

# Male Sexual Dysfunction

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- Read the enclosed course.
- Complete the questions at the end of the course.
- Return your completed Evaluation to NetCE by mail or fax, or complete online at [www.NetCE.com](http://www.NetCE.com). (If you are a physician, behavioral health professional, or Florida nurse, please return the included Answer Sheet/Evaluation.) Your postmark or facsimile date will be used as your completion date.
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### Faculty

**Mark Rose, BS, MA, LP**, is a licensed psychologist in the State of Minnesota with a private consulting practice and a medical research analyst with a biomedical communications firm. Earlier healthcare technology assessment work led to medical device and pharmaceutical sector experience in new product development involving cancer ablative devices and pain therapeutics. Along with substantial experience in addiction research, Mr. Rose has contributed to the authorship of numerous papers on CNS, oncology, and other medical disorders. He is the lead author of papers published in peer-reviewed addiction, psychiatry, and pain medicine journals and has written books on prescription opioids and alcoholism published by the Hazelden Foundation. He also serves as an Expert Advisor and Expert Witness to law firms that represent disability claimants or criminal defendants on cases related to chronic pain, psychiatric/substance use disorders, and acute pharmacologic/toxicologic effects. Mr. Rose is on the Board of Directors of the Minneapolis-based International Institute of Anti-Aging Medicine and is a member of several professional organizations.

### Faculty Disclosure

Contributing faculty, Mark Rose, BS, MA, LP, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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The division planners and director have disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

### Audience

This course is designed for healthcare and mental health providers involved in the assessment and/or treatment of male sexual dysfunction.

### Accreditations & Approvals



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 INTERPROFESSIONAL CONTINUING EDUCATION

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This course is considered self-study, as defined by the New York State Board for Social Work. Materials that are included in this course may include interventions and modalities that are beyond the authorized practice of licensed master social work and licensed clinical social work in New York. As a licensed professional, you are responsible for reviewing the scope of practice, including activities that are defined in law as beyond the boundaries of practice for an LMSW and LCSW. A licensee who practices beyond the authorized scope of practice could be charged with unprofessional conduct under the Education Law and Regents Rules.

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Successful completion of this CME activity, which includes participation in the evaluation component, enables the participant to earn up to 10 MOC points in the American Board of Internal Medicine's (ABIM) Maintenance of Certification (MOC) program. Participants will earn MOC points equivalent to the amount of CME credits claimed for the activity. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABIM MOC credit. Completion of this course constitutes permission to share the completion data with ACCME.

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NetCE designates this continuing education activity for 10 ANCC contact hours.



This activity was planned by and for the healthcare team, and learners will receive 10 Interprofessional Continuing Education (IPCE) credits for learning and change.

NetCE designates this continuing education activity for 12 hours for Alabama nurses.

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AACN Synergy CERP Category A.

NetCE designates this activity for 10 hours ACPE credit(s). ACPE Universal Activity Numbers: JA4008164-0000-23-003-H001-P and JA4008164-0000-23-003-H001-T.

Social workers completing this intermediate-to-advanced course receive 10 Clinical continuing education credits.

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### Individual State Nursing Approvals

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### About the Sponsor

The purpose of NetCE is to provide challenging curricula to assist healthcare professionals to raise their levels of expertise while fulfilling their continuing education requirements, thereby improving the quality of healthcare.

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### Disclosure Statement

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**Course Objective**

Many men with sexual dysfunction complaints are reluctant to discuss concerns with healthcare and mental health providers. The purpose of this course is to provide healthcare professionals with the information necessary to identify and appropriately treat male sexual dysfunction.

**Learning Objectives**

Upon completion of this course, you should be able to:

1. Outline the epidemiology of male sexual dysfunction.
2. Discuss the etiology of and risk factors for various forms of male sexual dysfunction.
3. Review of the physiology of male sexual arousal.
4. Define the diagnostic criteria of various male sexual disorders.
5. Describe components of the sexual, medical, and psychological history of men presenting with sexual dysfunction complaints.
6. Identify instruments used in the assessment and diagnosis of sexual problems in men.
7. Describe aspects of the diagnostic workup for male sexual dysfunction.
8. Identify cases in which urologic referral is indicated.
9. Evaluate treatment options for erectile dysfunction.
10. Discuss treatment approaches for other male sexual dysfunctions, including premature ejaculation.
11. Analyze the role of psychosocial approaches and interpreter assistance when treating male sexual dysfunction.

**Pharmacy Technician Learning Objectives**

Upon completion of this course, you should be able to:

1. Outline the epidemiology, etiology, and pathophysiology of male sexual dysfunction.
2. Describe the diagnosis and treatment of various sexual dysfunctions that may be experienced by men.

**INTRODUCTION**

Sexual dysfunction is a highly prevalent condition. Among U.S. adults 18 to 59 years of age, an estimated 31% of men and 43% of women have sexual function concerns. Sexual problems are most prevalent in older men and young women [1; 2; 3]. Male sexual dysfunction broadly includes sexual pain and/or diminished or loss of sexual desire/interest, arousal, function, or orgasm, and diagnosis requires patient distress in addition to impairment [4]. Sexual dysfunction is distressing for male patients and their partners and can adversely and profoundly impact patient quality of life and self-image. In addition, many patients are reluctant to discuss sexual concerns with their primary care providers [5; 6].

Before the 1990s, male sexual dysfunction was assumed to arise from psychological problems and was treated by psychological intervention. The 1998 introduction and success of sildenafil (Viagra) for the treatment of erectile dysfunction (ED) helped shift research and clinical focus to a biomedical paradigm. However, current understanding of sexual dysfunction incorporates a broader, more complex framework; sexual function is influenced by a complex interaction of physiologic, sociocultural, and psychological factors. Their relative contribution to sexual dysfunction across patients varies broadly, although physiologic contribution to sexual dysfunction is decidedly more prominent in men. Nonetheless, all patients presenting with sexual complaints should receive diagnosis and treatment based on assessment of five key biopsychosocial domains [4; 7; 8]:

- Medical factors
- Cultural or religious factors
- Individual vulnerability factors
- Relationship factors
- Partner factors



EVIDENCE-BASED  
PRACTICE  
RECOMMENDATION

Sections marked with this symbol include evidence-based practice recommendations. The level of evidence and/or strength of recommendation, as provided by the evidence-based source, are also included so you may determine the validity or relevance of the information. These sections may be used in conjunction with the course material for better application to your daily practice.

Almost all patients require a biopsychosocial treatment approach. Even strictly physiologic sexual dysfunction can result in patient demoralization, loss of confidence, relationship problems, or sex avoidance, all of which are effectively addressed by psychological treatment. Patients with purely psychogenic ED can benefit from oral sildenafil or similar medication, as this can greatly improve their confidence and decrease sexual anxiety or avoidance. Combining medication and psychosocial intervention is more effective than either one alone in most cases of male sexual dysfunction [9; 10].

The concept of sexual health has also evolved from a narrow focus on the prevention of sexually transmitted infections and unplanned pregnancy to one that encompasses broader elements of reproductive health and sexual function. Sexual health is now understood as the ability to have pleasurable and safe sexual experiences free from coercion, with sexual health and sexual relationships strongly inter-related to general health and fundamental to individual, family, and social life in all cultures throughout the adult lifespan [11]. Clinicians require familiarity with knowledge advances; comprehension of the diverse etiologies, risk factors, and management strategies in specific male sexual dysfunction; and skills development to initiate and address this important aspect of wellness and quality of life [6; 12].

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## EPIDEMIOLOGY

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Roughly 20% to 30% of adult men currently have at least one manifest sexual dysfunction (occurring “somewhat often,” “often,” “nearly always,” or “always”) [13]. A survey of 1,709 men 40 to 70 years of age found a 52% prevalence of past-year ED, with 17.2% minimal, 25.2% moderate, and 9.6% complete ED. ED severity, prevalence, and incidence increase with age, and higher ED rates are found in those with low education level, heart disease, hypertension, and diabetes. A Canadian survey of 3,921 male primary care patients 40 to 88 years of age found a roughly 50% prevalence of ED [14; 15; 16].

As noted, age and ED prevalence are highly associated. The prevalence of ED is 1% to 10% in men younger than 40 years of age, 2% to 9% in men 40 to 49 years of age, 20% to 40% in men 60 to 69 years of age, and 50% to 100% in men 70 years of age or older [13; 15; 17].

Among men older than 40 years of age, ED prevalence rates are 21% in whites, 24% in blacks, 20% in Hispanics, and 22% overall. In all groups, ED rates increased with older age. Across racial groups, ED risk was increased by diabetes, hypertension, and moderate or severe lower urinary tract symptoms [18].

A survey of adults 18 to 59 years of age reported past-year rates of premature ejaculation (PE) in 28.5%, lack of sexual interest in 15.8%, sexual performance anxiety in 17%, inability to achieve or maintain an erection in 10.4%, and lack of sexual pleasure in 8.1% [2]. The National Health and Social Life Survey (NHSLs) indicates a fairly steady 30% prevalence of PE through all adult age categories (in contrast to ED, which rises in prevalence with increasing age) [19]. PE is the most common sexual disorder in men younger than 40 years of age, and 30% to 70% of men experience some degree of PE at some time point [19; 20]. The prevalence of diagnosable PE varies from 8% to 30% for all age groups, with most studies reporting prevalence rates ranging from 12% to 19% [13]. Acquired PE is more prevalent than lifelong PE.

In male hypoactive sexual desire disorder (MHSD), problems with sexual desire are reported by 6% of younger men (18 to 24 years of age) and 41% of older men (66 to 74 years of age). It is a persistent problem in 1.8% of men [4].

The prevalence of genital pain in men during sexual intercourse has seldom been studied, and male sexual pain was removed as a diagnostic entity in the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) [4].



## ETIOLOGY AND RISK FACTORS

Suboptimal overall health commonly co-occurs with low sexual interest/desire, PE, and ED. Psychological difficulties, anxiety, low socioeconomic status, and unhealthy lifestyle are male sexual dysfunction risk factors [19; 21].

### GENERAL RISK FACTORS

#### Substance-Related Sexual Dysfunction

Substance effects contribute to a large proportion of sexual dysfunction in men, and certain drug classes are especially prone to inducing sexual dysfunction. These include antidepressants, neuroleptics, 5 $\alpha$ -reductase (5 $\alpha$ -R) inhibitors, and certain recreational or illicit drugs.

#### *Antidepressants*

Selective serotonin reuptake inhibitors (SSRIs) account for most antidepressant prescriptions, and primary care providers should have an appreciation of the impact of sexual side effects common to these agents. Antidepressant-induced sexual side effects largely result from increased serotonin (5-HT) neurotransmission via reuptake blockade of serotonin transporters, while antidepressants that primarily increase dopamine and norepinephrine neurotransmission produce markedly fewer sexual side effects.

In patients showing an otherwise positive therapeutic response, switching medications to an antidepressant with fewer sexual side effects is highly undesirable and should be avoided, if possible. Another strategy is antidepressant dose reduction, on the basis of a dose-response relationship in sexual side effects. The incidence of male sexual dysfunction (particularly ejaculatory delay) is much higher with SSRIs and serotonin-norepinephrine reuptake inhibitors, and much lower in antidepressants with primary adrenergic or dopaminergic mechanism. However, this can be a desired instead of adverse effect in men with PE, and the SSRI dapoxetine has been approved as first-line therapy for PE in more than 50 countries, but not in the United States [9;

22; 23; 24]. To date, no drug has been specifically approved by the U.S. Food and Drug Administration (FDA) for the treatment of PE [19]. However, the SSRIs sertraline, paroxetine, fluoxetine, and citalopram are used off-label for PE [24].

Tricyclic antidepressants (TCAs) with SSRI-like activity have a similar effect as SSRIs. The TCA most studied for treatment of PE is clomipramine. Studies suggest that the off-label, on-demand administration of clomipramine is more effective for PE than many SSRIs [19; 25; 26].

#### *Hyperprolactinemia Secondary to Neuroleptics*

Antipsychotic medications, also referred to as neuroleptics, are prescribed for schizophrenia, other psychotic disorders, and bipolar disorder and are widely prescribed off-label for mood and anxiety disorders, insomnia, and other psychiatric conditions. Though often effective for these uses, the prevalence of neuroleptic-induced sexual dysfunction is high [27]. A 12-month comparative trial of neuroleptic therapy for schizophrenia reported sexual dysfunction rates of 29% with olanzapine, 34% with quetiapine, 43% with risperidone, and 45% with haloperidol [28].

Hyperprolactinemia is the underlying factor in almost all neuroleptic-induced sexual dysfunction [27]. Neuroleptics over-ride normal pituitary inhibitory mechanism by facilitating prolactin synthesis and secretion, a mechanism shared by all D2 receptor antagonists. Among D2 antagonists, neuroleptics are the most widely prescribed and show the highest rates of drug-induced hyperprolactinemia [29; 30]. Some trials have found 100% hyperprolactinemia rates with risperidone and older first-generation phenothiazine neuroleptics [31; 32]. Verapamil induces hyperprolactinemia in 8.5% of patients by blocking hypothalamic dopamine [33]. In addition, opioids and cocaine can induce mild hyperprolactinemia through mu-opioid receptor action. Some patients with hyperprolactinemia remain asymptomatic, but men can develop ED, diminished libido, and hypogonadism [34; 35].

In patients with sexual dysfunction complaints while receiving neuroleptics, the Endocrine Society recommends the following [29]:

1. Measure serum prolactin.
2. If hyperprolactinemia is confirmed, determine the onset of sexual dysfunction relative to drug initiation.
3. If sexual dysfunction symptoms began shortly after initiation, drug-induced hyperprolactinemia is confirmed.
4. With symptom onset before initiation, focus on treating hyperprolactinemia.

### **5 $\alpha$ -Reductase Inhibitors**

The enzyme 5 $\alpha$ -R transforms testosterone into the potent androgen 5 $\alpha$ -dihydrotestosterone. The 5 $\alpha$ -R inhibitors finasteride and dutasteride were developed to block 5 $\alpha$ -R in order to produce an anti-androgenic effect. Both were U.S. Food and Drug Administration (FDA)-approved for treatment of benign prostate hyperplasia and male pattern hair loss [24]. However, 5 $\alpha$ -R is broadly distributed in central nervous system tissue, and inhibition blocks synthesis of several key hormones and neuroactive steroids. This effect was later found to result in numerous adverse effects, including impaired or complete loss of libido, erectile, and orgasm function; high Gleason grade prostate cancer; cardiac arrest and cardiovascular events; and depression [24]. In some patients, total sexual dysfunction has been irreversible, with significant emotional toll and impact on quality of life [36; 37; 38; 39; 40]. Treatment of 5 $\alpha$ -R inhibitor-induced post-treatment enduring sexual dysfunction has focused on endocrine interventions, but no approach has been successful [41; 42; 43].

In 2013, the Sexual Medicine Society of North America published a comprehensive review that acknowledged a link between 5 $\alpha$ -R inhibitors and persistent sexual dysfunction after treatment cessation but stopped short of stating a causal relationship had been established. They concluded more research was needed [44].

### **Illicit Drugs**

There is some evidence that illicit drug use, particularly heroin and cannabis, may cause sexual dysfunction in men [45; 46]. In one study, researchers hypothesized that “cannabis may actually have peripheral antagonizing effects on erectile function by stimulating specific receptors in the cavernous tissue” [45]. Use of opioids (such as heroin) and cocaine has been associated with mild hyperprolactinemia, with related impairment in sexual functioning. Although amphetamines are often illicitly used to enhance sexual experience, in one study of 1,159 male amphetamine abusers, the prevalence of ED was higher among the drug users (29.3%) than non-abusing controls (11.9%) [47]. A study of male drug abusers in a drug treatment program found that the participants were more likely than the general public to have ED, decreased sexual desire, and increased ejaculation latency [46].

### **Cigarette Smoking and Nicotine**

Cigarette smoking is an established sexual dysfunction risk factor in both men and women, although the link in men is strengthened by the adverse vascular effect that directly impacts erectile function [48].

The added risk, as odds ratio (OR), of developing ED from smoking was calculated using data from 28,586 study participants. Compared to nonsmokers, the odds of developing ED were 1.51 in current smokers and 1.29 in former smokers. Compared with never-smokers, the odds of developing ED were 1.23 in those who smoke 20 or more cigarettes and 1.60 in those who have smoked for more than 23 years (after correcting for education) [49; 50]. Smoking is linked to disrupted signaling and inhibited production of nitric oxide from excess generation of reactive oxygen species. This leads to impaired endothelium-dependent smooth muscle relaxation and the development of ED [51; 52].

