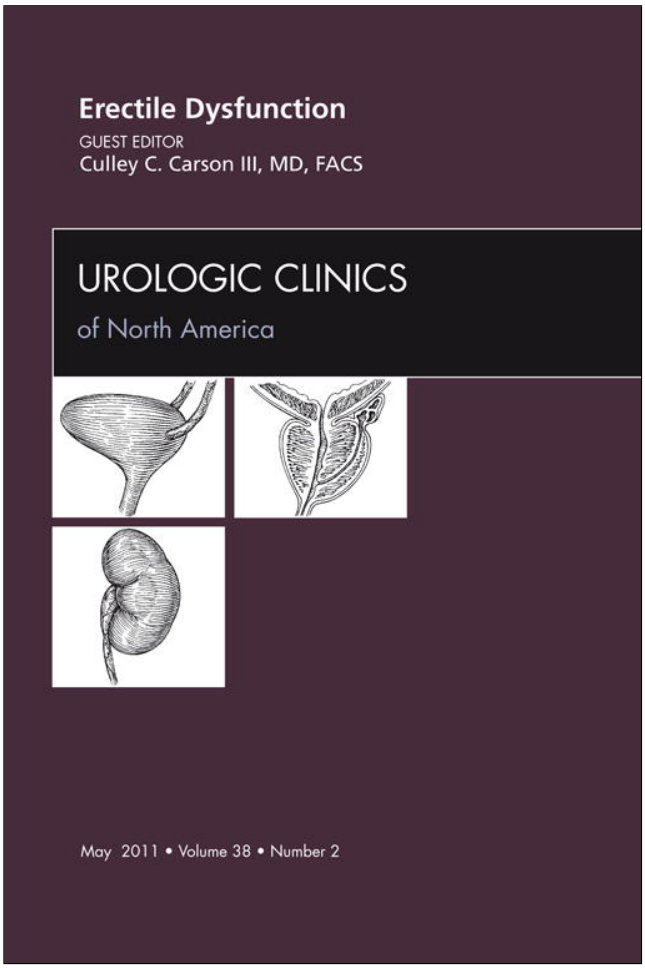

Erectile Dysfunction and Depression: Screening and Treatment

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KEYWORDS

• Depression • Erectile dysfunction • Sexual dysfunction
• Metabolic syndrome • Combination treatment

The comorbid conditions erectile dysfunction (ED) and depression are both highly prevalent in men. The National Comorbidity Survey found a lifetime prevalence of major depression of 12.7% for men in a representative sample of the US population, with minor depression affecting an estimated 10% of the population aged 15 to 54 years.[1] In the Massachusetts Male Aging Study, high depression scores were associated with frequent reports of moderate ED (for men aged 40–70 years), with the prevalence of severe, or complete, ED estimated at 10%.[2] Multiple regression analysis to control for all other predictors of ED still found that men with high depression scores were nearly twice as likely to report ED than nondepressed men.[3] Depression continues to be among the most common comorbid problems seen in men with ED, both in the community and in clinical samples.[2–5]

There is a very low rate of recognition of depression by urologists and other nonpsychiatric physicians. Lee and colleagues[6] determined that 33% of the 120 men presenting to a sexuality clinic had a major current psychiatric disorder. Of these 40 men, only one-third had been identified as having a mental disorder by the study urologist. Major depression was present in 15 (12.5%) of those men and was the second most common category of mental illness (chemical dependence was first). This failure to properly diagnose has 2 obvious negative consequences. First, the mental disorders detected were hardly trivial: 2 of the men required psychiatric hospitalization, 1 made a suicide attempt, and 1 required electroconvulsive therapy (ECT). Failure to properly diagnose is in itself serious and could have extremely deleterious consequences. Second, there is a growing body of evidence that underdiagnosed and untreated psychosocial-cultural factors contribute significantly to ED treatment discontinuation and failure.[7,8] In fact, Mallis and colleagues[9] determined that more than 50% of their study participants reported a lifetime history of psychiatric difficulties, concluding that obtaining a patient's psychosocial history is essential when evaluating and treating ED.

The effect of depression on the course of ED is multifaceted because of systemic pathophysiologic implications as well as psychological and behavioral ramifications. Although the relative contributions of organic and psychosocial-cultural causes to depression is open to discussion, there is little debate that depression can have a deleterious effect on the treatment of ED. Confounding this problem is the reality that a proper psychiatric diagnosis usually requires a 45- to 90-minute interview by a trained psychiatrist, whereas a urologist's time is often limited to

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15 to 30 minutes, almost all of it occupied with acquiring medical information. This article reviews the current knowledge about the relationship between ED and depression, the effect of treatments for depression on ED, ways to improve screening for depression, and treatment of ED in patients experiencing this common comorbidity.

Every patient who seeks treatment of ED should be screened for a major mood disorder (MMD) or depression. Depression in the medically ill is generally underdiagnosed and undertreated.[10] Patients with ED have an increased likelihood of depression and vice versa. In patients with ED, it is of course normal to have a distressed response to this condition. Indeed, distress or bother is generally a part of the diagnostic criteria for ED. Whereas many of these symptoms resolve themselves with the effective treatment of the ED, for those individuals who have significant depressive disorder (associated with ED rather than caused by ED), this is not the case. Failure to screen for MMD can result in significant risk to the patient in terms of both morbidity and mortality.

WHAT IS DEPRESSION?

