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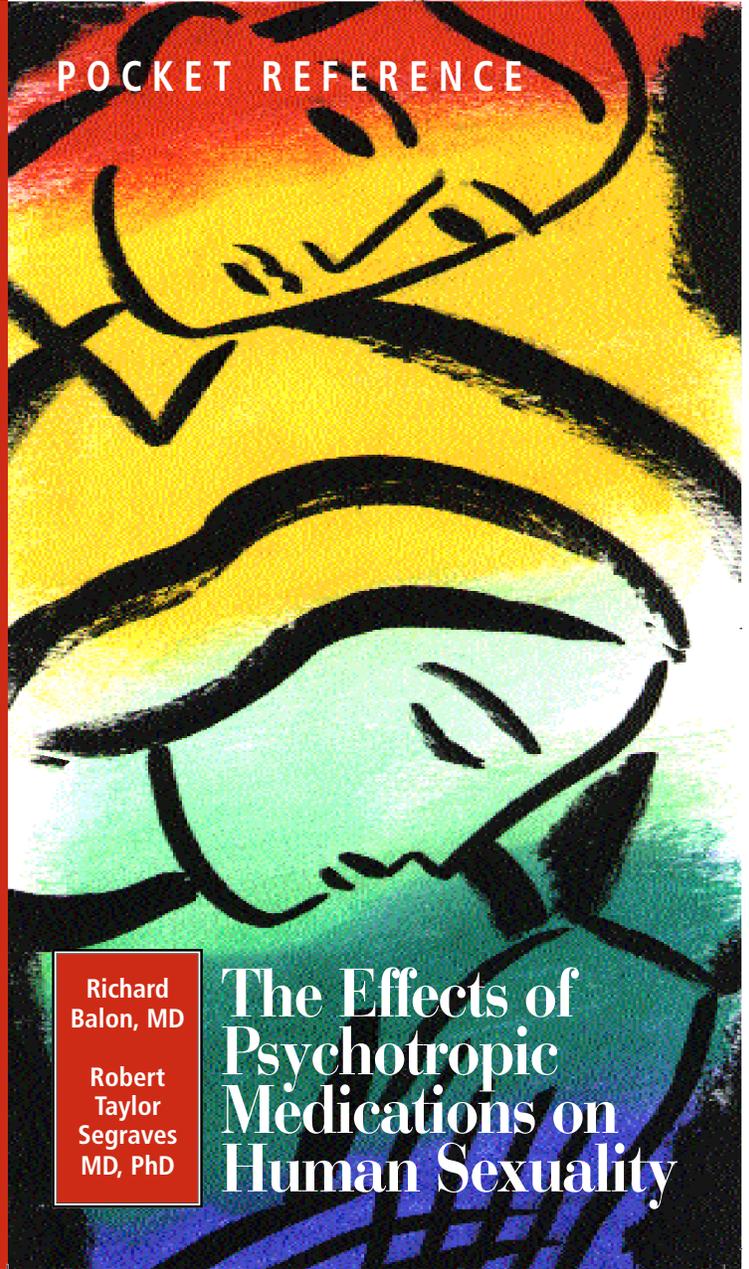
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The Effects of Psychotropic Medications on Human Sexuality



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The Effects of Psychotropic Medications on Human Sexuality

TWO SECTIONS:

The Effects of Antidepressants on Human Sexuality: Diagnosis and Management Update

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Sexual Dysfunction: Diagnosis and Treatment

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The Effects of Antidepressants on Human Sexuality: Diagnosis and Management Update 2007

By Richard Balon, MD

Abstract

What sexual dysfunction (SD) side effects are associated with antidepressant drugs and how can these side effects be managed? Until recently, few studies explored the effects of antidepressants in human sexuality. Now, the amount of information about this concern is growing. Initial studies have found that among the selective serotonin reuptake inhibitors (SSRIs), paroxetine may have the highest incidence of SD. Other studies show that patients treated with SSRIs experience significantly more SD than those treated with tricyclic antidepressants, whereas some research concludes that the effects of SSRIs on sexual function seem strongly dose-related. Importantly, these studies provide suggestions for techniques that may manage or diminish sexual dysfunction. This article offers insight into current research findings related to SD in antidepressant drug use and outlines several management strategies, such as the "antidotes" and "switching" strategies, among others, that may prove to be beneficial in diminishing SD. The direct questioning of SD patients is also an appropriate means of obtaining more accurate rates of incidence.

Introduction

Diagnosis and management of sexual dysfunction associated with antidepressants has been the topic of a series of articles published in *Primary Psychiatry* since 1995.¹⁻³ Still, even though sexual dysfunction (SD) has now been recognized as a serious side effect of antidepressant drugs, not all studies report SD. Some of the reports on efficacy and tolerability of antidepressants may still be reporting data from an era when not much attention was paid to SD, while other studies use old side effects—reporting tools that do not list SD, or spontaneous reporting, which does not yield the best information on SD. Finally, some studies may simply try to avoid the issue of sexual dysfunction for marketing reasons.

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Glossary

Anorgasmia

Inability to achieve orgasm, absence of orgasm

Drug holidays

Regular periods during which the patient is not given medication

Impaired erectile capacity

Persistent or recurrent inability to attain or to maintain an adequate erection until completion of sexual activity

Libido

Sexual desire, drive, interest

Priapism

Persistent penile erection accompanied by severe pain

Primary sexual dysfunction

Disturbance in sexual desire and in the psychophysiological changes that characterize the sexual response cycle, causing marked distress; the term "primary" refers to etiology

Nevertheless, the amount of information in the literature on SD associated with antidepressants has been steadily growing. Since the publication of the latest update on this topic in *Primary Psychiatry* in 1998,³ there have been numerous reports and articles published that either focused solely on SD or mentioned SD in the context of antidepressant tolerability. This review focuses on the more interesting and/or important publications in this area and does not cover every published article on SD associated with antidepressants.

What's New

Review Articles

Drs. Waldinger and Olivier⁴ discuss results of their own research on the effects of various selective serotonin reuptake inhibitors (SSRIs) on rapid or premature ejaculation. They conclude that out of four studied SSRIs—fluvoxamine, fluoxetine, paroxetine, and sertraline—fluvoxamine had by far the least disturbing effect on ejaculation. Citalopram was unfortunately not included in their studies. Segraves⁵ pointed out that delayed orgasm or ejaculation is the most clearly substantiated complaint with antidepressant use. Rosen and colleagues, in their comprehensive review on SSRIs and SD,⁶ came to the same conclusion: delayed ejaculation and absent or delayed orgasm are the most commonly associated sexual side effects from SSRIs. They also concluded that the effects of SSRIs on sexual function seem

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TABLE 1: Causes of sexual dysfunction in depressed patients

- Part of depressive symptomatology
- Concomitant medical illness
- Primary sexual dysfunction
- Side effect of antidepressant medication
- Side effect of other medication
- Combination of some or all of these factors

strongly dose-related and may vary among the group according to serotonin and dopamine reuptake mechanisms, induction of prolactin release, anticholinergic effects (eg, paroxetine), inhibition of nitric oxide synthetase, and propensity of the drug and/or its metabolite to accumulate over time. Some of the explanations seem to be contradictory, however, as in the case of paroxetine, for which both the lack of effects on the dopamine system and selectivity of paroxetine relative to dopamine reuptake (prolactin) are used to explain various effects.

