Exploring the Relationship Between Depression and Erectile Dysfunction in Aging Men

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Normal sexual function is a biopsychosocial process; sexual dysfunction almost always has organic and psychological components and 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 is one of the more common male sexual dysfunctions encountered in the clinical setting. Comorbidity between erectile dysfunction and depressive illness is high, but the causal relationship is unclear. The psychosocial distress that often accompanies erectile dysfunction might stimulate the development of depressive illness, or, as some data suggest, depression might cause erectile dysfunction. This article reviews the literature on the relationship between depression and erectile dysfunction, as well as the design of a new study that may provide some answers, and concludes that erectile dysfunction is a common, treatable condition that may cause or be the result of depression. Recent data suggest that sildenafil is an effective treatment for erectile dysfunction in men with comorbid depression. Erectile dysfunction should be considered a multifactorial condition that may require a multidisciplinary approach to treatment, especially when depression is present. *(J Clin Psychiatry 2002;63[suppl 5]:5–12)*

Erectile dysfunction is a common disorder of aging men, affecting up to 30 million men in the United States, with a prevalence of 40% in men 40 years of age that increases to approximately 70% at age 70.[1] Unipolar depressive disorders, such as major depressive disorder (MDD) and milder depressive syndromes (e.g., dysthymia, depressive disorder not otherwise specified), are syndromes characterized by a pervasive low mood and/or loss of pleasure or interest in activities, along with 2 or more associated symptoms (i.e., agitation, low energy, low libido, guilty feelings or low self-esteem, poor concentration, sleep or appetite disturbances, and/or thoughts of death). Among men, the lifetime prevalence of MDD is 10%, and the point prevalence in community samples is 3%. Among elderly men, milder depressive syndromes appear to be more common.

Although comorbidity between erectile dysfunction and depressive illness is apparently high, the causal relationship is unclear. Erectile dysfunction and the psychosocial distress that often accompanies it might stimulate the development of depressive illness in vulnerable individuals, or depression might cause erectile dysfunction (e.g., a subgroup of men with MDD develop a reversible loss of nocturnal penile tumescence while depressed).[2–5] A third factor, such as substance abuse or medical illness, may cause both conditions, or these conditions might be etiologically unrelated. Furthermore, the relationship between improvement in erectile dysfunction and the concurrent depression has not been explored. The impressive efficacy of sildenafil in men who are not depressed poses the important clinical question, Does the presence of depression affect erectile dysfunction treatment response?

MALE SEXUAL FUNCTION AND DYSFUNCTION

Sexual function in men can be divided into 4 overlapping phases: (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 commonly derives from the biological, psychological, or social arena, but virtually always affects all 3.

In clinical practice, the most commonly encountered male sexual dysfunctions are hypoactive sexual desire disorder, premature ejaculation, and erectile dysfunction. As defined by the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV),[6] these diagnoses require a great deal of clinical judgment and do not

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include frequency or duration criteria. This article focuses on erectile dysfunction and explores physiologic factors contributing to its development, the relationship between erectile dysfunction and depression, and current treatments.

Erectile Dysfunction

Erectile dysfunction is defined as the inability to obtain and maintain an erection sufficient for satisfactory intercourse. It is a para-aging phenomenon that affects approximately half of all men between the ages of 40 and 70 years.[1,7] Erectile dysfunction 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.[1,8]

Until the recent introduction of an effective oral agent, the only nonsurgical erectile dysfunction treatments with proven efficacy were the urethral suppository, penile self-injection therapy, and vacuum device therapy. The urethral suppository is a minimally invasive pharmacologic therapy for erectile dysfunction. A small pellet of the vasodilator medication alprostadil, preloaded in a sterile applicator, is inserted into the urethra prior to sexual intercourse. Penile self-injection therapy is a very effective nonsurgical treatment method[9] 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. Many men and their partners find these methods unacceptable. In a follow-up with patients for whom injection therapy is effective, about half of the patients have discontinued treatment.[10,11]

