Management of Erectile Dysfunction

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Erectile dysfunction (ED) is the most common sexual problem in men. The incidence increases with age and affects up to one third of men throughout their lives. It causes a substantial negative impact on intimate relationships, quality of life, and self-esteem. History and physical examination are sufficient to make a diagnosis of ED in most cases, because there is no preferred, first-line diagnostic test. Initial diagnostic workup should usually be limited to a fasting serum glucose level and lipid panel, thyroid-stimulating hormone test, and morning total testosterone level. First-line therapy for ED consists of lifestyle changes, modifying drug therapy that may cause ED, and pharmacotherapy with phosphodiesterase type 5 inhibitors. Obesity, sedentary lifestyle, and smoking greatly increase the risk of ED. Phosphodiesterase type 5 inhibitors are the most effective oral drugs for treatment of ED, including ED associated with diabetes mellitus, spinal cord injury, and antidepressants. Intraurethral and intracavernosal alprostadil, vacuum pump devices, and surgically implanted penile prostheses are alternative therapeutic options when phosphodiesterase type 5 inhibitors fail. Testosterone supplementation in men with hypogonadism improves ED and libido, but requires interval monitoring of hemoglobin, serum transaminase, and prostate-specific antigen levels because of an increased risk of prostate adenocarcinoma. Cognitive behavior therapy and therapy aimed at improving relationships may help to improve ED. Screening for cardiovascular risk factors should be considered in men with ED, because symptoms of ED present on average three years earlier than symptoms of coronary artery disease. Men with ED are at increased risk of coronary, cerebrovascular, and peripheral vascular diseases. (*Am Fam Physician.* 2010;81(3):305-312, 313. Copyright © 2010 American Academy of Family Physicians.)

► **Patient information**: A handout on erectile dysfunction, written by the author of this article, is provided on page 313.

Erectile dysfunction (ED) is defined by the National Institutes of Health as the inability to achieve or maintain an erection sufficient for satisfactory sexual performance.[1] ED is the most common sexual problem in men; it often causes serious distress, prompting men to seek medical attention they may not otherwise seek. It often has a profound effect on intimate relationships, quality of life, and overall self-esteem. ED may also be the presenting symptom or harbinger of undetected cardiovascular disease.[2] The economic impact of ED is multifactorial, with direct costs that include physician evaluation, pharmacotherapy, and diagnostic testing, and indirect costs that include lost time at work, lost productivity, and effects on the man's partner, family, and coworkers.

Prevalence

Many men associate advancing age with declining sexual function and an overall decreased quality of life. ED affects up to one third of men throughout their lives, and the incidence increases with age. A population-based study of U.S. health professionals found the prevalence of sexual dysfunction in men to be 12 percent in those younger than 59 years, 22 percent in those 60 to 69 years of age, and 30 percent in those older than 69 years.[3] Persons with type 2 diabetes mellitus have a threefold greater risk of ED compared with the general population.[4] Depression increases the risk of ED, but it is not clear if this relationship is causal.[5]

Pathophysiology

ED may result from organic causes (e.g., vascular, neurogenic, hormonal, anatomic, drug-induced), psychological causes, or a combination of both. A normal sexual erectile response results from the interaction between neurotransmitter, biochemical, and vascular smooth muscle responses initiated by parasympathetic and sympathetic neuronal triggers that integrate physiologic stimuli of the penis with sexual

perception and desire. Nitric oxide produced from endothelial cells after parasympathetic stimuli triggers a molecular cascade that results in smooth muscle relaxation and arterial influx of blood into the corpus cavernosum. This is followed by compression of venous return, which produces an erection.[6]

Diagnosis and Evaluation

There is no preferred, first-line diagnostic test for ED, and routine screening is not recommended. History and physical examination are sufficient in making an accurate diagnosis of ED in most cases. Penile duplex ultrasonography is not a useful diagnostic test for ED.[7] The American Urological Association (AUA) recommends that the initial evaluation of ED include a complete medical, sexual, and psychosocial history.[8] The medical history may reveal comorbid conditions, risk factors related to ED (*Table 1*),[9] or medications that contribute to ED (*Table 2*).[6] Sexual history should focus on erection adequacy, altered libido, quality and timing of orgasm, volume and appearance of ejaculate, presence of sexually-induced genital pain or penile curvature (Peyronie disease), and partner sexual function. The five-item version of the International Index of Erectile Function Questionnaire is a validated survey instrument that can be used to assess the severity of ED symptoms (*Table 3*).[10]