Even though lack of sexual desire has been reported less with antidepressants, the lack of sexual desire or hypoactive sexual desire disorder could be a diagnostic and management challenge during the treatment of depression. In her instructive review, Domeena Renshaw⁷ provides guidance to the management of this problem and concludes that sexual disinterest is highly treatable with brief supportive intervention. In addition, an interesting article by Holmes and colleagues⁸ focuses on SD in women. These last two articles do not deal solely with antidepressant-associated SD, but they provide very good guidance in distinct, less frequently studied areas.

Original Observations

Studies

Some of the published studies focused exclusively on SD with antidepressants. Ashton and colleagues⁹ reviewed charts of 596 patients seen in a private practice office. SDs were associated with SSRIs in 16.3% of their sample, with orgasmic delay or anorgasmia and hypoactive sexual desire being the most frequent dysfunctions. Interestingly, SDs were more frequent among men and married patients of both sexes, whereas psychiatric diagnosis and type of SSRI were unrelated to the occurrence of SD. About 46% of their patients with SD opted for a trial with either yohimbine, amantadine, or cyproheptadine. All three antidotes were safe and relatively effective, although yohimbine was more effective than amantadine or cyproheptadine. The obvious limitations of this

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study are its retrospective and descriptive character and lack of placebo control. Ashton and Rosen¹⁰ also studied what happens to SD "naturally." They monitored 132 SSRI medication trials in 97 patients in private practice. A small portion of the medication trials (9.8%) demonstrated accommodation to SSRI-induced SD or spontaneous remission. Unfortunately, due to the naturalistic character of this report, the description of the duration to accommodation to the effect of SSRIs is missing; it is not clear how long it took until the SD disappeared.

A group of 20 Spanish clinicians¹¹ conducted a prospective, observational, open, and multicentric study of SD associated with SSRIs in 344 outpatients (192 women, 152 men). The overall incidence of SD was 58.1%. The authors noted that significantly more patients reported SD when their physicians asked them about it directly (58%). Only 14% of patients spontaneously reported SD. They also observed that paroxetine provoked significantly more orgasm or ejaculation delay and impotence than fluvoxamine, fluoxetine, or sertraline ($P < 0.05$). Only 24.5% of patients "tolerated" their SD. SD was positively correlated with the dose of the antidepressant. Men showed higher incidence of SD than women, but women's SD was more intense than that of men. Only 5.8% of patients reported spontaneous remission of SD within 6 months, while 81.4% showed no improvement at the end of this period. Twelve out of 15 patients improved when switched to moclobemide (a monoamine oxidase inhibitor not available in the United States but available in Canada) and two of five patients improved when switched to amineptine (an antidepressant not available in the United States).

Piazza and coworkers,¹² in a small prospective study of 25 patients treated either with paroxetine or sertraline, observed that desire, arousal, and overall sexual functioning significantly improved in women, while orgasm delay, orgasm satisfaction, and overall sexual functioning significantly worsened in men (all measured by the Arizona Sexual Experience Scale [ASEX]—see the "Methodological Issues" section of this article). However, the results of this small study pose more questions than answers. The data on the frequency of SD in this study were missing. In addition, the group cells were small, and thus any significant gender differences need to be interpreted with caution.

Zajecka et al¹³ used the Rush Sexual Inventory (RSI) to assess SD in 42 patients treated with paroxetine, sertraline, and fluoxetine in an 8-week study. Males and females were found to experience similar rates of treatment-emergent SD (60% and 57%, respectively).

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Labbate and colleagues¹⁴ measured SD for at least 2 months in 61 patients treated with fluoxetine, paroxetine, or sertraline, using visual analogue scales. Orgasm appeared to be a primary sexual function affected by SSRIs. Anorgasmia was more frequent in women. Erection scores on the visual analogue scale (VAS) were also lower, though less dramatically. Lubrication, libido, and sexual frequency were not appreciably changed over 3 months. They did not report any differences among the three SSRIs.

Finally, Waldinger and colleagues conducted two studies examining the effect of SSRIs on ejaculation in male patients with rapid or premature ejaculation.^{4,15} In the first study, paroxetine delayed ejaculation most, whereas fluvoxamine delayed ejaculation least in men with lifelong rapid ejaculation.⁴ Results of the second study suggested that ejaculation-delaying side effects of some SSRIs in men with lifelong rapid ejaculation (less than 1 minute to ejaculation) may be generalized to men with less-rapid ejaculation (over 1 minute to ejaculation).¹⁵

Numerous published studies on efficacy and/or tolerability of antidepressants mention SD among the various side effects. Fawcett and colleagues,¹⁶ in an abstract published in *Psychopharmacology Bulletin*, noticed that significant improvement from baseline in sexual function was found in patients treated with nefazodone in a multicentric open-label study of 985 depressed patients. In an interesting meta-analysis of 36 double-blind trials of tricyclic antidepressants (TCAs) and SSRIs, Steffens and colleagues¹⁷ found that patients treated with SSRIs experienced significantly more SD than patients treated with TCAs (7.4% vs 5.9%). Simeon and colleagues¹⁸ reported that in a study on treatment of pathologic skin picking, 40% of 10 patients on fluoxetine and 9% of 11 patients on placebo reported impaired orgasm. In a double-blind, long-term comparison of clomipramine and milnacipram (not available in the United States),¹⁹ 19% of the clomipramine-treated depressed patients and 17% of milnacipram-treated patients reported treatment-emergent impotence.

The rates of SD were similar for placebo (20%), paroxetine (20%), and imipramine (28%) in a small study comparing paroxetine and imipramine in depressed HIV-positive patients.²⁰ Interestingly, erectile dysfunction was observed only in paroxetine-treated patients, albeit at a low rate of 8%. Paroxetine delayed ejaculation in 36% of males treated for social phobia with paroxetine²¹ in a randomized, double-blind, placebo-controlled study. In addition, 6.4% reported decreased libido and 9.1% of women reported SD with paroxetine in this study.

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TABLE 2: Antidepressants reported to cause significant changes in sexual functioning

Heterocyclics:

amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, maprotiline, nortriptyline, protriptyline, trimipramine

Monoamine oxidase inhibitors:

isocarboxazid, phenelzine, tranylcypromine

Selective serotonin reuptake inhibitors:

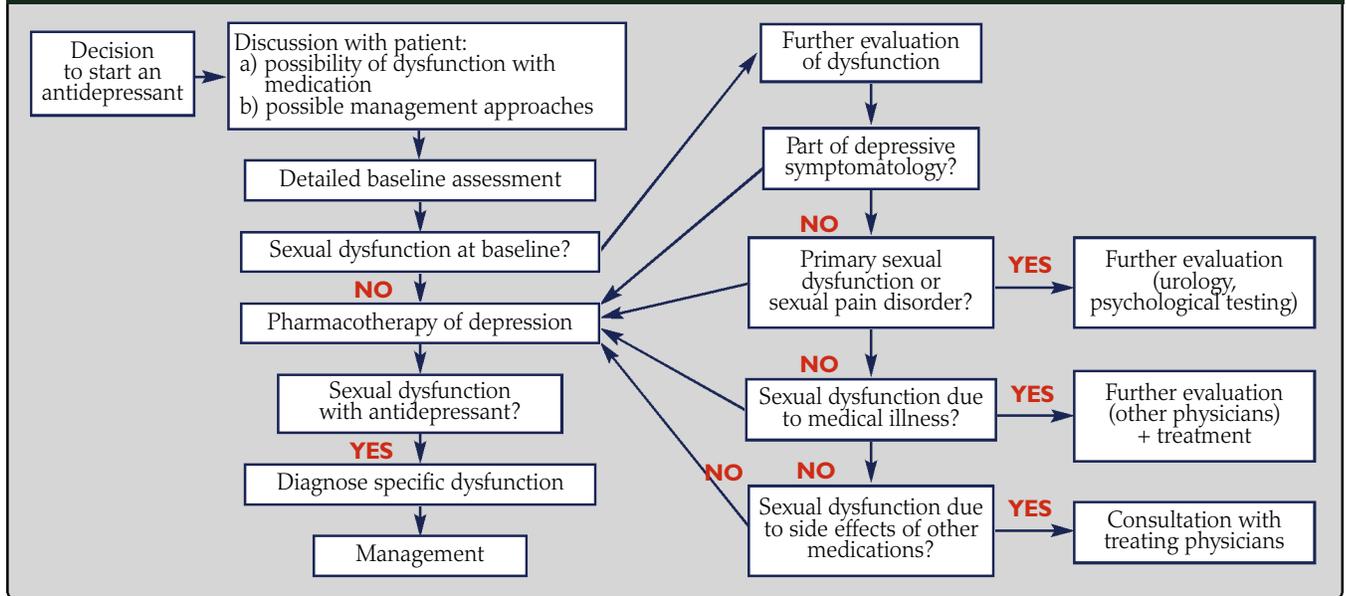
fluoxetine, fluvoxamine, paroxetine, sertraline

Other antidepressants:

trazodone, venlafaxine citalopram (occasionally reported to cause SD), mirtazapine (occasionally reported to cause SD, remedy SD)

Several studies with sertraline show various incidences of SD. Orgasm function was impaired in more sertraline-treated patients than in bupropion slow release (SR)-treated patients in a 16-week treatment study by Kavoussi and colleagues.²² A significantly greater proportion of sertraline-treated patients started to experience orgasm delay on treatment day 7. More men than women experienced orgasmic dysfunction among both groups. Keller and colleagues,²³ in a 12-week double-blind comparison of sertraline and imipramine in chronic depression, reported an incidence of SD (total includes delayed ejaculation, anorgasmia, impotence, and decreased libido) of 13.4% in sertraline-treated patients (426) and 12% in imipramine-treated patients (209). As a continuation of the 12-week acute treatment study,²³ Keller and colleagues²⁴ also conducted a 4-month maintenance phase treatment study with sertraline in chronic depression. This study included 161 patients who responded to sertraline during the 12-week acute phase of the study. Seventy-seven patients were assigned to sertraline up to 200 mg/day and 84 patients were assigned to placebo. Interestingly, the incidence of SD in sertraline-treated patients was 16.9%, while the incidence of SD in patients on placebo was 2.4% ($P < 0.01$). Finally, Pollack and colleagues²⁵ observed ejaculation failure in 15% of men on sertraline and 3% of men on placebo in a double-blind, flexible-dose study of sertraline in panic disorder patients. Unfortunately, researchers in this study did not examine other aspects of SD, or SD in women.

SD was observed in women treated with citalopram for premenstrual dysphoria in a double-blind, placebo-controlled study.²⁶ Citalopram was administered either continuously, semi-

FIGURE 1: General approach to diagnosis and management of sexual dysfunction associated with antidepressants

intermittently, or intermittently. The most common SD, reduced libido, was reported more frequently in the first treatment cycle in all treatment groups and in the placebo group. Reduced libido was much less common in the third treatment cycle, which suggests that SD declines with time. Finally, delayed ejaculation was noted in 11.4% of men on fluvoxamine and 4.3% of men on placebo in a double-blind, placebo-controlled study of fluvoxamine in social phobia.²⁷

Case Reports

Gagnon and colleagues²⁸ described the case of a woman who reported a sharp decrease in libido, disappearance of sexual fantasies, sexual numbness, and lack of sensations in the sexual organs, as well as anorgasmia while on paroxetine 10 mg/day. SD returned to pre-paroxetine levels when her paroxetine regimen was changed to 10 mg 3 days/week. Similarly to the observation in a study by Wikander et al,²⁹ Michael and Herrod²⁹ noted a com-

plete loss of interest in sex in a depressed male treated with citalopram. Libido returned within 7 days after discontinuation of citalopram. Mirtazapine has usually been reported to have a beneficial effect on sexual functioning (see the "Beneficial or Prosexual Side Effects of Antidepressants" section). However, Berigan and Harazin³⁰ reported on a case of a male who had an inability to ejaculate while on 30 mg of mirtazapine. He was able to achieve full orgasm within 5 days of discontinuing mirtazapine.

There have been numerous case reports of trazodone-induced priapism. Recently, Myrick and colleagues³¹ observed priapism in a cocaine dependent male 2 hours after the patient overdosed on trazodone. Cases of priapism with SSRIs have been extremely rare. Recently, Rand³² described intermittent priapism in a patient taking sertraline, dextroamphetamine, lisinopril, and ketoprofen. The patient was later switched to nefazodone with no further abnormal erectile function. Perera and Khan³³ presented a

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TABLE 3: Frequency of sexual dysfunction associated with antidepressant

Steffens et al¹⁷	5.9% w/TCAs 7.4% w/SSRIs
Zajacka et al⁷⁵	7.8% w/fluoxetine
Herman et al⁷⁶	8.9% w/fluoxetine
Keller et al²³	12% w/imipramine 13.4% w/sertraline
Ashton et al⁹	16.3% w/various SSRIs
Leinonen et al¹⁹	19% w/clomipramine
Jacobsen⁷⁷	34% w/fluoxetine
Stein et al²¹	36% w/paroxetine
Harrison et al⁷⁸	40% w/ phenelzine 30% w/imipramine
Balon et al⁷⁹	43.3% w/various antidepressants
Montejo-Gonzales et al¹¹	58.1% w/various SSRIs
Couper-Smartt and Rodham⁸⁰	71% w/various antidepressants
Monteiro et al⁸¹	96% w/clomipramine

case of a male with testicular pain and swelling upon withdrawal of 150 mg of imipramine daily.

Finally, there is an interesting report that presents a bridge to the section on beneficial sexual effects of antidepressants. Elmore and Quattlebaum³⁴ reported on three women who experienced undesirable sexual arousal or increased sexual desire and hypersexuality on various SSRIs (fluoxetine, fluvoxamine, paroxetine). Obviously, increased arousal, pelvic sexual sensations, and sexual fantasies with masturbation could be unpleasant and thus considered SD.