Dysregulated sympathovagal balance is a reliable acute nicotine effect and is associated with reduced erectile function tumescence. Nicotine may contribute to ED by inducing dysfunctional cardiac autonomic tone [53]. A series of highly controlled trials isolated nicotine effect (using nicotine gum) on sexual function in young, healthy, nonsmoking volunteers. In one study, nicotine reduced erectile response in 16 of 20 men, with a 23% reduction in physiologic sexual arousal. Nicotine did not affect subjective sexual arousal ratings [54].

In a separate four-week smoking cessation study, erectile function did not differ between continued- and quit-smokers at two weeks, likely due to quit-smokers receiving a high-dose nicotine patch. At four weeks, after all nicotine replacement was discontinued, erectile function significantly improved in those who quit smoking [55].

## MEDICAL CONDITIONS

### Endocrine Disorders

Hypogonadism is characterized by low testosterone levels and may adversely impact libido and erectile function. To some degree, nitric oxide release in the corporal endothelium is androgen dependent, and androgen deficiency decreases nocturnal erections and libido [56]. Hyperprolactinemia can also contribute to male sexual dysfunction, as discussed [56].

### Lower Urogenital and Benign Prostate Conditions

Several reports have linked lower urinary tract symptoms with male sexual dysfunction. Ejaculatory dysfunction, higher prevalence of ED, and reduced sexual desire were found in men with lower urinary tract symptoms, with symptom severity correlated with ED severity. Additionally, men with overactive bladder are significantly more likely to have ED than controls [13; 57; 58]. Any lifetime history of sexually transmitted infection shows an OR of 5.4 for non-pleasurable sex [59].

Acute and chronic lower urogenital infection, prostatodynia, and chronic pelvic pain syndrome are associated with ED, PE, and painful ejaculation. Men with chronic prostatitis or chronic pelvic pain syndrome have a 26% to 77% prevalence of PE [60; 61]. Antibiotic treatment of bacterial prostatitis in men with acquired PE led to a 2.6-fold increase in intravaginal ejaculation latency time (IELT) and improved ejaculatory control in 83.9% of subjects [62]. One study suggests that routine screening for chronic prostatitis may be beneficial for men presenting with PE [63].

## PSYCHOLOGICAL FACTORS

As noted, emotional and psychological factors can contribute to most types of male sexual dysfunction. For example, ED almost doubles in men with depression compared with those without depression. Also, male veterans with post-traumatic stress disorder (PTSD) have higher rates of sexual dysfunction than veterans without PTSD [64; 65].

## DYSFUNCTIONAL SEXUAL BELIEFS

“Macho” sexual beliefs, common among men, include the ability to always be ready for sex, to always satisfy the partner, and to maintain an erection until ending sexual activity. In a study of 575 men (288 heterosexual, 287 gay), these types of sexual beliefs were the main contributing factor in the association between frequency of unsuccessful sexual episodes (e.g., ED) and activation of incompetence schemas. These findings emphasize the importance of psychological interventions that target dysfunctional sexual beliefs [66].

## INTERNET PORNOGRAPHY

In the late 2000s, population-based surveys and clinical studies of treatment-seeking patients began observing marked increases in the rates of sexual dysfunction among younger, sexually active men. These trends defied established associations between age and onset of ED. For example, new ED diagnoses in active duty servicemen doubled from 2004 to 2013 [67]. Other studies found persistent problems in boys/men (16 to 21 years of age) of low sexual satisfaction (47.9%), low desire (46.2%), and ED (45.3%) [67].

These increases in sexual dysfunction rates among younger men cannot be explained by increases in the standard risk factors for organic ED in older men or psychogenic ED in younger men. However, access to high-speed, broadband Internet started becoming widespread in the mid-to-late 2000s, and growing evidence indicates that regular Internet pornography use may underlie the surge in sexual dysfunction rates. Sexual arousal is conditionable, especially before adulthood. Younger age of onset for regular Internet pornography use may lead to less enjoyment from, and greater preference over, partnered sex at an earlier age. In 2014, nearly 50% of college-age men reported first exposure to Internet pornography before 13 years of age, compared with 14% in 2008 [68].

Numerous studies have linked frequent Internet pornography use with arousal, attraction, and sexual performance problems, including difficulty orgasming, diminished libido, ED, negative impact on partnered sex, decreased enjoyment of sexual intimacy, lower sexual and relationship satisfaction, preference for Internet pornography over partnered sex, and greater brain activation response to pornographic images among men with low desire for sex with partners [67; 69; 70; 71; 72; 73].

### **ERECTILE DYSFUNCTION RISK FACTORS**

While purely psychogenic ED is now considered uncommon, a psychogenic component is frequently present with organic ED and other male sexual dysfunctions. In addition, numerous medical conditions are associated with ED, and almost any disease that alters nervous, vascular, or hormonal systems can adversely affect erectile function [17; 64]. ED originates from vasculogenic, neurogenic, endocrinologic, psychogenic, or anatomic etiology or from iatrogenic cause involving medical procedures or medication side effects [17; 64; 74].


A longitudinal study that controlled for comorbid factors found a 10-fold difference in relative risk for ED associated with older age, independent of health or previous ED. Diabetes, cancer, stroke, and hypertension increased ED risk, while physical activity, leanness, moderate alcohol consumption, and not smoking decreased ED risk [13; 75].

### **Cardiovascular Disease and Endothelial Dysfunction**

In most patients, ED and cardiovascular disease are viewed as clinical manifestations of a common pathophysiology. ED may be viewed as a sentinel event for cardiovascular disease; it often develops before cardiovascular disease because the smaller diameter of penile blood vessels creates susceptibility to plaque buildup before larger coronary, internal carotid, and femoral arteries. Coronary artery disease and ED share a generalized arteriopathy that may initially affect arterial inflow to the penile corpus cavernosum [56; 76].

The vascular endothelium is essential for regulating normal circulatory function, and the association between ED and vascular disease resides in vascular endothelial dysfunction [56; 77]. Endothelial and vascular smooth muscle dysfunction are highly prevalent in patients with ED and represent shared etiologic pathways for other vascular disease states such as cerebral vascular accidents, myocardial infarction, heart disease, hypertension, hyperlipidemia, low high-density lipoprotein (HDL), arteriosclerosis, and peripheral vascular disease [13]. Most risk factors of ED promote endothelial dysfunction, including hypertension, dyslipidemia, diabetes, depression, obesity, cigarette smoking, and metabolic syndrome [52; 77; 78; 79].





The Male Training Center for Family Planning and Reproductive Health asserts that asking males about problems with sexual function is particularly important to identify underlying cardiovascular disease among men who present with symptoms of sexual dysfunction routinely starting at 25 years of age.

([https://rhntc.org/sites/default/files/resources/mtc\\_male\\_prevrhc\\_2014.pdf](https://rhntc.org/sites/default/files/resources/mtc_male_prevrhc_2014.pdf). Last accessed February 21, 2023.)

Level of Evidence: Expert Opinion/Consensus Statement

ED is predictive of potential future cardiovascular events, and the presence of ED, particularly severe ED, significantly elevates patient risk of hypertension, ischemic heart disease, peripheral arterial disease, and stroke. ED development is a precursor to symptomatic coronary artery disease, with an average 39-month lead-time, and men with ED have a 65% to 85% increased risk of subsequent coronary artery disease. Some have concluded that ED is the most robust predictor of silent coronary artery disease, and the importance of careful cardiovascular risk evaluation in men with ED cannot be overemphasized [80; 81; 82; 83; 84].

Elevated mortality risk is associated with ED. The relationship between ED and increased risk of cardiovascular events and mortality was confirmed by analysis of 14 studies involving more than 90,000 patients. The presence of ED (vs. no ED) increased patient risk of cardiovascular events by 44%, all-cause mortality by 25% (mostly cardiovascular mortality), myocardial infarction by 62%, and cerebral vascular accidents by 39% [85; 86].

In 1,402 men followed over 20 years, ED in younger men markedly elevated the risk of future cardiac events, but the prognostic importance of ED substantially diminished in older men. Younger men with ED may be ideal candidates for cardiovascular risk factor screening and intervention [56; 82].

A prostate cancer prevention trial followed 9,457 men randomized to placebo over 19 years. New-onset ED was associated with an increased risk for cardiovascular events during follow-up. This elevated risk for cardiovascular events in earlier-onset ED was comparable to risk associated with current smoking or family history of myocardial infarction [56; 83].

While evidence stresses the importance of early cardiovascular evaluation in men with ED of unexplained etiology, impaired masturbation-induced erections in younger men are usually presumed psychogenic. To examine this assumption, young men (mean age: 29 years) presenting with weaker masturbatory erections and no sexual intercourse were evaluated for early cardiovascular risks associated with ED [87]. Compared to ED and healthy controls, these men demonstrated higher prevalence of early ED risk factors, including endothelial dysfunction, insulin resistance, elevated glycosylated serum protein, and abnormal nocturnal penile tumescence and rigidity. Endothelial dysfunction was a strong and independent risk factor for sexual dysfunction. In young men with weaker masturbatory erection without history of successful sexual intercourse, ED may be a sign of early cardiovascular risk [87].

### **Abnormal Cholesterol Levels**

Hypercholesterolemia can impair endothelium-mediated smooth muscle relaxation of corpus callosum tissue [52]. A study found ED risk inversely correlated with low HDL cholesterol levels but unrelated to elevated total cholesterol levels in older men, while in younger men ED correlated with abnormal HDL and elevated total cholesterol [88].

### **Sexual Activity and Cardiovascular Risk Assessment**

The Princeton Consensus (Expert Panel) Conference is a multispecialty collaboration dedicated to improving identification of men with ED who may require additional cardiovascular work-up and evaluation of cardiac risk associated with sexual activity in men with documented cardiovascular disease.

The most recent Princeton consensus (Princeton III) emphasizes that evaluation of exercise ability and use of stress testing should be conducted before ED treatment to ensure adequacy of patient cardiovascular capacity for the physical demands of sexual activity. Princeton III also emphasizes patient stratification by level of cardiac risk from sexual activity [74; 89]:

- Low risk: Patients without significant cardiac risk from sexual activity who are likely to perform modest-intensity exercise without symptoms
- Intermediate risk: Further evaluation with exercise stress testing is required before resuming sexual activity.
- High-risk: Cardiac conditions severe or unstable enough to impose significant risk from sexual activity. These patients require cardiologist referral, and sexual activity should be deferred until the cardiac condition has stabilized.

### Chronic Periodontitis

Chronic periodontitis is a bacterial disease that manifests as inflammation of gingival tissues and possibly of structures that support teeth. There is evidence that chronic periodontitis promotes endothelial dysfunction, which may lead to systemic vascular disease. Chronic periodontitis was found highly prevalent in men with ED; one study found men with severe chronic periodontitis were 3.29 times more likely to have ED than men without chronic periodontitis [90].

### Prostate Disease Treatment

Transurethral resection of the prostate for benign prostatic hyperplasia is associated with a 10% to 20% rate of ED from cauterization-induced nerve damage, but newer procedures using microwave, laser, or radiofrequency ablation have reduced ED rates to nearly 0%. Radical prostatectomy treatment of prostate cancer poses a significant risk of ED, but erectile function may be preserved if both nerves

that run through the lateral edges of the prostate are saved. Potency preservation is related to surgeon experience and patient age, with baseline erectile function maintained in 75% to 80% of men younger than 60 years of age, and 10% to 15% of men older than 70 years of age. At two-year follow-up of early-stage prostate cancer treatment, patient ability to achieve erection suitable for intercourse was 35% with radical prostatectomy, 37% with external beam radiotherapy, and 43% with brachytherapy [91].

A population-based cohort of 835 men with newly diagnosed prostate cancer was followed prospectively using the validated Prostate Cancer Symptom Indices (PCSI) instrument, which measures likely physical and psychological symptoms and the distress they cause following prostate cancer treatment. Patients were treated with external beam radiotherapy (EBRT), EBRT with androgen deprivation therapy (EBRT/ADT), brachytherapy, nerve-sparing radical prostatectomy, or non-nerve-sparing radical prostatectomy. EBRT and brachytherapy treatment groups resulted in similar PCSI scores through 24 months. Patients treated with EBRT/ADT and radical prostatectomy, with or without nerve sparing, had the lowest PCSI scores at all post-treatment time points. Preservation rates of useful sexual function at 24 months were 14.1% to 70.7% for EBRT; 8.4% to 52.3% for EBRT/ADT; 4.7% to 45.3% for nerve-sparing radical prostatectomy; and 4.8% to 34.5% for non-nerve-sparing radical prostatectomy [92].

### Trauma

ED can also result from trauma to the pelvic blood vessels or nerves. Bicycle riding for long periods is a known causal factor of ED, the result of vascular and nerve injury from direct compression of the perineum by the bicycle seat. However, bicycling for less than three hours per week may be modestly protective against ED, and some newer bicycle seats are designed to reduce perineal pressure [93; 94]. There is some evidence that surgical repair may improve ED in patients with a history of pelvic or perineal trauma [95].

## Diabetes

Diabetes is a recognized ED risk factor, and decreased sexual desire and orgasmic dysfunction are highly prevalent in men with diabetes [13]. Approximately 50% of patients with diabetes will develop ED, with an earlier onset than in those without diabetes [96]. Contributors to diabetes-induced ED include hyperglycemia and hypogonadism, which facilitate development of impaired vasodilatory signaling, smooth muscle cell hypercontractility, and veno-occlusive disorder [52; 97; 98]. Obesity and metabolic syndrome also elevate the risk of ED and are common in men with diabetes [13].

## Peyronie Disease

Peyronie disease can result in penile curvature and fibrosis. In severe cases of Peyronie disease, extensive scar tissue in the corpora may impede blood flow and result in ED [76].

## Lifestyle Risk Factors

Exercise and lifestyle modifications may improve erectile function. Weight loss may help by decreasing inflammation, increasing testosterone, and improving self-esteem. Patients should be advised to increase activity, reduce weight, and stop smoking, as these efforts can improve or restore erectile function in men without comorbidities. Optimal glycemic control in patients with diabetes and pharmacologic treatment of hypertension may be important in preventing or reducing sexual dysfunction [99]. A prospective cohort study of 31,742 men 53 to 90 years of age found physical activity associated with a 0.7 relative risk for ED and obesity associated with a 1.3 relative risk for ED [51; 75].

## Aging

Age is strongly linked to ED, due to increased oxidative stress, penile endothelial dysfunction, vascular changes, and decline of circulating steroids [52; 100].

## PREMATURE EJACULATION RISK FACTORS

Acquired PE is most commonly due to sexual performance anxiety, psychological or relationship problems, or ED; less commonly, prostatitis, withdrawal/detoxification from prescribed or recreational drugs, and, rarely, hyperthyroidism may be the cause [101]. Men with lifelong and acquired PE differ on some demographic and etiologic dimensions. Compared with men with lifelong PE, those with acquired PE are older, show slightly greater mean IELT, have higher rates of cardiovascular risk factors, and have more prevalent comorbidities of hypertension, ED, sexual desire disorder, diabetes, and chronic prostatitis [102; 103; 104].

## Psychological Factors

Psychological and interpersonal factors may cause or exacerbate acquired PE. Specific factors include the effects of early experience and sexual conditioning, sexual abuse, and attitudes toward sex internalized during childhood. Individual psychological factors may include poor body image, depression, performance anxiety, and alexithymia. Relationship factors include decreased intimacy or partner conflict. Anxiety is thought to activate the sympathetic nervous system and reduce ejaculatory threshold, leading to earlier ejaculation. Hypoactive sexual desire may lead to acquired PE from an unconscious desire to abbreviate the unwanted penetration or, conversely, may develop as a consequence of chronic and frustrating PE. Psychological factors and PE can be bi-directional, with either factor causing or exacerbating the other. An example is performance anxiety leading to PE, which further exacerbates the original performance anxiety [64; 105; 106; 107; 108].

### Comorbid Erectile Dysfunction

Up to 50% of patients with ED also experience PE, and while ED is unlikely to co-occur or cause lifelong PE, evidence confirms the association of acquired PE and ED [101]. These men may experience rapid ejaculation from performance anxiety or, with deliberate intensification of stimulation, complete ejaculation before loss of erection. Men with comorbid ED and PE may manifest a more severe variant of each disorder and experience lower sexual satisfaction and diminished response to treatment of PE [109; 110].