In March 1998, the U.S. Food and Drug Administration approved the first "on-demand" oral medication for the treatment of erectile dysfunction, sildenafil citrate. Sildenafil is a competitive inhibitor of cyclic guanosine monophosphate (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 erectile dysfunction associated with primarily psychogenic, primarily organic, and mixed etiologies in worldwide clinical trials involving over 3300 men and many of their partners.[12] The most frequently reported adverse events were 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.[13] Additionally, drugs that are potent inhibitors of the subclasses of hepatic cytochrome P450 (CYP) enzymes that metabolize sildenafil (CYP3A4 and CYP2C9), such as cimetidine, erythromycin, and protease inhibitors, may result in an increase in serum levels of sildenafil. Sildenafil doses may require adjustment in patients taking these types of compounds.

Table 1. Normal Sexual Function in Aging Men

Expected changes in sexual function
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 years; "use or lose" principle
Ejaculation: reduced volume of ejaculate, reduced force of expulsion, period of ejaculatory inevitability not as evident
Refractory period: prolonged

FACTORS CONTRIBUTING TO CHANGES IN SEXUAL FUNCTION

Age

The change in sexual function with age is multifactorial and variable.[7,8] 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 decrease in testosterone level may be associated with a reduction in libido and mood, although this is not well established.[14]

Medications and Substance Use

Many medications and substances have been reported to induce sexual dysfunction, particularly tobacco, antihypertensives, antiulcer drugs, alcohol, anxiolytics, mood stabilizers, antipsychotics, and antidepressants.[1,15] Depression itself is associated with decreased libido, diminished erectile function, and decreased sexual activity.[2,3] This, as well as 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 preexisting organic factors and to major depression complicates this association), and/or the release phase (e.g., delayed orgasm or anorgasmia). With serotonergic medications such as selective serotonin reuptake inhibitors (SSRIs), orgasmic delay appears to be most common, followed by decreased libido and then arousal difficulties.[16] Painful ejaculation occurs in some men taking tricyclic antidepressants.[17] In comparing classes of antidepressants, sexual dysfunction is reported most often with SSRIs, somewhat less frequently with monoamine oxidase inhibitors, and even less frequently with tricyclic antidepressants.[15]

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 (see below). Erectile dysfunction is more common among men with diabetes, heart disease, hypertension, and hyperlipidemia.[1,8]

Male Depressive Illnesses

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.[18] Among the elderly male community, MDD appears to be less common, but it may be replaced by milder depressive syndromes.[19] In an on-site expansion of the Epidemiologic Catchment Area study[20] that focused on the psychiatric status of community-dwelling elderly individuals, 465 men older than age 60 were interviewed. 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 (24%), and significant, isolated dysphoria was most common (73%).

TESTOSTERONE SECRETION IN MEN: THE RELATIONSHIP TO DEPRESSION AND ERECTILE DYSFUNCTION

Testosterone secretion in adult men has multiple determinants, and this androgen has neurobehavioral and metabolic actions. Central nervous system effects include organizing and activating actions on male sexual arousal and behavior, as well as some influence on energy and mood.[21] In animal models, testosterone plays a role in regulating male social behaviors, particularly those related to male-male competition, dominance, and submission.[21]

Testosterone secretion generally peaks at age 20 years and slowly declines thereafter, although not significantly until about age 50.[22–25] Among men in their eighth decade, mean free testosterone level is approximately 50% that of young adult men.[24] Reduction in circulating testosterone, or hypogonadism, is a common clinical syndrome with multiple etiologies (e.g., hypothalamic, pituitary, and/or testicular pathology). Loss of libido and lack of vigor, reduced musculoskeletal mass, and impaired fertility characterize postpubertal onset of hypogonadism.[26] Such sequelae are reversed with testosterone replacement.[21] In men who have normal testosterone levels (i.e., eugonadal men), administration of moderately supraphysiologic doses of testosterone has idiosyncratic mood-elevating and libido-enhancing effects.[26,27]

Testosterone and Sexual Function

Testosterone has complex and pervasive influences on sexual behavior.[28] Increased levels of plasma androgens at puberty are correlated with the onset of nocturnal emission, masturbation, dating, and infatuation. In parallel, males with an early onset of androgen secretion (i.e., precocious puberty) often develop an early interest in sexuality and erotic fantasies.[29] Suppression of testosterone secretion in eugonadal men leads to reduced sexual desire and activity and a decrease in spontaneous erections.[30] Hypogonadal men who experience similar symptoms have a dramatic increase in sexual desire, sexual activity, and frequency of spontaneous erections after testosterone replacement.[21] There appears to be a threshold testosterone level (which may vary from person to person) below which sexual function is impaired.