Several interesting conclusions could be drawn from the literature on SD published within the last 1 to 2 years. SD has been more systematically studied; however, the methodology of studies that focus on SD frequently remains poor. SD is a frequent side effect of antidepressants (17%⁹ to 58%¹¹). Better and higher estimates of SD are elicited when patients are asked directly about SD.¹¹ It remains unclear whether SD is more frequent among men⁹ or women.¹⁴ SD may be slightly more frequent with SSRIs than with TCAs.^{17,23} SD may occur even with very low doses of SSRIs, such as 10 mg of paroxetine daily.²⁸ Orgasm dysfunction is probably the most frequent SSRI-associated SD. Spontaneous

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remission of antidepressant-induced SD is possible, although low, about 5%¹¹ to 10%.¹⁰ Paroxetine may be associated with the highest frequency of SD among the SSRIs, particularly with anorgasmia.^{11,15} Interestingly, it seems that citalopram is frequently associated with decreased libido.^{26,30}

Beneficial or Prosexual Side Effects of Antidepressants

Improved Sexual Functioning

Bupropion has frequently been noted as beneficial to sexual functioning. Three new reports confirm the previous observations. Rowland and colleagues³⁵ treated 14 nondepressed diabetic men experiencing somatic erectile dysfunction with bupropion up to 450 mg/day in a single-blind study. Their results indicated that neither subjective nor objective measures of erectile and overall sexual functioning worsened during bupropion. In fact, several measures suggested a trend toward improved sexual functioning. Thus, the authors recommended using bupropion for treatment of depression in diabetic men or others for whom SD is a concern. Canive and colleagues,³⁶ in their open-label study of bupropion in posttraumatic stress disorder, noted that three patients who complained of SSRI-associated SD reported improvement in sexual functioning during bupropion treatment. Finally, Labbate³⁷ described a case of a male who experienced increased libido and unexpected spontaneous, pleasurable second ejaculation and orgasm during intercourse while treated for attention deficit disorder with bupropion-SR 450 mg/day. Sexual functioning returned to "normal" after he discontinued bupropion. Again, though pleasurable, these effects were ultimately of concern and led to the discontinuation of bupropion.

Mirtazapine has also been reported to improve sexual functioning. Boyarsky and colleagues³⁸ conducted an open-label study of sexual functioning as rated by the Arizona Sexuality Scale in depressed patients treated with mirtazapine up to 45 mg/day. Desire, arousal/lubrication, and ease/satisfaction of orgasm improved (by 41%, 52%, and 48%, respectively) in depressed women. In men, desire, arousal/erection, and ease/satisfaction of orgasm improved much more modestly (by 10%, 23%, and 14%, respectively). Farah³⁹ described four cases of improved libido (plus improved orgasm dysfunction in one of these cases) after addition of mirtazapine in SSRI-associated SD. Three of these patients were on paroxetine and one on fluoxetine.

As already noted, sexual functioning improved in depressed patients treated with nefazodone in one study.¹⁶

Finally, three cases of moclobemide-induced reversible hypersexuality in patients with stroke and Parkinson's disease were described by Korpelainen and colleagues.⁴⁰

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Premature Ejaculation

Two relatively new double-blind, placebo-controlled studies confirmed the effectiveness of fluoxetine 20 to 40 mg/day⁴¹ and 5 to 10 mg/day⁴² in premature ejaculation.

Methodological Issues

Three important methodological issues have emerged in the published literature during the last 1 to 2 years:

1) The Importance of Direct Questioning vs Spontaneous Reporting

As already discussed, Montejo-Gonzales et al¹¹ noted that significantly more patients reported SD when their physicians asked about it directly (58%) than when SD was spontaneously reported (14%). Direct questioning is clearly a better approach in eliciting reliable clinical information about SD.

2) The Development of a Rating Instrument

The use of rating instruments is still in development, though the use of questionnaires^{12,13} or VASs¹⁴ in research of SD has been more frequent.

Zajecka et al¹³ used the RSI to assess SD in 42 patients treated with paroxetine, sertraline, and fluoxetine in an 8-week study. RSI is a comprehensive, succinct, self-rated inventory that uses visual analogue items. Its completion takes about 7 minutes. The authors found RSI to be user friendly to both patient and clinician. However, the discriminant validity and test-retest reliability of this instrument still need to be established.

Clayton and colleagues⁴³ expanded on their previous work with the Changes in Sexual Functioning Questionnaire (CSFQ) in a study with 122 medical students, 33 residents, 32 bipolar patients, and 32 women treated for nonpsychiatric disorders. They

TABLE 4: Antidepressant-induced changes in sexual functioning

- Changes in libido (decreased or increased)
- Impaired erectile capacity
- Delayed ejaculation
- Painful ejaculation
- Priapism
- Impotence
- Partial or complete anorgasmia
- Clitoral engorgement

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concluded that CSFQ is a useful measure for assessing medication- and illness-related effects on sexual functioning in a systematic way. It is useful in assessing sexual functioning in both clinical and nonclinical populations and is capable of discriminating between those who have SD and those who do not.⁴³

A group of researchers from Arizona⁴⁴ described the development, reliability, and validity of their ASEX. The ASEX is a brief 5-item scale designed to assess the core elements most commonly impaired by antidepressants: drive, arousal, penile erection/vaginal lubrication, ability to reach orgasm, and satisfaction from orgasm (male and female versions of ASEX exist). Each item is rated in a 6-point Likert fashion, with lower scores reflecting enhanced sexual function and higher scores reflecting impaired sexual function. It seems to be a useful and easy to use rating scale. However, delayed ejaculation is not rated on this questionnaire.

Several questionnaires are available; however, none of them seems to be ideal and/or widely used. The ASEX is probably the easiest questionnaire to use.

3) The Effect of Antidepressants on Sexual Functioning in Nondepressed Subjects

As already noted, there was a tendency toward improvement of sexual functioning in nondepressed diabetic men treated with bupropion.³⁵ Nafziger and colleagues⁴⁵ reported on SD in 20 healthy volunteers on 150 mg of fluvoxamine/day. SD occurred in 20% of the healthy volunteers after 2 weeks on fluvoxamine and in 35% of subjects after 4 weeks of fluvoxamine. In a double-blind study, Knutsen and colleagues⁴⁶ studied effects of 20 mg/day of paroxetine (26 subjects) or placebo (25 subjects) on personality variables and social interaction in healthy volunteers. They noticed significantly delayed orgasm in men and women on paroxetine at week 4 (no specific numbers given).

It should be noted that the effect of moclobemide on sexual functioning remains unclear. Moclobemide-induced hypersexuality in three patients with neurological disorders⁴⁰ has been noted. However, in a study by Kennedy and colleagues,⁴⁷ moclobemide did not differ from placebo in its effect on sexual interest or sexual functioning in 60 healthy male and female volunteers.

