Sexual Side Effects of Antidepressants

Anthony J. Rothschild, M.D.

Patients with depressive disorders frequently have concurrent sexual problems. The sexual dysfunction is often masked by the mood disorder, and many patients have difficulty discussing these problems openly. Thus, sexual dysfunction often is detectable only by careful inquiry. The relationship between sexual dysfunction and depressive disorders is further complicated by antidepressant therapy, which itself may cause sexual dysfunction, increasing the risk of noncompliance and relapse. This article reviews studies indicating that antidepressants may cause 30% to 40% of patients who take them to develop some degree of sexual dysfunction. Management strategies for alleviating sexual dysfunction as a complication of antidepressant treatment are discussed in terms of supporting research studies as well as practicality. Spontaneous resolution of antidepressant-induced sexual dysfunctions rarely occurs, and dose reductions may jeopardize the antidepressant effect. Antidotes, drug holidays, and timing sexual relations with respect to antidepressant dose are effective for some patients, but only a few of these strategies have been studied with double-blind paradigms. Switching to antidepressants that cause sexual dysfunction at lower rates and data comparing rates of sexual dysfunction among antidepressants are discussed. *(J Clin Psychiatry 2000;61[suppl 11]:28–36)*

Sexual function is an important aspect of depressive illness and its treatment, and it is critical for physicians to assess sexual function during the initial evaluation and throughout treatment. Although sexual dysfunction secondary to antidepressants is a perplexing and common clinical problem, it is important to realize that effective antidepressant treatment does not need to compromise sexual function. Unfortunately, several myths exist about sexual dysfunction and depression. One such myth is that depressed patients do not care about their sexual function. Another is that most patients will continue to take their medications even if they are experiencing sexual dysfunction, as long as the treatment is helping their depression. A third myth is that patients will spontaneously report sexual problems to their doctor. And a fourth myth is that all antidepressants cause sexual dysfunction at the same rate.

Sexual dysfunction side effects can have an impact on adherence to antidepressant treatment, and thus it is critical for the physician to elicit reports of sexual dysfunction from patients. Sexual function should be assessed during the initial evaluation to establish a baseline for a given patient, allowing the physician to determine whether the patient is sexually active and/or whether sexual dysfunction is part of the patient's presenting clinical profile. It is also critical to consider the importance of sexual function when selecting an initial antidepressant for sexually active patients and to reassess sexual function periodically during the course of therapy so that the physician can detect any problems that may arise.

Sexual dysfunction is usually classified by where in the normal human sexual response cycle the problem occurs. Figure 1 is modified from the work of Masters and Johnson and colleagues.[1] They divided human sexual response into phases of desire, arousal, release, and resolution, which occur over time in response to sexual stimulation. In the curve, a woman has more than one orgasm during the release phase; therefore, the resolution phase is somewhat delayed. This reflects the fact that, generally speaking, women have a greater capacity for multiple orgasms than do men. Sexual dysfunction is usually classified according to the phase of the Masters and Johnson sexual response cycle in which the problem occurs. In the desire phase, problems include inhibited sexual desire or decreased libido. In the arousal phase, a patient could have inhibited sexual excitement, impotence, erectile dysfunction, or failure to achieve or maintain adequate vaginal lubrication. Problems in the release phase include delayed orgasm or ejaculation, no orgasm or ejaculation, or, in some cases, premature ejaculation.

CAUSES OF SEXUAL DYSFUNCTION

Sexual dysfunction has many causes, and the differentiation of treatment-induced symptoms from those that are illness induced can be a diagnostic challenge. Depressive illness itself can cause sexual problems (see below). Many medical illnesses can cause sexual dysfunction as

From the Department of Psychiatry, University of Massachusetts Medical School, Worcester.

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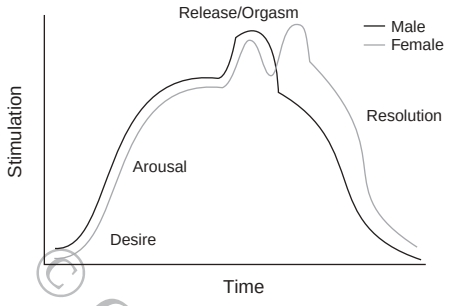
Reprint requests to: Anthony J. Rothschild, M.D., Department of Psychiatry, University of Massachusetts Medical School, 361 Plantation St., Worcester, MA 01605 (e-mail: rothscha@ummhc.org).

Figure 1. The Sexual Response Cycle[a]



[a]Adapted from Masters and Johnson et al.[1]

Table 1. Ten Key Sexual History Questions[a]

1. Are you generally satisfied with your sex life?
2. Have you noticed a sexual problem? If yes, describe.
3. Have you noticed decreased desire? If yes, describe.
4. Have you noticed problems achieving erection/vaginal lubrication? If yes, describe.
5. Have you noticed problems achieving ejaculation/orgasm? If yes, describe.
6. Is the orgasm less pleasurable?
7. Do you experience sexual dysfunction in all situations?
Spontaneous arousal intact?
Desire when not interacting with a partner?
Morning erections (men)?
8. Did this symptom(s) begin before, or coincident with, the onset of the depressive illness?
Did this symptom(s) begin before or after starting antidepressant therapy?
9. If treatment induced, did the sexual effects appear after a dosage increase?
10. Was there any change after discontinuing medication?

