Sex and antidepressants: When to switch drugs or try an antidote

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Antidepressants’ sexual side effects can often be managed—while preserving the antidepressant effect—by altering dosages, switching to another drug class, or adding an “antidote.” Understanding the benefits and risks of each strategy can help you:

- base treatment choices on your patient’s history and side-effect experience
- improve long-term compliance with antidepressant regimens.

### Effects vary by antidepressant class
Antidepressants may affect one or more phases of sexual functioning:

- desire (libido)
- arousal (erection or vaginal lubrication)
- orgasm/ejaculation.

Sexual symptoms linked to antidepressants range from diminished interest/arousal and delayed orgasm to heightened sexual functioning (Table 1). Resulting sexual dysfunction can impair quality of life and intimate relationships and discourage patients from taking antidepressants (Box).1,2

Although most reports have focused on SSRIs, all antidepressant classes have been associated with sexual dysfunction, with prevalence likely influenced by differences in neurotransmitter modulation (Table 2).1,3,4 The highest rates of sexual side effects have been reported with SSRIs, certain tricyclic antidepressants (TCAs), and monoamine oxidase inhibitors (MAOIs).

A recent study reported similarly high rates with mirtazapine, but its small sample size limits conclusions about side effect prevalence with this drug.1 Other studies have found significantly lower rates with bupropion and
nefazodone.

**TCAs'** sexual side-effect rates and types depend on how much each drug inhibits serotonin reuptake. Clomipramine appears to have the highest rates of sexual dysfunction—particularly anorgasmia—probably because it inhibits the serotonin transporter more than do other TCAs. In TCAs with lesser effects on serotonergic neurotransmission, alpha-adrenergic and cholinergic receptor blockade may cause sexual side effects—particularly erectile dysfunction (ED).

**Cholinergic agonists** such as bethanechol, 10 to 50 mg/d, may reverse sexual dysfunction caused by anticholinergic effects. Cyproheptadine—a nonselective serotonin receptor antagonist—has also shown benefit at 4 to 12 mg/d in treating TCA-related sexual side effects.

**MAOIs.** Sexual side effects appear to be more prevalent with MAOIs than with TCAs, perhaps similar to the rate seen with SSRIs. MAOIs directly increase serotonergic neurotransmission, and their substantial alpha-adrenergic antagonist effects may also produce sexual side effects.

Waiting for symptoms to subside may be appropriate, as anorgasmia caused by MAOIs may remit spontaneously. Sildenafil and cyproheptadine may reverse MAOI sexual side effects, although serious toxicity has been reported in a patient taking cyproheptadine and an MAOI.

**SSRIs.** Increased serotonergic neurotransmission is widely believed to cause SSRI sexual side effects. Resulting secondary effects—such as inhibited central dopamine release, increased prolactin secretion, and inhibited nitric oxide synthesis—may also play important roles.

In general, SSRIs appear to alter sexual functioning in 40% to 60% of patients—both men and women. Anorgasmia is the most commonly reported sexual symptom.

Although all SSRIs are associated with sexual dysfunction, some studies have found higher rates with paroxetine. One study associated paroxetine with significantly higher rates of ED compared with other SSRIs. The authors attributed this finding to paroxetine’s greater anticholinergic effects or to its directly decreasing nitric oxide synthesis.

**SSRI management strategies**

**Waiting.** The simplest, safest way to manage SSRI-related sexual dysfunction is to wait and see if side effects resolve spontaneously. Sexual side effects improve without treatment in approximately 20% of cases, although improvement is often incomplete. Moreover, several months may pass before symptoms diminish adequately, making this strategy impractical for patients with substantial sexual dysfunction.
**Dosing changes.** Because SSRIs’ sexual side effects appear to be dose-related, carefully reducing the dosage may reduce sexual dysfunction without compromising antidepressant efficacy. This strategy is most likely to sustain remission when you avoid dosages that have proven ineffective. For example, consider a patient who achieves remission of depressive symptoms when fluoxetine is increased from 20 to 40 mg/d. If sexual side effects emerge at 40 mg/d, relapse may be less likely at 30 mg/d than at 20 mg/d.

Other strategies that lessen sexual side effects for some patients include:

- dividing the dosage
- delaying dosing until after sexual activity
- allowing 2- to 3-day “drug holidays” over weekends, when sexual activity is more likely to occur.

Drug holidays probably would not help patients taking fluoxetine, as plasma concentrations would not drop sufficiently in 2 to 3 days to alleviate sexual side effects. Also, drug holidays are presumably safest for patients who are in maintenance treatment, are asymptomatic, and have no history of rapid symptom recurrence or withdrawal effects when discontinuing SSRIs.

**Switching medications.** When sexual side effects do not resolve spontaneously or with dose reduction, consider switching to an antidepressant with a lower incidence of sexual dysfunction.

Bupropion has been shown to improve sexual functioning in patients treated for depression. One study reported improved sexual functioning in patients with SSRI-induced sexual side effects who were switched to bupropion. Similar studies have shown benefits with substituting nefazodone or mirtazapine for an SSRI.

