

ERECTILE DYSFUNCTION (ED)

KEYWORDS: Erectile dysfunction, impotence, penis, phosphodiesterase inhibitors, sexual dysfunction.

LEARNING OBJECTIVES:

At the end of medical school, the medical student will be able to...

- Draw, identify and name the major anatomic regions of the penis involved with erections
- Describe the physiology of the normal penile erection
- List and briefly describe the major causes of erectile dysfunction (ED)
- List the important components of the history when interviewing a patient with ED
- Outline the important components of the physical exam of a patient with ED
- List the treatment options for erectile dysfunction and describe the mechanisms by which they work
- Describe the contra-indications and side-effects of phosphodiesterase inhibition for ED
- Describe when a patient with ED should be referred to a urologist

DEFINITION

Erectile dysfunction is defined as the inability to achieve and maintain an erection sufficient for satisfactory sexual intercourse. It is estimated to affect 20 to 30 million men in the US. It may result from impairment of one or more factors: psychological, neurologic, hormonal, arterial, and venous. More recently it has become clear that, in many cases, erection dysfunction can be a “silent marker” for the later development of cardiovascular disease.

THE PENILE ERECTION

Penile erection is a neurovascular event subject to psychological and hormonal modulation. Upon sexual stimulation, nerve impulses release neurotransmitters from the cavernous nerve terminals and relaxing factors from the endothelial cells in the penis resulting in (a) relaxation of smooth muscle in the arteries and arterioles supplying the erectile tissue. As a result, there is a several-fold increase in blood flow. Concomitantly, there is (b) relaxation of the sinusoidal smooth muscle within the paired corporeal bodies, facilitating rapid filling and expansion of the sinusoidal system (Figure 1). As a result, (c) venous plexuses located between the sinusoids and rigid tunic covering the penis are compressed resulting in almost total occlusion of venous outflow. These events effectively trap the blood within the corpora cavernosa and raise the penis from flaccid to erect position; in doing so, an intracavernous pressure of 100 mm Hg (full erection phase) is achieved. Both masturbation and sexual intercourse trigger the bulbocavernosus reflex, which causes the ischiocavernosus muscles to forcefully compress the blood-filled corpora cavernosa. During ejaculation, penile intracavernous pressures reach several hundred mm Hg (rigid erection phase). During this phase, vascular inflow and outflow temporarily cease. Detumescence results when erectile neurotransmitter release stops, when there is breakdown of second messengers by phosphodiesterases, or due to sympathetic discharge during ejaculation.

The penis is innervated by autonomic and somatic nerves. In the pelvis, the sympathetic and parasympathetic nerves merge to form the cavernous nerves, which enter the corpora cavernosa, corpus spongiosum and glans penis to regulate the blood flow during erection. The pudendal nerve, the somatic component, is responsible for penile sensation and the contraction and relaxation of the bulbocavernosus and ischiocavernosus muscles that surround the penis.

Nitric oxide released from nonadrenergic-noncholinergic neurotransmission and the endothelium is probably the principal neurotransmitter for penile erection. Within the muscle, nitric oxide activates a guanylyl cyclase that raises intracellular concentrations of cyclic guanosine monophosphate (GMP). Cyclic GMP in turn activates a specific protein kinase, which results in the opening of the potassium channels and hyperpolarization and causes sequestration of intracellular calcium and blocks calcium influx. As a result of this drop in cytosolic calcium, smooth muscle relaxation occurs leading to erection. On return to the flaccid state, cyclic GMP is hydrolyzed to guanosine monophosphate by phosphodiesterase type 5. Sildenafil, vardenafil and tadalafil are drugs currently FDA approved to treat erection dysfunction and they work by blocking phosphodiesterase enzyme activity.

