Erectile Dysfunction

Gretchen M. Irwin, MD, MBA

KEYWORDS

• Erectile dysfunction • Phosphodiesterase 5 inhibitor medication • Cardiac disease

KEY POINTS

- Erectile dysfunction is common but undertreated, because of patient reluctance to self-report.
- Patients with cardiac disease, hypertension, hyperlipidemia, and diabetes should be screened for erectile dysfunction.
- Patients with erectile dysfunction may have undiagnosed diabetes or cardiac disease and should be evaluated for these conditions.
- Oral medications can be used safely and easily by many patients for the treatment of erectile dysfunction, although patient education is critical for effective use.

INTRODUCTION

Erectile dysfunction is defined by the Fourth International Consultation on Sexual Medicine as the consistent or recurrent inability to attain and/or maintain penile erection sufficient for sexual satisfaction.[1] Erectile dysfunction is a common condition, affecting up to 30 million men in the United States.[2] Physicians should ask male patients about sexual health to identify men affected by erectile dysfunction, to identify potentially life-threatening underlying conditions associated with erectile dysfunction, and to improve overall quality of life for the patients.

PATHOPHYSIOLOGY AND RISK FACTORS

Erectile function is dependent on a complex interaction of vascular and neural processes. The internal pudendal artery supplies the majority of the blood flow to the penis through the cavernosal branches whereas venous outflow occurs through a network of easily compressible venules. When arousal occurs, parasympathetic activity from the sacral segments of the spinal cord initiates a cascade of events to release nitric oxide and increase intracellular cyclic guanosine monophosphate. Cyclic guanosine monophosphate increases result in vascular smooth muscle relaxation and

Disclosure: The author has nothing to disclose.
Wichita Family Medicine Residency, Department of Family and Community Medicine, Wesley Medical Center, University of Kansas School of Medicine, 1010 North Kansas, Wichita, KS 67214, USA
E-mail address: gdickson@kumc.edu

Prim Care Clin Office Pract ■ (2019) ■–■
https://doi.org/10.1016/j.pop.2019.02.006 **primarycare.theclinics.com**

an increase in blood flow into the corpora cavernosa. This rapid inflow of blood leads to compression of the venule network to decrease venous outflow, thereby raising intracavernosal pressure and resulting in erection. Erectile dysfunction, therefore, can result from any process that impairs either the neural or vascular pathways that contribute to erection.

Because aging is an independent risk factor for the development of erectile dysfunction, many men assume that sexual impairment is an inevitable consequence of growing older.[3–5] Up to one-third of 70 year old men, however, in a recent study reported no erectile difficulty.[6] Thus, a physician should still perform a thorough history and physical examination to rule out other causes before assuming that new-onset erectile dysfunction is solely the result of advancing age.

Risk factors for developing erectile dysfunction include tobacco use, obesity, sedentary lifestyle, and chronic alcohol use.[3–5] Such risk factors are believed to cause hormonal changes that result in low testosterone and impaired endothelial function, which contribute to the development of erectile dysfunction. Both hypothyroidism and hyperthyroidism also may result in significant hormonal derangements that can result in the development of erectile dysfunction.[7]

Patients who have previously been diagnosed with diabetes mellitus, hypertension, dyslipidemia, or depression also have a higher risk of developing erectile dysfunction.[3–5] Of men diagnosed with erectile dysfunction, approximately 40% have hypertension, 42% have hyperlipidemia, and 20% have diabetes.[8–10]

Medication side effects may account for as many as 25% of all cases of erectile dysfunction. In general, antihypertensives, antidepressants, and antipsychotic medications are most likely to cause impaired erectile function, although the exact mechanism is often not well defined. Specific medications that have been associated with erectile dysfunction include α-blockers, benzodiazepines, β-blockers, clonidine, digoxin, histamine H2-receptor blockers, ketoconazole, methyldopa, monoamine oxidase inhibitors, phenobarbital, phenytoin, selective serotonin reuptake inhibitors, spironolactone, thiazide diuretics, and tricyclic antidepressants. Although chronic diseases, such as diabetes mellitus and hypertension, are considered risk factors for developing erectile dysfunction, erectile dysfunction is a key risk factor for development of cardiovascular and metabolic disease.[11,12] Studies suggest that the degree of erectile dysfunction severity a patient experiences may correlate with cardiovascular disease risk, with erectile dysfunction onset preceding a cardiovascular event by up to 5 years.[13–15] Additionally, patients with erectile dysfunction are more likely to also have premature ejaculation, lower urinary tract symptoms associated with benign prostatic hypertrophy, and overactive bladder compared with the general male population.[9]

