Sexual Dysfunction and Depression

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Current Psychiatry Reports 2001, **3**:202–208
Current Science Inc. ISSN 1523-3782

Sexual functioning is generally impaired during depression. Interest in the relationship between sexual dysfunction and depression has risen substantially, prompted primarily by 1) the 1998 Food and Drug Administration approval of sildenafil citrate as the first oral therapy of erectile dysfunction, and 2) the widespread clinical use of selective serotonin reuptake inhibitors, which prominently impair orgasm, and possibly libido and arousal. In this paper, we first review the phenomenology of sexual dysfunction and important contributing factors, such as age and illness, and then focus on the clinical assessment and therapeutic interventions used for sexual dysfunction in depressed individuals.

Introduction

There are four overlapping phases of sexual function: 1) drive; 2) arousal, marked by erection in men and by vaginal lubrication and engorgement in women; 3) release, marked by orgasm and ejaculation; and 4) resolution, which involves some degree of refractoriness. Normal sexual function is a biopsychosocial process. In the setting of depressive illness, there may be impairment in any phase of sexual response. Most commonly, and perhaps related to a more general anhedonia, there is a reduction in sexual interest. In addition, about one third of depressed men develop a loss of nocturnal penile tumescence (NPT), suggesting that depression can impair the neurophysiology of arousal or genital vasocongestion. Despite these apparent depression-specific impairments, the evaluation of sexual function in depressed individuals must begin with the baseline context, *ie*, factors related to sexual functioning in general, such as age, relationship status, and illness.

Although sexual dysfunction and depression are highly comorbid, 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 sexual dysfunction might stimulate the development of secondary depressive illness in vulnerable individuals. Second, sexual dysfunction can be a symptom of depression. Third, antidepressant medication might lead to sexual dysfunction. Fourth, a common factor (*eg*, alcohol, tobacco, cardiovascular disease, or hypogonadism) might be etiologically related to both conditions. Finally, depression and sexual dysfunction, both relatively common, might be serendipitously comorbid and etiologically unrelated.

Normative Sexual Dysfunction

Hypoactive sexual desire disorder

Hypoactive sexual desire disorder (HSDD) is diagnosed when the patient is judged to have persistently or recurrently deficient (or absent) sexual fantasies and desire for sexual activity [1••,2]. Criteria that have been used in studying this disorder include a frequency of self-initiated sexual activity once every 2 weeks or less, along with a subjective lack of desire to engage in any sexual behavior, and absence of or decrease in sexual fantasy. Medical conditions that have been associated with HSDD include endocrine disorders (*eg*, hypogonadism, hypothyroidism, hyperprolactinemia), temporal lobe lesions, environmental toxins, medications, and substance use [2].

It is estimated that about one in five adults has HSDD [3••]. About half of patients seen in sex therapy clinics receive the diagnosis of HSDD, with women outnumbering men in this diagnosis [2]. Important determinants of sexual desire include age-related hormonal changes, and relationship factors. For example, decreased desire can be a passive-aggressive coping strategy for dealing with the controlling behavior of a partner. Patients with primary (lifelong) or global (cross-situational) low desire should be more intensively evaluated for organic etiologies, such as medical illness, endocrine factors, and substance or medication use.

Treatment typically consists of individual or couples psychotherapy. Pharmacologic treatment with folk medicines such as rhinoceros horn, or with psychotropic agents such as yohimbine, alcohol, dopamine agonists, stimulants, and antidepressants appears to stimulate nonspecific (*ie*, placebo) response [1••,2]. Testosterone replacement in women with deficient androgen levels appears to increase sexual desire and arousal [4]. Similarly, among men with unequivocally low testosterone levels, hormone replacement is often effective in increasing sexual desire [5]. Among men with normal testosterone levels, exogenous testosterone administration is no more effective than placebo [6]. Overall, treatment success for HSDD is not high.

Female sexual dysfunction

In a large, representative sample of American women between the ages of 18 and 59 years, one third reported that they lacked interest in sex, one fourth had difficulty achieving orgasm, and one fifth had trouble lubricating [3••]. The prevalence of female sexual dysfunction increases with age, and is associated with the presence of vascular risk factors and menopause [7]. Despite dramatic advances over the past decade in our understanding of the physiology and neuroanatomy of male erectile tissue, and the pathophysiology and treatment of male erectile dysfunction, there has been very little research activity focused on the mechanisms of female sexual dysfunction (FSD). It has been postulated that, similar to the most common pathophysiologic mechanism of male sexual dysfunction, females develop a reduction in pelvic blood flow with age, with a consequent impairment in arousal—specifically, vaginal lubrication and clitoral tumescence. Investigation of these phenomena has been based on indirect measures, such as photoplethysmography, thermal clearance, and other temperature-based methods, and has been hampered by the lack of an animal model. Despite its high prevalence, female sexual dysfunction is rarely reported to clinicians and remains mostly untreated [3••]. There is no pharmacologic treatment that has shown efficacy, or been FDA-approved, for female sexual dysfunction. There is some interest in using sildenafil for female sexual dysfunction, and there have been positive anecdotal reports and open trials [8]. However, in a recent 12-week, placebo-controlled trial in which 583 women with FSD were randomized to receive sildenafil (25–100 mg prior to sexual activity) or placebo, changes in sexual function were indistinguishable between the groups [9••].

