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Erectile dysfunction: A sentinel marker for cardiovascular disease in primary care

ABSTRACT

Erectile dysfunction (ED) is a common, age-related disorder that diminishes quality of life for affected men and their partners. While most ED is now recognized as organic in origin, both organic and psychogenic causes often conspire to reduce sexual function in men with ED. Vasculopathy has come to be recognized as the most common cause of ED, which has elevated ED's importance in the primary care setting as a sentinel to underlying cardiovascular disease. Identification of cardiovascular risk factors should be a routine part of the evaluation for ED and is as important as taking the patient's sexual, medication, and psychosocial histories. Involving the patient's partner in evaluation and management is often valuable. Treatment with phosphodiesterase type 5 inhibitors is effective in restoring sexual function for most men with ED, but patients and their partners should be encouraged to make an informed choice from among all available treatment options.

DEFINITION OF THE CONDITION

Erectile dysfunction (ED) is "the consistent or recurrent inability of a man to attain and/or maintain a penile erection sufficient for sexual performance," according to the First International Consultation on Erectile Dysfunction, convened by the World Health Organization in 1999.[1] This definition closely mirrors that of a National Institutes of Health consensus development panel, which further specified "recurrent inability" as being 3 months or greater in duration.[2]

* **Dr. Kuritzky** reported that he has received honoraria from Pfizer, Eli Lilly, ICOS, Bayer, and GlaxoSmithKline for teaching/speaking or consulting. **Dr. Miner** reported that he has received a research grant from Auxilium Pharmaceuticals and consulting fees from GlaxoSmithKline/Schering-Plough and Sanofi-Aventis for consulting and serving on speakers' bureaus.

PREVALENCE AND SOCIAL IMPLICATIONS

Reported prevalence has varied

Reviews of the epidemiologic literature on ED suggest that about 5% to 35% of men have moderate to severe ED, with differences in prevalence stemming from differences in how ED is defined, the age groups studied, concomitant medical conditions, and methodologic differences.[3]

One of the largest prevalence studies to date, the multinational Men's Attitudes to Life Events and Sexuality (MALES) study, involved interviews of 27,839 men aged 20 to 75 years from the general population in Europe and North and South America, and found a 16% overall prevalence of ED and a 22% prevalence in the United States.[4]

The Massachusetts Male Aging Study was a community-based, random-sample survey of 1,290 men aged 40 to 70 years who were asked to categorize their erectile function as either complete impotence, moderate impotence, minimal impotence, or no impotence.[5] A full 52% of the men reported some degree of ED, with 25% reporting moderate ED and 10% reporting complete ED.[5] These findings underscore how much the reported prevalence of ED depends on how the condition is defined.

An age-dependent disorder

Both of the above studies demonstrated that ED is an age-dependent disorder. In the Massachusetts Male Aging Study, between the ages of 40 and 70 years, the probability of complete impotence tripled (from 5.1% to 15%) and the probability of moderate impotence doubled (from 17% to 34%), while the probability of minimal impotence remained constant at 17%.[5] Among men at the upper end of the age range (70 years), only 32% reported that they were free of ED.[5] In the MALES study, though the overall prevalence of ED was lower because of how ED was defined, the prevalence again increased with age, rising steadily from 8% among men in their 20s to 37% among men in their 70s.[4]

The prevalence of ED, or at least of diagnosed and

recognized ED, is only expected to increase as improved awareness of the condition leads to a greater likelihood that physicians will diagnose it and as the group of men at risk grows with the aging of the overall US population.

Despite reduced quality of life, most cases go untreated

Sexual function is a high priority for men and their partners throughout the life span. Loss of sexual harmony reduces the quality of life of men and their partners. Early references cite the issue of performance anxiety and the shift from lovemaking as a sensual experience to one fraught with anxiety; during subsequent attempts at lovemaking, the ability to acquire or maintain an erection dominates the sexual experience.[6,7] Interventional trials indicate that restoration of sexual function improves quality of life both for men with ED and for their partners.[8]

Unfortunately, up to 70% of men with ED go untreated.[3] Many men fail to seek treatment because they mistakenly believe that ED is a normal part of aging. Others admit to embarrassment as the reason for not seeking treatment or discussing ED with their physicians. In the MALES study, only 58% of men with self-reported ED sought medical attention for it.[4]

A sentinel for cardiovascular disease

A final—and perhaps most significant—social implication of ED is its increasingly recognized status as an early marker of vascular disease, as detailed in the following section. Knowledge that a man has ED should prompt thorough scrutiny for traditional cardiovascular risk factors, since early detection may allow reduction of cardiovascular disease risk or attenuation of existing disease.