ED has been extensively characterized elsewhere. However, before proceeding further, it would be useful to define and characterize depression. It is a significant error to view depression as "only" a psychosocial-cultural phenomenon. A severe major depression is frequently organic in derivation and some think that depression is a systemic disease with distinct subtypes, each with unique organic pathophysiology.[10] Yet, it is clear that behavioral, psychosocial, and cultural factors also play a role in the cause of depression in much the same way they do in sexual dysfunction (SD) generally and ED specifically. Like ED, there are omnipresent psychogenic components existing in most depressed patients regardless of the degree of organicity. The degree of manifest dysfunction frequently exceeds the degree of organic impairment even in men who are "organically " depressed. In other words, like ED, despite the existence of organic pathogenesis, depression always has a psychogenic component, even if the depression was initially the result of constitution, illness, surgery, or other treatments.[11]

Depressed mood is common in everyday life and may be a normal and expectable reaction to adverse events. However, when depressed mood lasts for 2 weeks or more, is associated with certain other symptoms, such as insomnia and agitation, and causes serious distress or impairment in functioning, a diagnosis of a mood disorder should be considered. The algorithm required and the multiple terms used to diagnose specific mood disorders in the current the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition Text Revision) (DSM-IV-TR)[12] can be confusing for the uninitiated. **Box 1** provides the nomenclature used in DSM-IV-TR to categorize the various mood disorders.

Major depressive episode and major depressive disorder sound similar but are conceptually distinct. Major depressive episode denotes a period of at least 2 weeks marked by the presence of at least 5 of 7 specific symptoms, 1 of which must be either depressed mood or markedly diminished interest or pleasure. The term major depressive episode is not applied when the patient also meets the following criteria: (1) if the symptoms do not cause clinically significant distress or impairment for a manic episode, (2) if the symptoms are directly attributable to substance or medical condition, or (3) if the symptoms are because of bereavement (this last item is controversial). Many patients with a major depressive episode qualify for a diagnosis of major depressive disorder, either single episode or recurrent. But a diagnosis of major depressive disorder is only made if certain other disorders are ruled out (such as schizophrenia) and if the patient has never had a manic episode. The DSM-IV-TR recommends the diagnosis of major depressive disorder only for those patients who do not have a bipolar disorder, or what used to be called manic-depressive disorder. If there is a past history of a manic episode, the diagnosis is bipolar I disorder. If only milder manic-range episodes, called hypomanic episodes, have been present, the diagnosis is bipolar II disorder. Bipolar disorders are less common than major depressive disorders. However, the inadvertent prescription of an antidepressant to patients with bipolar disorder can destabilize them and is a major iatrogenic risk associated with primary care physicians (PCPs) or urologists prescribing antidepressants. Bottom line, the clinician initially consulted should screen every patient with ED for major mood disorders. However, once screened and identified as potentially having a major mental disorder, the patient should be referred to a mental health professional (MHP), typically a psychiatrist for sophisticated diagnostic typing.

Depression, like ED, occurs more frequently in the medically ill. Rates of depression have been shown to increase with the increasing number and acuity of medical illnesses.[13] For example, studies have found increased risk for major depression in patients with cardiovascular, endocrine, and inflammatory diseases at rates triple

Box 1
The current mood disorder nomenclature

Mood episodes
- Major depressive episode
- Manic episode
- Mixed episode
- Hypomanic episode

Depressive disorders
- Major depressive disorder
- Dysthymic disorder
- Depressive disorder not otherwise specified

Bipolar disorders
- Bipolar I disorder
- Bipolar II disorder (recurrent major depressive episodes with hypomanic episodes)
- Cyclothymic disorder
- Bipolar disorder not otherwise specified

Other mood disorders
- Mood disorders due to a general medical condition
- Substance-induced mood disorder
- Mood disorder not otherwise specified

Specifiers, describing current or most recent episode
- Severity/psychotic/remission specifiers for major depressive episode
- Severity/psychotic/remission specifiers for manic episode
- Severity/psychotic/remission specifiers for mixed episode
- Chronic specifier for a major depressive episode
- Catatonic features specifier
- Melancholic features specifier
- Atypical features specifier
- Postpartum onset specifier

Specifiers, describing course of recurrent episodes
- Longitudinal course specifiers (with and without full interepisode recovery)
- Seasonal pattern specifier
- Rapid cycling specifier

Adapted from Diagnostic and statistical manual of mental disorders, 4th edition, Text Revision (DSM-IV-TR). Washington, DC: American Psychiatric Association; 2000; with permission.

those of usual populations.[14–20] Furthermore, depression is an independent risk factor for those diseases including greater risk of mortality after acute myocardial infarction.[21,22]

ETIOLOGY: THE BIDIRECTIONAL RELATIONSHIP BETWEEN ED AND DEPRESSION

Correlations have been noted between depression and aspects of sexual function, including erectile function. Experiencing ED can of course be a cause or precipitator of a depression of greater magnitude. History taking is critical in determining whether depression is a consequence of the ED, or if ED is more determined by the depression and its treatments. Most cases of reactive depression resolve upon improvement of sexual function.[23,24] In fact, for a select subpopulation of depressed men with ED, the use of phosphodiesterase 5 (PDE5) inhibitors alone is adequate in resolving the depression.[25,26]

Shabsigh and colleagues[27] concluded that ED is associated with a high incidence of depressive symptoms independent of age, marital status, or comorbid conditions and that depressed patients with ED had a lower libido than patients who did not exhibit depression. These patients were also less likely than others to continue a treatment of ED. There is a link between depression and nocturnal penile tumescence (NPT). In an early case report, 2 severely depressed men with ED were noted to have virtually absent NPT, which normalized, with successful antidepressant treatment.[28] A subsequent series measuring NPT found that, compared with nondepressed controls, men with depression showed decreased total sleep tumescence time and were more likely to have absence of rigid nocturnal erections.[29–31]

