Chapter 103: Erectile Dysfunction

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CHAPTER SUMMARY FROM THE PHARMACOTHERAPY HANDBOOK

For the Chapter in the Schwinghammer Handbook, please go to Chapter 82, Erectile Dysfunction.

KEY CONCEPTS

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1. The incidence of erectile dysfunction is low in men younger than 40 years of age. The incidence increases as men age likely as a result of concurrent medical conditions that impair the vascular, neurologic, psychogenic, and hormonal systems necessary for a normal penile erection.

2. Many commonly used drugs have sympatholytic, anticholinergic, sedative, or antiandrogenic effects that may exacerbate or contribute to the development of erectile dysfunction. Clinicians should be familiar with these agents and be prepared to adjust drug regimens to minimize adverse effects of these drugs on a patient's erectile function.

3. The first step in clinical management of erectile dysfunction is to identify and, if possible, reverse the underlying causes. Risk factors for erectile dysfunction, including hypertension, diabetes mellitus, smoking, and chronic ethanol abuse, should be addressed and minimized.

4. Specific treatments for erectile dysfunction include vacuum erection devices (VEDs), pharmacologic treatments, psychotherapy, and surgery. Of these, phosphodiesterase type 5 inhibitors are the medications of first choice.

5. The ideal treatment of erectile dysfunction should have a fast onset, be effective, be convenient to administer, be cost -effective, have a low incidence of serious adverse effects, and be free of serious drug interactions.

6. Specific treatment is first initiated with the least invasive modality, including VEDs or oral phosphodiesterase type 5 inhibitors, followed by intracavernosal injections or intraurethral inserts, and finally by surgical insertion of a penile prosthesis.

7. Vacuum erection devices can have a slow onset of action (up to 20 minutes) during initial use and are not discreet; therefore, they are most effective for a couple in a stable relationship.

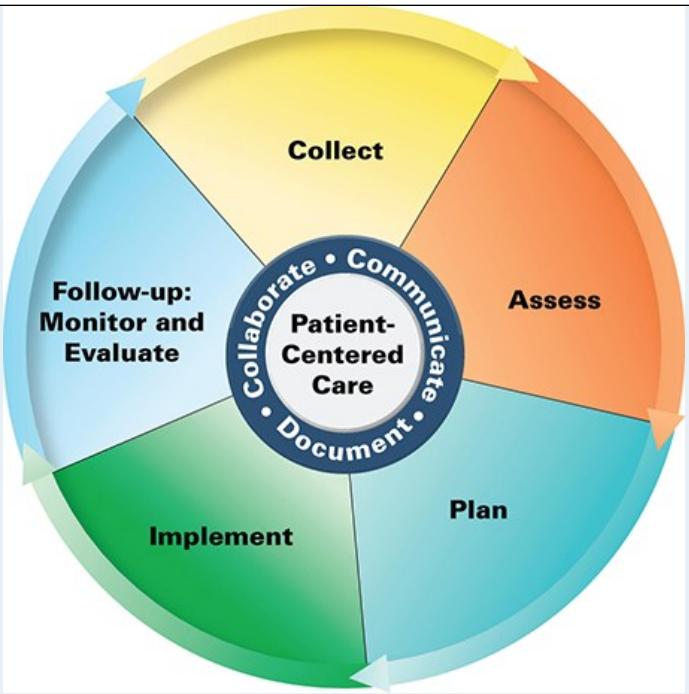
8. Although phosphodiesterase type 5 inhibitors are convenient and effective regardless of the etiology of erectile dysfunction, they fail in 30% to 40% of patients. Also, phosphodiesterase type 5 inhibitors are contraindicated in patients taking any dosage formulation of nitrate.

9. Testosterone supplementation should be reserved for symptomatic patients with primary, secondary, or mixed hypogonadism who have erectile dysfunction. Testosterone supplementation should not be used by patients with erectile dysfunction who have normal serum testosterone levels.

10. Although intracavernosal injections and intraurethral pellets of alprostadil are effective and independent of the etiology of erectile dysfunction, they fail in up to one-third of patients. To self-administer medication by these routes, patients require training to minimize administration-related adverse effects.

PATIENT CARE PROCESS

Patient Care Process for the Management of Erectile Dysfunction



Collect

- Patient characteristics (eg, age, race)
- Patient history (past medical history, marital/partner status, family history, social—sexual history, situations in which erectile dysfunction occurs, tobacco, recreational drug, or alcohol use, and medication history)
- Current psychologic status (emotional stressors, depression, performance anxiety) (see "Clinical Presentation" box)
- Objective data (see "Diagnosis" section)
  - BP, heart rate (HR), height, weight, and BMI
  - Physical examination to rule out hypogonadism and prostate dysfunction
  - Labs (eg, blood/serum glucose, lipids, testosterone)
  - Cardiovascular risk assessment, if indicated (see the "Diagnosis" section and Table 103-3)
- Administer International Index of Erectile Function screening questionnaire if feasible (see the "Diagnosis" section)
- Current and past medications, including prescription and nonprescription medications, or nonpharmacologic interventions for erectile dysfunction (see Table 103-4)
- If a patient is not responding to a phosphodiesterase type 5 inhibitor, details on how and when a patient is using the medication (see the "Efficacy" subsection under "Phosphodiesterase Type 5 Inhibitor" section)

Assess

- Patient and partner's pattern and frequency of sexual intercourse, their goals for treatment and expectations regarding therapy and its costs
- Patient's physical ability to engage in sexual intercourse
- Presence of conditions that are contraindications to sexual intercourse and to phosphodiesterase type 5 inhibitors (Table 103-3)

- Current use of medications contributing to erectile dysfunction (see Table 103-2)

Plan*

- Individualize treatment selection based on the patient's preferences for and perception of the effectiveness of various treatment options, out-of-pocket costs for treatment, and potential adverse effects; patients generally prefer a discreet treatment not obvious to sexual partners and not requiring careful attention to administration timing relative to sexual activity
- Optimize treatment for underlying causes of erectile dysfunction (eg, hypertension, coronary artery disease, dyslipidemia, diabetes mellitus, smoking, chronic ethanol abuse)
- Discontinue medications contributing to erectile dysfunction when possible (Table 103-2)
- Treat hypogonadism when present
- Initiate counseling or psychotherapy for psychogenic causes of erectile dysfunction
- Drug therapy regimen including specific agent(s), dose, route, frequency, and duration; specify the continuation and discontinuation of existing therapies (see Tables 103-4 and 103-5 and Figs. 103-2, 103-3, 103-5, and 103-6); consider the presence of concomitant diseases treatable with agents for erectile dysfunction (eg, daily tadalafil in men who also have benign prostatic hypertrophy)
- Nonpharmacologic or surgical intervention when medications are contraindicated or are not effective (see Figs. 103-2 and 103-3)
- Patient reeducation to salvage patient nonresponders to phosphodiesterase type 5 inhibitor, if appropriate (see "Efficacy" subsection under "Phosphodiesterase Type 5 Inhibitor" section)
- Monitoring parameters including efficacy (eg, BP, cardiovascular events, kidney health), safety (medication-specific adverse effects), and time frame (see Table 103-6)
- Patient education (eg, purpose of treatment, dietary and lifestyle modification, drug therapy)
- Referrals to other providers when appropriate (eg, physician, urologist)

Implement*

- Provide patient education regarding all elements of the treatment plan
- Schedule follow-up for several weeks after therapy initiation

Follow-up: Monitor and Evaluate

- Patient satisfaction with quality and quantity of penile erections
- Presence of adverse effects
- Adjust medication doses or switch to alternative agents as clinically indicated
- Consider alternative devices, drugs, combinations of drugs, or surgical intervention in patients who fail treatment with a single approach

****Collaborate with patient, caregivers, and other healthcare professionals.***

BEYOND THE BOOK

BEYOND THE BOOK

Many medications may cause or worsen erectile dysfunction. Based on the physiology of a normal erection, create a table in which you identify various classes of medications that interfere with the hormonal, vascular, neurologic, or psychogenic factors that are essential for a normal penile erection. In a separate column, identify medications that are most likely to interfere with those physiologic factors and are likely to cause erectile dysfunction.

INTRODUCTION

The National Institutes of Health Consensus Development Panel on Impotence[1] defines erectile dysfunction as the persistent or recurrent failure to achieve or maintain a penile erection to allow for satisfactory sexual intercourse. A persistent failure generally refers to erectile dysfunction for a minimum of 3 months. Patients may refer to the condition as impotence. Erectile dysfunction must be distinguished from disorders of libido or ejaculation, and of infertility, all of which are caused by different pathophysiologic mechanisms and are treated with alternative agents (Table 103-1). A patient may have one or more disorders of sexual and reproductive function. For example, an older man with primary hypogonadism could have both decreased libido and erectile dysfunction. Diagnosing the type of sexual disorders in a patient is key to initiating the most appropriate treatment.

Editors' note: In this and other chapters in Pharmacotherapy*, references to biologic gender (as assigned at birth) are used based on prior literature being discussed or anatomical or physiologic differences. We recognize that not all individuals identify with their gender at birth, and to the degree possible when discussing therapeutics, we avoid the use of references to gender. Use of gender in this chapter refers to the language used in prior studies, published guidelines, and other recommendations for diagnosis and treatment based on biological gender and does not necessarily reflect an individual's gender identity.*

TABLE 103-1

Types of Sexual Dysfunction in Men

Type of Dysfunction	Definition
Decreased libido	Decreased sexual drive or desire
Increased libido	Inappropriate and excessive sexual drive or desire
Erectile dysfunction (impotence)	Failure to achieve a penile erection suitable for satisfactory sexual intercourse
Delayed ejaculation/anejaculation	Commonly referred to as "dry sex"; ejaculation is delayed or absent
Retrograde ejaculation	Ejaculate passes retrograde into the bladder, instead of toward the anterior urethra (antegrade) and out of the penis
Infertility	Sperm are insufficient in number, have abnormal morphology, or have inadequate motility, and fail to fertilize the ovum

EPIDEMIOLOGY

The incidence of erectile dysfunction is low in men younger than 40 years but increases as men ages. The Massachusetts Male Aging Study, a cross-sectional survey of a random sample of 1,290 men in the Boston area, was conducted during the period from 1987 to 1989. The study reported an overall prevalence of 52% for any degree of erectile dysfunction in men aged 40 to 70 years, with an age-related increase in incidence ranging from 12.4

cases per 1,000 men per year in men aged 40 to 49 years, up to 46.4 cases per 1,000 men per year in men aged 60 to 69 years.[2] In men older than 70 years, the prevalence of erectile dysfunction increases and has been reported to be as high as 80%, depending on the population studied.[2] In the Health Professional Follow-up Study of more than 31,000 male health professionals aged 53 to 90 years, the prevalence of erectile dysfunction was 33%.[3] Interestingly, although the prevalence of erectile dysfunction increases with patient age, many patients fail to seek medical treatment. This may be due to a decrease in sexual activity as males age.

Erectile dysfunction is sometimes assumed to be a symptom of the aging process in men. However, more likely it results from concurrent medical conditions of the patient (eg, hypertension, arteriosclerosis, hyperlipidemia, diabetes mellitus, metabolic syndrome, or psychiatric disorders) or from medications that patients may be taking for these diseases.[1,2] For example, up to 50% of patients with diabetes mellitus develop erectile dysfunction, and medications such as diuretics are associated with a high incidence of erectile dysfunction.

PHYSIOLOGY OF A NORMAL PENILE ERECTION

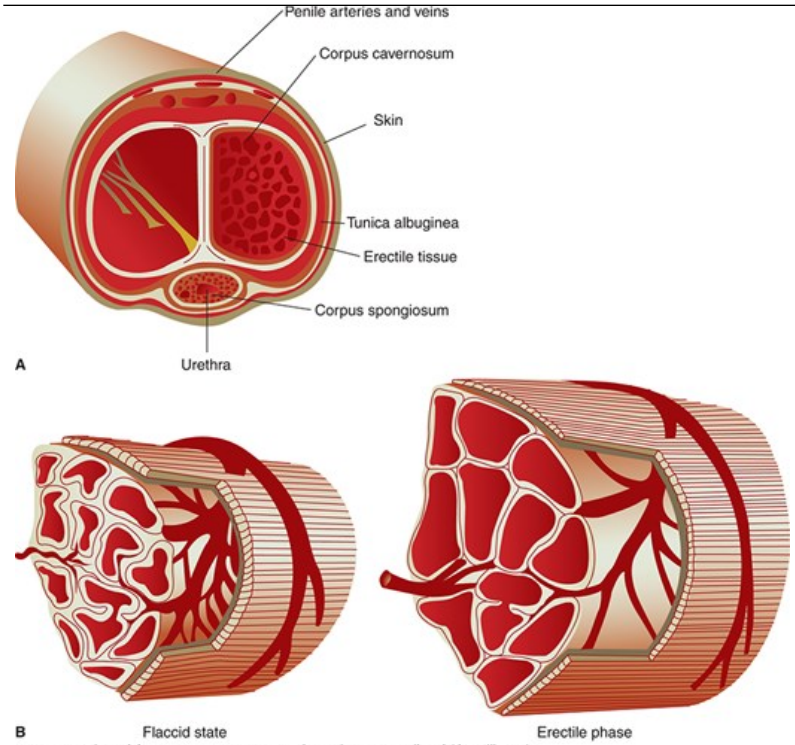
A normal penile erection requires full functioning of several physiologic systems: vascular, nervous, and hormonal. The patient also must be psychologically receptive to sexual stimuli.

Vascular System

The penis comprises two corpora cavernosa on the dorsal side and one corpus spongiosum on the ventral side. The corpus spongiosum surrounds the urethra and forms the glans penis. The corpora are composed of multiple interconnected sinuses, which can fill with blood to produce an erection. The corpora cavernosa are encased by the tunica albuginea, a fibrous tissue membrane, which has limited distensibility. In the flaccid state, arterial flow into and venous outflow from the corpora are balanced. During the erectile phase, arterial blood flow increases, and blood fills the sinusoids within the corpora. Blood traps in the corpora as the outflow of the subtunical veins is compressed against the tunica albuginea. This prolongs the erection (Fig. 103-1).

FIGURE 103-1

Microanatomy of and vascular changes in the penis in flaccid and erect states. *(Reprinted, with permission, from Walsh PC, ed. Campbell's Urology, 8th ed. Philadelphia, PA: WB Saunders; 2002:1595, 1697. Copyright © 2002 from Elsevier.)*



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

Arterial flow into the corpora is enhanced by acetylcholine-mediated vasodilation. Acetylcholine indirectly enhances arterial flow to the corpora and increases sinusoidal filling of the corporal tissue. That is, acetylcholine is a co-neurotransmitter, which works along with other nonpeptidergic intracellular neurotransmitters—including cyclic guanosine monophosphate (cGMP), cyclic adenosine monophosphate (cAMP), or vasoactive intestinal polypeptide—to produce vasodilation. In effect, cGMP and cAMP are secondary messengers that direct desired effects in target tissues.

Specifically, acetylcholine produces an erection probably through two different pathways. Through one pathway, in the presence of sexual stimulation to genital tissue, acetylcholine enhances the production of nitric oxide by endothelial cells and nonadrenergic–noncholinergic neurons. Nitric oxide enhances the activity of guanylate cyclase, which increases the conversion of cyclic guanosine triphosphate to cGMP. cGMP activates a cGMP-dependent kinase, which decreases intracellular calcium concentrations in smooth muscle cells of penile arteries and cavernosal sinuses. As a result, smooth muscle relaxation occurs, which enhances arterial blood flow to and blood filling of the corpora.[4] An erection results.

In an alternative pathway, acetylcholine or prostaglandin E enhances the activity of adenyl cyclase, which increases the conversion of cyclic adenosine triphosphate to cAMP, a potent muscle relaxant. Similar to cGMP, cAMP decreases intracellular calcium concentrations to produce smooth muscle relaxation in cells of the arteries and cavernosal sinuses. Arterial blood flow to and blood filling of the corpora are enhanced, and a penile erection results.

Nervous System and Psychogenic Stimuli

Some erections are mediated by a sacral nerve reflex arc (eg, erections can occur while the patient is sleeping). However, in the conscious patient, sensory sexual stimulation mediates erections via the central nervous system (CNS). That is, when a patient sees an attractive partner, hears sweet words, smells a particular scent, or tastes or touches a pleasant object, these situations can result in an erection. In this case, the patient's brain processes this information, and the nervous impulse is carried down the spinal cord to peripheral cholinergic nerves that innervate the vascular supply to the corpora, resulting in an erection.

The medial preoptic area of the hypothalamus is thought to be that portion of the brain responsible for integrating external stimuli. Here, dopamine exerts a proerectogenic effect, whereas alpha$_2$-adrenergic stimulation causes the penis to become and/or remain flaccid. After moving down the spinal cord, stimulatory nerve impulses travel to the penis by efferent peripheral nerves, including inhibitory sympathetic neurons (T_{11}-L_2), proerectogenic parasympathetic neurons (S_2-S_4), and proerectogenic somatic neurons (S_2-S_4).

In short, acetylcholine produces an erection by working along with other co-neurotransmitters, including cGMP and cAMP. Thus, an erection is mediated neurologically, maintained by arterial blood filling of the corpora, and sustained by occlusion of venous outflow from the corpora.

Detumescence, or the progression of an erect penis to a flaccid state, results from the actions of norepinephrine, which contracts vascular smooth muscle to decrease arterial inflow to the corpora and contracts sinusoidal tissue in the corpora. As a result, venous outflow from the corpora increases.

Hormonal System

Testosterone is principally produced by the testes at a daily rate of 4 to 8 mg and a normal physiologic serum concentration is 300 to 1,100 ng/dL (10.4-38.2 nmol/L). Production follows a circadian pattern with the highest blood levels in the morning and lowest levels in the evening. Physiologically active (free) testosterone comprises only 2% of circulating blood levels. About 44% of testosterone in the bloodstream is tightly bound to sex hormone-binding globulin and is inactive. Approximately 50% is reversibly bound to albumin and 4% is reversibly bound to corticosteroid-binding globulin; both of these portions of testosterone are in equilibrium with the 2% of testosterone that is not bound. Thus, the bioavailable portion of testosterone is normally 56% and comprises testosterone bound to albumin and corticosteroid-binding globulin, and the unbound or free portion.[5] However, the bioavailable percentage of testosterone can vary considerably with changes in sex hormone-binding globulin. Sex hormone-binding globulin increases with aging, hyperthyroidism, human immunodeficiency virus disease, and hepatic cirrhosis and decreases with obesity, diabetes mellitus, hypothyroidism, nephrotic syndrome, and corticosteroid use.[5]

Testosterone stimulates libido (sexual drive) and increases muscle mass in males. In addition, androgen receptors have been identified in the penile arterial endothelium and are thought to increase cavernosal levels of nitric oxide and cGMP, thereby enhancing vascular processes essential for a penile erection. In addition, androgens may enhance phosphodiesterase type 5 activity and may improve cavernosal nerve function.

ETIOLOGY/PATHOPHYSIOLOGY

Erectile dysfunction can result from any single abnormality or combination of abnormalities of the four systems necessary for a normal penile erection. Vascular, neurologic, or hormonal etiologies of erectile dysfunction are collectively referred to as *organic erectile dysfunction*. Approximately 80% of elderly patients with erectile dysfunction have the organic type. Patients who do not respond to psychogenic stimuli and have no organic cause for dysfunction have *psychogenic erectile dysfunction*.[6]

Diseases that compromise vascular flow to the corpora cavernosum (eg, peripheral vascular disease, arteriosclerosis, and essential hypertension) comprise the most common causes of organic erectile dysfunction.[7] Erectile dysfunction is increasingly recognized as a predictor of cardiovascular disease.[8] This is because penile arteries are small caliber blood vessels when compared to coronary or carotid arteries; the diameters are 1 to 2 mm, 3 to 4 mm, and 5 to 6 mm, respectively. As a result, erectile dysfunction could be one of the first signs of atherosclerosis and may predict future cardiovascular disease.[8]

In addition to decreasing arterial blood flow to the corpora cavernosa, atherosclerosis may cause erectile dysfunction by causing inflammation to or impairing the function of vascular endothelial cells. As a result, nitric oxide release is decreased. Since nitric oxide is essential for the relaxation of cavernosal sinusoidal tissue, tumescence is impaired.[8]

Neurological disorders cause 10% to 20% of all cases of organic erectile dysfunction. Diseases that impair nerve conduction to the central nervous system (eg, Parkinson's disease, epilepsy, stroke, spinal cord injury) or conditions that impair peripheral nerve conduction to the penile vasculature (eg, diabetes mellitus, alcoholic neuropathy) can cause erectile dysfunction.[9]

Patients must be in the proper mental frame of mind to be receptive to sexual stimuli. Patients who suffer from malaise, have reactive depression or performance anxiety, are sedated, or have Alzheimer's disease, hypothyroidism, or mental disorders commonly complain of erectile dysfunction. In most studies, patients with psychogenic erectile dysfunction generally exhibit a higher response rate to various interventions than do patients with organic erectile dysfunction because the former have less severe disease.