[a]Adapted from Ende et al.[4]

well, such as diabetes mellitus or hypothyroidism, among others. Various pharmacologic treatments can cause sexual side effects, including psychotropics, antihypertensives, and antiulcer drugs. Recreational drugs often cause sexual dysfunction; a particular culprit is alcohol.

Psychosocial and interpersonal factors can be causes of sexual dysfunction, including factors in the relationship between sexual partners as well as other kinds of environmental stressors, such as stress at work or stress caused by caring for a sick child or an elderly parent. Sexual dysfunction can also be the result of a primary sexual disorder (e.g., hypoactive sexual desire disorder, sexual aversion disorder). Casper and colleagues[2] reported that 70% to 80% of depressed patients have diminished libido as a symptom of their illness. In their study, severity of depressive illness and anxiety symptoms strongly influenced the disturbances in sleep, appetite, and sexual interest. All of these symptoms increased as the depression deepened. These data underscore the importance of establishing a patient's baseline sexual function before initiating antidepressant therapy. If the physician fails to do this, and 3 months later the patient complains of low libido, the physician cannot know whether the low libido is a lingering symptom of the depression, a side effect of treatment, or both. Sexual dysfunction is manageable regardless of whether it is depression related or treatment related, but these 2 etiologies will result in very different treatment strategies. Therefore, it is very important to obtain a sexual history right from the beginning and to continually reassess sexual function throughout the course of antidepressant therapy.

ASSESSMENT OF SEXUAL DYSFUNCTION IN DEPRESSED PATIENTS

Most patients report sexual dysfunction only in response to direct inquiry. In a study of treatment-emergent sexual dysfunction caused by clomipramine,[3] a questionnaire was used to elicit patient reports of side effects. Approximately one third of the patients taking clomipramine complained of sexual problems, prompting investigators to question all of the patients directly and specifically. Shortly after starting clomipramine therapy, 96% of patients had developed difficulty in achieving orgasm. Of those who acknowledged drug-induced anorgasmia at interview, 36% had not admitted any sexual difficulty on the questionnaire previously. The investigators later discovered that some patients were secretly reducing their dose of clomipramine in an attempt to regain orgasmic capacity. This study illustrates an important point: sexual function may be more important to patients than adherence to treatment, especially if patients are not totally convinced of the benefits of treatment. Another key point this study demonstrates is that when reviewing the literature, it is important to look at how the information on sexual dysfunction was obtained. Questionnaire studies reveal lower rates of sexual dysfunction than when investigators ask patients about sexual function directly and specifically.

In a busy practice, it is critical to have a systematic approach for obtaining information regarding a patient's sexual history. The basic questions listed in Table 1 (adapted from Ende et al.[4]) can help elicit a sexual history from patients. I usually ask these questions in the context of questions about the neurovegetative symptoms of depression (e.g., appetite, weight, sleep). Collecting information by asking these questions directly is important for establishing the presence of any sexual dysfunction as well as for determining any possible causes of the problem, identifying the management strategy, and selecting an appropriate antidepressant.

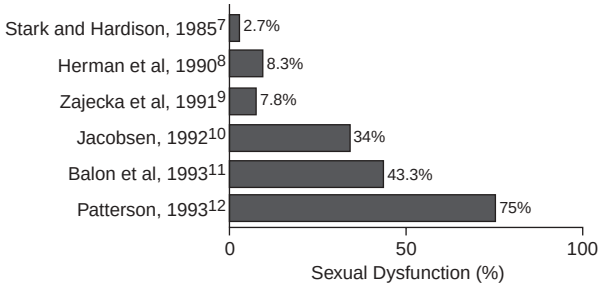
The first 2 questions are fairly general and provide the clinician with a bridge to a series of questions based on the classic phases of the human sexual response cycle discussed above. Question 3 addresses the desire phase. Question 4 addresses the arousal phase. Questions 5 and 6 address the release phase. Physicians should use terms that are appropriate to the gender of the patient. For example, one should refer to erection and ejaculation when interviewing a male patient and refer to vaginal lubrication

Table 2. Antidepressant Drugs Associated With Treatment-Emergent Sexual Dysfunction[a]

Phase (dysfunction)	Drugs
Desire (decreased libido)	Heterocyclics, fluoxetine, MAOIs, lithium
Arousal (erectile failure)	Heterocyclics, MAOIs, fluoxetine, trazodone
Release (ejaculation impairment, delayed or absent orgasm in men and women)	Heterocyclics, MAOIs, SSRIs, trazodone, venlafaxine

[a]Based on Segraves[5] and package insert for venlafaxine.[6] Abbreviations: MAOI = monoamine oxidase inhibitor, SSRI = selective serotonin reuptake inhibitor.