The relationship between depression and ED is complex, and it can be difficult to distinguish which occurred first. Depression can be a major consequence of ED, yet inversely, depression and its treatments can both cause ED.[32,33] Finally, although factors such as stress, alcohol, or hypogonadism can contribute to both depression and ED, it is quite plausible that a mechanism, as yet unknown, may lead to both ED and depression. Such an interaction can be understood in terms of several theoretical models that discuss how the mind and body both inhibit and excite sexual response, creating a unique dynamic balance.[34–38]

Bancroft[39] and Kaplan[40] both described a delicate balance between central excitatory and inhibiting mechanisms, adding greater understanding of the role of anxiety and other psychogenic factors in ED. Subsequently, Perelman[35–38]

postulated The Sexual Tipping Point (STP) model, which expanded this dual control concept to include all aspects of sexual functioning and dysfunction. This useful heuristic model defined a characteristic threshold for the expression of a sexual response for any individual, which could vary dynamically within and between individuals and for any given sexual experience (**Fig. 1**).[38]

Although the exact nature of a biological predisposition is not known, it is reasonable to conclude that the threshold for onset of either erectile difficulty and/or depression may have a distribution curve like that of numerous other human variables, such as height.[8,41,42] The specific threshold for any specific function is determined by multiple factors for any given moment or circumstance. One or another factor dominates, whereas the others recede in importance.[41–43] Determining whether the exact physiologic mechanisms of such thresholds are central, peripheral, and/or some combination requires further research.

These biological set points for erectile latency and depression (as well as other comorbid disease thresholds) are affected by multiple organic and psychogenic factors in varying combinations over the course of a man's life cycle. However, this pattern of biological susceptibility presumably interacts with a variety of circumstances and intrapersonal and interpersonal dynamics, in addition to environmental and medical risk factors, resulting in manifest disorders. These concepts can help us understand both ED and depression, as well as lead to identification of both the types and severity of factors that underlie both disorders. Clinicians can understand both ED and depression by recognizing how these predisposing, precipitating, and maintaining psychosocial-cultural causes, organic causes, and risk factors are all interrelated. Yet, ED and depression can both be elicited by a purely organic factor at one time and a completely cultural/environmental in another instance. There is a subsequent typical cascade of secondary