Psychogenic causes of erectile dysfunction appear to be more prevalent in men under the age of 40 years of age. Depression, performance anxiety, lack

of self-confidence, or partner-related problems are contributory.[10]

Diseases associated with hypogonadism, primary, secondary, or mixed, result in subphysiologic levels of testosterone, which cause diminished sexual drive (decreased libido) and secondary erectile dysfunction. Primary hypogonadism occurs with surgical removal of the testes for the treatment of prostate or testicular cancer or with testicular injury or disease. Secondary hypogonadism may result from hypothalamic or pituitary disorders of luteinizing hormone-releasing hormone or luteinizing hormone, respectively, or elevated prolactin levels, which can be associated with pituitary tumors, or can occur in patients with chronic renal failure.

Late-onset hypogonadism refers to the physiologic changes in testosterone in aging males. The etiology of hypogonadism is mixed. In addition to decreased Leydig cell function in the testes, hypothalamic release of luteinizing-releasing hormone is reduced, the circadian pattern of luteinizing hormone release from the pituitary gland is impaired, and sex hormone-binding globulin production increases.[11] Serum testosterone levels decrease starting at age 40 years by approximately 10% per decade of life. Thus, the prevalence of late-onset hypogonadism ranges from 3.2% and 5.1% in men aged 60 to 69 years and in men aged 70 to 79 years, respectively.[11,12] Symptoms include decreased libido, gynecomastia, small testes, reduced growth of body hair and beard, decreased muscle mass, and increased body fat. Decreased libido is associated with erectile dysfunction and loss of spontaneous morning erections. In addition, patients may complain of a depressed mood and tiredness, which may also contribute to erectile dysfunction. If left untreated, patients develop anemia and osteoporosis.

However, it must be noted that the relationship between erectile dysfunction and serum testosterone levels is complicated. Patients with normal serum testosterone levels may have erectile dysfunction, and patients with subnormal serum testosterone levels may have normal sexual function.[11]

Some patients have multiple factors contributing to the development of erectile dysfunction. Consider the typical older adult with cardiovascular disease, who is a smoker and has hypertension and diabetes mellitus, which are medically treated. The pathophysiology of erectile dysfunction in this patient includes vascular, neurologic, and hormonal origins. In addition, many common antihypertensive medications may cause erectile dysfunction.[13]

Social habits of patients have been linked to erectile dysfunction. The vasoconstrictor effect of cigarette smoking may compromise blood flow to the corpora and decrease cavernosal filling. Excessive ethanol intake may lead to androgen deficiency, peripheral neuropathy, or chronic liver disease, all of which can contribute to erectile dysfunction.

2 Medications may cause erectile dysfunction through similar pathophysiologic mechanisms (Table 103-2). Medications are responsible for approximately 10% to 25% of cases of erectile dysfunction. Two excellent reviews have been published.[14,15]

TABLE 103-2

Medication Classes That Can Cause Erectile Dysfunction

Drug Class	Proposed Mechanism by Which Drug Causes Erectile Dysfunction	Special Notes
Anticholinergic agents (antihistamines, antiparkinsonian agents, tricyclic antidepressants, phenothiazines)	Anticholinergic activity	• Second-generation nonsedating antihistamines (eg, loratadine, fexofenadine, or cetirizine) are associated with less erectile dysfunction than first-generation agents. • Selective serotonin reuptake inhibitor (SSRI) and multiple receptor reuptake inhibitor antidepressants cause less erectile dysfunction than tricyclic antidepressants. Of the SSRIs, paroxetine, sertraline, fluvoxamine, and fluoxetine cause erectile dysfunction more commonly than venlafaxine, nefazodone, trazodone, bupropion, duloxetine, mirtazapine, escitalopram, or vilazodone.[16] • Phenothiazines with less anticholinergic effect (eg, chlorpromazine) can be substituted in some patients if erectile dysfunction is a problem.

Dopamine antagonists (eg, metoclopramide, phenothiazines)	Inhibit prolactin inhibitory factor, thereby increasing prolactin levels	• Increased prolactin levels inhibit testicular testosterone production; decreased libido results.
Estrogens or drugs with antiandrogenic effects (eg, luteinizing hormone-releasing hormone superagonists, digoxin, spironolactone, ketoconazole, cimetidine)	Suppress testosterone-mediated stimulation of libido	• In the face of decreased libido, a secondary erectile dysfunction develops because of diminished sexual drive.[7]
CNS depressants (eg, barbiturates, narcotics, benzodiazepines, short-term use of large doses of alcohol, anticonvulsants)	Suppress perception of psychogenic stimuli	
Agents that decrease penile blood flow (eg, diuretics, peripheral β-adrenergic antagonists, or central sympatholytics [methyldopa, clonidine, guanethidine])	Reduce arteriolar flow to corpora	• Any diuretic that produces a significant decrease in intravascular volume can decrease penile arteriolar flow. • Spironolactone has estrogenic effects, and has a high potential to decrease libido and cause erectile dysfunction when used in large doses.[17] • First-generation beta blockers (eg, propranolol) or second-generation agents (eg, atenolol or metoprolol) are associated with more erectile dysfunction than newer generation agents (eg, nebivolol), which possess vasodilatory actions through blockade of alpha adrenoreceptors and release of nitric oxide.[17,18] • Safer antihypertensives include angiotensin-converting enzyme inhibitors, postsynaptic alpha$_1$-adrenergic antagonists (terazosin, doxazosin), calcium channel blockers, and angiotensin II receptor antagonists.[7,19]
Miscellaneous • Finasteride, dutasteride	Erectile dysfunction from 5-alpha reductase inhibitors is thought to result from inhibition of androgen-mediated nitric oxide production by vascular endothelial cells.[20]	• Sexual dysfunction has been reported to persist even after the 5-alpha reductase inhibitor is discontinued.[21]
Lithium carbonate	Unknown mechanism	
Gemfibrozil	Unknown mechanism	
Interferon	Unknown mechanism	
Clofibrate	Unknown mechanism	

Monoamine oxidase inhibitors (eg, phenelzine, isocarboxazid, tranylcypromine)	Unknown mechanism	
Opiates	Unknown mechanism	

SSRI, selective serotonin reuptake inhibitor.

Data from References 6,14,15.

DIAGNOSIS

With the availability in the late 1990s of effective medications for erectile dysfunction independent of the etiology, diagnostic evaluation of erectile dysfunction became streamlined. Key assessments include a description of the severity of erectile dysfunction, complete medical, psychosocial, and surgical histories, review of concurrent medications, physical examination, assessment of cardiac reserve, and selected clinical laboratory tests.[22]

To assess the severity of erectile dysfunction, the patient should be asked about the quality of sexual intercourse for the past 4 weeks to 6 months. A self-administered standardized questionnaire, such as the International Index of Erectile Function (IIEF), is often used. It is administered before initiation of any treatment and repeated at regular intervals during treatment to assess changes. The IIEF is considered a gold standard tool. It includes 15 questions about orgasmic function, libido, erectile function, intercourse satisfaction, and overall satisfaction.[22] Shorter versions of the IIEF are also used in clinical practice. For example, the IIEF-EF includes only the five or six questions that focus on erectile function. The patient responds to each question; each response is scored on a range of 1 to 5. For a six-question IIEF-EF, a score of 26 to 30 is considered normal function, 19 to 25 is mild erectile dysfunction, 13 to 18 is mild-to-moderate erectile dysfunction, 7 to 12 is moderate erectile dysfunction, and 6 or less is severe erectile dysfunction.[23] For a five-question IIEF-EF, a score of 22 to 25 is considered normal function, 17 to 21 is considered mild erectile dysfunction, 12 to 16 is mild-to-moderate erectile dysfunction, and 8 to 11 is moderate erectile dysfunction, and 1 to 7 is severe erectile dysfunction.[23]

Other commonly used questionnaires include the Sexual Health Inventory for Men, Erection Hardness Score, Erectile Dysfunction Inventory for Treatment and Satisfaction, and Treatment Satisfaction Score.[23]

A medical history should be obtained to identify concurrent medical illnesses (eg, hypertension, atherosclerosis, hyperlipidemia, diabetes mellitus, and depression) or surgical procedures (eg, perineal or pelvic) that are risk factors for or are associated with organic or psychogenic erectile dysfunction. Underlying diseases that have not responded to treatment should be addressed before specific treatment for erectile dysfunction is initiated. If the patient smokes cigarettes, drinks excessive amounts of ethanol, or uses recreational drugs, these social habits should be discontinued before specific treatment for erectile dysfunction is started.[24,25]

A complete listing of the patient's prescription and nonprescription medications and dietary supplements should be reviewed by the clinician, who should identify any drugs that could be contributing to erectile dysfunction. If possible, causative agents should be discontinued or the dose should be reduced.

A physical examination of the patient should include a check for hypogonadism (ie, signs of gynecomastia, small testicles, and decreased beard or body hair). The penis should be evaluated for diseases associated with abnormal penile curvature (eg, Peyronie's disease), which are associated with erectile dysfunction. Femoral and lower extremity pulses should be assessed to provide an indication of vascular supply to the genital area. Anal sphincter tone and other genital reflexes should be checked for the integrity of the nerve supply to the penis. A digital rectal examination in patients aged 50 years or older is needed to rule out benign prostatic hyperplasia, which may contribute to erectile dysfunction.

Erectile dysfunction is a potential marker for arteriosclerotic cardiovascular disease. Sexual intercourse and orgasm require a cardiac work equivalent

to that needed to vigorously climb two flights of stairs or to walk approximately 1.5 km. In addition, erectogenic drugs may stress the heart.[26] For this reason, a patient's cardiac reserve should be assessed before initiating the treatment for erectile dysfunction. According to the Princeton Consensus Conference guideline, the clinician should take a careful cardiovascular disease history and check for signs and symptoms of cardiovascular disease. Drug treatment for erectile dysfunction is recommended only in patients at low risk of cardiovascular events. Drug treatment should be avoided in patients at high risk of cardiovascular events. For patients at intermediate risk, treadmill testing is indicated; results will stratify patients into low- and high-risk groups, which should be managed accordingly. The risk assessment is described in Table 103-3 and detailed in the Third Princeton Consensus Panel recommendations.[19,26]

TABLE 103-3

Recommendations of the Third Princeton Consensus Conference for Cardiovascular Risk Stratification of Patients Being Considered for Phosphodiesterase Inhibitor Therapy

Risk Category	Description of Patient's Condition	Management Approach
Low risk	Has asymptomatic cardiovascular disease with <3 risk factors for cardiovascular disease Has well-controlled hypertension Has mild congestive heart failure (NYHA class I or II) Has mild valvular heart disease Has had a myocardial infarction >8 weeks ago	Patient can be started on phosphodiesterase inhibitor
Intermediate risk	Has ≥3 risk factors for cardiovascular disease Has mild or moderate, stable angina Had a recent myocardial infarction or stroke within the past 2-8 weeks Has moderate congestive heart failure (NYHA class III) History of stroke, transient ischemic attack, or peripheral artery disease	Patient should undergo a complete cardiovascular workup and treadmill stress test to determine tolerance to increased myocardial energy consumption associated with increased sexual activity. Then, reclassify in the low- or high-risk category
High risk	Has unstable or refractory angina, despite treatment Has uncontrolled hypertension Has severe congestive heart failure (NYHA class IV) Has had a recent myocardial infarction or stroke within the past 2 weeks Has moderate or severe valvular heart disease Has high-risk cardiac arrhythmias Has obstructive hypertrophic cardiomyopathy	Phosphodiesterase inhibitor is contraindicated; sexual intercourse should be deferred

NYHA, New York Heart Association.

Data from References 19,26.

Selected laboratory tests should be obtained to identify the presence of underlying diseases that could cause erectile dysfunction. These include a fasting serum blood glucose and lipid profile. Serum testosterone levels should be checked in patients older than 50 years and in younger patients who complain of decreased libido and erectile dysfunction. At least two early morning serum testosterone levels on different days, approximately 4 weeks apart, are needed to confirm the presence of hypogonadism. Within the normal physiologic range for serum total testosterone concentration, sexual drive is usually normal. Because of variability in circulating levels of sex hormone-binding globulin and the lack of precision of available assays, a patient's serum concentration of testosterone should always be interpreted in the context of the patient's symptoms and physical exam findings.[5]

The range of serum total testosterone levels that defines hypogonadism varies among various expert organizations. The Food and Drug Administration (FDA) defines hypogonadism when the serum testosterone concentration is less than 300 ng/dL (10.4 nmol/L) in an adult man, but treatment is indicated only in patients who have symptomatic hypogonadism.

CLINICAL PRESENTATION

CLINICAL PRESENTATION: Erectile Dysfunction

General

Men with erectile dysfunction are affected emotionally in different ways, and may present with

- Depression.
- Performance anxiety.
- Marital difficulties and avoidance of sexual intimacy (patients are often brought to a physician by their partners).
- Nonadherence to medications that the patient believes are causing erectile dysfunction.

Symptoms

- Erectile dysfunction or inability to have sexual intercourse, which may or may not be associated with decreased libido and ejaculatory disorders.

Signs

- IIEF questionnaire results are consistent with low satisfaction with the quality of erectile function.
- Medical history may identify concurrent medical illnesses or past surgical procedures that interfere with good vascular flow to the penis, damaged nerve function to the corpora, or mental disorders associated with decreased reception of sexual stimuli.
- Medication history may reveal prescription or nonprescription medications that could cause or contribute to erectile dysfunction.
- Physical examination may reveal signs of hypogonadism (eg, gynecomastia, small testicles, decreased body hair or beard, and decreased muscle mass), which may contribute to erectile dysfunction. The patient may have an abnormally curved penis when erect, decreased pulses in the pelvic region (suggesting impaired vascular flow to the penis), or decreased anal sphincter tone (suggesting impaired nerve function to the corpora). Men older than 50 years should undergo a digital rectal examination to determine whether an enlarged prostate is contributing to the patient's erectile dysfunction.

Assessments

- Conduct IIEF-EF to assess the severity of the patient's erectile dysfunction.[22,23]
- Complete a thorough medical history and check for any psychologic issues (eg, personal relationship issues), social habits (eg, smoking), that

might be contributing to erectile dysfunction.[22,24]

- Assess cardiac reserve based on the patient's medical history, signs and symptoms of cardiovascular disease, and treadmill testing, if indicated.

Laboratory Tests

- If the patient has signs of hypogonadism and complains of decreased libido, a serum testosterone concentration may be below the normal range, which would be consistent with a hormonal cause of erectile dysfunction. A low serum testosterone level should always be confirmed with a repeat blood level.
- If the patient has an enlarged prostate noted on digital rectal examination, blood prostate-specific antigen should be measured, especially if the patient is aged 50 or older. If elevated, the patient should be evaluated for a prostate disorder, which could contribute to erectile dysfunction.
- For patients with a history of cardiovascular disease, a fasting glucose and lipid profile is recommended to determine if treatment for risk factors for erectile dysfunction needs to be optimized.

TREATMENT

Desired Outcomes

The goal of treatment is to improve the quantity and quality of penile erections suitable for intercourse and considered satisfactory by the patient and his partner. Simple as this may sound, healthcare providers must ensure that patients and their partners have reasonable expectations before any therapies are initiated. Furthermore, only patients with erectile dysfunction should be treated. Patients who have normal sexual function should not seek—or be encouraged to seek—treatment in an effort to enhance sexual function or enable increased activity. Measures of improvement proposed include a minimum increase of at least 4 points in the IIEF-EF score or achievement of a total score of at least 20.[23] In addition, treatment should be well tolerated and be of reasonable cost.

General Approach to Treatment

3 The Third Princeton Consensus Conference recommendations are a widely accepted multidisciplinary approach to managing erectile dysfunction that maps out a stepwise treatment plan.[26] Since erectile dysfunction, cardiovascular disease, and tcardiovascularheir risk factors coexist in many patients, vigorous sexual intercourse can precipitate serious cardiovascular consequences in high-risk patients. Thus, the first step in clinical management of erectile dysfunction is to identify and, if possible, reverse underlying causes. Risk factors for erectile dysfunction, including hypertension, coronary artery disease, dyslipidemia, diabetes mellitus, smoking, or chronic ethanol abuse, should be addressed and minimized.[24,26] Patients should follow a heart-healthy lifestyle, which includes aerobic exercise, weight loss to achieve a normal body mass index, low cholesterol diet, no excessive ethanol intake, and no smoking.[7,17,27–29] In some cases, these types of interventions are sufficient to restore erectile function.[2,6,16,22] However, if erectile dysfunction does not respond to these measures, specific treatment is indicated.

4 5 6 Specific treatments of erectile dysfunction include vacuum erection devices (VEDs), pharmacologic treatments, and surgery. The ideal treatment of this disorder should have a fast onset, be effective, be convenient to administer, be cost-effective, have a low incidence of serious adverse effects, and be free of serious drug interactions (Table 103-4). Generally, when choosing from among treatment approaches, those that are least invasive are selected first; more invasive therapies are reserved for patients who do not respond to first-line agents.

TABLE 103-4

Dosing Regimens for Selected Drug Treatments for Erectile Dysfunction

Drug	Brand Name*	Initial Dose	Usual Range	Special Population Dose	Other

Phosphodiesterase Inhibitor					
Sildenafil	Viagra	50 mg orally 1 hour before intercourse	25-100 mg 1 hour before intercourse. Limit to one dose per day	In patients aged 65 years and older, start with 25 mg dose. In patients with creatinine clearance less than 30 mL/min (0.5 mL/s) or severe hepatic impairment, limit starting dose to 25 mg. In patients with mild-to-moderate hepatic impairment or those taking strong CYP3A4 inhibitors (eg, itraconazole, ketoconazole, or erythromycin), consider starting with 25 mg. In patients taking protease inhibitors, limit starting dose to 25 mg.	Generic formulations are available. Titrate dose so that erection lasts no more than 1 hour. High-fat foods decrease the rate of absorption by 1 hour. Avoid taking dose with grapefruit juice. Contraindicated with nitrates by any route of administration.
Vardenafil	Levitra[a]	5-10 mg orally 1 hour before intercourse	5-20 mg 1 hour before intercourse. Limit to one dose per day	In patients aged 65 years and older, start with 5-mg Levitra. No dosage adjustment is required in patients with decreased creatinine clearance or mild hepatic impairment. In patients with moderate hepatic impairment, start with 5-mg Levitra. Use not recommended in patients with severe hepatic impairment. In patients taking strong P450 CYP3A4 inhibitors (eg, atazanavir, erythromycin, clarithromycin, ketoconazole, itraconazole), limit starting dose to 2.5 mg in a 24-hour period. In patients on ritonavir, limit dose to 2.5 mg every 72 hours. Not recommended in patients with congenital prolonged QT interval or in patients taking Type 1A or Type 3 antiarrhythmics.	Generic formulations are available. Titrate dose so that erection lasts no more than 1 hour. High-fat foods decrease the rate of absorption by 1 hour. Avoid taking the dose with grapefruit juice. Contraindicated with nitrates by any route of administration.
	Staxyn[b]	10-mg tablet to dissolve on the tongue 1 hour before intercourse	10-mg tablet to dissolve on the tongue 1 hour before intercourse. Limit to one dose per day	Dose of Staxyn requires no adjustment in patients aged 65 years or older, patients with creatinine clearance less than 30 mL/min (0.5 mL/s), or those with mild hepatic impairment. Do not use in patients with moderate or severe hepatic	Generic formulations are available. Staxyn should be taken without any liquid or food. The tablet should be placed on the tongue where it will dissolve. No up-titration of dose is recommended. Do not

				impairment or those taking moderately or highly potent P450 CYP3A4 inhibitors. Do not initiate Staxyn in patients taking *alpha*-adrenergic antagonists.	substitute Staxyn for Levitra, or vice versa.
Tadalafil	Cialis	5-10 mg orally at least 30 minutes before intercourse OR 2.5-5 mg orally once daily	10-20 mg at least 30 minutes before intercourse. Limit to one dose per day 2.5-5 mg once daily. Limit to one dose per day	Dose of tadalafil requires no dosage adjustment in patients aged 65 years or older. In patients with creatinine clearance of 30-50 mL/min (0.5-0.83 mL/s), limit starting dose to 10 mg every 48 hours; if less than 30 mL/min (0.5 mL/s), limit starting dose to 5 mg every 72 hours. In patients with mild-to-moderate hepatic impairment, limit starting dose to 10 mg every 24 hours. Do not use in patients with severe hepatic impairment. In patients taking potent P450 CYP3A4 inhibitors, limit starting dose to 10 mg every 72 hours (if using it on demand) or 2.5 mg daily (if using a continuous daily regimen).	Generic formulations are available. Titrate dose so that erection lasts no more than 1 hour. Food does not affect rate or extent of drug absorption. Avoid taking dose with grapefruit juice. Contraindicated with nitrates by any route of administration. When taken with large amounts of ethanol, tadalafil may cause orthostatic hypotension.
Avanafil	Stendra	100 mg orally 15 minutes before intercourse	50-200 mg orally 15 minutes before intercourse. Limit to one dose per day	Dosage adjustment needed in patients aged 65 years or older. In patients with creatinine clearance of 30-89 mL/min (0.5-1.49 mL/s) or those with mild-to-moderate hepatic impairment, no dosage adjustment is needed. Not recommended if creatinine clearance is less than 30 mL/min (0.5 mL/s), if the patient has severe hepatic disease, or if the patient is taking potent P450 CYP3A4 inhibitors. If the patient is	Titrate dose so that erection lasts no more than 1 hour. May be taken with or without food. Avoid taking dose with grapefruit juice. Contraindicated with nitrates by any route of administration. When taken with large amounts of ethanol, avanafil may cause orthostatic hypotension.