PATHOGENESIS

ED is a neurovascular phenomenon modulated by hormonal and local biochemical interactions as well as by biomechanical mechanisms that influence neurovascular control.[9]

In the past, ED was believed to be largely psychogenic in origin. Today we recognize that most ED is organic in origin, although it is equally acknowledged that men with organic ED often will suffer significant psychological stress as a result. Once a man fails in his sexual performance, he usually will have fear or anxiety that the failure will recur. For this reason it often is oversimplistic to categorize ED as "solely organic" or "solely psychogenic"; rather, both components can contribute to reduce sexual function in men with ED.

Normal erectile function

Penile erection is a hemodynamic process that depends on the successful interaction of neurologic and endocrine factors and on coordination of the parasympathetic and sympathetic nervous systems.[10] With sexual stimulation, parasympathetic activity enhances production of cyclic guanosine monophosphate (cGMP), resulting in cavernosal smooth muscle relaxation and an influx of blood into the penis. This filling of the penis produces expansion of the sinusoidal spaces, compressing venous channels and thereby preventing outflow of blood to allow maintenance of a rigid erection.

What goes wrong in ED

ED results from physical (eg, hormonal, neurologic, vascular, or cavernosal) and/or psychological factors that disrupt this sequence. Physical causes of disruption include injury, surgery (eg, prostatectomy, proctocolectomy, vascular surgery), and comorbid conditions that affect the vasculature and peripheral nervous system (eg, diabetes, hypertension, dyslipidemia, peripheral arterial disease, obesity, coronary artery disease).

The role of the vascular system is noteworthy, as it is now generally accepted that most ED results from a vascular disturbance of the endothelium. This impairment in endothelial function typically results from vasculopathy, such as in dyslipidemia, hyperglycemia, smoking toxicity, or hypertension. ED arises from a combination of endothelial disturbance and abnormal smooth muscle function with blood flow abnormalities that lead to difficulties developing or maintaining an erection. The same factors that lead to oxidative stress and impair endothelial function in the cardiovascular and peripheral vascular beds play a fundamental role in the underlying pathogenesis and progression of ED[11] (see "ED as a marker of vascular disease" below).

Other contributors to ED include neurogenic factors (eg, diabetes, multiple sclerosis), endocrinologic factors (eg, hypogonadism, hyperprolactinemia), or psychogenic factors (eg, excessive sympathetic tone due to performance anxiety), although the etiology is less clear in these settings.

A key insight: The role of nitric oxide

Prior to the past decade, ED was managed by urologists, who generally used intracavernosal injection therapy, vacuum pumps, and penile prostheses as their primary tools. Most men with ED did not seek treatment because of the relative unpalatability of these choices. It was not simply the advent of oral medications that changed the tide; after all, oral yohimbine had been available for several decades. Rather, it took the availability of highly effective oral therapy, in the form of phosphodiesterase type 5 (PDE-5) inhibitors, to spur large numbers of men with ED to seek restoration of sexual function.

Critical in the development of highly effective oral therapy was elucidation of the role of nitric oxide. Nitric oxide is fundamental to vasodilation, including dilation of the corpora cavernosa. Insight into the relationship between nitric oxide production and successful vasorelaxation, together with the serendipitous discovery that PDE-5 inhibition enhances accumulation and survival of penile cGMP, enabled recognition of the critical nature of penile endothelial function. Although cGMP may be generated via the nitrergic nervous system or as a result of endothelial metabolism, defects in either pathway may lead to functional deficits in erection. PDE-5 inhibitors, by preventing cGMP breakdown, were shown to enhance erectile function. The advent of these medications, together with their ease of use, brought ED management into the primary care arena and brought the era of urologist-centered management to an end.

ED as a marker of vascular disease

Vasculopathy is now recognized as the most common cause of organic ED, and ED is considered one of the earliest manifestations of vascular disease. Indeed, vasculopathy should be suspected in a man presenting with ED until proven otherwise.