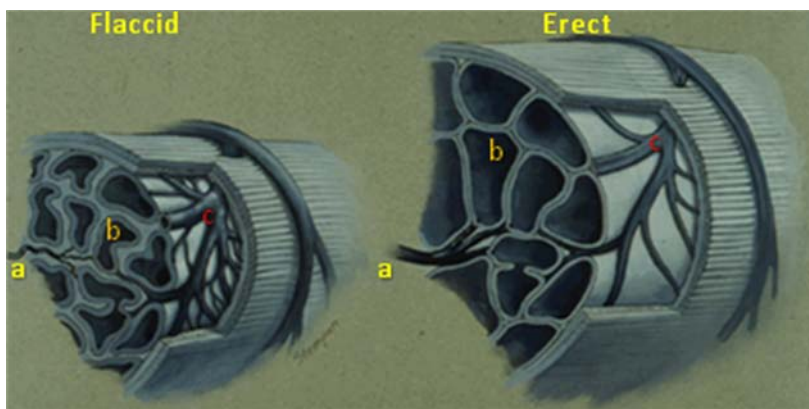


Figure 1. Anatomy of the Penis. The penile erection occurs as a result of 3 processes: a) smooth muscle relaxation among arteries and trabecular tissue increases blood flow, which b) lengthens and enlarges penis through sinusoidal filling, and c) expanded sinusoids compress the subtunical venous plexus, reducing venous outflow.

CAUSES OF ERECTILE DYSFUNCTION

Erectile dysfunction can be classified as psychogenic, organic (neurogenic, hormonal, arterial, venous or cavernosal and drug-induced), and mixed psychogenic and organic (Table 1). The last is the most common. Common causes of psychogenic erectile dysfunction include performance anxiety, strained relationship, lack of sexual arousability, and overt psychiatric disorders such as depression and schizophrenia. Neurologic disorders such as Parkinson's and Alzheimer's diseases, stroke, and cerebral trauma often cause erectile dysfunction by decreasing libido or causing inability to initiate the erectile process. In men with spinal cord injuries, the degree of erectile function depends largely on the nature, location and extent of the lesion. Hormonally, androgen deficiency results in a decrease in nocturnal erections and decreases libido. However, erection in response to visual sexual stimulation is preserved in men with hypogonadism, suggesting that androgen is not essential for erection. Hyperprolactinemia of any cause results in both reproductive and sexual dysfunction due to the inhibitory action of prolactin on gonadotropin-releasing hormone secretion, resulting in hypogonadotropic hypogonadism.

TABLE 1. CLASSIFICATION AND CAUSES OF ERECTILE DYSFUNCTION

CATEGORY	DISORDERS	PROBLEM
Psychogenic	Performance anxiety, Depression	Loss of libido, overinhibition, Impaired nitric oxide release
Neurogenic	Stroke, Spinal cord injury, Diabetic retinopathy	Lack of nerve impulse, or Interrupted transmission
Hormonal	Hypogonadism, Hyperprolactinoma	Inadequate nitric oxide release
Vasculogenic (arterial or venous)	Atherosclerosis, hypertension	Impaired arterial or venous flow
Medication-induced	Antihypertensives, Antidepressants, Alcohol, cigarette use	Central suppression, Vascular insufficiency

Vascular factors may also cause poor erections. Common risk factors associated with generalized penile arterial insufficiency include hypertension, hyperlipidemia, cigarette smoking, diabetes mellitus, and pelvic irradiation. Focal stenosis of the common penile artery most often occurs in men who have sustained blunt pelvic or perineal trauma (e.g., biking accidents). Poor venous occlusion during erection (veno-occlusive dysfunction) can also cause erectile dysfunction. This can result from degenerative changes (Peyronie's disease, old age, diabetes mellitus) or traumatic injury (penile fracture) to the tunica albuginea and structural alterations of the cavernous smooth muscle and endothelium.

