The Relationship Between Depression and Erectile Dysfunction

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Normal sexual function is a biopsychosocial process; sexual dysfunction almost always has organic and psychologic components, and it requires multidisciplinary, goal-directed evaluation and treatment. Factors such as aging, declining testosterone levels, medical illness, certain medications, and comorbid depressive illness can contribute to sexual dysfunction. Erectile dysfunction (ED) is the most common male sexual dysfunction encountered in the clinical setting. Comorbidity between ED and depressive illness is high, but the causal relationship is unclear, and likely bidirectional. In this article, we review the existing literature on the relationship between depression and ED.

Introduction

Erectile dysfunction (ED) is a common disorder of aging men with a prevalence of 5% in men 40 years of age, increasing to 15% to 25% at age 65 years and older [1,2]. Unipolar depressive disorders, such as major depressive disorder (MDD) and milder depressive syndromes (*eg*, dysthymia) affect 10% to 20% of men. Among elderly men, milder depressive syndromes appear to be more common.

Although comorbidity between ED and depressive illness is apparently high, the causal relationship is unclear. ED and the psychosocial distress that often accompanies it may trigger the development of depressive illness in vulnerable individuals; depression may induce ED (*eg*, a subgroup of men with MDD develop a reversible loss of nocturnal penile tumescence while depressed) [3–6]; a third factor, such as substance abuse or medical illness, may cause both conditions; or these conditions may be etiologically unrelated and are comorbid simply because of their high prevalence, particularly in older men.

Depression in Men

The lifetime prevalence of MDD in young adult men (15–54 years) is 12.7%, and the female-to-male adjusted odds ratio is 1.57 [7]. Among older men, MDD appears to be less common but may be replaced by milder depressive syndromes [8]. In an on-site expansion of the Epidemiologic Catchment Area study that focused on the psychiatric status of community-dwelling elderly individuals, 465 men older than age 60 were interviewed [9]. Of these men, 18% had some degree of depression. Notably, among the depressed men, MDD was rare (2.4%), milder depressive syndromes were more common, and significant, isolated dysphoria was most common (73%).

Male Sexual Function and Dysfunction

Sexual function can be divided into four overlapping phases: 1) drive; 2) arousal, marked by erection in men; 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 be biologic, psychologic, or social in origin, but virtually always affects all three. In clinical practice, the most commonly encountered male sexual dysfunctions are hypoactive sexual desire disorder, premature ejaculation, and ED. In the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV), these diagnoses are strikingly dependent on clinical judgment and do not include frequency or duration criteria [10]. This article focuses on ED and explores physiologic factors contributing to its development, the relationship between ED and depression, and current treatments.

Erectile dysfunction

Erectile dysfunction 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 [1,11]. ED is associated with, and presumably exacerbated by, poor health and is more common among men who smoke and those with diabetes, heart disease, hypertension, and hyperlipidemia [1,12].

Table 1. Expected changes in sexual function in aging men

Function	Change
Desire	Variably reduced, depending on testosterone level, desire of partner, length of time in relationship, baseline libido
Erection	Increased time to achieve erection, difficult to maintain; nocturnal penile tumescence time decreases from age 13, "use or lose" principle
Ejaculation	Reduced volume of ejaculate, reduced force of expulsion, period of ejaculatory inevitability not as evident
Refractory period	Prolonged

Factor Contributing to Changes in Sexual Function

Age

The change in sexual function with age is multidimensional and variable [11,12]. 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, and depression.

Age-associated changes in male sexual response include reduced libido; reduced number and frequency of morning erections; reduced penile sensitivity; reduced arousal, including an increase in the time needed to achieve erection and difficulty maintaining an erection; prolonged plateau phase; reduced ejaculatory volume and force of expulsion; and prolonged refractory period (Table 1). The normative decline in testosterone level may be associated with a reduction in libido and mood, although this is not well established [13•].

Medications and substance use

Many medications and substances have been reported to induce sexual dysfunction, particularly tobacco, antihypertensives, anti-ulcer drugs, alcohol, anxiolytics, mood stabilizers, antipsychotics, and antidepressants [1,14]. Depression itself is associated with decreased libido, diminished erectile function, and decreased sexual activity (see below) [3,4]. Sexual dysfunction as a symptom of depression, coupled with the paucity of controlled data regarding the effects of medications on sexual function, makes interpretation of data regarding antidepressant-induced sexual dysfunction difficult.

Most antidepressants are associated with sexual side effects. 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 pervasive anhedonia), the arousal phase (*eg,* erectile dysfunction, although the relationship to preexisting organic factors and to major depression complicates this association), and the release phase (*eg,* delayed orgasm or anorgasmia). With serotonergic medications such as selective serotonin reuptake inhibitors, orgasmic delay appears to be most common, followed by decreased libido and then arousal difficulties [15]. Painful ejaculation occurs in some men taking tricyclic antidepressants [16]. In comparing classes of antidepressants, sexual dysfunction is reported most often with serotonin reuptake inhibitors, somewhat less frequently with monoamine oxidase inhibitors, and even less frequently with tricyclic antidepressants [14].