### Partner's Impact

The association of PE and intimate relationship distress is bi-directional. Numerous studies show high levels of personal distress in men with PE and in their female partners [64]. Men with PE show low scores on self-esteem and self-confidence, and one-third experience anxiety connected to sexual situations. Men with PE have more interpersonal difficulties than men without PE, feel they are “letting their partner down” with PE, and believe their relationship quality would improve if they did not have PE. The negative impact of PE on single men may be greater, as it can impose a barrier to seeking and becoming involved in new relationships [111; 112]. PE can also negatively impact female partner sexuality and is correlated to overall female sexual dysfunction, low sexual satisfaction, and sexual distress [9; 107].

Partner inclusion in the treatment process is important, but not mandatory, for PE treatment success. Some patients may not understand the importance for partner involvement, and some partners may be reluctant to participate or to change the sexual interaction. A cooperative partner augments the power of treatment, and this is more likely to improve sexual and broader aspects of their relationship [9; 113].

### MALE HYPOACTIVE SEXUAL DESIRE DISORDER

Many factors may contribute to the etiology of MHSDD, including [4]:

- Vascular or neuropathic conditions
- Low serum testosterone
- Heavy/chronic alcohol use or cigarette smoking
- Use of antihypertensives or SSRIs
- Major depression or anxiety disorders
- Sexual assault or childhood sexual abuse
- Low physiologic arousal
- Stress and exhaustion
- Relationship problems (e.g., anger, hostility, poor communication, anxiety over relationship security)

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### PHYSIOLOGY OF MALE SEXUAL RESPONSE

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In men, sexual stimulation releases neurotransmitters from corpus cavernosum nerve endings and relaxation factors, including nitric oxide synthase, from endothelial cells lining the sinusoids. Increased nitric oxide synthase produces nitric oxide from L-arginine, which activates guanylate cyclase in the corpus cavernosum and results in the release of cyclic guanosine monophosphate (cGMP). cGMP induces vasodilation and smooth muscle relaxation in the arteries and arterioles that supply erectile tissue, which rapidly fill and expand from increased penile blood flow. This tissue expansion occludes venous outflow, and an erection is produced. The balance between contraction and relaxation is controlled by central and peripheral factors involving many transmitters and transmitter systems [52; 64; 114].



Erectile function depends on peripheral nerve status, integrity of the vascular supply, and biochemical events within the corpus cavernosum. Erection and orgasm are mediated by the autonomic nervous system, and sustaining and maintaining erection is controlled by the parasympathetic nervous system. Vascular and neurogenic components in male sexual response are mediated by hormonal status and extrinsic factors. Disruption to any of these systems can induce sexual dysfunction [56].

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## DIAGNOSTIC CRITERIA

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### DSM-5-TR DIAGNOSTIC CRITERIA FOR MALE SEXUAL DISORDERS

The American Psychiatric Association published the DSM-5 in 2013 and included several revisions to the male sexual dysfunction section including revised diagnostic criteria and deleted or renamed diagnostic conditions; these revisions also appear in the text revision, published in 2022 [4; 115]. Male dyspareunia, male sexual pain, and sexual aversion disorder are no longer listed. Male erectile disorder was renamed erectile disorder, hypoactive sexual desire disorder became male hypoactive sexual desire disorder, and male orgasmic disorder is now delayed ejaculation [4].

Male sexual disorders in the DSM-5-TR are characterized by a clinically significant inability to respond sexually or to experience sexual pleasure. All symptoms must meet the following criteria for diagnosis:

- Persistence for at least six months
- Symptoms cause significant distress to the individual
- Dysfunction cannot be better explained by nonsexual mental disorder, a medical condition, the effects of a drug or medication, severe relationship distress, or other significant stressors

Each diagnosed sexual disorder must also include the following qualifiers:

- Duration of the dysfunction
  - Lifelong (i.e., present since first sexual experience)
  - Acquired (i.e., developing after a period of relative normal sexual functioning)
- The context in which the dysfunction occurs
  - Generalized (i.e., not limited to certain types of stimulation, situations, or partners)
  - Situational (i.e., limited to specific types of stimulation, situations, or partners)

### Erectile Disorder

In order to reach a diagnosis of erectile disorder, at least one of the following three symptoms must be present in most or all (75% to 100%) sexual activity [4]:

- Marked difficulty in obtaining an erection during sexual activity
- Marked difficulty in maintaining an erection until the completion of sexual activity
- Marked decrease in erectile rigidity

The severity is classified as mild, moderate, or severe on the basis of patient level of distress over the symptoms.

### Premature Ejaculation

In men with PE, all or almost all (75% to 100%) sexual activity is marked by a pattern of ejaculation occurring during partnered sexual activity within one minute after penetration and before the individual wishes it [4]. The severity of PE is specified as:

- Mild: Within 30 to 60 seconds of penetration
- Moderate: Within 15 to 30 seconds of penetration
- Severe: Occurring before sexual activity, at the start of sexual activity, or within 15 seconds of penetration

### Male Hypoactive Sexual Desire Disorder

Patients with MHSDD experience low desire for sex and absence of sexual thoughts or fantasies. On most occasions, there is a marked delay, infrequency, or absence of orgasm during sexual activity and/or a tendency to ejaculate after less than one minute of sexual activity. These experiences cause clinically significant distress or interpersonal problems and are usually present (75% to 100% of the time) [4].

### Delayed Ejaculation

Delayed ejaculation is defined as an inability to climax during sex with a partner about 75% to 100% of the time, with either a delay in ejaculation or infrequent or absent ejaculation [4]. The ejaculatory delay is not considered pathologic if it is due to a deliberate effort to prolong sexual activity.

### INTERNATIONAL SOCIETY FOR SEXUAL MEDICINE DIAGNOSTIC CRITERIA FOR PREMATURE EJACULATION

Two major studies established normative IELT [116; 117]. One study indicated a median IELT of 5.4 minutes overall—6.5 minutes in men 18 to 30 years of age and 4.3 minutes in men 51 years of age and older. Condom use had no effect [116]. The other trial found a median 6.0 minutes [117]. Pooling both studies, IELT was less than one minute in 2.5%, and less than two minutes in 6% [118].

From the results of these trials and numerous other studies, definitions and diagnostic criteria for ejaculatory conditions were published by the International Society for Sexual Medicine (ISSM) in 2014 [118].

### Premature Ejaculation

The ISSM PE criteria combine lifelong PE and acquired PE and apply to intravaginal sex only [9; 101]:

- Ejaculation that always or nearly always occurs prior to or within about one minute of vaginal penetration from the first sexual experience (lifelong PE), or a clinically significant and bothersome reduction in latency time, often to about three minutes or less (acquired PE)
- The inability to delay ejaculation on all or nearly all vaginal penetrations
- Negative personal consequences, such as distress, bother, frustration, and/or the avoidance of sexual intimacy

### Subjective PE

Subjective PE is characterized by subjective perception of consistent or inconsistent short IELT and at least one of the following [9; 101]:

- Preoccupation with an imagined short ejaculatory latency or lack of control over the timing of ejaculation
- Actual IELT in the normal range or longer duration (i.e., ejaculation occurs after five minutes)
- Ability to control ejaculation (i.e., to withhold ejaculation at moment of imminence) diminished or lacking
- Preoccupation not better accounted for by another mental disorder

### Anteportal Ejaculation

Anteportal ejaculation occurs prior to penetration [9; 101]. It is considered the most severe form of PE and affects 5% to 20% of men with lifelong PE.

### Variable PE

Variable PE is a short ejaculatory latency that occurs irregularly and inconsistently, with some subjective sense of diminished ejaculatory control [9; 101]. Variable PE is not considered a sexual dysfunction, but rather a normal variation in sexual performance.

## ASSESSMENT AND DIAGNOSIS

### HISTORY AND CLINICAL ASSESSMENT

Independent of a specific complaint, assessment of any male sexual dysfunction follows the same underlying principle of addressing severity, onset, and duration of the problem; concurrent medical or psychosocial factors; and extent of patient and partner (if applicable) distress. A thorough patient history and clinical assessment is essential for accurate diagnosis and the creation of a patient-specific treatment plan. Specific areas to assess include the sexual, medical, and psychological history [119].

#### Sexual History

The sexual history should include information about previous and current sexual relationships; current emotional status; the onset, duration, and clinical course (stable or worsening) of the current problem and whether the problem is continuous, intermittent, or context-specific; and previous provider contact for sexual function concerns, including any treatments and treatment response. Partner sexual health status (when available) may be useful. A detailed description should be made of the rigidity and duration of both sexually stimulated and morning erections and problems with arousal, ejaculation, and orgasm. In patients with a sexual partner, clinicians should begin developing a sense of patient and partner distress surrounding the sexual dysfunction and whether the sexual dysfunction was antecedent to, or a consequence of, the current relationship. Sexual orientation and gender identity should be noted. Patients should also be asked whether they favor or oppose any specific treatment and the extent they wish to explore the cause of their sex concern [74; 119].



EVIDENCE-BASED  
PRACTICE  
RECOMMENDATION

According to the British Association for Sexual Health and HIV, sexual history taking should take place in a confidential, private environment.

(<https://www.bashhguidelines.org/media/1241/sh-guidelines-2019-ijsa.pdf>.)

Last accessed February 21, 2023.)

**Level of Evidence:** 1D (Strong recommendation based on non-analytic evidence, e.g. case reports or series or expert opinion)

#### ED

With possible ED, determine which sexual response aspect is dysfunctional by exploring whether [9; 76]:

- The patient has difficulty obtaining an erection.
- The erection is suitable for penetration.
- The erection can be maintained until the partner has achieved orgasm.
- Ejaculation occurs.
- Both partners experience sexual satisfaction.
- Erection suitable for penetration has been obtained, even briefly, or not.

#### PE

In patients with PE, patient and partner estimation of ejaculatory latency should be the measure for determining IELT in clinical practice [9]. To help identify PE, consider asking the following:

- Can you delay ejaculation before penetration?
- What is the time between penetration and ejaculation?
- Can you delay ejaculation?
- Do you and/or your partner feel bothered, annoyed, and/or frustrated by your PE?
- Is your PE affecting your relationship?
- Do you and/or your partner avoid sexual intercourse because of embarrassment?

Recommended questions to distinguish between ED and PE may include [9; 76]:

- Is your erection hard enough to penetrate?
- Do you have difficulty maintaining your erection until you ejaculate during intercourse?
- Do you ever rush intercourse to prevent loss of your erection?


To assess for lifelong versus acquired PE, ask:

- When did you first experience PE?
- Have you experienced PE since your first sexual experience on every/almost every attempt and with every partner?

The following questions can help evaluate relationship impact, previous treatment, and impact on quality of life:

- How upset is your partner over your PE?
- Does your partner avoid sexual intercourse?
- Is your PE affecting your overall relationship?
- Have you previously received any treatment for your PE?
- Do you avoid sexual intercourse because of embarrassment?
- Do you feel anxious, depressed, or embarrassed because of your PE?

Taking a thorough sexual history also allows the clinician to begin forming an objective opinion regarding the interpersonal relationship between the patient and his sexual partner [120]. In PE, two validated questionnaires with extensive data are the Premature Ejaculation Profile (PEP) and the Index of Premature Ejaculation (IPE). Both may be useful as adjuncts but should not replace a detailed sexual history [9; 121; 122].



**E B**  
EVIDENCE-BASED  
PRACTICE  
RECOMMENDATION

According to the Male Training Center for Family Planning and Reproductive Health, specific questions to include in the sexual history if the patient is experiencing sexual dysfunction such as inability to obtain and maintain an adequate erection for satisfactory sexual activity (e.g., impotence, erectile dysfunction), premature or delayed ejaculation, loss of libido, painful intercourse, and also priapism, a prolonged painful erection not associated with sexual desire.

([https://rhntc.org/sites/default/files/resources/mtc\\_male\\_prevrhc\\_2014.pdf](https://rhntc.org/sites/default/files/resources/mtc_male_prevrhc_2014.pdf). Last accessed February 21, 2023.)

**Level of Evidence:** Expert Opinion/Consensus Statement

### Medical History

Information should be obtained on general medical status and history and any current or past medical conditions that may affect sexual function. This should encompass details concerning hospitalization, diagnosis, treatment and response, and follow-up with healthcare professionals with positive history in any of the following [17; 52; 56; 74]:

- Cardiovascular disease
- Hypertension
- Type 1 and 2 diabetes
- Hyperlipidemia
- Prostate conditions (e.g., cancer, benign prostatic hyperplasia) and treatment (e.g., transurethral resection of the prostate, prostatectomy, irradiation, brachytherapy, androgen deprivation therapy)
- Urinary tract infection and lower urinary tract symptoms such as urinary incontinence, frequency, and urgency
- Pelvic trauma or surgery



### **Prescribed and Recreational Drug Use Assessment**

A detailed list of all medications taken in the past year should be obtained, including vitamins and supplements. Prescribed and recreational substances associated with male sexual dysfunction can be assessed with inquiry by drug class [17; 74]:

- Antidepressants
- Antipsychotic (neuroleptic) agents
- Lipid-lowering agents
- 5 $\alpha$ -R inhibitors
- Anabolic steroids
- Antihypertensive drugs
- Tobacco, alcohol, cannabis, and/or other recreational/illicit drugs

### **Psychological History**

Current or past history of psychiatric illness, diagnoses, and treatment should be obtained, as well as current or past contact with counselors, therapists, or other mental health practitioners. The reason for the contact and extent the concern was resolved should also be explored [76].

Significant stressors in the family, relationship, or work environment should be explored to assess patient psychological state, with particular attention to [74; 123]:

- Indications of depression
- Loss of libido
- Problems and tension in the sexual relationship
- Insomnia
- Lethargy
- Moodiness
- Stress from work or other sources

In patients with clinical depression, a two-question depression scale is recommended [74; 123]:

- During the past month, how often have you felt really down, depressed, or hopeless?
- During the past month, have you often been bothered by little interest or pleasure in doing things?

It is especially important to have the patient explain his own interpretation of the problem. To this end, questions such as the following may be asked:

- Did the onset of sexual dysfunction coincide with a specific event, such as a major operation or a divorce? Have you experienced the death of a spouse or family member?
- Do you have diminished sexual desire? If so, for how long? Is your diminished sexual desire a primary symptom, or is it a reaction to poor sexual performance?
- Do you experience performance anxiety?

Pure psychogenic ED is uncommon and is characterized objectively by the presence of good nocturnal and morning erections and negative findings on all other tests. However, a psychogenic component is usually present in men with organic ED. A history of highly variable erection function suggests a psychogenic cause.

Studies show that as the severity of depression increases, there is a decrease in libido and sexual satisfaction [124]. Loss of sexual interest and desire is the core feature of MHSDD and a common symptom of major depression. All patients with sexual interest and desire complaints should be screened for depression [4].

## PHYSICAL EXAMINATION

A physical examination should be performed for all patients with sexual complaints, with focus on genitourinary, endocrine, vascular, and neurologic systems. A genital examination is recommended and is essential with a history of rapid onset of pain during sex, penile deviation during erection, symptoms of hypogonadism, and current or past history of other urologic symptoms [76]. The physical exam should involve the following minimal exploration [120; 125]:

- Blood pressure
- Peripheral pulses
- Sensation
- Status of genitalia and prostate
- Size and texture of testes
- Presence of epididymis and vas deferens
- Any penile abnormalities, such as hypospadias or Peyronie disease
- Presence of lower urinary tract conditions

During the physical examination, unsuspected diagnoses may be revealed, such as Peyronie disease, prostatic enlargement or irregularity/nodularity, or signs and symptoms suggesting primary hypogonadism (e.g., small testes, altered secondary sexual characteristics). Referral for specialist evaluation is indicated in these cases. All patients older than 40 years of age should receive a digital rectal examination. Blood pressure and heart rate should be measured if they have not been assessed in the previous three to six months. Patients with cardiovascular disease require particular attention [74; 76; 125].

Because ED is a known marker of underlying cardiovascular disease in otherwise asymptomatic patients, men with unexplained ED should receive a thorough evaluation for cardiovascular risk factors. Men diagnosed with cardiovascular disease should be asked about ED as part of routine surveillance and management [76]. ED can improve screening sensitivity for asymptomatic cardiovascular disease in men with diabetes, and patients with diabetes should be asked about ED annually [74].

## QUESTIONNAIRES

Knowledge of the most widely used assessment and outcome measures in studies of male sexual dysfunction allows for better understanding of available research [126; 127; 128; 129; 130]. In the clinical diagnosis of ED, for example, the most commonly used tools are the Sexual Health Inventory for Men (SHIM) (score  $\leq 21$ ) and the International Index of Erectile Function (IIEF) (erectile function domain score  $\leq 25$ ). There are a variety of tools available to assess treatment response depending on the specific dysfunction and affected domain(s) (*Table 1*).

Validated questionnaires can be useful for obtaining objective data related to male sexual dysfunction and/or associated psychosocial concerns to assist clinicians in assessment and diagnosis.