Many drugs have been reported to cause erectile dysfunction. Central neurotransmitter pathways, including serotonergic, noradrenergic, and dopaminergic pathways involved in sexual function, may be disturbed by antipsychotics, antidepressants and centrally acting antihypertensive drugs. Beta-adrenergic blocking drugs may cause erectile dysfunction by potentiating alpha-1 adrenergic activity in the penis. Thiazide diuretics have been reported to cause erectile dysfunction, but the cause is unknown. Spironolactone can cause erectile failure as well as decrease in libido and gynecomastia. Cigarette smoking may induce vasoconstriction and penile venous leakage because of its contractile effect on the cavernous smooth muscle. Alcohol in small amounts improves erection and increases libido because of its vasodilatory effect and the suppression of anxiety; however, large amounts can cause central sedation, decreased libido and transient erectile dysfunction. Cimetidine, a histamine-H₂ receptor antagonist, has been reported to decrease libido and cause erectile failure; it acts as an antiandrogen. Other drugs known to cause erectile dysfunction are estrogens and drugs with antiandrogenic action such as ketoconazole and cyproterone acetate.

It is also true that sexual function progressively declines in "healthy" aging men. For example, the latent period between sexual stimulation and erection increases, erections are less turgid, ejaculation is less forceful, ejaculatory volume decreases, and the refractory period between erections lengthens. There is also a decrease in serum testosterone concentration in men with age and this may contribute to erectile dysfunction. About 50% of men with diabetes mellitus have

erectile dysfunction. In addition to the disease's effect on small vessels, it may also affect neurotransmitter delivery. Chronic renal failure has frequently been associated with diminished erectile function, impaired libido, and infertility. Men with angina, myocardial infarction, or heart failure may have erectile dysfunction from anxiety, depression, or concomitant penile arterial insufficiency.

ERECTILE DYSFUNCTION-DIAGNOSIS

Erectile dysfunction can be the presenting symptom of a variety of diseases such as diabetes mellitus, coronary artery disease, hyperlipidemia, hypertension, spinal-cord compression, and pituitary tumor. Therefore, a thorough history (medical, sexual and psychosocial), physical examination and appropriate laboratory tests aimed at detecting these diseases should be performed. A detailed psychosocial history may reveal deep-seated psychological problems or relationship conflicts that can only be successfully treated by mental health professionals. Standardized, validated survey instruments such as the SHIM-5 are now available to assess erectile dysfunction in affected individuals (Figure 2). Often, the particular characteristics of the erection problem can help with the diagnosis: in cases of arterial problems, prolonged stimulation may be required to achieve an erection; with venous leak an erection is easily achieved but lost very quickly. Physical examination should include evaluation of the breast, hair distribution, penis and testis, palpation of the femoral and pedal pulses and testing of genital and perineal sensation. Recommended laboratory tests include urinalysis, complete blood count, and measurement of fasting blood glucose, creatinine, cholesterol and triglycerides, and testosterone. If the man's testosterone concentration is low, serum free (or bioavailable) testosterone, prolactin, and lutenizing hormone should be measured.

OVER THE PAST 6 MONTHS:

1. How do you rate your confidence that you could get and keep an erection?		VERY LOW	LOW	MODERATE	HIGH	VERY HIGH
		1	2	3	4	5
2. When you had erections with sexual stimulation, how often were your erections hard enough for penetration (entering your partner)?	No SEXUAL ACTIVITY	ALMOST NEVER OR NEVER	A FEW TIMES (MUCH LESS THAN HALF THE TIME)	SOMETIMES (ABOUT HALF THE TIME)	MOST TIMES (MUCH MORE THAN, HALF THE TIME)	ALMOST ALWAYS OR ALWAYS
	0	1	2	3	4	5
3. During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?	DID NOT ATTEMPT INTERCOURSE	ALMOST NEVER OR NEVER	A FEW TIMES (MUCH LESS THAN HALF THE TIME)	SOMETIMES (ABOUT HALF THE TIME)	MOST TIMES (MUCH MORE THAN, HALF THE TIME)	ALMOST ALWAYS OR ALWAYS
	0	1	2	3	4	5
4. During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?	DID NOT ATTEMPT INTERCOURSE	EXTREMELY DIFFICULT	VERY DIFFICULT	DIFFICULT	SLIGHTLY DIFFICULT	NOT DIFFICULT
	0	1	2	3	4	5
5. When you attempted sexual intercourse, how often was it satisfactory for you?	DID NOT ATTEMPT INTERCOURSE	ALMOST NEVER OR NEVER	A FEW TIMES (MUCH LESS THAN HALF THE TIME)	SOMETIMES (ABOUT HALF THE TIME)	MOST TIMES (MUCH MORE THAN, HALF THE TIME)	ALMOST ALWAYS OR ALWAYS
	0	1	2	3	4	5