Theoretical Issues

Several articles discussing the possible theoretical underpinning of SD associated with antidepressants have appeared lately.⁴⁸⁻⁵² Reviewing the recent findings on SD with antidepressants,

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TABLE 5: Management approaches to antidepressant-induced sexual dysfunction

- Waiting for spontaneous remission of the dysfunction
- Reduction to the minimal effective dosage
- Switching to another agent: bupropion, nefazodone
- Using various secondary pharmacologic agents
- Vacuum erectile devices

News in Management of Sexual Dysfunction

- Waiting for spontaneous remission may not be successful as remission is infrequent
- Switching to bupropion, mirtazapine, nefazodone seems to be helpful
- Switching to citalopram in case of other SSRI-induced sexual dysfunction?
- Most promising antidotes: sildenafil, bupropion
- Other antidotes worth trying: mirtazapine, buspirone in higher doses
- Other possible antidotes: granisetron, terfenadine
- Unclear role of ginkgo biloba

Alcantara⁴⁸ proposed a possible role of dopamine in the SSRI-induced SD. According to this hypothesis, in addition to the inhibition of noradrenergic transmission, serotonergic drugs also block dopamine release through the inhibition that the 5-HT₂ receptors carry out on dopaminergic transmission. Increase of dopaminergic transmission seems to be useful in the reversal of SD (eg, bupropion?, amantadine?). Adding an argument to the discussion of the role of the adrenergic system in SD is a study by Meston and Heiman.⁴⁹ They found that in a double-blind, randomized, placebo-controlled study, oral ephedrine sulfate significantly increased vaginal pulse amplitude responses to erotic films and had no significant effect on subjective ratings of sexual arousal in 20 healthy, sexually functional women. The authors felt that ephedrine can significantly facilitate the initial stages of physiological sexual arousal in women.

Another interesting discussion has developed around the role of nitric oxide in sexual functioning. Melis and Argiolas⁵⁰ summarized the evidence of the role of nitric oxide in the control of penile erection and the relationship of nitric oxide production to the dopamine system. Sussman and Ginsberg⁵¹ and Sussman⁵² made a strong argument for at least the partial role of alteration in nitric oxide activity in mediation of the SSRI-associated SD. This is a very interesting and intriguing hypothesis. However, as

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Sussman points out,⁵² it does not fully explain effects of some compounds, such as ginkgo biloba, on SSRI-induced SD.

These articles illustrate the complexity of the mechanism of antidepressant-induced SD and the possible interaction of various neurotransmitter systems in the regulation of sexual functioning.⁴

Management Issues

As noted in previous reviews,³ not every management approach (waiting for spontaneous remission, reduction to the minimal effective dosage, drug holidays, switching to another antidepressant, using secondary pharmacological agent) has been rigorously studied. Nevertheless, references to almost all management approaches appeared in various reports.

Waiting for Spontaneous Remission

Even though this approach has not been studied directly as a management approach, at least two studies^{10,11} noted that spontaneous remission of SSRI-associated SD occurs in a small portion of patients. Ashton and Rosen¹⁰ observed that spontaneous remission or accommodation of SSRI-associated SD happened in 9.8% of their patients and that it was slow (no time frame given). Montejo-Gonzales and colleagues¹¹ reported spontaneous remission of SD within 6 months in 5.8% of their patients. As spontaneous remission occurs infrequently and is unpredictable, its use seems to be limited.

Reduction to the Minimal Effective Dosage or Partial Drug Holidays

Gagnon and colleagues²⁸ observed a gradual return of sexual functioning to premedication level after paroxetine was decreased from 10 mg/day to 10 mg 3 days/week in one patient. The patient's depression did not return after the decrease of paroxetine.

Switching to Another Antidepressant

Montejo-Gonzales and colleagues¹¹ noted that 12 of 15 patients with SSRI-induced SD improved when switched to moclobemide, and three of five patients improved when switched to amineptine (both drugs are not available in the United States). Several studies noted improvement of sexual functioning in depressed patients when treated with some non-SSRI antidepressants. Fawcett and colleagues¹⁶ reported significant improvement of sexual functioning in depressed patients treated with nefazodone in a large multicentric study. Boyarsky and colleagues³⁸ noted improved sexual functioning

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TABLE 6: New Findings in Antidepressant-Induced Sexual Dysfunction

- SSRIs may have even higher incidence of sexual dysfunction
- Direct questioning about sexual dysfunction is very important
- Spontaneous reporting keeps yielding low frequency of sexual dysfunction
- Mirtazapine has lower incidence of sexual dysfunction
- Mirtazapine may have beneficial effects on sexual functioning
- Citalopram may decrease libido
- Nitric oxide may play role in mediating SSRI-induced sexual dysfunction

in depressed patients treated with mirtazapine up to 45 mg/day. The improvement was more pronounced among women. Two studies^{35,36} noted improved sexual functioning in patients treated with bupropion. Finally, Pallanti and Koran⁵³ reported two cases in which citalopram (20–40 mg/day) did not cause sexual impairment in patients who had experienced such events with fluoxetine and paroxetine. However, as noted before, citalopram was cited causing decrease of libido in two reports.^{26, 29}

Results from several studies^{16,35,36,38} infer that switching to bupropion, mirtazapine, or nefazodone seems to be a successful management approach to antidepressant-induced SD. Switching to citalopram in cases of other SSRI-induced SD might be a management option⁵³; however, this approach requires more study.

Using Secondary Pharmacological Agents

A good number of reports addressing this management approach with various agents have been published. Guirguis⁵⁴ reviewed the development of orally active and safe remedies for erectile dysfunction, from herbal remedies to designer drugs. He paid special attention to sildenafil; however, he did not address specifically the issue of antidepressant-induced SD.

Bupropion

In addition to being used as an alternate antidepressant because of the lack of SD, bupropion has also been used as an “antidote” for SD. Four of eight patients with SD on various SSRIs (fluoxetine, paroxetine, sertraline) for at least 2 months experi-

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enced marked improvement of SD with an addition of 75 mg of bupropion per day.⁵⁵ Ashton and Rosen⁵⁶ treated 47 patients complaining openly of SD with SSRIs (fluoxetine, fluvoxamine, paroxetine, sertraline) and venlafaxine. The authors first asked patients to take bupropion (75–150 mg) 1 to 2 hours before sex. This approach was effective in 38% of patients. If patients reported lack of success, they were asked to titrate the dose to 75 mg tid and sustain it for 2 weeks. This approach was successful in 57% of the remaining patients. The overall response rate was 66%. Seven patients (15%) discontinued bupropion because of anxiety or tremor. Finally, there is one unsuccessful report by Spier⁵⁷ on the use of bupropion to counteract SD with SSRIs and venlafaxine. He added bupropion (75–300 mg) to four patients complaining of SD (impaired libido or orgasm) on SSRIs or venlafaxine, but none of them improved.

Buspirone

In a study by Landen and colleagues,⁵⁸ 119 patients with major depression were treated with either citalopram or paroxetine. After 4 weeks and failure to respond to the SSRI, buspirone (flexible dosage, 20–40 mg/day) or placebo was added. SD was evaluated weekly using structured interview. Before starting buspirone or placebo, 40% of patients reported some SD. During the 4 weeks of added treatment, 58% of patients on buspirone and 30% of patients on placebo reported improvement of SD. The onset of action was relatively fast—improvement occurred after the first week with no further improvement occurring after that. The differences between buspirone and placebo were more pronounced among women.

Gingko Biloba

Ellison and DeLuca⁵⁹ described a woman who suffered from diminished sexual desire, reduced arousal, delayed orgasm, and genital anesthesia on 60 mg of fluoxetine. Repeated trials of prn yohimbine or cyproheptadine were unsuccessful. After 2 weeks of daily use of 180–240 mg of ginkgo biloba extract, she reported improved level of desire, established arousal with lubrication, reversed delay of orgasm and restored genital sensation. Cohen and Bartlik⁶⁰ found ginkgo biloba (60–240 mg/day) to be successful in 84% of SD in an open study of 63 patients mostly on SSRIs. However, as Balon⁶¹ pointed out, Cohen and Bartlik’s response rate was really 68%, not 84%, and their study had many methodological flaws.

