

Dr. Burghardt: Treating SSRI-induced sexual dysfunction in men

Sildenafil for SSRI-induced sexual dysfunction in women

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Mrs. L, age 27, has a history of major depressive disorder with symptoms of anxiety. She was managed successfully for 2 years with bupropion XL, 300 mg/d, but was switched to venlafaxine, titrated to 225 mg/d, after she developed seizures secondary to a head injury sustained in a car accident. After the switch, Mrs. L's mood deteriorated and she was hospitalized. Since then, she's received several medication trials, including paroxetine, 30 mg/d, a selective serotonin reuptake inhibitor (SSRI), and the tricyclic antidepressant (TCA) nortriptyline, 75 mg/d, but she could not tolerate these medications because of severe xerostomia.

After taking sertraline, 150 mg/d, for 8 weeks, Mrs. L improves and has a Patient Health Questionnaire score of 6, indicating mild depression. Her initial complaints of diarrhea and nausea have resolved, but Mrs. L now reports that she and her husband are having marital difficulties because she cannot achieve orgasm during sexual intercourse. She did not have this problem when she was taking bupropion. Her husband occasionally takes the phosphodiesterase type 5 (PDE5) inhibitor sildenafil before intercourse, and Mrs. L asks you if this medication will help her achieve orgasm.

DSM-IV-TR defines sexual dysfunction as disturbances in sexual desire and/or in the sexual response cycle (excitement, plateau, orgasm, and resolution) that result in marked distress and interpersonal difficulty.¹ Sexual dysfunction can occur with the use of any

antidepressant with serotonergic activity; it affects an estimated 50% to 70% of patients who take SSRIs.² Sexual dysfunction can occur with all SSRIs; however, higher rates of sexual dysfunction are found with citalopram, fluoxetine, paroxetine, and sertraline.³ Studies have suggested there may be a dose-side effect relationship with SSRI-induced sexual dysfunction.⁴

Several factors can increase a patient's risk of sexual dysfunction and should be considered before prescribing an antidepressant or when a patient presents with new or worsening sexual dysfunction (*Table 1, page 30*).⁵ In general, nonserotonergic agents such as bupropion, mirtazapine, and nefazodone are associated with lower rates of sexual dys-



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Practice Points

- Sexual dysfunction can arise from environmental, social, medical, or drug effects and **requires a multifaceted approach to treatment.**
- When possible, **take a baseline sexual dysfunction measurement** to assess if selective serotonin reuptake inhibitor use is correlated with onset or worsening of sexual dysfunction.
- **Nonpharmacologic options should be considered** before and during pharmacotherapy.
- Sildenafil **may be useful for treating anorgasmia** in women taking serotonergic antidepressants.
- Phosphodiesterase type 5 inhibitors are **not FDA-approved for sexual dysfunction in women.**

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Table 1

Risk factors for sexual dysfunction

Sex	Risk factors
Women	History of sexual, physical, or emotional abuse, physical inactivity
Men	Severe hyperprolactinemia, smoking
Both sexes	Poor to fair health, genitourinary disease, diabetes mellitus, cardiovascular disease, hypertension, increasing age, psychiatric disorders, relationship difficulties

Source: Reference 5

Clinical Point

Although not FDA-approved for treating sexual dysfunction in women, adjunctive PDE5 inhibitor treatment may be beneficial

function. The pharmacology of these agents explains their decreased propensity to cause sexual dysfunction. These agents increase levels of dopamine in the mesolimbic dopaminergic system either by blocking reuptake (bupropion) or antagonizing the serotonin subtype-2 receptor and facilitating disinhibition of decreased dopamine downstream (nefazodone and mirtazapine).

One option for treating antidepressant-induced sexual dysfunction in women is PDE5 inhibitors, which are used to treat erectile dysfunction (ED). These medications ameliorate ED by inhibiting degradation of cyclic guanosine monophosphate by PDE5, which increases blood flow to the penis during sexual stimulation. Although these medications are not FDA-approved for treating sexual dysfunction in women, adjunctive PDE5 inhibitor treatment may be beneficial for sexual dysfunction in females because similar mediators, such as nitric oxide and cyclic guanosine monophosphate, involved in the nonadrenergic-noncholinergic signaling that controls sexual stimulation in men also are found in female genital tissue.⁶

When treating a woman with SSRI-induced sexual dysfunction, consider non-pharmacologic treatments both before and during pharmacotherapy (Table 2).^{7,8} See this article at CurrentPsychiatry.com for a table that compares pharmacokinetics, side effects, and drug interactions of the 4 FDA-approved PDE5 inhibitors—avanafil, sildenafil, tadalafil, and vardenafil.

