

Depression, antidepressants and sexual functioning in men

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ABSTRACT *In recent years, increased attention has been focused on antidepressant-associated sexual dysfunction, largely because of the widespread use of serotonin specific reuptake inhibitors (SSRIs) and the recognition that their side-effects can have a negative impact on treatment compliance. Yet the relationship between the depressive illness, the antidepressant medication used to treat it and treatment of emergent sexual dysfunction is complicated and multifactorial. For example, when a depressed man treated with an antidepressant medication seeks treatment for a sexual dysfunction, the clinician is faced with the responsibility of deciphering whether the sexual dysfunction is the result of a pre-existing medical disorder, a symptom of depression or a treatment-emergent adverse effect of antidepressant medication. In order to do this, the clinician needs to be knowledgeable about the salient aspects of normal sexual functioning, and the influences of age, depression and antidepressant medications. In this review, we discuss normal sexual functioning and dysfunction in men, the relationship between depression and sexual functioning, possible mechanisms for SSRI-associated sexual dysfunction and evolving pharmacologic treatment strategies.*

Normal sexual functioning

The sexual response cycle

There are four overlapping phases of male sexual function: (1) drive; (2) arousal, marked by erection; (3) release, marked by orgasm and ejaculation; and (4) resolution, which involves some degree of refractoriness. Normal sexual function is a biopsychosocial process. Sexual dysfunction may primarily derive from the biological, psychological or social arena, but virtually always affects all three.

Age and sexual functioning

Age-associated changes in male sexual response include: (1) reduced libido, (2) reduced number and frequency of morning erections, (3) reduced penile sensitivity, (4) reduced arousal, including an increase in the time needed to achieve erection

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and difficulty maintaining an erection, (5) prolonged plateau phase, (6) reduced ejaculatory volume and force of expulsion, and (7) prolonged refractory period. There is an age-associated decline in testosterone level that may be associated with a reduction in libido and mood, although this is not well established (Seidman & Walsh, 1999; Seidman & Roose, 1999).

The change in sexual function with age is multifactorial and variable (Seidman & Rieder, 1995; Mulligan *et al.*, 1988). Important co-factors include availability and health of a partner, relationship dynamics, fear of performance failure, chronic illness, substance and medication use, neuropathy and vascular insufficiency, and depression. Data from two large epidemiological studies suggest that sexual dysfunction is a para-aging phenomenon. In the Massachusetts Male Aging Study (MMAS), a cross-sectional, community-based, random sample survey of health in men aged 40 to 70, erectile dysfunction increased progressively with age (Feldman *et al.*, 1994). Data from the National Health and Social Life Survey (NHSLs), a cross-sectional, community-based, random sample survey of health and social life in 1410 men and 1749 women aged 18 to 59, reveal that 31% of men report having a sexual dysfunction (Laumann *et al.*, 1999). Overall, increasing age was associated with increasing erectile problems and with lack of sexual desire. Furthermore, the study found that erectile dysfunction was associated with low physical satisfaction, low emotional satisfaction and low general happiness. Despite these age-related changes, sexual interest and satisfaction appear to be maintained in the majority of men (Laumann *et al.*, 1999).

Depression and sexual functioning

Overview

Sexual functioning is a complex process, and sexual dysfunction can occur during any of the stages of sexual response. Although the causal relationship between sexual dysfunction and depressive illness is unknown, these conditions are highly co-morbid (Araujo *et al.*, 1998). Sexual symptoms are prominent in major depression, and often include decreased libido, erectile dysfunction, ejaculatory delay and decreased sexual satisfaction and pleasure (Seidman & Roose, 2000).

Depression and low libido

Low libido is the most common sexual dysfunction (Laumann *et al.*, 1999). Data from the NHSLs suggest several factors, such as decreased androgen production, decreased mood and vitality, medication side-effects and partner availability, that may contribute to loss of libido, particularly in aging men. Reduced libido is present in up to three quarters of depressed patients (Casper *et al.*, 1985) and is considered a 'classic vegetative symptom' of Major Depressive Disorder (MDD) (Nofzinger *et al.*, 1993b). This is commonly attributed to the pervasive anhedonia that often accompanies this depressive illness (Nofzinger *et al.*, 1993b).