### The International Index of Erectile Function

Widely used in clinical research and clinical practice, the IIEF is considered the criterion standard assessment instrument for ED [131]. This 15-question instrument evaluates five domains: erectile function, orgasmic function, sexual desire, intercourse satisfaction, and global satisfaction [132; 133].

A shorter version of the IIEF, the IIEF-5, was developed as a sexual health inventory for men and is useful for screening patients for ED. The IIEF-5 asks the patient the five questions below, as applied to the previous six months. Answers to the five questions are scored on a 0–5 scale. A score of 25 is typical in healthy men; a score  $\leq 11$  indicates moderate-to-severe ED [133; 134]:

- How do you rate your confidence that you could achieve and maintain an erection?
- When you had erections with sexual stimulation, how often were your erections hard enough for penetration?
- During sexual intercourse, how often were you able to maintain your erection after you had penetrated your partner?
- During sexual intercourse, how difficult was it to maintain your erection to the completion of intercourse?
- When you attempted sexual intercourse, how often was it satisfactory for you?

TREATMENT RESPONSE MEASURES	
Tool	Designed to Measure
International Index of Erectile Function (IIEF)	ED treatment response
Sex Effects Questionnaire (SEQ)	Male sexual dysfunction response
Self-Esteem and Relationships (SEAR) questionnaire	Changes in self-esteem during PDE5I therapy (discerns attribution of change to improvements in ED or in concomitant comorbidity)
Ageing Males' Symptoms (AMS) Score	Changes in mood and quality of life with testosterone therapy
Hospital Anxiety and Depression Scale	
Global Assessment Question (GAQ)	
Index of Sexual Life (ISL)	Changes in quality of sexual life of women with partners with ED
Intravaginal ejaculatory latency time (IELT)	PE treatment response, in time from vaginal penetration to intravaginal ejaculation
PDE5I = phosphodiesterase type 5 inhibitor.	
Source: [126; 127; 128; 129; 130]	

Table 1

### The Sexual Encounter Profile

Commonly used in pharmacotherapy trials for ED, the Sexual Encounter Profile (SEP) is a diary maintained after each sexual attempt. A series of yes/no questions regarding specific aspects of each encounter are asked [133; 135]:

- Were you able to achieve at least some erection (some enlargement of the penis)?
- Were you able to insert your penis into your partner?
- Did your erection last long enough for you to complete intercourse with ejaculation?
- Were you satisfied with the hardness of your erection?
- Were you satisfied overall with this sexual experience?

### The Global Assessment Question

The Global Assessment Question (GAQ) also has been used in clinical trials. The GAQ asks the following questions [133; 136]:

- Has the treatment you have been taking improved your erectile function?
- If yes, has the treatment improved your ability to engage in sexual activity?

### The Psychological and Interpersonal Relationship Scales

The Psychological and Interpersonal Relationship Scales (PAIRS) questionnaire measures the broader psychological and interpersonal outcomes concerning sexual dysfunction (specifically ED) and its treatment with three domains: sexual self-confidence, time concerns, and spontaneity. Patients rate their agreement or disagreement with a specific statement on a scale of 1 (strongly disagree) to 4 (strongly agree) [133; 137].

### The Self-Esteem and Relationship Questionnaire

The Self-Esteem and Relationship Questionnaire (SEAR) measures psychosocial outcomes in patients with ED by 14 items assessing two domains: sexual relationship and confidence. The confidence domain has two subscales: self-esteem and overall relationship [133; 138].

### The Erectile Dysfunction Inventory of Treatment Satisfaction

The Erectile Dysfunction Inventory of Treatment Satisfaction (EDITS) assesses patient satisfaction with their ED treatment. For each question, satisfaction is rated on a scale of 0 (extremely low treatment satisfaction) to 4 (extremely high treatment satisfaction) [133; 139].

## LABORATORY INVESTIGATIONS

Laboratory evaluation may be unnecessary for specific male sexual dysfunction diagnoses, but it can be a valuable window of opportunity for detecting potentially serious comorbidity that should not be missed. As noted, all men older than 30 years of age with ED should be considered at increased risk of cardiovascular disease, and evaluation of fasting plasma glucose level, serum creatinine, and plasma lipid levels is required [89]. Most laboratory testing is tailored to patient complaints and risk factors, but all patients should receive the following tests [74; 76]:

- Fasting glucose, hemoglobin A1c, and lipid profile (if not recently assessed)
- A morning sample of total testosterone:
  - If indicated, bioavailable or free testosterone should be assessed to corroborate total testosterone level.
  - Sexual function poorly correlates with total testosterone >350 ng/dL.

Urinalysis is also recommended. Presence of red blood cells, white blood cells, protein, or glucose can provide important evidence of a genitourinary disorder. Additional tests for selected patients include [74; 89]:

- Prostate-specific antigen, for detection or suspicion of prostate cancer and in all patients considered for testosterone therapy
- Prolactin and luteinizing hormone (LH) tests when low testosterone levels are detected
- Testosterone levels in all cases of phosphodiesterase 5 inhibitor (PDE5I) non-response

## Hormonal Testing

### Testosterone

Serum testosterone testing can be useful in patients with decreased sexual interest, delayed ejaculation, reduced ejaculate volume, PDE5I failure, or diabetes-related ED [119]. Testosterone level is measured to

identify hypogonadism, defined by the American Urological Association (AUA) as biochemically low testosterone levels and the presence of a cluster of symptoms including male sexual dysfunction and impairments in mood, energy, and body composition [140]. The prevalence of biochemical hypogonadism in middle-aged men is 2.1% to 12.8%, and the prevalence of low testosterone and hypogonadism symptoms in men 40 to 79 years of age is 2.1% to 5.7%. Hypogonadism rates are higher in men who are older, who are obese, with medical comorbidities, and/or with poor health status [30].

Serum total testosterone circulates as unbound or free total testosterone (2% to 3%) or bound to sex hormone-binding globulin (SHBG) (44%), albumin (50%), or corticosteroid-binding globulin (CBG) (4%). SHBG-bound testosterone is not bioavailable, but testosterone is weakly bound to CBG and albumin and easily and rapidly dissociates from both [141]. As such, bioavailable total testosterone refers to the sum of total testosterone that is CBG-bound, albumin-bound, and free. This represents the total testosterone fraction that is available to cells, but it should not be confused with cellular and tissue bioavailable total testosterone that bind to androgen receptors to produce androgenic action [141].

Professional organizations and regulatory agencies disagree over the serum testosterone levels that define hypogonadism, low testosterone, or the threshold for testosterone therapy. The FDA uses a cut-off total testosterone value of 300 ng/dL to define hypogonadism for clinical trials and drug development [141]. A consensus statement by several European and North American urology and andrology organizations recommends that treatment is not necessary for total testosterone >350 ng/dL [142]. This group concluded that total testosterone <230 ng/dL (with symptoms) may require testosterone therapy, and that total testosterone levels 230–350 ng/dL require repeat total testosterone measurement, use of SHBG values to calculate free testosterone, or direct measurement of free testosterone by equilibrium dialysis [142].



The AUA stresses that biochemical and clinical parameters are equally important as indicators of hypogonadism and that rigid interpretation of testosterone ranges should not dictate decisions concerning patient care. Rigid adherence to a predetermined cut-off value, such as 300 ng/dL, can lead to unnecessary treatment of asymptomatic men and treatment withheld from persistently symptomatic men. However, they note that free or bioavailable testosterone levels can help diagnose biochemical hypogonadism, especially with equivocal total testosterone values or lack of signs and symptoms. With free testosterone, values <65 ng/mL can support testosterone therapy [141].

A systematic overhaul is underway for analytic methods used in testosterone measurement. Some laboratories now use reliable and valid assays, but many still use older, less reliable assays. Potentially unreliable lab results and fluctuation in serum testosterone levels from diurnal, seasonal, and age-related temporal factors can complicate patient care and impose a risk of non-payment by insurance carriers that often require serum total testosterone <300 ng/dL for reimbursement. The AUA states that no patient should be denied coverage for testosterone treatment based solely on payer-defined cut-offs when clinical need for the treatment is established [141].

### ***Luteinizing Hormone***

LH levels vary according to physiologic requirements for testosterone. The hypothalamus regulates testosterone levels by releasing or inhibiting LH-releasing hormone, which activates pituitary production and release of LH. With a high LH level and a low testosterone level, primary testicular (Leydig cell) failure is suggested. Low levels of both LH and testosterone suggest a central defect [74].

### ***Thyroid-Stimulating Hormone***

Thyroid-stimulating hormone evaluation is appropriate in selected patients with ED or loss of sexual desire [74].

## **SPECIALIZED INVESTIGATIONS**

Specialized diagnostic tests are generally reserved for use in patients with [74; 76]:

- Primary ED (not caused by organic disease or psychogenic disorder)
- Pelvic or perineal trauma in younger patients who may benefit from vascular surgery
- Penile deformities that may need surgical correction
- Complex psychiatric or psychosexual disorders
- Complex endocrine disorders

### **Psychological/Psychiatric Assessment**

Psychological assessments can provide important insight into psychosocial contributors to or causation of male sexual dysfunction. Findings may also guide psychological therapy selection and treatment goals, such as reducing performance anxiety, understanding the context in which the patient or couple functions sexually, modification of sexual scripts through psychoeducation, or improving pharmacotherapy adherence [119; 143].

### **Nocturnal Penile Tumescence Testing**

Erections normally occur during rapid eye movement sleep. Nocturnal penile tumescence testing is used to measure and record nighttime erectile events to differentiate organic from psychogenic sexual dysfunction. Several bands are placed around the penis and connected to a device (e.g., a RigiScan monitor) and worn by the patient for two to three consecutive nights. With occurrence of an erection, the force and duration are measured. Inadequate or absent nocturnal erections suggest organic dysfunction, and a normal result strongly suggests psychogenic etiology [119].

### Vascular Testing

Determination of penile duplex cavernous artery flow after corporal vasoactive injection is commonly used with ultrasound to localize and measure blood flow through the cavernous vessels for assessment of penile circulation. A peak systolic blood flow more than 30 cm/second and a resistance index >0.8 represent normal results and additional vascular investigation is unnecessary. With abnormal findings, further testing involves arteriography and dynamic infusion cavernosometry and cavernosography (DICC), but only in appropriate candidates for vascular reconstructive surgery [144].

DICC is used for assessment of veno-occlusive mechanism function. Penile dye and fluid delivery induce an erection. The rise and fall of intra-penile pressure is measured and visualized to determine if the veno-occlusive mechanism is intact [145].

Arteriography, the most invasive diagnostic test, is usually reserved for high-flow priapism or planned vascular bypass. Penile angiogram visualizes the penile circulation to guide embolization in penile injury [146].

### Prostaglandin E1 Injection

Prostaglandin E1 (PGE1) may be injected into the corpus cavernosum to evaluate penile function. An erection developing within minutes indicates adequate penile vasculature and, depending on quality of the erection, establishes PGE1 injection as a therapeutic option [74].

### DIFFERENTIAL DIAGNOSES

As discussed, numerous substances, diseases, and conditions may account for the signs and symptoms of ED and PE. Excessive expectations by men with normal erectile and ejaculatory latency function should also be considered in the diagnostic process.

### ROLE OF THE PRIMARY CARE PROVIDER

Primary care providers are usually the first healthcare system contact by patients seeking help for sexual problems and play an essential role that includes [9]:

- Initial recognition and evaluation of undiagnosed signs, symptoms, or health concerns
- Health promotion through disease prevention, health maintenance, counseling, patient education, chronic illness management, and patient advocacy
- Coordination of care that promotes effective communication with patients and patient encouragement to be a partner in health

Primary care providers are ideally suited for assisting patients with sexual concerns, often with the value of personal, long-term patient relationships. The multifactorial contributors to sexual dysfunction can be appropriately evaluated by primary care providers, and the routine, long-term follow-up in primary care can help ensure the resolution of a sexual dysfunction.

An important responsibility of primary care providers is to identify sexual dysfunction and assist patients in feeling comfortable about getting help in the primary care clinic or through specialist referral. Primary care providers can normalize and universalize inquiry into sexual concerns, use screening questions to identify sexual dysfunction, and initiate assessment and treatment planning [9].

### Effective Patient Engagement

Many healthcare professionals are uncomfortable initiating discussion of patient sexual functioning, in many cases due to inadequate education, training, knowledge, skills, and confidence. A 2010 study showed that fewer than 50% of U.S. medical schools offer sexual health curricula [147]. A 2018 study sought to quantify the sexual health knowledge of undergraduate medical students. A 32-question survey evaluated six areas of knowledge: sexual function and dysfunction; fertility and reproduction; sexuality across the lifespan; sexual minority

health; society, culture, and behavior; and safety and prevention [148]. The 1,014 survey respondents scored an average of 66% correct, with the lowest scores (49% correct) on questions regarding safety and prevention and the highest scores (75% correct) on questions regarding sexuality across the lifespan [148]. Primary care providers understand the importance of sexual health but may avoid initiating discussion due to limited time, expertise, comfort, compensation, or litigation concerns. Men with sexual dysfunction are frequently reluctant to discuss their sexual problems and must be specifically asked. When clinicians fail to open the dialogue, sexual dysfunction remains unaddressed [119; 149].

Clinician awareness of patient comfort level is vital, given the highly sensitive nature of the presenting problem. Patient history-taking gives clinicians the opportunity to provide education about the sexual dysfunction and its treatment to patients and their partners, facilitate communication, and establish rapport. Validated psychometric questionnaires can be valuable for obtaining information that patients may be reticent in disclosing [119].

### SPECIALIST REFERRAL

Although most men with sexual dysfunction are successfully diagnosed and managed by their primary care physician, urologist referral remains an essential option in the following situations [51; 119]:

- Difficult-to-treat, oral-refractory dysfunction
- Second-line intracavernous or intraurethral vasoactive therapy, when outside the primary care practice pattern
- Peyronie disease or post-trauma penile deformity that contributes to the sexual dysfunction
- Severe vascular disease or poorly controlled diabetes
- ED resulting from congenital venous leak
- Patient or partner request for specific tests performed by urologists
- ED treatment in men with prostate cancer diagnosis

## TREATMENT

Following assessment and diagnosis, management options should be discussed with the patient to seek the best solution. Options are now available such that, regardless of etiology, every man who wishes to be sexually active can do so. As discussed, patients benefit when education, sexual counseling, partner involvement, and/or psychological therapy is combined with pharmacotherapy. Sexual dysfunction can be all-consuming and demoralizing and can invite fixation on restoration of normal sexual function. One treatment challenge is teaching men that sex entails more than achieving and maintaining an erection or delaying ejaculation [64].

### ERECTILE DYSFUNCTION

Before treating ED, reversible underlying causes should first be addressed [76]. This includes:

- Hormonal abnormalities (e.g., hyperthyroidism/hypothyroidism, hyperprolactinemia, hypogonadism)
- Post-traumatic arteriogenic ED in young patients
- Substance-induced ED

A tiered approach for ED treatment based on level of invasiveness is recommended by the British Society for Sexual Medicine, the Canadian Urological Association, the American College of Physicians, the European Association of Urology, and the AUA [74; 76; 119; 120; 150]. First-line therapy with oral PDE5Is is universally recommended in patients without contraindications. Also, vacuum erection devices may be a viable first option. Second-line therapy consists of intracavernous injection or intraurethral alprostadil, and third-line therapy involves penile prostheses.

## Phosphodiesterase Inhibitors

Phosphodiesterase inhibitors act through cGMP-specific PDE type 5 inhibition. PDE5 degrades cGMP in the corpus cavernosum, and the rates of PDE synthesis and degradation regulate tissue concentrations of cGMP. In the corpus cavernosum, PDE5 is the most prevalent cGMP-specific PDE, and PDE5Is enhance erectile function by increasing cGMP [52].

Sildenafil, vardenafil, tadalafil, and avanafil are PDE5Is FDA-approved for treating ED, and their safety and efficacy is established. All have efficacy rates around 60% to 70%, with lower rates in patients with severe neurologic damage, post-radical prostatectomy ED, diabetes, and severe vascular disease [151]. PDE5I selection is guided by intercourse frequency and patient preference [52; 74; 152].

Initially, PDE5Is were approved for on-demand use. Tadalafil is also approved for daily use of 2.5–5 mg in patients anticipating sexual activity more than twice per week [24]. This regimen may be more cost-effective in this context, and a marked reduction in adverse events has been suggested [76].

Vardenafil and sildenafil are also available in orodispersible tablet formulation, which offers improved convenience that patients may prefer over the oral tablet. Absorption of the agents in orodispersible tablet form is unaffected by food ingestion, and the bioavailability is improved relative to oral tablets. Safety and efficacy are equivalent between the vardenafil and sildenafil formulations [24; 153; 154; 155].