				taking moderate P450 CYP3A4 inhibitors (eg, erythromycin, fluconazole), the maximum recommended dose is 50 mg every 24 hours.	
Prostaglandin E_1					
Alprostadil intracavernosal injection	Caverject, Edex	2.5-mcg intracavernosally 5-10 minutes before intercourse	10-40 mcg 5-10 minutes before intercourse. Maximum recommended dose is 60 mcg. Limit to not more than one injection per day and not more than three injections per week with a 24-hour interval between doses. Give each dose over 5-10 seconds	In older adults, use the lowest effective dose. No specific dosage adjustment provided in labeling for patients with hepatic or renal impairment.	Titrate dose to achieve an erection that lasts 1 hour. Patient will require training on aseptic intracavernosal injection technique. Avoid intracavernosal injections in patients with sickle cell anemia, multiple myeloma, leukemia, severe coagulopathy, schizophrenia, poor manual dexterity, severe venous incompetence, severe cardiovascular disease, or Peyronie's disease.
Alprostadil intraurethral pellet	Muse	125-250 mcg intraurethrally 5-10 minutes before intercourse	250-1,000 mcg just before intercourse. Limit to not more than two doses per day	In older adults, use the lowest effective dose. No specific dosage adjustment provided in labeling for patients with hepatic or renal impairment.	Patient will require training on proper intraurethral administration techniques. Use applicator provided to administer medications to avoid urethral injury.
Testosterone Supplements[c]					
Methyltestosterone	Methitest	10 mg once daily	10-50 mg once daily	No dosage adjustment provided in labeling for patients with renal or hepatic impairment or older adults.	Not recommended for use due to extensive first-pass hepatic catabolism and because it is associated with hepatotoxicity. May cause fluid retention in patients with renal or hepatic disease.
Testosterone cypionate intramuscular injection	Depo-Testosterone	100-200 mg every 2-4 weeks	200-400 mg every 2-4 weeks (up to 6 weeks)	No dosage adjustment provided in labeling for patients with renal or hepatic impairment or older adults.	During the dosing interval, supraphysiologic serum concentrations of testosterone are produced

					during a portion of the dosing interval. This has been linked to mood swings and infertility.
Testosterone enanthate intramuscular injection		100-200 mg every 2-4 weeks	200-400 mg every 2-4 weeks (up to 6 weeks)	No dosage adjustment provided in labeling for patients with renal or hepatic impairment or older adults.	During the dosing interval, supraphysiologic serum concentrations of testosterone are produced during a portion of the dosing interval. This has been linked to mood swings and infertility.
Testosterone undecanoate intramuscular injection	Aveed	750 mg as a single dose	750 mg as a single dose on Day 0, Week 4, and then 750 mg every 10 weeks	No dosage adjustment provided in labeling for patients with renal or hepatic impairment or older adults. Contraindicated in patients with serious hepatic or renal disease.	Only available in facilities certified through a Risk Evaluation and Mitigation Strategy Program. Administer by deep intramuscular injection into gluteal muscle. Avoid intravascular injection, which can lead to pulmonary oil embolism.
Testosterone transdermal patch	Androderm	4 mg as a single dose at bedtime	2-6 mg as a single dose at bedtime. Titrate dose 2 weeks after initiating a dose. Multiple patches may be needed to achieve dose needed.	No dosage adjustment is provided in labeling for patients with renal or hepatic impairment or older adults.	When administered at bedtime, serum concentrations of testosterone in the usual circadian pattern are produced. Apply to those body sites recommended in the package labeling: upper arm, back, abdomen, and thigh. Rotate application sites every 7 days. May have to apply multiple patches at one time to achieve appropriate serum testosterone level. Avoid swimming, showering, or washing administration site for 3 hours after patch application.
Testosterone gel	AndroGel 1% (25 mg/2.5 g) Testim 1% (25	5-10 g of gel (equivalent to 50-100 mg testosterone, respectively) as a	5-10 g of gel (equivalent to 50-100 mg testosterone, respectively) as a	No dosage adjustment provided in labeling for patients with renal or hepatic impairment or older adults.	Cover application site to avoid inadvertent transfer to others. Avoid swimming, showering, or washing administration site for 2 hours after gel

	mg/2.5 g)	single dose in the morning	single dose in the morning. Titrate dose at 14-day intervals		application. Apply to those sites recommended in the product labeling. For Androgel, apply to shoulders, upper arms, or abdomen. For Testim, apply to shoulders or upper arms only. Children and women should avoid contact with unclothed or unwashed application sites. Patients should wash hands with soap and water after administration of transdermal testosterone product. For patients who have difficulty measuring the appropriate dose using tubes of gel, it is also available in premeasured dose packets or from a pump dispenser. REMS assessments must be submitted to the FDA.
	AndroGel 1.62% (20.25 mg/1.25 g)	2 pumps (equivalent to 40.5 mg testosterone) as a single dose in the morning	2-4 pumps (equivalent to 40.5-81 mg) as a single dose in the morning. Titrate dose 14-28 days after starting treatment	No dosage adjustment provided in labeling for patients with renal or hepatic impairment or older adults.	Apply to shoulders and upper arms. Avoid swimming, showering, or washing administration site for 2 hours after application. Same precautions as listed above for 1% gel. REMS assessments must be submitted to the FDA.
Testosterone transdermal spray	Fortesta 2% (10 mg/actuation)	4 sprays (equivalent to 40-mg testosterone) every morning	4-7 sprays (equivalent to 40-70 mg testosterone) every morning. Titrate dose up at 14- to 35-day intervals	No dosage adjustment provided in labeling for patients with renal or hepatic impairment or older adults.	Must prime pump by pushing on pump three times. Apply to front or inner thighs only. Cover application site to avoid inadvertent transfer to others. Avoid swimming, showering, or washing administration site for 2 hours after spray application. Children and women should avoid contact with unclothed or unwashed application sites. Patients should wash hands with soap and water after administration of transdermal testosterone

					product. REMS assessments must be submitted to the FDA.
Testosterone transdermal solution	Axiron (30 mg/actuation)	One pump spray (equivalent to 30-mg testosterone) to left or right axilla daily	One to four pump sprays (equivalent to 30-120 mg testosterone, respectively) to axilla daily. If dose is more than one pump spray, divide total dose between axillae. Titrate dose at 14- to 35-day intervals	No dosage adjustment provided in labeling for patients with renal or hepatic impairment or older adults.	Limit application to axilla. Apply antiperspirant or deodorant before Axiron. If applying multiple spray doses to an axilla, apply one spray, let dry, then apply second dose. Avoid swimming, showering, or washing administration site for 2 hours after application. REMS assessments must be submitted to the FDA.
Testosterone intranasal gel	Natesto (5.5 mg/actuation)	2 pump actuations in nostrils (equivalent to 1 pump actuation per nostril, total dose of 11 mg) three times a day	2 pump actuations in nostrils (equivalent to 1 pump actuation per nostril, total dose of 11 mg) three times a day. If serum testosterone level is not corrected with this dose, it is recommended to switch to an alternative testosterone supplement	No dosage adjustment provided in labeling for patients with renal or hepatic impairment or older adults.	Administer each dose 6 to 8 hours apart. Prime pump by inverting and depressing pump 10 times. Blow nose before application. After administration, press on nostrils and lightly massage. Do not blow nose or sniff for 1 hour after administration. Do not administer with any other intranasal product, except decongestants. Discontinue if patient has rhinitis. If patient develops severe rhinitis, temporarily switch to an alternative testosterone replacement product until rhinitis resolves. Avoid use in patients with chronic nasal conditions, sinusitis, or after nasal or sinus surgery.
Testosterone subcutaneous implant pellet	Testopel 75 mg/pellet	150-450 mg (equivalent to 2-6 pellets) as a single dose every 3-6 months	150-450 mg as a single dose every 3-6 months	No dosage adjustment recommended for renal or hepatic impairment or older adults.	Trained health professional is required to administer the dose. Use sterile implanter kit. Administration of the dose requires a forearm incision and local anesthesia to

					subcutaneously implant dose. Clinical onset is delayed for 3-4 months after initial dose. Generic formulations are available in higher strengths: 100 or 200 mg per pellet.

*Common brand names are included in this table. Medications may be available with other brand names or as generic formulation.

[a]Levitra brand was discontinued in April 2021. Vardenafil is available as generic formulation.

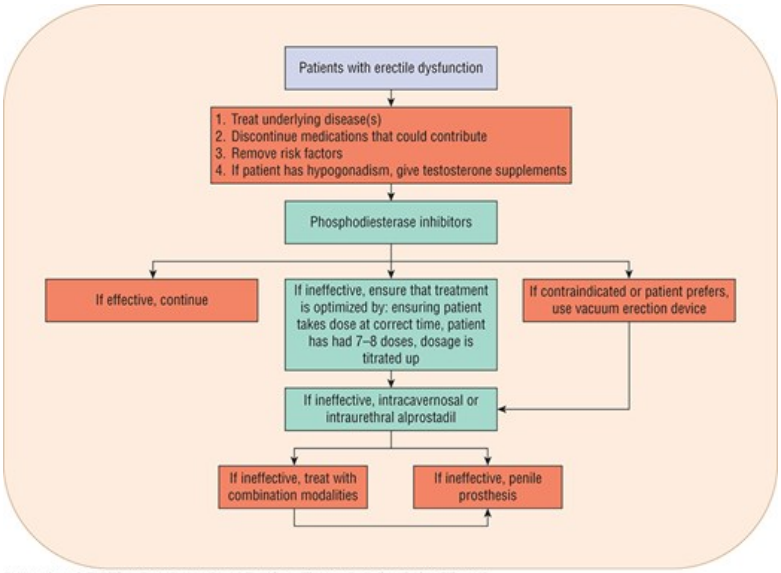
[b]Staxyn brand was discontinued in April 2021. Vardenafil is available as generic formulation.

[c]This listing includes only those testosterone supplements approved for treating hypogonadism associated with aging. Testosterone enanthate auto-injector and oral testosterone undecanoate are not included for this reason.

The British Society of Sexual Medicine,[16] 2018 American Urological Association,[22] and the Fourth International Consultation of Sexual Medicine[30] clearly identify oral phosphodiesterase type 5 inhibitors for first-line treatment. VEDs, intracavernosal injection of erectogenic agents, or intraurethral prostaglandin pellets are second-line treatments. Prescribing a particular agent for a patient should be individualized. Surgical intervention should be reserved for patients who fail to respond to first- and second-line treatments. A sample algorithm that guides the selection of treatment is shown in Fig. 103-2.

FIGURE 103-2

Algorithm for selecting treatment for erectile dysfunction.



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

Nonpharmacologic Therapy

Vacuum Erection Device

A vacuum erection device (VED) is a noninvasive medical device with few contraindications to use. It is available over-the-counter. A patient makes a one-time purchase, and the device can be used repeatedly.

A VED has two parts: a pump, which generates a negative vacuum pressure, and a cylinder, which is closed at one end (Fig. 103-3). The patient applies lubricant to and inserts his penis into the open end of the cylinder, which is then pushed up flush against his lower abdomen to create a vacuum chamber. The lubricant helps maintain a tight seal between the VED and the patient's abdomen. Then, the patient activates the pump to produce a vacuum pressure, which draws arteriolar blood into the corpora cavernosa. To prolong the erection, the patient places constriction bands or tension rings at the base of the erect penis. The bands or rings trap arteriolar blood in the corpora cavernosa and reduce venous outflow from the penis. With the assistance of loading cones to protect the glans, these bands or rings can be rolled over the glans penis onto the erect penile shaft. Alternatively, the bands or rings can be first threaded onto the plastic cylinder before the penis is inserted. Once the penis is erect, the band or ring can be rolled off the cylinder onto the base of the penis. However, some patients prefer to apply the band or ring before the penis is erect.[6,31]

FIGURE 103-3

Technique for using a vacuum erection device. (*Reprinted, with permission, from Osbon Erec Aid Esteem Vacuum Therapy System User Guide. Eden Prairie, MN: TIMM Medical Technologies.*)

Assemble your system according to the two-step procedure.

Step 1

Apply Osbon Personal Lubricant™ to the following:

1. two inches inside the open end of the cylinder;
2. the rim of the cylinder that meets the body to form the vacuum seal; and
3. the entire head of the penis.

Applying lubricant properly will help you achieve the best erection possible.

Tip: Trimming the pubic hair around the base of the penis with a pair of scissors may also prove helpful in creating an airtight seal.

Step 2

It is recommended that you stand for this step (the system can also be used when you are sitting or lying down).

Place the lubricated penis inside the cylinder with the label on the cylinder facing up. With one hand, hold the cylinder at a downward 45° angle with the open end snugly against the body.

Tip: Rotate cylinder slightly back and forth to make an airtight seal against the body, make sure the testicles are not drawn into the cylinder.

Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

The onset of action of the VED is 3 to 20 minutes; a faster onset of 2 to 3 minutes is associated with continued, more experienced use.[31] VEDs are not discreet. That is, a patient's use of a VED is evident to the partner. For this reason, VEDs appear to work best in older patients who are married or who have stable sexual relationships. In this group, VEDs could be considered first-line therapy, and the overall satisfaction rate can be as high as 60% to 80% (range, 27%-94%) in all patients, including those with diabetes mellitus and spinal cord injury.[30,31] VEDs may be used as second-line therapy in patients who do not respond to oral phosphodiesterase type 5 inhibitors,[22] which includes patients who have had a radical prostatectomy or those who do not respond to injectable drug treatments for erectile dysfunction. The combination of a VED with intracavernosal or intraurethral alprostadil[24,32] or a phosphodiesterase type 5 inhibitor is associated with a higher efficacy rate than the use of the VED alone.[16,32,33] As a result,

combination therapy sometimes is attempted before penile prosthesis surgery is considered in the patient who fails to respond to a VED alone.

Patients may discontinue using VEDs because they are inconvenient and not discreet. It has been reported that the dropout rate is as high as 56% during the first year of use.[31] Also, 6% to 11% of partners complain that the penis is cool to the touch or is discolored (bluish) in appearance, particularly when constriction bands are used.[22]

Vacuum erection devices are available with battery-operated pumps, which offer convenience, particularly in patients with arthritis of the hands. When choosing a device, patients should select one with a pop-off safety valve that minimizes the likelihood of excessively high vacuum pressure, which can cause penile discomfort, petechiae, or hematoma.[24,31]

Penile pain, bruising, or injury from VEDs most often is caused by the constriction bands used to sustain an erection. Because these rings trap blood in the corpora and reduce arteriolar flow into the penis, the penile shaft may feel cold and numb. If the constriction bands are applied for longer than 30 minutes, the penile shaft may turn blue and hurt.[22] Patients may complain that a hinge-like erection is produced in that the penis pivots on the rubber ring or tension band. Patients sometimes fail to ejaculate.[24]

Vacuum erection devices are contraindicated in patients with sickle cell disease or patients with a history of prolonged erections. These patients are prone to priapism, which can be exacerbated by the use of constriction bands with VEDs. The devices also should be used cautiously by patients taking warfarin, as this agent increases the likelihood of penile bruising during use of the device. Finally, VEDs are contraindicated in patients with severe penile curvature.

Pharmacologic Therapy

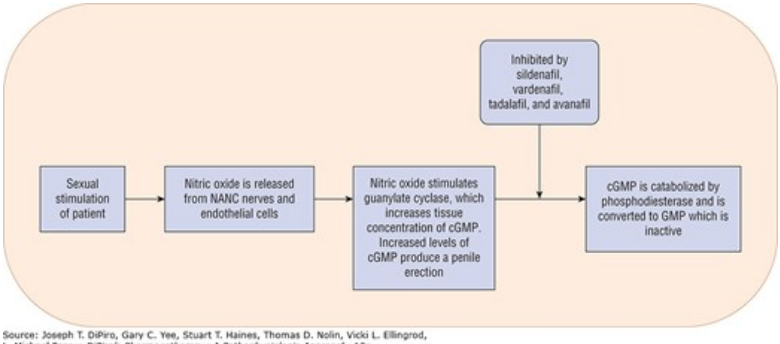
Phosphodiesterase Type 5 Inhibitors

Mechanism

In the presence of sexual stimulation, nitric oxide is released by neurons and endothelial cells in cavernosal tissue, thereby enhancing the activity of guanylate cyclase, the enzyme responsible for the conversion of guanylate triphosphate to cGMP (Fig. 103-4).[22] cGMP is a vasodilatory secondary messenger that activates protein kinase G, which decreases intracellular calcium levels, relaxes smooth muscle, enhances arterial flow to the corpora cavernosa, and increases blood filling of cavernosal sinuses. Catabolism of cGMP in cavernosal tissue is mediated by phosphodiesterase isoenzyme type 5.

FIGURE 103-4

Mechanism of action of phosphodiesterase type 5 inhibitors. All inhibit catabolism of cGMP, a vasodilatory secondary messenger. (cGMP, cyclic guanosine monophosphate; NANC, nonadrenergic noncholinergic.)



Four competitive, reversible inhibitors of the phosphodiesterase isoenzyme type 5 are marketed for erectile dysfunction in the United States (Table 103-5). Chemically, they are nonhydrolyzable analogs of cGMP and they act by decreasing catabolism and maintaining high concentrations of cGMP in the corpora cavernosa. In effect, this sustains a penile erection. However, these medications are not specific for phosphodiesterase isoenzyme type 5. They also inhibit other phosphodiesterase isoenzymes in other tissues and organs, which produces some of the unwanted side effects of this

medication class.[34]

TABLE 103-5

Pharmacodynamics and Pharmacokinetics of Phosphodiesterase Inhibitors

	Sildenafil (Viagra)	Vardenafil (Levitra/Staxyn)	Tadalafil (Cialis)	Avanafil[36,37] (Stendra)
Inhibits PDE-5	Yes	Yes	Yes	Yes
Inhibits PDE-1	Yes	Yes	Minimally	Minimally
Inhibits PDE-6	Yes	Yes	No	Mildly
Inhibits PDE-11	No	No	Yes	No
Onset of action (min)	60	25-60	30	15-30
Time to peak plasma level (hours)	0.5-1	0.7-0.9/1.5	2	0.5-0.8
Oral bioavailability (%)	40	15/21-44	36	15
Fatty meal decreases rate and/or extent of oral absorption?	Yes	Yes/No[a]	No	Yes. Fatty meal decreases rate but not extent of absorption.
Mean plasma half-life (hours)	3.7	4.4-4.8/4-6	18	5
Active metabolite	Yes	Yes/Yes	No	Yes
Is CYP 3A4 principally responsible for metabolism?	Yes	Yes	Yes	Yes
Other CYP enzymes responsible for metabolism	CYP 2C9, CYP 2C19, CYP 2D6, CYP 1A2	CYP 3A5, CYP 2C9	None	CYP 2C9
Percentage of dose excreted in feces	80	91-95/91-95	61	62
Percentage of dose excreted in urine	13	2-6/2-6	36	21
Clinical onset (minutes)	60	30/60	60	25-40
Duration (hours)	2-4, up to 12	4-5/4-6	24-36	6+

[a]When Staxyn is taken with water, the area under the curve decreases by 29%.

Data from References 34,35.

Selectivity of Other Phosphodiesterase Isoenzymes

More than 11 different phosphodiesterase isoenzymes have been identified; however, the physiologic effects of stimulation and inhibition of some of

these isoenzymes remain to be elucidated.[13,34] The four commercially available phosphodiesterase type 5 inhibitors exhibit variable selectivity for phosphodiesterase 5 as opposed to phosphodiesterase types 1, 6, and 11. These differences are displayed in Table 103-5.

