Management of Sexual Side Effects of Antidepressant Therapy

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Sexual dysfunction occurs in over one third of the general population and has many causes, including psychosocial factors, general medical illness, nonpsychiatric medication, psychiatric disorders, and psychotropic medications. Psychosocial causes are the most prevalent, but many frequently used medications, such as diuretics, β-blockers, and H_2-blockers, can also cause sexual dysfunction. Sexual dysfunctions occur in many psychiatric disorders, including mood disorders, schizophrenia, substance abuse, and anxiety disorders. In addition, over half the patients with major depression will have some sexual dysfunction. Although much attention has been paid to sexual dysfunction associated with the selective serotonin reuptake inhibitors (SSRIs), many other commonly used psychotropics are associated with a variety of sexual dysfunction, including haloperidol, benzodiazepines, stimulants, and drugs of abuse. With regard to SSRIs, sexual dysfunction occurs in 50% or more of such patients, which is substantially higher than the rates reported in the *Physicians' Desk Reference.* The reason for this discrepancy is that patients will not spontaneously report sexual problems and must be questioned about such problems directly. A variety of strategies exist to manage antidepressant-induced sexual dysfunction, including waiting, reducing the antidepressant dose, use of drug holidays, use of adjunctive pharmacotherapy, and switching antidepressants. Use of an antidepressant with a low prevalence of sexual side effects, such as bupropion, nefazodone, and mirtazapine, may also be considered. *(J Clin Psychiatry 1999;60[suppl 14]:27–30)*

Concern about the sexual side effects of the newer generation antidepressants has generated considerable attention in the press recently. Sexual dysfunction has emerged as a particular problem in the treatment of depression, because depression often requires long-term treatment. In the short term, sexual dysfunction may not be of great concern because reduced libido is part of the depression and the pain of depression spurs the desire for relief at any cost. Complying with medication that may cause sexual dysfunction after recovery, however, is a different issue.

Antidepressant medication is not the only cause of sexual dysfunction in depressed patients. There are many causes of sexual dysfunction in depression, including primary sexual dysfunction, sexual dysfunction associated with general medical and psychiatric disorders, and sexual dysfunction associated with treatments for psychiatric disorders. This article will review briefly all aspects of this issue, but will focus on management of antidepressant-induced sexual side effects.

Sexual dysfunction is encountered fairly frequently in the general population. Over one third of women, and perhaps as many men, have reported some kind of sexual dysfunction[1] (Table 1). The prevalence of sexual dysfunction is substantially higher in a depressed population prior to initiating treatment. According to a study by Matthew and Weinman[2] of depressed men, 31% reported decreased libido, 35% reported erectile dysfunction, and 47% reported delayed ejaculation at baseline. There are a number of factors that can contribute to this sexual dysfunction (Table 2). First and most importantly is the depression itself. Depressive illness causes a reduction in bodily drives, including libido and the ability to experience pleasure. Thus, patients who are acutely depressed rarely complain of sexual dysfunction because they have little or no interest in sex. Other psychiatric illnesses, including schizophrenia, substance abuse, and personality disorders, that are often comorbid with depression are also associated with sexual dysfunction. A variety of general medical conditions are associated with sexual dysfunction, including thyroid problems, cardiovascular problems, and diabetes. Sexual dysfunction can also be caused by any of a number of medicines that are used to treat general medical problems, including clonidine, atenolol, cimetidine, and phenytoin.[3] Finally, primary sexual dysfunction, as already noted, can be the cause of sexual dysfunction in patients with depression.

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Table 1. Prevalence of Sexual Dysfunction in the General Population[a]

Side Effect	%
Women	
Vaginismus	15
Low libido	34
Orgasmic disorder	24
Men	
Orgasmic disorder (ie, inhibited)	10
Premature ejaculation	29
Erectile disorder (ie, impotence)	10

[a]Data from reference 1. Based on personal interviews of sample of 3432 American men and women between ages 18 and 50.

