Drug Therapy

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ERECTILE DYSFUNCTION

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ERECTILE dysfunction is defined as the inability to achieve and maintain an erection sufficient to permit satisfactory sexual intercourse.[1] It has been estimated to affect 20 million to 30 million men in the United States.[2,3] It may result from psychological, neurologic, hormonal, arterial, or cavernosal impairment or from a combination of these factors. In this article we provide a brief overview of the physiology of erection and the pathophysiology of erectile dysfunction, followed by a discussion of drug treatment for the disorder.

PHYSIOLOGY OF PENILE ERECTION

Penile erection is a neurovascular event modulated by psychological factors and hormonal status. On sexual stimulation, nerve impulses cause the release of neurotransmitters from the cavernous nerve terminals and of relaxing factors from the endothelial cells in the penis, resulting in the relaxation of smooth muscle in the arteries and arterioles supplying the erectile tissue and a severalfold increase in penile blood flow. At the same time, relaxation of the trabecular smooth muscle increases the compliance of the sinusoids, facilitating rapid filling and expansion of the sinusoidal system (Fig. 1). The subtunical venular plexuses are thus compressed between the trabeculae and the tunica albuginea, resulting in almost total occlusion of venous outflow.[4,5] These events trap the blood within the corpora cavernosa and raise the penis from a dependent position to an erect position, with an intracavernous pressure of approximately 100 mm Hg (the phase of full erection).

During masturbation or sexual intercourse, both of which trigger the bulbocavernous reflex, the ischiocavernous muscles forcefully compress the base of the blood-filled corpora cavernosa and the penis becomes even harder, with an intracavernous pressure reaching several hundred millimeters of mercury (the phase of rigid erection). During this phase, the inflow and outflow of blood temporarily cease.[6] Detumescence can be the result of a cessation of neurotransmitter release, the breakdown of second messengers by phosphodiesterases, or sympathetic discharge during ejaculation. Contraction of the trabecular smooth muscle reopens the venous channels, the trapped blood is expelled, and flaccidity returns.

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Neurophysiology of Penile Erection

The penis is innervated by autonomic and somatic nerves. In the pelvis, the sympathetic and parasympathetic nerves merge to form the cavernous nerves, which enter the corpora cavernosa, corpus spongiosum, and glans penis to regulate blood flow during erection and detumescence. The somatic component, the pudendal nerve, is responsible for penile sensation and the contraction and relaxation of the extracorporeal striated muscles (bulbocavernous and ischiocavernous).

Penile Flaccidity

The maintenance of the intracorporeal smooth muscle in a semicontracted state (Fig. 2) results from three factors: intrinsic myogenic activity,[7] adrenergic neurotransmission,[8] and endothelium-derived contracting factors such as prostaglandin $F_{2\alpha}$ and endothelins.[9,10]

Penile Erection

Nitric oxide released during nonadrenergic, noncholinergic neurotransmission and from the endothelium is probably the principal neurotransmitter mediating penile erection.[11,12] Within the muscle, nitric oxide activates a soluble guanylyl cyclase, which raises the intracellular concentration of cyclic guanosine monophosphate (GMP). Cyclic GMP in turn activates a specific protein kinase, which phosphorylates certain proteins and ion channels, resulting in the opening of potassium channels and hyperpolarization of the muscle-cell membrane, sequestration of intracellular calcium by the endoplasmic reticulum, and blocking of calcium influx by the inhibition of calcium channels. The consequence is a drop in cytosolic calcium concentrations and relaxation of the smooth muscle (Fig. 3). During the return to the flaccid state, cyclic GMP is hydrolyzed to GMP by phosphodiesterase type 5. Other phosphodiesterases are also found in the corpus cavernosum, but they do not appear to have an important role in erection. Communication among smooth-muscle cells takes place through gap junctions in the membranes of adjacent cells, which allow the passage of ions and second messengers to synchronize muscle activity.[13]

PATHOPHYSIOLOGY OF ERECTILE DYSFUNCTION

Erectile dysfunction can be classified as psychogenic, organic (neurogenic, hormonal, arterial, cavernosal, or drug-induced), or mixed psychogenic and organic (Table 1). The last form is the most common.

