Antidepressant-Induced Sexual Dysfunction

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This article reviews current evidence regarding sexual side effects of antidepressant drugs. Controlled studies have demonstrated that some antidepressant drugs have adverse effects on orgasm and libido. Orgasmic dysfunction and ejaculatory delay appear to be common sexual side effects of the serotonin selective reuptake inhibitors (SSRIs). A variety of treatment options are available if a patient experiences antidepressant-induced sexual dysfunction. Often, modification of the pharmacologic regimen will restore sexual function while maintaining antidepressant activity. The frequency of sexual side effects reported with the SSRIs mandates that the clinician inquire about sexual function if these agents are used. Bupropion and nefazodone appear to have an unusually low incidence of sexual side effects.
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It is generally accepted among psychopharmacologists that treatment with antidepressant drugs, especially agents with strong serotonergic effects, is associated with sexual side effects. Although a variety of antidepressant-related sexual difficulties have been reported in the literature, most of the evidence is consistent in finding that orgasmic dysfunction and ejaculatory dysfunction are frequently associated with the serotonin selective reuptake inhibitors (SSRIs), including sertraline, fluoxetine, and paroxetine.

The exact incidence of sexual side effects among antidepressants is unknown. This information is lacking in part because clinicians and clinical investigators depend on the patient to spontaneously report sexual problems. Patients' willingness to report such problems varies considerably, and studies that use patient self-report have been shown to greatly underestimate the frequency of sexual problems.[1]

The purpose of this paper is to critically review the available evidence concerning sexual side effects associated with antidepressant medication. To put this review in perspective, it is important to remember that sexual problems are often part of the depressive syndrome itself and that successful psychopharmacologic treatment may reverse depressive symptoms, including sexual dysfunction. However, in other cases, psychopharmacologic intervention may induce a high incidence of sexual side effects.

ANTIDEPRESSANTS AND ANORGASMIA

Although a wide variety of side effects has been reported with antidepressant use, the most clearly substantiated complaint appears to be delayed orgasm or ejaculation. The first controlled study of the effect of antidepressant medication on sexual function was reported by Harrison and colleagues.[2,3] A sexual function questionnaire was administered to participants in the double-blind placebo-controlled trial of imipramine and phenelzine. Patients took between 60 and 90 mg of phenelzine or between 200 to 300 mg of imipramine for 6 weeks. The questionnaire was administered prior to treatment and at the end of treatment to both male and female subjects. Delayed orgasm was noted by 21% of the men taking imipramine and 30% of the men taking phenelzine. No delay was noted with placebo. Orgasmic delay was noted by 11% of women taking placebo, 27% of women taking imipramine, and 36% of women taking phenelzine. Monteiro and colleagues[1] studied the effect of clomipramine (a drug approved for obsessive-compulsive disorder in the United States but used extensively as an antidepressant in many other countries) on sexual function in patients of both sexes with obsessive-compulsive disorder. Information was obtained by direct questioning of patients. Ninety-six percent of patients who had previously been able to reach orgasm became anorgasmic while taking clomipramine. Only about one third of patients spontaneously reported their sexual difficulty, and a questionnaire including a question concerning sexual satisfaction did not distinguish the patients taking drug from those taking placebo. There was no sex difference in the frequency with which clomi-

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pramine interfered with orgasm. It is of note that two separate studies have established that the orgasmic delay induced by clomipramine can be used to treat premature ejaculation.[4,5] Thus, two independent lines of evidence support the observation that clomipramine can delay ejaculation.