Table 2. Causes of Sexual Dysfunction in Depressed Patients Prior to Starting Antidepressant Therapy

The depression itself
Other psychiatric illnesses
Concomitant general medical illness
Primary sexual dysfunction
Side effects of other medications
Combination of some or all of these factors

Table 3. Causes of Sexual Dysfunction: Psychotropic Medications for Mood Disorders

Mood stabilizers
Lithium
Carbamazepine
Tricyclic antidepressants (TCAs)
Imipramine
Clomipramine
Monoamine oxidase inhibitors
Phenelzine
Selective serotonin reuptake inhibitors (SSRIs)
Fluoxetine
Sertraline
Paroxetine
Fluvoxamine
Citalopram
Other
Venlafaxine

Nearly all psychotropic medications used in the treatment of patients with depression are associated with sexual dysfunction (Table 3). Monoamine oxidase inhibitors in particular can cause sexual dysfunction.

SEXUAL DYSFUNCTION ASSOCIATED WITH ANTIDEPRESSANTS

Prevalence

Table 4 lists the prevalence of sexual dysfunction associated with antidepressants as cited in the *Physicians' Desk Reference*,[4] which contains the package insert information for each antidepressant. These reported prevalence rates are lower than those reported in clinical studies (ranging from less than 1% to a maximum of 16%[5]), because they are derived from spontaneously reported, treatment-emergent side effects. In practice, patients will

Table 4. Prevalence of Sexual Dysfunction With Antidepressants

Drug Class	Physicians' Desk Reference %	Clinic[a] %
TCAs	N/A	2–95
SSRIs	2–16	4–75
Bupropion	3	3
Nefazodone	1	< 1
Mirtazapine	< 1	< 1

[a]Data adapted from reference 5.

Table 5. Attitudes About Sex in U.K. General Population and in Depressed Sample[a]

Attitude	Total Population, % (N = 6143)	Depressed Subpopulation, % (N = 1140)
Having a good sex life is fairly or very important	70	75
Loss of sexual interest would prompt visit to treating physician	3	2

[a]Data adapted from reference 7.

rarely report sexual problems spontaneously. However, if patients are specifically queried about sexual problems, they will report them, as is documented in the second column of Table 4. Some studies have found that most patients treated with tricyclic antidepressants (TCAs) or selective serotonin reuptake inhibitors (SSRIs) report sexual dysfunction associated with medication.

Consistent with this finding is a 1997 study by Modell et al.,[6] in which approximately three fourths of patients who were taking fluoxetine, paroxetine, or sertraline reported 1 or more sexual side effects, compared with bupropion, with which 14% of patients had sexual side effects. The most frequent side effects were libido reduction and delayed orgasm.

Do patients with depression care about sex? This question was addressed in a study conducted in the United Kingdom[7] (Table 5). In this door-to-door epidemiologic survey of over 6000 people, 70% reported that having a good sex life was fairly or very important to them. Among the 1140-person subsample of those who were depressed, 75% reported that having a good sex life was fairly or very important to them. These findings suggest that sex is as important to those who are depressed as it is to those who are not.

Long-Term Treatment

Because loss of libido is a core feature of depression, antidepressant-induced sexual dysfunction may not pose a large burden for patients in acute treatment. In addition, the pain and suffering caused by depression may make any increase in sexual dysfunction worth the "cost" of alleviation of depression. However, the situation is very different in long-term treatment. In long-term treatment, patients are

Table 6. Strategies to Manage Antidepressant-Induced Sexual Dysfunction

Wait	Adjunctive pharmacotherapy
Reduce antidepressant dose	Switch antidepressants
Drug holiday	Avoid the problem

generally well or much better, and the duration of treatment may extend for years. Therefore, anything that interferes substantially with sexual functioning is substantially more of a problem and will contribute strongly to noncompliance.

