

Major Depressive Disorder, Antidepressants, and Sexual Dysfunction

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Sexual dysfunction is a common problem with a number of causes, including psychosocial factors, general medical illness, psychiatric disorders, and psychotropic and nonpsychiatric medications. It is especially prevalent among patients with poor emotional health and has been strongly associated with antidepressant medications. Selective serotonin reuptake inhibitors (SSRIs) in particular have demonstrated a higher incidence of sexual dysfunction than other antidepressants that work through different mechanisms of action. Further supporting the relationship between sexual dysfunction and antidepressant mechanism of action, data from a number of studies indicate that bupropion, nefazodone, and mirtazapine alleviate symptoms of sexual dysfunction and are as effective as SSRIs at controlling depressive symptoms. Although a number of strategies besides drug substitution have been utilized to help manage antidepressant-induced sexual dysfunction, many patients remain suboptimally treated; as many as 42% of patients were found to passively wait for spontaneous remission. The addition of antidotal therapy has been proven to be among the effective management strategies for sexual dysfunction. However, due to a lack of systematic data, additional studies are warranted to further investigate these findings.

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Sexual dysfunction is a frequent problem that occurs in both healthy patients and patients with depression. According to the National Health and Social Life Survey, sexual dysfunction is more prevalent in women (43%) than men (31%);¹ furthermore, sexual dysfunction is more prevalent in both sexes with poor emotional health than in healthy controls.² Sexual dysfunction is a side effect that is particularly attributed to the use of antidepressant medication and represents a substantial problem, especially with regard to long-term treatment compliance. Approximately 36% of patients find antidepressant-induced sexual dysfunction to be an unacceptable side effect of treatment, constituting possible grounds for treatment discontinuation.³ Data suggest that the mechanism of action behind antidepressants is a key contributor to sexual dysfunction.^{3,4} A better understanding of these data and of the physiology and etiology of sexual dysfunction will lead to more effective management strategies, which may result in better therapeutic compliance.

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PHYSIOLOGY OF SEXUAL FUNCTIONING

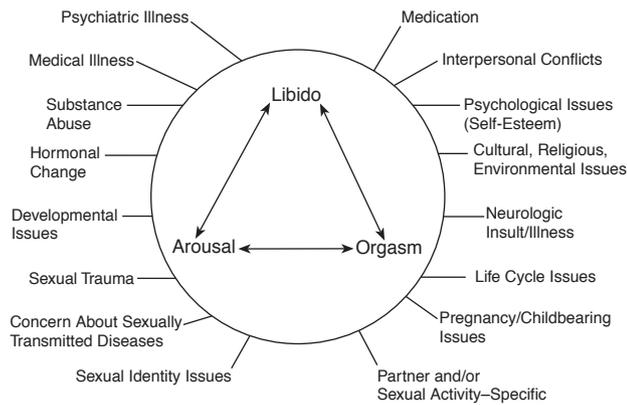
The role of hormones is of great interest with regard to sexual dysfunction. In women, estrogen, testosterone, and progesterone are all physiologic components of sexual function, whereas in men, testosterone is the primary physiologic component. Oxytocin appears to be related to orgasm and may influence feelings of desire. In addition to hormones, data have indicated that neurotransmitters also may have a significant physiologic effect on sexual functioning.⁵

The effect that dopamine and norepinephrine appear to have on sexual functioning could explain the diminished feelings of desire and arousal experienced by patients with depression. Dopamine appears to be related to motivated behaviors, including motivated sexual behaviors. Dopamine influences desire and the ability to become involved in sexual activity and may play a role in maintaining sexual focus. Norepinephrine stimulates sexual arousal and vasocongestion. To avoid persistent arousal with no release, serotonin (5-HT) systems are activated to suspend vasocongestion, thus turning off arousal. In addition, serotonin may diminish nitric oxide function and decrease genital sensation.⁵

ETIOLOGY OF SEXUAL DYSFUNCTION

Sexual dysfunction has many causes, including psychosocial factors, general medical illness, nonpsychiatric medication, psychiatric disorders, and psychotropic medi-