Two recent double-blind controlled studies have compared sexual side effects of sertraline with those of other antidepressants. In a multisite double-blind comparison of nefazodone and sertraline, Feiger and coworkers[6] studied 160 patients taking 100–600 mg of nefazodone or 50–200 mg of sertraline per day. Sexual function was assessed by a series of questions asked of each patient. Women taking nefazodone reported significantly greater ease reaching orgasm than women taking sertraline. Approximately 47% of women taking sertraline reported difficulty reaching orgasm. Of the men taking sertraline, 67% reported difficulty with ejaculation. The percentage of patients reporting orgasmic delay with nefazodone use was essentially unchanged from baseline. There was no significant difference between patients taking nefazodone and those taking sertraline on measures of libido, erection, and lubrication. Somewhat similar results were found in a multisite double-blind comparison of the effect of sertraline and bupropion sustained release (SR) on sexual function. In this study of patients receiving 50–200 mg of sertraline or 150–300 mg of bupropion SR, Kavoussi[7] found that 39% of patients taking sertraline experienced orgasmic delay versus 7% taking bupropion SR. This difference between the two drugs was statistically significant as soon as 7 days after drug administration. In contrast to the study of Feiger et al. that found no difference between sertraline and nefazodone, Kavoussi found significant differences between the effects of bupropion and sertraline on libido, lubrication, and erection. In all cases, the patients taking bupropion had higher levels of sexual function. In another double-blind study, patients who had orgasmic problems while taking sertraline were blindly assigned either to sertraline or nefazodone therapy for 8 weeks.[8] Seventy-one percent of the sertraline-treated patients had a continuation of orgasmic dysfunction, whereas only 30% of nefazodone-treated patients had orgasmic difficulties. It is unclear why such a large number of patients who were switched to nefazodone failed to have a restoration of orgasmic function. Mendels et al.[9] utilized the retardation of ejaculation by sertraline to successfully treat premature ejaculation, providing independent validation that sertraline is associated with ejaculatory delay.

To this author's knowledge, there have been no controlled studies assessing the association of fluoxetine or paroxetine with ejaculatory delay. However, a number of clinical series[10,11] have reported similar rates of delayed ejaculation in patients taking paroxetine, sertraline, or fluoxetine. These studies, which are based on retrospective case reports, report that approximately 30% of patients taking an SSRI will experience orgasmic or ejaculatory delay. Reinforcing the impression that paroxetine has an effect of delaying ejaculation is a report by Waldinger et al.[12] from the Netherlands that paroxetine is an effective agent for the treatment of premature ejaculation. Fluoxetine was originally listed as having an incidence of male ejaculatory problems of less than 2%.[13] In the *Physicians' Desk Reference*, female sexual problems are not mentioned in association with fluoxetine use. However, clinical series using fluoxetine have reported orgasmic disturbance in both sexes.[14] Clinicians who have utilized direct patient inquiry about sexual function have reported orgasmic delay to be present in 24% to 75% of patients.[15,16] The presence of sexual dysfunction in patients taking fluoxetine may be dose related, as some clinicians have reported successful restoration of sexual function by lowering the dose of fluoxetine. Again, there have been reports of successfully using fluoxetine to treat premature ejaculation.[17]

Two separate studies[18,19] have indicated that fluvoxamine, a drug approved for the treatment of obsessive-compulsive disorder in the United States, has approximately a 10%–12% incidence of sexual side effects—predominantly delayed orgasm and ejaculation. Both studies relied on spontaneous self-report by the patients and thus probably underestimated the true incidence of sexual problems associated with fluvoxamine. The cyclic antidepressants, including amitriptyline, amoxapine, desipramine, doxepin, maprotiline, nortriptyline, protriptyline, and trimipramine, have all been reported to be associated with orgasmic disorder, as has trazodone.[20] We have minimal evidence regarding the true incidence of anorgasmia associated with any of these drugs.