Strategies for treating antidepressant-induced sexual dysfunction include decreasing the dose, waiting, adding an "antidote," or switching, although none of these treatments has well-established efficacy.

Disease

Determining the impact of medical illness on sexual function is complicated by the effects of age and relationship dynamics. Reduced libido and loss of spontaneous or fantasy-related erectile function are clearly associated with hypogonadism [13•]. ED is more common among men with diabetes, heart disease, hypertension, and hyperlipidemia [1,12].

Comorbid Depression and Erectile Dysfunction

Erectile function in men with major depressive disorder

Loss of libido is a classic symptom of melancholic MDD and has played a prominent role in psychodynamic and other anecdotal descriptions of depressive illness. Systematically collected data confirm that MDD is frequently associated with decreased libido, diminished erectile function, and decreased sexual activity [3,4].

In some men, the presence of MDD is associated with a reversible impairment in sexual neurophysiology, leading to ED. Steiger *et al*. [17] assessed several parameters of nocturnal penile tumescence (NPT) in 25 men with an acute episode of depression compared with nondepressed control subjects. Although no statistically significant differences in NPT parameters were found between the depressed group and the control subjects, there was a complete lack of NPT in four of 25 depressed men that was reversed after antidepressant therapy.

In contrast, Thase *et al*. [3] demonstrated a significant reduction in NPT time and decreased penile rigidity in 34 depressed men compared with nondepressed control

subjects. NPT time was reduced by at least one standard deviation below the control mean in 40% of depressed men and was comparable to that in a group of 14 non-depressed 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 major depression [18]. Together, the results of these studies support the conclusion that erectile function as assessed by NPT is impaired or absent in some, but not all, depressed men, suggesting a neurophysiologic link between depression and ED.

Depressive symptoms among men with erectile dysfunction

The link between ED and depression among men who present with ED has not been systematically studied in clinical settings. There is, however, suggestive evidence from a large epidemiologic sample as well as from a sexual dysfunction clinic.

The Massachusetts Male Aging Study was a 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 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, levels of ED were graded as nil (48%), minimal (17%), moderate (25%), or complete (10%) [1]. Depression and anger were highly correlated with ED. Using the Center for Epidemiologic Studies Depression Scale cutoff of 16 (which is correlated with MDD), all men with this degree of depressive symptomatology had some (*ie,* minimal, moderate, or complete) ED [19••]. 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 [1].

Two large studies describing psychiatric diagnoses and 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) revealed that approximately one third had a comorbid psychiatric diagnosis (mostly affective, anxiety, or personality disorders) [20,21]. Men with ED had high levels of depressive, somatic, and anxious symptoms and scored very high on measures of overall psychological distress (*eg,* using one well-validated instrument that measures such distress, these men scored in the 92nd percentile of the normative population).

Finally, multiple studies have demonstrated a strong positive correlation between ED and reduced quality of life, impaired social and occupational functioning, and substance abuse [22]. Successful treatment of ED appears to reverse much of this morbidity [23].

Treatment of Erectile Dysfunction

Until the recent introduction of effective oral agents, the only nonsurgical ED treatments with proven efficacy were penile self-injection therapy and vacuum device therapy. Penile self-injection therapy is an effective nonsurgical treatment [24] that involves the injection of vasodilator medications into the penis using a small needle. After the initial test injections in the urologist's office, patients receive instructions in the self-injection technique. Once they have learned the proper technique and reached the satisfactory dose of the medication, patients receive medication and supplies for home injections. Follow-up is conducted through periodic visits to ensure compliance and to supply additional medication. The most commonly utilized injectable medication is alprostadil, which is available as a ready-to-use kit under the brand name Caverject (Pharmacia and Upjohn, Peapack, NJ). Many men and their partners find these methods unacceptable. Follow-up studies of patients for whom injection therapy was effective determined that about half of the patients had discontinued treatment [25,26]. The urethral suppository is a minimally invasive pharmacologic therapy for ED. A small pellet of alprostadil, preloaded in a sterile applicator, is inserted into the urethra prior to sexual intercourse.