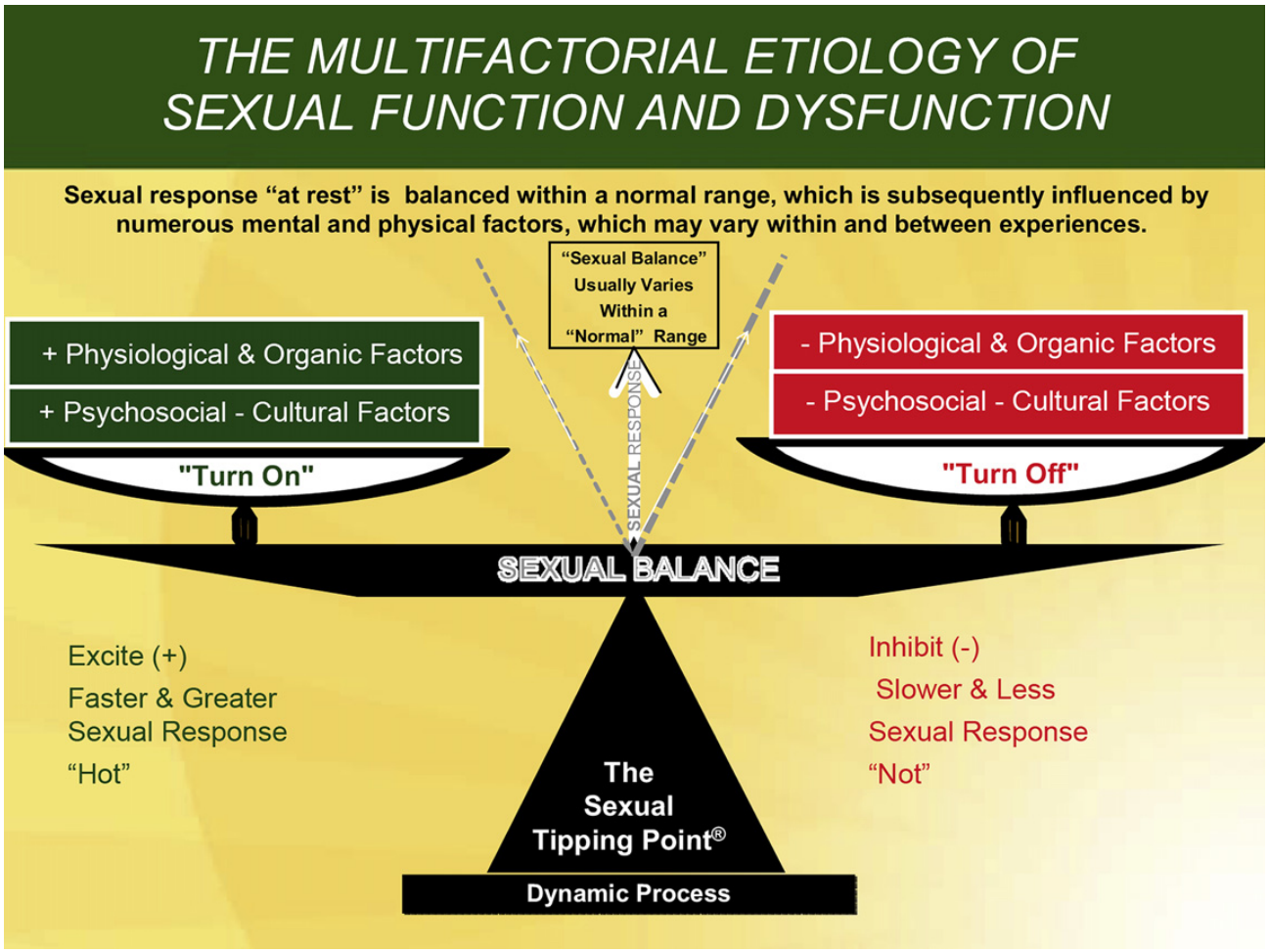

Fig. 1. The Sexual Tipping Point is the characteristic threshold for the expression of a sexual response for any person that may vary within and between sexual experiences. This model demonstrates both the mental and physical contributors to sexual function and dysfunction. At rest, the range of sexual response is normally balanced around neutral by these same dynamically opposing inhibitory and excitatory forces. At rest, a given individual is usually neither "turned on" nor "turned off"; "sexual balance" usually varies within a "normal range." (*Adapted from* Perelman MA. The Sexual Tipping Point: a mind/body model for sexual medicine. J Sex Med 2009;6:630; with permission.)

physiologic and psychosocial consequences that exacerbate the end points of the depressed mood, energy level, appetites, and sexual function. To further explore the cause of comorbid ED and depression, the next section focuses on some of the key factors. Although there is a spurious risk of oversimplifying a multidimensional nuanced cause, clarity of presentation requires such an organizational structure.

Depression, ED, and the Metabolic Syndrome

Clinicians have often observed that men with depression and hypogonadism often report a similar set of symptoms: fatigue, lack of sexual energy, depressed mood, and a sense of diminished psychological well-being. It may be difficult to determine the correct diagnosis, and the 2 conditions may also coexist in the same patient. Some evidence suggests that testosterone supplementation may benefit at least some men who are depressed, particularly those with low serum testosterone levels. Studies by Kupelian and colleagues[44] and Pope and colleagues[45] have successfully documented the potential role for testosterone augmentation therapy in depressed men with testosterone levels in the low-normal range.

The multiple biological mechanisms that can be involved causing ED (including type 2 diabetes, insulin resistance, abdominal obesity, hypertension, and dyslipidemia) characterize the metabolic syndrome. Recent advances in understanding the systemic effects of depression have suggested that depression can exacerbate, can contribute to, and is highly associated with this syndrome. In particular, older men may develop a major depressive episode along with ED, sometimes in association this metabolic syndrome.[46,47] There are of course other endocrine concerns, which are discussed by Guay elsewhere in this issue.

Psychogenic

Psychological issues often involve personality disorders, loss, and stresses of life, such as financial pressures. Relationship problems and other psychosocial events/stresses frequently contribute to, result from, or sometimes cause both ED and depression. The relevance of psychogenic factors should especially be considered for men with acquired and/or situational ED. Alterations in perceptual and attention processes (negative cognitions) can directly result in both mood and erectile variations.[48,49] In addition, performance anxiety may lead a man to engage in behaviors such as "spectatoring" during intercourse, which focuses attention away from arousing stimulus and instead on negative cognitions and consequently has a dampening effect on both erectile capacity and mood.[50] Thought affects the body biologically, not just psychologically. "In the anxious individual, there can be over-activity of the sympathetic system leading to increased smooth muscle tone. Alternatively, signals from the brain of an individual with a psychogenic issue can override the erotogenic parasympathetic output from the sacral spinal cord."[4]

Treatments for Depression Resulting in ED

Drugs, whether prescribed or taken recreationally, are perhaps one of the most common causes of diminished sexual capacity. Commonly prescribed medications are known to affect erectile function. For a detailed discussion of pharmacology and sex, the reader is recommended to the International Society for Sexual Medicine (ISSM) Consultation texts on Sexual Medicine.[51] Some of the most important groups of pharmacologic agents to consider are antidepressants, centrally acting antihypertensive drugs, central nervous system depressants, β-adrenoceptor antagonists, and any drug that has an anticholinergic action.[4] It is ironic that antidepressants seem to be independently associated with male sexual disorders.[23] It is difficult to separate the ED risk of antidepressants from ED associated with depression. In individual cases, a thorough baseline history of erectile function before antidepressant treatment usually helps in clarifying the cause of the ED.

The chronic nature of depression in many cases and the subsequent need for long-term administration of antidepressants has enriched our knowledge of the sexual side effects of these medications. Estimates of the percentage of patients affected in later studies are likely to be more accurate than the estimates in earlier studies that relied on spontaneous reporting, which is known to underestimate the true incidence.[52–56] Side effects of antidepressant treatment on sexual function are a serious issue for patients and their partners. Semipermanent interruption of sexual function by these medications is a significant barrier to medication adherence.