Granisetron

In a case report by Nelson and colleagues,⁶² a woman complaining of near complete loss of sexual interest and delay in

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orgasm on 40 mg of fluoxetine reported a complete recovery from her SDs after taking 1 mg of granisetron, a 5-HT₃ antagonist approved for the treatment of nausea associated with chemotherapy.

Mirtazapine

As already mentioned, Farah³⁹ used mirtazapine to counteract SD in four patients reporting SD (mostly lack of libido and delayed orgasm) on SSRIs. All four patients reported improvement of their SD after addition of 15 mg of mirtazapine at bedtime.

Sildenafil

Not surprisingly, sildenafil has been the most frequently reported antidote for antidepressant-induced SD during the last 2 years. At least 16 case reports⁶³⁻⁷¹ (some reports describe more than one case) and one small study with 14 patients⁷² reported successful treatment of antidepressant-induced SD. Twenty-six of the patients (14 cases, 12 in the small open study) reported SD associated with SSRIs; two with mirtazapine,⁷² one with nefazodone,⁶⁸ and one with phenelzine.⁶⁹ In several cases, other medications were used in addition to antidepressants. Interestingly, even though sildenafil is only indicated for male erectile dysfunction,

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tion, 10 reported cases were that of women, who mainly reported improvement of anorgasmia. The effective dose of sildenafil was 50 to 100 mg, 1 to 2 hours prior to intercourse, with 50 mg being the most frequently used dose. In the case of phenelzine-induced SD,⁶⁹ even 25 mg of sildenafil was effective. Surprisingly, sildenafil was frequently used as first line management for SD, even though it was also used in several cases of other antidotes' failure.

As Balon⁷³ pointed out, clinical practice outstripped research in the case of sildenafil in antidepressant-induced SD. Even though sildenafil has not been systematically studied for this indication, it is becoming frequently used. There are also many unanswered questions about sildenafil in antidepressant-induced SD. Is it really working? Placebo studies are needed to answer this question. Is sildenafil really working for SD in women? Is sildenafil better than other antidotes?

Finally, a cautionary note for those who would like to use sildenafil in antidepressant-induced SD. Sildenafil should only be used in healthy subjects, it is officially indicated only in erectile dysfunction, patients should be educated about its use and infrequent side effects, and patients should be warned that concurrent use of organic nitrates is contraindicated.

Terfenadine

One male experiencing anorgasmia on fluoxetine started to experience orgasms while taking terfenadine 50 mg/day for hay fever.⁷⁴ Despite remission of his hay fever, he decided to stay on terfenadine to alleviate fluoxetine-associated SD.

Two of the management approaches—switching to another antidepressant with a low incidence of SD (bupropion, mirtazapine, nefazodone), or using an “antidote,” seem to dominate the news on strategies for management of antidepressant-induced SD. The most promising antidote seems to be sildenafil, yet it needs to be carefully studied in this indication. Addition of bupropion, mirtazapine or buspirone seems to be another possible “antidote” strategy. The effectiveness of ginkgo biloba for antidepressant-induced SD is still unclear. Lowering the dose of an antidepressant may be successful occasionally. Spontaneous remission of SD is rather infrequent. Switching within the same class (eg, SSRIs: from fluoxetine to citalopram) may be occasionally helpful.⁵³ Not surprisingly, no reports on drug holidays have appeared lately.

Conclusion

SD associated with antidepressants is an important clinical problem in the management of various disorders, namely mood and anxiety. The recent reports on frequency of SD with antide-

TABLE 7: Various treatment strategies for different types of sexual dysfunction associated with antidepressants

Decreased Libido

- Drug holidays
- Small dose of neostigmine before coitus
- Substitution of another antidepressant

Erectile problems

- 50-100 mg sildenafil 1 hour prior to intercourse
- Dose reduction
- Drug holidays
- Bethanechol, 30 mg 1-2 h before coitus
- Substitution of another antidepressant

Ejaculatory/orgasmic dysfunction

- Wait for spontaneous remission
- Drug holidays
- Coadminister another drug
(eg, bethanechol, dextroamphetamine, yohimbine, or buspirone)
- Substitution of another antidepressant

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pressants (up to 60%) confirm the previous reports on its fairly high incidence. SD is quite frequent especially with SSRIs, and the frequency of SSRI-induced SD may be even higher than TCA-induced SD. Among the SSRIs, paroxetine probably has the highest frequency of SD. Spontaneous remission of antidepressant-induced SD occurs rather infrequently. Priapism may very rarely occur with antidepressants other than trazodone.

Again, relying on spontaneous reporting of SD by patients may not be the best strategy. Direct questioning about SD yields much higher rates of SD than spontaneous reports. More questionnaires for SD have appeared, and ASEX seems to be the easiest one to use. SD also occurs in healthy subjects administered antidepressants. This observation seems to confirm the fact that the dysfunction is drug induced and not disease related.

Several of the newer antidepressants—bupropion, mirtazapine, and nefazodone—seem to have lower incidences of SD or even prosexual effects. SSRIs have been shown to be beneficial in the treatment of premature ejaculation.

The most frequent and reliable management strategies of antidepressant-induced SD seem to be switching to another antidepressant or using an “antidote.” Bupropion, mirtazapine, and nefazodone seem to be the antidepressants to be switched to; however, switches within the same class of drugs may yield positive results (eg, from fluoxetine to citalopram). The antidotes reported as being successful include bupropion, buspirone, ginkgo biloba, granisetron, mirtazapine, sildenafil, and terfenadine. Sildenafil and bupropion seem to be the antidotes with the highest chance of success. Nevertheless, caution is necessary as sildenafil needs to be studied more in antidepressant-induced SD, and it should not be used in patients with cardiac problems or those patients taking nitrates.¹¹

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Effects of Antipsychotic, Antianxiety, and Mood-Stabilizing Agents on Sexual Function

By Robert Taylor Segraves, MD

Abstract

What are the effects of antipsychotic, antianxiety, and mood-stabilizing agents on sexual function, and how do we manage these types of disorders? Serotonergic antidepressants have been recognized for their association with various forms of sexual dysfunction, which may contribute to patient non-compliance and inaccurate prevalence of drug-induced sexual dysfunction. Steps to take in the management of sexual dysfunction caused by serotonergic antidepressants include lowering dosages, switching agents, and adding sildenafil to the regimen.

Introduction

It is widely recognized that serotonergic antidepressants are associated with sexual dysfunction, that this may be a cause of treatment noncompliance, and that patients tend to underreport the prevalence of drug-induced sexual dysfunction. However, the effects of other psychotropic agents on sexual function are not as well documented or recognized. The available evidence suggests that certain antipsychotic agents and antianxiety drugs may also have sexual side effects.