These uncontrolled studies suggest that switching some patients to a non-SSRI antidepressant may diminish sexual side effects while continuing antidepressant efficacy. Bupropion or nefazodone may be more effective for this purpose, as mirtazapine showed a high rate of sexual side effects in a large observational study.

Use caution when switching from an SSRI to nefazodone, as cytochrome P-450 2D6 isoenzyme inhibition may increase levels of mCPP—a nefazodone metabolite with anxiogenic properties. To avoid this interaction, taper the SSRI before starting nefazodone.

Switching medications may not be ideal for patients with an unacceptable depression relapse risk, characterized by severe dysfunction, suicidal ideation, or past treatment resistance.
Using an antidote

Adding a second medication to antidepressant therapy is another strategy to consider. An antidote seems most practical when:

• a patient clearly benefits from an antidepressant regimen
• the risk of losing efficacy with a new medication is high
• reducing the dosage or waiting for sexual dysfunction to resolve spontaneously are impractical or have failed.

Most reports of sexual side effect antidotes have been open-label trials of drugs thought to:

• improve some aspect of sexual functioning as with dopamine or noradrenergic agonists)
• or block antidepressant mechanisms suspected of contributing to sexual side effects (as with serotonin receptor antagonists or cholinergic agonists).

Unfortunately, controlled trials with many of these strategies have been less than promising (Table 3). Several trials reported high placebo-response rates—which may complicate assessment of any sexual side effect treatment—and most produced negative results. Two notable exceptions have been sildenafil and bupropion.

Sildenafil, a phosphodiesterase-5 inhibitor, showed greater benefit than placebo in a prospective trial of 90 depressed men (mean age 45) diagnosed with sexual dysfunction caused by an SSRI. The men took sildenafil, 50 to 100 mg, 1 hour before sexual activity.

After 6 weeks, 55% of sildenafil-treated patients were rated as much/very much improved on the Clinical Global Impression Scale adapted for Sexual Function, compared with 4% of those taking placebo, a statistically significant difference. Measures used to assess sexual function showed that arousal, erectile function, and orgasm improved significantly, with a lesser effect on desire. This suggests that adjunctive sildenafil reduces SSRIs’ sexual side effects, and this benefit may extend beyond improving ED.

Sildenafil improves peripheral vasodilatation due to smooth muscle relaxation caused by enhanced nitric oxide release. Other sexual side effects—such as delayed orgasm/ejaculation—may improve because of indirect effects of increased penile and clitoral blood flow caused by vasodilatation.

Sildenafil treatment was well-tolerated; the most common side effects were headache (40.5%), flushing (16.7%), dyspepsia (7.1%), nasal congestion (11.9%), and transient visual disturbances (11.9%).
**Bupropion** has also shown therapeutic efficacy for SSRI-related sexual dysfunction in a 4-week, placebo-controlled trial of 55 patients (mean age 39) diagnosed with SSRI-induced sexual dysfunction. Compared with the placebo group, those receiving add-on bupropion SR, 150 mg bid, improved significantly more in sexual desire and frequency of sexual activity, as measured by the Changes in Sexual Functioning Questionnaire.

Measures of arousal, orgasm, and global sexual functioning did not differ significantly between the two groups. Bupropion added to SSRI treatment was well-tolerated; most-commonly reported side effects were irritability (12%), dry mouth (12%), and headache (15%).

**Other ED treatments.** Two additional phosphodiesterase-5 inhibitors have become available in the past year. Like sildenafil, tadalafil and vardenafil are indicated for treating ED. They may be useful as alternatives for patients who do not respond to or tolerate sildenafil, although no published studies have examined their use in antidepressant-induced sexual dysfunction.

**Recommendation.** Based on the evidence, it seems reasonable to start with bupropion or sildenafil when considering an antidote for sexual side effects caused by SSRIs or other medications with strong serotonergic effects. Determining which agent would be “first-line” depends on patient factors, as summarized in Table 4.30,31 For example:

- Bupropion has been reported to augment SSRIs’ antidepressant effects and thus may provide added benefit in patients with residual depressive symptoms.

- Bupropion is more effective than sildenafil for improving sexual desire and thus would be preferred for patients in whom this sexual dysfunction symptom is prominent.

- Sildenafil appears to be more effective than bupropion for improving overall sexual satisfaction for men experiencing substantial erectile dysfunction.

**References**

5. Monteiro WO, Noshirvani HF, Marks IM, Lelliott PT. Anorgasmia from clomipramine in
Related resources


Drug brand names

Amantadine • Symmetrel
Bethanechol • Duvoid, Urecholine, Urabeth
Bupropion SR • Wellbutrin SR
Buspirone • Buspar
Citalopram • Celexa
Clomipramine • Anafranil
Cyproheptadine • Periactin
Fluoxetine • Prozac
Granisetron • Kytril
Methyphenidate • Ritalin
Mianserin • Bolvidon, Norval
Mirtazapine • Remeron
Nefazodone • Serzone
Paroxetine • Paxil
Pramipexole • Mirapex
Ropinirole • Requip
Sertraline • Zoloft
Sildenafil • Viagra
Tadalafil • Cialis
Vardenafil • Levitra
Venlafaxine • Effexor

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