Efficacy and side effect differences between PDE5Is reflect the varying enzymatic selectivity and pharmacokinetic properties. Sildenafil and vardenafil are cross-reactive for PDE6, and dominant PDE6 expression in the retina helps account for side effects of visual disturbance (<2% of patients) with both drugs. Tadalafil cross-reacts with PDE11; while expressed in cardiac tissue, the testes, and the ante-

rior pituitary, complications from PDE11 inhibition are unknown [52]. Possible long-term consequences of visual disturbance side effects are concerning and were evaluated in 277 patients with pulmonary arterial hypertension associated with connective tissue disease or following congenital heart disease repair. Sildenafil up to 80 mg three times per day for  $\geq 18$  months was not associated with visual change and did not show adverse effects on best corrected visual acuity, contrast sensitivity, color vision, visual field, slit lamp examinations, funduscopy, or intraocular pressure during the study period [156].

## Pharmacokinetic Differences

The clinical effect of PDE5Is is influenced by pharmacokinetic properties that include bioavailability, maximum plasma concentration ( $C_{max}$ ), time duration to reach  $C_{max}$  ( $T_{max}$ ), and time required to eliminate half the drug from plasma ( $t_{1/2}$ ) (Table 2) [157]. Sildenafil, vardenafil, and avanafil have broadly similar  $T_{max}$ , which predicts a similar time of onset of action. The  $t_{1/2}$  value of tadalafil is longer than other PDE5Is, possibly from slower intestinal absorption and/or hepatic degradation. The extended  $t_{1/2}$  of tadalafil provides a longer therapeutic effect. The  $C_{max}$  of vardenafil is significantly lower than with sildenafil and tadalafil, likely from lower bioavailability [157]. PDE5Is are degraded in the liver, and interactions with the CYP3A4 inhibitor ketoconazole, for example, may prolong their effect duration. PDE5I duration of effect is inconsistently associated with elimination rate from plasma. Molecular mechanisms that can contribute to this have been suggested [158]. Thus, there may be a persistence of biochemical effects after the inhibitor is cleared from cells (i.e., memory effect). Because inhibitors bind tightly to PDE5 in muscle cells, for example, this could significantly retard their exit from these cells and prolong their effects [52; 158].



PHARMACOLOGIC CHARACTERISTICS OF PDE5Is <sup>a</sup>				
Characteristic	Sildenafil 100 mg	Vardenafil 20 mg	Tadalafil 20 mg	Avanafil 200 mg
Bioavailability (oral)	38% to 41%	15%	≥36%	85% to 94%
T <sub>max</sub> median (range)	60 minutes (30 to 120 minutes)	60 minutes (30 to 120 minutes)	120 minutes (30 to 360 minutes)	30 to 45 minutes
Maximal concentration	560 mcg/L	20.9 mcg/L	378 mcg/L	2,600 ng/mL
Reduction of maximal concentration after a fatty meal	29%	18%	No effect	39%
Plasma elimination half-life	3 to 5 hours	4 to 5 hours	17.5 hours	5.3 to 10.6 hours
CYP450 isoenzyme	3A4, 2C9	3A4	3A4	3A4
Active metabolite	Yes	Yes	None	Negligible
Consider dose adjustment with:	Age older than 65 years Hepatic or renal impairment Concurrent use of potent 3A4 inhibitors (e.g., ritonavir, erythromycin) Concurrent cimetidine	Age older than 65 years Hepatic or renal impairment Concurrent use of potent 3A4 inhibitors (e.g., ritonavir, erythromycin)	No adjustment for age older than 65 years in the absence of hepatic or renal impairment Hepatic or renal impairment Concurrent use of potent 3A4 inhibitors (e.g., ritonavir, erythromycin)	Unneeded in patients older than 65 years of age
Absolute contraindications	Regular or intermittent use of organic nitrates			
Use with $\alpha$ -blockers	Risk for significant hypotension with concurrent use of non-selective $\alpha$ -blockers			
<sup>a</sup> Under fasting conditions T <sub>max</sub> = time-to-maximum plasma concentration.				
Source: [52; 74; 119; 159; 160]				Table 2

### Tolerability and Safety

Adverse events common to PDE5Is include headache, flushing, dyspepsia, nasal congestion, and dizziness (**Table 3**) [74; 160; 161]. Tadalafil may cause back pain/myalgia in up to 6% of patients. Adverse events are generally mild in nature, usually resolve with continuous use, and resulted in few dropouts in clinical trials. PDE5Is are considered safe in patients with cardiovascular disease, and PDE5Is do not adversely affect total exercise time or time to ischemia during exercise testing in men with stable angina [162]. PDE5Is may even be beneficial in cardiovascular disease, and sildenafil has been approved for treatment of pulmonary arterial hypertension [52; 163].

Clinical trial results and post-marketing data of sildenafil, tadalafil, and vardenafil have demonstrated no increase in myocardial infarction rates in patients receiving PDE5Is compared to expected rates in age-matched male populations [74]. Sildenafil does not alter cardiac contractility, cardiac output, or myocardial oxygen consumption according to available evidence. Chronic or on-demand use is well-tolerated, with a similar safety profile [74]. Single-dose avanafil 100 mg and 800 mg in healthy male subjects did not cause significant changes in QTc interval or ventricular repolarization [160].

PREVALENCE OF COMMON ADVERSE EVENTS WITH PDE5Is				
Adverse Event	Sildenafil	Vardenafil	Tadalafil	Avanafil
Headache	16%	14.5%	23%	6.5%
Flushing	14%	9.5%	7.5%	6.5%
Dyspepsia	10%	4%	6%	—
Nasal congestion	6%	3%	9.5%	2%
Dizziness	3%	2%	<2%	1.5%
Abnormal vision	6%	<2%	<1%	—
Back pain	3.5%	—	6%	2%
Myalgia	4.5%	—	7.5%	—
Nasopharyngitis	6.5%	—	—	3%

Source: [24; 74; 160; 161] Table 3

### Drug-Drug Interactions

Use of nitrates are absolutely contraindicated in all patients taking PDE5Is due to potentially severe hypotension resulting from cGMP accumulation. Organic nitrates include nitroglycerine, isosorbide mononitrate, isosorbide dinitrate, and other nitrate preparations used to treat angina [24]. Amyl nitrite or butyl nitrate (“poppers”) used recreationally are also dangerous [74].

Duration of interaction between organic nitrates and PDE inhibitors varies according to the specific agents involved. If a patient develops angina while using a PDE inhibitor, other anti-angina agents should be used instead of nitroglycerin until at least 24 hours after the last dose of sildenafil or vardenafil, at least 48 hours after the last dose of tadalafil, and at least 12 hours after the last dose of avanafil [24; 74; 162].

In general, the adverse effect profiles of PDE5Is are not amplified by antihypertensive medications, even in patients taking several antihypertensive agents [74]. However, all PDE5Is interact to some degree with  $\alpha$ -blockers, possibly resulting in orthostatic hypotension under certain conditions [164; 165]. Sildenafil should be used cautiously in patients prescribed  $\alpha$ -blockers (especially doxazosin). Hypotension is most likely to occur within four hours of  $\alpha$ -blocker use. The recommended sildenafil starting dose is 25 mg in these patients [24]. Var-

denafil should be initiated only when the patient has reached dose stabilization on  $\alpha$ -blocker therapy. Concurrent vardenafil and tamsulosin therapy is not associated with significant hypotensive effect. Tadalafil amplifies the hypotensive properties of doxazosin but not tamsulosin 0.4 mg. Single-dose avanafil 200 mg combined with stable-dose doxazosin or tamsulosin lacks appreciable effect [160].

Alcohol and PDE5Is both act as mild vasodilators, and the blood pressure-lowering effects of each compound may be synergistic with concurrent ingestion. Significant alcohol consumption (more than three standard drinks) combined with PDE5Is can increase the potential of orthostatic signs and symptoms, including increased heart rate, decreased standing blood pressure, dizziness, and headache [24; 160].

PDE5Is are substrates of, and predominantly metabolized by, CYP3A4, and drugs that inhibit the CYP3A4 pathway will inhibit the metabolic breakdown of PDE5Is [160]. Strong CYP3A4 inhibitors can substantially increase systemic exposure, maximum blood concentration, and half-life of single-dose PDE5Is. As such, PDE5Is should not be used in patients taking strong CYP3A4 inhibitors, including ketoconazole, itraconazole, clarithromycin, nefazodone, ritonavir, saquinavir, nelfinavir, indinavir, atazanavir, and telithromycin [24; 160].

Moderate CYP3A4 inhibitors are likely to increase PDE5I exposure, and patients taking concomitant moderate CYP3A4 inhibitors should only be prescribed lowest-dose PDE5Is no more than once every 24 hours. Moderate CYP3A4 inhibitors include erythromycin, amprenavir, aprepitant, diltiazem, fluconazole, fosamprenavir, and verapamil. Other CYP3A4 inhibitors, such as grapefruit juice, are likely to increase avanafil exposure [160].

Drugs that act as CYP3A4 inducers, including rifampin, phenobarbital, phenytoin, and carbamazepine, can accelerate PDE5I metabolism and elimination. In patients taking these medications, higher doses of PDE5Is may be required [160].

### **PDE5I Non-Response**

Guidelines recommend at least six maximum-dose PDE5I trials with sexual stimulation before classifying a patient as a non-responder [74]. The most common reasons for PDE5I nonresponse are incorrect drug use (e.g., failure to take an adequate dose, failure to engage in sexual stimulation) or lack of efficacy. Non-response management depends on identifying the underlying cause [74]. Inadequate counseling is a common cause of incorrect PDE5I use, and patient education may salvage apparent non-response by addressing dose, timing, and need for sexual stimulation. It is also important for patients to be aware of the window of efficacy after ingestion and initiation of sex. For sufficient effect, most patients need to wait 60 minutes after taking sildenafil and vardenafil and 120 minutes after tadalafil. Sildenafil absorption is delayed by a meal, and vardenafil absorption may be delayed by a fatty meal. The normal efficacy window is 6 to 8 hours for sildenafil and vardenafil and up to 36 hours for tadalafil [74].

In patients using PDE5Is correctly, switching agents may lead to patient response. While not approved for daily use independent of regular on-demand use, daily sildenafil or vardenafil dosing may salvage some non-responders to intermittent dosing [74; 76]. In patients with hypogonadism, normalizing testosterone may improve PDE5I response. Patients should also be questioned regarding where they obtain their medications, as illicitly obtained PDE5Is may differ in purity or dose [74].

Adequate sexual stimulation is necessary for PDE5I efficacy because the drugs' action is dependent on release of nitric oxide by parasympathetic nerve endings in penile erectile tissue. The usual trigger for nitric oxide release is sexual stimulation, but some patients may incorrectly believe that the drugs act independent of any stimulation [74].

Some patients preferentially respond to specific PDE5Is. A randomized controlled trial of sildenafil and tadalafil non-responders found 17% and 14% response rates, respectively, after switching to the alternate PDE5I [166]. This may be due to pharmacokinetic variation between the two drugs, but with identical mechanism of action, the possibility is raised of an unidentified mechanism that contributes to preferential PDE5I response [74].

Another option, cabergoline, was evaluated in 402 patients with ED (21 to 59 years of age) who were not responding to sildenafil. Following weekly dosing at 0 mg or 0.5–1 mg for six months (92% study completion rate), mean improvements from baseline included weekly intercourse episodes (45.5% cabergoline, 15% placebo), IIEF intercourse satisfaction domain scores (+50% cabergoline, -9% placebo), and IELT (51.4% cabergoline, 16% placebo). Adverse events (12.2% versus 2.0%) and withdrawals due to adverse events (5.9% versus 1.01%) were more frequent with cabergoline [167]. In the United States, cabergoline is approved for use in the treatment of hyperprolactinemia [24].

### **Efficacy of PDE5Is in Subpopulations**

Clinical trials have further evaluated efficacy, safety, or tolerability with PDE5Is in general ED populations or in subgroups with comorbid medical or psychiatric conditions. PDE5Is are effective in men with ED and untreated depression and in antidepressant-induced ED. Sildenafil efficacy (0 mg or 25–100 mg for six weeks) was assessed in 202 men with ED and mild-to-moderate untreated depressive symptoms (not major depressive disorder). At baseline screening, men with ED were more likely to have depression compared with men without ED, and ED severity was a predictor of depression. Compared with placebo, sildenafil led to significantly greater changes from baseline in Beck Depression Inventory-II scores and significant improvement in all IIEF domains and Sex Effects Questionnaire components. Adverse events were mild and consistent with PDE5I therapy [126].

ED is associated with significant loss in quality of life and self-esteem. In one study, 841 patients with ED received sildenafil (0, 25, 50, or 100 mg) for 14 weeks to assess self-esteem changes and their causality during sildenafil therapy. Patients receiving sildenafil showed significantly greater changes (versus placebo) in all SEAR component and IIEF domain scores. This finding was maintained in all subgroups with ED comorbidities of hypertension, hyperlipidemia, benign prostatic hypertrophy, or depression. In patients receiving sildenafil, a highly significant correlation was found between improvements in self-esteem subscale scores and erectile function domain scores. The physiologic and emotional benefits of sildenafil treatment of ED were confirmed overall and in men with common ED comorbidities [127].

### **Partner Effect**

Initiation of sildenafil at 50 mg or 100 mg was assessed for effects on the sexual experience and anxiety level anticipating the next intercourse attempt. After 12 weeks, 56% receiving 100 mg and 39% receiving 50 mg reported no anxiety concerning

the next intercourse attempt. Changes in functional scores from baseline were comparable. Measures of treatment satisfaction and sexual experience significantly favored those receiving 100 mg, and adverse events were not increased with the higher dose. The authors conclude that sildenafil 100 mg can be initiated instead of titrated, based on anxiety-reduction benefits and tolerability [128].

Partners' quality of sexual life is strongly impaired by ED, and their involvement in ED treatment is important for adherence and long-term efficacy but remains difficult. Without concurrent sex therapy, open-label sildenafil treatment of ED was assessed using the Index of Sexual Life (ISL) for impact on female partners in 67 couples. After 14 weeks, women showed a 79.0% positive response rate. Mean sex life satisfaction scores increased 40% from baseline, and a significant correlation was found between final scores on ISL sex life satisfaction, IIEF erectile function, and SEAR confidence domain. Both partners reported high levels of treatment satisfaction [129].

### **Phentolamine**

Early trials of phentolamine showed some success in patients with nonspecific ED, and it became viewed as a promising oral “on-demand” approach for ED treatment. A review of randomized, double-blind, placebo-controlled trials of oral phentolamine in ED found the mean change in erectile function was significantly higher with active drug (40 mg and 80 mg) than placebo, with three to four times as many patients on phentolamine reporting being satisfied or very satisfied (versus placebo). At 40-mg and 80-mg doses, 55% to 59% of men achieved vaginal penetration. ED was resolved or improved in 53% of men with 80 mg and 40% with 40 mg. All responses were consistent regardless of concomitant medication, and there were no severe adverse events. The most common side effects were nasal congestion (10%), headache (3%), dizziness (3%), and tachycardia (3%). Although phentolamine is concluded to be safe, well-tolerated, and efficacious as ED treatment,



it has not yet received FDA approval for this indication [24; 52; 64; 168; 169]. Intracavernous injections of phentolamine are a mainstay of the second-line treatment of neurogenic sexual dysfunction and have been found to be highly successful in the spinal cord injury population [76; 170].

### **Yohimbine**

Yohimbine, a bark extract, is a selective  $\alpha$ 2-blocker with central and peripheral effects and has been used as ED treatment for more than a century. In studies, yohimbine was found modestly more effective than placebo [171]. Orally administered yohimbine may benefit some patients with ED, and there has been renewed interest in this agent, particularly when combined with an oral PDE5I. Yohimbine is considered safe with few known adverse effects, and typical dosing is one tablet (5.4 mg) taken three times per day [52].

### **Sublingual Apomorphine**

Apomorphine (APO) is a dopamine D1- and D2-receptor agonist with higher affinity for D2 and is absorbed through the oral mucosa to produce erection [52]. The overall results of five clinical trials with sublingual APO 2 mg and 3 mg showed statistically significant improvements (versus placebo) in erectile function. Sublingual APO efficacy is weakly dose-related, and limited efficacy in patients with organic ED has led to suggestions that APO was best suited for mild ED [172; 173]. Subsequent comparisons between sublingual APO and sildenafil found sildenafil more effective and preferred by patients.