Testosterone and Depression

Although the symptoms of hypogonadism (e.g., loss of libido, dysphoria, fatigue, irritability, and appetite loss)[21,31] overlap with the signs and symptoms of depression, it is not known what proportion of hypogonadal men meet criteria for MDD and, for those who do, which dysfunction is primary. Furthermore, it is unclear whether a specific hypothalamic-pituitary-gonadal (HPG) measure (e.g., total testosterone, free testosterone) might be associated with psychiatric symptoms and, if so, at which absolute or relative level. For example, symptomatic hypogonadism apparently develops only when the total testosterone level drops below a certain threshold, typically "set" between 200 and 300 ng/dL. Yet this threshold has generally been used to assess for HPG dysfunction in relatively young men (e.g., young men with testosterone levels below 250 ng/dL often have symptoms of sexual dysfunction, such as impaired nocturnal erections and low libido).[31] In contrast, standards for determining the relevance of decreasing testosterone levels among healthy aging men—i.e., "normative" gonadal hypofunction—may need to account for other age-related phenomena,

such as changes in end-organ responsiveness and changes in HPG secretory patterns.

A recently published epidemiologic study demonstrated a significant inverse association between free testosterone and depressive symptoms. The Rancho Bernardo Study[32] 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 years (mean ± SD = 70.2 ± 9.2 years) 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 score was positively correlated with these same factors. In multiple linear-regression analyses, adjusting for these potentially confounding covariates, free testosterone concentration was significantly associated with BDI score (–0.302; adjusted standard error = 0.11, p = .007); there was no significant 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 and/or the depressive symptoms that evolve with age (i.e., male "climacteric") has long been an area of intense speculation and anecdote.[21] Yet very few studies have systematically addressed these issues using standard psychiatric methodology. For example, none of the numerous controlled testosterone replacement trials completed over the past 3 decades has described the prevalence of prereplacement psychiatric illness followed by systematic monitoring of psychiatric symptoms during testosterone replacement.[14] 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, perhaps not unlike the dysphoric/irritable/fatigue syndrome of female hypogonadism (i.e., menopause).

COMORBID DEPRESSION AND ERECTILE DYSFUNCTION

Erectile Function in Men With MDD

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.[2,3]

In some men, the presence of MDD is associated with a reversible impairment in sexual neurophysiology, leading to erectile dysfunction. Steiger and colleagues[33] 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 4 of 25 depressed men that was reversed after antidepressant therapy.

In contrast, Thase and coworkers[2] 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 with that in a group of 14 nondepressed men with a diagnosis of erectile dysfunction due to organic causes. These findings were confirmed in a repeat study[34] with a new group of 51 men with major depression. Together, the results of these studies support the conclusion that erectile capacity as assessed by NPT is impaired or absent in some, but not all, depressed men, suggesting a neurophysiologic link between depression and erectile dysfunction.

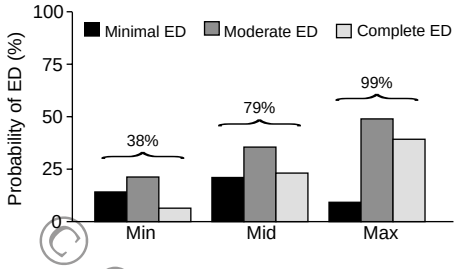
Depressive Symptoms Among Men With Erectile Dysfunction

