



Depression and Erectile Dysfunction

Stanley Althof, PhD

Depression and erectile dysfunction (ED) are highly prevalent among men, and the conditions coexist and interact in ways that remain unclear. Data from the Massachusetts Male Aging Study (MMAS) show that among men aged 40 to 70 years, the overall prevalence of mild, moderate, and severe ED is 52%.¹ The prevalence of severe, or complete, ED is estimated at 10% in the same group. The overall lifetime prevalence of major depression is estimated at 16% in the general population, and minor depression affects an estimated 10% of the population aged 15 to 54 years.² Depression increases the risk for ED, but whether the relationship is causal is unclear. This article reviews current knowledge about the relationship between ED and depression, the effect of depression treatments on sexual dysfunction, and ways to improve treatment of ED in patients who take antidepressants.

Depression and ED: A Two-way Street?

The nature of the relationship between depression and ED is complex and remains unclear. Some investigators believe that the onset of ED causes some men to become depressed. Others believe that current or past depression causes sexual dysfunction, including low sexual desire and ED itself. A third mechanism, as yet unknown, may lead to both ED and depression.³

Compared to men who are not depressed, men with major depression are approximately twice as likely as others to have ED. Diminished libido and reduced sexual activity overall have been associated with depression, as well.⁴ Men with major depressive disorder may experience the loss of nocturnal erections.⁵ Men

with ED often feel emasculated, have diminished self-esteem, and tend to withdraw from their partners.^{6,7}

Shabsigh et al⁸, reported on the increased incidence of depression among men with ED. In their study, 100 men were categorized as having ED only, benign prostatic hypertrophy (BPH) only, or both ED and BPH. The participants were screened for depressive symptoms using the Primary Care Evaluation of Mental Disorders and the Beck Depression Inventory. Depressive symptoms were reported by 54% of men with only ED, 56% of men with ED and BPH, and 21% in men with BPH only. Men with ED were more than two-and-a-half times more likely than men without ED to report symptoms of depression, a difference that achieved statistical significance ($P < .005$). In turn, men who reported having symp-

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toms of depression also had lower libido than those without depressive symptoms ($P < .0001$). Thirty-three of the subjects had been previously treated for ED. Of these, 15 men who were not depressed but had ED and were previously treated, 100% persisted with treatment and reported being pleased with the outcome. In contrast, only 39% of the 18 patients with ED and depressive symptoms continued treatment, a statistically significant difference ($P < .00021$). Based on their findings, the authors concluded that ED is associated with high incidence of depressive symptoms independent of age, marital status, or comorbid conditions and that depressed patients with ED had a lower libido than patients

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who did not exhibit depression and were less likely than others to continue a treatment for ED.⁸

Araujo et al⁹, also assessed the relationships among ED, aging, and depression. Using data from the MMAS, a cross-sectional, population-based multidisciplinary survey of health in normal men aged 40 to 70 years, depressive symptoms were tested as a predictor of ED. The investigators determined that ED was associated with depressive symptoms even after controlling for potential confounders, with an odds ratio (OR) of 1.82, and that depressive symptoms and ED were related in middle-aged men. This relationship was robust and independent of aging, demographic factors, anthropometric and lifestyle factors, health status, medication use, and hormones.⁹

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Research conducted by Mallis et al¹⁰, suggests that psychiatric problems often go undiagnosed among men with ED. This group evaluated 103 consecutive patients, aged 20 to 76 years, who sought help at an andrology clinic for the management of ED. Most of the participants (71%) had moderate or severe ED. In addition, more than 63% of patients also had a psychiatric condition, including a depressive disorder in 25%, anxiety disorders in 12%, comorbid depression and anxiety in 7%, and a personality disorder in 6%. More than half of the study participants reported a lifetime history of psychiatric difficulties, prompting the investigators to conclude that obtaining a patient's psychosocial history is essential when evaluating and treating ED.¹⁰

Antidepressant Medication and ED

Several classes of medications, including beta-blockers, thiazide diuretics, and certain antipsychotic medications have been linked to new-onset ED in some men.¹¹ It is ironic that depression is associated with ED, and that tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitor (SSRI) antidepressants also seem to be independently associated with male sexual dysfunction.¹¹ In contrast, bupropion, an antidepressant that is not an SSRI or TCA, seems to have few adverse effects on sexual function.