About 10% of women have never experienced orgasm, and a majority of women have situational orgasmic difficulties [10]. The diagnosis of orgasmic disorder is subclassified into *situational*, *generalized*, and *mixed situational*, and depends on the clinician's judgement regarding the patient's sexual experience, age, and adequacy of stimulation [11]. Orgasmic disorder is effectively treated by a combined masturbation and sex therapy approach with individuals, couples, or groups, or with bibliotherapy [12]. All of these methods focus on issues of body image, relaxation, self-stimulation, acceptance of sexual feelings, tolerance of higher levels of arousal, loss of control, and partner functioning [12].

Male sexual dysfunction

The most common male sexual dysfunctions are HSDD, premature ejaculation (PE), and erectile dysfunction (ED). As currently defined by the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV), these diagnoses require a great deal of clinical judgment, and do not include frequency or duration criteria.

Premature ejaculation (PE) is defined as persistent or recurrent ejaculation with minimal sexual stimulation before, on, or shortly after penetration, or before the person wishes it. An important component of the definition of PE is the patient's perception of lack of control over ejaculation. Generally, ejaculation occurs too quickly (less than 1 minute) and before, or soon after penetration into the vagina. Ejaculation occurring after vaginal penetration is less easily defined as premature. Some experts describe ejaculation as premature if a man is unable to continue intercourse for more than 1 minute without ejaculating, whereas others believe that men should be able to satisfy their healthy partners more than 50% of the time. Clearly, there are many couples for whom neither of these definitions would be satisfactory, and the most useful definition is probably an attitudinal one: ejaculation is premature if either partner perceives it to be.

Premature ejaculation is treated with behavior modification and, more recently, SSRIs. The pause-squeeze technique involves start and stop behavior therapy combined with a frenulum squeeze procedure. Although the technique appears to result in considerable improvement early on, a 3-year follow-up study evaluating treatment and assessing long-term benefits found that 75% of the patients showed no sign of lasting improvement over pretreatment baseline, and there was no effect in 25% at the time of treatment termination [13]. Although no drugs are currently approved by the FDA for the treatment of PE, several serotonergic antidepressants have been investigated. In double-blind, placebo-controlled trials using patient and partner assessments, clomipramine 25 mg and 50 mg used 6 hours prior to coitus [14], paroxetine 40 mg [15], sertraline 50 to 200 mg [16], and fluoxetine 20 to 40 mg [17] have been shown to produce significant ejaculatory delay, *ie*, 4 to 10 minutes increased latency to ejaculation.

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 para-aging phenomenon that affects more than half of all men between the ages of 40 and 70 years [18•]. ED is associated with, and exacerbated by, poor health; it is more common among men with diabetes, heart disease, hypertension, cigarette smoking, and hyperlipidemia [18]. Indeed, some evidence suggests that ED is a sentinel for cardiovascular disease [19]. Treatments for erectile dysfunction include oral medication (*ie*, the phosphodiesterase inhibitor, sildenafil), penile self-injection and urethral suppository therapy, vacuum device therapy, and surgical treatments.

Factors contributing to sexual dysfunction

Age

The change in sexual function with age is multifactorial and variable. Important determinants include availability and health of a partner, relationship dynamics, fear of performance failure, chronic illness, substance and medication use, neuropathy, and vascular insufficiency.

With age, females experience a reduction in pelvic muscle tension, relaxation of the urethral meatus (with some urinary incontinence associated with orgasm), reduction in orgiastic rectal contractions, vaginal dryness associated with the decline in estrogen, reduced libido (possibly associated with a decline in androgen levels [5]), and reduced engorgement (possibly due to pelvic vascular insufficiency). There is some decrease in the intensity of orgasm, and an increase in the time needed to achieve orgasm. Estrogen replacement and estrogen creams can be effective for postmenopausal vaginal changes, as can use of water-soluble lubricants (*eg*, vaginal jelly). Testosterone replacement may be effective for reduced libido [4].