Significant tolerability or safety issues seem lacking. Adverse events of nausea, headache, dizziness, and yawning are more frequent with sublingual APO than placebo. Two trials suggested that APO did not differ from placebo in serious adverse events [172; 173]. Because of sildenafil's superiority, sublingual APO never reached broad acceptance and is not FDA-approved for treatment of ED [24; 52].

### **Trazodone**

Trazodone is an antidepressant drug that selectively inhibits central 5-HT uptake and increases central dopamine transmission without peripheral norepinephrine reuptake inhibition. Positive clinical results have been reported but have not been replicated in controlled trials [52]. However, trazodone may have some efficacy in men with ED who are anxious or depressed. Pilot studies found trazodone beneficial in SSRI-induced sexual dysfunction and in psychogenic ED when combined with sildenafil [52; 174; 175]. The most frequent side effects are sedation and headache [17].

### **Cabergoline**

A four-month study of cabergoline (0.5 mg/day) in 50 men with psychogenic ED found the drug to be well tolerated. With cabergoline (but not placebo), hormone levels normalized in most patients; significant interactions were observed between serum prolactin and testosterone levels and improvements in erectile function, sexual desire, and orgasmic function. Patient and partner sexual satisfaction were also enhanced. Mean improvement from baseline in IIEF erectile function domain score was 41% higher with cabergoline than with placebo [176]. A 2015 survey of sexual health providers demonstrated an overall treatment success of 40%, with most providers commonly using cabergoline, bupropion, or oxytocin [177]. However, this survey measured only anecdotal results; there was no proven efficacy or superiority of any drug due to a lack of placebo-controlled, randomized, blinded, comparative trials [72].

### **Intranasal Bremelanotide**

Bremelanotide is a synthetic heptapeptide with strong binding affinity and agonist action with melanocortin receptor 4, and several trials have evaluated intranasal bremelanotide in the treatment of ED [178]. In healthy volunteers without use of visual sexual stimulation (erotic films), significantly increased erectile activity was found, with duration of erections with rigidity approximately 140 minutes

with 20 mg bremelanotide versus 21 minutes with placebo [179]. In men with mild-to-moderate ED, bremelanotide 20 mg with visual sexual stimulation increased erectile activity three-fold and significantly increased duration of erection and penile rigidity [179]. In patients with ED, comparison of sildenafil 25 mg alone versus sildenafil 25 mg plus bremelanotide 7.5 mg found the combination resulted in significantly prolonged time of increased base rigidity (>60%) over the 2.5 hour trial. The combination was well tolerated, without significantly increased side effects over sildenafil or bremelanotide alone [180; 181]. No serious side effects have been reported in healthy or ED subjects [52].

It is important to note that these studies involved no more than 32 subjects. Bremelanotide may have clinical efficacy in ED, but larger trials are required to determine efficacy and adverse events before regulatory approval and possible clinical introduction is possible [52]. Bremelanotide is not currently approved for the treatment of MHSDD [24].

### **Intraurethral PGE1 Pharmacotherapy**

The Medicated Urethral System for Erections (MUSE) involves urethral insertion of a small intra-urethral alprostadil suppository [74]. The vasodilator alprostadil is absorbed through the urethral mucosa and into the corpus spongiosum. The drug is then transferred to the corpus callosum to produce retrograde filling of the cavernosal bodies through the deep dorsal vein and its circumflex branches, producing erection [182].

Alprostadil and alprostadil/prazosin combination produce erections in the majority of patients with chronic organic ED [183]. Intraurethral alprostadil has been found to produce full penile enlargement in 75.4% and intercourse success in 63.6% of men with chronic ED [184]. A trial of 1,511 men with chronic ED of diverse organic etiology found successful intercourse in 64.9% with alprostadil versus 18.6% with placebo. Painful erection and urethral burning occur in <10% [185].

Intraurethral alprostadil is a reasonable option when PDE5I are contraindicated or in PDE5I failure, particularly for men with post-prostatectomy ED [120]. Ease of administration makes it preferred in men experiencing difficulty with intracavernosal injections or wishing to avoid self-injections [120]. Intraurethral alprostadil has been successfully used with sildenafil when each agent alone failed [52].

### **Intracavernosal Injection Pharmacotherapies**

Patients lacking oral therapy response may benefit from intracavernosal injection of the vasodilators papaverine, phentolamine, PGE1 (alprostadil), or vasoactive intestinal polypeptide (VIP), alone or in combination [120]. Intracavernosal vasodilator injection directly into the penis relaxes corpus cavernosum smooth muscle to facilitate erection. Optimal dose and combination are tailored, and patients should be instructed in proper technique [52].

#### ***Papaverine***

The introduction of intracavernosal papaverine to the U.S. market in 1993 marked the modern era of clinically effective ED pharmacotherapy. While effective in inducing erections, papaverine is no longer used as monotherapy due to the risks of fibrosis and priapism, but it is highly effective and safer in intracavernosal combination therapy [52; 120].

#### ***Phentolamine***

Intracavernosal phentolamine alone seldom produces a satisfactory erectile response, but is widely used in combination with papaverine or with VIP [52; 74; 120].

#### ***PGE1***

PGE1 is the most widely used agent for intracavernosal delivery and is second-line therapy for PDE5I failure [64; 120]. The optimal dose and combination should be tailored to reach the target of an adequately rigid erection for less than 30 minutes. These medications can be obtained in standard formulation or from a compounding pharmacy with dose and combination specified by the prescribing physician [186].

High efficacy rates are reported, with one study finding 94% of men with ED achieved erections suitable for penetration after PGE1 injection [187]. Sparse data indicate that the rate of improved erections with PGE1 is greater than with papaverine, moxisylyte, linsidomine, sodium nitroprusside, or combined linsidomine plus urapidil, and comparable to papaverine plus phentolamine [74]. PGE1 plus papaverine is superior to PGE1 alone [17].

The rates of penile pain (>10%) with PGE1 are higher than with moxisylyte or papaverine plus phentolamine. Pain is significantly less frequent with slower PGE1 injection and when PGE1 is combined with lidocaine or procaine (but not sodium bicarbonate) [17].

PGE1 is highly effective with normal corpus cavernosum vasculature, but some trials have found high nonresponse rates. The exact cause is unclear, but it is probably due to the increased prevalence of compromised but asymptomatic vascular function in men with ED [52].

### ***Vasoactive Intestinal Polypeptide***

VIP is a potent vasodilator that inhibits contractile activity in many types of smooth muscle and stimulates adenyl cyclase and cAMP formation. Intracavernosal injection of VIP alone does not induce erections, but VIP combined with intracavernosal papaverine or phentolamine has produced full erections in men lacking response to intracavernosal papaverine or papaverine plus phentolamine. Positive findings with VIP plus papaverine with or without phentolamine have been repeated in several trials, including a study of 304 patients with psychogenic ED [188]. VIP plus phentolamine is approved by several European countries for use in ED, but it is not approved in the United States [24; 52].

### **ED Associated with Hormonal Abnormalities**

Underlying hormonal abnormalities substantially elevate the risk of male sexual dysfunction and, if undetected, can result in patient non-response to first-line therapies. Common endocrine system abnormalities include hypogonadism and hyperprolactinemia.

### ***Testosterone Therapy***

Hypogonadism causation should be determined before testosterone is initiated, with baseline assessment and safety monitoring performed in accordance with current authoritative guidelines [29; 30; 150; 189]. Testosterone levels peak around 8:00 a.m., and testosterone measurements should be obtained in the morning, when possible. Elevated serum androgen levels can potentially stimulate prostate growth and increase the risk of activating latent cancer, so all patients receiving testosterone should receive periodic prostate examinations that include digital rectal examination, prostate-specific antigen level, and complete blood count [76].

PDE5Is do not address hypogonadism symptoms (e.g., fatigue, loss of libido) that impair erectile function [190]. In one study, poor PDE5I response was associated with serum testosterone <300 ng/dL; serum testosterone normalization in PDE5I non-responders resulted in improved erectile function and normal PDE5I response [191]. Despite these data, salvaging PDE5I failure with testosterone is controversial [190].

Younger patients with significantly depressed serum testosterone levels should receive testosterone as first-line treatment. Restoration of nocturnal erection should be monitored and, if needed, a PDE5I added at a second stage. In older men with late-onset hypogonadism or borderline testosterone deficiency and chronic ED, PDE5Is should be able to restore sexual function, but any medications affecting testosterone levels should be discontinued and any underlying conditions treated. In these patients, testosterone therapy should be added if testosterone levels remain low, PDE5Is fail to alleviate ED, or signs and symptoms of hypogonadism are evident [10].

Efficacy comparison of different testosterone formulations for improving sexual dysfunction found intramuscular injection to be the least effective for improved erectile function. Transdermal testosterone is more effective in intercourse success and satisfaction when combined with PDE5Is. Testosterone 100 mg gel is more effective than testosterone transdermal in intercourse frequency, and combined testosterone, co-dergocrine, and isosorbide dinitrate cream is more effective than testosterone alone for improved erections and successful intercourse [17]. Side effect comparison found application site skin reactions with transdermal but not gel testosterone, and greater frequency of mild headache with combination testosterone, co-dergocrine, and isosorbide dinitrate cream than cream testosterone [17].

As noted, up to 75% of men with type 2 diabetes experience male sexual dysfunction, particularly ED, and hypogonadism is highly prevalent in men with type 2 diabetes [130]. In the primary care setting, long-acting testosterone undecanoate (0 mg or 1,000 mg) was evaluated in 199 men with hypogonadism (total testosterone  $\leq 12$  nmol/L, free testosterone  $\leq 250$  pmol/L) and type 2 diabetes for a total of 82 weeks. At 30 weeks, IIEF erectile function, intercourse satisfaction, sexual desire, overall satisfaction, and orgasm domain scores significantly improved from baseline with testosterone undecanoate. Benefit began at six weeks, and all IIEF sexual function measures continued to improve significantly up to 18 months. At 30 weeks, 46% of patients receiving testosterone undecanoate (compared with 17% of those receiving placebo) felt treatment had improved their health, which increased to 70% after 52-week open-label therapy. Depression at baseline was associated with markedly lower sexual function and psychological response. Erectile function scores were unchanged at 30 weeks in a subgroup taking PDE5I therapy, but substantially improved after 52-week open-label. Improvement was greatest in less obese, older, and non-depressed patients. There were no significant adverse events. Results suggest that men with type 2 diabetes may require substantially longer testosterone undecanoate trials than the guideline recommendations of three to six months [130].

A separate study found that adding testosterone to sildenafil showed no added benefit beyond sildenafil alone in men without diabetes [192]. Men 40 to 70 years of age with ED and low testosterone (total testosterone  $< 330$  ng/dL or free testosterone  $< 50$  pg/mL) received daily transdermal gel containing 0 g or 10 g testosterone for 14 weeks. Treatment with testosterone alone was not studied. Divergent findings may have reflected younger age, shorter trial duration, or less stringent inclusion criteria.

A gradual, age-related decline in total serum testosterone levels begins in men in their mid-30s and continues at an average rate of 1.6% per year [142; 193]. The incidence of low testosterone in the United States is approximately 20% in men 60 years of age and older, 30% in men 70 years of age and older, and 50% in men 80 years of age and older [194].

In January 2020, the American College of Physicians (ACP) published guideline recommendations for testosterone treatment of men with age-related low testosterone (**Table 4**) [189]. The recommendations are based on an evidence review of 38 randomized controlled trials [195]. The average of age of participants was 66 years; the average baseline total testosterone level was  $\leq 300$  ng/dL. Participants were followed for 6 to 36 months.

The role of testosterone therapy for the management of age-related low testosterone remains controversial. The FDA requires all testosterone medications labeling to clearly state that the products are approved for use only in persons with low testosterone levels due to known causes [196].

### **Cabergoline**

In one small study, men with hyperprolactinemia were evaluated for treatment response to six months of cabergoline 0.5–1.5 mg per week or bromocriptine 5–15 mg per day. Baseline characteristics included libido impairment (100%), ED (59%), infertility (35%), and bilateral galactorrhea (29%). After six months, sperm parameters, RigiScan-measured erectile frequency, and mean serum prolactin were normalized in both groups. The cabergoline group showed more rapid and evident improvement in sex-



**AMERICAN COLLEGE OF PHYSICIANS RECOMMENDATIONS FOR TESTOSTERONE  
TREATMENT IN MEN WITH AGE-RELATED LOW TESTOSTERONE**

Recommendation	Evidence Level	Comments
Discuss initiation of testosterone treatment in men with sexual dysfunction who desire improved sexual function.	Conditional recommendation; low-certainty evidence	Discussion should include potential benefits, harms, costs, and patient preferences.
Re-evaluate symptoms within 12 months and periodically thereafter.	Conditional recommendation; low-certainty evidence	Discontinue testosterone treatment when no improvement in sexual function is achieved.
Consider intramuscular rather than transdermal formulations when initiating testosterone treatment to improve sexual function.	Limited direct evidence; no substantial differences in clinical effectiveness, benefits, or harms between intramuscular and transdermal applications	Costs for intramuscular formulations are considerably lower.
Do not initiate testosterone treatment to improve energy, vitality, physical function, or cognition.	Conditional recommendation; low-certainty evidence	Evidence shows little to no benefits for common concerns of aging. Evidence on long-term harms is lacking.
<i>Source: [189]</i>		<i>Table 4</i>

ual function. Significant increases in serum testosterone and dihydrotestosterone levels occurred with cabergoline only. Side effects were mild with cabergoline and mild-to-moderate with bromocriptine [197]. One single-center study retrospectively analyzed the records of 498 patients with hyperprolactinemia. The cabergoline group received an average dose of 1.5 mg/week. The bromocriptine group received an average of 3.8 mg/day. Treatment durations were similar. Baseline prolactin levels, frequency of galactorrhea, amenorrhea, oligomenorrhea, erectile dysfunction, infertility, and visual impairment were similar between the two groups. Cabergoline was found to be more effective than bromocriptine in controlling symptoms, normalizing serum prolactin levels, and shrinking prolactinomas [198].

### Vacuum Devices

Vacuum devices are plastic cylinders that draw blood into the penis to induce erection. The cylinder is placed over the penis, air is pumped out to cause a partial vacuum, and a constricting band is placed at

the base of the penis when erection is produced. The erection is maintained until the constricting band is released, recommended to not exceed 30 minutes. Vacuum devices are effective in 60% to 90% of patients, are inexpensive and generally safe, and work better with practice. However, many patients lose interest due to assembly, transportation, and spontaneity difficulties [76; 199; 200]. The use of PDE5Is has eclipsed the use of vacuum devices for the treatment of ED [201].

### Penile Implants

Penile implants involve the placement of semirigid or inflatable prosthetic devices within the corpora and are the last recommended option for ED when less invasive approaches fail, when penile reconstruction is required, or following radical prostatectomy when a nerve-sparing procedure was unsuccessful or not performed [200]. Men treated with radiation therapy are also good candidates for penile implants [202; 203].



The American Urological Association asserts that clinicians may offer penile prosthesis surgery to patients with Peyronie disease with erectile dysfunction and/or penile deformity sufficient to prevent coitus despite pharmacotherapy and/or vacuum device

therapy.

(<https://www.auanet.org/guidelines-and-quality/guidelines/peyronies-disease-guideline>. Last accessed February 21, 2023.)

**Level of Evidence:** C (Randomized controlled trials with serious deficiencies of procedure or generalizability or extremely small sample sizes or observational studies that are inconsistent, have small sample sizes, or have other problems that potentially confound interpretation of data)

Semirigid implants involve implantation of two matching cylinders into the corpus cavernosum to provide rigidity sufficient for penetration. Primary drawbacks include cosmetic and concealment concerns from the penis remaining semi-erect and destruction of the natural erectile mechanism during implantation [202; 203].

Inflatable implants consist of two cylinders inserted into the corpus cavernosum, a pump placed in the scrotum to inflate the cylinders, and a reservoir within the cylinders or placed beneath the lower abdomen fascia. They usually remain functional for 7 to 10 years before needing replacement. With improvements in these devices, failure occurs in less than 10% of patients [202; 203].

One analysis compared the cost of penile implantation following failed first-line PDE5I treatment with alternate PDE5Is, intracorporal injections with alprostadil or trimix, and inflatable penile prosthesis placement [204]. Over a 10-year period, penile implants were more cost effective (\$22,009) compared with alprostadil (\$62,890), trimix (\$48,617), and alternate PDE5I (\$52,883).

