

Long-Term Side Effects of SSRIs: Sexual Dysfunction and Weight Gain

Robert M. A. Hirschfeld, M.D.

Selective serotonin reuptake inhibitors are associated with a variety of side effects, many of which are resolved during the first couple of weeks of treatment. Side effects that emerge or persist after 1 month of treatment include sexual dysfunction and weight gain. Although these adverse events are serious, they can be managed successfully if recognized early.

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Most side effects associated with selective serotonin reuptake inhibitors (SSRIs) occur early and are short lived. Gastrointestinal (GI) activation (e.g., nausea, vomiting, and diarrhea) and central nervous system (CNS) activation (e.g., insomnia, somnolence, and sedation) tend to disappear within the first week of treatment. In contrast to the GI and CNS side effects, sexual dysfunction and weight gain can persist and/or emerge after 1 month of treatment. Clinicians must consider possible side effects and educate patients to ensure compliance. Adverse events can be managed successfully if they are recognized early.

SEXUAL DYSFUNCTION

Sexual dysfunction is encountered frequently in the general population and is associated with a variety of general medical and psychiatric conditions. Possible causes of sexual dysfunction include a variety of general medical conditions (e.g., thyroid problems, cardiovascular problems, and diabetes) and the medicines used to treat them. Sexual dysfunctions are a common symptom in many psychiatric disorders, including mood disorders, anxiety disorders, and schizophrenia. Depression has long been associated with sexual problems, so much so that it is estimated that more than 50% of patients with major depressive disorder will have some sexual dysfunction as a symptom of their depression.¹

Patients with depression often experience a reduction in bodily drives, including libido and the ability to experience pleasure. Antidepressant therapy, although effective for treating the negative symptoms of depression, frequently induces or exacerbates sexual dysfunction.^{2–5} Determining whether or not sexual dysfunction exists prior to initiating antidepressant therapy, then, is an important first step in treating patients with depression. Patients who report a change in sexual functioning within 8 to 12 weeks of starting treatment with an antidepressant are most likely experiencing a side effect of the medication rather than a core symptom of the depression.⁶ Sexual dysfunction is generally not a major problem in acute treatment of depression. It is, however, a major problem that frequently leads to noncompliance in long-term treatment.

Selective serotonin reuptake inhibitors (e.g., citalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline), drugs that affect both serotonin and norepinephrine reuptake (e.g., mirtazapine, nefazodone, and venlafaxine), and bupropion, which enhances dopamine and norepinephrine neurotransmission, are among the newer antidepressants typically used to treat depression. Of these, SSRIs appear to be most likely to cause sexual dysfunction.^{2,5,7}

Although a low incidence of sexual side effects (i.e., < 15%) is stated on the product labeling for these newer antidepressants, a review of published studies between 1986 and 2000 suggests that between 30% and 60% of SSRI-treated patients may experience some form of treatment-induced sexual dysfunction,⁵ and data from another study placed the incidence with some antidepressants even higher (up to 70% of patients when directly questioned).⁸

Because patients rarely report sexual dysfunction spontaneously, systematic direct inquiry is a critical component of assessing sexual dysfunction both at baseline and throughout treatment.^{2,4} In one of the few studies to use consistent methodology and a validated rating scale, Clayton et al.⁴ confirmed that SSRIs and venlafaxine

From the Department of Psychiatry and Behavioral Sciences, University of Texas Medical Branch, Galveston.

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Corresponding author and reprints: Robert M. A. Hirschfeld, M.D., University of Texas Medical Branch, 1.302 Rebecca Sealy Building, 301 University Blvd., Galveston, TX 77555-0188 (e-mail: rohirsch@utmb.edu).

extended release (XR) are related to higher rates of sexual dysfunction than bupropion or nefazodone. This multicenter, cross-sectional study was conducted at 1101 U.S. primary care clinics and enrolled 4534 women and 1763 men who were already receiving antidepressant treatment with bupropion immediate release (IR), bupropion sustained release (SR), citalopram, fluoxetine, mirtazapine, nefazodone, paroxetine, sertraline, venlafaxine, or venlafaxine XR. The prevalence of sexual dysfunction was measured using the Changes in Sexual Functioning Questionnaire. The incidence of sexual dysfunction was highest for paroxetine (43%) and mirtazapine and venlafaxine (both 41%). The investigators then looked at a subgroup of this population in which any sexual problem could be attributed solely to the medication and not to other preexisting conditions. The subgroup consisted of 798 patients, aged 18 to 40 years, all of whom either had many sexual side effects during a previous antidepressant treatment or had never taken an antidepressant. Patients had to have had at least 3 months of treatment with the current antidepressant and could not be taking concomitant medications or have a comorbid medical illness that would affect sexual functioning. Also, patients must have had at least some sexual enjoyment in their past. In this subpopulation, the investigators found little difference among the SSRIs. The incidence of sexual dysfunction ranged from 7% to 30%, with patients taking SSRIs suffering from sexual dysfunction 4 to 6 times more often than patients treated with bupropion SR.