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 and difficulty maintaining an erection, 5) prolonged plateau phase, 6) reduced ejaculatory volume and force of expulsion, and 7) prolonged refractory period [20].

Illness

The effects of age and psychosocial variables often complicate the determination of the specific impact of medical illnesses on sexual function. The following relationships have been consistently demonstrated: 1) lower libido and loss of spontaneous or fantasy-related erections in men with hypogonadism; and 2) ED is more common among men with diabetes, heart disease, hypertension, and hyperlipidemia.

Depression and Sexual Dysfunction

Depression and hypoactive sexual desire disorder

Loss of libido is a classic symptom of major depressive disorder (MDD), and has played a prominent role in psychodynamic and other psychologic formulations of depressive illness. Systematic studies suggest that low libido is present in up to 75% of depressed patients [21,22].

Depression and erectile dysfunction

Depression and erectile dysfunction (ED) are frequently comorbid, particularly in middle-aged and elderly men. The relationship between depression and ED appears to be bidirectional: the presence of or alteration in one of these conditions may be the cause, consequence, or modifier of the other [23]. For example, in depressed men, ED may be a symptom of depression or a treatment-emergent adverse event of antidepressant medication. Alternatively, men with ED may develop a secondary depression as a reaction to the biopsychosocial stress commonly associated with loss of sexual functioning.

The relationship between depression and ED has been studied in population-based and clinical samples. The most compelling evidence for a strong association between depression and ED comes from the Massachusetts Male Aging Study (MMAS). The MMAS was an ongoing, cross-sectional, community-based, random-sample survey of health and aging in men aged 40 to 70 years. It was conducted in 11 randomly selected towns in the Boston area between 1987 and 1989, and it had a response rate of 76% (n = 1290). Based on the subjects' responses to nine questions that were highly correlated with biologic measures of erectile response, ED was graded as nil (48%), minimal (17%), moderate (25%), or complete (10%) [18]. Using the Center for Epidemiologic Studies Depression Scale (CES-D) cutoff of 16 (which is highly correlated with MDD), all men with this degree of depressive symptomatology had some (*ie*, minimal, moderate, or complete) ED. Maximal level of anger (either suppression or expression, as defined by Spielberger's anger scales) was associated with approximately 75% overall ED, double the ED prevalence among men who reported minimal anger [18•].

In clinical studies of men with MDD, it has been shown that a subgroup of depressed men have a reversible impairment in sexual neurophysiology. Roose *et al*. [24] first reported the observation that nocturnal penile tumescence (NPT) was impaired in depressed men and returned to normal following remission. Subsequently, Steiger *et al.* [25] assessed several parameters of NPT in 25 men with an acute episode of depression, as compared with nondepressed control subjects. Although no statistically significant differences in NPT parameters were found between the depressed and control subjects, there was a complete lack of NPT in four of 25 depressed men, which was reversed after antidepressant therapy.

In contrast, Thase *et al.* [26] demonstrated a significant reduction in NPT time and decreased penile rigidity in 34 depressed men compared with nondepressed controls. NPT time was reduced by at least one standard deviation below the control mean in 40% of depressed men, and was comparable with that in a group of 14 nondepressed men with a diagnosis of ED due to organic causes. These findings were confirmed in a repeat study with a new group of 51 men with MDD [21]. Together, the results of these studies support the conclusion that erectile function as assessed by NPT is impaired in some, but not all, depressed men, suggesting a neurophysiologic link between depression and ED.

Finally, the link between ED and depression among men who present with ED has not been systematically studied. There is, however, suggestive evidence from two large studies describing psychiatric symptoms among men presenting to the Johns Hopkins Sexual Behaviors Consultation Unit from 1976 to 1979 (n = 199) and from 1984 to 1986 (n = 223) [27]. Men with ED had high levels of depressive, somatic, and anxious symptoms, and scored very high on measures of overall psychologic distress (*eg*, using one well-validated instrument that measures such distress, these men scored in the 92nd percentile of the normative population).

Depression and testosterone

Although the symptoms of hypogonadism (*eg*, loss of libido, dysphoria, fatigue, irritability, and appetite loss) overlap with the signs and symptoms of depression, it is not known what proportion of hypogonadal men meet criteria for MDD or another depressive illness (*eg*, dysthymia) and, for those who do, which dysfunction is primary. Furthermore, it is unclear whether a specific hypothalamic-pituitary-gonadal (HPG) measure (*eg*, total testosterone or free testosterone) might be associated with psychiatric symptoms and, if so, at which absolute or relative level. For example, symptoms such as low libido and loss of nocturnal erections apparently develop only when the total testosterone level drops below a certain threshold, typically set between 200 and 300 ng/dL. However, the impact of decreasing testosterone levels among healthy aging men may require the establishment of a different set of standards for HPG assessment in older men, which take into account other age-related phenomena, such as changes in end-organ responsiveness and HPG secretory patterns.

