

Sexual Dysfunction Associated with Anti-depressant Medications

a report by

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Introduction

Approximately 20% of women and 10% of men will experience a major depressive episode in their lifetime. Although the newer generation of medications used to treat depression are generally easier to tolerate and safer to use than the older antidepressants (tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs)), there has been greater recognition of sexual side effects caused by the newer generation. Anti-depressant medications may affect all phases of the sexual response cycle – libido, arousal, and orgasm – causing potentially serious impairment for both men and women. Depression and other psychiatric disorders for which antidepressants may be prescribed may also cause difficulties with sexual function.

The prevalence, assessment, and treatment of sexual dysfunction (SD) related to antidepressants will be discussed in the following article.

Baseline Rates of Sexual Dysfunction

Any discussion of SD secondary to specific disorders or treatments must acknowledge relatively high rates of SD reported in the general population. According to the National Health and Social Life Survey (NHLS) of people aged 18 to 59 in the US, 43% of women and 31% of men complain of some form of SD.¹ Specific complaints in women were low sexual desire (32%), inability to achieve orgasm (26%), and absence of pleasure in sex (23%). A survey of people aged 18 to 75 in the UK shows similar rates, with 41% of women and 34% of men complaining of a current sexual problem.² There is no substitute for good patient history when assessing sexual side effects. By recognizing that the base rates in non-ill general populations are rather high, wrongly attributing SD to a medication or illness may be avoided.

Depression and Sexual Dysfunction

Decreased sexual desire is a common complaint of unipolar depressed patients. Depressed women may also report decreased sexual arousal, trouble with vaginal lubrication, and difficulty achieving orgasm. Although few antidepressant trials in the past have prospectively gathered information about sexual function, more clinicians are recognizing the importance of asking about sexual function and some clinical medical trials are collecting data about the sexual side effects of medication. According to Kennedy et al., depressed women may have more difficulty with the early stages of sexual activity (desire and arousal) than with the later stages of orgasm and resolution.³ Prior to treatment, depressed women in their study complained of decreased sexual drive (50%), decreased sexual arousal (50%), difficulty obtaining vaginal lubrication (40%), and difficulty achieving orgasm (15%).³

Antidepressants and Sexual Dysfunction

Selective serotonin reuptake inhibitors (SSRIs) are generally regarded as first-line anti-depressant therapy. These medications significantly enhanced the armamentarium available to treat depressive and anxiety disorders, with their improved tolerability and safety in overdose compared with TCAs and MAOI antidepressants. Although the older generation of medications also caused SD, many of their other side effects (such as orthostatic hypotension, sedation, anticholinergic effects and weight gain) may have overshadowed the sexual side effects for most patients. In addition to the SSRIs there are several other classes of anti-depressant medications available, some of which offer advantages in the sexual realm.

Most reports comparing SSRIs have found few differences among the various medications in rates of



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1. Laumann E O, Paik A, Rosen R C, "Sexual Dysfunction in the United States: Prevalence and Predictors", *JAMA* (1999), 281 (6) pp. 537–544.
2. Dunn K M, Croft P R, Hackett G I, "Satisfaction in the Sex Life of a General Population Sample", *J. Sex Marital Ther.* (2000), 26 (2) pp. 141–151.
3. Kennedy S H, Dickens S E, Eisfeld B S, Bagby R M, "Sexual Dysfunction before Antidepressant Therapy in Major Depression", *J. Affect. Disord.* (1999), 56 (2-3) pp. 201–208.

related SD. Montejo et al. report the following rates of antidepressant-associated SD in a sample of 1,022 outpatients (610 women and 412 men):

- citalopram (an SSRI), 72.7%;
- paroxetine (an SSRI), 70.7%;
- venlafaxine (a serotonin and norepinephrine (NE) reuptake inhibitor (SNRI)), 67.3%;
- sertraline (an SSRI), 62.9%;
- fluvoxamine (an SSRI), 62.3%;
- fluoxetine (an SSRI), 57.7%;
- mirtazapine (a tetracyclic compound that blocks alpha-2 autoreceptors, serotonin type-2 receptors, and serotonin type-3 receptors), 24.4%;
- nefazodone (a phenylpiperazine antidepressant that blocks neuronal reuptake of serotonin and NE and blocks post-synaptic serotonin type-2 receptors, which has been withdrawn from the US and UK markets), 8%;
- amineptine (a TCA with dopamine reuptake blocking properties), 6.9%; and
- meclobemide (a short-acting reversible inhibitor of monoamine oxidase), 3.9%.⁴