Add the numbers corresponding to questions 1-5. TOTAL: _____

The Sexual Health Inventory for Men further classifies ED severity with the following breakpoints:

1-7 Severe ED 8-11 Moderate ED 12-16 Mild to Moderate ED 17-21 Mild ED

Figure 2. Sexual Health Inventory for Men (SHIM) that is used clinically to assess the degree of erectile dysfunction.

The physician should then assess the findings, inquire about the goals and preferences of the man (and his partner), and discuss further diagnostic and therapeutic options. If the man is taking a drug known to cause erectile dysfunction or recreational drugs, or has vascular risk factors, a change in medication or life-style may be helpful. If primary hypogonadism is detected, androgen therapy is the treatment of choice. Importantly, PDE5 inhibitors are contraindicated in those taking nitrate medication and also in men for whom sexual intercourse is inadvisable due to cardiovascular risk factors. This goal-directed approach to diagnosis and treatment of erectile dysfunction, tailored to the individual’s health status and goals, is outlined in Figure 3.

Importantly, erectile dysfunction not just a sexual health issue. □ In many men, ED may be a serious harbinger of life-threatening cardiovascular conditions. A recent JAMA study followed men age 55 and older over for 7 years and assessed them for both erectile dysfunction and cardiovascular disease, including heart attack and stroke. In patients with a new onset of erectile dysfunction there was an associated 25% increased risk for heart attacks, strokes, angina, or mini-strokes, compared to men with no erectile dysfunction. If men already had ED at the onset of the study, the risk for cardiovascular disease was 45% higher than those with no ED. □ In fact, ED is as important a cardiovascular disease risk factor as is smoking or a family history of heart disease. Physiologically, this kind of associated risk makes sense, as the cells that form plaques

in the arteries of the penis are the same cells that form plaques the arteries anywhere else in the body. Indeed, previous research has shown that among patients who seek help for ED, nearly 20% had undiagnosed high blood pressure, 15% had diabetes, and 5% already had significant coronary artery disease.

