

Sexual Functioning and SSRIs

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This article reviews the literature concerning the relationship between sexual functioning and selective serotonin reuptake inhibitors (SSRIs). Reduced sexual functioning is a common depressive symptom that typically improves after successful antidepressant treatment. On the other hand, sexual dysfunction has been observed in a substantial proportion of patients treated with all classes of antidepressants. In particular, SSRI use has been shown to be associated with sexual dysfunction. A number of pharmacologic interventions have been found to be helpful in anecdotal case reports. Unfortunately, the lack of placebo-controlled studies in this area limits our ability to draw firm conclusions on the efficacy of such interventions. Three classes of drugs have primarily been used to counteract sexual side effects of SSRIs: serotonin receptor antagonists, α_2 -adrenergic receptor antagonists, and dopaminergic agents. An open trial from our group suggests the potential usefulness of oral sildenafil in the treatment of antidepressant-associated sexual side effects, but further studies are needed.

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Changes in sexual functioning (in particular, diminished or absent libido) can be symptoms of depression.¹ When sexual dysfunction is an integral component of a depressive disorder, one would expect that as depression improves with antidepressant treatment, so too will sexual function.² However, emergence or exacerbation of sexual dysfunction as a side effect of antidepressant therapy has been reported with some drugs in all antidepressant classes, including monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants (TCAs), and selective serotonin reuptake inhibitors (SSRIs).^{3,4} The most common symptoms of sexual dysfunction reported by both men and women during antidepressant treatment are listed in Table 1.¹

The emergence or the worsening of preexisting sexual dysfunction among patients treated with antidepressants is typically accompanied by psychological and behavioral changes in both those who suffer from it and their partners. Table 2 lists the potential consequences of sexual dysfunction as a result of antidepressant treatment.⁵

Distinguishing between sexual dysfunction as a symptom of major depression or as a side effect of antidepressant therapy poses a challenge to the physician.¹ The first

step is to take a careful medical and medication history to assess conditions, such as diabetes, and the use of other medications known to affect erectile function, such as antihypertensives. When appropriate, the patient can be referred to a urologist or internist. Generally, if a patient reports a change in sexual functioning within 8 to 12 weeks of starting treatment with an antidepressant, it is highly probable that it is a side effect of the medication.

Psychiatrists and primary care physicians need to be aware of the prevalence of sexual dysfunction associated with antidepressant treatment and to specifically assess sexual functioning in these patients in order to institute interventions.

PREVALENCE OF SEXUAL DYSFUNCTION WITH SSRIs

SSRIs are the most prescribed pharmacologic treatments for depressive disorders worldwide. Although they have a common mechanism of action, their pharmacologic profiles differ; therefore, some of the SSRIs are associated with higher frequency of sexual dysfunction than others.

A retrospective study by Shen and Hsu⁶ showed that 30% of 110 women receiving SSRIs experienced sexual side effects, including loss of libido, delayed orgasm, or anorgasmia. In this study, no statistically significant differences were found in frequency of sexual side effects for fluoxetine, paroxetine, and sertraline. Another retrospective study found an overall rate of sexual dysfunction of 16% among 596 men and women, with 23% of men and 13% of women receiving SSRIs reporting sexual side effects.⁷ The most frequent sexual dysfunction reported by the male patients was difficulty in achieving orgasm (65%).

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Table 1. Most Common Sexual Side Effects Reported During Antidepressant Treatment^a

Erectile dysfunction
 Diminished libido
 Arousal difficulties
 Delayed or absent orgasm
 Ejaculatory dysfunction
 Anorgasmia

^aFrom Lane.¹

A prospective study by Jacobsen⁸ showed that 34% of 160 patients who were successfully treated for depression with fluoxetine reported the onset of sexual side effects, including decreased libido, decreased sexual function, or both. Another prospective study assessed treatment-emergent sexual side effects in 42 patients receiving paroxetine, sertraline, or fluoxetine using the Rush Sexual Inventory Scale,⁹ a systematic inquiry approach. Of those patients, 60% of men and 57% of women experienced treatment-emergent sexual dysfunction. In men, the most commonly reported changes in sexual function were delay or loss of ability to achieve orgasm and decreased intensity of orgasm.

In a double-blind, placebo-controlled trial of 128 patients treated for major depression with an SSRI, 25% of paroxetine-treated patients and 7% of fluoxetine-treated patients reported treatment-emergent sexual dysfunction, with this difference being statistically significant ($p < .05$).⁴

MANAGEMENT OF ANTIDEPRESSANT-INDUCED SEXUAL DYSFUNCTION

A number of interventions aimed at managing antidepressant-induced sexual dysfunction are available to the clinician. Such interventions can be broadly classified into 3 groups: dose reduction/switching, nonpharmacologic (psychotherapeutic) interventions, and use of concomitant medications (on either a daily or p.r.n. basis). Side effects that occur early in treatment frequently will diminish over time, so clinicians may first choose to wait and see whether an intervention is truly necessary.

