausal, non-depressed control group. Before successful antidepressant treatment, mean total testosterone and bioavailable testosterone were significantly lower in the treatment group relative to controls. Following antidepressant treatment, these parameters significantly increased from baseline levels and were comparable to controls. The authors state the significant increase in testosterone to normal levels following antidepressant therapy suggests that testosterone may be involved in the etiology of depression for some women [38].

Sublingual Testosterone Plus Bupirone or Sildenafil

Androgen receptor gene polymorphism, encoded by the nucleotides cysteine, adenine, and guanine, may influence the effect of testosterone on female sexual functioning and treatment. In one study, 21 pre- and postmenopausal women with SSRI-induced sexual dysfunction received daily sublingual testosterone 0.5 mg, plus bupirone 10 mg or sildenafil 50 mg. Women using low-dose SSRIs showed marked improvement in sexual function from both treatments relative to placebo. Sublingual testosterone combined with sildenafil or bupirone may be beneficial in subgroups of women with SSRI-induced sexual dysfunction [39].

Bremelanotide and Flibanserin

Beginning in 2015, two medications have been approved for the treatment of hypoactive sexual desire disorder in premenopausal women—bremelanotide and flibanserin. Flibanserin is a mixed 5-HT_{1A} agonist/5-HT_{2A} antagonist, while bremelanotide is a synthetic heptapeptide with strong binding affinity and agonist action with melanocortin receptor 4. There is some evidence that flibanserin may be safely added to a stable SSRI or SNRI treatment regimen in premenopausal women with remitted or mild depression [49]. However, the efficacy of addressing SSRI/SNRI-associated sexual dysfunction was not analyzed. It is important to note that these medications are specifically approved to treat low female sexual desire not the result of the effects of a medication, so their use in the management of antidepressant-associated sexual dysfunction is off-label.

Saffron

Saffron (*Crocus sativus* L.) has shown beneficial aphrodisiac effects, but little is known of its efficacy in the management of medication-induced sexual dysfunction. A random controlled trial evaluated saffron 30 mg/day in 38 women with SSRI-induced

sexual dysfunction, stabilized on fluoxetine for major depression. After four weeks of treatment, the saffron group had significantly greater improvement in total FSFI score and arousal, lubrication, and pain domains, but not desire, satisfaction, or orgasm domains. Side effects were similar between the two groups. Saffron may safely and effectively improve some fluoxetine-induced sexual problems, including arousal, lubrication, and pain [40].

Maca Root

Maca root (*Lepidium meyenii*) has been suggested as an option for the management of antidepressant-related sexual side effects in postmenopausal women. In one small study, women given maca root were approximately twice as likely as the placebo group to experience remission of sexual side effects [52].

POST-TREATMENT ENDURING SEXUAL DYSFUNCTION

Post-SSRI sexual dysfunction is little known in the broader medical community and, when reported, has been partially attributed to psychologic factors [12]. However, the adverse impact from antidepressant-induced sexual side effects and post-SSRI sexual dysfunction may be worse than the condition for which treatment has been sought [41].

In the first review of post-SSRI sexual dysfunction in 2008, Bahrack and Harris challenged conventional wisdom that sexual side effects resolve with SSRI cessation, stating that research literature had failed to include systematic follow-up to support this assumption [42]. This emerging problem is supported by a convergence of case reports, consumer reports, and robust evidence from efficacy studies of healthy men documenting SSRI-induced delayed ejaculation persisting long after SSRI cessation. Internet drug consumer sites may provide a database of this qualitative information not captured within research paradigms or existing post-market pharmacovigilance mechanisms [42].

In 2014, the broader category of post-treatment enduring sexual dysfunction (PTESD) was investigated and 120 cases (mean age: 30.9 years) were identified. Highest rates occurred with SSRI agents (11.2% to 15.5%), venlafaxine (7.8%), isotretinoin (6.0%), and finasteride (5.2%). Women comprised 20% of SSRI cases, and all of the isotretinoin and finasteride cases occurred in men. PTESD occurred following medication exposure of 3 to 5,840 days, and a common feature was sexual side effect onset after medication was discontinued. The consequences of PTESD were severe, including several well-documented cases of suicide. The longest case was 18 years, from a brief exposure to fluoxetine at 18 years of age [43].

In a data report from 2017 including 300 cases of enduring sexual dysfunction, the highest rates of PTESD occurred with isotretinoin (18%), escitalopram (14%), citalopram (13.7%), and paroxetine (13.3%) [48]. The duration of the treatment ranged from a single dose to more than 16 years. The report also found that many cases of sexual dysfunction appeared or became worse when treatment came to an end. Subjects consistently reported difficulty maintaining romantic relationships and 30% reported that their work had been affected [48].

PTESD symptoms can include the entire spectrum of male and female sexual dysfunction, but the triad of penile or clitoral anesthesia, loss of libido, and loss of function is the core characteristic of PTESD, across all identified drug classes and agents [43; 44; 48]. Pleasureless orgasm has also been reported [45; 48].

Efforts to manage PTESD have involved serotonin and dopamine system modulation with the 5HT-1 agonist buspirone, the 5HT-2 and 5HT-3 antagonists trazodone and mirtazapine, and dopamine agonists (e.g., pramipexole, cabergoline, bupropion, dexamphetamine). Phosphodiesterase type 5 inhibitors, testosterone, ketamine, donepezil, and metformin have all been tried for PTESD. However, none of these have helped. This treatment-refractory characteristic may reflect epigenetic

changes in PTSD [43]. Additional research into the underlying etiology of persistent sexual dysfunction following antidepressant cessation will hopefully give insight into an effective treatment.

CONSIDERATIONS FOR NON-ENGLISH-PROFICIENT PATIENTS

In this multicultural landscape, interpreters are a valuable resource to help bridge the communication and cultural gap between clients/patients and practitioners. Discussions of depression and sexuality can be sensitive, and removing possible language barriers using professional interpreters is recommended for patients for whom English is not their first language. Interpreters are more than passive agents who translate and transmit information back and forth from party to party. When they are enlisted and treated as part of the interdisciplinary clinical team, they serve as cultural brokers who ultimately enhance the clinical encounter. In any case in which information regarding diagnostic procedures, treatment options and medication/treatment measures are being provided, the use of an interpreter should be considered.

CONCLUSION

Identifying and adhering to an effective antidepressant regimen can be challenging, and the presence of sexual side effects makes the task even more difficult. These side effects are relatively common, particularly with SSRIs/SNRIs, but they may be under-reported and undertreated as a result of the stigma surrounding mental health care and patients' and healthcare providers' reluctance to discuss sexual topics. This course has briefly outlined the demographics of antidepressant-associated sexual dysfunction and gender-specific manifestations. Enriching one's knowledge of sexual side effects and approaches to management will improve patients' adherence to antidepressant therapy and overall quality of life.

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