The link between erectile dysfunction and depression among men who present with erectile dysfunction 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 it had a response rate of 76% (N = 1290). On the basis of the subjects' responses to 9 questions that were highly correlated with biological measures of erectile response, their levels of erectile dysfunction were graded as nil (48%), minimal (17%), moderate (25%), or complete (10%).[1] Depression and anger were highly correlated with erectile dysfunction. Using the Center for Epidemiologic Studies Depression Scale cutoff of 16 (suggesting likely MDD), nearly all men with this degree of depressive symptomatology had some (i.e., minimal, moderate, or complete) erectile dysfunction[35] (Figure 1). Maximal level of anger (either suppression or expression, as defined by Spielberger's anger scales) was associated with approximately 75% overall erectile dysfunction, double the erectile dysfunction prevalence among men who reported minimal anger.[1]

Two large studies[36,37] describing psychiatric diagnoses and symptoms among men presenting to the Johns

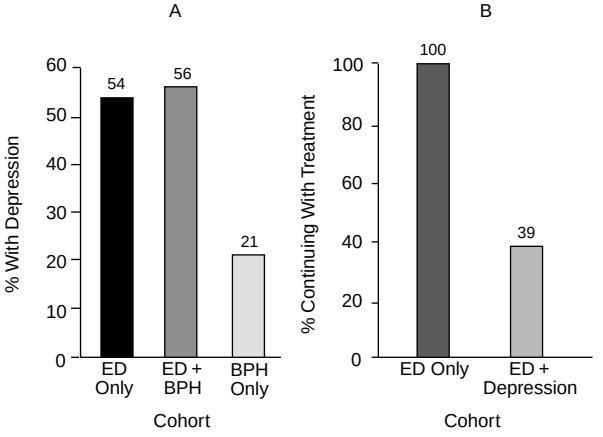
Figure 1. Erectile Dysfunction (ED) and Depression Are Highly Correlated (N = 1290)[a]



[a]Adapted from Feldman et al.,[1] with permission. Association of psychological indexes with age-adjusted probability of impotence imputed by discriminant analysis. Labels refer to minimum (Min), midrange (Mid), and maximum (Max) values observed in impotence substudy subjects.

According to data from the Massachusetts Male Aging Study, after adjustment for age, a higher probability of ED was directly correlated with heart disease, hypertension, and diabetes. ED was also highly correlated with an index of depression. At the maximum degree of depression, the combined age-adjusted probability of any degree of ED was around 99%, compared with approximately 79% at midscale and 38% at the least depressed extreme.

Figure 2. Depression in Men With Erectile Dysfunction (ED)[a]



[a]Adapted from Shabsigh et al.,[40] with permission. Panel A: Depression was assessed in 120 consecutive patients presenting to a urologic clinic with ED alone, with ED and benign prostate hyperplasia (BPH), or with BPH alone. Depression was measured with the Beck Depression Inventory and Primary Care Evaluation of Mental Disorders rating scales. Panel B: Compliance with treatment for ED in men with (N = 18) and without (N = 15) depressive symptoms. ED treatments were either penile intracavernosal injection or vacuum device ($p < .00021$).

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). Men with erectile dysfunction had high levels of depressive, somatic, and anxious symptoms and scored very high on measures of overall psychological distress (e.g., 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 erectile dysfunction and reduced quality of life,[38] impaired social and occupational functioning, and substance abuse.[39]

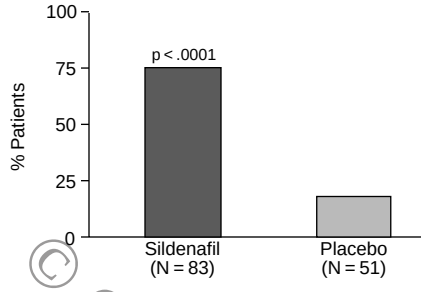
Treatment of Erectile Dysfunction in Depressed Men

Shabsigh and colleagues[40] conducted a study of 120 men who presented to a urologic clinic with erectile dysfunction, benign prostate hyperplasia (BPH), or both. The study was designed to investigate the hypothesis that men with erectile dysfunction have a higher incidence of concomitant depressive symptoms compared with age-matched controls and that depressive symptoms may have an impact on the success of erectile dysfunction therapy. All 120 men were screened for depressive symptoms with a questionnaire that incorporated the Primary Care Evaluation of Mental Disorders survey (PRIME-MD) and the BDI. Patients were divided into 3 groups on the basis of their diagnostic evaluations: erectile dysfunction only, BPH only, and concomitant erectile dysfunction and BPH.