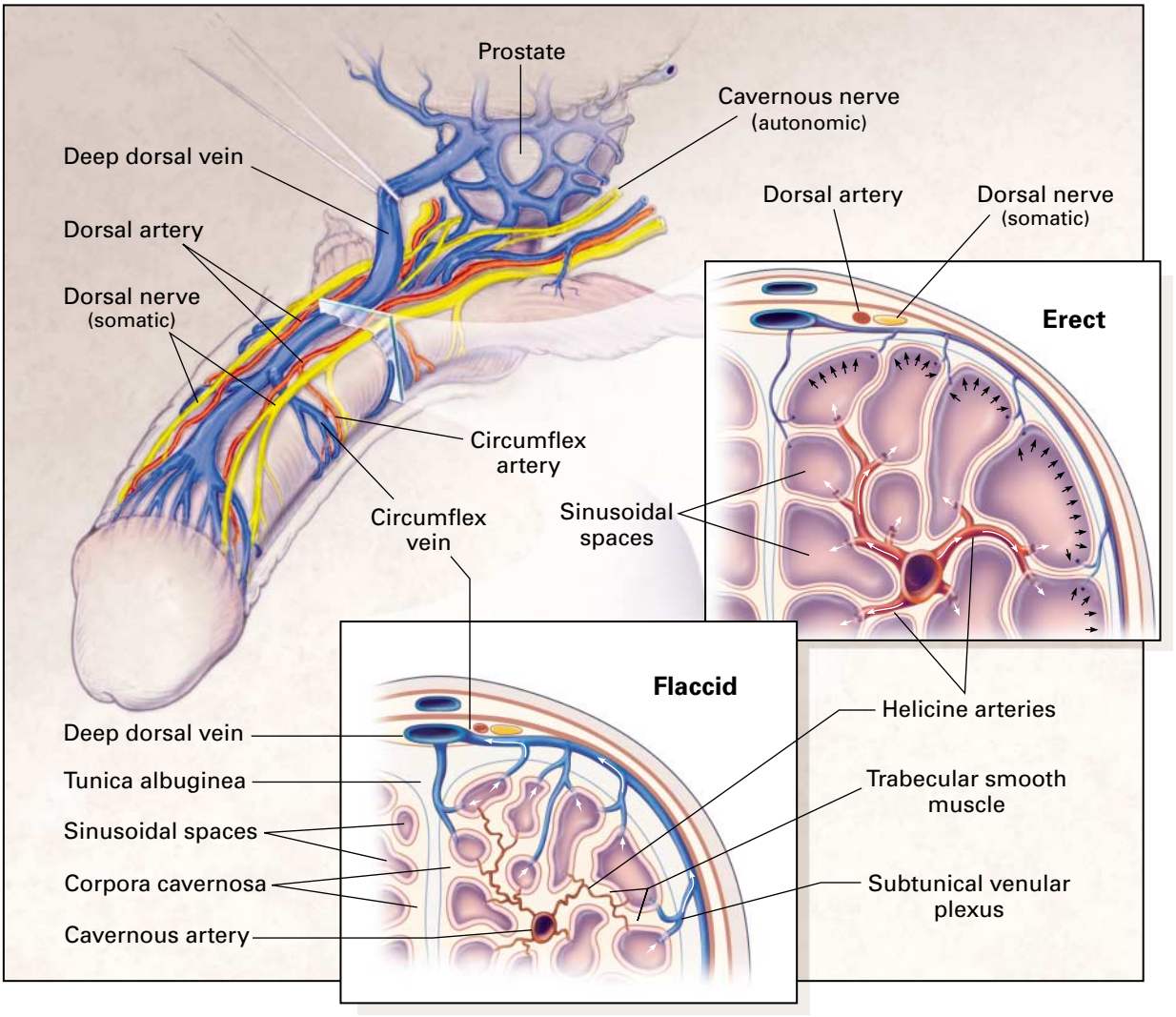

Figure 1. Anatomy and Mechanism of Penile Erection.

The cavernous nerves (autonomic), which travel posterolaterally to the prostate, enter the corpora cavernosa and corpus spongiosum to regulate penile blood flow during erection and detumescence. The dorsal nerves (somatic), which are branches of the pudendal nerves, are primarily responsible for penile sensation. The mechanisms of erection and flaccidity are shown in the upper and lower inserts, respectively. During erection, relaxation of the trabecular smooth muscle and vasodilatation of the arterioles results in a severalfold increase in blood flow, which expands the sinusoidal spaces to lengthen and enlarge the penis. The expansion of the sinusoids compresses the subtunical venular plexus against the tunica albuginea. In addition, stretching of the tunica compresses the emissary veins, thus reducing the outflow of blood to a minimum. In the flaccid state, inflow through the constricted and tortuous helicine arteries is minimal, and there is free outflow via the subtunical venular plexus.

Psychogenic Erectile Dysfunction

Common causes of psychogenic erectile dysfunction include performance anxiety, a strained relationship, lack of sexual arousability, and overt psychiatric disorders such as depression and schizophrenia. The strong association between depression and erectile dysfunction has been confirmed in two recent studies.[14,15] In men with schizophrenia, decreased libido is the main problem reported; neuroleptic drugs improve libido but lead to difficulties with erection, orgasm, and sexual satisfaction.[16]

Neurogenic Erectile Dysfunction

Neurologic disorders such as Parkinson's disease, Alzheimer's disease, stroke, and cerebral trauma often cause erectile dysfunction by decreasing libido or preventing the initiation of an erection. In men with spinal cord injuries, the degree of erectile function de-