The physical examination should assess blood pressure and heart rate; body habitus, for central obesity; and cardiovascular, neurologic, and genitourinary systems, including penile, testicular, and digital rectal examinations (*Figure 1*).[8,9,11-14] The AUA and World Health Organization recommend limited diagnostic testing in men with ED. This may include a fasting serum glucose level and lipid panel, thyroid-stimulating hormone test, and morning total testosterone level.[8,11] Additional diagnostic testing and urologic evaluation may be warranted in cases of ED refractory to standard therapies (*Table 4*).[11] Clues to the diagnosis of ED are listed in *Table 5*.

Table 1. Risk Factors for Erectile Dysfunction

Advancing age

Cardiovascular disease

Cigarette smoking

Diabetes mellitus

History of pelvic irradiation or surgery, including radical prostatectomy

Hormonal disorders (e.g., hypogonadism, hypothyroidism, hyperprolactinemia)

Hypercholesterolemia

Hypertension

Illicit drug use (e.g., cocaine, methamphetamine)

Medications (e.g., antihistamines, benzodiazepines, selective serotonin reuptake inhibitors)

Neurologic conditions (e.g., Alzheimer disease, multiple sclerosis, Parkinson disease, paraplegia, quadriplegia, stroke)

Obesity

Peyronie disease

Psychological conditions (e.g., anxiety, depression, guilt, history of sexual abuse, marital or relationship problems, stress)

Sedentary lifestyle

Venous leakage

Information from reference 9.

Table 2. Medications and Substances That May Cause or Contribute to Erectile Dysfunction

Medication class or substance	Examples
Analgesics	Opiates
Anticholinergics	Tricyclic antidepressants
Anticonvulsants	Phenytoin (Dilantin), phenobarbital
Antidepressants	Lithium, monoamine oxidase inhibitors, selective serotonin reuptake inhibitors, tricyclic antidepressants
Antihistamines	Dimenhydrinate, diphenhydramine (Benadryl), hydroxyzine (Vistaril), meclizine (Antivert), promethazine (Phenergan)
Antihypertensives	Alpha blockers, beta blockers, calcium channel blockers, clonidine (Catapres), methyldopa, reserpine
Anti-Parkinson agents	Bromocriptine (Parlodel), levodopa, trihexyphenidyl
Cardiovascular agents	Digoxin, disopyramide (Norpace), gemfibrozil (Lopid)
Cytotoxic agents	Methotrexate
Diuretics	Spironolactone (Aldactone), thiazides
Hormones	5-alpha reductase inhibitors, corticosteroids, estrogens, luteinizing hormone-releasing hormone agonists, progesterone
Illicit drugs, alcohol, and nicotine	Amphetamines, barbiturates, cocaine, heroin, marijuana
Immunomodulators	Interferon-alfa
Tranquilizers	Benzodiazepines, butyrophenones, phenothiazines

Information from reference 6.

Treatment

LIFESTYLE MODIFICATIONS

First-line therapy for ED is aimed at lifestyle changes and modifying pharmacotherapy that may contribute to ED[8] *(Table 2[6])*. Sedentary lifestyle, a significant risk factor for cardiovascular disease, may also be a modifiable risk factor for ED.[15] Obesity nearly doubles the risk of ED[3]; one study determined that one third of men who were obese improved their ED with moderate weight loss and an increase in the amount and duration of regular exercise.[14] The risk of moderate or total ED is almost double in men who smoke compared with nonsmokers.[16] Patient education should be aimed at increasing exercise, losing weight to achieve a body mass index (BMI) less than 30 kg per m^2, and stopping smoking.

PHARMACOTHERAPY

Phosphodiesterase type 5 (PDE5) inhibitors are the most effective oral drugs in the treatment of ED,[9,12] and should be considered first-line therapy.[8,14,17] Retail sales of sildenafil (Viagra), tadalafil (Cialis), and

Table 3. Five-Item Version of the International Index of Erectile Function Questionnaire

Questions	Scores				
	1	2	3	4	5
Over the past six months:					
1. How do you rate your confidence that you could get and keep an erection?	Very low	Low	Moderate	High	Very high
2. When you had erections with sexual stimulation, how often were your erections hard enough for penetration?	Almost never or never	A few times*	Sometimes†	Most times‡	Almost always or always
3. During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?	Almost never or never	A few times*	Sometimes†	Most times‡	Almost always or always
4. During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?	Extremely difficult	Very difficult	Difficult	Slightly difficult	Not difficult
5. When you attempted sexual intercourse, how often was it satisfactory for you?	Almost never or never	A few times*	Sometimes†	Most times‡	Almost always or always

NOTE: *The score is the sum of the above five question responses. Erectile dysfunction is classified based on these scores: 17 to 21 = mild; 12 to 16 = mild to moderate; 8 to 11 = moderate; 5 to 7 = severe.*

*—Much less than one half the time.