Figure 1. Potential Causes of Sexual Dysfunction During Antidepressant Therapy^a



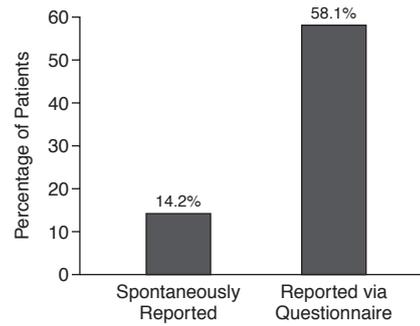
^aReprinted with permission from Zajecka.⁶

cations (Figure 1).⁶ Some patients experience a primary sexual disorder that predates their depression, whereas others have a psychiatric illness that could contribute to problems with sexual function. Psychotic illnesses also contribute to sexual dysfunction, as do neurologic illnesses and genitourinary trauma or infections. A number of psychotropics, including antidepressants, antipsychotic medications, benzodiazepines, and narcotics, can cause sexual dysfunction; additionally, there are more than 100 nonpsychotropics known to cause sexual dysfunction.⁷ Drugs of abuse and alcohol can factor into sexual dysfunction as well, as can psychosocial and situational changes. For example, if a depressed patient's spouse has just started a job that calls for an overnight shift, then that patient may report an increase in dissatisfaction with his or her sex life that is unrelated to the depression or antidepressant treatment.

PREVALENCE OF SEXUAL DYSFUNCTION

Antidepressant-induced sexual dysfunction is often underestimated. A high frequency of sexual dysfunction has been found with monoamine oxidase inhibitors, selective serotonin reuptake inhibitors (SSRIs), venlafaxine, and tricyclic agents (particularly those with a high serotonin reuptake blocker profile such as clomipramine).⁴ Patients taking antidepressants are not likely to spontaneously report sexual dysfunction to their physicians but are more likely to report problems when directly questioned by a physician (Figure 2).^{4,8} The Changes in Sexual Functioning Questionnaire (CSFQ), developed by Clayton et al.,⁹ and the Arizona Sexual Experiences Scale (ASEX), developed by McGahuey et al.,¹⁰ are the primary instruments utilized in the United States and Europe for accurate measurement of sexual dysfunction. In addition, the Psychotropic-Related Sexual Dysfunction Questionnaire

Figure 2. Reports of Antidepressant-Induced Sexual Dysfunction^a



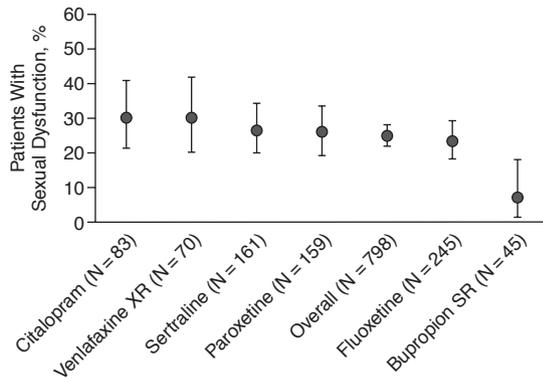
^aData from Montejo-Gonzalez et al.⁸

(PRSexDQ)^{3,11} has been shown to have adequate feasibility and psychometric properties as a measure of sexual dysfunction, and it has been used in different samples of depressed and schizophrenic patients on medication. The PRSexDQ consists of 7 items that ask about changes in sexual dysfunction since beginning antidepressant treatment, the types of problems experienced, and the tolerability of those changes.

To demonstrate the prevalence of sexual dysfunction in the United States, a large, cross-sectional, observational study⁴ was conducted in which 8312 patients receiving antidepressant monotherapy were invited to complete the CSFQ. Of these patients, 70% (N = 6297; women, N = 4534; men, N = 1763) chose to participate. Of the 30% of patients who declined, the majority cited that they were either too busy or too sick; only 6% said they would not participate because it was too intimate a topic, indicating that most patients are willing to discuss their sex lives if asked. Of the overall clinical population that chose to participate, a target population (N = 802) was identified that was free of possible age-associated sexual dysfunction and comorbid illnesses or concomitant medications that might affect sexual function. Total CSFQ scores indicated that 37% of the overall clinical population exhibited significant global sexual dysfunction. CSFQ scores in the target population indicated that the prevalence of sexual dysfunction ranged from 7% to 30%, depending on the antidepressant medication, with an average prevalence of 24%.