Men with traditional risk factors for cardiovascular disease—hypertension, smoking, dyslipidemia, diabetes, overweight, sedentary lifestyle—are now recognized to also be at risk for ED. These risk factors are more common in men with ED than in those without ED.[12–17] For instance, in a survey of 2,869 men aged 20 to 80 years, hypertension, hyperlipidemia, and diabetes each increased the risk of ED twofold to threefold.[16] The individual components of the metabolic syndrome—central obesity, high blood pressure, elevated triglyceride level, low high-density lipoprotein cholesterol level, and glucose intolerance—are also risk factors for ED.

Endothelial dysfunction is believed to be the common initiator of ED and other atherosclerotic diseases.[18] Men with ED but no other clinical cardiovascular disease were found to have reduced flow-mediated vasodilation in the brachial artery in response to sublingual nitroglycerin, indicating endothelial dysfunction and abnormal smooth muscle relaxation.[11] Evidence is accumulating that endothelial dysfunction is an early functional change thought to precede atherosclerotic changes in the cerebrovascular, coronary, and peripheral circulations.

In addition to its commonality of risk factors with cardiovascular disease, ED is a marker of potential or occult cardiovascular disease.[19,20] A secondary analysis of data from the Prostate Cancer Prevention Trial demonstrated that men with ED have a significantly greater chance of experiencing a cardiovascular event (angina, myocardial infarction, cerebrovascular accident, transient ischemic attack, congestive heart failure, or cardiac arrhythmia) than men without ED.[20] This study, which enrolled men aged 55 years or older, also showed that incident ED (the first report of ED of any grade) may predict the risk of later cardiovascular events as effectively as does smoking, dyslipidemia, or a family history of myocardial infarction.[20]

Other studies have pointed to similar conclusions. A prospective angiographic study of men with ED of vascular origin showed that 19% had angiographically documented silent coronary artery disease.[13] Separately, Ponholzer et al found that men with moderate to severe ED had a 65% increased risk for developing coronary artery disease within 10 years, based on Framingham risk profile assessment, compared with men without ED;[16] analysis of the actual event data from this study is still awaited.

ED and sexual function may be a useful tool for stratifying risk in men with known or suspected coronary artery disease. A recent prospective study of men referred for nuclear stress testing found that those with ED exhibited more severe coronary artery disease and left ventricular dysfunction and had shorter exercise times and lower Duke treadmill scores compared with men without ED.[21]

These findings all support the results of studies linking ED with prevalent and incident cardiovascular disease.[11,22–24] The literature consistently demonstrates that signs of penile endothelial dysfunction (ie, ED) are often evident in patients with existing coronary artery disease, cerebrovascular disease, or peripheral arterial disease that has not yet manifested.[25] The presence of ED should be a wake-up call to clinicians that vasculopathy in nonpenile beds is likely. Given that more than 50% of men do not have warning signs of coronary artery disease prior to their first cardiovascular event,[20] ED could be a sentinel marker for the presence of occult vascular disease in asymptomatic men. Thus, ED is clearly a potential marker of a man's vascular health.

EVALUATION

The examination and history should be directed to identify recognized contributors to ED: diabetes, hypertension, dyslipidemia, cigarette smoking, hypogonadism, cardiovascular disease, medications known to cause ED, past surgical procedures, and psychosocial contributors such as relationship problems or depression. In the primary care setting, this can often

be streamlined if the patient's history is known. If not known, a pertinent sexual, medical, and psychosocial history can be performed efficiently within the time constraints of the typical office visit.

Sexual history

ED can develop at any age, but because its prevalence rises steeply at about age 40 years,[5] it is wise to particularly inquire about sexual health for men at this age and beyond. Such inquiry is appropriate at any age, however, especially as it can also address safe sexual practices.[26]

Because some recognized vasculopathies (diabetes, uncontrolled hypertension, marked dyslipidemia) accelerate the process of endothelial dysfunction, men who have such disorders merit inquiry about their sexual function, regardless of age. Indeed, the case has been made that inquiry into sexual health should be one of the "vital signs of lifestyle" asked of all patients.[27]

Disorders during the desire phase of the sexual cycle (libido) can be elicited by asking if the patient still feels desire or has sexual thoughts or fantasies.[28] Difficulty in the desire phase may be a sign of hypogonadism, relationship difficulties, medication-induced ED, or depression.