Limited evidence for sildenafil

Case reports, a few small open-label trials, and 1 prospective, randomized controlled

trial (RCT) have evaluated sildenafil as an adjunctive treatment for serotonergic antidepressant-associated sexual dysfunction in women.^{6,9} Nurnberg et al⁶ examined the efficacy of adjunctive sildenafil in women with SSRI-induced sexual dysfunction. This 8-week, placebo-controlled, double-blind, RCT used a flexible dose (50 or 100 mg), intention-to-treat design to assess the effect of sildenafil on 98 premenopausal women whose depression was in remission. Ten patients were taking the serotonin-norepinephrine inhibitor venlafaxine, 1 was taking the TCA clomipramine, and 87 were receiving an SSRI. Patients were instructed to take sildenafil or placebo 1 to 2 hours before sexual activity. The primary outcome was mean change from baseline on the Clinical Global Impression-Sexual Function (CGI-SF) scale.

Women taking sildenafil showed significant improvement compared with those taking placebo, with a treatment difference between groups of 0.8 (95% CI, 0.6 to 1.0; $P = .001$). Additionally, 23% of sildenafil-treated patients reported no improvement with the intervention, compared with 73% of patients receiving placebo. Secondary outcomes using 3 validated scales that evaluated specific phases of sexual function found that patients' orgasmic function significantly benefited from sildenafil treatment, while desire, arousal, and overall satisfaction were not significantly different.

Although these findings seem to support sildenafil for treating serotonergic antidepressant-associated sexual dysfunction in women, the study had a relatively small treatment effect in a well-defined patient population; therefore, replication in



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Table 2

Management strategies for SSRI-induced sexual dysfunction

Intervention	Comments
Nonpharmacologic	
Lifestyle modifications	Encourage healthy eating, weight loss, smoking cessation, substance abuse treatment, or minimizing alcohol intake to improve patient self-image and overall health
Cognitive-behavioral therapy	Patients can identify coping strategies for reducing symptom severity and preventing worsening sexual dysfunction
Sex therapy	May benefit patients with relationship difficulties
'Watch and wait'	Spontaneous resolving (or 'adaptation') of sexual dysfunction with antidepressants can take ≥ 6 months. Studies have found adaptation rates generally are low (~10%)
Pharmacologic	
Drug holiday	May be an option for patients taking antidepressants with shorter half-lives and patients taking lower doses. Be cautious of empowering patients to stop their own medications as needed
Dosage reduction	Serotonergic antidepressant-induced sexual dysfunction may be related to dose. Little research has been conducted on this method and the patient's clinical status must be considered
Dose timing	Instructing a patient to take the antidepressant after his or her usual time of sexual activity (eg, patients who engage in sexual activity at night should take the antidepressant before falling asleep). This may allow the drug level to be lowest during sexual activity
Switching medications	Case reports, retrospective studies, and RCTs suggest switching to a different antidepressant with less serotonergic activity may be appropriate, particularly if the patient has not responded to the current antidepressant
Adjunctive therapy	RCTs support adjunctive bupropion (≥ 300 mg/d) or olanzapine (5 mg/d) as treatment for SSRI-induced sexual dysfunction in women Studies have found no improvement in sexual functioning with adjunctive buspirone, granisetron, amantadine, mirtazapine, yohimbine, ephedrine, or ginkgo biloba in women
RCTs: randomized controlled trials; SSRI: selective serotonin reuptake inhibitor	
Source: Reference 7,8	

future trials and different patient populations is warranted. Overall, sildenafil was well tolerated, despite patient reports of headaches, flushing, visual disturbances, dyspepsia, nasal congestion, and palpitations. Finally, cost vs benefit should be considered; PDE5 inhibitors may not be covered by insurance or may require prior authorization.

CASE CONTINUED

Symptoms resolve

Bupropion is not an appropriate choice for Mrs. L because of her seizure risk. Mirtazapine is ruled out because in the past she experienced excessive somnolence that impaired

her ability to function. You are not comfortable prescribing nefazodone because of its risk of hepatotoxicity or suggesting that Mrs. L take a "drug holiday" (stop taking any antidepressants for a short period) because of the risk of depressive relapse. You suggest that Mrs. L continue to take sertraline because sometimes antidepressant-induced sexual dysfunction resolves after ≥ 6 months of treatment with the same agent, but she is adamant that her relationship with her husband will deteriorate if she waits that long. She also declines cognitive-behavioral therapy because her job doesn't allow the time or flexibility to commit to the sessions.