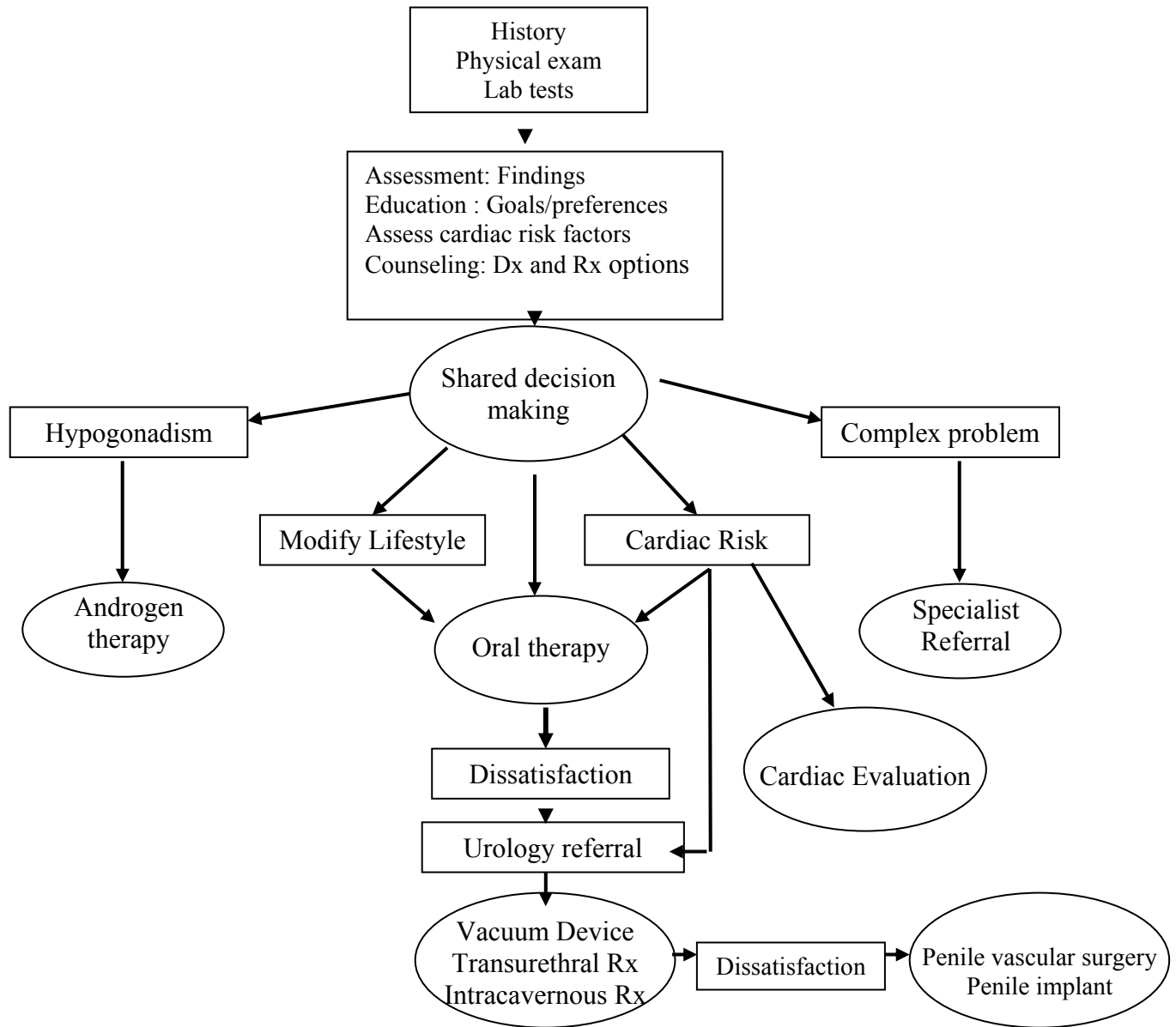


Figure 3. Goal-directed, algorithmic approach to the diagnosis and treatment of erectile dysfunction.

ERECTILE DYSFUNCTION-TREATMENT

Lifestyle changes. In general, most physicians suggest treatments that proceed from least to most invasive. Healthy lifestyle changes like quitting smoking, losing excess weight, and

increasing physical activity may help some men regain sexual function. Discontinuing drugs with harmful side effects is another effective treatment.

Psychotherapy. Until other treatments became more popular in the 1980s and 1990s, psychotherapy was the mainstay of ED treatment. Psychotherapy attempts to treat ED by decreasing the anxiety associated with intercourse. The patient's partner can help by gradually developing better intimacy and stimulation.

Drug Therapy. Drugs for treating ED can be taken orally, injected directly into the penis, or inserted into the urethra at the tip of the penis. In March 1998, the FDA approved sildenafil, the first pill to treat ED. Since that time, vardenafil and tadalafil have also been approved. These drugs are all phosphodiesterase (PDE) inhibitors. Taken an hour before sexual activity, they work by enhancing the effects of nitric oxide, which relaxes smooth muscles in the penis during sexual stimulation and allows increased blood flow. While these drugs improve the response to sexual stimulation, they do not trigger an automatic erection. The majority of men with ED will respond to these drugs and for this reason, they are considered first line therapy for ED.