DIAGNOSIS

A diagnosis of erectile dysfunction can be readily made by a primary care physician. A patient is unlikely to spontaneously self-report erectile dysfunction, however. Rather, a physician should inquire about erectile dysfunction symptoms in at-risk patients.[16]

Once a patient has reported erectile dysfunction symptoms, a physician must take a careful history to determine the extent of symptoms as well as the contribution to symptoms by associated chronic diseases, medication use, or psychosocial issues. Onset of symptoms, severity, degree of impact on daily life, and situational factors that exacerbate symptoms are critical issues to discuss with patients. Many physicians prefer the use of validated questionnaires to help both diagnose and track treatment effectiveness for patients with erectile dysfunction. Examples of validated

questionnaires that may be used include the Erection Hardness Score, Sexual Health Inventory for Men, and International Index of Erectile Function.[17,18] Furthermore, a physician should discuss psychosocial issues with patients, such as current relationship dynamics, individual views of sexuality and sexual function, and current life stressors.[19]

In addition to thorough sexual, past medical, past surgical, medication, and psychosocial histories, a diagnosis of erectile dysfunction requires an appropriate physical examination. A physician should assess pulse, blood pressure, and weight given the association of erectile dysfunction with obesity and hypertension. Patients also should be assessed for signs consistent with testosterone deficiency because low testosterone can contribute to erectile dysfunction and may alter treatment recommendations. Several studies have shown a link between erectile dysfunction and osteoporosis.[20,21] In 1 study, men with erectile dysfunction were noted to have a 3-fold increase in incidence of osteoporosis compared with men without erectile dysfunction, independent of other risk factors, such as diabetes or hypertension.[21] It is believed that low androgens, high inflammation causing endothelial dysfunction, and/or reduced nitric oxide activity may play a role in increased bone reabsorption.[21] Physicians counsel patients about the importance of maintaining good bone health.[20] Laboratory studies are not required to diagnose erectile dysfunction, but, given the association with chronic disease, men with newly diagnosed erectile dysfunction should have a hemoglobin A_{1c} and lipid panel evaluated. Young men who develop erectile dysfunction should be screened for coronary vascular disease because these men may have up to a 50% increase in risk of future cardiac events.[22] A morning testosterone should be obtained, because a result less than 300 mg/dL in the setting of testosterone deficiency symptoms warrants treatment of low testosterone as well as erectile dysfunction. Treating both conditions may have an additive benefit for patients. Emerging evidence suggests that mean platelet volume and platelet distribution width may be elevated in men with diabetes at risk of erectile dysfunction, although routine ordering of platelet studies currently is not recommended.[23]

TREATMENT

Multiple treatment modalities exist for erectile dysfunction. Although patients often start with oral medication therapy, other options, such as a surgically implanted penile prosthesis or intraurethral and intracavernosal therapies, should be discussed with patients at the outset. Patient preferences after a discussion of risks and benefits should guide treatment. Ultimately, the goal of treatment should be to improve patient quality of life by restoring sexual function when possible and improving overall health by mitigating risk factors for cardiac and metabolic disease.

Lifestyle changes should be recommended to all patients. Improved diet to facilitate lower blood pressure and weight loss, increased physical activity, and elimination of tobacco use can improve effectiveness of treatment while decreasing risk of concomitant chronic disease. Treatment of chronic diseases, such as diabetes, hypertension, hyperlipidemia, hypothyroidism, depression, and low testosterone, can improve erectile dysfunction symptoms as well as improve effectiveness of oral medication treatment of erectile dysfunction.[7] Improved blood pressure control has been demonstrated to improve erectile dysfunction symptoms as well as decrease men's risk of acquiring erectile dysfunction.[24] The impact of treatment of metabolic disease should not be underestimated because treatment with 40 mg of simvastatin for 6 months significantly improved sexual health related quality of life for men over age 40 years with untreated erectile dysfunction.[25]

Many patients elect to treat erectile dysfunction with oral medications. Approved medications include 4 phosphodiesterase type 5 (PDE5) inhibitors, namely sildenafil, tadalafil, vardenafil, and avanafil. Each medication works by inhibiting the PDE5 enzyme action on cyclic guanosine monophosphate. Erection hardness and duration increase with accumulation of cyclic guanosine monophosphate in the penile cavernosa. Men with disrupted penile vasculature will not benefit from PDE5 inhibitor medications.