Clinicians should be aware that the sexual side effects of antidepressant medications are quite variable.[57,58] The mechanisms by which selective serotonin reuptake inhibitor (SSRI) antidepressants impair sexual function is the focus of ongoing research, but it is presumed to be caused by differential action of the relevant neurotransmitters. For instance, serotonin is known to act as an inhibitor of sexual response, so that drugs such as SSRIs,

which increase serotonin levels, probably inhibit sexual function.[59] In addition, there is speculation that some SSRI antidepressants by centrally inhibiting nitric oxide synthetase may be involved in SSRI-related ED.[60] However, the primary sexual side effect associated with SSRIs is their effect on ejaculation and orgasm, with libido being second. Although SSRIs may also have a secondary effect on the erectile capacity, ED is the least common of the sexual negative effects with approximately 10% occurrence rate; however, in some cases, it has been reported to be irreversible.[58,61]

DIAGNOSIS AND SCREENING

The history obtained by PCPs and urologists is frequently limited to an end-organ focus and fails to reveal significant psychosocial barriers to successful restoration of sexual health. These obstacles or resistances represent an important cause of nonresponse and treatment discontinuation.[62] These barriers manifest themselves in varying levels of complexity, which individually and/or collectively must be understood and managed for the pharmaceutical treatment to be optimized.[63–65] Only recently have clinicians begun incorporating sex therapy concepts and have recognized that resistance to lovemaking is often emotional. Most of these barriers to success can be managed as part of the treatment, yet too few clinicians are trained to do so.[64,66]

Screening

Although the patient is initially evaluated for ED, there is a secondary goal of evaluating the management algorithm for any other significant disease or disorder. When depression is suspected, the physician must explore the mental status of the patient with an emphasis on assessing this mood disorder. This assessment can be done by the examining clinician alone or by working within a multidisciplinary team. The primary goal of the evaluation visit is to obtain the necessary information to assess the nature of the ED and to begin developing a treatment plan. Guidance for brief screening or a "sex status" examination of the patient with ED has been well described elsewhere.[8,67] Therefore, it is only briefly summarized in the following section, whereas specific screening techniques and questionnaires for depression are highlighted.

The Sexual Status Examination or Sex Status Exam

The sex status focuses on finding potential physical and specific psychosocial factors relating to the disorder.[68] It is also important to ascertain why the patient is seeking assistance at that particular time. The clinician should first obtain a clear and detailed description of the patient's sexual symptoms, as well as information about the onset and progression of symptoms. The details of the physical and emotional circumstances surrounding the onset of a difficulty are important for the assessment of both physical and psychological causes. The ideal history is an integrated, fluid assessment, in which the patient's response is continuously reevaluated during follow-up. The successful treatment of ED requires answers to 3 key questions regarding diagnosis, cause, and treatment: (1) Does the patient really have a sexual disorder and what is the differential diagnosis? (2) What are the underlying organic and/or psychosocial factors? (3) Should the patient be treated or not? Do the underlying organic and psychosocial factors require priority treatment, or can the treatment of these factors be bypassed or concurrent? These decisions are dynamic and should be consistently reevaluated as the treatment proceeds.[67]

The methodology used to answer these questions is a focused history. Obviously, the clinician must determine whether the patient has an illness or is taking a drug that could be causing the symptom. However, this article presumes that the necessary assessment steps and procedures, including physical examination, as well as laboratory tests have been conducted in a manner consistent with the parameters recommended by Broderick elsewhere in this issue. By the end of the evaluation visit, the physician should have already ascertained or identified the necessary next steps to determine the extent to which there is an endocrine (eg, diabetes, androgens), neurogenic, vascular, psychogenic, and/or drug-related basis to the patient's ED. However, the clinician should not arbitrarily separate the psychosocial/sexual history from the medical history. An integrated medical and sexual history yields a significant amount of information regarding all aspects of a man's sexual health and relationships.

It is not necessary to do an exhaustive sexual and family history for most evaluations. The investigation of these issues should be selective so that the interview does not become unnecessarily lengthy. The clinician should briefly screen all patients for obvious psychopathology that would significantly interfere with the initiation of treatment of ED. Yet, the clinician will also want to know whether psychiatric symptoms, if present, are the cause and/or the consequence of the sexual disorder. If the patient is depressed, the

severity of his depression must be clarified. Any patient who experiences major depression should be queried about suicide risk.

For all men, clinicians should assess the living and marital/dating status. Contextual factors, including difficulties with the current interpersonal relationship and whether the partner has an SD, should be clarified. The clinician may grasp the couple's interactions from the first interview's sex status. Numerous partner-related nonsexual issues may adversely affect the outcome. The degree of acrimony should be monitored when the patient describes his complaints, including is the anger, resentment, hurt, or sadness a maintaining or precipitating factor, or are the emotions more mild manifestations of the frustrations of daily life. Severe marital strife will inevitably require a referral to an MHP, albeit it may not be successfully accepted.[35,64,65] The single patient with ED must be assessed in the same manner as if the patient was in a relationship. The patient's sexual symptom may or may not relate to difficulties in his relationships. Needless to say, sexual orientation issues, for both single and coupled men, require the same, if not even greater sensitivity on the clinician's part.

Questionnaires

Chochinov and colleagues[10] were able to demonstrate that the mere asking of a single question, "Are you depressed?" was at least as effective as questionnaires in detecting depression. Yet, some clinicians may choose to use current or future instruments to facilitate the history-taking process. Two such instruments are briefly described below, but such instruments must be incorporated in a manner that does not interfere with rapport. The Patient Health Questionnaire-9 (PHQ-9) rating scale, developed specifically for the medical office practice,[69,70] is a convenient way to screen medical office patients for major depressive episode. It can be completed either by the patient himself or by the practitioner interviewing the patient. The PHQ-9 scale is easily scored to provide a measure of depression severity, and includes an item asking specifically about suicidal thoughts. In addition, the Depression in the Medically Ill Scale is a 10-item questionnaire that is 85% effective in detecting depression without the necessity of a psychiatric evaluation, which can be used by busy clinicians as a screening device.[10]

WHEN TO REFER?