The possible effects of antidepressant treatment on sexual function are a serious issue for patients and their partners. Consider that most patients with depression

who are treated with antidepressants typically start with a 6- to 9-month course of medication. This is sometimes extended to a year, and some patients are candidates for life-long therapy. Permanent interruption of sexual function by these medications is a significant barrier to compliance. In fact, no more than half of patients who are given a prescription for an antidepressant refill it more than 3 times, according to Lin et al¹², based on their study of patients treated in primary care. Sexual side effects of antidepressants probably contribute to the difficulty of maintaining patients on treatment. Initially, patients are grateful for the antidepressant effects of these medications. By three months patients struggle with the sexual side effects of their medication and many discontinue, against the advice of their physician.

In a randomized, double-blind, multicenter trial, Segraves et al¹³, compared sustained-release bupropion with the SSRI sertraline and determined that the two agents were similarly effective in treating moderate and severe depression. The sexual side effects of the two medications were quite different, however. A total of 248 patients with normal sexual functioning and moderate to severe major depression were randomized to receive bupropion sustained-release (SR) (100-300 mg/d) or sertraline (50-200 mg/d) for 16 weeks. Of these, 63% of the men and 41% of the women treated with sertraline developed sexual dysfunction during the study. In contrast, only 15% and 7% of the men and women, respectively, who were assigned to bupropion SR reported sexual dysfunction. Four patients dropped out of the study because of sexual side effects, and all of these had been assigned to the sertraline group.¹³

In a study that included 107 outpatients being treated for depression, Modell et al¹⁴, conducted a direct comparison of the sexual side effects associated with bupropion and the SSRIs fluoxetine, paroxetine, and sertraline. Compared to their sexual function before treatment, patients treated with bupropion reported significant improvements in libido, arousal, and orgasm intensity and duration. In contrast, the use of an SSRI was associated with significant decreases in libido, arousal, and duration and intensity of orgasm. Only 27% of patients treated with SSRIs reported no adverse sexual side effects, compared with 86% of bupropion-treated patients who reported no sexual problems. Further, 77% of patients in the bupropion group reported that at least one facet of their sexual functioning was enhanced by treatment.¹⁴ The results of other trials of SSRI-associated ED are summarized in Table 1.¹⁵⁻²²

The mechanisms by which SSRI antidepressants might impair sexual function are unknown. It has been speculated that since serotonin is known to act as an inhibitor of sexual response, drugs like SSRIs, which increase serotonin levels, might well inhibit sexual function.²³ Some

SSRI antidepressants are known to centrally inhibit nitric oxide synthetase. Because nitric oxide is an essential part of the signaling system that triggers erections, it is likely that this mechanism may be involved in SSRI-related ED.²⁴ The primary sexual side effect associated with SSRIs impacts ejaculation and orgasm. Sexual desire and erections are affected to a lesser extent.

Hypogonadism, Depression, and ED

Clinicians have often observed that men with depression and hypogonadism often report a similar set of