Patients taking paroxetine reported a significantly greater incidence of decreased vaginal lubrication and erectile dysfunction compared with fluoxetine, fluvoxamine, sertraline, citalopram, venlafaxine, mirtazapine, and nefazodone ($p < 0.05$). In addition, paroxetine led to greater intensity of delayed orgasm compared with mirtazapine, fluoxetine, fluvoxamine, sertraline, citalopram, and venlafaxine ($p < 0.005$) and to greater intensity of decreased vaginal lubrication compared with fluoxetine, fluvoxamine, and sertraline ($p < 0.005$). In the overall sample, 59.1% of subjects reported treatment-emergent SD, and more men (62.4%) than women (56.9%) reported SD.⁴ Women, however, reported greater intensity of decreased libido, delayed orgasm, and anorgasmia than men.⁴

The largest epidemiological study of antidepressant-associated SD to date is a cross-sectional, observational study of 6,297 patients carried out by Clayton et al.⁵ In this study, immediate-release bupropion, an antidepressant that blocks the reuptake of dopamine and NE without effect at serotonin receptors, was the least likely to cause SD, with 22% of patients taking this medication reporting SD.⁵ Paroxetine, an SSRI, showed the highest rate of SD at 43%.⁵ The authors identified a group of patients ($N = 798$) who were unlikely to develop antidepressant-associated SD; these subjects were generally younger and had reported no history of antidepressant-related SD. In this group, rates of SD ranged from 7% for sustained-release bupropion to 30% for citalopram and extended-release venlafaxine. For both groups SSRIs and SNRIs were therefore associated with higher rates of SD than bupropion, a non-serotonergic antidepressant.

Although most reports focus on antidepressants worsening sexual function, some individuals experience improvement in sexual function when their depression is treated. Both libido dysfunction and psychological arousal difficulty associated with depression have been shown to improve with anti-depressant therapy.⁶

Treatment of Antidepressant-associated SD

Treating antidepressant-associated SD may be categorized into four general approaches:

- adaptation or tolerance through waiting, dose adjustment, or drug holiday;
- avoidance by preferentially prescribing medications that cause fewer adverse sexual side effects;
- augmentation with or switching to an antidepressant with fewer sexual side effects after SD has emerged; and
- use of antidotes.

Some people find that their antidepressant-induced SD remits with time. It is difficult to estimate the rate of development of tolerance, but some studies suggest a range of 20% to 40%. For some patients, a period of watchful waiting may therefore be a reasonable approach

4. Montejo A L, Llorca G, Izquierdo J A, Rico-Villademoros F, "Incidence of Sexual Dysfunction Associated with Antidepressant Agents: A Prospective Multicenter Study of 1022 Outpatients. Spanish Working Group for the Study of Psychotropic-Related Sexual Dysfunction", *J. Clin. Psychiatry*, (2001), 62 (Suppl 3) pp. 10–21.
5. Clayton A H, Pradko J F, Croft H A, Montano C B, Leadbetter R A, Bolden-Watson C et al., "Prevalence of Sexual Dysfunction among Newer Antidepressants", *J. Clin. Psychiatry*, (2002), 63 (4) pp. 357–366.
6. Piazza L A, Markowitz J C, Kocsis J H, Leon A C, Portera L, Miller N L et al., "Sexual Functioning in Chronically Depressed Patients Treated with SSRI Antidepressants: A Pilot Study", *Am. J. Psychiatry*, (1997), 154 (12) pp. 1,757–1,759.

to take. Dose adjustment is not a practical approach in most cases because the dose needed to maintain remission of depression is the same as that used to attain remission. A drug holiday (skipping medication on Friday and Saturday in an attempt to improve sexual function over the weekend) is another approach, but it hinders spontaneity, may put patients at risk of serotonin discontinuation syndromes, and may inadvertently encourage non-adherence to medication.

Augmenting with or switching to novel action antidepressants are popular but relatively unproven options for treating antidepressant-induced SD. Antidepressants are not interchangeable. The odds ratio of switching a true medication responder/remitted patient to another antidepressant and maintaining efficacy with a second agent is between 0.65 and 1.2, approximating a coin flip. Keeping these caveats in mind, two novel action antidepressants (bupropion and mirtazapine) seem to have fewer sexual side effects than antidepressants that block the reuptake of serotonin.