Medication interactions are an important consideration before prescribing PDE5 inhibitor medications to patients. PDE5 inhibitors have been shown to interact with antidepressant, antifungal, antiretroviral, and antihypertensive medications. Undoubtedly, however, the most significant interaction occurs between PDE5 inhibitors and nitrate medications. Concomitant use can result in severe hypotension for patients. Men on chronic nitrate medications should not use PDE5 inhibitors. Men who use occasional sublingual nitrates for treatment of angina should not use the nitrate medication and a PDE5 inhibitor within 24 hours of each other. Although medication interactions should be considered prior to prescribing PDE5 inhibitor medications, the presence of significant cardiac or renal disease alone should not be considered a contraindication for treatment. Men should be healthy enough to engage in sexual intercourse, although even dialysis patients have been shown appropriate candidates for use of PDE5 inhibitor medication.[26]

When prescribing PDE5 inhibitor medications, physicians should consider the differences in onset of action and efficacy to help determine the best choice for an individual patient. Avanafil has the shortest onset of action at 15 minutes to 30 minutes as well as the smallest window of effectiveness, with time of effectiveness at only 6 hours. Sildenafil and vardenafil have similar onsets of action at 30 minutes to 60 minutes, respectively, and similar lengthg of effectiveness at 12 hours and 10 hours, respectively. Both of these medications can be less effective if taken with a high-fat meal. Tadalafil requires 60 minutes to 120 minutes for onset of action but can have effect for up to 36 hours. Tadalafil can be taken daily or on an as-needed basis, although no efficacy benefit has been shown for 1 dosing strategy over the other. In a meta-analysis of 82 trials, 1 report suggests that sildenafil, 50 mg, is most likely to be effective whereas tadalafil, 10 mg, is most tolerable for patients.[27] Treatment should be optimized for individual patients, with a trial of medications and titration of doses to find the best effect for the least side effects. **Table 1** summarizes available medication options.

To increase the effectiveness of oral medications, physicians should ensure that patients have been educated on proper use, including the timing of medication in relation to planned intercourse and to mealtimes. Studies suggest that, of patients who failed oral medication therapy for erectile dysfunction, more than half were successful when given additional education on how to use the medication.[28,29]

Table 1
Medications for use in erectile dysfunction

	Onset of Action	Effectiveness Time	Dosage
Avanafil	15–30 min	6 h	50 mg, 100 mg, or 200 mg, once daily, as needed
Sildenafil	30–60 min	12 h	20 mg, 25 mg, 50 mg, or 100 mg, once daily, as needed
Tadalafil	60–120 min	36 h	10 mg or 20 mg, once daily, as needed, *OR* 2.5 mg or 5 mg daily
Vardenafil	30–60 min	10 h	10 mg or 20 mg once daily, as needed

If men cannot or choose not to take an oral medication, intraurethral or intracavernosal alprostadil may be an option. Alprostadil can be inserted as a pellet via a delivery catheter in the meatus or may be injected into the corpus cavernosa. Although there may be some initial reluctance to use alprostadil delivery systems, many men who do initiate therapy report high satisfaction with the medication. In 1 study of 596 men, the overall satisfaction rate with alprostadil treatment was 78.3%, with 86% of patients willing to recommend alprostadil therapy to friends.[30]

Nonpharmacologic options for treatment of erectile dysfunction include vacuum devices and penile prosthesis. Vacuum devices and prostheses have been shown effective and result in high patient and partner satisfaction. Men who have undergone prostate surgery for prostate cancer or benign prostatic hypertrophy who experience erectile dysfunction may find vacuum devices particularly effective.[31] Investigational treatments include extracorporeal shock wave therapy, intracavernosal stem cell therapy, and platelet-rich plasma therapy.

Erectile dysfunction can be diagnosed and managed by primary care physicians. Patients should be referred, however, to urology for additional diagnostic and treatment interventions when men are young, have a history of pelvic trauma, have failed prior erectile dysfunction therapies, have lifelong erectile dysfunction, or have concomitant Peyronie disease.[32] Referral to cardiology may be warranted in the setting of strong family history or severe personal history of cardiac disease to evaluate if a patient is healthy enough for intercourse and for medical treatment of erectile dysfunction. Many men have either a psychological component that contributes to erectile dysfunction or experience psychological distress as a result of erectile dysfunction. Accordingly, men should be encouraged to seek psychotherapy in additional to medical therapy because several studies have shown outcomes are better with combined therapy than either modality alone.[32,33]

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