In this study,⁴ SSRIs and serotonin-norepinephrine reuptake inhibitors (SNRIs) were generally associated with higher incidence of sexual dysfunction than were other antidepressants with different mechanisms of action, indicating that the mechanism of action was integral to antidepressant-related sexual dysfunction. Of all the antidepressants included, bupropion sustained release (SR)—which does not have a direct effect on serotonin function—had the lowest associated prevalence of sexual dysfunction at 7% (Figure 3). The prevalence of sexual

Figure 3. Prevalence of Antidepressant-Induced Sexual Dysfunction in Patients Without Other Probable Causes of Sexual Dysfunction³



³Reprinted with permission from Clayton et al.⁴ Sexual dysfunction is defined as a Changes in Sexual Functioning Questionnaire score at or below the gender-specific threshold total score. Bars represent the 95% confidence interval (CI). Data were included only for antidepressant groups with a CI range less than 30 percentage points.

Abbreviations: SR = sustained release, XR = extended release.

dysfunction among patients taking bupropion SR was significantly lower than that among patients taking citalopram, paroxetine, sertraline, or venlafaxine extended release (XR).

THERAPEUTIC MECHANISMS OF ACTION

A number of studies have been conducted to further illustrate that the mechanism of action is the key to antidepressant-induced sexual dysfunction. Studies that compared bupropion, a norepinephrine-dopamine reuptake inhibitor, and mirtazapine, a noradrenergic and specific serotonergic antidepressant, with the SSRIs seem to support this hypothesis.

A randomized study¹² of 456 patients with major depression examined the effects of bupropion SR (N = 150) versus fluoxetine (N = 154) versus placebo (N = 152) on sexual functioning. The onset of sexual dysfunction, specifically orgasm dysfunction, occurred as early as week 2 of the trial and continued throughout the study in approximately 30% of patients who were taking fluoxetine. This rate was significantly more than the approximate 10% to 11% of patients experiencing dysfunction who were taking bupropion SR or placebo ($p < .001$). These data were similar to previous results regarding sertraline.¹³ When compared with patients taking bupropion SR (N = 118) or placebo (N = 117), a greater percentage of patients taking sertraline (N = 109) experienced orgasm dysfunction (10% bupropion SR versus 11% placebo versus 36% sertraline; $p < .05$). A recent study¹⁴ comparing patients with depression taking escitalopram (N = 266), bupropion extended release (XL) (N = 263), or placebo

(N = 256) identified, by investigator interview, a significantly greater number of escitalopram-treated patients who experienced orgasm dysfunction in the first week of treatment compared with bupropion- or placebo-treated patients. These differences continued throughout the 8-week study (30% escitalopram versus 15% bupropion XL and 9% placebo with $p < .001$) and were mirrored in self-rated changes in CSFQ total scores.

A small study¹⁵ of patients switched from an SSRI to mirtazapine also indicates that the mechanism of action may play an important part in the etiology of antidepressant-induced sexual dysfunction. Nineteen depressed patients with SSRI-induced sexual dysfunction whose depression was in remission were switched to mirtazapine for up to 6 weeks. Eleven of those patients experienced a return to normal sexual functioning, and an additional 2 saw marked improvement. A naturalistic 6-month study¹⁶ tracked depressed patients who were treated with mirtazapine. At baseline, 48 (61.5%) of 78 patients were experiencing sexual dysfunction, but by the 6-month follow-up, it had resolved in 27 (71.1%) of the 38 completers.

Duloxetine and agomelatine are among some of the newer drugs being examined as alternatives to SSRIs. Sexual functioning was assessed using the ASEX in 4 double-blind placebo- and paroxetine-controlled trials¹⁷ of duloxetine in patients with major depression. The incidence of treatment-emergent sexual dysfunction was significantly lower in patients treated with duloxetine than in patients treated with paroxetine, although both rates were higher than observed in patients taking placebo. Agomelatine has a dual mechanism of action: a resynchronization of circadian rhythms by its melatonin receptor agonist activity and antagonism of 5-HT_{2C}. Sexual dysfunction associated with agomelatine has been found to be similar to that with placebo and lower than that with fluoxetine, paroxetine, and venlafaxine.^{18,19} A placebo-controlled study of agomelatine is currently underway in healthy subjects to further examine its effects on sexual dysfunction.