Phosphodiesterase isoenzyme 1 is found in the peripheral vasculature. Inhibition of this isoenzyme has been linked with peripheral vasodilation, which can lower blood pressure, and cause flushing and reflex tachycardia, particularly in patients taking nitrates, alpha-adrenergic antagonists, or some antihypertensives.[37] Among the phosphodiesterase type 5 inhibitors, tadalafil and avanafil have much less selectivity for phosphodiesterase type 1 as compared with phosphodiesterase type 5. As a result, tadalafil and avanafil are less likely to cause hypotension as compared with sildenafil and vardenafil.[36,37]

Phosphodiesterase isoenzyme type 6 is localized to the rods and cones of the retina. Inhibition of this isoenzyme has been associated with blurred vision and cyanopsia. Sildenafil is the most potent inhibitor of phosphodiesterase isoenzyme type 6, vardenafil is an intermediate inhibitor, and tadalafil and avanafil are the least potent inhibitors.[35,37]

Phosphodiesterase isoenzyme type 11 is localized to skeletal muscle. Inhibition of this isoenzyme has been associated with myalgia and back muscle pain. Tadalafil exerts the greatest inhibitory activity against phosphodiesterase type 11.[35,37]

Efficacy

Because of their apparent effectiveness, convenient oral route of administration, and comparatively low incidence of serious adverse effects, phosphodiesterase type 5 inhibitors are first-line therapy for erectile dysfunction. They allow for discreet use. Although not based on direct comparison trials, all four commercially available phosphodiesterase type 5 inhibitors are considered to be equally effective and comparable in safety and tolerability.[13,34] Patient preference studies show that some patients may choose a particular agent because of the preferences of the sexual partner or the onset, duration, or cost of a specific medication.[38] For example, for a patient with infrequent sexual intercourse, sildenafil or vardenafil is a good choice; for a patient with frequent sexual intercourse, tadalafil may be preferred; and for a patient with unscheduled periodic intercourse, a fast-acting agent like vardenafil ODT may be preferred.[39]

Usual starting and maintenance dose regimens are included in Table 103-4.

In the presence of sexual stimulation and in doses of 25 to 100 mg, sildenafil produces satisfactory erections in 56% to 82% of patients, independent of the etiology of erectile dysfunction. Similar results are documented in the product labeling for the other agents in this class (65%-80% for vardenafil, 62%-77% for tadalafil, and 57%-77% for avanafil). The change in IIEF-EF score for a phosphodiesterase inhibitor is approximately 5.6 to 7.4 points.[25] Response rates are in the lower range for patients with diabetes mellitus or after radical prostatectomy, or those with severe vascular disease, probably due to neuropathy, or surgery-related nerve damage.[22] The effectiveness of the drugs appears to be dose-related.

Approximately 30% to 40% of patients do not respond to phosphodiesterase type 5 inhibitors.[22] At least half of nonresponders benefit from education on proper use of the drugs.[32] Therefore, follow-up is always recommended after a phosphodiesterase type 5 inhibitor is initiated to see if additional education is needed for the following points: (a) patients must engage in sexual stimulation (foreplay) for the best response;[16,22] (b) sildenafil and vardenafil should be taken on an empty stomach, at least 2 hours before meals, for the fastest response, but tadalafil and avanafil can be taken without regard to meals; (c) patients who do not respond to the first dose should continue with the phosphodiesterase type 5 inhibitor for at least seven to eight doses before failure is declared, as increasing success rates are reported with sequential dose administration;[16,32] (d) some patients require dosage titration up to 100-mg sildenafil, 20-mg vardenafil, 20-mg tadalafil, or 200-mg avanafil for a response;[13] (e) patients should avoid excessive alcohol intake, which can cause drowsiness and hypotension and worsen erectile dysfunction; (f) treatment of concomitant medical illnesses that contribute to erectile dysfunction (eg, diabetes mellitus, hypertension, and hypogonadism) should be optimized (if the patient has depression because of divorce or loss of a sexual partner, or has performance anxiety, psychologic counseling may be helpful).[22]

The phosphodiesterase type 5 inhibitors should not be used by patients with normal erectile function. Also, according to FDA-approved labeling, the drugs should not be used in combination with other forms of therapy for erectile dysfunction because prolonged erections (which may lead to priapism) may result.[22] Phosphodiesterase type 5 inhibitors should be avoided in patients predisposed to developing priapism, including men with sickle cell anemia, leukemia, or multiple myeloma.

Long-term use of phosphodiesterase type 5 inhibitors for up to 10 consecutive years continues to be effective and is not associated with tachyphylaxis.[6] The voluntary discontinuation rate among patients has been reported as high as 50% after 6 to 24 months of treatment, despite a positive treatment response.[13] This phenomenon is likely due to the high out-of-pocket costs of phosphodiesterase type 5 inhibitors, the inconvenient process of obtaining the medication, adverse drug effects, the patient's loss of interest in sexual intercourse, partner-related problems (marital problems/no partner) or the efficacy of the medication being below the patient's expectations because of worsening of the patient's underlying erectile dysfunction disease.[6,40,41]

Despite the initial effectiveness of phosphodiesterase type 5 inhibitors and the measures to salvage patients with reeducation, some patients with severe vascular or neurologic disease will show minimal or no response to maximum doses of a phosphodiesterase type 5 inhibitor. Various strategies have been attempted in this subgroup of patients, including the following:

1. The effectiveness of switching from one phosphodiesterase type 5 inhibitor to another when the patient does not respond to an initial agent is controversial, although it is clear that some patients prefer one agent over another.[24] Controlled clinical trials in larger patient groups are needed before this strategy is used as routine treatment.
2. Switching the patient from an as needed to a daily regimen of tadalafil may be reasonable when the patient has difficulty coordinating the timing of tadalafil before meals or sexual intercourse.[6,42] However, a daily dose regimen is more expensive than an on-demand regimen.
3. Adding an as-needed shorter-acting phosphodiesterase inhibitor to a low daily dose of tadalafil regimen.[16]
4. High-dose phosphodiesterase type 5 inhibitor treatment (eg, sildenafil 200 mg) has been used anecdotally. However, such doses are also associated with a higher frequency of adverse effects.[43]
5. In older patients (age greater than or equal to 65 years) with late-onset hypogonadism and erectile dysfunction, correcting the former with testosterone supplementation improves the response to a phosphodiesterase type 5 inhibitor.[22,32]
6. Phosphodiesterase type 5 inhibitors have been combined with intracavernosal or intraurethral alprostadil in selected patients. This allows combining agents with 2 different vasodilatory MOA.[22,44]

Pharmacokinetic parameters of the phosphodiesterase inhibitors are listed in Table 103-5.[35]

Sildenafil and the conventional oral formulation of vardenafil have similar pharmacokinetic profiles. Both drugs have a 1-hour onset of action and short duration of action. Oral absorption is significantly delayed by 1 hour when either drug is taken within 2 hours of a fatty meal.[35] An oral disintegrating tablet (ODT) formulation of vardenafil, which dissolves on the tongue, has 1.2- to 1.4-fold higher bioavailability than the conventional oral tablet when taken without water. Unlike the conventional tablet, the ODT formulation should be taken without water, which allows discretion, and is not susceptible to a drug-food interaction. In addition, the ODT dissolves on the tongue and does not require swallowing. Thus, patients with dysphagia, who comprise almost 25% of patients who are 50 years of age or older, could easily use this formulation.[34,39] When compared with the other phosphodiesterase type 5 inhibitors, tadalafil has a slower onset of action of 2 hours and a prolonged duration of action up to 36 hours. Food does not affect the rate of absorption of tadalafil. Tadalafil offers greater spontaneity for patients, as one dose can last through an entire weekend and it allows for multiple acts of sexual intercourse over multiple days with a single dose. Avanafil has an onset of action of 15 minutes; its onset is faster than, but is similar in duration to sildenafil and vardenafil. A high-fat meal will delay the absorption and reduce total amount absorbed by avanafil.[16,24,37]

The onset of action of these agents has undergone reexamination to assess how soon after drug administration patients can expect to have an erection suitable for intercourse. Although up to 50% of patients may develop an erection within 20 to 30 minutes of sildenafil 100 mg, vardenafil 20 mg, tadalafil 20 mg, or avanafil 200 mg, the rest of the patients may require a full hour to achieve an adequate erectile response.[35] Therefore, patients should be instructed to allow adequate time for the drug to work. In addition, sildenafil and vardenafil have been reported to be effective in some patients up to 12 hours after dosing, and tadalafil is effective up to 36 hours after dosing, which is long after plasma concentrations have declined. It has been hypothesized that this may be due to the continued intracellular action of the phosphodiesterase type 5 inhibitor. Further study is needed to determine if avanafil's duration of action is longer than 6 hours.

Concomitant ingestion of ethanol with phosphodiesterase type 5 inhibitors can result in orthostatic hypotension and drowsiness. Therefore, the manufacturer recommends that patients avoid ethanol when taking these medications.

All four phosphodiesterase type 5 inhibitors are hepatically catabolized principally by the cytochrome P450 3A4 microsomal isoenzyme. Other P450 isoenzymes and/or other hepatic enzymes are minor routes of catabolism (see Table 103-5). Sildenafil has an active metabolite, which is excreted primarily in the urine. Tadalafil has a clinically insignificant active metabolite. However, 36% of tadalafil drug is renally eliminated. Thus, both sildenafil and tadalafil doses should be reduced in patients with significant renal impairment. Vardenafil and avanafil have active metabolites that are largely excreted in feces. No specific dosage reduction of these medications is recommended in patients with reduced renal function because of the intermittent nature of the dosing schedule. However, avanafil is not recommended when the creatinine clearance is less than 30 mL/min (0.5 mL/s) (see Table 103-5).

Dosing

The usual oral doses of the phosphodiesterase type 5 inhibitors are listed in Table 103-4. Sildenafil, vardenafil (oral swallow tablets), and avanafil should be taken on demand at least 30 to 60 minutes before sexual intercourse. Vardenafil ODT and tadalafil should be taken 15 minutes and 2 hours, respectively, before sexual intercourse. The agents vary as to whether doses must be adjusted for patients aged 65 years and older and those with compromised hepatic or renal function. Patients should be advised to take no more than the amount prescribed and not more than one dose per day.[45] Doses higher than those recommended have been described in the published literature (eg, sildenafil 200 mg).[43] However, such dosing regimens have not consistently produced improved erectile responses.

For patients who do not respond to an adequate course of on-demand phosphodiesterase type 5 inhibitors for erectile dysfunction, daily low dosing of tadalafil may improve endothelial function in cavernosal tissue. That is, regular use of phosphodiesterase type 5 inhibitors may activate endothelial nitric oxide synthase, increase local concentrations of cGMP, which may increase oxygen tension, improve blood flow, and reduce endothelial damage and fibrosis in the corpora cavernosa.[46] Other potential advantages of this daily low dosing regimen include a lower potential for dose-related adverse effects and increased spontaneity of sexual intercourse. However, disadvantages of the daily low-dose regimen are the high cost of treatment; patients with more severe erectile dysfunction, who may require higher doses of a phosphodiesterase type 5 inhibitor, may not respond.[22,28,47] Although clinical trials of daily dosing of tadalafil 10 and 20 mg[48,49] have been published, the only FDA-approved labeling is for daily dosing of tadalafil 2.5 or 5 mg.

Adverse Effects

Most adverse effects of the phosphodiesterase type 5 inhibitors are mild or moderate and are self-limited; and tolerance to the adverse effects develops with continued use.[28,47,50,51] The rates of drug discontinuation because of adverse effects are low, ranging from 2.1% to 25%, and are similar for all four agents. In usual doses, the most common adverse effects are headache (11%), facial flushing (12%), dyspepsia (5%), nasal congestion (3.4%), and dizziness (3%), all of which are dose-related and result from vasodilation or smooth muscle relaxation secondary to inhibition of phosphodiesterase isoenzyme type 1 or 5 in cardiac or vascular tissues.[47,50] However, some differences in the adverse reaction profile do exist. Sildenafil and vardenafil use is associated with more vascular and ocular adverse effects due to its inhibition of phosphodiesterase type 1 and 6, and tadalafil is associated with more lower back and limb pain and myalgia due to its greater inhibition of phosphodiesterase type 11.[35,50-52] Avanafil may be the best-tolerated agent because of its highly selective inhibition of phosphodiesterase type 5 and short half-life.[36-38,53]

Sildenafil and vardenafil produce an 8 to 10 mm Hg decrease in systolic and a 5 to 8 mm Hg decrease in diastolic blood pressure starting approximately 1 hour after a dose is taken and lasting for 4 hours. Most patients are asymptomatic as a result of these blood pressure changes, but some patients, particularly those taking multiple antihypertensives or nitrates or those with baseline hypotension, may develop dizziness or palpitations. Avanafil and tadalafil produce decreases in systolic and diastolic blood pressure that are smaller than those associated with sildenafil and vardenafil, although the decrements may be greater when they are used along with other antihypertensives or α-adrenergic antagonists.[47] All phosphodiesterase type 5 inhibitors must be used with caution in patients with cardiovascular disease because of the cardiac risk inherent to vigorous sexual activity. The management approach for such patients, as described in the recommendations of the Princeton Consensus Guideline Conference III,[26] should be applied to all the patients in whom phosphodiesterase type 5 inhibitors are being considered for use (see Table 103-3). If a patient who has

cardiovascular disease develops angina during sexual intercourse after having taken a phosphodiesterase type 5 inhibitor, the patient should immediately stop and rest for the next 5 to 10 minutes. If angina does not resolve after 20-30 minutes, or if the patient develops additional anginal symptoms, the patient should be taken to the nearest emergency room.[54]

Sildenafil, vardenafil, and avanafil cause increased sensitivity to light, blurred vision, or transient loss of blue–green color discrimination in 2% to 3% of patients. This adverse effect is dose-related with the incidence increasing to 40% to 50% in patients taking sildenafil 200 mg.[47,55] These effects result from inhibition of phosphodiesterase type 6 in the photoreceptor cells of retinal rods and cones. Visual adverse effects commonly occur 1 to 2 hours after oral dosing when peak serum concentrations are achieved.[55] Avanafil has moderate and tadalafil has minimal to no inhibitory activity against phosphodiesterase type 6, and they are associated with a lower incidence of visual adverse effects (less than 1%) when compared to sildenafil and vardenafil.[47] Nevertheless, according to current product labeling, all phosphodiesterase type 5 inhibitors should be stopped immediately if the patient reports vision loss and should be used cautiously in patients at risk for retinitis pigmentosa, a genetic disease associated with retinal phosphodiesterase deficiency.

Nonarteritic anterior ischemic optic neuropathy (NAION) is a sudden, unilateral, painless blindness, which may be irreversible. Isolated cases of NAION have been associated with phosphodiesterase type 5 inhibitor use.[50] NAION has developed at variable and unpredictable times after starting a phosphodiesterase type 5 inhibitor, ranging from 6 hours to months or years after the first dose. Although a cause–effect relationship has not been established, it has been proposed that the blood pressure-lowering effects of these medications may decrease blood flow to the optic nerve and lead to a sudden unilateral decrease in vision.[56] Because NAION may lead to permanent vision loss, the FDA has required inclusion of warnings on the product labeling of phosphodiesterase type 5 inhibitors. Specifically, before receiving these agents, patients at risk for NAION should be evaluated by an ophthalmologist, risk factors for NAION should be addressed, and the patient should be cautioned against using a phosphodiesterase type 5 inhibitor.[47,50,56]

Patients at risk of NAION include a wide variety of patients: those with glaucoma, macular degeneration, diabetic retinopathy, dyslipidemia, or hypertension, those who have undergone eye surgery or have experienced eye trauma, patients who are aged 50 years or more, or smokers. A patient who experiences sudden vision loss in one eye while taking a phosphodiesterase type 5 inhibitor should be evaluated for NAION before continuing treatment. If NAION is present, the phosphodiesterase type 5 inhibitor should be discontinued as there is a 15% to 25% risk of developing NAION in the other eye in the ensuing 5 to 10 years.[56]

Acute unilateral hearing loss has also been reported after use of a phosphodiesterase type 5 inhibitor. A cause–effect relationship has not been established. In the cases reported, the hearing loss occurred within 1 to 3 days of starting treatment; it was variably accompanied by tinnitus or vertigo, and often resulted in residual hearing loss despite discontinuation of the phosphodiesterase type 5 inhibitor.[47] The product labeling now includes a warning that a phosphodiesterase type 5 inhibitor should be immediately stopped, and the patient should see a physician if sudden hearing loss develops.[50]

Priapism is a rare adverse effect of phosphodiesterase type 5 inhibitors, particularly sildenafil and vardenafil. Priapism has been associated with excessive doses of the phosphodiesterase type 5 inhibitor or when they are used along with other erectogenic drugs.[24]

Sildenafil use has been associated with an increased risk of melanoma. The proposed mechanism is that phosphodiesterase type 5 inhibition activates *BRAF*, a human gene that produces a protein that causes proliferation of melanoma cells. However, a cause–effect relationship has not been established.[57,58]

Recommendations for adverse effect monitoring are included in Table 103-6.

TABLE 103-6

Drug Monitoring Table

Drug	Adverse Drug Reaction	Monitoring Parameter	Comments

Phosphodiesterase Inhibitor			
Sildenafil	• Headache • Flushing • Dyspepsia • Nasal congestion • Cyanopsia • NAION • Hypotension • Priapism • Hearing loss	• Clinical symptoms of erectile dysfunction • Visual complaints, loss of vision • Hearing loss • Blood pressure • Pulse	• Discontinue sildenafil if the patient has any visual or hearing loss and refer the patient to a physician • If the patient is taking any antihypertensives, stabilize blood pressure before starting sildenafil • If the patient develops priapism, he should proceed to the emergency department • If the patient has a bleeding disorder, use cautiously
Vardenafil	• Headache • Flushing • Dyspepsia • Nasal congestion • Cyanopsia • NAION • Hypotension • QT interval prolongation on EKG • Priapism • Hearing loss	• Clinical symptoms of erectile dysfunction • Visual complaints, loss of vision • Hearing loss • Blood pressure • Pulse • Palpitations or dizziness	• Discontinue vardenafil if the patient has any visual or hearing loss and refer the patient to a physician • If the patient is taking any antihypertensives, stabilize blood pressure before starting vardenafil • If the patient has palpitations or dizziness, check EKG. If QT prolongation is present, refer the patient for appropriate medical care • If the patient develops priapism, he should proceed to the emergency department • If the patient has a bleeding disorder, use cautiously
Tadalafil	• Headache • Flushing • Dyspepsia • Nasal congestion • Cyanopsia • Hearing loss • NAION • Hypotension • Lower backor lower extremity pain or myalgia • Priapism	• Clinical symptoms of erectile dysfunction • Visual complaints, loss of vision • Hearing loss • Blood pressure • Pulse • Palpitations or dizziness • Myalgia	• Discontinue tadalafil if the patient has any visual or hearing loss and refer the patient to a physician • If the patient is taking any antihypertensives, stabilize blood pressure before starting tadalafil • If the patient develops priapism, he should proceed to the emergency department • If the patient has a bleeding disorder, use cautiously • Muscle pain is dose-related
Avanafil	• Headache • Flushing • Dyspepsia • Nasal congestion • Cyanopsia	• Clinical symptoms of erectile dysfunction • Visual	• Discontinue avanafil if the patient has any visual or hearing loss and refer the patient to a physician • If the patient is taking any antihypertensives, stabilize blood pressure before starting avanafil • If the patient develops priapism, he should proceed to the emergency