A recently published epidemiologic study demonstrated a significant inverse association between free testosterone and depressive symptoms. The Rancho Bernardo Study [28] was a population-based study of virtually all adult residents of a southern California community. In a 10- to 15-year follow-up study that included 82% of the surviving community residents, 856 men aged 50 to 89 (mean 70.2 years, standard deviation = 9.2) completed the Beck Depression Inventory (BDI), and had a morning blood sample drawn for determination of total and free testosterone. The free testosterone level was inversely correlated with age, lack of regular exercise, and weight loss over the preceding 10 to 15 years; BDI was positively correlated with these same factors. In multiple linear-regression analyses, adjusting for these potentially confounding covariates, free testosterone concentration was strongly associated with BDI score (B = -0.302, adjusted standard error = 0.11, P = 0.007); there was a complete absence of an association between BDI score and total testosterone level. These data support an association between HPG axis functioning—particularly as measured by free testosterone—and depressive symptoms in older men, and warrant more detailed analysis and follow-up.

Because of the well-accepted psychiatric effects of low testosterone and excess testosterone, as well as a presumed relationship between MDD and low testosterone, the use of exogenous androgens to treat MDD or the depressive symptoms that evolve with age (*ie*, male climacteric) has long been an area of intense speculation and clinical case reports [29]. Yet, very few studies have systematically addressed these issues using standard clinical trials methodology. For example, none of the numerous controlled testosterone replacement trials completed over the past three decades has described the prevalence of prereplacement psychiatric illness followed by systematic monitoring of psychiatric symptoms during testosterone replacement. It is unlikely that all hypogonadal men develop MDD, because there is no apparent increase in MDD among cohorts of aging men to parallel the decrease in testosterone levels. It is possible, however, that a low-grade affective syndrome develops [30], perhaps not unlike the dysphoric-irritable-fatigue syndrome of female hypogonadism (*ie*, menopause).

Treatment

Antidepressant-induced sexual dysfunction

Most antidepressants are associated with sexual side effects. Sexual side effects have a large impact on patients' satisfaction with their treatment regimen, can promote medication noncompliance and depressive relapse, and are associated with reduced quality of life and relationship satisfaction [31•]. Antidepressants may cause sexual side effects in the drive phase (*eg*, decreased libido, although this is difficult to distinguish from the decrease in sexual satisfaction associated with anhedonia); the arousal phase (*eg*, erectile dysfunction, although the relationship to preexisting organic factors and to MDD itself complicates this association); or the release phase (*eg*, delayed orgasm or anorgasmia). The most consistent estimates are that about one third of patients on SSRIs develop sexual dysfunction [32]. Sexual dysfunction is reported somewhat less frequently with monoamine oxidase inhibitors, even less with tricyclic antidepressants, and uncommonly with nefazodone, bupropion, and mirtazepine.

Although low libido and ED are reported during SSRI treatment, the rates are not substantially different from base rates in the general population. In contrast, a significant proportion of patients taking SSRIs report problems occurring during the orgasm phase (*ie*, delayed ejaculation in men and anorgasmia in women); such problems are uncommon in the general population [31•,32,33]. The presumed mechanism of orgasmic dysfunction is via 5-HT_2 receptor activation, which is inhibitory to ejaculation, through ascending serotonergic projections to the medial preoptic area and descending serotonergic pathways to the lumbosacral motor nuclei. Such activation apparently leads to an increase in genital sensory threshold, and the experience of genital anesthesia.

Strategies for treating SSRI-induced sexual dysfunction include 1) decreasing the dose; 2) waiting for tolerance to develop; 3) switching to an antidepressant that does not have sexual side effects (*eg*, nefazodone, bupropion, or mirtazepine); and 4) adding an antidote. In anecdotal case reports, the following antidotes have been reported: the alpha2-adrenergic receptor antagonist, yohimbine [34]; the 5-HT2 receptor antagonists, nefazodone [35] and cyproheptadine [36]; the 5-HT3 receptor antagonist, granisetron [37]; the dopamine agonists, amantadine [38] and bupropion [39]; psychostimulants [40]; and other agents, such as ginkgo biloba [41] and sildenafil citrate [42,43]. In uncontrolled trials, response rates greater than

50% have been reported for many of these agents [44]. Yet, in the only well-designed, placebo-controlled, prospective study, amantadine and buspirone were not distinguishable from placebo in women with SSRI-associated sexual dysfunction [45•]. Furthermore, all of these reports varied in dosing, follow-up, gender specificity, sexual dysfunction specificity, and methodology for determining sexual dysfunction remission. Indeed, none of these strategies has achieved widespread clinical acceptance.