No PDE inhibitor should be used more than once a day. Men who take nitrate-based drugs such as nitroglycerin for heart problems should not use these drugs because the combination can cause a sudden drop in blood pressure. One of these medications may cause a sudden drop in blood pressure when taken with an alpha-blocker.

Oral testosterone can reduce ED in some men with low natural testosterone levels, but it is often ineffective and may cause liver damage. Other forms of testosterone may be safer than oral testosterone, however, only a small proportion of ED (estimated at 6%) is due to low testosterone. Other drugs—including yohimbine hydrochloride, dopamine and serotonin agonists, and trazodone—may be effective for ED, but studies to substantiate these claims are inconsistent.

Intracavernosal Injections. Many men achieve stronger erections by injecting drugs into the penis, causing it to become engorged with blood. Drugs such as papaverine hydrochloride, phentolamine, and alprostadil (a prostaglandin E2) widen blood vessels and can help induce and maintain erections. These drugs may create unwanted side effects, however, including persistent erection (known as priapism) and scarring.

Intraurethral Injections. A system for inserting a pellet of alprostadil into the urethra is marketed as MUSE. The system uses a prefilled applicator to deliver the pellet about an inch deep into the urethra. An erection will begin within 8 to 10 minutes and may last 30 to 60 minutes. The most common side effects penile pain, warmth or burning sensation in the urethra; redness from increased blood flow to the penis; and minor urethral bleeding or spotting.

Vacuum Erection Devices. Mechanical vacuum devices induce erections by creating a partial vacuum, which draws blood into the penis, engorging and expanding it. The devices have three components: a plastic cylinder, into which the penis is placed; a pump, which draws air out of the cylinder; and an elastic band, which is placed around the base of the penis to maintain the erection after the cylinder is removed and during intercourse by preventing blood from flowing back into the body.

Penile Surgery. Surgical procedures to improve erections are performed for 3 reasons: to implant a device that can cause the penis to become erect, to reconstruct arteries and increase penile blood flow, and to occlude veins that allow blood to leak out of the penis and cause ED. Implanted devices, known as penile prostheses, are excellent at restoring erections in men with ED. Implants are devices, however and have complications that include mechanical breakdown, erosion and infection. Malleable implants consist of paired solid rods, which are inserted surgically into the corpora cavernosa. The user manually adjusts the position of the penis and, therefore, the rods. Adjustment does not affect the width or length of the penis. Inflatable implants consist of paired cylinders that are surgically inserted inside the penis and then expanded using pressurized fluid from a co-implanted fluid reservoir and a pump. The cylinders are inflated by pressing on the scrotal pump and reproduce a more natural erection with expansion of both the width and length of the penis.

Surgery to repair arteries can reduce ED caused by blockages. The best candidates for such surgery are young men with localized blockage of an artery because of pelvis injury or fracture. The procedure is almost never successful in older men with diffuse vascular disease due to atherogenesis. Surgery to tie off veins permitting blood to leak from the penis has the opposite goal: to reduce leakage of blood out of the penis that causes ED. Given the complexity of the venous drainage patterns from the penis, this type of penile surgery is rarely done.

SUMMARY

1. The normal penile erection involves relaxation of cavernous arteries, filling of venous sinusoidal spaces within the corpora cavernosal bodies and constriction of the subtunical venous plexus system.
2. Nitric oxide released from nonadrenergic-noncholinergic neurotransmission and the endothelium is the principal neurotransmitter for penile erection.
3. Erectile dysfunction is a common, age related and very treatable urologic condition that can have psychogenic, arterial, venous neurogenic and hormonal causes.
4. The clinical evaluation of ED involves a patient and goal-directed approach that incorporates the use of validated survey tools and laboratory testing for testosterone, cholesterol and lipids as appropriate.
5. Treatment with oral PDE5 inhibitors is effective for most men with mild to moderate ED.

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