Management/Alleviation of Sexual Dysfunction

Educating patients about treatment options and possible side effects will help them anticipate side effects and adhere to treatments. Further, patients and clinicians must rule out other general medical conditions and the medicines prescribed to treat them, which could be contributing factors. The cause of the sexual dysfunction must be determined before attributing this negative effect to SSRI treatment. Once SSRI-induced sexual dysfunction has been identified, several strategies may be used to manage or alleviate symptoms.

Wait for tolerance to develop. This strategy may be best employed if sexual dysfunction is reported early in therapy, since it may be a temporary condition.

Reduce dose. Dose reduction may improve sexual function, but lowering the dose may decrease therapeutic efficacy and exacerbate depressive symptomatology. When reducing the current antidepressant dose, it is important to maintain the drug at a therapeutic level.

Take a drug holiday. A brief drug holiday may provide improvement in sexual functioning without the return of depressive symptoms. In a study⁹ of 30 outpatients with unipolar major depression (DSM-III-R) who reported worsening of sexual functioning during treatment with fluoxetine, paroxetine, or sertraline, patients discontinued

their SSRI after the Thursday morning dose and restarted on Sunday at 12:00 noon over the course of 4 consecutive weekends. Ratings for depression and sexual function were performed in person on Thursday and by telephone on Monday morning. Patients receiving paroxetine and sertraline reported "much" or "very much" improved sexual functioning for at least 2 of the 4 weekend drug holidays, while fluoxetine-treated patients reported no improvement (presumably due to the shorter half-lives of paroxetine and sertraline). Depression scores as measured by the Hamilton Rating Scale for Depression (HAM-D) at baseline and after discontinuation were not significantly different. Sexual dysfunction returned in all patients after they restarted their SSRIs.

Augment with another medication. In general, adjunctive pharmacotherapy involves dopamine agonists, serotonin (5-HT) antagonists, and α_2 antagonists (Table 1). Caution is warranted when utilizing adjunctive pharmacotherapy, however, because these agents have side effects of their own. Although anecdotal reports support their use, few controlled studies of these medications used in this way have been conducted.

Switch medications. Switching to an agent not associated with sexual dysfunction is another viable strategy. In an 8-week trial,¹⁰ 11 patients (8 women, 3 men) with a diagnosis of major depressive disorder (DSM-IV) were switched from their SSRI to bupropion SR. These patients had experienced remission of depression. From baseline to week 2, bupropion SR was added to the current SSRI therapy. From weeks 2 to 4, the SSRI was tapered and discontinued. From baseline to week 4, scores on the Changes in Sexual Functioning Questionnaire showed improved sexual functioning with no changes in HAM-D scores, indicating that depression had not returned. Six (55%) of 11 patients completed the substitution trial without adverse events.

Initiate treatment with an antidepressant that has a low incidence of sexual dysfunction. In patients who complain of sexual dysfunction as a symptom of their depression and in those who express concern about sexual dysfunction as a potential side effect of antidepressant therapy, it may be best to initially use a drug not associated with sexual dysfunction, such as bupropion or nefazodone. Results of several studies have shown the efficacy of bupropion SR in major depressive disorder with no exacerbation of sexual adverse events.¹¹⁻¹⁴ In a placebo-controlled, double-blind study¹¹ of 456 patients with recurrent major depressive disorder (DSM-IV), bupropion SR and fluoxetine were both effective against the symptoms of depression. At week 2 of this 8-week study, however, adverse sexual events were reported in the fluoxetine-treated group that were significant compared with the bupropion SR and placebo ($p < .001$) groups.