STRATEGIES TO MANAGE ANTIDEPRESSANT-INDUCED SEXUAL DYSFUNCTION

Simply waiting to see if the problem resolves itself may work as a way of dealing with antidepressant-induced sexual dysfunction (Table 6). This is particularly true if the dysfunction occurs early in therapy, since it may not continue. Unfortunately, though, antidepressant-induced sexual dysfunction does tend to persist.

Many side effects, including sexual dysfunction, are dose dependent. Therefore, reducing the dose of the antidepressant may improve sexual function. However, dose reduction must be done with caution, because lowering the dose may decrease the therapeutic efficacy of the medication and exacerbate depressive symptomatology.

Drug holidays are also an option. These involve stopping or substantially reducing the antidepressant for 1, 2, or 3 days (or sometimes longer). The utility of the drug holiday was tested by Rothschild,[8] who asked patients taking sertraline, paroxetine, or fluoxetine to take 3-day drug holidays. This strategy improved orgasmic function, sexual satisfaction, and libido in approximately one half of the patients taking sertraline or paroxetine.[8] However, it was not useful with the patients treated with fluoxetine, a finding that is almost certainly explained by the substantially longer half-life of fluoxetine as compared with the other 2 antidepressants. Many physicians recommend against drug holidays because of concerns about discontinuation reactions or concerns that drug holidays may foster noncompliance.

Another strategy is to utilize adjunctive pharmacotherapy to ameliorate the antidepressant-induced sexual dysfunction. In general, this strategy involves agents that antagonize serotonin or α_2-noradrenergic neurotransmission or stimulate the dopamine system. Table 7 lists a variety of medications that have been utilized to manage antidepressant-induced sexual dysfunction. There are no controlled studies of these medications used in this way, but there are many anecdotal reports. Some of these drugs can be used on a p.r.n. basis, but most require ongoing administration. This practice can create problems, because these medications have side effects of their own. For example, yohimbine may increase agitation and anxiety substantially, and cyproheptadine may cause drowsiness.

Table 7. Pharmacotherapy for SSRI-Induced Anorgasmia

Drug	Mechanism	Dosage (mg/d)
Cyproheptadine[a]	5-HT antagonist	4–8
Buspirone	5-HT_{1A} partial agonist	15–45
Yohimbine[a]	Adrenergic antagonist (α_2)	5.4–10.8
Amantadine	Dopamine agonist	100–400
Methylphenidate	Dopamine agonist	10–30
Bupropion	Unknown	75–150
Mirtazapine	$5\text{-HT}_2 + 5\text{-HT}_3$ antagonist	15–45

[a]With prn dosing.

Yet another strategy involves switching from an antidepressant associated with sexual dysfunction to one that is not associated with sexual dysfunction, such as bupropion, nefazodone, or mirtazapine. This strategy was tested by Walker et al.,[9] who enlisted sexually active male and female patients experiencing sexual dysfunction on fluoxetine therapy and switched them to bupropion therapy. The 22 female and 17 male patients reported substantial improvement in sexual functioning.[9] With regard to orgasm dysfunction, 84% reported complete resolution and 10% partial resolution, leaving only 6% with no resolution of this dysfunction. In addition, 81% reported much or very improved libido following the medication switch.

Gelenberg et al.[10] employed a similar design to examine improvement in SSRI-induced sexual dysfunction after switching to mirtazapine. After 6 weeks, there was substantial improvement in sexual functioning in men and modest improvement in sexual functioning in women. Specifically, 58% of the sample (71.4% of the men and 50% of the women) experienced a return to normal sexual functioning, and 11% of the sample experienced a significant increase in sexual functioning. All patients maintained their antidepressant response (Hamilton Rating Scale for Depression score ≤ 18).

The best strategy is to avoid the problem altogether; that is, treat from the start with an antidepressant that has little to no sexual association with dysfunction, such as bupropion, nefazodone, or mirtazapine.