In a recent report, 90 men who were taking SSRIs and reported treatment-emergent ED were randomized to receive either sildenafil or placebo. Augmentation with sildenafil was associated with improvement in sexual dysfunction (Nurnberg *et al.*, Paper presented at the Annual Meeting of the American Psychiatric Association. Chicago: May, 2000) . However, all of the enrolled men had multiple sexual problems at baseline (mean, 3.5 problems). Thus, given the established efficacy of sildenafil for ED, specific improvement in ejaculatory delay could not be distinguished from improvement in erectile function in this sample. This is particularly important because for the majority of men with SSRI-induced sexual dysfunction, persistent ejaculatory delay despite improved ED appears to be the norm.

To date, we have treated 13 men (age range 33–76 years) with high-dose sildenafil for ejaculatory delay in the setting of SSRI use. At the first follow-up (*ie*, following sildenafil 25–50 mg), eight of 10 men who reported any degree of ED at baseline reported fully improved erectile function, but persistent anorgasmia. All 13 men were advised to increase their sildenafil doses as tolerated (up to a maximum 200 mg). Overall, nine of 13 men had a substantial clinical improvement in ejaculatory delay on higher-dose sildenafil (all used at least 100 mg, five men used 200 mg); notably, the four nonresponders were all using 100 mg and chose not to increase the dose. One patient complained of blue-tinged vision at 200 mg, one had a mild headache at 200 mg. There were no other significant adverse events. These data suggest that anorgasmia may require a higher sildenafil dose for response than does ED.

Treatment of erectile dysfunction in depressed men

Regardless of the etiologic relationship, depression is more frequent in patients with ED, and may impact negatively on ED treatment outcome. Shabsigh *et al*. [46] conducted a study of 100 men who presented to a urologic clinic with ED, benign prostatic hyperplasia (BPH), or both, and were screened for self-reported depression, defined as above-threshold scores on two questionnaires (*ie*, the Primary Care Evaluation of Mental Disorders Survey [PRIME-MD] and the Beck Depression Inventory [BDI]). Men with ED (n = 66) were 2.6 times more likely to report depression than were men with BPH alone (n = 34). Moreover, among men who received ED treatment (with either penile intracavernosal injection or a vacuum device), all 15 patients in the non-depressed ED group continued treatment and were satisfied with the outcome, whereas only seven of 18 (39%) of patients in the depressed ED group continued treatment. Thus, in this sample of men treated for ED, depression was highly associated with treatment discontinuation.

We recently conducted a placebo-controlled, parallel-group, double-blind study of 50 to 100 mg of sildenafil or placebo in 160 men with ED and comorbid minor depression [47•]. Patients were older than 18 years, were in stable heterosexual relationships, and had been experiencing ED for over 6 months. Subthreshold MDD was diagnosed as a score of at least 12 on the 24-item Hamilton Rating Scale for Depression (HAM-D) and two to four DSM-IV major depressive episode criteria, with at least one being depressed mood or loss of interest or pleasure in most activities every day for 2 weeks. The standard diagnosis of MDD involves five major depressive episode criteria, and such patients were excluded. Baseline psychiatric evaluations were made and repeated 4 weeks later. Patients with a persistent HAM-D score greater than or equal to 12 were randomized to sildenafil or placebo for 12 weeks.

An ED responder was defined by a score of greater than or equal to 22 on the erectile function domain (range 1–30) of the International Index of Erectile Function, as well as affirmative responses to two questions regarding improvement in erections and ability to have intercourse. The HAM-D and BDI scores were significantly reduced in ED responders (10.6 and 10.7, respectively) compared with ED nonresponders (2.3 and 3.7, respectively; $P < 0.001$). Although the majority of men who were ED responders were in the sildenafil treatment group (83% vs 17%), it is interesting to note that even among the small number of ED responders treated with placebo, there were similar improvements in their depression scores. The results of this study suggest that depressed men who respond to ED treatment show robust improvement in depressive symptoms, and support the concept of depression secondary to medical illness.

Conclusions

The relationship between sexual dysfunction and depression is complex and bidirectional, and the causal relationship remains unclear. Sexual dysfunction and the psychosocial distress that frequently accompanies it may precipitate the development of depression in vulnerable individuals, depression might cause sexual dysfunction, or both conditions might coexist independently.

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