Three drugs may have extremely low or no sexual side effects. These drugs are bupropion, nefazodone, and mirtazapine. In an open trial, patients taking fluoxetine have had their orgasmic dysfunction relieved by the discontinuation of the offending agent and substitution of bupropion.[21] Ninety-four percent of women in this trial who were anorgasmic while taking fluoxetine had the problem resolved by the substitution of bupropion. As previously reported, in a double-blind comparison with sertraline, only 7% of patients taking bupropion SR experienced orgasmic delay.[7] This is probably at the same level as a placebo response. Unfortunately, this study did not include a placebo condition. The early studies also indicated that nefazodone has an extremely low rate of sexual dysfunction, perhaps close to placebo levels. It is unclear whether mirtazapine will also produce an extremely low incidence of sexual dysfunction. Early clinical trial data suggest a minimal effect on sexual behavior. A double-blind study incorporating direct physician questioning about sexual behavior will be necessary to establish whether this new drug has a high incidence of sexual dysfunction. Table 1 lists antidepressants and their probable frequency of causing

Table 1. Incidence of Antidepressant-Induced Anorgasmia*

Phenelzine	30%
Clomipramine	96%
Imipramine	20%–30%
Fluoxetine	20%–75%
Sertraline	20%–67%
Paroxetine	20%–30%
Venlafaxine	20%–30%

*Data from references 1–3, 6, 7, 10, 15, 16.

Table 2. Treatment of SSRI-Induced Anorgasmia*

Yohimbine	1–2 tablets	prn, tid
Cyproheptadine	4–8 mg	prn
Amantadine	100–400 mg	prn
Bupropion	75 mg	Daily
Dextroamphetamine	20 mg	Daily
Pemoline	18.75 mg	Daily
Buspirone	15–60 mg	Daily or prn

*Data from reference 76.

orgasmic problems. To date, there has been insufficient study to indicate whether or not mirtazapine will be devoid of sexual side effects. Its 5-HT_2 blockade plus its α_2 antagonism suggest that it may prove to be devoid of sexual problems.

Other Orgasmic Problems Associated With Antidepressant Use

Painful ejaculation has been reported with imipramine[14] and amoxapine.[22,23] There have been episodic case reports of spontaneous orgasm accompanied by yawning apparently induced by both clomipramine[24] and fluoxetine.[25,26]

Medical Management of Antidepressant-Induced Anorgasmia

A variety of strategies for managing antidepressant-induced anorgasmia have been reported to be successful. Unfortunately, most of the strategies have been documented only in case reports or small clinical series. The major strategies reported are (1) waiting for tolerance to develop, (2) dose reduction, (3) alteration of dosing regimen, (4) substituting a different antidepressant, and (5) coadministering another agent to counteract the anorgasmia induced by the prescribed antidepressant. There have been reports of tolerance developing sometimes after months of chronic dosing with both monoamine oxidase inhibitors[27] and sertraline.[28] Dose reduction has been reported to restore normal sexual function while maintaining antidepressant efficacy with both fluoxetine and phenelzine.[16,29] Drug-induced anorgasmia can sometimes be circumvented by timing coitus to occur before the latest drug dose or on drug holidays. This technique has been reported to be successful with both sertraline and clomipramine.[30,31] Drug substitution has been reported to be successful in a large clinical series when bupropion was substituted for fluoxetine[8] and in a controlled study in which nefazodone was substituted for sertraline.[21] A variety of drugs have been reported to be successful in reversing antidepressant-induced anorgasmia when coadministered as an antidote. Bethanechol, a cholinergic agent, has been reported to reverse anorgasmia induced by imipramine,[32] protriptyline,[33] and amoxapine.[34] The usual strategy reported is to give 10–20 mg of bethanechol 1 to 2 hours prior to planned coitus.[35]

Cyproheptadine, a 5-HT_2 antagonist with antihistaminic and adrenolytic properties, has also been reported by some authors to be useful in the treatment of antidepressant-induced sexual dysfunction. There have been case reports that this drug is effective in reversing anorgasmia induced by clomipramine,[36] nortriptyline,[37] imipramine,[38] tranylcypromine,[39] fluoxetine,[40,41] and fluvoxamine.[42] Cyproheptadine is ineffective in some patients[43] and can reverse antidepressant activity of fluoxetine if taken on a daily basis.[44,45] For this reason, it is usually given on an as-needed basis prior to coitus. Usual doses are 4–8 mg taken before planned coitus. Excessive drowsiness may interfere with the desired outcome.