Depression and erectile dysfunction

Erectile dysfunction (ED) is defined as the inability to obtain and maintain an erection sufficient for satisfactory intercourse or other sexual expression. It is a paraaging phenomenon that affects more than half of all men between the ages of 40 and 70 years (Seidman & Rieder, 1995; Feldman *et al.*, 1994). ED is associated with and presumably exacerbated by, poor health: it is more common among men with diabetes, heart disease, hypertension and hyperlipidemia, and among men who smoke (Mulligan *et al.*, 1988; Feldman *et al.*, 1994).

Accumulating data support a strong link between ED and depression (Araujo *et al.*, 1998; Seidman & Roose, 2000; Laumann *et al.*, 1999; Shabsigh *et al.*, 1998). In the MMAS all men with a CES-D score of 16 or over (a score which correlates with a diagnosis of major depressive disorder) had erectile dysfunction and 41% had complete erectile failure (Araujo *et al.*, 1998). Overall, among depressed men the likelihood of having ED was twice that of non-depressed men, even after controlling for potentially confounding variables.

In middle-aged and elderly men, depression and erectile dysfunction (ED) are common and frequently co-morbid (Simon *et al.*, 1999; Araujo *et al.*, 1998; Feldman *et al.*, 1994). The relationship between depression and ED appears to be bi-directional: the presence of, or alteration in, one of these conditions may be the cause, consequence, or modifier of the other (Araujo *et al.*, 1998; Feldman *et al.*, 1994; Seidman & Roose, 2000). For example, in depressed men, ED may be a symptom of depression or a treatment-emergent adverse event of antidepressant medication (Seidman *et al.*, 1999). Alternatively, men with ED may develop a 'secondary' depression as a reaction to the biopsychosocial stress commonly associated with loss of sexual functioning (Zurowski *et al.*, 1994). Notably, in a recent randomized clinical trial in which men with ED and minor depression received sildenafil or placebo, those who had an improvement in ED also had a significant improvement in depression (Seidman *et al.*, 2001).

Finally, although systematic data are limited, the clinical consensus is that many men presenting with sexual dysfunction have psychiatric problems. In two separate studies done at the John Hopkins Sexual Consultation Unit, men presenting for evaluation of sexual dysfunction had systematic psychiatric evaluations. Study 1 was carried out between 1976 and 1979 and included 199 patients; study 2 was done from 1984 to 1986 and included 223 patients. In both studies roughly one-third of men with erectile dysfunction also met criteria for a co-morbid psychiatric diagnosis, predominantly affective disorder, and, even in men who did not meet full diagnostic criteria, there were high levels of depressive and anxious symptoms (Derogatis *et al.*, 1981; Fagan *et al.*, 1988).

Thus, although ED and depression are highly co-morbid, the causal relationship is unclear. There are five models, not mutually exclusive, which may be used to understand the coexistence of both conditions. First, the psychosocial distress that is invariably part of ED might stimulate the development of 'secondary' depressive illness in vulnerable individuals. Second, ED can be a symptom of depression: MDD is associated with decreased libido, diminished erectile function,

and decreased sexual activity (Seidman & Roose, 2000). Furthermore, a subgroup of men with MDD develop a reversible loss of nocturnal penile tumescence (Roose *et al.*, 1982; Nofzinger *et al.*, 1993; Steiger *et al.*, 1993), suggesting that depressive illness can interfere with erectile neurophysiology. Third, antidepressant medication might lead to ED, although loss of libido and delayed ejaculation appear to be more common side-effects (Seidman *et al.*, 1999). Fourth, a common factor (e.g. alcohol (Araujo *et al.*, 1998), cardiovascular disease (Morley *et al.*, 1988), or hypogonadism (Seidman, 2000) might be etiologically related to both conditions. Finally, depression and ED, both relatively common, might be serendipitously co-morbid and etiologically unrelated. Whatever the etiology, co-morbid ED and depression is a complicated and multifactorial problem that requires thorough biopsychosocial evaluation and treatment.

Medication-induced sexual dysfunction

Many medications and substances have been reported to induce sexual dysfunction, particularly antihypertensives, anti-ulcer drugs, alcohol, sedative/hypnotics, mood stabilizers, antipsychotics, and antidepressants. Importantly, depression itself is associated with decreased libido, diminished erectile function, and decreased sexual activity (Gitlin, 1997). This, and the paucity of controlled data regarding the effects of medications on sexual function, makes interpretation of antidepressant-induced sexual dysfunction difficult.