Patient acceptance is very high and nearly 100% express satisfaction, partially from failure of prior therapies and the high motivation level in these

patients [200]. Some evidence suggests additional benefit with PDE5Is following implantation, with enhanced sexual stimulation and sensation [205]. Possible complications include infections (2%), device erosion through the urethra or skin (2%), and painful erections (1%). The development of an antibiotic-coated device has further reduced the infection rate. Pre-implantation education should advise patients that implants do not lengthen the penis as much as normal erections [206; 207].

### Evaporative Gel

In 2023, the FDA approved a topical gel that may be applied to the head of the penis immediately before sexual intercourse in those experiencing ED [266]. This gel, approved as a device, works via a physical evaporative action, leading to a temperature drop followed by an increase in temperature, which in turn creates a strong sensory signal, stimulating nerve endings. The gel consists of Water, ethanol, propylene glycol, glycerin, and carbomer potassium hydroxide and is available over the counter as Eroxon [266].

### Treatment of Vasculogenic ED

Normal erectile function depends on adequate arterial inflow and venous outflow occlusion. Following normal filling of corporal sinusoids, suprasystolic intracavernosal pressure is required for erection. This filling and required pressure are compromised by impaired cavernosal smooth muscle relaxation and also by compromised arterial inflow or venous leakage, termed vasculogenic ED [149].

With vasculogenic ED, PDE5I failure can occur despite sufficient endothelial and smooth muscle relaxation. Several novel endovascular treatments have been developed, including a drug-eluting stent utilizing zotarolimus; endovascular venous embolization therapy with histoacryl-lipiodol for venous leak involvement; and percutaneous angioplasty of distal penile vasculogenic lesions microsurgical arterial reconstruction. Surgical revascularization procedures for ED secondary to pelvic artery trauma include microsurgical penile artery bypass for focal stenosis secondary to blunt pelvic trauma [74; 149].

Vasculogenic ED etiology is complex and multifactorial. These interventions are generally reserved for men with a focal arterial lesion or pelvic arterial trauma and are considered inappropriate in the presence of generalized vascular disease [149].

## Alternative Therapies

### Myo-Inositol/Folic Acid Combination

As many as 70% of men with type 2 diabetes develop ED, the result of neuropathic, vascular, smooth muscle, and fibrous tissue damage. Myo-inositol can prevent or reverse vascular endothelial dysfunction, reduce endothelial elevations in reactive oxygen species, potentiate nitrenergic or vasculo-myogenic relaxation, and preserve nitric oxide signaling through metabolic, superoxide scavenging, and nitric oxide signaling preservation actions [208; 209]. In addition, folic acid may reverse nitric oxide synthase uncoupling to improve endothelial dysfunction in patients with type 2 diabetes independent of effect on homocysteine [210].

Myo-inositol/folic acid (myo-inositol 4 g/folic acid 400 mcg) was evaluated in 176 men with type 2 diabetes (50 to 70 years of age) who received active drug or placebo daily. After three months, mean IIEF-5 scores improved 40%, from 12 to 20 (out of 25), with myo-inositol/folic acid but slightly worsened with placebo. Sexual function scores improved 27% with myo-inositol/folic acid and were unchanged with placebo. Diary entries of sexual activity were 50% greater with myo-inositol/folic acid than with placebo. Both groups were unchanged from baseline in bulbocavernosus reflex and all penile hemodynamic variables. The authors conclude that myo-inositol/folic acid deserves consideration as a therapeutic agent in men with diabetes-related ED [211].

### Tradamix

Reactive oxygen species are vital signaling molecules in cardiovascular cells, but enhanced production increases nitric oxide inactivation. Reactive oxygen species importantly contribute to endothelial dysfunction that often underlies ED. Tradamix is an herbal supplement developed for use in older men

with sexual dysfunction. The three constituents (*Ecklonia bicyclis*, *Tribulus terrestris*, and glucosamine oligosaccharide) have activity as reactive oxygen species scavengers, androgen receptor agonists, and nitric oxide modulators [212; 213]. Two trials have evaluated Tradamix efficacy. Doses of the constituents *E. bicyclis*, *T. terrestris*, and glucosamine oligosaccharide were 300, 450, 250 mg, respectively, in the ED trial, and 150, 396, 144 mg, respectively, in the low libido trial [212; 213].

The ED trial enrolled 177 men (average age: 64 years) with IIEF erectile function scores less than 26 (indicating at least mild dysfunction). After three months of treatment, significantly greater improvement was found with Tradamix than placebo on measures of intercourse satisfaction, orgasmic function, sexual desire, overall satisfaction, ejaculation control, and sexual quality of life. In patients with moderate arterial dysfunction, Tradamix resulted in significantly greater improvement (vs. placebo) in peak systolic velocity, erectile function, ejaculation control, and sexual quality of life [212].

In another study, 70 men (mean age: 67.3 years) with low libido with or without ED were randomized to daily Tradamix (group A) or tadalafil 5 mg (group B) treatment. After two months of treatment, group A experienced significant increases in mean total (671 ng/dL vs. 230 ng/dL) and free (120 pg/mL vs. 56 pg/mL) testosterone, while group B remained unchanged from baseline. Normal erectile function significantly increased in both groups, with higher rates in group B, and IIEF total scores significantly increased in both groups, as did sexual quality of life scores. Side effects with tadalafil (occurring in less than 15% of treated patients) included headache, nasopharyngitis, back pain, dizziness, and dyspepsia. No side effects were reported with Tradamix [213].

Both trials used highly restrictive enrollment criteria to exclude medications, medical conditions, past treatment, or anatomical causation of ED or low libido. It is also important to note that this product is patented, and some investigators are financial stakeholders. In addition, the herbal and dietary

PHARMACOTHERAPIES FOR PREMATURE EJACULATION			
Drug	Regimen	Dose	IELT Increase
Dapoxetine	On demand	30–60 mg	2.5- to 3-fold
Clomipramine	On demand	12.5–50 mg	4-fold
Clomipramine	Daily	12.5–50 mg	6-fold
Sertraline	Daily	50–200 mg	5-fold
Fluoxetine	Daily	20–40 mg	5-fold
Citalopram	Daily	20–40 mg	2-fold
Paroxetine	Daily for 30 days, then on demand	10–40 mg	11.6-fold
Paroxetine	On demand	10–40 mg	1.4-fold
Paroxetine	Daily	10–40 mg	8-fold
Topical lidocaine/prilocaine	On demand	2.5%/2.5%	4- to 6-fold

IELT = intravaginal ejaculation latency time.

Source: [24; 215] Table 5

supplement industry is unregulated in the United States, and this has led to quality and purity concerns. Because Tradamix is produced in Italy, safety concerns surrounding similar domestic products may not be fully applicable.

### Extracorporeal Shockwave Therapy

Low-intensity extracorporeal shockwave therapy is a novel, non-invasive approach to the treatment of erectile dysfunction that involves the application of acoustic waves applied to the corpora cavernosa, with the goal of revascularizing the area and improving the blood supply [214]. As such, shockwave therapy is the only modality that aims to cure erectile dysfunction. According to one review, several preliminary trials showed benefit on patient-reported erectile function scores, but results of randomized trials are conflicting [214]. More information is necessary before this approach can be incorporated into routine practice.

### Ineffective or Unsafe Treatments

Some treatments for ED are either ineffective, not safe, or lack sufficient evidence, and their use may preclude other treatments known to be effective. These include trazodone, oral apomorphine, statins as ED monotherapy, L-arginine alone or combined with other agents, yohimbine, ginseng, and various

types of topical treatments [264].

### PREMATURE EJACULATION

Agents that increase serotonin neurotransmission are first-line therapy for PE. SSRIs and the TCA clomipramine are the preferred agents, though they are used offlabel for PE treatment, as none are FDA-approved for this indication [24; 215; 216; 217]. Topical local anesthetic agents may also be effective (**Table 5**).

For first-line therapy for premature ejaculation, the AUA recommends daily SSRIs, on-demand clomipramine or dapoxetine (where available), or topical penile anesthetics [265]. The second-line option is on-demand dosing of tramadol in men who have failed first-line therapy; the preferred third-line approach is  $\alpha$ 1-adrenoreceptor antagonists.

### Dapoxetine

Dapoxetine is a rapid-acting, short half-life SSRI with a pharmacokinetic profile supporting use as on-demand treatment for PE. Dapoxetine has received regulatory approval for PE treatment in more than 50 countries, but not yet in the United States. This drug is considered the best option in PE treatment and has received the highest ratings on efficacy and safety evidence [9; 215].



## Other SSRIs and TCAs

The exact neurologic circuitry target of SSRIs in PE is unknown. Aside from dapoxetine, paroxetine seems more effective for ejaculatory delay than other SSRIs. Daily treatment with doses of paroxetine 10–40 mg, clomipramine 12.5–50 mg, sertraline 50–200 mg, fluoxetine 20–40 mg, or citalopram 20–40 mg is often effective in delaying ejaculation. On-demand treatment is also available with clomipramine, paroxetine, sertraline, and fluoxetine. On-demand dosing three to six hours before intercourse is modestly effective and well tolerated but is substantially less effective than daily treatment. On-demand treatment can be combined with an initial trial of daily treatment or continuous low-dose daily treatment [9].

With daily treatment, the onset of ejaculation delay is usually 5 to 10 days. Full therapeutic effect requires two to three weeks of treatment but is usually sustained with long-term use. Adverse effects start in the first week and may disappear within two to three weeks; they include fatigue, yawning, mild nausea, diarrhea, or perspiration. SSRI side effects of decreased libido and ED may be less common in non-depressed patients with PE (versus depressed men) taking SSRIs. SSRIs are contraindicated in men with history of bipolar depression or bipolar disorder [9; 218; 219].

## PDE5Is

The ISSM practice guideline states that, aside from acquired PE secondary to comorbid ED, use of PDE5Is as PE treatment is not supported [9]. Vardenafil is probably an exception, showing particular benefit in PE and significant improvement in IELT among treated patients. Vardenafil is highest in PDE5 specificity among PDE5Is, and PDE5 is expressed in male genital tract regions directly involving the ejaculatory mechanism. In addition, a subgroup of patients with PE exhibits high levels of chronic anxiety, particularly men with lifelong PE. Adrenergic hyperactivity is associated with chronic anxiety, and vardenafil decreases peripheral adrenergic tone, which improves ejaculatory function [10; 220; 221].

## Tramadol

Tramadol is a mild mu-opioid receptor agonist, and its action as a norepinephrine and 5-HT transporter reuptake inhibitor distinguishes it from other opioids and may account for its efficacy in the treatment of PE. Overall, tramadol is moderately effective in lifelong and acquired PE, with efficacy similar to dapoxetine, but high-level studies have not been conducted [222]. Tramadol has abuse potential, and serotonin syndrome may result from concurrent use of SSRIs or other serotonergic agents. Tramadol may be considered when other therapies have failed, especially in countries where dapoxetine is not available [9; 215].

## Topical Local Anesthetic Agents

Topical local anesthetics, including lidocaine and/or prilocaine cream, gel, or spray formulations, are moderately effective as PE treatment. Topical local anesthetics may induce ejaculatory delay by diminishing glans sensitivity and inhibiting the spinal reflex arc responsible for ejaculation [223].

In one study, a lidocaine-prilocaine spray under development applied to the penis five or more minutes before intercourse produced a 6.3-fold increase in IELT and associated improvements in measures of ejaculatory control and sexual satisfaction [224]. These results were replicated in a larger trial [225]. Reports of penile hypoesthesia and transfer to the partner were minimal and primarily attributed to aspects of the formulation [224]. Significant penile hypoesthesia and possible transvaginal absorption, vaginal numbness, and female anorgasmia are associated with other topical local anesthetics unless a condom is used [226; 227]. In all, the evidence supports use of topical local anesthetics for PE [9].

## Future Directions

Botulinum toxin A may be a safe and effective means to prolong ejaculatory latency without affecting other aspects of sexual behavior, but dose-ranging Phase II clinical trials were discontinued due to lack of efficacy in interim analysis. Until efficacy data become available, botulinum toxin A should not be considered standard care in PE [265].

Modafinil is a wake-promoting agent used for the treatment of narcolepsy. Several preclinical studies support modafinil as a potential treatment for PE. An uncontrolled trial of on-demand modafinil in men with lifelong PE reported a significant two-fold change in IELT. The short-acting modafinil d-isomer is in pre-clinical trials as an investigational drug for “on demand” treatment of PE [265].

### **MALE HYPOACTIVE SEXUAL DESIRE DISORDER**

Treatment options for MHSDD may include relationship counseling and psychotherapy, testosterone therapy, PDE5Is for ED, or the squeeze technique for PE. Very few studies of MHSDD therapies have been published [4].

### **MALE ORGASM DYSFUNCTION**

Anorgasmia refers to persistent or frequent absence of orgasm after normal sexual arousal. Etiology is often psychological but can also be substance-related. A surge in serum prolactin is observed during the post-ejaculatory refractory period, which diminishes erectile and ejaculatory potential. Cabergoline inhibits prolactin, and its efficacy (0.5 mg twice weekly) in male anorgasmia was evaluated in 72 anorgasmic patients. Data showed orgasm improvement in 69%, of whom 52% returned to normal orgasm. Mean therapy duration for non-responders and responders was 214 and 296 days, respectively. Pre- and post-treatment testosterone and prolactin levels did not significantly differ. Patient age was unrelated to outcome, but treatment response was associated with therapy duration and concurrent testosterone replacement therapy [228].

### **PORNOGRAPHY-INDUCED SEXUAL DYSFUNCTION**

In younger patients, erectile and libido problems during partnered sex but not when masturbating have been considered psychogenic. Younger patients now asked about sexual function may assume masturbation refers to use of Internet pornography and may be incorrectly diagnosed with performance anxiety

when their partnered-sex difficulties are related to use of Internet pornography. This diagnosis may be followed by prescriptions for psychoactive medications or PDE-5 inhibitors [67].

To avoid incorrect diagnoses and unneeded pharmacotherapy, ask the patient whether he can achieve a satisfactory erection (and climax as desired) masturbating without Internet pornography. If he cannot, but can easily achieve these goals with Internet pornography, his sexual dysfunction may be associated to its use. Healthcare providers should screen for psychosocial problems but should avoid assuming psychological cause of otherwise unexplained sexual dysfunction in men younger than 40 years of age. Little treatment guidance is available for these patients, but case studies show that after six to nine months of total abstinence from Internet pornography, pornography-induced ED resolves and normal sexual function returns [67].

### **HYPERPROLACTINEMIA-INDUCED SEXUAL DYSFUNCTION**

The Endocrine Society recommends that hyperprolactinemia be managed the same regardless of cause and that patients should not be treated for biochemically detected hyperprolactinemia in the absence of symptoms [29]. If a medication is inducing the hyperprolactinemia, it should be stopped or switched, if feasible. With neuroleptic-induced hyperprolactinemia, it is often possible to switch to the neuroleptic aripiprazole, which has mixed dopamine agonist/antagonist activity, or to another neuroleptic with lower dopamine antagonist potency. If this is not possible, cabergoline should be added.

Cabergoline has greatest efficacy among the dopamine agonists used in hyperprolactinemia therapy and a mild side effect profile that facilitates adherence and efficacy. The greatest concern in treating neuroleptic-induced hyperprolactinemia (in patients with psychotic disorders) has been psychosis exacerbation, but this adverse event is uncommon and can be attenuated [29].

### Risk of Psychosis Exacerbation

Risks of psychosis exacerbation with cabergoline can be mitigated by close initial monitoring, restricting use to patients stabilized on their neuroleptic, and tailoring cabergoline dose to hyperprolactinemia severity. A trial using terguride, a dopamine agonist similar to cabergoline, for neuroleptic-induced hyperprolactinemia in patients with schizophrenia found unacceptably high rates of insomnia, agitation, and aggravation of hallucinations during the initial two to four weeks of therapy. While terguride is contraindicated for neuroleptic-induced hyperprolactinemia, these findings show the early onset of psychosis exacerbation with dopamine agonist treatment [229].

A successful risk mitigation approach was confirmed in a trial involving 80 patients with schizophrenia and hyperprolactinemia stabilized on neuroleptics. Measures used to assess the participants were the Positive and Negative Syndrome Scale (PANSS) for psychopathology and the Arizona Sexual Experiences (ASEX) Scale for sexual dysfunction. Daily cabergoline 0.25 mg, 0.5 mg, or 1 mg was matched to baseline prolactin <50, 50–99, or >100 ng/mL, respectively. At six-month follow-up, mean prolactin reduction was comparable in all dose groups. Combining all subjects showed significant reductions in prolactin (73.3 to 27.1 ng/mL), ASEX scores (19.1 to 15.0), and PANSS scores from baseline. No psychosis exacerbation was observed. With stabilized neuroleptic dose and cabergoline matched to hyperprolactinemia severity, cabergoline may improve sexual functioning without psychotic exacerbation in patients with schizophrenia and hyperprolactinemia-induced sexual dysfunction [230].