MANAGEMENT STRATEGIES

Antidepressant-induced sexual dysfunction is often undertreated. The ELIXIR study²⁰ examined management strategies for SSRI-induced sexual dysfunction in 4557 patients and found that it was often not optimally treated; as many as 42% of patients passively waited for spontaneous remission, whereas 39% of patients were switched to a different antidepressant. Drug holidays and adjunctive treatment were rarely proposed. Waiting for spontaneous remission to occur is an ineffective strategy because so few patients experience it, perhaps as few as 5% to 10%.³ A number of other strategies have been utilized to help manage antidepressant-induced sexual dysfunction, in-

cluding dose adjustments, drug holidays, drug substitution, antidotal therapy, and nonpharmacologic strategies, although in many cases their efficacy remains insufficiently proven or unknown.

Dose Adjustments

Antidepressant-induced sexual side effects can be dose related, and gradual reduction of the dose may be useful in some patients. This management strategy is especially useful in patients who are experiencing other side effects as well. However, it should be attempted only in patients who have responded well to the medication, and the clinician and patient should be watchful for any signs of relapse or discontinuation symptoms.⁶

Drug Holidays

Drug holidays, in which a patient is advised to skip his or her antidepressant treatment for a day or two, can be effective but can also undermine treatment compliance. Even if the patient is instructed to take the antidepressant every day except on the weekends, for example, that patient may decide to skip other days as well. In addition, with short-acting SSRIs, drug holidays can result in drug discontinuation symptoms and relapse of depressive symptoms.

Drug Substitution

Substituting one SSRI with another SSRI may help alleviate sexual side effects; however, few patients (about 10%) benefit from this method of management. Substituting SSRIs with drugs that work through a different mechanism of action, including bupropion,^{13,21–23} nefazodone,^{4,24} and mirtazapine,^{15,25} appears to be a more effective option, as discussed above.

Antidotal Therapy

Studies have indicated that the addition of antidotes may prove to be an effective option for managing antidepressant-induced sexual dysfunction; however, there is a lack of systematic data to support these results. Although most of the available data to date are from case reports, case series, and open-label trials, they conclude that antidotal therapy may alleviate symptoms of sexual dysfunction while encouraging patients to maintain adherence to effective antidepressant treatment regimens.^{23,26} Agents commonly used as antidotes and evaluated in placebo-controlled trials currently include drugs approved for the treatment of erectile dysfunction, such as sildenafil, as well as buspirone and bupropion.

The benefits of sildenafil for the treatment of erectile dysfunction and other aspects of sexual function in men taking SSRIs have been shown in a small, randomized, placebo-controlled trial (N = 90).²⁶ A placebo-controlled trial²⁷ evaluating the use of buspirone in patients taking SSRIs found that buspirone alleviated SSRI-induced sexual dysfunction, particularly in women. A small placebo-

controlled trial (N = 42)²³ found that bupropion SR also reduced SSRI-induced sexual dysfunction. Larger studies are needed to further investigate these findings.

Nonpharmacologic Treatment

Some nonpharmacologic treatments may help alleviate sexual dysfunction in some patients. Talking with patients about their sexual problems may be enough to help some patients, while others may want to seek couples sex therapy or try different sexual techniques. Another important recommendation that the clinician can make is for the patient to resist avoiding sexual activity; maintaining a sex life may help improve sexual functioning.

CONCLUSION

Sexual dysfunction is a frequent problem that occurs in both healthy patients and patients with depression, although the prevalence is higher in patients with poor emotional health than in healthy controls. Sexual dysfunction has been particularly associated with the use of SSRIs and SNRIs, and data suggest that the mechanism of action is the key to antidepressant-related sexual dysfunction. Treatment with bupropion, nefazodone, or mirtazapine appears to alleviate symptoms of sexual dysfunction without compromising antidepressant efficacy. In addition, use of antidotes may prove an effective option for managing antidepressant-induced sexual dysfunction; however, there is a lack of systematic data in this area, and further studies are warranted. Physicians should focus more attention on this problem because the combination of several factors, such as the impairment in the quality of life and the risk of dropouts due to sexual dysfunction, can have a negative effect on treatment. Taking a psychosexual clinical history prior to initiating antidepressant treatment is always needed to identify antidepressant-induced sexual side effects. In addition, sexual side effects should be an important factor when selecting antidepressants for long-term treatment.