	• Hearing loss • NAION • Hypotension • Priapism	complaints, loss of vision • Blood pressure • Pulse • Palpitations or dizziness • Hearing loss	department • If the patient has a bleeding disorder, use cautiously
Prostaglandin E_1			
Alprostadil, intracavernosal	• Penile pain • Hematoma at injection site • Priapism • Hypotension • Fibrotic nodules along penile shaft • Decreased blood pressure • Dizziness	• Clinical symptoms of erectile dysfunction • Presence of hematoma or fibrotic nodules • Blood pressure • Pulse	• Penile pain responds to acetaminophen • To avoid hematoma, apply pressure to injection site for 5-10 minutes after injection • If the patient develops priapism, he should proceed to the emergency department • Fibrotic nodules are rare but may occur after repeated injections. These may cause curvature of the penis during an erection and this requires assessment by a urologist • Hypotension and dizziness are uncommon and are associated with inadvertent venous injection of the drug
Alprostadil, intraurethral	• Aching pain in penis, testicles, legs, and perineum • Urethral burning, bleeding, or tearing • Priapism • Hypotension • Dizziness • Female partner may experience vaginal pain and burning sensation	• Clinical symptoms of erectile dysfunction • Urethral injury as evidenced by pain, bleeding, or tissue damage • Blood pressure • Pulse	• Burning pain usually resolves spontaneously. If urethral injury is suspected, this requires assessment by a urologist. Pain experienced by the female partner is due to leakage of medication from male urethra into vagina. Pain will usually resolve spontaneously • If the patient develops priapism, he should proceed to the emergency department • Hypotension and dizziness are uncommon, occurring in only 2%-3% of patients, and are associated with systemic absorption of the drugs • Alprostadil is embryotoxic and contact must be avoided if the female sex partner is pregnant. Males should use condoms if female is pregnant
Testosterone Supplements			
Methyltestosterone	• Sodium and water retention • Hyperlipidemia • Polycythemia • Gynecomastia • Sleep apnea, worsening • Increased libido • Mood swings	• Clinical symptoms of erectile dysfunction • Physical exam for edema • Blood pressure • Serum lipids,	• Discontinue if the patient has signs of hepatoxicity. If hematocrit exceeds 55% (0.55), methyltestosterone should be discontinued. Testosterone supplements may worsen lower urinary tract symptoms (LUTS) in patients with BPH. It is contraindicated in patients with untreated prostate cancer or men with breast cancer. May increase the risk of nonfatal myocardial infarction or death. Use precautiously in patients with a significant cardiovascular history. Discontinue if venous thromboembolism is suspected

	• Oligospermia • Hepatotoxicity • Venous thromboembolism • Prostate enlargement	hematocrit, hepatic transaminases, prostate-specific antigen, serum testosterone	
Testosterone cypionate or enanthate Testosterone undecanoate	• Sodium and water retention • Hyperlipidemia • Polycythemia • Gynecomastia • Sleep apnea, worsening • Increased libido • Oligospermia • Mood swings • Hepatotoxicity • Venous thromboembolism • Prostate enlargement • Injection site pain, pruritis • Pulmonary oil microembolism (POME), testosterone undecanoate only • Anaphylactic reactions • Prostate enlargement • Sodium and water retention • Hyperlipidemia • Polycythemia • Gynecomastia • Sleep apnea, worsening • Increased libido • Oligospermia • Mood swings • Hepatotoxicity	• Clinical symptoms of erectile dysfunction • Physical exam for edema • Blood pressure • Serum lipids, hematocrit, hepatic transaminases, prostate-specific antigen • Clinical symptoms of erectile dysfunction • Physical exam for edema, cough, shortness of breath • Blood pressure • Serum lipids, hematocrit, hepatic transaminases, prostate-specific antigen	• Discontinue if the patient has signs of hepatoxicity. If hematocrit exceeds 55% (0.55), testosterone supplement should be discontinued. Testosterone supplements may worsen LUTS in patients with BPH. It is contraindicated in patients with untreated prostate cancer or men with breast cancer. These formulations produce supraphysiologic serum concentrations of testosterone. Mood swings have been reported with these agents. May increase the risk of nonfatal myocardial infarction or death. Use cautiously in patients with a significant cardiovascular history. Discontinue if venous thromboembolism is suspected • Discontinue if the patient has signs of hepatoxicity. If hematocrit exceeds 55% (0.55), testosterone supplement should be discontinued. Testosterone supplements may worsen LUTS in patients with BPH. It is contraindicated in patients with untreated prostate cancer or men with breast cancer. These formulations produce supraphysiologic serum concentrations of testosterone. Mood swings have been reported with these agents. May increase the risk of nonfatal myocardial infarction or death. Use cautiously in patients with a significant cardiovascular history. Discontinue if venous thromboembolism is suspected • Signs of POME include cough, dyspnea, chest pain, and syncope, usually within 30 minutes of testosterone undecanoate injection. This medication should only be administered by a healthcare provider or in setting which is certified through a Risk Evaluation and Mitigation Strategy program
Testosterone patch	• Sodium and water retention	• Clinical symptoms of	• Testosterone supplements may worsen LUTS in patients with BPH. It is contraindicated in patients with untreated prostate cancer or men with

	• Hyperlipidemia • Gynecomastia • Sleep apnea, worsening • Increased libido • Contact dermatitis • Application site erythema, pruritus • Prostate enlargement	erectile dysfunction • Physical exam for edema • Blood pressure • Serum lipids, hematocrit, hepatic transaminases, prostate-specific antigen, serum testosterone	breast cancer. Contact dermatitis has been associated with the alcohol-based agent used to enhance transdermal drug absorption. It responds to topical corticosteroids. Of significance, hepatotoxicity has not been reported with transdermal patches. May increase the risk of nonfatal myocardial infarction or death. Use precautiously in patients with a significant cardiovascular history. Discontinue if venous thromboembolism is suspected. Adverse effects of mood swings and polycythemia are less likely with patch than with injectable formulations
Testosterone transdermal gel/spray/axillary solution	• Sodium and water retention • Hyperlipidemia • Polycythemia • Gynecomastia • Sleep apnea, worsening • Increased libido • Dermatitis • Application site erythema • pruritis, • Prostate enlargement	• Clinical symptoms of erectile dysfunction • Physical exam for edema • Blood pressure • Serum lipids, hematocrit, hepatic transaminases, prostate-specific antigen, serum testosterone	• Do not interchange topical formulations. Testosterone supplements may worsen LUTS in patients with BPH. It is contraindicated in patients with untreated prostate cancer or men with breast cancer Use is contraindicated in pregnant women or women who are likely to become pregnant, or women who breast feed infants. Women and children who have inadvertent skin exposure to these formulations may become virilized. If hematocrit exceeds 55% (0.55), testosterone supplement should be discontinued. May increase the risk of nonfatal myocardial infarction or death. Use precautiously in patients with a significant cardiovascular history. Discontinue if venous thromboembolism is suspected. With transdermal sprays, REMS assessments must be submitted to the FDA
Testosterone gel, intranasal	• Rhinorrhea, nose bleeds, nose pain • Sore throat • Sodium and water retention • Hyperlipidemia • Polycythemia • Gynecomastia • Sleep apnea, worsening • Increased libido • Dermatitis • Application site erythema • pruritis, • Prostate	• Clinical symptoms of erectile dysfunction • Physical exam for edema • Blood pressure • Serum lipids, hematocrit, hepatic transaminases, prostate specific antigen, serum testosterone	• Discontinue if severe rhinitis occurs. • Testosterone supplements may worsen LUTS in patients with BPH. It is contraindicated in patients with untreated prostate cancer or men with breast cancer. Use is contraindicated in pregnant women or women who are likely to become pregnant, or women who breast feed infants. Women and children who have inadvertent skin exposure to these formulations may become virilized. If hematocrit exceeds 55% (0.55), testosterone supplement should be discontinued. May increase the risk of nonfatal myocardial infarction or death. Use precautiously in patients with a significant cardiovascular history. Discontinue if venous thromboembolism is suspected. With transdermal sprays, REMS (risk evaluation and mitigation strategies) assessments must be submitted to the US Food and Drug Administration

	enlargement		
Testosterone subcutaneous implant	• Sodium and water retention • Hyperlipidemia • Polycythemia • Gynecomastia • Sleep apnea, worsening • Increased libido • Mood swings • Oligospermia • Hepatotoxicity • Prostate enlargement • Pain and infection at the implant site	• Clinical symptoms of erectile dysfunction • Physical exam for edema • Blood pressure • Serum lipids, hematocrit, hepatic transaminases, prostate specific antigen, serum testosterone	• Subcutaneous pellet implant may be extruded with loss of the dose. Androgen-related adverse effects may persist for a long time after drug administration unless the implant is removed. If hematocrit exceeds 55% (0.55), testosterone implant should be removed. Testosterone supplements may worsen LUTS in patients with BPH. It is contraindicated in patients with untreated prostate cancer or men with breast cancer. May increase the risk of nonfatal myocardial infarction or death. Use cautiously in patients with a significant cardiovascular history. Discontinue if venous thromboembolism is suspected

LUTS, lower urinary tract symptoms.

Drug Interactions

Approximately 8% of patients taking organic nitrates may develop sudden, severe hypotension if they also take a phosphodiesterase type 5 inhibitor. Decreased blood pressure results from two major factors: (a) organic nitrates on their own produce hypotension and (b) organic nitrates are nitric oxide donors, which can stimulate the activity of guanylate cyclase and increase tissue levels of cGMP.[35,54] For this reason, phosphodiesterase type 5 inhibitor use is contraindicated in patients taking nitrates given by any route at scheduled times or intermittently. Furthermore, nitrates should be withheld for 24 hours after sildenafil, vardenafil, or avanafil administration and for 48 hours after tadalafil administration.[26,35] Furthermore, if a patient who has taken a phosphodiesterase type 5 inhibitor requires medical treatment of angina, non-nitrate-containing agents (eg, calcium channel blocker, β-adrenergic antagonist, and morphine) should be used.

If severe hypotension occurs after exposure to nitrates and a phosphodiesterase type 5 inhibitor, the patient should be placed in a Trendelenburg position and aggressive fluid administration initiated. If severe hypotension continues, parenteral β-adrenergic agonists (eg, dopamine) should be administered cautiously.[26]

Once a phosphodiesterase type 5 inhibitor has been discontinued, a nitrate may be taken 24 hours after the last dose of sildenafil, vardenafil, or avanafil, or 48 hours after the last dose of tadalafil.[54]

Interestingly, dietary sources of nitrates, nitrites, or L-arginine (a precursor for nitrates) do not interact with phosphodiesterase type 5 inhibitors. This is because dietary sources do not increase circulating or tissue levels of nitric oxide in humans.

The phosphodiesterase type 5 inhibitors have a low potential to interact with most antihypertensive medications.[16,17,19] However, small decreases in blood pressure with clinically symptomatic orthostatic hypotension have been described in some patients taking phosphodiesterase type 5 inhibitors and α-adrenergic antagonists. The degree of hypotension that develops is dependent on several factors: (a) stability of patient's blood pressure prior to taking both drugs; (b) dose of the α-adrenergic antagonist used; (c) particular α-adrenergic antagonist used; (d) particular phosphodiesterase type 5 inhibitor used; and (e) timing of administration of both drugs. The drug interaction produces less hypotension when the patient has stable blood pressure prior to taking both drugs; a low dose of alpha-adrenergic antagonist is taken; a uroselective (eg, tamsulosin or silodosin) or extended-release formulation of an α-adrenergic antagonist (eg, alfuzosin, or modified-release doxazosin) is used; tadalafil is preferentially prescribed over

sildenafil, vardenafil, or avanafil; and an interval of 4 to 6 hours separates the doses of the α-adrenergic antagonist and phosphodiesterase type 5 inhibitor.[24,39]

Hepatic metabolism of all four phosphodiesterase type 5 inhibitors can be inhibited by strong enzyme inhibitors of CYP 3A4, including fluvoxamine, fluoxetine, nefazodone, verapamil, diltiazem, cimetidine, erythromycin, clarithromycin, itraconazole, ketoconazole, fluconazole itraconazole, atazanavir, indinavir, ritonavir, saquinavir, and grapefruit juice. Potent CYP 3A4 inhibitors may increase plasma levels of phosphodiesterase type 5 inhibitors by threefold or more. Lower starting doses of phosphodiesterase type 5 inhibitor should be used in these patients to minimize dose-related adverse effects, including cyanopsia, hypotension, flushing, nasal congestion, and priapism (see Table 103-4). Similarly, CYP 3A4 inducers, including rifampin, carbamazepine, phenytoin, and phenobarbital, can decrease plasma levels of phosphodiesterase type 5 inhibitors. Higher starting doses of phosphodiesterase type 5 inhibitors should be used in these patients.

If used with type 1A antiarrhythmics (eg, quinidine or procainamide) or type 3 antiarrhythmics (eg, sotalol, amiodarone), vardenafil can prolong the QT interval. This is a unique drug interaction of vardenafil and not a pharmacologic class effect.

Testosterone Replacement Regimens

Mechanism

Testosterone replacement regimens supply exogenous testosterone and restore serum testosterone levels to the normal range of 300 to 1,100 ng/dL (10.4-38.2 nmol/L). In so doing, testosterone replacement regimens correct symptoms of hypogonadism, which include malaise, loss of muscle strength, depressed mood, and decreased libido.[11]

Testosterone can directly stimulate androgen receptors in the CNS and is thought to be responsible for maintaining normal sexual drive. In addition, testosterone may stimulate nitric oxide synthase, thereby increasing cavernosal concentrations of nitric oxide, and enhancing the effects of phosphodiesterase type 5 in cavernosal tissue.[11] Testosterone may also enhance relaxation and blood filling of the corpora cavernosa by downregulating RhoA-ROCK, an enzymatic pathway responsible for calcium transport into penile smooth muscle cells.[59]

Indications

Although multiple guidelines on testosterone replacement have been published, 4 commonly used ones include the recommendations from the Endocrine Society,[12] British Society for Sexual Medicine,[16] American Urological Association,[60] and the European Association of Urology.[61] A recent comparison of published guidelines is also available.[62]

Testosterone replacement regimens are indicated in symptomatic patients with primary, secondary, or mixed hypogonadism, as confirmed with serum concentrations of testosterone. Although the threshold serum total testosterone level that defines hypogonadism varies with specific published guidelines, usually a serum total testosterone less than 230- to 350 ng/dL (8.0-12.2 nmol/L) is used.[11,12,60]

Serum testosterone concentrations typically are measured in the early morning between 7 am and 11 am because the secretion pattern of this hormone follows a circadian pattern, with highest serum concentrations in the morning hours and the lowest level at night (approximately 10 pm). A low measured serum testosterone level is confirmed with a repeat measurement on a separate day, optimally 4 weeks later. Confirmation of a low serum testosterone level is essential because of an approximate 10% intra-individual variation of measured levels and variable performance characteristics of various testosterone assays.[11,12,60,61] Simultaneous serum luteinizing hormone levels help to distinguish patients with primary hypogonadism, who have elevated luteinizing hormone levels, from those with secondary hypogonadism, who have decreased luteinizing hormone levels.[12] In men with equivocal serum total testosterone levels, it is recommended to obtain free testosterone levels.[63]

Testosterone replacement regimens should never be administered to men with normal serum testosterone levels, patients who have asymptomatic hypogonadism, or patients with isolated erectile dysfunction as the only sign of hypogonadism.

Efficacy

Testosterone replacement regimens restore muscle strength and sexual drive, promote erythropoiesis, and improve mood, cognition, and bone

density in adult patients with hypogonadism.[12,59,60] Testosterone replacement regimens do not directly correct erectile dysfunction; instead, they improve libido, thereby correcting secondary erectile dysfunction. Although testosterone replacement regimens may correct the serum testosterone level within days, observable clinical improvements make take weeks after the start of testosterone replacement. For example, increased libido may be evident at 6 weeks, improvements in erectile dysfunction or increase in muscle mass may take months. For this reason, a minimum effective clinical trial is considered 3 to 6 months.[12,60]

No additional benefit has been demonstrated for large doses of testosterone, which can increase the serum testosterone level from the low end to the upper end of the normal range or to the above-normal range.[60]

Testosterone replacement regimens can be administered parenterally, orally, transdermally, or intransally (see Table 103-4).[63] Intramuscular injections of testosterone enanthate and cypionate are the preferred treatment for symptomatic patients with primary or secondary hypogonadism because they are effective, inexpensive, and not associated with the bioavailability problems or hepatotoxic adverse effects of oral androgens.[60] Patients generally require dosing every 2 to 4 weeks. A longer-acting depot intramuscular formulation of testosterone undecanoate, which can be dosed every 10 weeks, offers greater convenience but is more expensive than testosterone enanthate or cypionate. Testosterone undecanoate has been associated with pulmonary oil embolism and anaphylactic reactions that can necessitate hospitalization.[60] For this reason, testosterone undecanoate is restricted to settings certified through a Risk Evaluation and Mitigation Strategies Program. A subcutaneous implant of testosterone pellets lasts 3 to 6 months, but it requires a surgical incision in the forearm. Extrusion has been reported in up to 8.5% of treated patients and results in loss of drug effect.

Oral formulations are associated with hepatotoxicity and are not recommended.[60] Although convenient for the patient, testosterone patches, gels, and sprays are much more expensive than testosterone enanthate or cypionate.[60] An intranasal testosterone gel formulation avoids inadvertent transfer of testosterone to others, as can occur with some other transdermal gel formulations. However, the intranasal formulation must be taken 3 times a day, which is inconvenient.[63] Therefore, the transdermal and nasal formulations should be reserved for patients who refuse injectable testosterone.

The ideal testosterone replacement regimen would mimic the normal circadian pattern of serum testosterone concentrations such that peak and trough concentrations occur in the early morning and late afternoon, respectively; produce serum concentrations in the normal range; produce serum concentrations of dihydrotestosterone and estradiol, which are metabolites of testosterone, that mimic the normal physiologic pattern; and produce minimal adverse effects. The ideal replacement regimen should be inexpensive and be convenient for the patient to use. Table 103-4 compares commercially available testosterone replacement regimens for these characteristics and shows that an ideal regimen has yet to be identified.[59–62]

The dropout rate with testosterone supplementation is high. Approximately 30% and 85% of patients stop testosterone replacement after 6 and 12 months, respectively. The reasons for this include the cost of the medication, slow onset of response, and inadequate perceived benefit.[12]

Pharmacokinetics

Natural testosterone has poor oral bioavailability because of extensive first-pass hepatic metabolism; therefore, large doses must be taken. To improve oral bioavailability, alkylated derivatives were formulated. Of these derivatives, methyltestosterone and fluoxymesterone are more resistant to hepatic catabolism and can be taken in smaller daily doses, which are theoretically safer. However, oral alkylated derivatives of testosterone are not metabolized to dihydrotestosterone or estradiol, are associated with a higher incidence of serious hepatotoxicity, and therefore are not preferred for management of hypogonadism.

Several testosterone esters have been formulated for intramuscular injection, with different durations of action (see Table 103-4). The shorter-acting testosterone propionate, which required dosing three times per week, has been discontinued and replaced with testosterone cypionate or enanthate, which can be dosed every 2, 4, or 6 weeks in most patients. These testosterone formulations produce supraphysiologic serum testosterone levels 2 to 4 days after each dose, which have been linked to mood swings and polycythemia in some patients.[60]

After the first and second doses, which are given 4 weeks apart, intramuscular injections of testosterone undecanoate generally last 10 weeks. An even longer-acting parenteral testosterone is available as a subcutaneous implant for dosing every 3 to 6 months.[60]

Transdermal testosterone replacement regimens can be delivered as once-daily patches or gel. For convenience, the gel is available in premeasured

dose packets or in a pump dispenser. Testosterone patches increase serum testosterone levels to the normal range in 2 to 6 hours. Serum testosterone levels return to baseline 24 hours after patch or gel administration. However, unlike oral or injectable supplements, transdermal testosterone patches applied at bedtime or testosterone gel applied each morning produce physiologic patterns of serum testosterone levels throughout the day. Although these formulations are often described as producing more "natural" hormone levels, the clinical importance of this biochemical effect is unknown.[60]

The original Testoderm brand patch was formulated for scrotal application. Scrotal skin is thinner and has a richer vascular supply than does the skin on the arms or thighs. Therefore, application of Testoderm patches produced excellent absorption of the hormone. However, the patch could detach when the scrotum became damp or moist, when the patient exercised, or if the scrotum was excessively hairy. Due to its inconvenient site of application, the scrotal patch is no longer commercially available in the United States.

For improved convenience, Androderm patches are formulated for application to the upper arms, back, abdomen, or thighs. The addition of absorption enhancers and adhesives has been linked to a higher incidence of contact dermatitis with Androderm patches compared with the original Testoderm scrotal patch or to gel formulations.

When compared to patches, testosterone gel 1% formulation (AndroGel) is applied in much larger doses (5 or 10 g each day) to the skin of the shoulders, upper arms, or abdomen. The hormone is absorbed quickly, within 30 minutes, but several hours may be required for complete absorption of the dose. For this reason, the patient should be reminded to wait at least 2 hours after application before showering. To prevent inadvertent transfer of testosterone gel to others, the patient should thoroughly wash his hands with soap and water after administration of a dose, allow the application site to dry undisturbed for several minutes before dressing or covering it, and ensure that there is no contact with clothing contaminated with the gel by children and female members of the household.[60]

A high-strength testosterone gel (1.62%) formulation is also available. It allows administration of a daily dose with a smaller amount of gel. It should be applied to the shoulder or upper arms.