Figure 2. Fluoxetine and Sexual Dysfunction[a]



[a]Reported incidence of sexual dysfunction may reflect growing awareness.

and orgasm when interviewing a female patient. If a response indicates the presence of a problem, physicians should ask the patient to elaborate and to describe the particular problem he or she is experiencing. Question 7 addresses whether the sexual dysfunction is situational. The ability to achieve spontaneous erection in several circumstances, for instance, in the morning or with masturbation, in most instances rules out organic causes. Sporadic erectile dysfunction is more likely to have a psychological cause than organic cause. Question 8 addresses the onset of sexual dysfunction relative to that of the depressive illness and to the initiation of antidepressant therapy. This is important because depression itself can cause sexual dysfunction and the problem may or may not be treatment related even if it occurs in the context of treatment. The remaining questions further clarify the relationship between sexual symptoms and antidepressant medication.

SEXUAL DYSFUNCTION SECONDARY TO ANTIDEPRESSANTS

Sexual dysfunction has been attributed to specific classes of antidepressants and to other psychotropic and nonpsychotropic agents. Sexual dysfunction may occur during treatment with heterocyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), the monoamine oxidase inhibitors (MAOIs), and other antidepressants. Inability to ejaculate, delayed ejaculation, and problems with orgasm are particularly characteristic sexual side effects of antidepressants. As shown in Table 2, many of the commonly prescribed antidepressants have been shown to cause problems in various phases of the Masters and Johnson human sexual response cycle (see Figure 1). As is described below, notable exceptions include nefazodone, bupropion, and possibly mirtazapine.

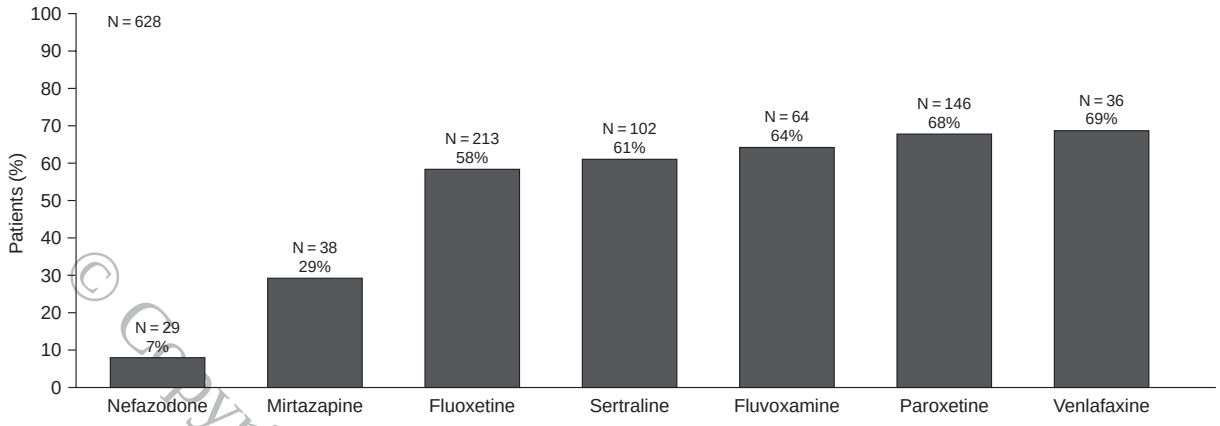
Figure 2 depicts the steady and dramatic increase in the reported incidence of sexual dysfunction among depressed patients treated with fluoxetine over the years since the drug was first introduced. Although these data might appear to indicate a rapid increase in the incidence of sexual dysfunction, what they really reflect is a growing awareness of a problem among patients and a change in the way data are gathered by research clinicians regarding sexual dysfunction. As was discussed above, people are generally quite reluctant to talk about sexual problems with their doctor, and that evidently includes patients in antidepressant clinical trials. Unfortunately, in some of these earlier studies, the investigators did not ask patients directly about sexual function. If a patient complained about sexual dysfunction, it was recorded, but the information was not elicited proactively. Left on their own, patients were much more likely to think that any sexual problem they were having was related to something in their relationship with their partner than to think that the problem had anything to do with the antidepressant medication they were taking. Now that the issues have been so widely discussed in the media, the level of awareness among patients may have risen. However, this does not change the fact that it is the physician's responsibility to elicit information about the sexual health of patients by direct and explicit inquiry.

In a recent prospective, multicenter study of the frequency of sexual dysfunction in 628 patients treated with an antidepressant,[13] patients were interviewed with a sexual dysfunction questionnaire that included questions about decreased libido, delayed orgasm and anorgasmia, delayed ejaculation, inability to ejaculate, impotence, and general sexual satisfaction. As is shown in Figure 3, antidepressant-induced sexual dysfunction occurred frequently. Nefazodone and mirtazapine had lower rates of sexual dysfunction than other antidepressants. Sexual dysfunction was positively correlated with dose. The patients experienced substantial improvement in sexual functioning when the dose was decreased or the medication was discontinued. Men showed a higher incidence of sexual dysfunction than women, but women's sexual dysfunction was more intense than that of men.

