Chapter 81: Erectile Dysfunction

INTRODUCTION

- *Erectile dysfunction* (ED) is the persistent failure (minimum of 3 months) to achieve a penile erection suitable for sexual intercourse. Patients often refer to it as impotence.

PATHOPHYSIOLOGY

- ED 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 ED are referred to as *organic ED*. Patients who do not respond to psychogenic stimuli and have no organic cause for dysfunction have *psychogenic ED*.
- The penis has two corpora cavernosa and one corpus spongiosum, which contain interconnected sinuses that fill with blood to produce an erection that is sustained by occlusion of venous outflow from the corpora.
- Acetylcholine works with other neurotransmitters (ie, cyclic guanylate monophosphate [cGMP], cyclic adenosine monophosphate [cAMP], or vasoactive intestinal po1ypeptide) to produce penile arterial vasodilation and ultimately an erection.
- Organic ED is associated with diseases that compromise vascular flow to the corpora cavernosum (eg, peripheral vascular disease, arteriosclerosis, and essential hypertension), impair nerve conduction to the brain (eg, spinal cord injury and stroke), or impair peripheral nerve conduction (eg, diabetes mellitus). Secondary ED is associated with hypogonadism.
- Psychogenic ED is associated with malaise, reactive depression or performance anxiety, sedation, Alzheimer disease, hypothyroidism, and mental disorders. Patients with psychogenic ED generally have a higher response rate to interventions than those with organic ED.
- Social habits (eg, cigarette smoking and excessive ethanol intake) and medications (**Table 81-1**) can also cause ED.

TABLE 81-1

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.

		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; depressed 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 a decreased libido, a secondary erectile dysfunction develops because of diminished sexual drive.
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. Safer antihypertensives include angiotensin-converting enzyme inhibitors, postsynaptic α_1-adrenergic antagonists (terazosin, doxazosin), calcium channel blockers, and angiotensin II receptor antagonists.
Miscellaneous Finasteride, dutasteride Lithium carbonate Gemfibrozil Interferon Clofibrate Monoamine oxidase inhibitors (eg, phenelzine, isocarboxazid, tranylcypromine) Opioids	Unknown mechanism	

CLINICAL PRESENTATION

- Signs and symptoms of ED can be difficult to detect. The patient's partner is often the first to report ED to the healthcare provider.
- Nonadherence to drugs thought to cause ED can be a sign of ED.

DIAGNOSIS

- Key diagnostic assessments include description of ED severity, medical, psychological, and surgical histories, review of concurrent medications, physical examination, assessment of cardiac reserve, and laboratory tests (ie, serum blood glucose, lipid profile, and testosterone level).

- Assess the severity of ED with a standardized questionnaire, such as the International Index of Erectile Function (IIEF).

TREATMENT

- Goals of Treatment: The goal is to improve the quantity and quality of penile erections suitable for intercourse.
- The first step in management of ED is to identify and, if possible, reverse underlying causes. Psychotherapy can be used as monotherapy for psychogenic ED or as an adjunct to specific treatments.
- Treatment options include vacuum erection devices (VEDs), drugs (**Table 81-2**), and surgery. Although no option is ideal, the least invasive options are chosen first (**Figure 81-1**).

TABLE 81-2

Dosing Regimens for Selected Drug Treatments for Erectile Dysfunction

Drug	Brand Name[a]	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 age 65 years and older, start with 25 mg dose. In patients with creatinine clearance less than 30 mL/min (0.5 mL/sec) 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 every 48 hours.	Generic formulations are available. Titrate dose so that erection lasts no more than 1 hour. High-fat foods decrease rate of absorption by 1 hour. Avoid taking dose with grapefruit juice. Contraindicated with nitrates by any route of administration.
Vardenafil	Levitra	5–10 mg orally 1 hour before intercourse	5–20 mg 1 hour before intercourse. Limit to one dose per day	In patients age 65 years and older, start with 5 mg Levitra. No dosage adjustment is required in patients with decreased creatinine clearance. 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,	Titrate dose so that erection lasts no more than 1 hour. High-fat foods decrease rate of absorption by 1 hour. Avoid taking dose with grapefruit juice. Contraindicated with nitrates by any route of administration.