†—About one half the time.

‡—Much more than one half the time.

Adapted with permission from Rosen RC, Cappelleri JC, Smith MD, Lipsky J, Peña BM. Development and evaluation of an abridged, 5-item version of the International Index of Erectile Function (IIEF-5) as a diagnostic tool for erectile dysfunction. Int J Impot Res. 1999;11:322.

Diagnosis and Treatment of Erectile Dysfunction

Obtain a comprehensive medical, sexual, and psychosocial history; assess vital signs; perform a risk factor analysis and a detailed examination of the cardiovascular, neurologic, and genitourinary systems

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Complete the five-item version of the International Index of Erectile Function Questionnaire to categorize erectile dysfunction severity (Table 3)

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Obtain a fasting serum glucose level and lipid panel, thyroid-stimulating hormone test, morning total testosterone level

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Definable medical etiology | No definable medical etiology

Maximize treatment of:
- Coronary artery disease
- Diabetes mellitus
- Hormonal disorders (e.g., hypogonadism, hypothyroidism)
- Hypercholesterolemia
- Hypertension
- Metabolic syndrome
- Neurologic conditions (e.g., Alzheimer disease, multiple sclerosis)
- Obesity
- Vascular disease

Consider:
- Screening for psychological causes (e.g., anxiety, depression, guilt, history of sexual abuse, marital or relationship problems, stress)
- Referral for behavior therapy, either individual or with partner
- Removal of negative psychosocial factor(s)

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First-line therapy:
- Lifestyle and pharmacotherapy modification (Table 2)
- Oral therapy with phosphodiesterase type 5 inhibitors (ensure patient is not taking nitrates)
- Testosterone supplementation if patient has clinical hypogonadism

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Second-line therapy:
- Intraurethral or intracavernosal alprostadil (Caverject)
- Vacuum pump devices

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Consider referral to urologist for implantation of an inflatable penile prosthesis if other methods fail

Consider screening for undetected cardiovascular disease

Figure 1. Algorithm for the diagnosis and treatment of erectile dysfunction.

Adapted from references 8, 9, and 11 through 14.

vardenafil (Levitra) approached $1.48 billion in 2007.[18] Sildenafil has been found to be effective and safe in cases of ED associated with diabetes mellitus[17,19] and spinal cord injury,[20] and in men with sexual dysfunction secondary to antidepressant therapy.[21] Compared with placebo, sildenafil has been shown to improve erections (74 versus 21 percent; number needed to treat [NNT] = 2)[22] and results in more frequent intercourse attempts (57 versus 21 percent; NNT = 3).[23] Approximately one third of men with ED do not respond to therapy with PDE5 inhibitors. These agents are not effective for improving libido.[24]

The three PDE5 inhibitors are considered to be relatively similar in effectiveness, but there are differences in dosing, onset of action, and duration of therapeutic effect *(Table 6)*.[25] There are no rigorous data to suggest that one PDE5 inhibitor is superior to another. An open-label trial found that patients preferred tadalafil and vardenafil over sildenafil,[26] yet most evidence supports equal effectiveness between sildenafil and vardenafil.[27] PDE5 inhibitors are generally well tolerated, with mild transient adverse effects of headache, flushing, dyspepsia, rhinitis, and abnormal vision. Headache is the most commonly reported adverse effect, occurring in approximately 10 percent of patients.