Dose Reduction/Switching

Sexual side effects appear to be dose-related and may be improved by a reduction in dosage.¹⁰ This approach, of course, carries the risk of decreasing the antidepressant dose to subtherapeutic levels and should therefore be used with caution. Another approach is to switch to an antidepressant associated with less frequent sexual side effects than the SSRIs. However, this path necessitates that patients be closely monitored after switching to the new antidepressant to ensure that antidepressant efficacy is maintained. In addition, a switch to another antidepressant is typically accompanied by a potentially disruptive period when the benefits of the discontinued medication are faded

Table 2. Potential Consequences of Antidepressant-Induced Sexual Dysfunction^a

Psychological distress
 Reduced quality of life
 Self-esteem issues
 Relationship difficulties
 Feelings of rejection in partner
 Diminished motivation to approach partner in a relationship or to seek a partner
 Noncompliance with drug treatment

^aFrom Fava et al.⁵

ing while the new medication has not yet shown significant clinical effects. For this reason, the switching strategy is typically used only in nonresponders and partial responders experiencing sexual side effects and not among patients who have shown robust responses to a particular antidepressant.

Nonpharmacologic (Psychotherapeutic) Interventions

Although behavioral and cognitive-behavioral techniques have been used extensively by sex therapists for decades, little is known about the efficacy of these approaches in antidepressant-induced sexual dysfunction. Thus, a great need exists for studies on these types of interventions among populations treated with antidepressants and experiencing sexual side effects.

Use of Concomitant Medications (daily or p.r.n.)

The use of concomitant medications aimed at managing sexual side effects is based primarily on proposed mechanisms involving certain neurotransmitter systems and receptor subtypes and has been widely reviewed.¹ For example, a proposed mechanism for the occurrence of sexual dysfunction during SSRI treatment is that of the stimulation of serotonin 5-HT₂ and 5-HT₃ receptors. This, in turn, suggests that the use of medications that block those receptors may help with this type of side effect. Three general groups of medications are used in the treatment of antidepressant-induced sexual dysfunction: α_2 -adrenergic receptor antagonists, serotonin 5-HT₂ or 5-HT₃ receptor antagonists, and dopaminergic agents.

While some pharmacologic interventions are used on a daily basis, other medications are taken as needed (p.r.n.) to counteract the sexual side effects of SSRIs. The p.r.n. approach is acceptable to many patients since it appears to be less intensive and to decrease the possibility of noncompliance with treatment (e.g., patients tend to associate the idea of sexual activity with that of taking the counteracting medication). An additional advantage of a p.r.n. intervention is that the placebo effect may be potentiated. On the other hand, because the patient typically takes the medication 30 to 60 minutes before engaging in sexual activities, planning is necessary. This course of action may decrease the spontaneity of sex and may result in partners

Table 3. Anecdotal Reports Concerning the Potential Usefulness of Agents in the Management of Antidepressant-Induced Sexual Dysfunction

The α_2 -adrenergic receptor antagonist yohimbine ¹⁴
The serotonin 5-HT ₂ receptor antagonist nefazodone ¹⁵
The serotonin 5-HT ₂ receptor antagonist cyproheptadine ¹⁶
The serotonin 5-HT ₃ receptor antagonist granisetron ¹⁷
The α_2 -adrenergic receptor antagonist and the serotonin 5-HT ₂ and 5-HT ₃ receptor antagonist mirtazapine ¹⁸
The dopaminergic agents amantadine ¹⁹ and pramipexole ²⁰
The psychostimulants dextroamphetamine and methylphenidate ²¹
The dopaminergic/noradrenergic agent bupropion ²²
<i>Ginkgo biloba</i> ²³
Sildenafil ^{24,25}

feeling pressured to have sex or “to perform” at a designated time.

When a medication is instead taken daily to counteract the unwanted sexual side effects of antidepressants, no pre-sex planning is required, perhaps allowing for greater spontaneity and a greater comfort level of both patient and partner. Taking this medication on a daily basis, however, will be more costly, and compliance with both antidepressant and concomitant therapy may become an issue. Finally, the frequency of sexual activity may seem disproportionate to the intensity of treatment, and the potential for side effects and drug-drug interactions may be increased with this approach.