Clinical Point

In one small RCT, women's orgasmic function significantly benefited from sildenafil, while desire and arousal were not different

See this article at
[CurrentPsychiatry.com](https://www.psychiatry.com)
 for a table that compares
 4 FDA-approved PDE5
 inhibitors

Clinical Point

Overall, sildenafil was well tolerated, despite patient reports of headaches, flushing, visual disturbances, and other effects

Related Resources

- Nurnberg HG. An evidence-based review updating the various treatment and management approaches to serotonin reuptake inhibitor-associated sexual dysfunction. *Drugs Today (Barc)*. 2008;44(2):147-168.
- NIH Medline Plus. Sexual problems in women. www.nlm.nih.gov/medlineplus/sexualproblemsinwomen.html.
- Sturpe DA, Mertens MK, Scoville C. What are the treatment options for SSRI-related sexual dysfunction? *J Fam Pract*. 2002;51(8):681.

Drug Brand Names

Amantadine • Symadine, Symmetrel	Nefazodone • Serzone
Avanafil • Stendra	Nitroglycerin • Nitrostat
Bupropion • Wellbutrin, Zyban	Nortriptyline • Pamelor
Bupirone • BuSpar	Olanzapine • Zyprexa
Citalopram • Celexa	Paroxetine • Paxil
Clomipramine • Anafranil	Sertraline • Zoloft
Fluoxetine • Prozac	Sildenafil • Viagra
Granisetron • Kytril	Tadalafil • Cialis
Mirtazapine • Remeron	Vardenafil • Levitra
	Venlafaxine • Effexor

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You prescribe sildenafil, 50 mg, and instruct Mrs. L to take 1 tablet 1 to 2 hours before

sexual activity. This treatment improves her ability to achieve orgasm. She tolerates the drug well and after 8 weeks of treatment her CGI-SF score improves from 6 at baseline, indicating extreme dysfunction, to 2, indicating normal function. Ten months into her sertraline treatment, Mrs. L discovers she no longer requires sildenafil to achieve orgasm.

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Table

Phosphodiesterase type 5 inhibitors: A comparison

Medication	Dose range ^a	Pharmacokinetics	Side effects	Significant drug interactions
Avanafil	50 to 200 mg, 30 minutes before sexual activity	Bioavailability: N/A (high-fat meal delays Tmax by 60 minutes and reduces Cmax by 24% to 39%; clinically insignificant) Half life: 5 hours Metabolism: CYP3A4	Headache, flushing, nasal congestion, nasopharyngitis, backache	Strong CYP3A4 inhibitors (increased avanafil levels) Contraindicated within 12 hours of nitrate use (eg, nitroglycerin)
Sildenafil	25 to 100 mg, 1 to 2 hours before sexual activity	Bioavailability: 41% (food/high-fat meal delays Tmax by 60 minutes and reduces Cmax by 29%) Half life: 4 hours Metabolism: CYP3A4	Headache, flushing, erythema, indigestion, insomnia, visual disturbances (blue vision)	Strong CYP3A4 inhibitors (increased sildenafil levels) Contraindicated within 24 hours of nitrate use
Tadalafil	10 to 20 mg, 30 minutes before sexual activity	Bioavailability: N/A (not affected by food) Half life: 17.5 hours (duration of action up to 36 hours) Metabolism: CYP3A4	Headache, flushing, indigestion, nasal congestion, dizziness, myalgia, and back pain	Strong CYP3A4 inhibitors (increased tadalafil levels) Contraindicated within 48 hours of nitrate use
Vardenafil	5 to 20 mg, 30 minutes to 2 hours before sexual activity	Bioavailability: 15% for film-coated tablet (high-fat meal reduces Cmax by 18% to 50%) Half life: 4 to 5 hours Metabolism: CYP3A4	Headache, flushing, indigestion, nasal congestion, dizziness, visual disturbances (blue vision)	Strong CYP3A4 inhibitors (increased vardenafil levels) Contraindicated within 24 hours of nitrate use

^aTypical dose range for treatment of erectile dysfunction

Cmax: maximum concentration; CYP: cytochrome P450; Tmax: time to maximum concentration

Source: Micromedex® Healthcare Series [Internet database]. Greenwood Village, CO: Thomson Healthcare. Accessed October 10, 2012