MANAGEMENT STRATEGIES FOR ANTIDEPRESSANT-INDUCED SEXUAL DYSFUNCTION

If a physician has done a careful history and has come to the conclusion that the sexual dysfunction is being caused by the patient's antidepressant treatment, what step should be taken next? There are a number of strategies discussed

Figure 3. Comparative Incidence of Antidepressant-Induced Sexual Dysfunction[a]



[a]Data from Montejo-Gonzalez et al.[13] Based on self reports from Sexual Dysfunction Questionnaire.

in the literature, each with pros and cons. One strategy is to wait and see if the side effect goes away.[8] In my experience, this is unlikely to happen with sexual dysfunction. In that respect, sexual dysfunction is similar to the side effect of weight gain. Over time, patients tend to accommodate to side effects such as dry mouth, sedation, constipation, or nausea. With weight gain or sexual dysfunction, however, waiting for the patient to accommodate to the side effect usually does not work.

Dose reduction of the antidepressant is another strategy that has been proposed.[8,13–15] However, this strategy runs counter to the current recommendations for the long-term treatment of depression: same drug, same dose. Some experts used to recommend tapering dosages for maintenance treatment of depression, but recent data suggest that this strategy is not a good idea. Thus, the idea of decreasing the antidepressant dose as an approach to alleviating sexual side effects runs very much counter to what we are learning about the most effective strategies for the acute and long-term treatment of depression.

Timing sexual activity in relation to the time of antidepressant administration is an interesting idea. This idea came from a study[16] in which patients on a once-a-day regimen of either sertraline or clomipramine were instructed to have sexual relations either an hour before or an hour after taking their once-a-day medication. This was the time of day in which the blood level of the antidepressant was presumed to be at its lowest point. This strategy allowed some people to have a return of sexual function. Of course, it is not necessarily a very convenient strategy, nor is it conducive to spontaneity in sexual relations.

Augmentation Therapy for SSRI-Induced Sexual Dysfunction

Numerous pharmacologic agents have been successfully used for treatment of sexual dysfunction induced by antidepressants, although none has been approved by the U.S. Food and Drug Administration (FDA) for this purpose. Unfortunately, most of the information regarding these augmentation strategies comes from anecdotal case reports of a small number of patients, not double-blind comparative studies.

Amantadine. Amantadine has been found to ameliorate SSRI-related sexual dysfunction in male and female patients.[17] Doses of amantadine typically used are 75 to 100 mg b.i.d. or t.i.d. or 100 to 400 mg as needed at least 2 days prior to coitus. The mechanism of action is most likely through its dopaminergic agonist effects.

Bupropion. The addition of bupropion as an augmentation therapy for the improvement of SSRI-associated sexual dysfunction has been described in case reports.[18,19] In a prospective, open, nonrandomized study of 47 patients receiving SSRI treatment,[20] augmentation with bupropion, 75 to 150 mg 1 to 2 hours before sexual activity, successfully relieved a variety of sexual dysfunctions in 38% of patients. Further increase of the bupropion dosage to 75 mg 3 times daily resulted in improvement in an additional 28% of patients. There was a trend that approached statistical significance for female patients receiving paroxetine or fluoxetine to be especially responsive to bupropion augmentation therapy. Side effects of anxiety and tremor led to discontinuation in 7 (15%) of the patients.

Clinicians should be aware of the potential for drug interactions when combining SSRIs and bupropion. Numerous case reports document serious adverse effects resulting from coadministration of bupropion in patients receiving fluoxetine or in the washout period after fluoxetine discontinuation. These have included tremor, anxiety and panic attacks, mild clonic jerks and bradykinesia, delirium, and seizures.[20–24] Fluoxetine has the potential to inhibit both the cytochrome P450 3A4 (CYP3A4) and the CYP2D6 hepatic isoenzymes that are believed to be at least partially responsible for the metabolism of bupropion and one of its major metabolites, hydroxybupropion, respectively.[25]

Buspirone. Buspirone is an antianxiety agent that has been used successfully as an augmentation therapy for overcoming SSRI-induced sexual dysfunction. In a retrospective study of 16 patients with SSRI-induced sexual dysfunction,[26] buspirone (5–10 mg 3 times a day) was effective in reversing sexual dysfunction in 11 patients (69%). Several patients reported that "as needed" use of buspirone on days when sexual relations were anticipated was equally effective. In a placebo-controlled trial designed to explore the efficacy of buspirone as an add-on treatment for patients not responding to an SSRI alone, Landen and colleagues[27] added buspirone (flexible dosage, 20–60 mg/day) or placebo in a double-blind paradigm to an SSRI for 4 weeks. At baseline, all patients met the criteria for a major depressive episode according to DSM-IV and had received citalopram or paroxetine for a minimum of 4 weeks. At endpoint, the mean ± SD daily dose of buspirone was 48.5 ± 1.0 mg. Sexual dysfunction was evaluated using a structured interview. Before starting medication with buspirone or placebo, 40% of patients (47/117) reported at least one kind of sexual dysfunction (decreased libido, ejaculatory dysfunction, orgasmic dysfunction). During the 4 weeks of treatment, 56% to 59% of patients treated with buspirone reported an improvement in sexual functioning compared with 25% to 30% in the placebo group. The difference between the placebo and buspirone was more pronounced in women than men. The response was evident during the first week, with no further improvement during the course of the 4-week study. The improvement in sexual functioning with the addition of buspirone was not due to an antidepressant effect of buspirone.