Both erectile dysfunction groups experienced significant depression: 54% of men (26 of 48) with erectile dysfunction and 56% of men (10 of 18) with erectile dysfunction and BPH reported depressive symptoms, compared with 21% of men (7 of 34) with BPH alone (Figure 2). Men with erectile dysfunction had a decreased libido compared with men without erectile dysfunction. Patients with erectile dysfunction were 2.6 times more likely to report depressive symptoms than men with BPH alone. A total of 15 patients in the erectile dysfunction group who did not experience depression and 18 patients with erectile dysfunction and depression were treated for their erectile dysfunction with either penile intracavernosal injection or a vacuum device. All 15 patients (100%) in the erectile dysfunction–only group continued treatment and were satisfied with the outcome. In contrast, only 7 (39%) of 18 patients in the group with erectile dysfunction and depression continued treatment. Thus, patients with erectile dysfunction and depression were more likely to discontinue erectile dysfunction treatment than patients with erectile dysfunction and no depressive symptoms, indicating that depression significantly affected treatment outcome in this study. These observations emphasize that erectile dysfunction is a multifactorial condition and that a multidisciplinary approach involving both urologic and psychiatric treatment is important.[40]

The erectile dysfunction treatments used in the above study were limited to the vacuum device and penile injections. Since completion of that study, oral sildenafil has become available to treat erectile dysfunction. Sildenafil has been proven effective for the treatment of erectile dysfunction by enabling an erectile response to sexual stimulation.

Figure 3. Efficacy of Sildenafil in Men With Depression[a]



[a]Adapted from Price,[41] with permission. The efficacy of sildenafil was determined in a subpopulation of patients (N = 134) enrolled in 10 randomized, double-blind, placebo-controlled clinical trials who were diagnosed with concurrent erectile dysfunction and depression. In answer to the question of whether treatment had improved their erections, 76% of depressed patients in the sildenafil group answered positively, compared with 18% of depressed patients in the placebo group.

Table 2. Sildenafil and Placebo in Men With Erectile Dysfunction (ED) and Minor Depression: Results After 12 Weeks of Treatment[a]

Question	Sildenafil (N = 70)	Placebo (N = 76)
GEQ1 (Did the treatment improve your erections?)*	82%†	20%
GEQ2 (Did the treatment improve your ability to have sexual intercourse?)*	83%†	19%

[a]Data from Rosen et al.[43] This placebo-controlled, parallel-group, double-blind study was designed to answer the following questions: (1) Is sildenafil an effective treatment for ED in men with concurrent depression? and (2) What effect does the alleviation of ED have on depressive symptoms?

The study, which enrolled 160 men with ED and comorbid minor depression, compared 50 to 100 mg of sildenafil with placebo. Inclusion criteria were age at least 18 years, ED of greater than 6 months' duration, a stable heterosexual relationship of at least 6 months, and comorbid minor depression. Depression was defined as a score of greater than 12 on the 24-item Hamilton Rating Scale for Depression and 2 to 4 symptoms indicative of a major depressive episode based on the DSM-IV, at least one of which was depressed mood or loss of interest or pleasure in most activities all day/every day for 2 weeks. Exclusion criteria included use of organic nitrates, major psychiatric disorder, recent stroke or significant cardiovascular disease, use of androgens or antidepressants, use of other ED therapies, and retinitis pigmentosa.

After 12 weeks of treatment, men in sildenafil groups had significantly higher scores on the International Index of Erectile Function than men in the placebo group ($p < .0001$). Significantly more men in the sildenafil group than in the placebo group gave positive answers to the 2 global efficacy questions (GEQs). Investigators concluded that sildenafil is effective and well tolerated by men with ED and comorbid depression.

*Percentage of positive response.

†$p < .0001$ vs. placebo.