Yohimbine, an α_2 antagonist, has been found to reverse anorgasmia associated with clomipramine, fluoxetine, sertraline, paroxetine, and fluvoxamine. The usual dosing strategy is 5.4 to 10.8 mg taken 1–2 hours prior to planned sexual activity. In some patients, yohimbine may cause agitation or elicit panic attacks.[46–48]

Other approaches reported to be helpful in reversing SSRI-induced anorgasmia include the addition of amantadine,[49–51] bupropion,[52] dextroamphetamine,[53,54] pemoline,[54] or buspirone.[55] The information concerning antidotes for drug-induced anorgasmia are listed in Table 2.

ANTIDEPRESSANTS AND ERECTILE DYSFUNCTION

Although the evidence linking antidepressant use to orgasmic delay is fairly convincing, the evidence linking antidepressant use to erectile dysfunction is less clear. The situation is difficult to evaluate as erectile dysfunction may occur as part of the presenting symptomatology of major affective disorder.[56] Case reports have suggested that a variety of antidepressant drugs may be associated with erectile failure. These include fluoxetine, paroxetine, sertraline, venlafaxine,[11,57] imipramine, desipramine, nortriptyline, amitriptyline, doxepin, protriptyline, amoxapine, trazodone, maprotiline, and tranylcypromine.[58] The few double-blind studies done have not usually confirmed an adverse effect of antidepressant drugs on erectile function. For example, Harrison and coworkers,[2] in a double-blind, placebo-controlled study of imipramine and phenelzine, found minimal evidence that either drug interfered with erectile function. In a double-blind, placebo-controlled study that used volunteers and that included nocturnal penile tumescence as a dependent measure, Kowalski and coworkers[59] found that amitriptyline and mianserin both decreased the magnitude and duration of

nocturnal erections. However, these same subjects reported minimal change in their waking sexual function. A controlled study of the effect of lithium carbonate on erectile function suggests that lithium may interfere with erectile function.[60] To my knowledge, this study is the only controlled study that has examined the effect of lithium on erectile function. Reports by some clinicians have been consistent with a proposed adverse effect of lithium on erectile function,[61,62] whereas those by others have not.[63]

Medical Management of Antidepressant-Induced Erectile Dysfunction

There is minimal evidence regarding the use of antidotes to treat antidepressant-induced erectile dysfunction. Isolated case reports have suggested that bethanechol taken prior to coitus may be helpful.[35] A large clinical series[64] found that patients experiencing erectile failure while taking a variety of antidepressants had the problem relieved with the substitution of bupropion. Similarly, nefazodone does not appear to cause erectile problems as a drug side effect. Drug substitution would appear to be the preferred approach for treating antidepressant-induced erectile problems.

ANTIDEPRESSANT THERAPY AND LIBIDO

Untreated affective disorder has been found to be associated with decreased libido, and the successful treatment of affective disorder is frequently associated with the return of normal libido.[65,66] Thus, the correct interpretation of the association between antidepressant therapy and alterations of libido can be quite difficult. It is difficult to know when the complaint is secondary to the disease process or its treatment. If an antidepressant drug has a delayed effect of decreases libido, one could observe a biphasic effect such that libido increases as the depression lifts and then decreases as the drug effect on libido exerts itself. A large number of antidepressants have been reported to cause changes in libido. Drugs reported to decrease sex drive include phenelzine, tranylcypromine, amitriptyline, clomipramine, desipramine, doxepin, imipramine, maprotiline, nortriptyline, protriptyline, alprazolam, lithium, fluoxetine, paroxetine, sertraline, and venlafaxine.[20,35,57] It is also of note that both bupropion[7,67] and trazodone[35] have been reported to increase libido above the level existing prior to depression.