Most antidepressants are associated with sexual side-effects. Antidepressants may cause sexual side-effects in the drive phase (e.g. decreased libido—although this is difficult to distinguish from the decrease in sexual satisfaction associated with pervasive anhedonia); the arousal phase (e.g. erectile dysfunction—although the relationship to pre-existing organic factors and to major depression complicates this association); and/or the release phase (e.g. delayed orgasm or anorgasmia). With SSRIs orgasmic delay appears to be most common, followed by decreased libido and arousal difficulties (Ashton *et al.*, 1997). The best estimates are that about one-third of patients on SSRIs develop sexual dysfunction (Balon *et al.*, 1993; Gitlin, 1997). Sexual dysfunction is reported somewhat less frequently with MAOIs, even less with TCAs, and rarely with nefazodone, bupropion and mirtazepine (Gitlin, 1997).

Strategies for treating antidepressant-induced sexual dysfunction include decreasing the dose, waiting, adding an 'antidote', or switching (Gitlin, 1997). None has well established efficacy.

Treatment

As with diagnosing the sexual dysfunction, it is also important, when trying to assess the proper treatment for this problem, that the root of the illness is adequately investigated. The appropriate treatment is largely indicated by the underlying cause of the sexual problem. Although some aspects are the same, treatment of sexual illnesses caused by pre-existing conditions, depression and medication is handled somewhat differently. If the sexual dysfunction is found to be unrelated to a medical

condition (e.g. hypogonadism), medication or psychosocial conflict, there are no known treatments of established efficacy but psychotherapy and erectogenic agents are commonly used.

If, however, it is discovered that the patient complaining of a sexual problem also has an untreated depressive illness, it is important that the depression be treated to remission before treating the sexual dysfunction as an illness separate from the depression. As is often noted, depressed men suffer a decrease in erectile function that reverses with effective treatment of the depressive illness (Roose & Seidman, 2000).

However, in treating the underlying depression, clinicians may encounter a second difficulty in that the depression medication they are using may actually cause the sexual dysfunction to worsen. In this case, the situation becomes more complicated. Since many of the SSRIs have some negative effect on sexual function, the clinician must balance the medication treatment of the depression with that of the sexual problem. Although it is important to treat the depression to remission, it is also important to realize that this treatment may have a negative effect on sexual function. For example, SSRI-associated sexual dysfunction can lead to patient dissatisfaction and medication noncompliance. In this setting, a strategy that is often effective is treating both complaints simultaneously. If the sexual dysfunction persists after effective treatment of the depressive illness or is a result of an antidepressant medication used for this treatment, the clinician may want to investigate treatments aimed specifically at the sexual dysfunction. The following is a guide to some of the current treatments available.

Until the recent introduction of an effective oral agent for ED, the only non-surgical treatments with proven efficacy were the urethral suppository, penile self-injection therapy and vacuum device therapy. However, many men and their partners find these methods unacceptable: in six-month follow-up with patients for whom injection therapy is effective, about half of the patients have discontinued (Van Driel *et al.*, 1991; Althof *et al.*, 1992). In 1998 the first 'on-demand' oral medication for the treatment of erectile dysfunction, sildenafil (Viagra), was introduced. It is a competitive inhibitor of cyclic GMP-specific phosphodiesterase type 5 (PDE5), the predominant isozyme causing the breakdown of cyclic guanosine monophosphate (GMP) in the human corpus cavernosum.

The pharmacokinetics of sildenafil are ideal for an 'on demand' oral agent for treating erectile dysfunction. Following oral administration, the drug is rapidly absorbed and reaches peak serum levels in about an hour. The serum half-life is three to five hours and many men observe improved early morning erections and a.m. sexual function following administration of sildenafil the night before. The effects of sildenafil are dose proportional following the administration of dosages between 1.25 mg and 200 mg. The clinically effective dose range is between 25 and 100 mg. When administered in doses of up to 200 mg to healthy normal volunteers, Sildenafil produced no significant alterations in heart rate, blood pressure and laboratory tests. The most common adverse effects following doses of 90 mg or more were headache and facial flushing, which were mild to moderate (Seidman *et al.*, 1999). Sildenafil has demonstrated significant efficacy in ED associated with primarily psychogenic, primarily organic and mixed etiologies in worldwide clinical trials.

Conclusion

Male sexual dysfunction is a common, multifactorial condition that is associated with age and antidepressant use. Within the context of antidepressant treatment, SSRI induced SD is important to identify because it may complicate and compromise effective depression treatment and medication compliance. Although SD is a common disorder that becomes more prevalent with age, it is not an inevitable consequence of aging and should not be regarded as such.

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