Dosing

Table 103-4 lists the usual doses for testosterone replacement regimens. Three to 6 months is considered as an adequate treatment trial with a particular dose.[12] Thus, a dose should not be increased until the patient has used one particular dose for at least this time period. The recommended target serum testosterone level is the mid normal range,[11,60] or 450 to 600 ng/dL (15.6-20.8 nmol/L).[60,62] Repeated serum testosterone levels that exceed the normal range or produce adverse effects will necessitate a dosage reduction or increased interval between drug doses. Table 103-7 provides guidance on the timeline for monitoring serum testosterone levels based on the particular testosterone formulation used. After starting treatment, patients should be reassessed in 1 to 3 months. The patient's libido, mood, and quality of life may improve in 3 to 4 weeks, erectile function may improve in 6 months, but other symptoms of hypogonadism (eg, bone density) may take longer to resolve. If the patient responds to treatment and serum testosterone levels have returned to normal, the patient can be followed up annually. At each visit, the use of a validated self-assessment tool (eg, Androgen Deficiency in Aging Men Questionnaire) can assist the physician in gauging the patient's response to treatment.[64]

TABLE 103-7

Timing of Serum Testosterone Level Monitoring in Patients on Testosterone Replacement Regimens

When to Monitor Serum Testosterone Levels	
Oral testosterone tablets/capsules	2-3 hours after dose for peak level only.
Intramuscular testosterone cypionate or enanthate Intramuscular testosterone undecanoate	Midpoint of dosing interval or measure trough level right before the fourth dose. Just before each subsequent injection or measure level halfway between 10-week dosing interval.
Transdermal testosterone gel	Depending on the formulation, just before dose in the morning 2-4 weeks after start of therapy or after a dose adjustment.[65]
Transdermal patch	Before the next dose 2 weeks after start of therapy or after a dose adjustment.
Axillary solution	2-8 hours after application and 2 weeks after starting therapy or after a dosage adjustment.
Intranasal testosterone gel	1 month after starting treatment, measure trough level right before a dose
Testosterone subcutaneous implant	3-6 months after implantation, obtain trough level just before next dose

Data from Reference 60.

Once an optimal dose of a patient's testosterone replacement regimen has been established and the patient has received treatment for at least 3 months, the prescriber should consider discontinuing the regimen if the patient's symptoms of hypogonadism show no improvement.[66]

Before initiating any testosterone replacement regimen in patients 40 years and older, patients should be screened for breast cancer, benign prostatic hyperplasia, and prostate cancer. All are testosterone-dependent conditions and theoretically could be worsened by exogenous administration of testosterone. However, no confirmed cases of prostate cancer caused by testosterone supplementation in a hypogonadal patient have been documented.[67] Nevertheless, untreated prostate cancer is a contraindication to androgen supplementation. To screen for prostate disorders, a prostate-specific antigen serum concentration should be obtained, and a digital rectal examination of the prostate performed particularly in men who are 50 years of age or older. These tests are generally repeated at 1-year intervals after treatment is started. Also, since testosterone supplementation has been reported to worsen severe sleep apnea or edema of congestive heart failure, caution should be exercised in using testosterone in patients with these disorders.[12,60]

Other baseline tests that are recommended include hematocrit and liver function tests. These should be repeated 3 and 6 months after the start of a testosterone replacement regimen. If normal, these tests can be repeated annually thereafter. If the hematocrit exceeds 55% (0.55), the testosterone replacement regimen should be withheld to avoid polycythemia and its consequences.

Adverse Effects

Testosterone replacement regimens can cause sodium retention, which can lead to weight gain, or exacerbate hypertension, congestive heart failure, and edema (Table 103-6). Although serum lipoprotein perturbations may occur, testosterone replacement regimens have a neutral effect in that they decrease both total cholesterol and high-density lipoprotein cholesterol levels. Two retrospective studies associated testosterone supplementation

with an increased risk of myocardial infarction and stroke.[68,69] Although these studies did not show a cause–effect relationship and are considered inconclusive, the FDA included a labeling warning that testosterone supplementation may lead to cardiovascular disease and physicians should discuss this potential risk with patients before initiating treatment. This was prompted by a significant increase in testosterone use in the United States, inadequate monitoring of serum testosterone levels prior to and during testosterone supplementation, and the potential hazards of using testosterone supplementation in elderly patients with cardiovascular risk factors.[70]

Since then, some prospective clinical trials have documented the safe use of testosterone replacement regimens in patients with risk factors for cardiovascular disease and these were included in a recent meta-analysis.[66,71] Nevertheless, in view of the product labeling, prescribers are advised to discuss the potential risks of testosterone replacement regimens with patients before initiating treatment, and to carefully monitor patients for adverse effects.[62] For patients who have had a myocardial infarction, stroke, or worsening of congestive heart failure, a testosterone replacement regimen should be delayed for at least 6 months.[11,61]

Gynecomastia can occur because of conversion of testosterone to estrogen in peripheral tissues. This has been reported most often in patients with liver cirrhosis or those who are obese.

Oral alkylated testosterone replacement regimens have caused hepatotoxicity, ranging from mild elevations of hepatic transaminases to serious liver diseases, including peliosis hepatis (hemorrhagic liver cysts), hepatocellular and intrahepatic cholestasis, and benign or malignant tumors. For this reason, parenteral or transdermal testosterone replacement regimens are preferred.

Transdermal testosterone patches may cause contact dermatitis, which responds well to topical corticosteroids. This adverse effect has been associated with the presence of permeation enhancers, which are added to patch formulations. If the dermatitis from the patch formulation becomes problematic, testosterone gel is associated with a lower incidence of contact dermatitis.

Erythrocytosis occurs most often in patients receiving parenteral testosterone formulations. If the increase in hematocrit is mild, decreasing the dose of testosterone replacement is all that is needed. However, if the hematocrit exceeds 55% (0.55) testosterone injections should be stopped and can be replaced with a transdermal testosterone product.[60]

Although testosterone supplementation in men with late-onset hypogonadism has not been shown to cause prostate cancer, it should not be given to men with known prostate cancer that has not been treated.[60,72]

Alprostadil

Mechanism

Alprostadil, also known as prostaglandin E_1, stimulates adenyl cyclase, resulting in increased production of cAMP, a secondary messenger that activates protein kinase A, which decreases intracellular calcium concentrations and causes smooth muscle relaxation of the arterial blood vessels and sinusoidal tissues in the corpora. This results in enhanced blood flow to and blood filling of the corpora.[38,51] Because it does not require nitric oxide to produce its clinical effects, patients with erectile dysfunction due to diseases that are associated with an impaired nitric oxide pathway (eg, diabetes mellitus, post radical prostatectomy, patients in whom phosphodiesterase type 5 inhibitors are contraindicated, and patients who fail phosphodiesterase type 5 treatment) may respond to alprostadil.[38,39]

Alprostadil is commercially available as an intracavernosal injection (Caverject and Edex) and as an intraurethral insert (medicated urethral system for erection [MUSE]).

Indications

Both commercially available formulations of alprostadil are FDA approved as monotherapy for management of erectile dysfunction.

The efficacy of the intracavernosal injection may be related to the excellent bioavailability of the drug when injected directly into the corpora cavernosum. In contrast, intraurethral alprostadil doses generally are several hundred times larger than intracavernosal doses. This is because intraurethral alprostadil must be absorbed from the urethra, through the corpus spongiosum, and into the corpus cavernosum, where it exerts its full

proerectogenic effect.

Although several other agents, including papaverine and phentolamine, have been used off-label for intracavernosal therapy, alprostadil is preferred. This is because intracavernosal alprostadil has been approved by the FDA for erectile dysfunction, it does not require extemporaneous compounding, and it has a low potential for causing prolonged erections and priapism.

Both formulations of alprostadil are considered more invasive than VEDs or phosphodiesterase type 5 inhibitors. For this reason, intracavernosal alprostadil is generally prescribed after patients do not respond to or cannot use less invasive interventions. Intracavernosal alprostadil is preferred over intraurethral alprostadil because of its greater effectiveness. Intracavernosal alprostadil may be preferred in patients with diabetes mellitus, who are accustomed to injectable drug therapy and may have peripheral neuropathies, which decrease the patient's perception of pain upon injection. Intraurethral alprostadil is generally reserved as a treatment of last resort for patients who do not respond to other less invasive and more effective forms of therapy, and who refuse surgery.

Intracavernosal Alprostadil

Efficacy

The overall efficacy of intracavernosal alprostadil is 70% to 90%.[22] Three characteristics of intracavernosal alprostadil include the following:

1. The effectiveness of alprostadil is dose related. The mean duration of erection is directly related to the dose of alprostadil administered and ranges from 12 to 44 minutes.
2. A higher percentage of patients with psychogenic and neurogenic erectile dysfunction respond to alprostadil at a lower dose compared to patients with vasculogenic erectile dysfunction.
3. Tolerance does not appear to develop with continued use of intracavernosal alprostadil at home.

10 Although 70% to 75% of patients respond to intracavernosal alprostadil, a high proportion of patients elect to discontinue its use over time. Depending on the study and the length of observation, 30% to 50% of patients voluntarily discontinue therapy, usually during the first 6 to 12 months, and this increases to 54% and 67% after 2 to 4 years, respectively.[22,38] After 10 years, less than 5% of patients continue intracavernosal injections. Common reasons for discontinuation include lack of perceived effectiveness; inconvenience of administration; an unnatural, nonspontaneous erection; needle phobia; penile pain, loss of interest; or cost of therapy.

Approximately one-third of patients do not respond to usual doses of intracavernosal alprostadil. In these patients, intracavernosal alprostadil has been used successfully along with VEDs. Such combination therapy can be attempted by patients before transitioning to more invasive surgical procedures.[32] Alternatively, intracavernosal injections of synergistic combinations of vasoactive agents that act by different mechanisms have been used. For example, papaverine is a nonspecific phosphodiesterase inhibitor that increases cavernosal concentrations of cAMP and cGMP, and phentolamine is an alpha-adrenergic antagonist that blocks detumescence (thereby prolonging an erection). Intracavernosal drug combinations typically produce an erection that lasts longer than an erection produced by any one of the agents in the mixture. In addition, because of the low dosage of each agent in the combination, fewer systemic and local fibrotic adverse effects develop compared with high-dose monotherapy. For example, when used in low-dose combination regimens, papaverine is less likely to induce hypotension and liver dysfunction, and phentolamine is less likely to induce tachycardia and hypotension.[6,22] However, such intracavernosal drug combinations are not commercially available and must be extemporaneously compounded. Several different two- or three-drug formulations have been used, but no one formulation is considered a standard.[22,32] Finally, intracavernosal alprostadil has been used in combination with phosphodiesterase type 5 inhibitors; however, this use is an unlabeled indication.[22,32]

Pharmacokinetics

Intracavernosal injection should be administered into only one corpus cavernosum. From this injection site, the drug will reach the other corpus cavernosum through vascular communications between the two corpora. Alprostadil acts rapidly, with an onset of 5 to 15 minutes. The duration is directly related to the dose. Within the usual dosage range of 2.5 to 20 mcg, the duration of erection is not more than 1 hour. Higher doses are expected

to exhibit a longer duration of action. Local 15-hydroxy dehydrogenase in the corpora cavernosum quickly converts alprostadil to inactive metabolites. Any alprostadil that escapes into the systemic circulation is deactivated on first pass through the lungs. Hence, the plasma half-life of alprostadil is approximately 5 to 10 minutes, and the potential for systemic and local adverse effects is negligible.[22,30] Dose modification is not necessary in patients with renal or hepatic disease.

Dosing

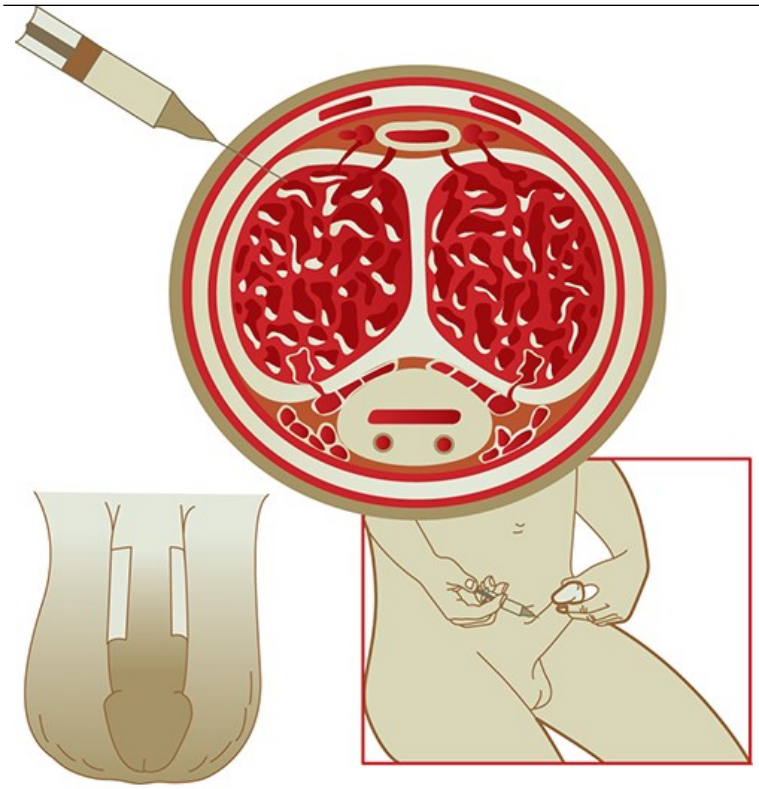
The usual dose of intracavernosal alprostadil is 10 to 20 mcg, with a maximum recommended dose of 60 mcg. Doses greater than 60 mcg have not produced any greater improvement in penile erection but may cause hypotension or prolonged erections lasting more than 1 hour. The dose should be administered 5 to 10 minutes before intercourse. The manufacturer recommends that patients be slowly titrated up to the minimally effective dosage to minimize the likelihood of hypotension. Under a health professional's supervision, patients should be started with a 1.25-mcg dose, which can be increased in increments of 1.25 to 2.50 mcg at 30-minute intervals up to the lowest dose that produces a firm erection for 1 hour and does not produce adverse effects. In clinical practice, this process is rarely done because it is time-consuming.[28] Thus, many physicians start the patient on 10 mcg and move quickly up the dosage range to identify the best dose for the patient. To avoid adverse effects, patients should receive not more than one injection per day and not more than three injections per week with a 24-hour interval between doses (see Table 103-4).

Intracavernosal injections should be performed using a 0.5-in. (1.3 cm), 27- or 30-gauge needle. A tuberculin syringe or a syringe prefilled with diluent as supplied by the manufacturer should be used to ensure precise measurement of doses. Patients with needle phobia, poor vision, or poor manual dexterity can use commercially available autoinjectors to facilitate administration of intracavernosal alprostadil.[30]

Intracavernosal injections require that the patient or the sexual partner practice good aseptic techniques (to avoid infection), have good manual skills and visual ability, and be comfortable with injection techniques. When practicing self-injection, the patient should use one hand to firmly hold the glans penis against his thigh to expose the lateral surface of the shaft. The injection should be made at right angles into one of the lateral surfaces of the proximal third of the penis. The injection should never be made into the dorsal or ventral surface of the penis. This will prevent inadvertent injection of the drug into arteries on the dorsal surface or the urethra on the ventral surface. After the injection, the penis should be massaged to help distribute the drug into the opposite corpus cavernosum. Injection sites should be rotated with each dose. Finally, manual pressure should be applied to the injection site for 5 minutes to reduce the likelihood of hematoma formation (Fig. 103-5).

FIGURE 103-5

Technique for administration of intracavernosal injections. (*Source: Caverject [package insert]. New York, NY: Pfizer Inc.; 2006.* https://www.pfizer.com/products/product-detail/caverject. *Accessed November 1, 2018.*)



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

Once the optimal dosage of intracavernosal alprostadil is established, the patient should return for routine medical follow-up every 3 to 6 months. Some patients subsequently require dosage adjustment, largely attributed to worsening of the underlying disease that is contributing to the erectile dysfunction.

Adverse Effects

Intracavernosal alprostadil is most commonly associated with local adverse effects. Hematoma and bruising at the injection site occur most often during the first year of therapy. These effects are largely the result of poor injection technique. To minimize the risk of injection site hematomas, patients should apply pressure to the injection site for 5 minutes after each dose. Similarly, infection at the injection site has been reported. Meticulous aseptic technique is necessary to prevent this complication.

Cavernosal plaques or areas of fibrosis at injection sites form in approximately 2% to 12% of patients.[51] When they occur, the patient should suspend further injections for 2 to 4 months or until the plaques resolve. These plaques may cause penile curvature, similar to Peyronie's disease, which makes sexual intercourse difficult or impossible. The cause of corporal fibrosis and plaque formation is unknown. This adverse effect may be caused by poor injection technique or by alprostadil itself. Although patients have developed corporal fibrosis, alprostadil may be less likely to cause this adverse effect compared to other intracavernosal drug combinations, such as phentolamine or papaverine. Unlike cavernosal fibrosis associated with large doses and repeated administration of papaverine, penile scarring secondary to alprostadil appears to be unpredictable.

Alprostadil causes penile pain in approximately 10% to 44% of patients. The pain has been described as a burning discomfort or dull pain near the injection site or during the erection, which generally does not persist after the penis becomes flaccid. The pain usually is mild, generally does not require discontinuation of therapy, and often abates even with continued treatment.[22] However, 2% to 5% of patients discontinue taking alprostadil because of severe pain. The pain can be managed by oral analgesics (eg, acetaminophen), if necessary. One investigator has recommended adding procaine to intracavernosal alprostadil, but this may mask the signs of more serious adverse effects of the drug or of penile injury during intercourse, and is not recommended. The mechanism of this adverse reaction is poorly understood. Alprostadil may intrinsically produce pain. In addition, the pain may be a result of the pH of the parenteral solution. Alprostadil is acidic, and the commercially available Caverject formulation is buffered with

sodium citrate, a weak base, to reduce pain on injection.[6]

Priapism, a prolonged, painful erection lasting more than 1 hour, occurs in 1% to 15% of treated patients. It occurs most often during the dose titration period and is rare thereafter. Blood sludging in the corpora can lead to tissue hypoxia and irreversible cavernosal fibrosis and scarring. The risk for this complication is greatest for erections that persist beyond 4 to 6 hours. Patients are advised to seek medical attention immediately when drug-induced erections last more than 4 hours, as this may progress to a urologic emergency.[22] Its management includes supportive care, including analgesics for pain and sedatives for anxiety. In addition, needle aspiration of sludged blood in the corpora or intracavernosal injection of α-adrenergic agonists (eg, phenylephrine) has been used. These procedures facilitate venous drainage of the corpora, allowing venous outflow to "catch up" with arterial inflow.[6,30]

The likelihood of prolonged erections with intracavernosal alprostadil is dose related. Therefore, to prevent this adverse effect, the lowest effective dose should be used, and the dose should be titrated to ensure that the duration of the erection is not more than 1 hour.

Intracavernosal alprostadil rarely causes systemic adverse effects, owing to the agent's local catabolism in cavernosal tissue and rapid deactivation in pulmonary tissue (if any of the drug escapes into the systemic circulation). However, large doses greater than 20 mcg are associated with dizziness and hypotension in some patients and is one reason why such large doses are not commonly used.

Intracavernosal injection therapy should be used cautiously by patients at risk for priapism, including patients with sickle cell disease, leukemia, or multiple myeloma. It should be used cautiously by patients who may develop bleeding complications secondary to injections, including patients with thrombocytopenia or those taking anticoagulants. It also should be used cautiously by patients who use poor-quality injection technique, including patients with psychiatric disorders, obese patients (who may not be able to reach or see the penile injection site), patients who are blind, patients with severe arthritis, or patients with abnormal penile anatomy.[22,24]

Intraurethral Alprostadil

Efficacy

10 Intraurethral alprostadil inserts are marketed as MUSE, which contains a medication pellet inside a prefilled urethral applicator. Multiple studies show this product has an overall effectiveness rate of 43% to 65%[22] compared with 70% to 90% for intracavernosal alprostadil. Its decreased effectiveness and inconvenient administration method have resulted in this product being considered a second- or third-line treatment option for patients with erectile dysfunction.[67] However, some patients have responded to intraurethral alprostadil even though they did not respond to intracavernosal alprostadil or sildenafil.[73]

Intraurethral alprostadil has been combined with a VED to improve treatment response.[30,32]

The voluntary dropout rate is high and has been reported to be 57% and 75% after 3 and 15 months, respectively.[22] Intraurethral alprostadil should be avoided in patients with urethral stricture or urethritis, or if the female partner is pregnant.

Pharmacokinetics

Following intraurethral instillation, alprostadil is absorbed quickly through the urethra, into the corpus spongiosum, and then into the corpora cavernosum.[24] As much as 80% of each dose is absorbed by the urethra and corpus spongiosum in less than 10 minutes, with peak absorption occurring in 20 to 25 minutes. An estimated 20% of each dose is delivered to the corpora cavernosum. As with intracavernosal injections of alprostadil, any drug absorbed into the systemic circulation is rapidly metabolized on first pass through the lungs.