Comparisons of bupropion SR with sertraline in double-blind studies of patients with major depressive dis-

Table 1. Adjunctive Pharmacotherapy for SSRI-Induced Anorgasmia

Drug	Mechanism	Dosage (mg)
Cyproheptadine (as needed)	5-HT antagonist	4–8
Buspirone	5-HT _{1A} partial agonist	15–45
Mirtazapine	5-HT ₂ + 5-HT ₃ antagonist	15–45
Yohimbine (as needed)	Adrenergic antagonist (α_2)	5.4–10.8
Amantadine	Dopamine agonist	100–400
Methylphenidate	Dopamine agonist	10–30
Bupropion	Dopamine and norepinephrine reuptake agonist	75–100
Sildenafil	cGMP-specific PDE-5 inhibitor	50–150

Abbreviations: 5-HT = serotonin, cGMP = cyclic guanosine monophosphate, PDE-5 = phosphodiesterase-5, SSRI = selective serotonin reuptake inhibitor.

order have reaped similar results.^{12–14} Both agents were effective in treating depression, but sertraline was associated with sexual dysfunction, whereas bupropion SR was not.

WEIGHT GAIN

About 55% of adults in the United States (approximately 97 million people) are overweight or obese.¹⁵ In addition, the average American adult gains approximately 3 lb (1.35 kg) per year, which is the amount of weight gain associated with the newer antidepressants in most long-term studies. In fact, 5% to 10% of antidepressant-treated patients gain a substantial amount of weight (7% or more of their body weight). For depressed patients who have substantial weight gain, other causes, such as hypothyroidism or the medications used to treat other medical conditions, must be considered. The prevalence of weight gain associated with social, cultural, genetic, and other medical conditions is very difficult to differentiate from weight gain caused specifically by antidepressant treatment. To further confound the issue, reports of changes in weight among SSRI-treated patients have been inconsistent and vary among drugs.

An interesting and not-yet-understood phenomenon in some SSRI-induced weight change is the tendency toward weight loss during acute treatment followed by weight gain during long-term treatment.¹⁶ Fluoxetine, for example, is well recognized for anorectic action during short-term treatment; however, a review¹⁷ of long-term follow-up studies in patients with depression and in obese nondepressed subjects has shown the opposite effect.

Results of long-term studies of the effects of paroxetine on weight are also inconsistent.^{18–20} In one study,¹⁸ patients with major depressive disorder (DSM-IV) were randomly assigned to up to 32 weeks of treatment with paroxetine, sertraline, or fluoxetine. A significantly higher mean percentage of change in weight from baseline to endpoint was found among paroxetine-treated patients (+3.6%) compared with a small mean increase in weight in sertraline-

treated patients (+1.0%), while a slight mean decrease in weight in fluoxetine-treated patients (–0.2%) was reported. A significantly higher proportion of paroxetine-treated patients (25.5%) gained $\geq 7\%$ in weight compared with the other treatment groups (sertraline, 4.2%; fluoxetine, 6.8%). Yet, in a placebo-controlled study¹⁹ of paroxetine in 566 patients with generalized anxiety disorder (DSM-IV), weight gain was not listed as a side effect after 24 weeks of treatment at 20 to 60 mg/day.

Weight gain during antidepressant treatment may be associated with improvement in patients who have weight loss as a symptom of depression or it may be a residual symptom in patients who overeat when depressed.²¹ Weight gain that continues after depressive symptoms have remitted is likely to be a side effect of antidepressant treatment and frequently leads to premature discontinuation of a therapy that provided an otherwise favorable response. Many of the newer antidepressants, including the SSRIs and bupropion, have some effect on weight change. Recovery from depression or clinical improvement,²² appetite increase or carbohydrate craving,²³ and changes in 5-HT_{2C} receptor activity²⁴ are the possible mechanisms for SSRI-induced weight gain.

Management/Alleviation of Weight Gain

As a first step, educating patients about treatment options and possible side effects will help them anticipate side effects and adhere to treatments. Further, patients and clinicians must rule out increases in weight caused by the psychiatric illness itself or general medical conditions (e.g., hypothyroidism) and the medications prescribed to treat them. The cause of the weight gain must be determined before attributing this negative effect to SSRI treatment. Several steps can then be initiated to manage treatment-emergent weight gain.

Improve diet and initiate an exercise program. Weight gain can be managed with a healthy diet and exercise if they are employed early.

Initiate adjunctive medication. Adjunctive pharmacotherapy is also an option. The stimulants topiramate and sibutramine can help to reduce weight in patients who have experienced antidepressant-induced weight gain. Actively treating the side effects of a drug to which the patient has shown an otherwise good response may have significant benefits over switching to an alternative treatment. In an attempt to induce weight loss among 15 patients with anxiety disorder (DSM-IV) who had experienced SSRI-induced weight gain (mean \pm SD = 13.0 \pm 8.4 kg [28.6 \pm 18.5 lb]),²⁵ open-label topiramate was added to the SSRI regimen at a starting dose of 50 mg/day and titrated up to a mean \pm SD dose of 135.0 \pm 44.1 mg/day for approximately 10 weeks. Patients lost a mean \pm SD of 4.2 \pm 6.0 kg (9.3 \pm 13.3 lb). Although these results support the use of topiramate in managing SSRI-induced weight gain, the open-label design and uncontrolled as-

pects (for example, changes in diet or physical activity) indicate a need for further investigation.