### Risk of Heart Valve Abnormalities

Cabergoline efficacy in sexual dysfunction due to hyperprolactinemia is widely recognized, and increasing evidence suggests efficacy in male sexual dysfunction without hyperprolactinemia causation. However, endorsement of cabergoline for sexual dysfunction treatment was curtailed by reports of heart valve abnormalities from cabergoline use and by FDA warnings of this serious adverse risk [231].

There is some controversy regarding the magnitude of this risk, but steps can be taken to mitigate it.

Cabergoline is an ergot alkaloid used in the treatment of Parkinson disease and Cushing (off-label) disease (in addition to hyperprolactinemia) [24]. Cabergoline lowers prolactin levels through binding pituitary gland D2 receptors and inhibiting prolactin synthesis. It is a D4 and 5-HT1A receptor agonist; both receptors play important roles in regulating male sexual functioning [24; 232].

Cabergoline is also a 5-HT2B receptor agonist, and other 5-HT2B agonists have been associated with cardiac-valve regurgitation [24]. In 2011, the FDA required changes to safety labeling warning that cabergoline was associated with fibrotic complications and cardiac valvulopathy; and that valvulopathy screening with echocardiogram (ECG) should be performed before and every 6 to 12 months after starting cabergoline [231]. This FDA action was based on retrospective data from patients with Parkinson disease associating high-dose cabergoline (3–6 mg/day) with a risk of valvular abnormalities [231].

However, it is not possible to determine a causal relationship between cabergoline and valvulopathy from retrospective data. This requires pre-treatment patient evaluation for pre-existing cardiac valvulopathy; assessment of risk factors for developing valvulopathy (e.g., altered cardiovascular system mechanical environments from hypertension or functional cardiac disease); and use of an untreated comparison group to control for high population rates of valvular abnormalities [233; 234; 235; 236].

In a study of 11 men and 29 women (mean age: 38.7 years) with hyperprolactinemia treated with cabergoline for 60 months, baseline ECG found trace mitral, aortic, pulmonic, and tricuspid regurgitations in 20%, 2.5%, 10%, and 40% of patients, respectively, and none with clinically relevant valvulopathy. A 24-month ECG found no changes from baseline, and with 60-month ECG, none had developed significant valvulopathy. No correlation was found between cumulative dose (median: 149 mg) and valve regurgitation prevalence or grade.

Cabergoline use for five years did not increase risk of significant cardiac valve regurgitation in patients with hyperprolactinemia [237].

The AACE/ACE investigated valve disease cabergoline treatment of hyperprolactinemia [238]. While the Parkinson disease data suggest cumulative cabergoline exposure is important and minimizing exposure may be appropriate in some contexts, they concluded there is no conclusive evidence that cabergoline causes clinically significant cardiac valve disease at usual hyperprolactinemia doses and that similar regulatory agency directives in the future should use an evidence basis [238].

A separate investigation of valvular abnormalities with cabergoline for hyperprolactinemia reviewed 21 studies and confirmed cabergoline-associated valvulopathy in 3 of 1,812 patients (0.17%). The authors concluded the probability of clinically significant valvular heart disease was very low in the absence of a murmur [239]. A 2014 guideline for clinical endocrinologists stated pre-cabergoline ECG should be reserved for patients with heart disease history or cardiovascular screening exam findings (e.g., heart murmur), with annual ECG limited to patients requiring cabergoline  $\geq 3$  mg/week [234].

The Endocrine Society conducted a literature review to clarify the risk of valvular abnormalities with cabergoline. They concluded that patients needing long-term, very high-dose cabergoline may require periodic ECG to assess valvular abnormalities, and patients receiving typical cabergoline doses (1–2 mg/week) will probably not require regular ECG screening [29].

### FIRST-LINE TREATMENT SELECTION IN PATIENTS WITH MULTIPLE SEXUAL DYSFUNCTIONS

Up to 50% of men with ED also experience PE, and men with sexual dysfunction often present with multiple sexual comorbidities. Unfortunately, the process of initial therapy selection in these patients was largely unaddressed by practice guidelines until recently [10; 240].


Men complaining of PE require careful assessment to rule out ED, subclinical ED, erectile compromise from systemic factors, and genital/lower urinary tract infection. When impaired erectile function is identified, ED (and not PE) should be addressed first by pharmacotherapy with or without cognitive-behavioral therapy. While concurrent treatment of PE and comorbid ED has been recommended, the approach of using two drugs to treat PE, which may resolve by treating the underlying cause of ED with a PDE5I, lacks merit. A better approach is to treat ED first; if PE remains symptomatic, dapoxetine should be prescribed [10].

Loss of erection before ejaculation is one sign of ED, but some men with ED condition themselves to ejaculate before erectile loss [241]. When PE onset occurs before ED, dapoxetine should be used, as PDE5I use in lifelong PE lacks an evidence basis [10; 242].

### PSYCHOSOCIAL APPROACHES

Sexual dysfunction treatment that includes a psychological component is broadly endorsed. Pharmacotherapy for sexual dysfunction cannot address important psychosocial features, including performance anxiety and poor self-confidence; partner sexual dysfunction; relationship conflict or poor communication; sexual factors in the relationship (e.g., sexual scripts, sexual satisfaction); and contextual factors (e.g., life stressors) [9]. Even when sexual dysfunction is primarily physiologic, virtually all patients experience negative psychological and interpersonal effects from their sexual dysfunction. These include interpersonal conflict, depression, performance anxiety, and avoidance of sex. If unaddressed, these will interfere with the efficacy of medical therapies [243; 244].





For men being treated for ED, the American Urological Association recommends referral to a mental health professional be considered to promote treatment adherence, reduce performance anxiety, and integrate treatments into a sexual relationship.

([https://www.auanet.org/guidelines-and-quality/guidelines/erectile-dysfunction-\(ed\)-guideline](https://www.auanet.org/guidelines-and-quality/guidelines/erectile-dysfunction-(ed)-guideline). Last accessed February 21, 2023.)

**Level of Evidence:** C (Randomized controlled trials with serious deficiencies of procedure or generalizability or extremely small sample sizes or observational studies that are inconsistent, have small sample sizes, or have other problems that potentially confound interpretation of data)

The efficacy of modestly effective medical therapies often increases when psychological or educational interventions are added, and combined psychological and medical interventions are consistently found superior to either treatment alone in men with ED or PE [245; 246; 247]. Many men with ED or PE significantly improve with medication, but a significant percentage stop their medication due to cost, side effects, improper dose, and/or partner or personal resistance to taking medication [248; 249]. PDE5Is give many men with psychogenic ED renewed confidence to engage in sexual activity and motivation to address psychological or interpersonal issues that complicate intimate life. Medication is beneficial in patients with PE as they learn behavioral techniques for arousal level sensitization and extended ejaculatory latency [10].

Clinicians often observe that patient change with positive medication response evokes change in the partner, such as men with restored erectile function whose partners no longer desire sex or develop sexual pain disorders. In these cases, psychosocial intervention is critical [10].

Psychotherapy should be initiated before medication in patients with severe depression, with substance abuse disorders, or in abusive/chaotic relationships, as medication has little benefit in this context.

Medical therapy alone is appropriate for cases in which the sexual dysfunction has a clear medical precipitant, couples in a high-quality relationship, or patients with few psychological concerns [10].

## Patient Counseling

### Sex Education

Providers should identify and dispel myths about sex that can negatively influence sexual behavior and contribute to or maintain sexual dysfunction, and the value of basic sex education for this goal should not be overlooked. Many men lack knowledge of basic sexual and reproductive anatomy and physiology. Education should address the diverse range of “normal” sexual function and distorted sexual beliefs or misinformation propagated by popular media and society [7].

### Lifestyle Modification

Lifestyle and behavior change should be emphasized to all patients with sexual dysfunction to help optimize sexual functioning. Simple suggestions can be highly beneficial. Reminding patients that changing lifestyle to health-promoting behaviors through diet, exercise, smoking cessation, and stress reduction can improve physical well-being and self-esteem, which may improve physiologic and psychological aspects of sexual desire and response [7].

This is especially true in men with ED. Every modifiable risk factor of ED (e.g., smoking, excessive alcohol, physical inactivity, abdominal obesity, metabolic syndrome, diabetes, hypertension) promotes metabolic conditions strongly linked with a pro-inflammatory state. This can lead to endothelial dysfunction and ED from decreasing nitric oxide availability. Lifestyle and nutrition strongly influence vascular nitric oxide production, testosterone levels, and erectile function. Lifestyle modification that reduces clinical inflammation may help improve erectile function and may potentially decrease ED or even restore absent erectile function in men with obesity or metabolic syndrome [250; 251; 252].

### Specific Psychological Interventions

Sex therapy and cognitive-behavioral therapy are the major psychological treatment approaches for sexual dysfunction in the empirical literature. Traditional sex therapy aims to improve an individual's or couple's erotic experiences while reducing anxiety and self-consciousness about sexual activity [7]. Cognitive-behavioral sex therapy includes emphasis on modifying thought patterns or beliefs that interfere with intimacy and sexual pleasure [253].

In PE, psychological interventions can help men develop sexual skills that promote ejaculatory delay, broaden the sexual script of the couple, increase sexual self-confidence, and reduce performance anxiety. Psychotherapy is also used in resolving psychological and interpersonal issues for the man, partner, or couple that were antecedent to or consequence of the PE [106; 254]. Current approaches integrate psychodynamic, systems, behavioral, and cognitive approaches within a short-term psychotherapy model, delivered in an individual, couples, or group format [9]. The squeeze and stop-start techniques are the most common behavioral strategies for PE. Both are designed to help men recognize mid-level ranges of excitement. Men with variable PE should receive education and reassurance, while men with subjective PE may require psychotherapy referral [255].

Performance anxiety can interfere with sexual functioning by diverting focus from erotic input to performance-related concerns, embarrassment, or guilt. Cognitive-behavioral therapy may improve ability and satisfaction by diminishing sex-associated anxiety and cognitive distortions [256].

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## CONSIDERATIONS FOR NON-ENGLISH-PROFICIENT PATIENTS

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As a result of the evolving racial and immigration demographics in the United States, interaction with patients for whom English is not a native language is inevitable. Because patient education is such an important aspect of the care of patients with sexual dysfunction, it is each practitioner's responsibility to ensure that information and instructions are explained in such a way that allows for patient understanding. When there is an obvious disconnect in the communication process between the practitioner and patient due to the patient's lack of proficiency in the English language, an interpreter is required. (In many cases, the terms "interpreting" and "translating" are used interchangeably, but interpreting is specifically associated with oral communication while translating refers to written text.) Frequently, this may be easier said than done, as there may be institutional and/or patient barriers.

Depending upon the patient's language, an interpreter may be difficult to locate. Or, an organization may not have the funds to bring in an interpreter. Also, bringing in an interpreter creates a triangular relationship with a host of communication dynamics that must be negotiated [257]. Many view interpreters merely as neutral individuals who communicate information back and forth. However, another perspective is that the interpreter is an active agent, negotiating between two cultures and assisting in promoting culturally competent communication and practice [258; 259]. In this more active role, the interpreter's behavior is also influenced by a host of cultural variables such as gender, class, religion, educational differences, and power/authority perceptions of the patient [258; 259]. Consequently, an intricate, triangular relationship develops between all three parties. Another factor affecting the communication process is the fact that many interpreters are not adequately trained in the art of interpretation in mental health and general health settings, as there are many technical and unfamiliar terms. An ideal interpreter goes beyond being merely proficient

in the needed language/dialect [260]. Interpreters who are professionally trained have covered aspects of ethics, impartiality, accuracy, and completeness [261]. They are also well-versed in interpreting both the overt and latent content of information without changing any meanings and without interjecting their own biases and opinions [261]. Furthermore, knowledge about cross-cultural communication and all the subtle nuances of the dynamics of communicating in a mental health or general health setting is vital [259; 260].

On the patients' side, they may be wary about utilizing interpreters for a host of reasons. They may find it difficult to express themselves through an interpreter [262]. If an interpreter is from the same community as the patient, the client/patient may have concerns about sharing private information with an individual who is known in the community and the extent to which the information disclosed would remain confidential. This is of particular concern when sensitive topics such as sexuality are discussed. In some cases, raising the issue of obtaining an interpreter causes the patient to feel insulted that his or her language proficiency has been questioned. Finally, if an interpreter is from a conflicting ethnic group, the patient may refuse having interpreter services [257]. The ideal situation is to have a well-trained interpreter who is familiar with health and mental health concepts.

If an interpreter is required, the practitioner should acknowledge that an interpreter is more than a body serving as a vehicle to transmit information verbatim from one party to another [262]. Instead, the interpreter should be regarded as part of a collaborative team, bringing to the table a specific set of skills and expertise [262]. Several important guidelines should be adhered to in order to foster a beneficial working relationship and a positive atmosphere.

A briefing time between the practitioner and interpreter held prior to the meeting with the patient is crucial. The interpreter should understand the goal of the session, issues that will be discussed, specific terminology that may be used to allow for advance preparation, preferred translation formats,

and sensitive topics that might arise [260; 262; 263]. It is important for the patient, interpreter, and practitioner to be seated in such a way that the practitioner can see both the interpreter and patient. Some experts recommend that the interpreter sit next to the patient, both parties facing the practitioner [261].

The practitioner should always address the patient directly. For example, the practitioner should query the patient, "How do you feel?" versus asking the interpreter, "How does she feel?" [261]. The practitioner should also always refer to the patient as "Mr./Mrs. D" rather than "he" or "she" [262]. This avoids objectifying the patient.

At the start of the session, the practitioner should clearly identify his/her role and the interpreter's role [262]. This will prevent the patient from developing a primary relationship or alliance with the interpreter, turning to the interpreter as the one who sets the intervention [260]. The practitioner should also be attuned to the age, gender, class, and/or ethnic differences between the patient and the interpreter [262]. For example, if the patient is an older Asian male immigrant and the interpreter is a young, Asian female, the practitioner should be sensitive to whether the patient is uncomfortable given the fact he may be more accustomed to patriarchal authority structures. At the conclusion of the session, it is advisable to have a debriefing time between the practitioner and the interpreter to review the session [260; 262; 263].

In this multicultural landscape, interpreters are a valuable resource to help bridge the communication and cultural gap between clients/patients and practitioners. Interpreters are more than passive agents who translate and transmit information back and forth from party to party. When they are enlisted and treated as part of the interdisciplinary clinical team, they serve as cultural brokers, who ultimately enhance the clinical encounter. In any case in which information regarding diagnostic procedures, treatment options and medication/treatment measures are being provided, the use of an interpreter should be considered.

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## CONCLUSION

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Sexual dysfunction is distressing for male patients and their partners and can have a profoundly negative impact on patient quality of life and self-image. However, providers often find discussion of patient's sexual concerns difficult, due in part to a lack of knowledge, skills, and confidence in their ability to initiate discussion and assess and treat sexual dysfunction. This course has outlined appropriate approaches to the assessment, diagnosis, and treatment of male sexual dysfunction in order to enhance patient-provider communication and improve patient outcomes and well-being.

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## RESOURCES

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**American Association of Sexuality  
Educators, Counselors, and Therapists**

<https://www.aasect.org>

**American Sexual Health Association**

<http://www.ashasexualhealth.org>

**American Urological Association**

<https://www.auanet.org>

**Sexuality Information and Education  
Council of the United States**

<https://siecus.org>

**Society for Sex Therapy and Research**

<https://sstarnet.org>

### Implicit Bias in Health Care

The role of implicit biases on healthcare outcomes has become a concern, as there is some evidence that implicit biases contribute to health disparities, professionals' attitudes toward and interactions with patients, quality of care, diagnoses, and treatment decisions. This may produce differences in help-seeking, diagnoses, and ultimately treatments and interventions. Implicit biases may also unwittingly produce professional behaviors, attitudes, and interactions that reduce patients' trust and comfort with their provider, leading to earlier termination of visits and/or reduced adherence and follow-up. Disadvantaged groups are marginalized in the healthcare system and vulnerable on multiple levels; health professionals' implicit biases can further exacerbate these existing disadvantages.

Interventions or strategies designed to reduce implicit bias may be categorized as change-based or control-based. Change-based interventions focus on reducing or changing cognitive associations underlying implicit biases. These interventions might include challenging stereotypes. Conversely, control-based interventions involve reducing the effects of the implicit bias on the individual's behaviors. These strategies include increasing awareness of biased thoughts and responses. The two types of interventions are not mutually exclusive and may be used synergistically.



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