Several mechanisms have been proposed to account for the effects of buspirone for the reduction of SSRI-induced sexual side effects. In animal models, activation of postsynaptic serotonin-1A (5-HT_{1A}) receptors results in a shorter ejaculation latency.[28] Buspirone has partial agonist effects at 5-HT_{1A} receptors and may also suppress SSRI-induced elevation of prolactin by this mechanism.[29] In addition, buspirone also interacts with dopamine receptors.[30] Given the reports of prosexual effects attributed to indirect dopaminergic agonists such as amantadine and bupropion (see above) and methylphenidate (see below), the involvement of dopamine in the effects of buspirone on sexual functioning is also a possibility. Another possible mechanism is that the major metabolite of buspirone, 1-pyrimidinylpiperazine (1-PP), is an α_2 antagonist (similar to yohimbine; see below), which has been shown to facilitate sexual behavior in animals.[31] Buspirone is an appealing choice as an augmentation therapy for treating SSRI-induced sexual dysfunction because other reports exist that adjunctive buspirone therapy may augment the therapeutic efficacy of SSRI treatment.[32–35]

Cyproheptadine. Cyproheptadine, a medication with many actions including antiserotonergic and antihistaminic effects, has been used to treat sexual dysfunction side effects with the tricyclic antidepressants (TCAs) and the MAOIs. In recent years, the successful use of cyproheptadine to treat sexual dysfunction side effects from SSRIs has been reported. However, the improvement induced by cyproheptadine is at times transitory. Moreover, sedation and fatigue are common side effects.[36] Arnott and Nutt[37] reported on a 63-year-old man who had recurrent unipolar depression with pronounced obsessive thoughts and was successfully treated with cyproheptadine for fluvoxamine-induced anorgasmia. Ashton and colleagues[17] reported improvement in sexual functioning in 8 (42%) of 19 patients receiving cyproheptadine at doses of 4 to 16 mg/day for SSRI-induced sexual dysfunction. One concern regarding cyproheptadine is that some reports have described a worsening of depressive symptoms with this antiserotonergic medication.[38–42]

Psychostimulants. Case reports have suggested that psychostimulants may be effective in alleviating SSRI-induced sexual dysfunction. Bartlik and colleagues[43] described good results with low-dose dextroamphetamine (5 mg) in 1 patient and methylphenidate (5–25 mg) in 4 patients. The psychostimulant was administered approximately 1 hour before intercourse to patients with SSRI-induced inhibited orgasm or ejaculation. In another report,[44] a 46-year-old man on sertraline treatment who had erectile dysfunction, decreased libido, and orgasmic difficulty experienced significant improvement when pemoline (18.75 mg/day) was added to his medication regimen. Bartlik and colleagues[43] have raised the possibility that low dosages of psychostimulants may enhance orgasmic function, whereas higher dosages may have the opposite effect.

Sildenafil. Sildenafil citrate is a new medication indicated for the treatment of erectile dysfunction from an organic or psychogenic cause in men. Taken orally, sildenafil acts as a potent and selective inhibitor of cyclic guanosine 3',5'-monophosphate (cGMP) phosphodiesterase (PDES) enzyme. This inhibition causes an increased level of cGMP in the corpus cavernosum, which results in smooth muscle relaxation and inflow of blood to the corpus cavernosum.

Recently, several reports in the literature have described the successful use of sildenafil for SSRI-induced sexual dysfunction. Fava and colleagues[45] reported on the successful use of sildenafil augmentation of SSRI- and mirtazapine-induced sexual dysfunction in 9 men and 5 women. Additional cases of sildenafil augmentation for antidepressant-induced sexual dysfunction have been reported by several other groups.[46–54] Oral sildenafil treatment was well tolerated, with no discontinuation from adverse events. Currently, the use of sildenafil is approved by the FDA only for the treatment of male erectile dysfunction and has not yet been approved for use in women or as an antidote for antidepressant-induced sexual dysfunction.

Yohimbine. Yohimbine, an α_2-adrenoceptor antagonist, has been reported to alleviate sexual dysfunction side effects from TCAs and SSRIs.[55] Segraves[56] successfully treated 10 cases of SSRI-induced anorgasmia (5 men, 5 women) with

yohimbine (5.4 mg as needed) taken approximately 1 to 2 hours before intercourse. In a retrospective case review[17] of 21 patients taking yohimbine for SSRI-induced sexual dysfunction, 17 (81%) showed partial or complete improvement in sexual functioning. Caution should be used when prescribing yohimbine to patients with anxiety or panic attacks because yohimbine can cause sympathomimetic reactions such as anxiety and agitation.