This strategy was tested in a study of bupropion (sustained release) and sertraline in a sample of patients with major depression who previously had normal sexual function. At the end of that 16-week trial of 122 patients taking bupropion and 126 taking sertraline, 7% of the bupropion patients compared with 39% of the sertraline patients ($p < .001$) experienced orgasm delay or failure at the end of the study.

Another study compared sexual functioning in 100 sexually active patients with major depression treated with either nefazodone (N = 50) or sertraline (N = 50). In that 6-week study, only 6% of the men treated with nefazodone had difficulty with ejaculation at the termination of the study, compared with 49% of those treated with sertraline

($p < .05$). Among 16% of the women, there was a modest reduction in difficulty with orgasm (compared with baseline) in the nefazodone group, whereas at the termination of the study, 27% of the women in the sertraline group complained of always, usually, or frequently having difficulty having orgasm.[11]

Boyarsky et al. (B. K. Boyarsky, M.D.; W. Haque, M.D.; M. R. Rouleau, M.Ed.; et al., unpublished data, 1999) performed a 12-week, open-label, flexible-dose study in which depressed patients with sexual dysfunction were treated with mirtazapine. Women had substantial improvement in sexual functioning (desire, 41%; arousal/lubrication, 52%; and satisfaction of orgasm, 48%), while men improved modestly (desire, 10%; arousal/erection, 23%; and satisfaction of orgasm, 14%). No patients in this study experienced an aggravation of sexual dysfunction resulting from mirtazapine treatment.

DISCUSSION

Focusing on sexual dysfunction in patients being treated for depression is useful. Although it may not loom large as a problem during acute treatment, it is a major issue in long-term treatment, and long-term treatment is recommended for many patients because the clinical course of depression is often characterized by recovery, recurrence, and chronicity. In a 15-year follow-up of patients with depression, only 1 in 11 patients recovered from the depressive episode and remained well.[12]

Evidence from a number of studies has shown that continuation treatment for an episode of depression must last a minimum of 3 months after acute stabilization of symptoms and should probably last 6 to 9 months.[13] During this time, patients will be well and hopefully able to function normally sexually.

In patients at high risk for recurrence, maintenance therapy should be considered. This includes patients who have had recurrent depressions, who are suffering from comorbid psychiatric conditions, whose episodes were more severe, or who were in control during continuation.[14,15] For these patients, we may be talking about years of therapy, and antidepressant-induced sexual dysfunction would be very problematic.

The strategies discussed in this article all have moderate success, but some are associated with creating the problems. Therefore, the last strategy, that of avoiding the problem, is particularly attractive.

CONCLUSION

Sexual dysfunction is frequent in the general population and even more so in depressed patients. Although it is a frequent problem in depressed patients, it is rarely an issue that arises in acute treatment, because depressed patients often have loss of libido and anhedonia as a result of their depression. However, it becomes a problem as patients get better and wish to resume normal sexual functioning. It is important for physicians to ask about treatment-emergent sexual dysfunction, because patients often will not spontaneously complain of it, but nonetheless will discontinue therapy because of it. Among the strategies to deal with treatment of antidepressant-induced sexual side effects are waiting, reducing the antidepressant dose, trying a drug holiday, employing adjunctive pharmacotherapy, switching antidepressants, or initially using an antidepressant that is not associated with sexual dysfunction.

Drug names: amantadine (Symmetrel), atenolol (Tenormin), bupropion (Wellbutrin), buspirone (BuSpar), carbamazepine (Tegretol and others), cimetidine (Tagamet), citalopram (Celexa), clomipramine (Anafranil), clonidine (Catepres), cyproheptadine (Periactin and others), fluoxetine (Prozac), fluvoxamine (Luvox), haloperidol (Haldol and others), methylphenidate (Ritalin), mirtazapine (Remeron), nefazodone (Serzone), paroxetine (Paxil), phenelzine (Nardil), phenytoin (Dilantin and others), sertraline (Zoloft), venlafaxine (Effexor), yohimbine (Yocon and others).

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