The onset after intraurethral insertion is similar to that of intracavernosal injection, 5 to 10 minutes, and the duration is 30 to 60 minutes.

Dosing

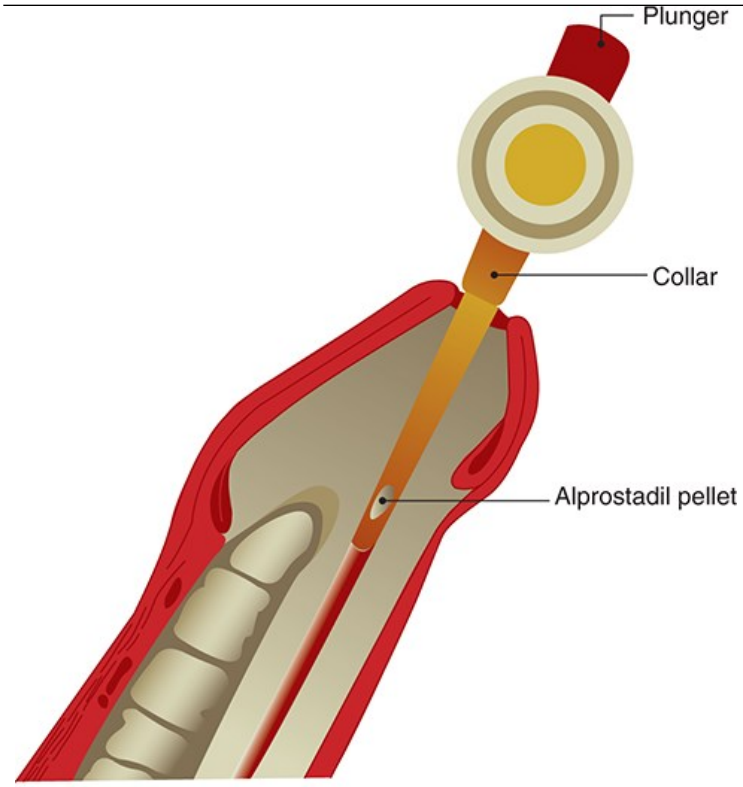
The usual dosage range of intraurethral alprostadil is 125 to 1,000 mcg, but 500 mcg is typically needed in most patients.[22] It is recommended that the first dose be administered under the supervision of a health professional.[24] The dose should be administered 5 to 10 minutes before sexual

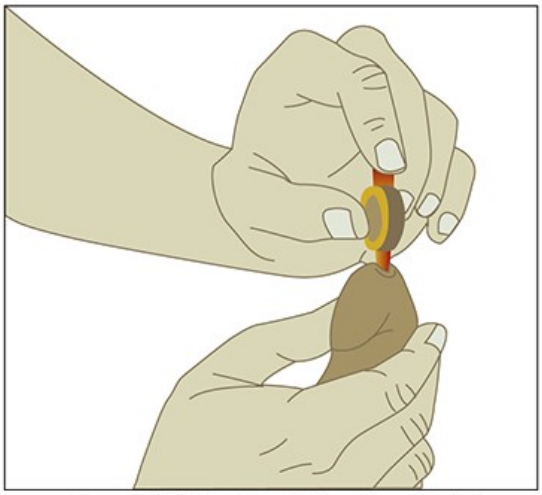
intercourse. Not more than two doses per day are recommended. Before administration, the patient should be advised to empty his bladder, voiding completely (see Table 103-4).

Similar to intracavernosal injection treatments, intraurethral insertion of alprostadil requires good manual and visual skills to minimize the risk of urethral injuries. Intraurethral alprostadil is supplied in a prefilled intraurethral applicator. The patient should void first to moisten the urethra. With one hand the patient holds the glans penis, and with the other hand, the patient inserts the intraurethral applicator 0.5 in. (1.3 cm) into the urethra. The drug pellet is then pushed into the urethra. The penis should be massaged to enhance drug dissolution in the urethral fluids and drug absorption (Fig. 103-6).

FIGURE 103-6

Technique for administration of intraurethral alprostadil with a medicated urethral system for erection applicator. (*Source: Muse [package insert]. Mountain View, CA: Vivus, Inc.; 2003.* https://medlibrary.org/lib/rx/meds/muse. *Accessed November 1, 2018.*)





Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

Adverse Effects

The urethra can be injured because of an improper administration technique. Injuries can lead to urethral bleeding or stricture and difficulty voiding. Patients should receive complete education about optimal administration procedures before starting treatment.

Urethral pain has been reported in 24% to 43% of patients. Usually, it is mild and does not require discontinuation of treatment. Approximately 6% of female sexual partners may experience vaginal burning, itching, or pain, which probably is related to transfer of alprostadil from the man's urethra to

the woman's vagina during intercourse.[22,30]

Prolonged painful erections (priapism) have been rarely reported. Syncope and dizziness have been reported rarely (only 2%-3% of patients) and likely are related to use of excessively large doses.

Unapproved Agents

A variety of other commercially available and investigational agents have been used for management of erectile dysfunction. Although it is beyond the scope of this chapter to discuss all of them, some of the more commonly used agents are discussed here.

Yohimbine

Yohimbine, a tree-bark derivative also known as *yohimbe*, is widely used as an aphrodisiac. Yohimbine is a central alpha$_2$-adrenergic antagonistic that increases catecholamines and improves mood. Some investigators believe that yohimbine has peripheral proerectogenic effects. Yohimbine may reduce peripheral alpha-adrenergic tone, thereby permitting a predominant cholinergic tone, which could result in a vasodilatory response.[22,51] The usual oral dose is 6 to 15 mg three times per day.

Based on a meta-analysis of published studies that concluded that yohimbine is only mildly efficacious for psychogenic erectile dysfunction, the American Urological Association has cautioned against the use of yohimbine.[22] In addition, yohimbine can cause many systemic adverse effects, including anxiety, insomnia, tachycardia, and hypertension.

Papaverine

Papaverine is a nonspecific phosphodiesterase type 5 inhibitor that decreases metabolic catabolism of cAMP in cavernosal tissue. As a result of enhanced tissue levels of cAMP, smooth muscle relaxation occurs. Cavernosal sinusoids fill with blood, and a penile erection results.

Papaverine is not FDA approved for erectile dysfunction. Intracavernosal papaverine alone is not commonly used for management of erectile dysfunction because the large doses required to achieve a therapeutic effect also produce dose-related adverse effects, such as priapism, corporal fibrosis, hypotension, and hepatotoxicity.[22] Papaverine is more often administered in lower doses combined with phentolamine and/or alprostadil. A variety of formulas have been used, but no one mixture has been proven better than other mixtures. Combination formulations are considered safer and are associated with the potential for fewer serious adverse effects than high doses of any one of these agents.

A portion of each papaverine dose is systemically absorbed, and its prolonged plasma half-life of 1 hour contributes to adverse effects. The usual dose of papaverine is 7.5 to 60 mg when used as a single agent for intracavernosal injection. When used in combination, the dose decreases to 0.5 to 20 mg.

If treated with papaverine, patients with a history of underlying liver disease or alcohol abuse should undergo liver function testing at baseline and every 6 to 12 months during continued treatment.

Phentolamine

Phentolamine is a competitive nonselective α-adrenergic blocking agent. It reduces peripheral adrenergic tone and enhances cholinergic tone. As a result, it improves cavernosal filling and is proerectogenic.[22]

Phentolamine has most often been administered as an intracavernosal injection. Monotherapy is avoided because large doses are required for an erection, and at these large doses systemic hypotensive adverse effects would be prevalent. Most often, phentolamine has been used in combination with other vasoactive agents for intracavernosal administration. A ratio of 30-mg papaverine to 0.5 to 1 mg phentolamine is typical, and the usual dose ranges from 0.1 to 1 mL of the mixture. Such a mixture minimizes systemic hypotensive adverse effects.

Hypotension is the most common adverse effect of intracavernosal phentolamine. It is more common and more severe with large doses or in patients with a poor injection technique who have injected into a vein (rather than the cavernosa). Prolonged erections have been reported in patients who used excessive doses of intracavernosal medications in combination.

Surgical Therapy

Penile Prostheses

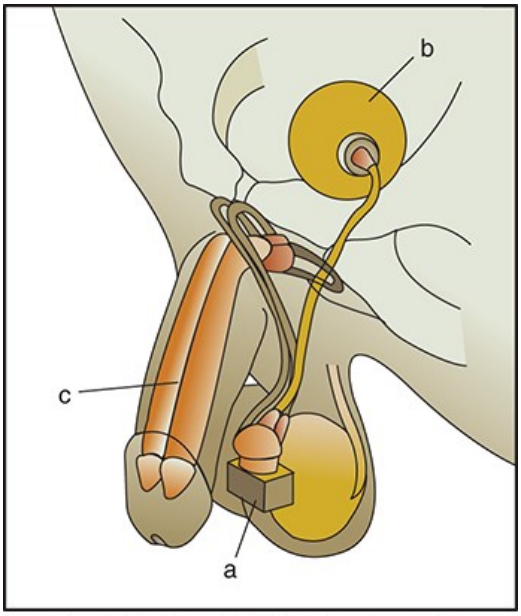
Surgical insertion of a penile prosthesis is the most invasive treatment of erectile dysfunction. It is reserved for patients who do not respond to or who are not candidates for less invasive medical treatments or devices.

Prosthesis insertion requires anesthesia, an operating room, and a skilled urologist. Two prostheses are widely used: malleable and inflatable. Malleable or semirigid prostheses consist of two bendable rods that are inserted into the corpora cavernosa. The patient appears to have a permanent erection after the procedure; the patient is able to bend the penis into position at the time of intercourse.[22,31,74,75]

The inflatable prosthesis has several mechanical parts, including a pump, reservoir, and fillable cylinders. Once it is manually activated, a pump transfers fluid from a reservoir into the cylinders in the corpora cavernosa. The inflatable prosthesis produces a more natural erection, and for this reason, it is associated with a higher patient satisfaction rate than a malleable prosthesis.[72,73] The patient develops an erection only when the device is activated. Inflatable prostheses are available as 2- or 3-piece devices; fewer mechanical parts are associated with fewer malfunctions. With improvements in technology, inflatable devices can be placed during shorter surgical procedures and have a low 10-year mechanical failure rate (5%-15%) as compared with the original inflatable prostheses (Fig. 103-7).[22,74]

FIGURE 103-7

Example of surgically implanted penile prosthesis. (a, activation mechanism; b, reservoir with fluid for inflating prosthesis; c, inflatable rods in corpora.) *(Reprinted from the National Institutes of Health/National Institute of Diabetes and Digestive and Kidney Diseases.)*



Penile prostheses provide penile rigidity suitable for vaginal intercourse and are associated with a greater than 90% patient satisfaction rate, which is generally higher than that observed with any other drug treatment or VED. The surgical success rate after insertion is 82% to 98%.[74]

Adverse effects of prosthesis insertion can occur early or late after the surgical procedure. The most common early complication is infection. Late complications include mechanical failure of the prosthesis, erosion of the rods through the penis, or late-onset infection. Although some salvage procedures have been devised, in many cases the prosthesis requires removal.[75]

EVALUATION OF THERAPEUTIC OUTCOMES

The primary therapeutic outcomes of specific treatments for erectile dysfunction include (a) improvement in the quantity and quality of penile erections suitable for intercourse and (b) avoidance of adverse drug reactions and drug interactions.

At baseline and after the patient has completed a clinical trial period of several weeks with a specific treatment for erectile dysfunction, the physician should conduct assessments to determine whether the quality and quantity of penile erections have improved. A patient's level of satisfaction is highly individualized, depending on his lifestyle and expectations. Therefore, a patient who has successful intercourse once per week might be completely satisfied, whereas another patient might judge this to be unsatisfactory. Patients with unrealistic expectations in this regard must be identified and counseled by clinicians to avoid adverse effects of excessive use of erectogenic agents.

Failure to improve the quality and quantity of penile erections suitable for intercourse after an appropriate clinical trial period with a specific treatment for erectile dysfunction occurs in a significant percentage of patients. In this case, physicians generally take the following steps to:

1. Ensure that the patient has been prescribed a maximum tolerated medication dose and has an adequate clinical trial of a specific treatment before discarding it as ineffective.
2. Switch to another drug (see Fig. 103-2).
3. Reserve surgical treatment for patients who do not respond to drug treatment.

CONCLUSION

Erectile dysfunction is a common disorder of aging men. Its incidence is higher in patients with underlying medical disorders that compromise the vascular, neurologic, hormonal, or psychogenic systems necessary for a normal penile erection. Medications are common causes of erectile dysfunction. By correcting the underlying etiology, erectile dysfunction can often be reversed without the use of specific treatments. When treatment of erectile dysfunction is needed, the least invasive options should be used first because they produce the lowest incidence of serious adverse effects. Phosphodiesterase type 5 inhibitors are first-line treatment. If this fails or if the patient cannot use a phosphodiesterase type 5 inhibitor, a VED or intracavernosal injection or intraurethral alprostadil can be initiated. If this treatment fails, the patient can attempt a combination of intracavernosal alprostadil and VED, combination intracavernosal therapy, or intraurethral alprostadil. If this treatment fails, the patient may require insertion of a penile prosthesis. Some insurance companies do not reimburse for drug treatments for erectile dysfunction, so cost is an important issue for patients. Clinicians should provide clear and simple advice. Patient confidentiality and privacy, which are extremely important to men with erectile dysfunction, should be maintained at all times.

ABBREVIATIONS

cAMP	cyclic adenosine monophosphate
cGMP	cyclic guanosine monophosphate
CNS	central nervous system
IIEF	International Index of Erectile Function
LUTS	lower urinary tract symptoms
NAION	nonarteritic anterior ischemic optic neuropathy
REMS	risk evaluation and mitigation strategies
VED	vacuum erection device

REFERENCES

1. NIH Consensus Development Panel on Impotence. Impotence. NIH Consensus Development Panel on Impotence. *JAMA.* 1993;270(1):83–90. [PubMed: 8510302]

2. Johannes CB, Aranjo AB, Feldman HA, et al. Incidence of erectile dysfunction in men 40–69 years old: Longitudinal results from the Massachusetts Male Aging Study. *J Urol.* 2000;163(2):460–463. [PubMed: 10647654]

3. Bacon CG, Mittleman MA, Kawachi I, et al. Sexual function in men older than 50 years of age: Results from the health professionals follow-up study. *Ann Intern Med.* 2003;139(3):161–168. [PubMed: 12899583]

4. Andersson KE. Mechanisms of penile erection and basis for pharmacological treatment of erectile dysfunction. *Pharmacol Rev.* 2011;63(4):811–859. doi: 10.1124/pr.111.004515

5. Livingston M, Kalansooriya A, Hartland AJ, et al. Serum testosterone levels in male hypogonadism: Why and when to check-a review. *Int J Clin Pract.* 2017(Nov);71(11):e12995. doi: 10.1111/ijcp.12995

6. McMahon CG. Current diagnosis and management of erectile dysfunction. *Med J Aust.* 2019(Jun);210(10):469–476. doi: 10.5694/mja2.50167

7. Patel JP, Lee EH, Mena-Hurtado CI. Evaluation and management of erectile dysfunction in the hypertensive patient. *Curr Cardiol Rep.* 2017(Aug);19(9):89. doi: 10.1007/s11886-017-0889-z

8. Imprialos K, Koutsampasopoulos K, Manolis A, Doumas M. Erectile dysfunction as a cardiovascular risk factor: Time to step up? *Curr Vasc Pharmacol.* 2021;19(3):301–312. doi: 10.2174/1570161118666200414102556

9. Moussa M, Papatsoris A, Abou Chakra MA, et al. Erectile dysfunction in common neurological conditions: A narrative review. *Arch Ital Urol Androl.* 2020(Dec 21);92(4). doi: 10.4081/aiua.2020.4.371

10. Nguyen HMT, Gabrielson AT, Hellstrom WJG. Erectile dysfunction in young men—A review of the prevalence and risk factors. *Sex Med Rev.* 2017(Oct);5(4):508–520. doi: 10.1016/j.sxmr.2017.05.004

11. Nieschlag E. Late-onset hypogonadism: A concept comes of age. *Andrology*. 2020(Nov);8(6):1506–1511. doi: 10.1111/andr.12719

12. Bhasin S, Brito JP, Cunningham GR, et al. Testosterone therapy in men with hypogonadism: An Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab.* 2018(May 1);103(5):1715–1744. doi: 10.1210/jc2018-00229

13. Voznesensky I, DeLay KJ, Hellstrom WJG. Advances in pharmacotherapy for erectile dysfunction and associated cardiac output. *Expert Opin Pharmacother.* 2016(Dec);17(17):2281–2289. doi: 10.1080/146566.2016.1241766

14. Imprialos KP, Stavropoulos K, Doumas M, et al. Sexual dysfunction, cardiovascular risk, and effects of pharmacotherapy. *Curr Vasc Pharmacol.* 2018(Jan);16(2):130–142. doi: 10.2174/1570161115666170609101502

15. Razdan S, Greer AB, Alameddine M, et al. Effect of prescription medications on erectile dysfunction. *Postgrad Med J.* 2018(Mar);94(1109):171–178. doi: 10.1136/postgradmedj-2017-135233

16. Hackett G, Kirby M, Edwards D, et al. British Society for Sexual Medicine guidelines on adult testosterone deficiency, with statements for UK practice. *J Sex Med.* 2017(Dec);14(12):1504–1523. doi: 10.1016/J.JSXM.2017.10.067

17. Hernandez-Cerda J, Bertomeu-Gonzalez V, Zuazola P, Cordero A. Understanding erectile dysfunction in hypertensive patients: The need for good

patient management. *Vasc Health Risk Manag.* 2020(Jun 12);16:231–239. doi: 10.2147/VHRM.S223331

18. Manolis A, Doumas M, Ferri C, Mancia G. Erectile dysfunction and adherence to antihypertensive therapy: Focus on β-blockers. *Eur J Intern Med.* 2020(Nov);81:1–6. doi: 10.1016/j.ejim.2020.07.009

19. Patel JP, Lee EH, Mena-Hurtado CI, Walker CN. Evaluation and management of erectile dysfunction in the hypertensive patient. *Curr Cardiol Rep.* 2017;19:89. doi: 10.1008/s11886-017-0889-z

20. Corona G, Tirabassi G, Santi D, et al. Sexual dysfunction in subjects treated with inhibitors of 5α-reductase for benign prostatic hyperplasia: A comprehensive review and meta-analysis. *Andrology*. 2017(Jul);5(4):671–678. doi: 10.1111/andro.12353

21. Traish AM. Post-finasteride syndrome: A surmountable challenge for clinicians. *Fertil Steril.* 2020 Jan;113(1):21–50. doi: w.1016/j.fertnstert.2019.11.030

22. Burnett AL, Nehra A, Breau RH, et al. Erectile dysfunction: AUA Guideline. *J Urol.* 2018(Sep);200(3):633–641. doi: 10.1016/j.juro.2018.05.004

23. Yafi FA, Huynh LM, Ahlering T, Rosen R. What is a "validated questionnaire"? A critical review of erectile function assessment. *J Sex Med.* 2020(May);17(5):849–860. doi: 10.1016/j.jsm.2020.02.005.

24. Bennett N Jr. Sexual dysfunction-behavioral, medical, and surgical treatment. *Med Clin N Am.* 2018(Mar);102(2):349–360. doi: 10.1016/j.mcna.2017.10.010

25. Capogrosso P, Ventimiglia E, Oreggia D, et al. Medical treatment of erectile dysfunction: Too many medical prescriptions. *Urologia.* 2017(Aug 17;84(3):121–129. [PubMed: 28708203]

26. Nehra A, Jackson G, Miner M, et al. The Princeton III Consensus recommendations for the management of erectile dysfunction and cardiovascular disease. *Mayo Clin Proc.* 2012(Aug);87(8):766–778. doi: 10.1016/j.mayocp.2012.06.015

27. Duca Y, Calogero AE, Cannarella R, et al. Erectile dysfunction, physical activity and physical exercise: Recommendations for clinical practice. *Andrologia.* 2019(Jun);51(5):e13264. doi: 10.1111/and.13264.