Postsynaptic serotonin antagonists. Nefazodone, a potent 5-HT_2 antagonist, has been used as an augmentation therapy for SSRI-induced sexual dysfunction. Reynolds[57] described a 31-year-old man with anorgasmia during sertraline treatment that was relieved by the addition of 100 mg of nefazodone 1 hour before sexual relations. Mirtazapine, a tetracyclic antidepressant with antagonistic activity at 5-HT_3 and α_2 receptors, may also be used as an antidote therapy for SSRI-induced sexual dysfunction. Finally, Nelson and colleagues[58] reported that 1 mg of the 5-HT_3 antagonist granisetron administered 1 hour before intercourse improved libido and ability to achieve orgasm in a 46-year-old woman with fluoxetine-induced sexual dysfunction.

Ginkgo biloba. *Ginkgo biloba*, an extract derived from the leaf of the Chinese gingko tree, has been reported to be effective for the alleviation of antidepressant-induced sexual dysfunction in 1 nonblind study.[59] The rate of response ranged from 46% with fluoxetine to 100% with nefazodone, paroxetine, and sertraline. Dosages of *Ginkgo biloba* ranged from 60 mg q.d. to 120 mg b.i.d. (average = 209 mg/day). The common side effects were gastrointestinal disturbances, headache, and general central nervous system activation.

Drug Holidays

In 1994, some of our patients with sexual dysfunction side effects from SSRIs informed us that they had tried stopping their medication for a day or 2 and that this resulted in an improvement in sexual functioning without a worsening of depressive symptoms. We decided to study this systematically with the hope of adding another strategy for addressing sexual dysfunction side effects from SSRIs.[60] We studied 30 patients (10 taking fluoxetine, 10 taking paroxetine, and 10 taking sertraline) in whom there was no question that the sexual dysfunction was secondary to the SSRI. Patients were instructed to take their antidepressant in the morning (most were already doing this) Sunday through Thursday and then skip the doses scheduled for Friday and Saturday. On Thursday afternoon (prior to stopping the medication) and on Monday morning (after the weekend drug holiday), we rated patients on measures of sexual functioning and symptoms of depression as measured by the Hamilton Rating Scale for Depression (HAM-D). Each of the 30 patients performed the drug holiday on 4 different occasions. With the 2 SSRIs that have a relatively short half-life, sertraline and paroxetine, we found that about half of the patients had improvement in libido, sexual satisfaction, and orgasm function for at least 2 of the 4 weekends. With fluoxetine, a drug that has a longer half-life, we did not see any improvement in libido, sexual satisfaction, or orgasm function. No worsening of depressive symptoms was noted in any of the 3 groups. Two patients (1 taking sertraline and 1 taking paroxetine) had slight increases in HAM-D scores each time the drug holiday was implemented. We do not yet know the impact of this strategy on the overall efficacy of long-term antidepressant therapy, but the study does indicate that this is a potential strategy for addressing treatment-induced sexual dysfunction that may be effective for patients taking sertraline or paroxetine. It is worth noting that no significant symptoms of withdrawal or discontinuation were observed in any of the patients in this study. This finding may have been due in part to the fact that the dosages that the patients were taking prior to the drug holiday were at the lower end of the dose range.

Switching Antidepressants

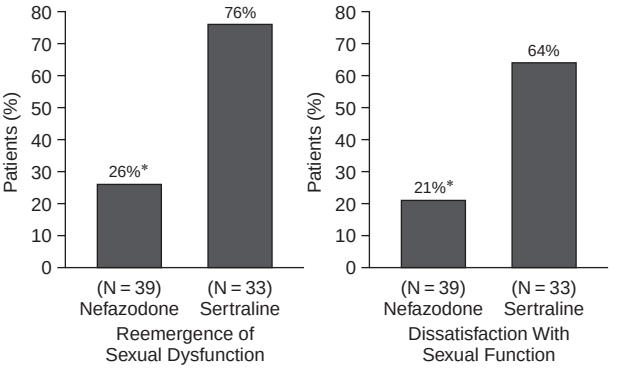
Switching antidepressants is another strategy available for addressing treatment-induced sexual dysfunction. Before switching therapies, however, several questions should be considered. First, will the new antidepressant maintain efficacy for the depressive disorder? In particular, for a patient who is achieving overall antidepressant efficacy from an SSRI but is suffering from sexual dysfunction, should treatment be switched to a drug such as bupropion that is nonserotonergic with more dopaminergic and noradrenergic type of activity, or should it be switched to a drug such as nefazodone, which is serotonergic but has a mechanism of action very different from that of the SSRIs? The question is, will this patient respond to the new antidepressant as he or she did to the medication that is currently causing the sexual dysfunction? And the final question is, will different side effects occur with the new antidepressant that were not present with the current antidepressant?