When a patient with a variety of psychopathologic states (eg, stress, phobias, personality disorders) is evaluated for sexual complaints, the clinician must consider whether that patient's emotional conflicts are too severe for a focused treatment of the sexual problem and whether such treatment should either be safely postponed for another time or occur concurrently with treatment of the emotional distress. With more severe situations, the modal choice is likely to be a simultaneous initiation of the SD treatment along with a referral to an MHP to facilitate patient management. Yet, a person who is currently addicted to drugs and/or alcohol is not a suitable candidate for treatment until he has been detoxified and is off the drug. However, it is usually not necessary to postpone treatment of ED.[40,67]

Combination Therapy: Who and When?

Typically, PCPs and urologists integrate counseling with their sexual pharmaceutical armamentarium to treat ED. If an antidepressant is needed, they might consider initially prescribing themselves depending on the presenting symptoms, their own expertise, and level of interest. However, in the presence of an MMD, a referral to a psychiatrist is strongly recommended. What follows is a general algorithm for evaluating the referral necessity for any comorbidity.

Whether or not a clinician works alone or in combination with a psychiatrist or other health care specialists is determined by the complexity of the case.[51,63,65] The treating clinician would diagnose the patients as having mild, moderate, or severe treatment obstacles (TOs) to the successful restoration of sexual function and satisfaction. TOs could either be organic, pharmaceutical, and/or psychosocial-cultural in any combination. However, the TO categories would be segmented as follows: (1) mild TOs, no significant or mild obstacles to successful medical treatment of ED; (2) moderate TOs, some significant obstacles to successful medical treatment of ED; and (3) severe TOs, substantial to overwhelming obstacles to successful medical treatment of ED[65]; Althof, 2003, #9076.[63] This characterization would be based on an assessment of all the available information obtained during the evaluation. The physician would continue treatment and/or make referrals based on the progress obtained. The matrix determining who might treat is presented in **Table 1**.

Clearly, a multidisciplinary team including multiple medical specialists and a sex therapist could attempt to treat almost every case. However, treatment by a team is a labor-intensive approach and frequently unrealistic, both economically and geographically in terms of available expertise and manpower. However, in a common clinical practice

Table 1
ED management guidelines based on treatment obstacles

	Mild TOs	Moderate TOs	Severe TOs
Solo Physician	Frequently	Sometimes	Rarely
Multidisciplinary Team	Frequently	Frequently	Frequently

Data from Perelman M. Combination therapy for sexual dysfunction: integrating sex therapy and pharmacotherapy. In: Balon R, Segraves RT, editors. Handbook of Sexual Dysfunction. Boca Raton (FL): Taylor & Francis; 2005. p. 13–41.

scenario, the physician who first evaluates a patient with ED (this would of course be true for all SDs) could integrate counseling with the needed medical treatment, often resulting in a successful outcome.[71] Presumably, in such a scenario, a PDE5 would probably be chosen. Indeed, for some patients this prescription might adequately treat a mild depression effectively as well.[26]

Again, all does not have to be accomplished in the first visit, when using a case management approach based on Perelman's combination treatment STP model.[71] Such an approach always includes: (1) a thorough evaluation including a focused sex history or sex status exam; (2) integration of sexual pharmaceuticals with counseling for psychosocial-cultural factors while recognizing that the prescribed pharmaceuticals are both potentially restorative, as well as therapeutic probes (illuminators of failure or nonresponse; (3) integration of weaning and/or relapse prevention when possible; and (4) continued follow-up and referral as needed. ED is recognized as a progressive disease in terms of the underlying organic abnormality, which may play a role in altering the threshold for response and potential reemergence of dysfunction. Perelman recommended that the clinician schedule booster or follow-up sessions to help the patient stay the course and provide opportunity for additional treatment when necessary[64,65,72]; Perelman, 2005, #102132.[8] Generally speaking, treatment of ED should be started as soon as possible, with reevaluations of the patient's responses occurring as treatment proceeds. Retaking a quick current and mental health sex status provides a convenient model for managing follow-up.

Returning specifically to the issue of comorbid depression and ED, most patients seeking treatment of ED will not be manifesting such severe symptoms that a referral would be required. Many PCPs who more and more are the first ones a man with ED seeks treatment from are themselves willing and able to treat mild to moderate depression as well as the ED concurrently. In addition, there are numerous organically determined reasons for making referral to a multiplicity of medical specialists (gynecologists, neurologists, endocrinologists, etc) when necessary and appropriate.[65] However, the next section highlights what to expect when the severity of the patient's depression requires referral to a psychiatrist for adjunctive treatment. In fact, the value of working with a board-certified psychiatrist when diagnosing and treating a severe depression could not be overemphasized.

WHAT TO EXPECT AFTER MAKING A REFERRAL?

Generally, the psychiatrist works with the referring physician to optimize the treatment of both the depression and the ED while also helping with the management of any other comorbid medical conditions. The psychiatrist typically provides pharmacotherapy for depression, and like any qualified mental health specialist, may also provide psychotherapy for both depression and ED. It is hoped that all the practitioners caring for the patient have special training and experience in the treatment of men with sexual issues.