REVIEW QUESTION

Mr. A is a 44-year-old married man who is a high-school teacher. He presented at a mental health clinic, referred by his primary care physician, because of an episode of sadness with anxiety, sleeping difficulties, feelings of guilt, and unexplained fatigue and tiredness, which started 4 or 5 months previously. His wife reported that for the last 3 to 4 months the patient had clearly decreased his daily activities, showing no interest in hobbies or socializing. He had pessimistic thoughts about his job, although according to his wife, he had no reason to be concerned. He had also lost interest in maintaining what had been an active sex life with his wife.

A treatment regimen including paroxetine, 20 mg q.d., and lorazepam, 1 mg p.r.n., was started. After 3 or 4 weeks, Mr. A showed overall clinical improvement. His sleep patterns and anxiety levels returned to normal. No adverse events were reported, but when the patient was asked about any change in his sexual relationships, he stated that his sexual interest was lower than before but it was not a problem for him. His wife, however, stated that in fact he showed no interest in sexual activity and experienced ejaculatory problems. After 65 days of treatment, clinical improvement was maintained, but his wife was still concerned about their sexual relationship. Mr. A. also reported that his erectile functioning was intensively compromised and that he had developed performance anxiety. After 4 months of treatment, Mr. A's relationship with his wife began to deteriorate because of his lack of sexual interest; she even began to suspect that he was being unfaithful to her.

What therapeutic strategy or strategies would you recommend for Mr. A?

Drug names: bupropion (Wellbutrin and others), buspirone (BuSpar and others), citalopram (Celexa and others), clomipramine (Anafranil and others), duloxetine (Cymbalta), escitalopram (Lexapro), fluoxetine (Prozac and others), lorazepam (Ativan and others), mirtazapine (Remeron and others), paroxetine (Paxil, Pexeva, and others), sertraline (Zoloft), sildenafil (Viagra), venlafaxine (Effexor).

Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, bupropion, buspirone, and sildenafil are not approved by the U.S. Food and Drug Administration as antidotes for sexual dysfunction.