Table 4. Additional Testing in the Workup of Erectile Dysfunction

Optional diagnostic tests

Laboratory investigations (complete blood count; free testosterone, luteinizing hormone, and prolactin levels; sex hormone-binding globulin test; urinalysis)

Psychological or psychiatric consultation

Specialized evaluation and diagnostic tests

In-depth psychosexual and relationship evaluation

Neurophysiologic testing (vibrometry; bulbocavernosus reflex latency; cavernosal electromyography; somatosensory evoked potential test; pudendal and sphincter electromyography)

Nocturnal penile tumescence and rigidity assessment

Psychiatric evaluation

Specialized endocrinologic testing (hypothalamic-pituitary-gonadal function studies; magnetic resonance imaging of the sella turcica)

Vascular diagnostics (duplex ultrasonography; penile pharmacocavernosometry and pharmacocavernosography; penile arteriography; computed tomography or magnetic resonance imaging; nuclear imaging)

Adapted with permission from Jardin A, Wagner G, Khoury S, et al. Recommendations of the 1st International Consultation on Erectile Dysfunction. In: Jardin A, Wagner G, Khoury S, et al., eds. Erectile Dysfunction. Plymouth, U.K.: Health Publication Ltd, 2000:718-719.

Table 5. Clues to the Diagnosis of Erectile Dysfunction

Clinical clue	Suggested diagnosis
History	
Altered or impaired partner sexual function	Psychological causes (e.g., anxiety, depression, guilt, history of sexual abuse, marital or relationship problems, stress)
Decreased appearance and volume of ejaculate	Chronic prostatitis, normal aging process, obstruction of ejaculatory duct(s), retrograde ejaculation
Decreased libido	Chronic fatigue syndrome, hypogonadism, hypothyroidism, psychological conditions
Impaired quality and timing of orgasm, including anorgasmia	Alcohol abuse, Cushing syndrome, hyper- or hypothyroidism, medications (e.g., antihistamines, antipsychotics, beta blockers, selective serotonin reuptake inhibitors, thiazides, tricyclic antidepressants), psychological causes, surgery of the pelvis or prostate
Presence of sexually-induced genital pain	History of sexual abuse, genital piercings, sexually transmitted infections (e.g., genital herpes)
Physical examination	
Assessment of body habitus for central obesity	Cushing syndrome, diabetes mellitus, metabolic syndrome
Decreased perineal sensation	Cauda equina syndrome, spinal stenosis, surgery of the pelvis or prostate, trauma
Decreased peripheral pulses	Atherosclerotic and peripheral vascular disease
Elevated blood pressure	Atherosclerotic vascular disease, cerebrovascular disease
Enlarged prostate on digital rectal examination	Benign prostatic hyperplasia, prostate cancer
Penile curvature	Peyronie disease, ruptured corpora cavernosum, venous leakage
Tachycardia	Anxiety, hyperthyroidism, stimulant abuse, underlying cardiovascular disease
Testicular abnormalities	Epididymitis, hypogonadism, testicular cancer, varicocele
Thyroid goiter	Hyper- or hypothyroidism

Rare but important adverse effects include dizziness, syncope, and nonarteritic anterior optic neuropathy (predominantly from crossover phosphodiesterase type 6 inhibition). PDE5 inhibitors should not be taken concomitantly with nitrates because this may lead to a synergistic effect, resulting in a potentially serious, even fatal, decrease in blood pressure. PDE5 inhibitors are metabolized by the cytochrome P450 3A4 and may affect metabolism of protease inhibitors and antifungal medications.

Intracavernosal pressure and PDE5 activity are androgen-dependent. The prevalence of hypogonadism (defined as a morning serum total testosterone level less than 300 ng per dL [10.41 nmol per L]) in men with ED is estimated to be 5 to 10 percent.[13,28] In men with hypogonadism, testosterone supplementation is superior to placebo in improving erections and sexual function. Response rates are higher in primary versus secondary testicular failure, and with transdermal versus oral or intramuscular testosterone.[13] Supplementation is also associated with improved satisfaction with erectile function and sexual desire.[29] Men with hypogonadism who failed a trial of sildenafil were found to have significant improvement in erectile function with the addition of testosterone supplementation.[30] Testosterone supplementation may result in erythrocytosis, elevated serum transaminase levels, exacerbation of untreated sleep apnea, benign prostatic hyperplasia, and an increased risk of adenocarcinoma of the prostate. Men receiving testosterone

Table 6. Phosphodiesterase Type 5 Inhibitors for Erectile Dysfunction

Drug	Standard dose*	Recommended time between dosing and intercourse	Onset of action	Duration†
Sildenafil (Viagra)	50 to 100 mg	One hour	14 to 60 minutes	Up to four hours
Tadalafil (Cialis)	10 to 20 mg	One to 12 hours	16 to 45 minutes	Up to 36 hours
Vardenafil (Levitra)	10 to 20 mg	One hour	25 minutes	Up to four hours

*—Maximum recommended dose per 24 hours is the maximum strength dose for each agent.
†—Duration during which successful erections may be achieved following a dose of medication.