				atazanavir, erythromycin, clarithromycin, ketoconazole, itraconazole), limit starting dose to 2.5 mg every 24 hours. 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.	
	Staxyn	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 65 years or older, patients with creatinine clearance less than 30 mL/min (0.5 mL/sec), or those with mild hepatic impairment. Do not use in patients with moderate or severe hepatic impairment or those taking moderately or highly potent P450 CYP3A4 inhibitors. Do not initiate Staxyn in patients taking α-adrenergic antagonists.	Staxyn should be taken without any liquid or food. The tablet should be placed on the tongue where it will dissolve. No uptitration of dose is recommended. Do not 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 65 years or older. In patients with creatinine clearance of 30–50 mL/min (0.5–0.83 mL/sec), limit starting dose to 10 mg every 48 hours; if less than 30 mL/min (0.5 mL/sec), 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 not 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 15–30 minutes before	50–200 mg orally 15–30 minutes	In patients with creatinine clearance of 30–89 mL/min (0.5-1.49 mL/sec) or those with mild-	May be taken with or without food. Avoid taking dose with grapefruit juice. When taken with large amounts

		intercourse	before intercourse. Limit to one dose per day.	to-moderate hepatic impairment, no dosage adjustment is needed. Not recommended if creatinine clearance is less than 30 mL/min (0.5 mL/sec), if the patient has severe hepatic disease, or if the patient is taking potent P450 CYP3A4 inhibitors. If the patient is taking moderate P450 CYP3A4 inhibitors (eg, erythromycin, fluconazole), the maximum recommended dose is 50 mg every 24 hours.	of ethanol, avanafil may cause orthostatic hypotension.
Prostaglandin E_1					
Alprostadil intracavernosal injection	Caverject, Edex	2.5 mcg intracavernosally 5–10 minutes before intercourse	10–20 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	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 disease.
Alprostadil intraurethral pellet	Muse	125–250 mcg intraurethrally 5–10 minutes before intercourse	250–1000 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					
Methyltestosterone	Android, Testred,	10 mg once daily	10–50 mg once daily	No dosage adjustment provided in labeling for patients with	Not recommended for use due to extensive first-pass hepatic catabolism

	Methitest			renal or hepatic impairment or older adults.	and because it is associated with hepatotoxicity. May cause fluid retention in patients with renal or hepatic disease.
Testosterone buccal system	Striant	30 mg every 12 hours, morning and evening	30 mg every 12 hours, morning and evening	No dosage adjustment provided in labeling for patients with renal or hepatic impairment or older adults.	Time the dose so that buccal system is removed before every morning and evening toothbrushing. Place buccal system just above incisor tooth in the mouth and hold in place for 30 seconds to adhere. To remove, slide buccal system down toward the tooth. With each dose, rotate site of administration to the alternate side of the mouth. Buccal tablet may become detached during eating. If this occurs, discard and replace with new buccal system. Do not chew or swallow buccal system.
Testosterone cypionate intramuscular injection	Depo-Testosterone	200–400 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.
Testosterone enanthate intramuscular injection	Delatestryl	200–400 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.
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	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 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

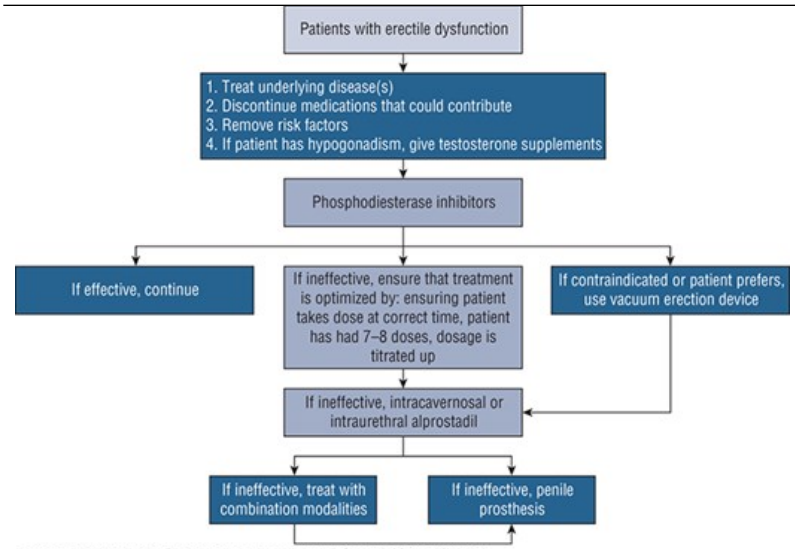
					time to achieve appropriate serum testosterone level. Avoid swimming, showering, or washing administration site for 3 hours after patch application.
Testosterone gel	AndroGel 1% (25 mg/2.5 g), Testim 1% (25 mg/2.5 g)	5–10 g of gel (equivalent to 50–100 mg testosterone, respectively) as a single dose in the morning	5–10 g of gel (equivalent to 50–100 mg testosterone, respectively) as a single dose in the morning. Titrate dose up at 14-day intervals	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 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 1.6% (40.5 mg/2.5 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 left or right axilla daily. 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.	Limit application to axilla. Apply antiperspirant or deodorant before Axiron. If applying multiple spray doses, apply one spray, let dry, then apply second dose to each axilla. Avoid swimming, showering, or washing administration site for 2 hours after application. REMS assessments must be submitted to the FDA.
Testosterone subcutaneous implant pellet	Testopel	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. Should use sterile implanter kit. Administration of the dose requires a forearm incision and subcutaneous dose implant under local anesthesia. Clinical onset is delayed for 3–4 months after initial dose. Generic formulations are available in higher strengths: 100 or 200 mg per pellet.