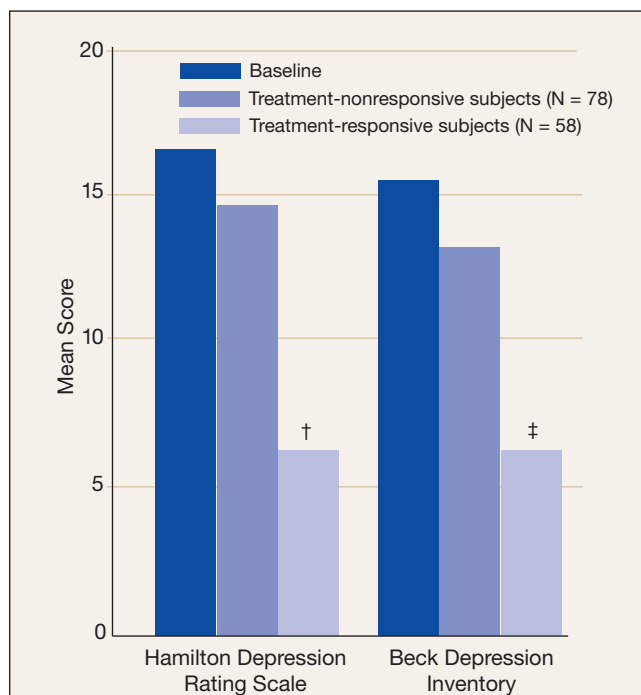


Figure. Baseline and endpoint depression scale scores of 136 men with erectile dysfunction and comorbid depressive disorder not otherwise specified who were randomly assigned to 12 weeks of treatment with sildenafil or placebo, by response to treatment.*

* = treatment response defined as participants answering “yes” to two global efficacy questions (“Did treatment improve your erections?” and “Did treatment improve your ability to have sexual intercourse?”) and scoring at least 21 on the erectile function domain of the International Index of Erectile Function.

† = Significantly lower than score of treatment-nonresponsive subjects ($F = 75.2$, $df = 1, 122$, $P < .001$).

‡ = Significantly lower than score of treatment-nonresponsive subjects ($F = 28.6$, $df = 1, 123$, $P < .001$).

Reprinted with permission from Seidman SN, Roose SP, Menza MA, Shabsigh R, Rosen RC. Treatment of erectile dysfunction in men with depressive symptoms: results of a placebo-controlled trial with sildenafil citrate. *Am J Psychiatry*. 2001;158(10):1623-1630.

symptoms: fatigue, lack of sexual energy, depressed mood, and a sense of diminished psychological well-being. Some evidence suggests that testosterone supplementation may benefit at least some men who are depressed, particularly those with low serum testosterone levels. Patients who present to a urology clinic with these symptoms are likely to be tested for hypogonadism and possibly treated with androgen replacement. Rarely are they evaluated for depression, treated, or referred. Similarly, patients who present to a psychiatry clinic with this set of symptoms are likely to be started on antidepressants. Only rarely are such patients evaluated for hypogonadism and treated or referred.

Pope et al²⁵, conducted an 8-week randomized, placebo-controlled trial designed to test the efficacy of testosterone transdermal gel in men with refractory depression and low-normal testosterone levels. The participants were aged 30 to 65 years. A group of 56 men with refractory depression were screened, 24 (42.9%) of these men had morning serum total testosterone levels of 350 ng/dL or less. The normal range is 270 to 1070 ng/dL. Twenty-two of the men were randomized to receive 1% testosterone gel, 10 g/day (12 men) or a placebo of identical appearance (10 men). All subjects continued to take their customary antidepressant, and 10 and 9 men in the testosterone and placebo groups, respectively, completed the 8-week study. The investigators reported that compared to men in the placebo group, those in the testosterone gel group had significantly more improvement in their Hamilton Depression Rating Scale (HDRS) scores, including the vegetative and affective subscales. The members of the testosterone and placebo groups also exhibited significant differences on the Clinical Global Impression severity scale. No changes were noted on the Beck Depression Inventory. The investigators concluded that although their findings were preliminary and derived from a small patient group, they pointed to a possible role for testosterone therapy in depressed men with testosterone levels in the low-normal range.²⁵

Treatment of ED and Depression: Mutually Beneficial?