Antipsychotic Drugs

Establishing the effects of antipsychotic drugs on sexual function is complicated by two factors: psychotic illness itself may be associated with decreased sexual activity, and obtaining a reliable sexual history from someone with psychotic illness may be extremely troublesome. In spite of these difficulties, there is convincing evidence from clinical reports that traditional antipsychotic agents

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TABLE 1: Antipsychotic Agents and Sexual Dysfunction

Agent	Average Dose	Patients Experiencing SD
Risperidone	5.5 mg/day	8.2%
Olanzapine	9.5 mg/day	2%
Haloperidol	5.8 mg/day	25%
Clozapine	115 mg/day	0%

such as chlorpromazine, haloperidol, and others are associated with sexual dysfunction. Although problems with libido and erectile dysfunction have been reported, the most commonly reported problems have been disturbances of ejaculation and orgasm. Ejaculatory problems have been reported with fluphenazine, haloperidol, thioridazine, trifluoperazine, chlorpromazine, and mesoridazine.¹ Of the traditional antipsychotic drugs, thioridazine appears to have the highest rate of sexual dysfunction. In one series of studies, slightly less than half of the patients on therapeutic levels of thioridazine had significant sexual problems.²

Sexual difficulties have been reported in both male and female patients. In a recent report, Aizenberg and his colleagues³ studied the presence of sexual problems in schizophrenic subjects both on and off medication. He found that untreated patients exhibited decreased sexual desire, and that neuroleptic medication restored sexual desire while creating sexual arousal and orgasm problems. One interpretation of this finding is that treatment of psychotic illness may allow patients to experience interpersonal closeness with less difficulty while, ironically, causing sexual disorders. Isolated cases of priapism have also been reported with both the traditional and atypical antipsychotics.

The mechanism of antipsychotic-induced sexual dysfunction is unknown. Some authors have postulated that α_1 -adrenergic blockade might be the mechanism by which antipsychotic agents influence both erectile and ejaculatory function.⁴ In a study of patients on neuroleptics, Ghadirian and colleagues⁵ reported that the presence of sexual dysfunction correlated with elevation of prolactin levels. This finding

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TABLE 2: Medical Management of Antipsychotic-Induced Sexual Dysfunction

- 1.** Attempt dose reduction
- 2.** Wait for tolerance to develop
- 3.** Switch to newer agent
- 4.** Consider adding sildenafil to therapeutic regimen

suggests that the new atypical antipsychotics might have a lower incidence of sexual side effects. The atypical antipsychotics cause less prolactin elevation and have fewer tendencies to cause dystonias and tardive dyskinesia. Atypical antipsychotics include clozapine, risperidone, quetiapine, and olanzapine. As they cause less prolactin elevation, they would be expected to have a lower incidence of drug-induced sexual side effects than the older, traditional antipsychotics. Current evidence suggests that this may be the case. In a large, open clinical trial employing a standardized sexual interview, Montejo⁶ studied the effects of risperidone, olanzapine, haloperidol, and clozapine on sexual function in 106 outpatients and found that the newer atypical antipsychotics, which have less effect on prolactin elevation, had much lower frequencies of sexual side effects than traditional antipsychotics (Table 1).

Another important finding of this study was that spontaneous patient self-report detected only about 15% of actual sexual side effects. Much higher levels of sexual dysfunction were found by direct physician interview. This suggests that the treating physician needs to inquire directly concerning sexual side effects, as many patients may be reluctant to bring up the matter themselves. Most other studies, with a few exceptions, have also reported a low incidence of sexual dysfunction with newer atypical antipsychotics than with traditional drugs. Among the atypical antipsychotics, clinicians have been consistent with finding a higher incidence of sexual dysfunction with risperidone than with olanzapine.⁷ The incidence of sexual side effects on risperidone appears to be dose-dependent.⁸

Treatment-emergent sexual side effects can logically be managed in a variety of ways. First, one would attempt to see if a lower dose would be sufficient for antipsychotic efficacy

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and possibly lead to a restoration of function. Second, one could wait for tolerance to develop. A recent study suggests that tolerance may develop after 18 weeks of therapy.⁹ A third approach would be to try to switch drugs. With a few exceptions, most evidence suggests that the new antidepressants have a lower incidence of sexual dysfunction than the older agents. In particular, olanzapine appears to have minimal sexual side effects. Another possibility is the use of sildenafil. Several clinicians have had success reversing antipsychotic-induced sexual dysfunction with sildenafil (Table 2).^{10,11}

Mood Stabilizers

The effects of drugs on sexual function in patients with bipolar illness has been difficult to study because patients with bipolar illness have fluctuations in sexual activity that are related to phases of the illness. For example, many bipolar patients will have an increase in sexual activity, sexual interest, and number of sexual partners during manic episodes, whereas decreased sexual interest and even sexual dysfunction may mark depressive episodes. Therefore, it is difficult to ascertain whether a decrease in sexual activity on lithium is a pharmacological side effect or a therapeutic effect.

A number of clinicians have noted an effect of lithium in decreasing libido and causing erectile dysfunction.¹² In a double-blind study of a small sample of bipolar patients, Vinarova and coworkers¹³ found that some patients on therapeutic doses of lithium developed erectile problems while those on placebo did not. However, Ghadirian and colleagues¹⁴ did not find a significant relationship between lithium blood level and sexual dysfunction in a study of patients on lithium carbonate. They concluded that lithium did not have a major effect on erectile function, as 49% of patients on lithium plus benzodiazepines had sexual problems compared to only 14% of patients treated with lithium alone. However, in a study of patients on lithium, Aizenberg and co-workers¹⁵ concluded that about 20% had a reduction in sexual thoughts and erectile function while on lithium alone.

Of the anticonvulsants used in bipolar disease, only valproic acid is Food and Drug Administration approved for this indication. Other anticonvulsants frequently utilized to treat bipolar disorder include lamotrigine, gabapentin, and carbamazepine. In the psychiatric literature, there is minimal evi-

Effects of Antipsychotic, Antianxiety, and Mood-Stabilizing Agents on Sexual Function

dence suggesting an adverse effect on sexual function with the use of any of these agents. Much of the evidence concerning the effect of anticonvulsants on sexual function is in the neurological literature. Establishing a clear relationship between sexual dysfunction and anticonvulsant use is difficult in this population, as epilepsy itself may be associated with sexual dysfunction.¹⁶ A possible mechanism for a relationship between anticonvulsant use and sexual dysfunction is the effect of anticonvulsant therapy on androgen metabolism.¹⁷ Certain anticonvulsants appear to increase sex hormone-binding globulin and thus may decrease the amount of bioavailable androgen. Long-term use of carbamazepine has been reported to be associated with an increase in serum hormone-binding globulin and a decrease in the free androgen index. This effect was particularly noted after 5 years of treatment and was proposed as a possible mechanism by which anticonvulsant therapy could lead to hyposexuality.¹⁸

The available evidence does not permit definitive recommendations regarding medical management of sexual dysfunction induced by mood stabilizers. First, one would want to be certain that the purported change in sexual function is the result of medication and not of the natural progression of the disease. The available data would suggest that an attempted switch from lithium to valproic acid or one of the other anticonvulsants might be indicated if sexual function is a reason for possible medication noncompliance. Such a switch would need to be undertaken with great caution in severe illness. To this author's knowledge, no one has studied the efficacy of sildenafil in reversing lithium-induced sexual dysfunction. It would be expected to work and might eventually prove to be the preferred strategy (Table 3).