In March 1998, the US Food and Drug Administration (FDA) approved the first "on-demand" oral medication for the treatment of ED, sildenafil (Viagra; Pfizer, New York, NY). Sildenafil is a competitive inhibitor of cyclic GMP–specific phosphodiesterase type 5 (PDE5), the predominant isozyme causing the breakdown of cyclic GMP in the human corpus cavernosum. After sexual stimulation, neurogenically mediated release of nitric oxide induces the formation of cyclic GMP by guanylate cyclase within the corpus cavernosum smooth muscle. Sildenafil amplifies the effect of sexual stimulation by retarding the degradation of cyclic GMP by PDE5. It is not effective in the absence of sexual stimulation. Sildenafil has demonstrated significant efficacy in ED associated with primarily psychogenic, primarily organic, and mixed etiologies in worldwide clinical trials [27]. The most frequently reported adverse events are headache, facial flushing, and indigestion. The only absolute contraindication to the administration of sildenafil is the concomitant use of organic nitrates in any form at any time. This class of drugs may precipitate hypotension and syncope in the presence of sildenafil [28]. Additionally, drugs that are potent inhibitors of the subclasses of hepatic P450 enzymes that metabolize sildenafil (CYP3A4 and CYP2C9), such as cimetidine, erythromycin, and protease inhibitors, may result in an increase in serum levels of sildenafil. However, these increases do not appear to be associated with an increase in the type or severity of adverse events seen when sildenafil is administered alone.

In April 2000, the FDA approved a second oral medication for the treatment of nonorganic ED, apomorphine (Uprima; TAP Pharmaceuticals, Deerfield, IL). Apomor-

phine is a centrally acting dopamine agonist. It has been available since 1869 and has been utilized parenterally as an emetic agent and as an anti-Parkinsonian drug. Uprima is a novel sublingual formulation of apomorphine that is rapidly absorbed following sublingual administration, with clinical effects within 20 to 45 min in the presence of sexual stimulation. In multicenter double-blind clinical trials, more than 1000 patients with ED with no major organic component were randomized to placebo or apomorphine 2, 4, or 6 mg. Global efficacy was as follows: apomorphine 2 mg, 44% to 46%; apomorphine 4 mg, 52% to 58%; apomorphine 6 mg, 60%; and placebo 31% to 38% ($P < 0.001$ for all apomorphine doses compared with placebo). The primary side effects were nausea, syncope, and sedation (Reproductive Health Drugs Advisory Committee, FDA Briefing Package. Uprima, April 10, 2000).

Treatment of erectile dysfunction in depressed men

Shabsigh *et al*. [29] conducted a study of 120 men who presented to a urologic clinic with ED, benign prostate hyperplasia, or both, and who completed self-report depression symptom inventories, the Primary Care Evaluation of Mental Disorders Survey (PRIME-MD) and the Beck Depression Inventory (BDI). Criteria for the diagnosis of "depression" were a BDI score of greater than 15 and four or more depressive symptoms from the PRIME-MD. Overall, depression was more commonly reported by men with ED (55%) than those with only benign prostate hyperplasia (21%). A total of 15 patients in the ED group who did not experience depression and 18 patients with ED and depression were treated for their ED with either penile intracavernosal injection or a vacuum device. All 15 (100%) patients in the ED-only group continued treatment and were satisfied with the outcome. In contrast, only 7 of 18 (38.9%) who had ED and depression continued treatment [29].

In a retrospective analysis of patients who took part in the placebo-controlled prerelease sildenafil clinical trials, 134 men were diagnosed with depression [30]. Of those who received sildenafil, 76% responded positively to the global efficacy question ("Did the treatment improve your erections?"), compared with 18% of those who received placebo.

We recently conducted a placebo-controlled, parallel-group, double-blind study of 50 to 100 mg of sildenafil or placebo in 146 men with ED and comorbid subthreshold MDD. Patients were older than 18 years, were in stable heterosexual relationship, 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 all day or every day for 2 weeks. The standard diagnosis of MDD involves five major depressive episode criteria, and such patients were excluded. Follow-up HAM-D, BDI, and Clinical Global Impression scores were assessed at week 12 [31].

Men with ED and depression were treated for 12 weeks with sildenafil or placebo. An "ED responder" was defined by a score of greater than 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: 1) Did the treatment improve your erections? and 2) Did the treatment improve your ability to have sexual intercourse? Among the responders, 83% were treated with sildenafil and 17% received placebo ($P < 0.0001$). Moreover, depressive symptoms decreased significantly in ED responders: the mean HAM-D score among ED-responders decreased from 16.8 to 7.0; among ED-nonresponders, it decreased from 16.8 to 13.6. Although the majority of men who were ED responders were in the sildenafil treatment group, even among the small number of ED responders treated with placebo, there were similar improvements in their depression scores [31].

Conclusions

Erectile dysfunction is a multifactorial condition. Precipitating factors include cardiovascular disease, diabetes, smoking, relationship problems, anxiety, and depression. It is a common disorder that becomes more prevalent with age, but it is not an inevitable consequence of aging. More studies are needed to fully understand the complex relationship between ED and depression and to determine the most appropriate treatment for men with both disorders.

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