Switching from SSRIs to bupropion. Some clinical trial data are available regarding the impact on sexual functioning of switching from fluoxetine, an SSRI, to bupropion. Walker and colleagues[61] managed patients on fluoxetine treatment with sexual dysfunction by stopping their fluoxetine and switching them to bupropion. On switching, 64% reported a much or very much improved satisfaction with overall sexual functioning. However, 36% of the patients who were switched to bupropion subsequently discontinued the drug, in some cases because they did not get an antidepressant response and in other cases because they developed new side effects such as agitation. Thus, while switching to another antidepressant agent sounds like an attractive strategy for dealing with treatment-induced sexual dysfunction, it is not always a simple matter.

Switching from SSRIs to nefazodone. Ferguson and colleagues[62] reported on an 8-week, double-blind study that involved switching from sertraline, an SSRI, to nefa-

zodone. In the protocol, a 1-week washout period was followed by a 7- to 10-day, single-blind placebo phase. The patients without organic sexual dysfunction at the end of the single-blind phase were then randomly assigned to double-blind treatment with nefazodone at 200 mg/day or sertraline at 50 mg/day for 7 days. At day 8, dosages of nefazodone and sertraline were doubled for the remaining 7 weeks. At the end of the 8-week, double-blind study, no significant difference was found in mean total HAM-D scores in the patients who were switched to nefazodone from sertraline compared with the patients who were switched back to the sertraline. In terms of discontinuation rates, with nefazodone, 12% discontinued because of adverse events and 10% discontinued because of lack of efficacy. With sertraline, 26% discontinued because of adverse events and 3% discontinued because of lack of efficacy. As shown in Figure 4, a significantly lower percentage of nefazodone-treated patients reported dissatisfaction with sexual function compared with patients treated with sertraline. Although both treatments were well tolerated with an excellent safety profile, at the 8-week endpoint, 26% of the nefazodone-treated patients had a reemergence of sexual dysfunction, whereas 76% of the sertraline-treated patients had a reemergence of sexual dysfunction. Twenty-one percent of the patients taking nefazodone were dissatisfied with sexual functioning, whereas 64% of the patients taking sertraline were dissatisfied with sexual functioning. These differences were highly statistically significant.

Figure 4. Switching From a Selective Serotonin Reuptake Inhibitor to Nefazodone: Report of an 8-Week Double-Blind Study[a]



[a]Adapted from Ferguson et al.[62] and data on file, Bristol-Myers Squibb Company. Data are from 75 sertraline-treated patients who experienced sexual dysfunction upon either switching to nefazodone or restarting sertraline.
*p < .001 vs. sertraline (last-observation-carried-forward analysis).

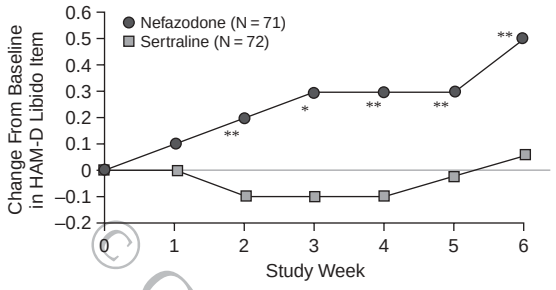
INITIAL ANTIDEPRESSANT SELECTION FOR SEXUALLY ACTIVE PATIENTS

Although patients may not be concerned with their sexual functioning when they first present with depressive symptoms, as the depression improves they become more aware of their sexual problems. Thus, it may be important to consider selecting an antidepressant initially that will have minimal effect on sexual function. Just as we consider other common side effects when prescribing initial therapy, such as dry mouth or fatigue, so we should also consider the potential impact of the medication on sexual functioning; both because sexual dysfunction is important in people's lives and also because patients are likely to be on antidepressant therapy for a considerable period of time.

A few antidepressants have been shown to induce sexual dysfunction side effects at a significantly lower rate than the SSRIs. In a double-blind 6-week study comparing nefazodone with sertraline, Feiger and colleagues[63] observed that nefazodone had a significantly lower rate of sexual dysfunction side effects than sertraline. Of the 160 patients enrolled in the study, approximately two thirds of each group were sexually active at entry into the study. Using the libido item of the HAM-D, item 14, as a measure of sexual function, the investigators demonstrated significantly more improvement in sexual desire in patients treated with nefazodone than patients treated with sertraline beginning as early as week 2 and continuing throughout treatment (Figure 5). This improvement in sexual interest occurred whether or not the patients were sexually active. However, no improvement was noted for patients taking sertraline. Using detailed questioning of the patients in the study, Feiger and colleagues observed that in women, nefazodone was significantly superior to sertraline on measures of ease of achieving orgasm and satisfaction with the ability to achieve orgasm at week 6 of the study (Figure 6). Similar results were observed in men who were asked about difficulty with ejaculation and ability to enjoy sex (Figure 7). A dramatic increase in the percentage of men who reported difficulty with ejaculation was observed in patients taking sertraline compared with only a slight increase among those men treated with nefazodone. In fact, by the end of the study, two thirds of the men taking sertraline reported difficulty with ejaculation. An increased percentage of men treated with nefazodone reported an ability to enjoy sex, whereas the percentage among men treated with sertraline decreased.