Table 3. Effect of Alleviation of Erectile Dysfunction (ED) on Depressive Symptoms at 12 Weeks[a]

Measure	Baseline Score	ED Optimal Responder Score (N = 58)	ED Nonresponder Score (N = 78)
HAM-D	16.1	6.4*	14.2
BDI	15.6	6.4*	13.7

[a]Data from Menza et al.[42] Abbreviations: HAM-D = Hamilton Rating Scale for Depression, BDI = Beck Depression Inventory. After 12 weeks of treatment, those who were optimal ED responders, including sildenafil- (N = 48) and placebo-treated (N = 10) subjects, showed significant improvements in depressive symptoms as indicated by the decrease in both their HAM-D and BDI scores to 6.4 ($p < .0001$). Optimal ED responders were those subjects who answered "yes" to global efficacy questions 1 and 2 and had a score in the range of 22–30 in the erectile function domain of the International Index of Erectile Function at week 8, week 12, or a specific visit.

*$p < .0001$ vs. ED nonresponders (analysis of covariance).

At the 8th World Meeting on Impotence Research in August 1998, a meta-analysis of patients who took part in the sildenafil clinical trials and who had concomitant conditions was presented.[41] Among the conditions analyzed was depression. Of the 134 men in the clinical trials diagnosed with depression, 76% of those in the sildenafil group responded positively to the global efficacy question "Did the treatment improve your erections?" compared with only 18% in the placebo group (Figure 3). The meta-analysis concluded that sildenafil was effective for treating erectile dysfunction in men with depression.

This extensive meta-analysis of all patients with diagnosed depression in the clinical trials of sildenafil demonstrated the efficacy of sildenafil in this population. However, a prospective study was needed not only to further establish the efficacy of sildenafil in depressed men with erectile dysfunction but also to determine whether successful treatment of erectile dysfunction would improve depressive symptoms.

We recently conducted a placebo-controlled, parallel-group, double-blind study of 50 to 100 mg of sildenafil or placebo in 160 men with erectile dysfunction and comorbid minor depression. Patients were older than 18 years, were in stable heterosexual relationships, and had been experiencing erectile dysfunction 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 2 to 4 DSM-IV major depressive episode criteria, with at least one of which was 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 5 major depressive episode criteria, and such patients were excluded. Baseline psychiatric evaluations (Structured Clinical Interview for DSM-IV/HAM-D) were made and repeated 4 weeks later. Patients with a HAM-D score > 12 were also assessed with the BDI and randomly assigned to sildenafil or placebo (week 0). Follow-up HAM-D, BDI, and Clinical Global Impressions scale scores were assessed at weeks 8 and 12.[42,43]

Men with erectile dysfunction and depression were treated for 12 weeks with sildenafil or placebo. An "erectile dysfunction optimal responder" was defined by those subjects who answered "yes" to global efficacy questions 1 and 2 (GEQ1 and GEQ2) and had a score in the range of

22 to 30 in the erectile function domain of the International Index of Erectile Function at week 8 or 12 or at a specific visit (GEQ1 was "Did the treatment improve your erections?" and GEQ2 was "Did the treatment improve your ability to have sexual intercourse?"). Among the responders, 83% were treated with sildenafil and 17% received placebo ($p < .0001$) (Table 2).[43] Furthermore, the HAM-D and BDI scores dropped significantly in erectile dysfunction responders, whether treated with sildenafil or placebo, compared with those patients who did not respond to treatment (Table 3).[42]

The results of this study suggest that sildenafil is an effective treatment for erectile dysfunction in men with comorbid depression. This study may provide important clues to the relationship between erectile dysfunction and depression.

CONCLUSION

Erectile dysfunction is a multifactorial condition. Precipitating factors include cardiovascular disease, diabetes, smoking and other lifestyle factors, relationship concerns, anxiety, and depression. It is a common disorder that becomes more prevalent with age, but it is not an inevitable consequence of aging. Erectile dysfunction is treatable in nearly all cases.

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

Sildenafil has been shown to be an effective treatment for erectile dysfunction in men with depression. More studies are needed to fully understand the complex relationship between erectile dysfunction and depression and to determine the most appropriate treatment for men with both disorders.

Drug names: alprostadil (Caverject and others), cimetidine (Tagamet and others), sildenafil (Viagra).

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