Difficulties with arousal or erection can be elicited by asking if the patient has trouble obtaining and maintaining an erection.[28] If the patient reports erectile difficulty, inquire about onset, frequency, and any relationship to medical treatments or stressful events. The line of inquiry should then include questions about specific times and circumstances in which the patient gets erections (eg, in the morning, with masturbation, during sexual activity with his partner) and how firm these erections are. For example, ED in a patient who has strong morning erections but poor erections with his partner is likely to have a psychogenic component.

Standardized questionnaires can assist in the diagnosis of ED and facilitate discussion of sexual health, especially when the patient is reluctant to initiate such discussion. The Sexual Health Inventory for Men is a five-item survey with four questions that pertain to the ability to attain and maintain an erection and the frequency of erections sufficient for intercourse.[29] The results of this and any other questionnaire on sexual health must be interpreted in the context of the patient's psychosocial factors, including desire and the opportunity to have sexual relations. Although this and other questionnaires can help identify the presence of ED, they do not elucidate its etiology.

Involve the partner

Whenever possible and when the patient is in agreement, including the patient's sexual partner in the evaluation and management process is wise.[30] An Italian study reported that 40% of men with ED had never discussed the problem with their partner.[31]

Because most men with ED are in midlife or beyond, their similarly aged partners may be suffering burdens that make the resumption of harmonious sexual intimacy more difficult (eg, menopausal lubrication deficits, changes in libido, pain syndromes, interrupted sleep). This further argues for incorporating the partner into discussion of treatment plans. Moreover, partner involvement may enhance the chance of treatment success. Women whose partners were treated for ED have been found to experience improvements in sexual arousal, orgasm, and sexual satisfaction,[32] and quality-of-life scores of both patients and their partners have been shown to improve following treatment of ED.[33]

Medication history

Taking a medication history can uncover a drug that may be responsible for ED, such as a narcotic analgesic, a benzodiazepine, or another central nervous system depressant prescribed for chronic pain. In current practice, the medications most associated with sexual dysfunction are hydrochlorothiazide and selective serotonin reuptake inhibitors, although the latter are more commonly associated with orgasmic dysfunction than with ED.

A comparative trial assessing sexual function in hypertensive men receiving either an angiotensin receptor blocker or a beta-blocker showed a higher incidence of ED in men taking the beta-blocker.[34] Although this finding might seem to be an indictment of beta-blockers, it could equally well reflect a salutary effect of angiotensin receptor blockers. Substantial controversy surrounds the potential role of beta-blockers in causing sexual dysfunction.

Because sexual dysfunction has been reported in data sets for dozens of medications, it is worth reviewing the patient's medication history to identify any clear temporal relationships between a particular drug and sexual dysfunction. If such a relationship exists, it is reasonable to substitute an alternate medication or, when possible, attempt a drug holiday or medication cessation.

Physical examination

The traditional physical examination includes blood pressure measurement and a genital examination to assess testicular size. Testicles that are small (< 2 cm) or appear atrophic to palpation should prompt confirmation of testosterone status. Other physical findings associated with ED include penile plaques (Peyronie

TABLE 1
Profile of pharmacologic therapies for erectile dysfunction[41,42]

Therapy	Standard dose	Recommended interval between dosing and intercourse	Duration of action
Oral phosphodiesterase type 5 inhibitors			
Sildenafil	50–100 mg	1 hr	⩾ 4 hr
Tadalafil	10–20 mg	0.5–12 hr	36 hr
Vardenafil	10–20 mg	0.5–1 hr	< 5 hr
Intracavernosal injection			
Alprostadil*	5–40 µg	10–30 min	1–4 hr
Intraurethral suppository			
Alprostadil pellet*	0.5–1 mg	5–10 min	1 hr

*The only medication approved by the US Food and Drug Administration for this method of administration.

disease), which may cause painful or deviated erections and thus lead to sexual dysfunction, and an enlarged prostate, which can be identified by digital rectal examination.

A vascular examination, including palpation of the femoral vessels and listening for bruits, may be appropriate, and neurologic examination may be helpful.