An evolving area of ED research encompasses the possibility that successful treatment of ED may lead to improvements in depressive symptoms. Seidman et al⁵, conducted a 12-week, randomized, double-blind, placebo-controlled trial at 20 urology clinics to assess how sildenafil treatment affected mild-to-moderate comorbid depression in men with ED. Participants included 152 men (mean age, 56 years) who had had ED for at least 6 months (mean, 5.7 years). Each man had also received a Diagnostic and Statistical Manual of

Mental Disorders, Fourth Edition diagnosis of depressive disorder not otherwise specified, and a HDRS score of at least 12. Participants were randomized to receive flexible-dose treatment with sildenafil or placebo. Sildenafil caused major improvements in ED; 48 men in the sildenafil group and 10 in the placebo group met response criteria. A total of 78 men did not respond, including 18 in the sildenafil group and 60 in the placebo group. Among sildenafil responders, HDRS scores decreased by 10.6; in nonresponders, scores decreased by just 2.3. (Decreases in HDRS scores indicate that a patient's depression has improved.) In 76% of men who responded to sildenafil, HDRS scores decreased by at least 50%. Among nonresponders, only 14% achieved comparable decreases in HDRS scores. The results are illustrated in Figure 1.⁵ The investigators concluded that sildenafil provided effective treatment of ED in men with mild-to-moderate depression and that improvements in ED were associated with improvements in mood and quality of life, as well.⁵

Nurnberg et al²⁶, assessed the use of sildenafil in men who had developed iatrogenic sexual dysfunction

during treatment SSRI or nonselective serotonin reuptake inhibitor antidepressants. Designed as a retrospective, parallel-group, randomized, double-blind, placebo-controlled trial, the study enrolled 90 men who had been treated to remission of major depression but had developed ED during treatment. Subjects were randomized to receive sildenafil (50 mg adjustable to 100 mg before sexual activity) or placebo. The study continued for 6 weeks. The primary outcome measure was each subject's score on the Clinical Global Impression-Sexual Function (CGI-SF). Other measures included the International Index of Erectile Function, Arizona Sexual Experience Scale, Massachusetts General Hospital-Sexual Functioning Questionnaire, and HDRS. According to the CGI-SF scores, 54.5% of sildenafil users reported being "much improved" or "very much improved," compared with only 4.4% of patients assigned to placebo. This was a statistically significant difference ($P < .001$). Compared with patients in the placebo group, those assigned to sildenafil reported improvements in erectile function, arousal, ejaculation, orgasm, and overall satisfaction. Members of both the

Table 1. Prevalence of Antidepressant-Induced Erectile Dysfunction¹⁵

Study	Men (n)	Type	Antidepressants	% Sexual Dysfunction	% ED
Keller Ashton et al ¹⁶	167	Retrospective	Fluoxetine	23.4	10
			Paroxetine		
			Sertraline		
			Venlafaxine		
Jacobsen ¹⁷	160	Prospective	Fluoxetine	34	
Montejo-Gonzalez et al ¹⁸	152	Prospective	Fluoxetine	58	16
			Fluvoxamine		9.5
			Paroxetine		34
			Sertraline		16
Fava et al ¹⁹	63	Double-blind, placebo-controlled	Fluoxetine	7	7
			Paroxetine	25	25
Labbate et al ²⁰	12	Prospective	Fluoxetine	N/A	58
			Paroxetine		
			Sertraline		
Clayton et al ²¹	183	Cross-sectional observational	Bupropion	7	N/A
			Citalopram	30	
			Fluoxetine	24	
			Paroxetine	27	
			Sertraline	27	
			Venlafaxine	30	
			Overall	24	
Nelson et al ²²	1466	Double-blind, placebo-controlled	Duloxetine	46	N/A
			Paroxetine	61	

Adapted with permission from Rosen RC, Marin H. Prevalence of antidepressant-associated erectile dysfunction. *J Clin Psychiatry*. 2003;64 (suppl 10):5-10.

sildenafil and placebo groups remained in remission from depression during the study, and the authors speculated that the use of sildenafil might prevent some men from discontinuing depression medication because of sexual side effects.²⁶