If a patient with ED fulfills the criteria for major depression, the recommendation to the patient and referring physician should be to treat the depression. A referring physician should expect that if the patient is indeed diagnosed as having an MMD, treatment options (depending on severity) are likely to include psychopharmacology, psychotherapy, more rarely ECT, and when necessary, psychiatric hospitalization. The side-effect burden of these treatments, once the depression has lifted, requires collegial consultation to determine the best balance of treatment for the patient seeking improvement in sexual functioning. Discussion with the patient, his partner, when possible and appropriate, and the psychiatrist can help guide the decision whether or not concurrent treatment of the ED should be attempted or postponed. Both the referring physician and the psychiatrist should be aware of the particular risk of drug treatments and maintain

the following cautionary viewpoint. Because many antidepressants carry the risk of erectile toxicity, there is a theoretical concern that depressed men may be at a particular risk of ED from long-term antidepressant treatment. Therefore antidepressants with the lowest risk of sexual side effects should be selected. Once treatment of ED is initiated, men on antidepressants should be asked regularly and specifically about the quality of their erections (with partner, with self-stimulation, and on awakening). If at all possible, the antidepressant treatment should be discontinued if ED recurs or worsens (Stephen Snyder, MD, New York, NY, USA, personal communication, January 2011).

There are several strategies for minimizing harm to erections, particularly during antidepressant treatment. These strategies may be summarized under the following general headings: (1) wait for spontaneous remission, (2) drug holiday, (3) decrease dosage (4) antidepressant selection and switching agents, and (5) antidotes.[53,73] These strategies are all discussed later, but only choices 4 and 5 represent truly valid approaches. Several reviews of this topic provide tables summarizing the advantages of one drug or method over the others.[4,23,53,74] However, the research underlying such studies frequently uses different methodologies and different thresholds for diagnosing SD, thus limiting the value of such comparison tables (Taylor Segraves, MD, Cleveland, OH, USA, personal communication, February 2011). Instead, in this article, the drugs mentioned are identified in **Box 2** with the relevant research summarized within the text.

Like urology, the concept of watchful waiting has its adherents, however, meta-analysis suggests that less than 10% of patients experience spontaneous improvement from the initially developed antidepressant sexual side effects.[57,75] A drug holiday may make a difference for a small percentage of patients, but the risk of depression reoccurrence makes this an imprudent strategy because skipping medicine can certainly lead to relapse.[76] Although reducing dose has a theoretical appeal, there is no indication that the antidepressant affect can be maintained at a level in which no sexual side effects occur. Finally, sudden discontinuation can cause a serotonin discontinuation syndrome with symptoms including lightheadedness, nausea, vomiting, irritability, electric shock paresthesias, and sudden depression, among others.[53]

Switching medications in combination with altering dosage and using multiple medications to achieve an individualized optimized response is a common strategy. The basis for this popularity

Box 2
Names of medicines mentioned in this article and their customary dosages

SSRIs

- Fluoxetine (Prozac), 20 to 80 mg
- Sertraline (Zoloft), 50 to 200 mg
- Paroxetine (Paxil), 20 to 60 mg
- Fluvoxamine (Luvox), 150 to 300 mg
- Citalopram (Celexa) 20 to 60 mg
- Escitalopram (Lexapro), 10 to 20 mg

Norepinephrine and dopamine reuptake inhibitors

- Venlafaxine (Effexor), 75 to 375 mg
- Duloxetine (Cymbalta), 30 to 120 mg
- Desvenlafaxine (Pristiq), 50 to 100 mg
- Trazodone extended release (Oleptro), 150 to 375 mg

Tricyclic antidepressants

- Clomipramine (Anafranil), 75 to 225 mg

Other antidepressants

- Bupropion (Wellbutrin), 225 to 450 mg
- Nefazodone (Serzone), 300 to 600 mg
- Mirtazapine (Remeron), 15 to 45 mg

Antidotes

- Amantadine (Symmetrel), 100 to 200 mg
- Buspirone (BuSpar), 20 to 60 mg
- Cyproheptadine (Periactin), 4 to 12 mg
- *Gingko biloba*, 120 to 240 mg
- Granisetron (Kytril), 2 mg
- Yohimbine (Yocon, Aphrodyne), 5.4 to 32.4 mg

PDE5 inhibitors

- Sildenafil (Viagra), 50 to 100 mg
- Tadalafil (Cialis for use as needed), 10 to 20 mg, (Cialis for daily use), 2.5 mg and 5 mg
- Vardenafil (Levitra), 10 to 20 mg

Stimulants

- Methylphenidate (Ritalin, Concerta, Focalin, and others), 15 to 60 mg
- Mixed amphetamine salts (Adderall), 15 to 60 mg
- Dextroamphetamine (Dexedrine), 10 to 60 mg

Courtesy of Adam Ashton, MD; with permission.

is determined by the numerous studies demonstrating variability of side effects noted both between and within given individuals in response to different antidepressants.[56,58,77–96] The methodological limitations independent of the popularity of these studies and the ubiquity of this strategy among psychiatrists should be remembered. For instance, Segraves[58] in a multicenter trial compared sustained-release bupropion with the SSRI sertraline. It was determined that the 2 drugs were similarly effective in treating depression but the side-effect profiles varied, with the sertraline patients having more sexual disorders than those assigned to the bupropion SR group. Similarly Modell and colleagues[82] compared the sexual side effects associated with bupropion and the SSRIs fluoxetine, paroxetine, and sertraline. Patients using SSRIs experienced significant decreases in libido, arousal, and duration and intensity of orgasm. In contrast, patients treated with bupropion reported significant improvements in libido, arousal, and orgasm intensity and duration. Only 27% of patients treated with SSRIs reported no adverse sexual side effects, compared with 86% of bupropion-treated patients who reported no sexual problems, with some reporting improvement in some aspect of their sexual functioning. Generally speaking, clinicians agree that the incidence of SD with bupropion, mirtazapine, moclobemide, nefazodone, and, maybe, reboxetine is lower than with other drugs. Norepinephrine and dopamine reuptake inhibitors, such as duloxetine, are also being used regularly now by psychiatrists. Segraves and colleagues[52,61] recommend duloxetine for depressed patients with sexual problem who need a selective and nonselective serotonin reuptake inhibitors.