A small number of controlled studies with adequate methodology have examined the effect of antidepressant medication on libido. In a previously mentioned multisite, placebo-controlled, double-blind study comparing sertraline and bupropion SR,[7] libido was found to return to significantly higher levels for patients taking bupropion SR than for those taking sertraline. In fact, there was some evidence that libido in bupropion SR–treated patients exceeded levels experienced prior to the onset of depression. In the double-blind, placebo-controlled comparison of imipramine and phenelzine previously mentioned,[2] decreased libido was noted in approximately 30% of patients taking phenelzine and 20% taking imipramine compared with about 10% taking placebo.

Treatment of Antidepressant-Induced Decreased Libido

Two open-label studies, one involving a switch from multiple antidepressants to bupropion and the other involving a switch from fluoxetine to bupropion,[21,64] noted an increase in libido upon discontinuing the other drug or drugs and starting bupropion. Similarly, studies to date have shown no libido decrement associated with switching from sertraline to nefazodone.[8] One author has reported that 7.5 to 15 mg of neostigmine[68] given prior to coitus restored libido, and another author recommended 5.4 mg of yohimbine t.i.d.[15] Isolated reports have found that libido disturbances coexisting with other sexual problems resolve with the addition of buspirone,[55] amantadine,[49] or cyproheptadine.[43] The weight of the evidence would suggest drug substitution of bupropion or nefazodone as a preferred strategy for treating antidepressant-induced libido disturbances.

OTHER ANTIDEPRESSANT-INDUCED SEXUAL SIDE EFFECTS

Vaginal anesthesia[69] and penile anesthesia[70] have been reported with fluoxetine, and painful ejaculation has been reported with imipramine, amoxapine, and clomipramine.[14] Penile priapism has been reported with trazodone.[71] Clitoral priapism has been reported with bupropion.[72] Improved erectile function has been reported with both fluoxetine[73] and trazodone[74] in case reports.

MECHANISMS BY WHICH ANTIDEPRESSANTS MIGHT INFLUENCE SEXUAL FUNCTION

Laboratory research in animals has indicated that dopaminergic, noradrenergic, serotonergic, cholinergic, GABAergic, and opiate neurotransmitter systems are involved in the regulation of sexual behavior. These studies can be useful in generating hypotheses regarding the mechanisms by which psychotropic agents might influence sexual behavior in the human. However, one needs to remember that there are numerous limitations in extrapolating to the human from these studies. First, the indices used in studying sexual behavior in the laboratory animal (e.g., intromission latency, copulatory efficiency) are often quite dissimilar to the measures investigators and clinicians employ when studying humans. There may also be differences in species regarding the neurotransmitters involved. In addition to these difficulties, many of the neurotransmitters which might be involved are present in the

peripheral as well as the central nervous system, and actions at one site in the central nervous system might be quite different from actions in another part of the nervous system. Drugs such as the SSRIs may influence serotonin in numerous serotonin subsystems. The impact of these drugs may vary considerably between individuals, depending on the particular subsystems that are activated in given individuals.[75] This could partially explain why most individuals experience orgasmic delay while taking fluoxetine, whereas a few individuals have been reported to experience spontaneous orgasm while taking the same drug.[76]

The neurophysiologic responses involved in sexual behavior include a complex sequencing of events within a network of interconnected regulatory centers in the brain, brain stem, spinal cord, and peripheral nervous system. Orgasm can be conceptualized as the sensory experience of a series of spinal cord reflexes that are triggered when sensory stimuli reach threshold levels. Higher nervous system centers are believed to exert inhibitory control over these spinal cord reflexes. In the monkey, ejaculation can be activated by stimulation of the anterior thalamus and preoptic area.[77] In general, studies have found that increased central serotonergic activity is inhibitory to ejaculation. Studies of receptor subtypes have suggested that 5-HT_2 receptors are inhibitory to ejaculation,[78–80] whereas other serotonergic receptors may be facilitatory. Adrenergic,[81] cholinergic,[82] and dopaminergic[83] influences on the central nervous system have been found to facilitate ejaculation in laboratory studies employing animal models. Peripherally, efferent signals for ejaculation travel in the hypogastric nerve, which synapses with a series of short adrenergic nerves. Stimulation of the hypogastric nerve elicits ejaculation. Both adrenergic and cholinergic fibers are present in the peripheral organs involved in orgasm. The role of the cholinergic fibers is unclear.