TABLE 3: Medical Management of Sexual Dysfunction on Mood Stabilizers

1. Determine if SD is medication-induced or a phase of illness
2. If on lithium, determine whether patient can be safely switched to anticonvulsant therapy
3. Consider adding sildenafil to therapeutic regimen

SD=sexual dysfunction

**TABLE 4: Pharmacological Management of
Antianxiety Drug-Induced Sexual Dysfunction**

1. Consider switching type of benzodiazepine
2. Consider switching to buspirone
3. Consider adding sildenafil to therapeutic regimen

Minor Tranquilizers

Benzodiazepines have been reported by various clinicians to cause difficulties in orgasm and ejaculation. The drugs implicated include alprazolam,¹⁹ chlordiazepoxide,²⁰ and diazepam.²¹ This author reported the successful use of lorazepam to delay ejaculation in a man with premature ejaculation.²² One double-blind study demonstrated a dose response relationship between orgasm delay and increasing doses of diazepam in women.²¹ Some reports have suggested that these drugs may also interfere with erection and that certain benzodiazepines may have a greater tendency to cause sexual dysfunction than others.²³ To date, the evidence is insufficient to permit a definitive conclusion regarding differences among benzodiazepines.

Buspirone appears to be devoid of sexual side effects, may facilitate sexual activity in patients with generalized anxiety disorders,²⁴ and has been successfully utilized to reverse antidepressant-induced ejaculatory difficulties.²⁵

Conclusion

Antipsychotic agents are associated with both erectile and ejaculatory problems. There is reason to believe that the tendency to cause these problems may be less in the newer prolactin sparing antipsychotic agents. Benzodiazepines have been shown to cause problems with orgasm. Among the mood stabilizers, there is suggestive evidence that lithium carbonate may cause erectile problems in some patients.

Medical management of antianxiety drug-induced sexual dysfunction would include the following: 1) attempting to reduce dosage; 2) switching agents if necessary; and 3) adding sildenafil to the regimen.

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DSM-IV Criteria for Sexual Dysfunction

Sexual Desire Disorders

Hypoactive Sexual Desire Disorder

- A. Persistently or recurrently deficient (or absent) sexual fantasies and desire for sexual activity. The judgment of deficiency or absence is made by the clinician, taking into account factors that affect sexual functioning, such as age and the context of the person's life.
- B. The disturbance causes marked distress or interpersonal difficulty.
- C. The sexual dysfunction is not better accounted for by another axis I disorder (except another sexual dysfunction) and is not due exclusively to the direct physiologic effects of a substance (eg, drug abuse, a medication) or a general medical condition.

Sexual Aversion Disorder

- A. Persistent or recurrent extreme aversion to, and avoidance of, all (or almost all) genital sexual contact with a sexual partner.
- B. The disturbance causes marked distress or interpersonal difficulty.
- C. The sexual dysfunction is not better accounted for by another axis I disorder (except another sexual dysfunction).

Sexual Arousal Disorders

Female Sexual Arousal Disorder

- A. Persistent or recurrent inability to attain, or to maintain until completion of the sexual activity, an adequate lubrication-swelling response of sexual excitement.
- B. The disturbance causes marked distress or interpersonal difficulty.
- C. The sexual dysfunction is not better accounted for by another axis I disorder (except another sexual dysfunction) and is not due exclusively to the direct physiologic effects of a substance (eg, drug abuse, a medication) or a general medical condition.

Male Erectile Disorder

- A. Persistent or recurrent inability to attain, or to maintain until completion of the sexual activity, an adequate erection.
- B. The disturbance causes marked distress or interpersonal difficulty.
- C. The erectile dysfunction is not better accounted for by another axis I disorder (other than a sexual dysfunction) and is not due exclusively to the direct physiologic effects of a

DSM-IV Criteria for Sexual Dysfunction

substance (eg, drug abuse, a medication) or a general medical condition.

Orgasmic Disorders

Female Orgasmic Disorder (formerly Inhibited Female Orgasm)

- A. Persistent or recurrent delay in, or absence of, orgasm following a normal sexual excitement phase. Women exhibit wide variability in the type or intensity of stimulation that triggers orgasm. The diagnosis of Female Orgasmic Disorder should be based on the clinician's judgment that the woman's orgasmic capacity is less than would be reasonable for her age, sexual experience, and the adequacy of sexual stimulation she receives.
- B. The disturbance causes marked distress or interpersonal difficulty.
- C. The orgasmic dysfunction is not better accounted for by another axis I disorder (except sexual dysfunction) and is not due exclusively to the direct physiologic effects of a substance (eg, drug abuse, a medication) or a general medical condition.

Male Orgasmic Disorder (formerly Inhibited Male Orgasm)

- A. Persistent or recurrent delay in, or absence of, orgasm following a normal sexual excitement phase during sexual activity that the clinician, taking into account the person's age, judges to be adequate in focus, intensity, and duration.
- B. The disturbance causes marked distress or interpersonal difficulty.
- C. The orgasmic dysfunction is not better accounted for by another axis I disorder (except another sexual dysfunction) and is not due exclusively to the direct physiologic effects of a substance (eg, drug abuse, a medication) or a general medical condition.

Premature Ejaculation

- A. Persistent or recurrent ejaculation with minimal sexual stimulation before, on, or shortly after penetration and before the person wishes it. The clinician must take into account factors that affect duration of the excitement phase, such as age, novelty of the sexual partner or situation, and recent frequency of sexual activity.
- B. The disturbance causes marked distress or interpersonal difficulty.
- C. The premature ejaculation is not due exclusively to the direct effects of a substance (eg, withdrawal from opioids).

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GUIDED CLINICAL INTERVIEW QUESTIONNAIRE

**By Richard Balon, MD, and
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Questions to ask when clinically assessing sexual functioning prior to and during treatment:

Women & Men:

1. Are you involved in a sexual relationship now?
2. Has your sexual drive or desire changed since I saw you last, or since you have started medication? Has there been a change in the frequency of your sexual fantasies during the same time period?
3. Any change in the frequency of sexual activity initiated by you (intercourse/ masturbation)?
4. Has there been change in your ability to reach orgasm, in your ability to get excited (during intercourse and/or masturbation)?
5. Does it take you more or less time to reach orgasm, or to reach full sexual pleasure (orgasm, climax, ejaculation)?
6. Have you experienced any change or difficulty in reaching orgasm? Is the difficulty partial or complete (ie, no orgasm/no full pleasure)? Have you noted any pain during orgasm?
7. Are the changes in your sexual functioning/ enjoyment happening during sexual encounters with your partner only? During masturbation? Possibly with another partner?
8. Is your sexual functioning an issue in your relationship? Has (Have) your partner(s) complained about your sexual performance/functioning?
9. Are any of the mentioned changes in sexual functioning causing you any distress?
10. What are your thoughts regarding the cause of your difficulties? (eg, lack of energy? stress? depression? medication? problem in the relationship? underlying medical problem?)
11. Is there anything we did not discuss that you would like to mention?

Men:

12. Have you had any difficulty lately getting an erection during intercourse and/or masturbation? Any physical changes in your erection? Have you been unable to get an erection at all? Do you require manual stimulation to maintain your erection during intercourse?
13. Are you getting any erections unrelated to sexual activity, eg, when waking up in the morning? Are these erections firm enough for penetration if you were to attempt penetration?
14. Have you experienced any pain during erection and/or ejaculation?