REFERENCES

- Laumann EO, Paik A, Rosen RC. Sexual dysfunction in the United States: prevalence and predictors. *JAMA* 1999;281:537-544
- Casper RC, Redmond DE Jr, Katz MM, et al. Somatic symptoms in primary affective disorder: presence and relationship to the classification of depression. *Arch Gen Psychiatry* 1985;42:1098-1104
- Montejo AL, Llorca G, Izquierdo JA, et al, for the Spanish Working Group for the Study of Psychotropic-Related Sexual Dysfunction. Incidence of sexual dysfunction associated with antidepressant agents: a prospective multicenter study of 1022 outpatients. *J Clin Psychiatry* 2001;62(suppl 3):10-21
- Clayton AH, Pradko JF, Croft HA, et al. Prevalence of sexual dysfunction among newer antidepressants. *J Clin Psychiatry* 2002;63:357-366
- Clayton AH. Sexual function and dysfunction in women. *Psychiatr Clin North Am* 2003;26:673-682
- Zajacka J. Strategies for the treatment of antidepressant-related sexual dysfunction. *J Clin Psychiatry* 2001;62(suppl 3):35-43
- Hirschfeld RM. Management of sexual side effects of antidepressant therapy. *J Clin Psychiatry* 1999;60(suppl 14):27-30; discussion 31-25
- Montejo-Gonzalez AL, Llorca G, Izquierdo JA, et al. SSRI-induced sexual dysfunction: fluoxetine, paroxetine, sertraline, and fluvoxamine in a prospective, multicenter, and descriptive clinical study of 344 patients. *J Sex Marital Ther* 1997;23:176-194
- Clayton AH, McGarvey EL, Clavet GJ. The Changes in Sexual Functioning Questionnaire (CSFQ): development, reliability, and validity. *Psychopharmacol Bull* 1997;33:731-745
- McGahuey CA, Gelenberg AJ, Laukes CA, et al. The Arizona Sexual Experience Scale (ASEX): reliability and validity. *J Sex Marital Ther* 2000;26:25-40
- Montejo AL, Garcia M, Espada M, et al, for the Spanish Working Group for the Study of Psychotropic-Related Sexual Dysfunction. Psychometric characteristics of the Psychotropic-Related Sexual Dysfunction Questionnaire. *Actas Esp Psiquiatr* 2000;28:141-150
- Coleman CC, King BR, Bolden-Watson C, et al. A placebo-controlled comparison of the effects on sexual functioning of bupropion sustained release and fluoxetine. *Clin Ther* 2001;23:1040-1058
- Coleman CC, Cunningham LA, Foster VJ, et al. Sexual dysfunction associated with the treatment of depression: a placebo-controlled comparison of bupropion sustained release and sertraline treatment. *Ann Clin Psychiatry* 1999;11:205-215
- Clayton AH, Croft H, Horrigan JP, et al. Bupropion extended release compared with escitalopram: effects on sexual functioning in 2 randomized, double-blind, placebo-controlled studies. *J Clin Psychiatry* 2006;67:736-746
- Gelenberg AJ, McGahuey C, Laukes C, et al. Mirtazapine substitution in SSRI-induced sexual dysfunction. *J Clin Psychiatry* 2000;61:356-360
- Saiz-Ruiz J, Montes JM, Ibanez A, et al. Assessment of sexual functioning in depressed patients treated with mirtazapine: a naturalistic 6-month study. *Hum Psychopharmacol* 2005;20:435-440
- Delgado PL, Brannan SK, Mallinckrodt CH, et al. Sexual functioning assessed in 4 double-blind placebo- and paroxetine-controlled trials of duloxetine for major depressive disorder. *J Clin Psychiatry* 2005;66:686-692
- Rouillon F. Efficacy and tolerance profile of agomelatine and practical use in depressed patients. *Int Clin Psychopharmacol* 2006;21(suppl 1):S31-S35
- Servier and Novartis sign licensing agreement for a novel treatment of major depressive disorder. Mar 29, 2006. Available at: <http://www.servier.com/pro/neurosciences/general/Valdoxan.asp>. Accessed Apr 18, 2006
- Bonierbale M, Lancon C, Tignol J. The ELIXIR study: evaluation of sexual dysfunction in 4557 depressed patients in France. *Curr Med Res Opin* 2003;19:114-124
- Kavoussi RJ, Seagraves RT, Hughes AR, et al. Double-blind comparison of bupropion sustained release and sertraline in depressed outpatients. *J Clin Psychiatry* 1997;58:532-537
- Croft H, Settle E Jr, Houser T, et al. A placebo-controlled comparison of the antidepressant efficacy and effects on sexual functioning of sustained-release bupropion and sertraline. *Clin Ther* 1999;21:643-658
- Clayton AH, Warnock JK, Kornstein SG, et al. A placebo-controlled trial of bupropion SR as an antidote for selective serotonin reuptake inhibitor-induced sexual dysfunction. *J Clin Psychiatry* 2004;65:62-67
- Feiger A, Kiev A, Shrivastava RK, et al. Nefazodone versus sertraline in outpatients with major depression: focus on efficacy, tolerability, and effects on sexual function and satisfaction. *J Clin Psychiatry* 1996;57(suppl 2):53-62
- Koutouvidis N, Pratikakis M, Fotiadou A. The use of mirtazapine in a group of 11 patients following poor compliance to selective serotonin reuptake inhibitor treatment due to sexual dysfunction. *Int Clin Psychopharmacol* 1999;14:253-255
- Nurnberg HG, Hensley PL, Gelenberg AJ, et al. Treatment of antidepressant-associated sexual dysfunction with sildenafil: a randomized controlled trial. *JAMA* 2003;289:56-64
- Landen M, Eriksson E, Agren H, et al. Effect of buspirone on sexual dysfunction in depressed patients treated with selective serotonin reuptake inhibitors. *J Clin Psychopharmacol* 1999;19:268-271