Switch to a medication that is not associated with weight gain. Bupropion is not associated with weight gain and may be an appropriate drug to switch to for many patients. Both short-term²⁶ and long-term²⁶⁻²⁸ studies have demonstrated a modest weight-reducing to weight neutral effect in both the standard and SR formulations.

In a long-term relapse-prevention study²⁶ of patients with major depression, responders to open-label bupropion SR (N = 423) were randomly assigned to 44 weeks of double-blind treatment with bupropion SR (300 mg/day) or placebo. The mean changes from baseline weight during the double-blind phase in the bupropion SR group were statistically significant compared with baseline ($p < .001$).

Initiate treatment with an antidepressant that has a low incidence of weight gain. As with sexual dysfunction, patients concerned about weight gain may be more compliant with antidepressant treatment if the initial treatment strategy involves an agent not associated with weight gain. Patients diagnosed with obesity (body mass index = 30 to 44 kg/m²) who had depressive symptoms (Beck Depression Inventory scores between 10 and 30) but not a current diagnosis of major depression were enrolled in a 26-week double-blind, placebo controlled study evaluating the efficacy of bupropion SR in reducing weight and depressive symptoms.²⁷ In addition to bupropion SR therapy, a 500-kcal/day-deficit diet was instituted. The initial dose of bupropion SR was 300 mg/day but was increased to 400 mg/day for patients who had lost < 5% of baseline weight at week 12. The bupropion SR group (N = 193) lost an average of 4.4 kg (9.8 lb) 4.6% of baseline weight compared with 1.7 kg (3.8 lb) 1.8% of baseline weight lost by the placebo group ($p < .001$, last observation carried forward). More patients in the bupropion SR group than in the placebo group lost at least 5% of baseline weight ($p < .05$ at week 4; $p < .001$ at weeks 6 to 26). In addition, depressive symptoms improved more in the bupropion SR group than in the placebo group among patients with a history of major depression ($p < .05$ at weeks 4 to 26). Improvement in depressive symptoms was associated with weight loss $\geq 5\%$ regardless of treatment ($p < .0001$).

SUMMARY

Several methods for managing treatment-emergent sexual dysfunction have been successful. One method is to reduce the current antidepressant dose while maintaining the drug at a therapeutic level. Drug holidays can be useful in some patients who are compliant and don't have significant problems with discontinuation. In general, adjunctive pharmacotherapy with stimulants can be extremely helpful. Switching to or initiating treatment with an antidepressant that is associated with a low incidence of

treatment-emergent sexual dysfunction should also be considered.

Similarly, treatment-emergent changes in weight may be managed by first discussing weight gain as a possible side effect with the patient, and if it is an unacceptable risk for the patient, begin treatment with an agent less likely to induce weight gain. For patients who have substantial weight gain, first rule out other causes such as hypothyroidism or other medications that can cause an increase in weight. Weight gain can be managed effectively with patient education, a healthy diet, and exercise if these strategies are employed early. Adjunctive pharmacotherapy and switching to an antidepressant that is not associated with weight gain are also effective strategies.

The positive news is that long-term treatment with antidepressants, particularly the newer agents, is not fraught with a significant side effect burden. While sexual dysfunction and weight gain can be serious side effects of treatment, they can be managed if recognized and dealt with early in treatment.

Drug names: amantadine (Symmetrel and others), bupropion (Wellbutrin and others), buspirone (BuSpar and others), citalopram (Celexa), cyproheptadine (Periactin and others), fluoxetine (Prozac and others), methylphenidate (Ritalin, Metadate, and others), mirtazapine (Remeron and others), nefazodone (Serzone and others), paroxetine (Paxil and others), risperidone (Risperdal), sertraline (Zoloft), sibutramine (Meridia), sildenafil (Viagra), topiramate (Topamax), venlafaxine (Effexor).

Disclosure of off-label usage: The author of this article has determined that, to the best of his knowledge, amantadine, bupropion, buspirone, cyproheptadine, methylphenidate, mirtazapine, sildenafil, and yohimbine are not approved by the U.S. Food and Drug Administration for the treatment of SSRI-induced sexual dysfunction and sibutramine and topiramate are not approved for the treatment of antidepressant-induced weight gain.

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