Unfortunately, most reports of efficacy of medications for treating sexual dysfunction are only anecdotal, and no placebo-controlled trials of these interventions, with the exception of the studies by Michelson et al.,¹¹ Masand et al.,¹² and Nelson et al.,¹³ have been published. The lack of a placebo control limits our ability to draw firm conclusions on the efficacy of any of these interventions, as the placebo response rate, as suggested by the findings of Michelson et al.¹¹ and Nelson et al.,¹³ is fairly high in this patient population. Table 3 lists the agents that have been shown to be associated with improvement of antidepressant-induced sexual dysfunction in anecdotal reports. In addition to the α_2 -adrenergic receptor antagonists, the serotonin 5-HT₂ or 5-HT₃ receptor antagonists, and the dopaminergic agents, recent reports have suggested the usefulness of *Ginkgo biloba*²³ and oral sildenafil citrate.^{24,25}

Several open trials of pharmacologic interventions aimed at managing antidepressant-induced sexual dysfunction have been reported. In a study by Jacobsen,⁸ 8 of 9 patients reported improvement in SSRI-induced sexual dysfunction with yohimbine (5.4 mg t.i.d.), although 2 withdrew owing to adverse events. One issue related to the use of yohimbine is the possibility that this drug will trigger panic attacks in patients with a history of these attacks, and yohimbine can therefore cause patients significant anxiety. In a study using bupropion,²⁶ 66% of 47 patients reported improvement in sexual function. In another study

with bupropion,²⁷ 50% of 8 patients reported marked improvement in sexual dysfunction. Although a 3-week, double-blind study¹² failed to show any statistically significant difference in efficacy between bupropion sustained release, 150 mg once daily, and placebo among 30 patients with SSRI-induced sexual dysfunction, the short duration of the study and the use of a relatively low dose of bupropion once daily limit the generalizability of these findings. A study by Nelson et al.¹³ failed to show a significant difference in efficacy between the serotonin 5-HT₃ receptor antagonist granisetron (1–1.5 mg) and placebo among 20 patients with antidepressant-induced sexual dysfunction. Finally, the use of *Ginkgo biloba*²⁸ was associated with a 76% response rate among men treated for antidepressant-induced sexual dysfunction in a study of 30 men.

A retrospective study among patients with SSRI-induced sexual dysfunction found the response rates of 71% for yohimbine, 40% for cyproheptadine, and 26% for amantadine.⁷ Although treatments were not randomized, making accurate comparisons of the response rates across these 3 agents impossible, the results are consistent with the findings of the double-blind prospective study¹¹ on amantadine and buspirone that found no difference between study drugs and placebo for treatment of SSRI-induced sexual dysfunction.

On the other hand, a double-blind study²⁹ found buspirone (20–60 mg/day) superior to placebo in treating sexual dysfunction (response rates: 58% vs. 30%) among 47 patients treated with SSRIs. Since this study included only patients who had SSRI-induced sexual dysfunction but were also nonresponders to the SSRI treatment, one cannot rule out the possibility that the greater improvement in sexual dysfunction with buspirone was due to the augmenting effect of this drug on the depression itself.

Open Trial of Oral Sildenafil Citrate

We⁵ have recently conducted an open trial of sildenafil in the treatment of 9 men with antidepressant-induced sexual dysfunction. Patients were determined to have sexual dysfunction according to their responses to the Massachusetts General Hospital Sexual Functioning Questionnaire, a brief self-rating scale recently validated by Labbate and Lare.³⁰ Patients were administered sildenafil at a daily dose of 57 ± 18 mg for at least 4 weeks, with a mean interval between visits of 6.1 ± 2.8 weeks.

Among the 9 men with antidepressant-induced sexual difficulties, sildenafil was associated with significant improvements in erectile dysfunction. Only 1 patient reported adverse events. None of the patients discontinued treatment prematurely. Interpretation of the results of this study is limited by the small sample size and the absence of a placebo arm; nonetheless, the results suggest that sildenafil is generally efficacious in men with antidepressant-induced erectile dysfunction. In further support of our find-

ings, a recently published subanalysis³¹ of combined data from 10 phase 2/3 double-blind, placebo-controlled dose trials of sildenafil in males with erectile dysfunction while on concomitant SSRIs showed a significantly greater improvement with sildenafil compared to placebo.

CONCLUSIONS

In summary, sexual dysfunction may be an integral component of depressive disorders and may improve with SSRI antidepressant treatment. However, sexual dysfunction is a frequent dose-dependent side effect of SSRIs, the most commonly prescribed antidepressants. Common management has been to wait for tolerance to develop, reduce the dosage, or, in the case of partial and nonresponse, switch to another antidepressant. Use of concomitant medications in the treatment of SSRI-induced sexual dysfunction is highly prevalent, but to date, no double-blind, placebo-controlled trials have established the efficacy of these treatments. Some treatments are associated with unwanted side effects, such as panic attacks with yohimbine. Simple, effective, and reliable treatment of SSRI-induced sexual dysfunction would improve patient compliance with antidepressant therapy, as well as their quality of life.

Drug names: amantadine (Symmetrel and others), bupropion (Wellbutrin), buspirone (BuSpar), cyproheptadine (Periactin), fluoxetine (Prozac), granisetron (Kytil), methylphenidate (Ritalin and others), mirtazapine (Remeron), nefazodone (Serzone), paroxetine (Paxil), pramipexole (Mirapex), sertraline (Zoloft), sildenafil (Viagra), trazodone (Desyrel and others), yohimbine (Yocon and others).

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