Laboratory tests

Because ED is a sentinel for vasculopathy in other compartments, laboratory testing should seek cardiovascular risk factors. Basic initial laboratory tests for suspected ED are fasting serum glucose level and a lipid panel, especially low-density and high-density lipoprotein cholesterol. Testosterone levels should be considered in those men with ED who also have metabolic syndrome, diabetes mellitus, or decreased libido, given that low testosterone may be associated with these conditions.[9,35,36] Morning serum total testosterone should also be considered as an additional laboratory test in patients whose ED is refractory to initial therapy, as should prolactin, luteinizing hormone (if testosterone is < 200 ng/dL or the patient is < 50 years old), and thyroid-stimulating hormone.

Some experts suggest urinalysis to detect potential renal disease or infection, although these are rarely associated with ED.[37] A complete blood count and metabolic panel may identify a potential hematologic disorder or renal or liver disease.

TREATMENT

Lifestyle changes

Given the important vascular component of ED, behavioral modifications such as weight loss, increased exercise, and smoking cessation are an appropriate foundation for ED therapy, although data from controlled trials on the effects of individual lifestyle changes on ED are limited.

Some data are starting to emerge, however. A recent study of obese men with ED (but without diabetes, hypertension, or hyperlipidemia) found that reducing calorie intake and increasing physical activity was associated with improved sexual function in about one third of obese men.[38] An Iranian study of smoking cessation in men with ED found that ED status improved at 1-year follow-up in at least 25% of men who stopped smoking during the study period compared with 0% of continuing smokers.[39] The benefit was greatest in younger men and in those with less severe ED prior to smoking cessation.[39]

Data on incident ED from a cohort study led to somewhat different conclusions: among men without ED at baseline, midlife adoption of lifestyle changes to reverse the effects of smoking, obesity, and alcohol consumption may be too late to reduce the risk of ED, although increased physical activity may reduce ED risk even if adopted in midlife.[40]

Oral drug therapy (PDE-5 inhibitors)

The goal of therapy for ED is restoration of sexual function. There are several types of therapy options, and the choice among them should be an informed decision by the patient and his partner based on the efficacy, risks, benefits, and costs of each option. Most patients and their partners will, given all available choices, elect an oral agent—specifically, a PDE-5 inhibitor—but this is not to say that the other options detailed below (intracavernosal injection therapy, vaccum constriction devices, intraurethral suppositories) may not have a role.

The three PDE-5 inhibitors available in the United States—sildenafil, tadalafil, and vardenafil—are similarly effective in improving and maintaining erections suitable for intercourse, though they differ somewhat in pharmacokinetics and dosing **(Table 1)**.[41,42] Clinical trials demonstrate that PDE-5 inhibitor therapy successfully enables almost three quarters of men with ED to achieve an erection adequate to complete intercourse,[37] although results are highly dependent on the patient population studied—eg, diabetic men and post-prostatectomy patients are less likely to respond.[33]

All PDE-5 inhibitors are approximately equally efficacious, and there are no large head-to-head randomized trials to suggest that one agent has meaningfully superior efficacy over another.[43] In preference trials, some patients express distinct preference for one PDE-5 inhibitor over another, but this too is hard to predict. Most couples at midlife and beyond have sexual activity no more than once within 24 hours, and any of the available PDE-5 inhibitors can be effective in this setting. The only area where these agents appear to differ is in half-life, as tadalafil has a longer half-life than the other two PDE-5 inhibitors, which translates to a longer duration of action **(Table 1)**.[41,42] Some clinicians allow patients to try all three PDE-5 inhibitors to determine their personal preference.

All PDE-5 inhibitors require sexual stimulation to achieve an erection.

The side effect profiles of the three PDE-5 inhibitors are very similar, and all three agents are contraindicated in patients taking long-acting nitrates or nitroglycerin.[43]

Because absorption of sildenafil may be meaningfully reduced by food, it is best not to take it in close proximity to meals, especially high-fat meals. Vardenafil shows some diminution in absorption after a high-fat meal, but not enough to impair efficacy. Absorption of tadalafil is not affected by food.[41]

Patients should be instructed that near-maximal concentrations are reached about 1 hour after administration of sildenafil and vardenafil and about 2 hours after administration of tadalafil.[41] Some patients achieve a therapeutic response within 15 minutes, but since most do not experience such rapid onset, it is wise to suggest the more conservative timing at first.[44] Over time, patients will become more and more familiar with the time to onset of action.