The current evidence concerning the effect of antidepressants on orgasm could probably be accommodated by the hypothesis that orgasm is regulated by a balance of cholinergic and adrenergic influences and that 5-HT_2 receptors inhibit adrenergically mediated ejaculation. This hypothesis would account for the absence of an effect of nefazodone and bupropion on ejaculation as well as the correction of SSRI-induced anorgasmia by drugs that have adrenergic effects such as yohimbine and dextroamphetamine and by drugs that have antiserotonergic effects such as cyproheptadine and buspirone (by stimulating the serotonin autoreceptor).

Lubrication and erection are the result of reflex vasodilation of the genital vasculature. The genitalia in both sexes have a dual innervation—a sympathetic outflow from T12 (thoracic vertebra) to L4 (lumbar vertebra) and a parasympathetic outflow from S2 (sacral vertebra) to S4. The postganglionic neurotransmitter responsible for erection is unclear.[84] Cholinergic fibers are considered to have only a minor role in erection, although they may enhance the lubrication or erection response by suppressing adrenergic tone or enhancing the action of an endothelium-derived relaxing factor that may be nitric oxide.[85,86] The effect of nitric oxide may be mediated by stimulation of guanylate cyclase and production of cyclic guanosine monophosphate (a second messenger). The observation that sildenafil, an inhibitor of cyclic guanosine monophosphase–specific phosphodiesterase, facilitates penile erection supports this hypothesis.[87] Stimulation and ablation experiments in laboratory animals have identified cerebral areas associated with erection. These include the preoptic area and anterior hypothalamus.[77] Maeda et al.,[88] after a series of stimulation and ablation experiments, proposed that dopaminergic stimulation may activate the raphe-hippocampal serotonergic pathway, which enhances the septohippocampal cholinergic pathway eliciting penile erection. In this model, 5-HT_1 and 5-HT_3 play a regulatory role. This model may offer a basis for understanding how antidepressant drugs with serotonergic action may influence the erectile process.

CONCLUSION

In this decade, our knowledge of the sexual side effects of psychotropic drugs has increased dramatically. Psychiatric clinicians have become much more knowledgeable about these side effects, and a beginning knowledge base is accumulating concerning the sexual side effect profiles of the major antidepressants as well as ways to counteract antidepressant-induced sexual disorders. The frequency with which such side effects occur and patient reticence to spontaneously report such problems mandate that clinicians routinely inquire about the sexual behavior of their patients who are taking psychotropic agents.

Drug names: alprazolam (Xanax), amantadine (Symmetrel), amitriptyline (Elavil and others), amoxapine (Asendin), bethanechol (Urecholine), bupropion (Wellbutrin), buspirone (BuSpar), clomipramine (Anafranil), cyproheptadine (Periactin and others), desipramine (Norpramin and others), dextroamphetamine (Dexedrine), doxepin (Sinequan and others), fluoxetine (Prozac), fluvoxamine (Luvox), imipramine (Tofranil and others), maprotiline (Ludiomil), mirtazapine (Remeron), nefazodone (Serzone), neostigmine (Prostigmin), nortriptyline (Pamelor and others), paroxetine (Paxil), pemoline (Cylert), phenelzine (Nardil), protriptyline (Vivactil), sertraline (Zoloft), tranylcypromine (Parnate), trazodone (Desyrel and others), trimipramine (Surmontil), venlafaxine (Effexor), yohimbine (Yocon and others).

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