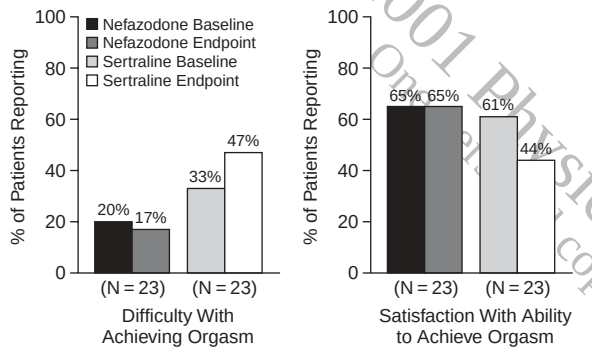
In a study comparing bupropion sustained release (SR) with sertraline, Kavoussi and colleagues[64] reported a lower frequency of self-reported orgasm dysfunction in patients treated with bupropion SR compared with sertraline. This study permitted rapid upward titration of the sertraline dose at 50-mg increments at weekly intervals to a maximum of 200 mg/day after 3 weeks and did not permit downward titration of the dose. This dosing schedule may have resulted in an exaggerated incidence of orgasm delay in the sertraline group. Another limitation of this study is the fact that the investigators used self-report questionnaires as opposed to direct interviews of the patients. A previous study[3] has demonstrated that direct interviewing of patients is a more

Figure 5. Six-Week, Double-Blind Comparison of Nefazodone Versus Sertraline: Effects on Desire[a]



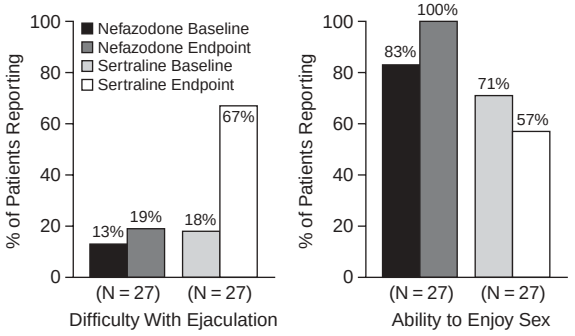
[a]Data from Feiger et al.[63] Abbreviation: HAM-D = Hamilton Rating Scale for Depression.
*p ≤ .05 vs. sertraline. **p ≤ .01 vs. sertraline.

Figure 6. Six-Week, Double-Blind Comparison of Nefazodone Versus Sertraline: Results in Women[a]



[a]Data from Feiger et al.[63]

Figure 7. Six-Week, Double-Blind Comparison of Nefazodone Versus Sertraline: Results in Men[a]



[a]Data from Feiger et al.[63]

reliable and accurate means of assessing sexual dysfunction than self-report questionnaires.

Although no double-blind studies comparing mirtazapine with SSRIs have specifically looked at differences in rates of sexual dysfunction side effects, results from double-blind efficacy studies comparing mirtazapine with placebo, as well as the proposed mechanism of action of mirtazapine, suggest that it may also have a lower rate of sexual dysfunction compared with the SSRIs.[65]

SUMMARY

In summary, depressed patients care as much about their sexual functioning as do members of the general population. Sexual dysfunction can have a negative impact on the patients' quality of life and may lead to medication noncompliance and then relapse. Patients usually do not spontaneously report their sexual problems, and thus it is critical for physicians to assess sexual function during the initial evaluation and throughout treatment. A variety of management strategies are available to deal with the problem of treatment-induced sexual dysfunction. However, it is also important to consider the importance of sexual functioning when selecting initial antidepressant therapy for sexually active patients. Some agents, such as nefazodone, bupropion, and possibly mirtazapine, are much less likely to compromise sexual functioning compared with the SSRIs and other classes of antidepressant drugs.

Drug names: amantadine (Symmetrel and others), bupropion (Wellbutrin), buspirone (BuSpar), citalopram (Celexa), clomipramine (Anafranil and others), cyproheptadine (Periactin), dextroamphetamine (Dexedrine and others), fluoxetine (Prozac), fluvoxamine (Luvox), granisetron (Kytril), methylphenidate (Ritalin and others), mirtazapine (Remeron), nefazodone (Serzone), paroxetine (Paxil), pemoline (Cylert), sertraline (Zoloft), sildenafil (Viagra), trazodone (Desyrel and others), venlafaxine (Effexor), yohimbine (Yocon and others).

Disclosure of off-label usage: The author of this article has determined that, to the best of his knowledge, the following agents mentioned in this article are not approved by the U.S. Food and Drug Administration for the treatment of sexual dysfunction: amantadine, bupropion, buspirone, cyproheptadine, dextroamphetamine, granisetron, methylphenidate, mirtazapine, nefazodone, pemoline, sildenafil, and yohimbine.

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