Some noted psychiatrists think that the drugs with the most frequent sexual side effects are the tricyclic antidepressants.[52,97–99] Among the SSRIs, paroxetine has the worst reputation for side effects, which may ironically be related to why it is frequently used as an off-label treatment of premature ejaculation.[57,82,100,101] Of related concern, antipsychotics are somewhat notorious for having persistent sexual side effects after discontinuing medication.[102] However, the second-generation antipsychotics (eg, aripiprazole) can sometimes be used without adding significant burden to the sexual side effect profile beyond that existing for the antidepressant being augmented (Adam Ashton, MD, Amherst, NY, USA, personal communication, February 2011).

Although some might question whether to use an SSRI at all in a patient with depression and ED, the answer depends on considering the whole array of sexual symptoms. The SSRIs can affect all 4 components of sexual function, including desire, arousal/erection, orgasm, and resolution. In this situation, a careful sexual history can help determine whether a trial of an SSRI antidepressant is reasonable. For instance, a depressed man with psychogenic ED who is a rapid ejaculator and has good sexual desire would be a good candidate for an SSRI. Yet conversely, a man with organic ED who has difficulty ejaculating and lacks sexual desire would be a poor candidate for an SSRI, and for such a patient, it may be preferable to prescribe a non-SSRI such as bupropion. However, it is worth remembering that some men find improved sexual function in all 4 phases in response to successful treatment of their depression whether by drugs, cognitive-behavioral psychotherapy, and/or both. As mood improves there is less anhedonia, and a happier person is more likely to have sex.

Augmenting the primary antidepressant with antidotes is a very commonly used approach. Regrettably, the results are often less than totally satisfactory, and like “switching,” usually require a considerable trial and error process to find the correct dosage and/or the most effective dosing schedule.[53] A number of these antidotes are only briefly discussed below because none of them met with the success originally predicted for them. The 5-hydroxytryptamine receptor 1A (5-HT_{1A}) agonist buspirone has been reported to improve sexual functioning in patients treated for generalized anxiety disorder[103] and to assist in reversing SSRI-induced SD.[104] However, buspirone is not frequently used in the United States for either purpose. While frequently discussed in the nutraceutical literature, *Gingko biloba* probably has only exceedingly modest effect in treating SSRI-induced SD.[105–107] A few case studies have suggested benefit from cyproheptadine in reversing SSRI-induced SD.[108–111] Recently, urologists have discussed using midodrine to treat anejaculation in men with spinal cord injuries, as well as those with SSRI side effects. Most found it ineffective, with proponents acknowledging noticeable variability in response from patient to patient.[112] A variety of psychostimulants (dopamine-releasing agents with enhancing noradrenergic benefits) have been reported, again with mixed and minimal success.[113] The centrally acting presynaptic α_2-antagonist yohimbine that is approved to treat male erectile disorder[114] has been described in studies dating back to more than 25 years.[53,115–117] The results of these studies on reversing SSRI-induced SD are both conflicting and generally poor.[53,111,118–120] However, the most important work to date in the pharmacologic

management of ED and depression was after the release of the PDE5 inhibitors.[53]

An important use of sildenafil in cases of depression is to counteract the effect of antidepressants.[4,121,122] Fava and colleagues[123] also assessed the safety and efficacy of sildenafil with ED caused by SSRI antidepressants, with those randomized to receive sildenafil reporting significant improvement in the number of successful sexual intercourse attempts per week. For ED in particular, the likely use of any of the PDE5 inhibitors by the initially consulting physician will work well with the drugs used by most psychiatrists for treating men with comorbid ED and depression. Although it is clear that additional research is needed, until more is known, the strategies outlined earlier can be used to assist many of the patients experiencing a comorbid ED and depression.[53]

Generally, in addition to pharmacotherapy, the psychiatrist also provides psychotherapy for both the depression and the ED. Psychotherapeutic treatment by MHP adds benefit, improves the chance of long-term success, and specifically can improve patients' adherence to medical treatments for ED and depression. Although there are a wide variety of psychotherapeutic techniques, a combination treatment using cognitive-behavioral approach, integrated with the use of as-needed antidepressant medication is recommended.[26,124–128]

SUMMARY

Sexuality is a complex interaction of biology, culture, intrapersonal and interpersonal psychology. A biopsychosocial model of SD provides a compelling argument for a combination treatment, which integrates counseling and pharmaceuticals. It is certainly a primary goal of pharmaceutical companies to develop new drugs for the treatment of depression, which do not have negative sexual side effects. While more research is needed, it seems probable that combination therapy will be the treatment of choice for all SDs, as new pharmaceuticals are developed for desire, arousal, and orgasm problems in both men and women.[64,65,67,101] Obtaining a sex status or focused sex history and continuous reassessment based on follow-up are the foundations of this approach. Restoration of lasting and satisfying sexual function requires a multidimensional understanding of all the forces that created the problem, whether a solo clinician or multidisciplinary team approach is used. All clinicians need to carefully evaluate their own competence and interest when considering the treatment of a man's ED so that the patient receives optimized care regardless of the modalities used. The initially consulted physician for a man with ED must screen for a MMD, given the high incidence of comorbidity. The consulting psychiatrist is expected to suggest both pharmacologic and psychotherapeutic strategies because psychosocial issues always arise when medicating a man's mood and sexuality.

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