More recently, Fava et al²⁷, also assessed the safety and efficacy of sildenafil with ED caused by SSRI antidepressants in a multicenter, 6-week, randomized, flexible-dose, double-blind, placebo-controlled trial conducted in the United States, United Kingdom, Germany, and Canada. The subjects included 152 men aged 18 and older who had major depressive disorder that had been treated to remission with an SSRI but who also had SSRI-induced ED. Some were randomized to receive sildenafil (N = 71), and the others received placebo (N = 71). The primary outcome measures were questions derived from the International Index of Erectile Function questionnaire about frequency of penetration and the maintenance of erections after penetration. Compared to patients on placebo, those randomized to receive sildenafil reported significantly better mean scores on the International Index of Erectile Function questionnaire and reported a significant improvement in the number of successful sexual intercourse attempts per week. Depression remained in remission in all subjects, regardless of whether they received sildenafil or placebo.²⁷

Some possible management strategies for treating patients with SSRI-associated sexual dysfunction are shown in Table 2.²⁸ Clinicians can consider adding a phosphodiesterase-5 (PDE-5) inhibitor such as sildenafil, tadalafil, or vardenafil to the regimen and/or switching the patient to a non-SSRI antidepressant such as bupropion, mirtazapine, or nefazodone.

Conclusion

Depression and ED have a complicated relationship. Depression increases the risk of ED, and ED may lead to depression. Further, certain antidepressants, especially those in the SSRI class, may cause ED or other sexual dysfunction as a side effect. Treatment with a PDE-5 inhibitor may help restore sexual function in a patient taking antidepressants, and restoration of sexual function may help alleviate depressed mood. Depression and low testosterone levels may cause similar symptoms, making it difficult to determine the correct diagnosis. The two conditions may also coexist in the same patient, and preliminary evidence suggests that testosterone treatment may help alleviate symptoms of depression in patients with low testosterone levels.

Management Strategies for SSRI-associated Sexual Dysfunction

1. Start with an antidepressant that is not associated with sexual dysfunction. Bupropion, mirtazapine, or nefazodone may be a useful strategy for sexually active patients.
2. Switch to an antidepressant that has a lower incidence of sexual dysfunction. Several studies have documented the usefulness of switching to an antidepressant with a lower incidence of sexual dysfunction, such as bupropion, mirtazapine, and nefazodone. This strategy may work with some patients, but it may be difficult to implement in cases where several other antidepressants have been tried and the offending agent is the only one that has been helpful in alleviating depression.
3. Wait for spontaneous remission of dysfunction or for tolerance to develop. This approach may require a long wait, which is not always acceptable to the patient; the effectiveness of this strategy is low.
4. Reduce the dose of antidepressant to the minimal effective dose. With some antidepressants, associated sexual dysfunction seems to be dose dependent, and decreasing the dose might be helpful. However, this approach requires careful, continuous assessment of depressive symptoms, as depression may recur after the dose is lowered.
5. Introduce drug holidays or partial drug holidays. The antidepressant can be discontinued (holiday) or the dose decreased (partial holiday) for a brief period (eg, 2–3 days), with sexual activity scheduled at the end of the period. This approach carries risks, however, as withdrawal symptoms may occur, anxiety may worsen, and nonadherence may be encouraged.
6. Suggest that sexual activity be scheduled around the daily dose of antidepressant, so that sexual activity occurs just before the patient takes the entire daily dose of the antidepressant. The evidence of efficacy for this strategy is limited. It may work with some short-half-life antidepressants.
7. Add “antidotes” or “augmenting” agents. Numerous antidotes or augmenting agents have been described as useful in alleviating SSRI-associated sexual dysfunction. The following is a partial list of agents that have been reported to be useful: amantadine, bethanechol, bromocriptine, bupropion, cyproheptadine, dextroamphetamine, ginkgo biloba, granisetron, loratadine, methylphenidate, mirtazapine, nefazodone, neostigmine, pemoline, pramipexole, ropinirole, sildenafil, tadalafil, trazodone, vardenafil, and yohimbine.

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