Patients should be instructed about the timing of administration, the need for sexual stimulation, the expected success rate, and the fact that the first few doses may not be successful. Based on data from sildenafil trials (similar data are not available for the other PDE-5 inhibitors), patients should be made aware that any PDE-5 inhibitor should be tried six to eight different times at full dose before it is deemed ineffective. Because patient misadventure and misadministration may occur despite the best instructions, it is wise to ask patients to return after whatever interval is required for this six- to eight-dose trial period. For most couples, this will be 3 to 4 weeks, but the interval should be tailored to the couple's preference.

Intracavernosal injection therapy

Another approach to ED involves injection of alprostadil, a prostaglandin, into the corpora cavernosa **(Table 1)**. Despite the development of intracavernosal injection products that are fully appropriate to primary care settings, most primary care providers have not been trained in their use.[45] Additionally, most patients will prefer methods of treatment other than injection. Nonetheless, an occasional patient may prefer intracavernosal injection therapy for personal reasons, and it is an option for patients who are intolerant of or unresponsive to PDE-5 inhibitors or in whom those drugs are contraindicated.

Vacuum constriction devices

Vacuum constriction devices (VCDs) consist of a cylinder that is placed over the penis and a pump that creates a vacuum within the cylinder. The negative pressure generated within the cylinder causes blood to flow into the corpora cavernosa, facilitating erection. Once an erection is achieved, a constrictor ring is placed around the base of the penis so that blood is retained within the corpora cavernosa.

Prior to the availability of PDE-5 inhibitors, VCDs were used successfully in many men with ED. The device can be viewed as cumbersome, however, and VCD-induced erections can differ from "spontaneous" erections in color and/or temperature as a result of the constriction ring. Still, VCDs have essentially no serious side effects, can work in ED of multiple etiologies,[46] and are economical; for these reasons a VCD may be a viable option for couples who are attracted by its simplicity, avoidance of systemic medications, or cost.[45,47]

Long-term continuation rates with VCDs vary widely (35% to 81%),[48–50] but in our experience, dropout rates are inversely related to the thoroughness of initial instruction in VCD application and use. Frequent reasons for VCD discontinuation include inadequate penile rigidity, the "unnaturalness" of the erection produced, pain from the pressure of the constriction ring, difficulty in use, and failure to ejaculate.[51]

Intraurethral alprostadil suppositories

Like intracavernosal injection therapy, another treatment approach employs the prostaglandin alprostadil but applies it topically as a urethral suppository using an applicator **(Table 1)**. The penis is then massaged to dissolve the alprostadil pellet, after which venous flow delivers alprostadil to the corpora cavernosa, where it will induce erection.[52] The patient generally needs to be standing when the pellet is inserted and walk around for about 10 minutes before the erection will develop. Pellet insertion should be preceded by urination to moisten the urethra and ease insertion. The patient should be instructed on the proper technique for inserting the suppository, which requires that the initial insertion be done in the primary care provider's office.[41,43]

Because of lower levels of efficacy (30% success rate),[53] local adverse effects, and relatively high cost, intraurethral suppositories do not enjoy as widespread popularity as other forms of therapy for ED.

Treatment for psychogenic factors

Cognitive-behavioral interventions and relationship counseling are among the treatment approaches for psychogenic ED. These interventions are often combined with pharmacologic therapy. Primary care clinicians should consider referral to a sexual therapist if psychogenic factors are the cause of, or contribute to, ED.

APPROPRIATE FOLLOW-UP

After treatment is prescribed, follow-up is important to evaluate treatment success, monitor for adverse effects, and adjust the dose or type of treatment as necessary. There is no evidence-based guidance for the follow-up schedule, which should be tailored to the couple's preference and usual frequency of sexual activity. Generally, follow-up should be sufficiently soon so that obstacles to successful treatment can be promptly addressed, and should be at least periodic thereafter.

WHEN TO REFER

The role of the primary care clinician in ED management will depend on personal preference. It may vary from simple identification of ED and subsequent referral, to the use of oral medications, VCDs, intracavernosal injection, and uretheral suppositories. Despite the typically supportive relationship between primary care clinicians and their patients, some patients may prefer the relative anonymity of a consultant for a condition as intimate as ED.

Referral to a urologist is appropriate for complex cases of ED, when an anatomic problem such as Peyronie disease is present, or when there is a lack of treatment success.[28] As noted, referral to a sex therapist should be considered when relationship problems appear to be the cause of ED or an important contributor to it.

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