A majority of the evidence for antidotes comes from single case reports or case series, and few reports focus on the treatment of women with SD. Many medications that appear to work with open-label treatment fail to perform to a higher level than placebo drugs in controlled trials. Open-label reports suggest that the following medications may improve antidepressant-induced SD:

- amantadine (100mg to 200mg/day);
- bethanechol (10mg 30 minutes prior to sexual activity);
- cyproheptadine (4mg to 12 mg, one to two hours prior to sexual activity, or 4mg to 12 mg/day);
- ginkgo biloba (60mg to 900mg/day);
- granisetron (1mg to 1.5mg, one to two hours prior to sexual activity);
- loratadine (2.5mg to 15mg/day);
- methylphenidate (10mg to 40mg/day);
- mianserin (7.5mg to 15mg/day); and
- yohimbine (5.4mg three times daily).

Although open-label reports of bupropion as an antidote showed promise, the first randomized controlled trial of adding sustained release bupropion (150 mg/day) or placebo to an SSRI showed no differences between the groups.⁷ A more recent controlled study of sustained-release bupropion found increased desire for and frequency of sexual activity in patients (48 women and seven men) taking bupropion compared with the placebo when added to an SSRI; global sexual functioning, sexual interest, arousal, and orgasm were no different between groups.⁸ Double-blind, placebo-controlled trials of buspirone, amantadine, granisetron, mirtazapine, yohimbine, and olanzapine failed to support use of these medications.

The Use of Sildenafil for Antidepressant-associated SD

The research group at the University of New Mexico, led by Dr George Nurnberg, has carried out extensive work with the use of the selective phosphodiesterase type-5 inhibitor sildenafil to reverse serotonergic antidepressant-induced SD. This class of medication competitively and selectively inhibits cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type-5 (PDE-5). With sexual stimulation in men, nitric oxide (NO) is released locally, and the PDE-5 inhibitor leads to increased levels of cGMP in the corpus cavernosum, causing smooth muscle relaxation and blood inflow into the corpus cavernosum. Vardenafil and tadalafil are PDE-5 inhibitors that were released after sildenafil.

The New Mexico research group published the first double-blind placebo-controlled trial of the use of sildenafil for antidepressant-induced SD in men. In this trial, with 90 men taking a serotonergic antidepressant in depressive remission, sildenafil significantly improved sexual functioning on the primary outcome measure, the Clinical Global Improvement (CGI) scale ($p < 0.001$).⁹ On the CGI, 54.5% of sildenafil-treated subjects and 4.4% of placebo-treated subjects reported a categorical improvement of very much improved or much improved. On the secondary measures (the International Index of Erectile Function, IIEF; the Arizona Sexual Experience scale, ASEX; and the Massachusetts General Hospital – Sexual Functioning Questionnaire, MGH), sildenafil-treated subjects improved from baseline to end-point when compared with subjects receiving placebo ($p < 0.001$ for all). For both groups of subjects, depression remained in remission and the participants were able to continue taking their antidepressants uninterrupted at the same doses that allowed them to achieve remission.

Sildenafil and the other PDE-5 inhibitors are not approved for use in women. Several open-label reports suggest efficacy for the use of sildenafil for antidepressant-induced SD in women.¹⁰⁻¹² In the last of these, the group reported on the use of sildenafil (50mg to 100mg) one hour prior to sexual activity in 10 women with remitted depression, without pre-existing SD, who complained of antidepressant-induced anorgasmia. Nine of these 10 women reported reversal of their sexual symptoms. The mechanism of action of sildenafil and the other PDE-5 inhibitors in women is very likely analogous to that in men, with clitoral erection, labial swelling, and vaginal lubrication being the desired results in women. The research group is carrying out a double-blind, placebo-controlled trial of sildenafil in remitted depressed women, similar to the

trial in men, at the time of press. Hormonal measures are being included in this trial in an attempt to identify markers of treatment response.

Conclusions

Major advances in the treatment of depression, anxiety, and related disorders have occurred in the last 15 years. The newly-developed medications have fewer side effects than older medications, but sexual dysfunction has emerged as an important and common side effect that limits use of antidepressants in some patients. New data on the prevalence of SD in the general population

has underscored the importance of obtaining a good sexual function history prior to antidepressant initiation. Many treatments have been proposed for antidepressant-induced SD, but none has proven efficacy. PDE-5 inhibitors show great promise in the management of antidepressant-induced SD and seem to have a clear role for managing SD due to antidepressants in men. More data and controlled trials in women are awaited. The best approach to secondary SD at this time may be to assess for pre-existing dysfunction, inform the patient of the potential for sexual side effects, encourage open communication about treatment-emergent effects, and consider the use of PDE-5 inhibitors. ■

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9. Nurnberg H G, Hensley P L, Gelenberg A J, Fava M, Lauriello J, Paine S, "Treatment of Antidepressant-Associated Sexual Dysfunction with Sildenafil: A Randomized Controlled Trial", *JAMA* (2003), 289 (1) pp. 56–64.
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