[a]Common brand names are included in this table. Medications may be available with other brand names.

FIGURE 81-1

Algorithm for selecting treatment for erectile dysfunction.



Source: Terry L. Schwinghammer, Joseph T. DiPiro, Vicki L. Ellingrod, Cecily V. DiPiro: *Pharmacotherapy Handbook, 11e*

Nonpharmacologic Treatment

Vacuum Erection Device

- First-line therapy for older patients in stable relationships. Onset of action is slow (ie, 3–20 minutes). An erection can be prolonged through use of constriction bands or tension rings.
- Consider VEDs as second-line therapy after failure of oral or injectable drugs. Response rate improves with addition of **alprostadil** or a phosphodiesterase inhibitor (PI).
- VEDs are contraindicated in patients with sickle cell disease or a history of prolonged erections. Use cautiously in patients taking warfarin as the likelihood of penile bruising is increased.

Surgery

- Surgical insertion of a penile prosthesis, the most invasive treatment for ED, is used after failure of less invasive treatments and for patients who are not candidates for other treatments.

Pharmacologic Treatments

Phosphodiesterase Type 5 Inhibitors

- Phosphodiesterase mediates catabolism of cGMP, a vasodilatory neurotransmitter in the corporal tissue.
- PIs are selective for isoenzyme type 5 in genital tissue. Inhibition of this isoenzyme in nongenital tissues (eg, peripheral vascular tissue, tracheal smooth muscle, and platelets) can produce adverse effects.
- Available agents (**avanafil, sildenafil, tadalafil**, and **vardenafil**) have different pharmacokinetic and pharmacodynamics profiles (**Table 81-3**). They are considered equally effective and comparable in safety despite no comparative clinical trial data.
- PIs are first-line therapy for younger patients. Effectiveness appears to be dose related; nonresponse rate is 30%–40%. Patient education is critical for clinical success.
- Hepatic metabolism of all four PIs can be inhibited by enzyme inhibitors of CYP 3A4. Use a lower starting dose to minimize dose-related adverse effects.

- Avoid exceeding prescribed doses due to increased frequency of adverse effects and inconsistent erectile responses.
- In usual doses, the most common adverse effects include headache, facial flushing, dyspepsia, nasal congestion, and dizziness that are all dose related.
- Sildenafil and vardenafil decrease systolic/diastolic blood pressure by 8–10/5–8 mm Hg for 1–4 hours after a dose. Although most patients are asymptomatic, multiple antihypertensives, nitrates, and baseline hypotension increase the risk of developing adverse effects. Avanafil is associated with similar decreases in blood pressure. Tadalafil is not associated with blood pressure decreases, but use with caution in patients with cardiovascular disease because of the inherent cardiac risk associated with sexual activity.
- Guidelines are available for stratifying patients on the basis of their cardiovascular risk (**Table 81-4**).
- Use PIs cautiously in patients at risk for retinitis pigmentosa and by pilots who rely on blue and green lights to land airplanes. Evaluate patients with sudden vision loss before continuing treatment.
- Tadalafil inhibits type 11 phosphodiesterase, which is thought to account for the dose-related back and muscle pain seen in 7%–30% of patients.
- PIs are contraindicated in patients taking nitrates. Use cautiously in patients taking α-adrenergic antagonists.

TABLE 81-3

Pharmacodynamics and Pharmacokinetics of Phosphodiesterase Inhibitors

	Sildenafil (Viagra)	Vardenafil (Levitra/Staxyn)	Tadalafil (Cialis)	Avanafil (Stendra)
Inhibits PDE-5	Yes	Yes	Yes	Yes
Inhibits PDE-1	Yes	Yes	Minimally	Minimally
Inhibits PDE-6	Yes	Yes	No	Moderately
Inhibits PDE-11	No	No	Yes	No
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 of oral absorption?	Yes	Yes/No[a]	No	No
Mean plasma half-life (hours)	3.7	4.4–4.8/4–6	18	4–5
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 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)	30	30/60	45	25–40
Duration (hours)	4–12	4–5/4–6	24–36	6+

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

TABLE 81-4

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 CHF (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 CHF (NYHA class III) History of stroke, transient ischemic attack, or peripheral artery disease	Patient should undergo complete cardiovascular workup and treadmill stress test to determine tolerance to increased myocardial energy consumption associated with increased sexual activity. Then, reclassify in low- or high-risk category
High risk	Has unstable or refractory angina, despite treatment Has uncontrolled hypertension Has severe CHF (NYHA class IV) Has had a recent myocardial infarction or stroke within 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

CHF, congestive heart failure; NYHA, New York Heart Association.