Information from reference 25.

supplementation require more frequent monitoring of hemoglobin, serum transaminase, and prostate-specific antigen levels, and prostate examinations.[31]

SURGICAL AND PROCEDURAL THERAPY

Alprostadil (Caverject) is a viable second-line therapeutic option for the treatment of ED. It should initially be administered in the physician's office at the lowest dose and sequentially titrated to an adequate erectile response while monitoring for syncope. The physicians should also provide education on self-administration.[8] Intracavernosal alprostadil is more effective, better tolerated, and preferred by men over the intraurethral form.[32] Common adverse effects of intraurethral alprostadil include local penile pain, urethral bleeding, dizziness, and dysuria. Common adverse effects of intracavernosal alprostadil include penile pain, edema and hematoma, palpable nodules or plaques, and priapism. Patients should be informed about the potential for occurrence of prolonged erections and should seek emergent medical evaluation for rigid erections lasting longer than four hours. Priapism is most commonly treated with aspiration of blood from the corpus cavernosum under local anesthetic. If this treatment is insufficient, then intracavernosal injections of phenylephrine should be performed with hemodynamic monitoring to watch for severe hypertension, tachycardia, or arrhythmia.

Vacuum pump devices are a noninvasive second-line option *(Figure 2)*. They are contraindicated in men with sickle cell anemia or blood dyscrasias, and in those taking anticoagulants. If used properly, adverse effects and potential risks are negligible, yet there may be a substantial learning curve. When first- and second-line therapies have failed, surgical implantation of an inflatable penile prosthesis can be considered in consultation with a urologist *(Figure 3)*. Patients should be counseled regarding risks, benefits, and expectations of this procedure. The AUA does not endorse penile venous reconstructive surgery or surgeries to limit venous outflow from the penis. Penile arterial reconstructive surgery is controversial and more rigorous trials are needed to prove short- and long-term effectiveness.[16]

ALTERNATIVE THERAPIES

Korean red ginseng (*Panax ginseng*) at 900 mg three times daily has been reported to improve erections but

Figure 2. Erec-Tech vacuum therapy system.

Figure 3. Coloplast Alpha-1 inflatable penile prosthesis.

not overall sexual experience.[33] Yohimbine has shown superiority over placebo for treatment of ED with limited adverse effects,[34] but is not recommended by the AUA because of questions about its safety and effectiveness.[8] Some dietary supplements marketed for treatment of ED obtainable via the Internet (e.g., Super X, Stamina-Rx) contain PDE5 inhibitors (sildenafil 30 mg and tadalafil 20 mg, respectively). Although these and other similar products claim to be free of any adverse effects, they have the same risks as PDE5 inhibitors.[35]

BEHAVIOR THERAPY

When there is no obvious medical etiology for ED, psychosocial factors should be explored. The potential clue that psychosocial factors may be a cause is that a man is able to achieve normal erections and orgasm through masturbation or sex with a partner other than the "index case" partner with whom he has erectile dysfunction (e.g., a spouse with whom there is substantial conflict). Group or individual cognitive behavior therapy; psychosexual therapy, including sensate focus technique; and therapy aimed at improving relationship difficulties may help to improve sexual dysfunction in men. A 2007 Cochrane review found that men who received group therapy plus sildenafil had more successful intercourse and were less likely to drop out of the study compared with those who received only sildenafil.[36] When comparing psychosocial interventions versus alprostadil injections and vacuum pump devices, no differences in effectiveness were found.[36] In some cases, education about medical and psychosocial etiologies of ED in conjunction with physician reassurance may prove adequate to restore normal male sexual function.

Link to Cardiovascular Disease

Men with ED should be considered for cardiovascular risk screening.[15] ED rates differ significantly in patients with established coronary artery disease (CAD). On average, ED symptoms present three years earlier than CAD symptoms.[37] Men with ED have a 75 percent increased risk of peripheral vascular disease.[38] The Prostate Cancer Prevention Trial determined that men with ED have a significantly greater likelihood of having angina, myocardial infarction, stroke, transient ischemic attack, congestive heart failure, or cardiac arrhythmia compared with men without ED.[39] Because most men are asymptomatic before an acute coronary syndrome, ED may serve as a sentinel marker for prompting discussions centered on promotion of cardiovascular risk stratification and modification.

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