28. Mitidieri E, Cirino G, d'Emmanuele di Villa Bianca RD, Sorrentino R. Pharmacology and perspectives in erectile dysfunction in man. *Pharmacol Ther.* 2020(Apr);208:107493. doi: 10.1016j.pharmthera.2020.107493 0163-7258

29. La J, Roberts NH, Yafi FA. Diet and men's sexual health. *Sex Med Rev.* 2018(Jan);6(1):54–68. doi.org/10.1016/jsxmr.2017.07.004 [PubMed: 28778698]

30. Hatzimouratidis K, Salonia A, Adaikan G, et al. Pharmacotherapy for erectile dysfunction: Recommendations from the Fourth International Consultation for Sexual Medicine (ICSM 2015). *J Sex Med.* 2016(Apr);13(4):465–488. doi: 10.1016/j.jsxm.2016.01.016

31. Trost LW, Munarriz R, Wang R, et al. External mechanical devices and vascular surgery for erectile dysfunction. *J Sex Med.* 2016(Nov);13(11):1579–1617. doi: 10.1016/j.jsxm.2016.09.008

32. Lee M, Sharifi R. Non-invasive management options for erectile dysfunction when a phosphodiesterase type 5 inhibitor fails. *Drugs Aging*. 2018(Mar);35(3):175–187. doi: 10.1007/s40266-018-0528-4

33. Zhang DL, Chen Z, Wang FX, et al. Adding a vacuum erection device to regular use of tadalafil improves penile rehabilitation after posterior urethroplasty. *Asian J Androl.* 2019(Nov-Dec);21(6):582–586. doi: 10.4103/aja.aja_50_19

34. Scaglione F, Donde S, Hassan TA, Jannini EA. Phosphodiesterase type 5 inhibitors for the treatment of erectile dysfunction: Pharmacology and clinical impact of the sildenafil citrate orodispersible tablet formulation. *Clin Ther.* 2017(Feb);39(2):370–377. doi: 10.1016/j.clinthera.2017.01.001

35. Hong JH, Kwon YS, Kim IY. Pharmacodynamics, pharmacokinetics, and clinical efficacy of phosphodiesterase-5 inhibitors. *Expert Opin Drug Metab Toxicol.* 2017(Feb);13(2):199–192. doi: 10.1080/1742555.2017.1244265

36. Boeri L, Capogrosso P, Ventimiglia E, et al. Avanafil-a further step to tailoring patient needs and expectations. *Expert Rev Clin Pharmacol.* 2016(Sep);9(9):1171–1181. doi: 10.1080/17512433.2016.1195261

37. Zurawin JL, Stewart CA, Anaissie JE, et al. Avanafil for the treatment of erectile dysfunction. *Expert Rev Clin Pharmacol.* 2016(Sep);9(9):1163–1170. doi: 10.1080/17512433.2016.1212655

38. Le TV, Tsambarlis P, Hellstrom WJG. Pharmacodynamics of the agents used for the treatment of erectile dysfunction. *Expert Opin Drug Metab Toxicol.* 2019(Feb 4);15(2):121–131. doi: 10.1080/17425255.2019.1560421

39. Zucchi A, Costantini E, Scroppo FI, et al. The first-generation phosphodiesterase 5 inhibitors and their pharmacokinetic issues. *Andrology*. 2019(Nov);7(6):804–817. doi: 10.1111/andr.12683

40. Yafi FA, Jenkins L, Albersen M, et al. Erectile dysfunction. *Nat Rev Dis Primers*. 2016(Feb 4);2:16003. doi: 10.1038/nrdp.2016.3

41. Corona G, Rastrelli G, Burri A, et al. First-generation phosphodiesterase type 5 inhibitors dropout: A comprehensive review and meta-analysis. *Andrology*. 2016(Nov);4(6):1002–1009. doi: 10.1111/andr.12255

42. Peng Z, Yang L, Dong Q, et al. Efficacy and safety of tadalafil once-a-day versus tadalafil on-demand in patients with erectile dysfunction: A systematic review and meta-analyses. *Urol Int.* 2017;99(3):343–352. doi: 10.1159/000477496

43. McMahon CG. High dose sildenafil as a salvage therapy for severe erectile dysfunction. *Int J Impot Res.* 2002;14(6):533–538. [PubMed: 12494291]

44. Moncada I, Martinez-Salamanca J, Ruiz-Castane E, Romero J. Combination therapy for erectile dysfunction involving a PDE5 inhibitor and alprostadil. *Int J Impot Res.* 2018(Oct);30(5):203–208. [PubMed: 30050072]

45. Irwin GM. Erectile dysfunction. *Prim Care*. 2019(Jun);46(2):249–255. doi: 10.1016/j.pop.2019.02.006

46. Osmonov DK, Junemann KP, Bannowsky A. The "Kiel Concept: Of long-term administration of daily low-dose sildenafil initiated in the immediate post-prostatectomy period: Evaluation and comparison with the international literature on penile rehabilitation. *Sex Med Rev.* 2017(Jul);5(3):387–392. doi.org/10.1016/jsxmr.2017.03.002 [PubMed: 28372960]

47. Ventimiglia E, Capogrosso P, Montorsi F, Salonia A. The safety of phosphodiesterase type 5 inhibitors for erectile dysfunction. *Expert Opin Drug Saf.* 2016;15(2):141–152. doi: 10.1517/14740338.2016.1131818

48. McMahon C. Efficacy and safety of daily tadalafil in men with erectile dysfunction previously unresponsive to on demand tadalafil. *J Sex Med.* 2004(Nov);1(3):292–300. doi: 10.1111/j.1743-6109.04042

49. McMahon C. Comparison, efficacy, and tolerability of on demand tadalafil and daily dosed tadalafil for the treatment of erectile dysfunction. *J Sex Med.* 2005(May);2(3):415–425. doi: 10.1111/j.1743-6109.2005.20360.x

50. Yafi FA, Sharlip ID, Becher EF. Update on the safety of phosphodiesterase type 5 inhibitors for the treatment of erectile dysfunction. *Sex Med Rev.* 2018(Apr);6(2):242–252. doi: 10.1016/j.sxmr.2017.08.001

51. Gul M, Serefoglu EC. An update on the drug safety of treating erectile dysfunction. *Expert Opin Drug Saf.* 2019(Oct);18(10):965–975. doi: 10.1080/1440338.2019.1659244

52. Gong B, Ming M, Xie W, et al. Direct comparison of tadalafil with sildenafil for the treatment of erectile dysfunction: A systematic review and meta-analysis. *Int Urol Nephrol.* 2017(Oct);49(10):1731–1740. doi: 10.1007/s11255-017-1644-5

53. Madiera CR, Tonin FS, Fachi MM, et al. Efficacy and safety or oral phosphodiesterase 5 inhibitors for erectile dysfunction: A network meta-analysis and multicriteria decision analysis. *World J Urol.* 2021(Mar);39(3):953–962. doi/org/10.1007/s00345-020-03233-9 [PubMed: 32388784]

54. Kloner RA, Goggin P, Goldstein I, et al. A new perspective on the nitrate-phosphodiesterase type 5 inhibitor interaction. *J Cardiovasc Pharmacol Ther.* 2018(Sept);23(5):375–386. doi: 10.1177/1074248418771896

55. Moschos MM, Nitoda E. Pathophysiology of visual disorders induced by phosphodiesterase inhibitors in the treatment of erectile dysfunction. *Drug Des Devel Ther.* 2016(Oct 19);8:3407–3413. doi: 102147/DDDT.S118015

56. Pomeranz HD. Erectile dysfunction agents and nonarteritic anterior ischemic optic neuropathy. *Neurol Clin.* 2017(Feb);35(1):17–27. doi: 10.1016/j.ncl.2016.08.007

57. Loeb S, Ventigmiglia E, Salonia A, et al. Meta-analysis of the association between phosphodiesterase inhibitors (PDE5Is) and risk of melanoma. *J Natl Cancer Inst.* 2017(Aug);109(8):djx086. doi: 10.1093/jnci/djx086

58. Han X, Han Y, Zheng Y, et al. Use of phosphodiesterase type 5 inhibitors and risk of melanoma: A meta-analysis of observational studies. *Onco Targets Ther.* 2018(Feb);11:711–720. doi: 10.2147/OTT.s142637

59. Rastrelli G, Guaraldi F, Reismann Y, et al. Testosterone replacement therapy for sexual symptoms. *Sex Med Rev.* 2019(Jul);7(3):464–475. doi: 10.1016/j.sxmr.2018.11.005

60. Mulhall JP, Trost LW, Brannigan RE, et al. Evaluation and management of testosterone deficiency: AUA guideline. *J Urol.* 2018(Aug);200(2):423–32. doi: 10.1016/j.juro.2018.03.115

61. Dohle GR, Arver S, Bettochi C, et al. EAU guidelines office, 2018. Available at https://uroweb.org/guideline/male-hypogonadism/. Last accessed October 2, 2021.

62. Salter CA, Mulhall JP. Guideline of guidelines: Testosterone therapy for testosterone deficiency. *BJU Int.* 2019(Nov);124(5):722–729. doi: 10.1111/bju.14899

63. Anon. Testosterone nasal gel (Natesto) for hypogonadism. *Med Lett Drugs Ther.* 2015 (May 11);57(1468):73–74. [PubMed: 25941957]

64. Morely JE, Charlton E, Patrick P, et al. Validation of a screening questionnaire for androgen deficiency in aging males. *Metabolism*. 2000(Sept);49(9):1239–1242. doi: 10.1053/meta.2000.8625

65. Sansone A, Sansone M, Selleri R, et al. Monitoring testosterone replacement therapy with transdermal gel: When and how? *J Endocrinol Invest.* 2019(Dec);41(12):1491–1496. doi.org/10.1007/s40618-019-01082-x

66. Elkhoury FF, Rambhatla A, Mills JN, Rajfer J. Cardiovascular health, erectile dysfunction, and testosterone replacement: Controversies and correlations. *Urology*. 2017(Dec);110:1–8. doi: 10.1016/j.urology.2017.07.030

67. Karakus S, Burnett AL. The medical and surgical treatment of erectile dysfunction: A review and update. *Can J Urol.* 2020(Aug); 27(S3):28–35. [PubMed: 32876000]

68. Vigen R, O'Donnell CI, Baron AE, et al. Association of testosterone therapy with mortality, myocardial infarction and stroke in men with low testosterone levels. *JAMA.* 2013(Nov);310(17):1829–1836. doi: 10.1001/jama.2013.280386

69. Finkle WD, Greenland S, Ridgeway GK, et al. Increased risk of nonfatal myocardial infarction following testosterone therapy prescription in men. *PLoS One*. 2014(Jan);9(1):e85805. doi: 10.1371/jouornal.pone.00885805.ecollection2014

70. Elsherbiny A, Tricomi M, Bhatt D, Dandapantula HK. State-of-the-art: a review of cardiovascular effects of testosterone replacement therapy in adult males. *Curr Cardiol Rep.* 2017(Apr);19(4):35. doi: 10.1007/s11886-017-0838-x

71. Corona G, Rastrelli G, Pasquale G, et al. Testosterone and cardiovascular risk: Meta-analysis of interventional studies. *J Sex Med.* 2018;15(6):820–838. doi: 10.1016/j.jsxm.2018.04.641

72. Santella C, Renoux C, Yin H, et al. Testosterone replacement therapy and the risk of prostate cancer in men with late-onset hypogonadism. *Am J Epidemiol.* 2019(Sep);188(9):1666–1673. doi: 10.1093/aje/kwz138

73. Engel JD, McVary KT. Transurethral alprostadil as therapy for patients who withdrew from or failed prior intracavernous injection therapy. *Urology*. 1998(May);51(5):687–692. doi: 10.1016/s0090-4295(98)0093-4

74. Barnard JT, Cakir OO, Ralpah D, Yafi FA. Technological advances in penile implant surgery. *J Sex Med.* 2021(Jul);18(7):1158–1166. doi: 10.1016/j.jsxm.2021.04.011

75. Scherzer NK, Dick B, Gabrielson AT, et al. Penile prosthesis complications: Planning, prevention, and decision making. *Sex Med Rev.* 2019(Apr);7(2):349–359. doi.org/10.1016/j.sxmr.2018.04.002 [PubMed: 30033128]

SELF-ASSESSMENT QUESTIONS

1. Which of the following medications for erectile dysfunction would be a good choice for a patient with dysphagia?

   A. Avanafil tablet

   B. Tadalafil tablet

   C. Sildenafil tablet

   D. Vardenafil ODT

   E. Testopel implant

2. After taking sildenafil 100 mg, taken on demand on four separate occasions, the patient returns to the physician's office to complain that the medication is not working. His erectile dysfunction has not responded to treatment. The most appropriate action that the physician should take at this time is

   A. Discontinue sildenafil and switch the patient to a vacuum erection device.

   B. Switch the patient from on-demand sildenafil to daily sildenafil 10 mg.

   C. Continue current regimen for a total of 7 to 8 doses and review the instructions for proper use.

   D. Increase the sildenafil dose to 20 mg and instruct the patient to try this the next time.

   E. Combine sildenafil 10 mg with intracavernosal alprostadil and instruct the patient to take both on demand.

3. If vardenafil is taken with rifampin, the drug interaction may result in:

   A. Decreased efficacy of vardenafil

   B. Priapism

   C. Increased blood pressure

D. Acute hearing loss

E. Nausea and vomiting

4. Which one of the following statements about phosphodiesterase type 5 inhibitors is correct?

A. If a patient is taking doxazosin, blood pressure should be stabilized before starting the phosphodiesterase type 5 inhibitor.

B. If the patient has taken a nitrate, all phosphodiesterase type 5 inhibitors should be held for at least 1 week.

C. Sildenafil prolongs the QT interval in patients taking quinidine or procainamide.

D. The combination of erythromycin and a phosphodiesterase type 5 inhibitor will result in severe coughing.

E. The combination of a phosphodiesterase type 5 inhibitor and intracavernosal alprostadil will likely result in hypotension.

5. If a patient develops an acute, painless loss of vision in one eye while taking sildenafil 100 mg on demand, the most appropriate counseling information is

A. Discontinue sildenafil and do not start another phosphodiesterase type 5 inhibitor.

B. Discontinue sildenafil and start vardenafil.

C. Discontinue sildenafil and start tadalafil.

D. Continue sildenafil 100 mg on demand.

E. Continue sildenafil but reduce dose to 50 mg on demand.

6. Which one of the following statements about intracavernosal alprostadil is correct?

A. Alprostadil inhibits adenylate cyclase and increases the level of epinephrine in cavernosal tissue.

B. It has a low potential to produce systemic adverse effects.

C. Alprostadil should always be combined with other erectogenic drugs.

D. When administering a dose, both sides of the corpora cavernosa must be injected with alprostadil.

E. When administering a dose, alprostadil should be injected into an arm vein.

7. Which one of these testosterone supplements is most often associated with hepatotoxicity?

A. Oral alkylated testosterone tablets

B. Transdermal testosterone gel

C. Intranasal testosterone gel

D. Transdermal testosterone patch

E. Testosterone undecanoate injections

8. Which one of these testosterone supplements must be administered at a facility with a REMS program?

A. Transdermal testosterone gel

B. Intranasal testosterone gel

C. Oral alkylated testosterone tablets

D. Testosterone undecanoate injections

E. Testosterone enanthate injections

9. Which one of the following adverse effects of testosterone supplements necessitates discontinuing its use?

A. Azoospermia

B. Hematocrit of 55% (0.55)

C. Gynecomastia

D. Serum creatinine of 2 mg/dL (177 µmol/L)

E. Doubling of ALT and AST over baseline

10. When should the Princeton Consensus Panel guidelines be used?

A. To assess patients for cardiac side effects of phosphodiesterase type 5 inhibitors

B. To identify patients who can be treated safely with medications for erectile dysfunction

C. To monitor a patient's therapeutic response to alprostadil

D. To assess the severity of a patient's erectile dysfunction

E. To diagnose the type of sexual dysfunction that a patient has

11. Which one of the following statements about the phosphodiesterase type 5 inhibitors–nitrate interaction is correct?

A. Transdermal nitrates can be used safely with phosphodiesterase type 5 inhibitors.

B. When compared to vardenafil, tadalafil has less potential to interact with nitrates.

C. All nitrates by any route of administration are contraindicated in a patient taking any phosphodiesterase type 5 inhibitor.

D. The interaction produces dry mouth, constipation, and decreased sweating.

E. If taken in low enough doses, phosphodiesterase inhibitors will not interact with nitrates.

12. Which one of the following drugs commonly causes erectile dysfunction?

A. Nifedipine

B. Enalapril

C. Nebivolol

D. Hydrochlorothiazide

E. Irbesartan

13. Which of the following statements about VED's is correct?

A. VED is only available with a prescription.

B. Penile pain is a common reason why patients cannot tolerate its use and discontinue use after a few attempts.

C. A rubber ring may be applied to the erect penis to prolong the erection.

D. Prior to activating the VED, lidocaine jelly should be applied to the penis.

E. A male patient with severe arthritis of both hands is a contraindication to VED use.

14. Which statement about Caverject is correct?

A. An excessive dose may result in priapism.

B. It works by decreasing intracavernosal production of cAMP.

C. It is considered first-line treatment of erectile dysfunction.

D. Pulmonary oil embolism has been associated with its use.

E. Multiple doses during the day can be given.

15. Which one of the following statements is correct about phosphodiesterase type 5 inhibitors used for the treatment of erectile dysfunction?

A. They are 100% effective in all patients.

B. They improve libido, and correct erectile dysfunction and ejaculation disorders.

C. Sildenafil exhibits no significant drug–food interactions.

D. They enhance sexual performance in patients with normal erectile function.

E. Patients should take no more than one dose per day.

SELF-ASSESSMENT QUESTION-ANSWERS

1. **D.** Vardenafil ODT is an oral dispersible tablet formulation of vardenafil. It is considered convenient to use because it does not require that the patient swallow the tablet or take it with water. Instead, it dissolves quickly in the patient's saliva when put on the tongue. It ideal for patients with dysphagia.

2. **C.** A minimum clinical trial of a particular dosing regimen of a phosphodiesterase inhibitor is 7 to 8 doses. Therefore, the most prudent course is to allow the patient to have a minimal clinical trial with one dosing regimen before increasing the dose, switching to another phosphodiesterase type 5 inhibitor, or switching to another treatment for erectile dysfunction.

3. **A.** Vardenafil principally is metabolized to inactive metabolites by hepatic CYP3A4 enzymes. Therefore, rifampin, a CYP3A4 inducer would be expected to enhance vardenafil's catabolism and decrease sildenafil's efficacy.

4. **A.** Both doxazosin, an alpha-adrenergic antagonist, and phosphodiesterase type 5 inhibitors can decrease blood pressure. Therefore, it is recommended that a patient's blood pressure should be stabilized on doxazosin before starting a phosphodiesterase 5 inhibitor.

5. **D.** Nonarteritic anterior ischemic optic neuropathy presents as a sudden painless loss of vision in one eye. Although a cause–effect relationship has not been established between phosphodiesterase type 5 inhibitors and NAION, there is an association. Because there is an increased risk of NAION in the fellow eye, the manufacturer recommends discontinuation of the phosphodiesterase type 5 inhibitor if NAION is suspected, and not rechallenging with a phosphodiesterase type 5 inhibitor.

6. **C.** Intracavernosal alprostadil has a low potential to cause systemic side effects because it is catabolized by enzymes in the corpora cavernosa. This treatment is considered second-line treatment for management of erectile dysfunction.

7. **A.** Oral alkylated testosterone formulations, for example, fluoxymesterone, should be avoided as they may cause peliosis hepatis, hepatocellular

and intrahepatic cholestasis, and benign and malignant liver tumors.

8. **D.** Testosterone undecanoate may cause severe allergic reactions and pulmonary oil embolism. For this reason, it must be administered at a facility with a REMS program.

9. **B.** A severely increased hematocrit may lead to polycythemia and its sequelae, including hypertension, thrombosis, vertigo, tinnitus, and other neurologic symptoms.

10. **B.** The Princeton Consensus Panel guidelines identify patients who can and cannot safely engage in sexual activity. Therefore, it identifies patients who can be safely treated with medications for erectile dysfunction.

11. **C.** Because of the potential for severe hypotension when nitrates and phosphodiesterase type 5 inhibitors are taken together, any nitrate by any route of administration is contraindicated when a patient is taking a phosphodiesterase type 5 inhibitor.

12. **D.** Thiazide diuretics are one of the most common causes of erectile dysfunction, whereas angiotensin II antagonists, angiotensin converting enzyme inhibitors, and certain beta-adrenergic antagonists are considered safer antihypertensive agents to use in sexually active male patients.

13. **C.** Once the vacuum erection device pulls blood into the corpora cavernosa, the erection can be maintained by threading a rubber ring on to the base of the penis. The maximum duration that the rubber ring should remain on the penile shaft is 30 minutes.

14. **B.** Caverject or alprostadil works by stimulating adenyl cyclase, which increases production of cAMP, a vasodilatory neurotransmitter in the corpora cavernosa. Excessive doses can result in priapism.

15. **E.** The daily dose of phosphodiesterase type 5 inhibitor should be limited to one dose per day in order to prevent priapism.