Reprinted with permission from 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;87(8):766–778.

Testosterone-Replacement Regimens

- **Testosterone**-replacement regimens restore serum testosterone levels to the normal range (300–1100 ng/dL; 10.4–38.2 nmol/L). These

regimens are indicated for symptomatic patients with hypogonadism as confirmed by both a decreased libido and low serum testosterone concentrations.

- Testosterone-replacement regimens correct secondary ED by improving libido. Improved muscle strength, sexual drive, and mood are observed within days or weeks of initiating treatment; however, improvements in ED or increased muscle mass may take months.
- Oral, buccal, parenteral, and transdermal products are available (see **Table 81-2**). Injectable regimens are preferred because they are effective, inexpensive, and do not have the bioavailability problems or adverse hepatotoxic effects of oral regimens. Testosterone patches, gels, and sprays are more expensive than other forms and should be reserved for patients who refuse injections.
- Screen patients 40 years and older for breast cancer, benign prostatic hyperplasia (BPH), and prostate cancer before starting therapy. Continue treatment for 3–6 months before an increase in dosage is considered.
- Testosterone replacement can cause sodium retention which can result in weight gain or exacerbate hypertension, congestive heart failure, and edema; gynecomastia; serum lipoprotein changes; and erythrocytosis.
- Oral testosterone-replacement regimens can cause hepatotoxicity, ranging from mildly elevated hepatic transaminases to serious liver diseases including peliosis hepatitis, hepatocellular and intrahepatic cholestasis, and benign or malignant tumors.
- Topical testosterone patches may cause contact dermatitis that responds to topical corticosteroids.

Alprostadil

- **Alprostadil**, or prostaglandin E_1, stimulates adenyl cyclase to increase production of cAMP, a neurotransmitter that ultimately enhances blood flow to and blood filling of the corpora.
- Alprostadil is approved as monotherapy for the management of ED. It is generally prescribed after failure of VEDs and PIs and for patients who cannot use these therapies. The intracavernosal route is more effective than the intraurethral route.
- *Intracavernosal* alprostadil is effective in 70%–90% of patients, but 30%–50% discontinue therapy during first 6–12 months. Perceived ineffectiveness, inconvenience of administration, unnatural, nonspontaneous erection, needle phobia, loss of interest, and cost of therapy are reasons given for discontinuation.
- *Intracavernosal* alprostadil is used successfully in combination with VEDs or vasoactive agents (eg, papaverine and phentolamine) that act by different mechanisms.
- *Intracavernosal* alprostadil acts rapidly, with an onset of 5–15 minutes. Duration of action is dose related and, within the usual dosage range, lasts less than 1 hour. To avoid adverse effects, the maximum number of injections is one daily and three weekly, with at least 24 hours between doses.
- Usual dose is 10–20 mcg up to a maximum of 60 mcg. The manufacturer recommends slow dose titration, but in clinical practice, most patients start with 10 mcg and titrate quickly.
- Local adverse effects occur during the first year of therapy, including cavernosal plaques or fibrosis at the injection site (2%–12% of patients), penile pain (10%–44%), and priapism (1%–15%). Penile pain is usually mild and self-limiting, but priapism (ie, painful, drug-induced erection lasting >1 hour) necessitates immediate medical attention.
- Use cautiously in patients at risk of priapism (eg, sickle cell disease, leukemia, or multiple myeloma) and bleeding complications secondary to injections.
- Instill *intraurethral* alprostadil, 125–1000 mcg 5–10 minutes before intercourse after emptying the bladder. No more than two doses daily are recommended.
- *Intraurethral* administration is associated with mild pain in 24%–32% of patients. Prolonged painful erections are rare.
- Female partners may experience vaginal burning, itching, or pain, which is probably related to transfer of alprostadil during intercourse.

Unapproved Agents

- A variety of commercially available and investigational agents have been used for management of ED. Examples include **yohimbine** (6–15 mg orally three times daily), **papaverine** (7.5–60 mg [single-agent therapy] or 0.5–20 mg [combination therapy] intracavernosal injection), and **phentolamine** (0.5–1 mg in combination with 30 mg papaverine; dose administered ranges from 0.1 to 1 mL of the mixture as an intracavernosal injection).

EVALUATION OF THERAPEUTIC OUTCOMES

- The primary therapeutic outcomes for ED are improving the quantity and quality of penile erections suitable for intercourse and avoiding adverse drug reactions and interactions.
- Assess the patient at baseline and after a treatment trial period of 1–3 weeks.
- Identify patients with unrealistic expectations and counsel accordingly to avoid adverse effects due to excessive use of erectogenic agents.

See Chapter 99, Erectile Dysfunction, authored by Mary Lee and Roohollah Sharifi, for a more detailed discussion of this topic.