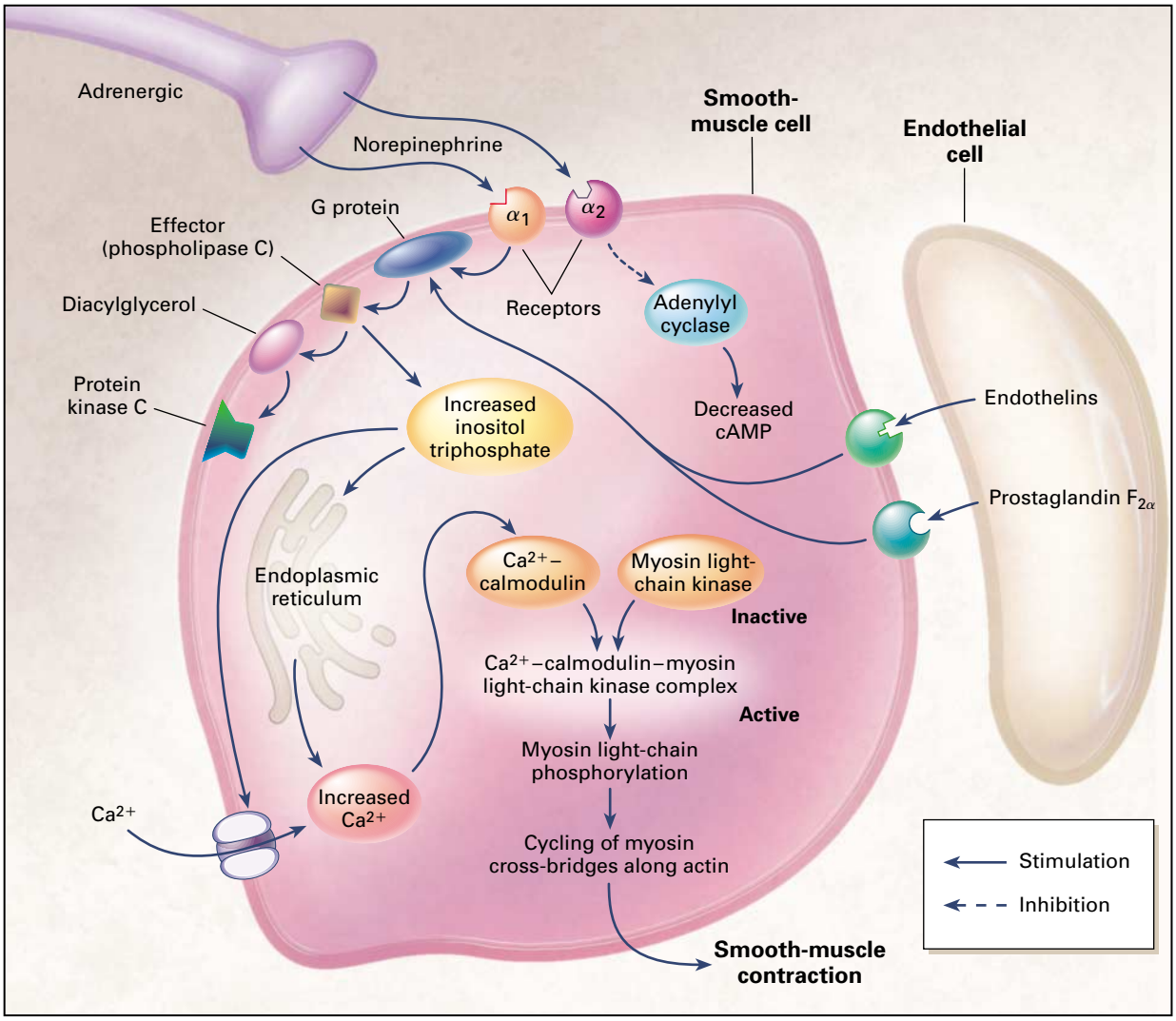

Figure 2. Molecular Mechanism of Penile Smooth-Muscle Contraction.

Norepinephrine from sympathetic nerve endings, and endothelins and prostaglandin $F_{2\alpha}$ from the endothelium, activate receptors on smooth-muscle cells to initiate the cascade of reactions that results in elevation of intracellular calcium concentrations and smooth-muscle contraction. Protein kinase C is a regulatory component of the calcium-independent, sustained phase of agonist-induced contractile responses.

Figure 3 (facing page). Molecular Mechanism of Penile Smooth-Muscle Relaxation.

Cyclic AMP (cAMP) and cyclic GMP (cGMP), the intracellular second messengers mediating smooth-muscle relaxation, activate their specific protein kinases, which phosphorylate certain proteins to cause opening of potassium channels, closing of calcium channels, and sequestration of intracellular calcium by the endoplasmic reticulum. The resultant fall in intracellular calcium leads to smooth-muscle relaxation. Sildenafil inhibits the action of phosphodiesterase (PDE) type 5, thus increasing the intracellular concentration of cGMP. Papaverine is a nonspecific phosphodiesterase inhibitor. GTP denotes guanosine triphosphate, and eNOS endothelial nitric oxide synthase.

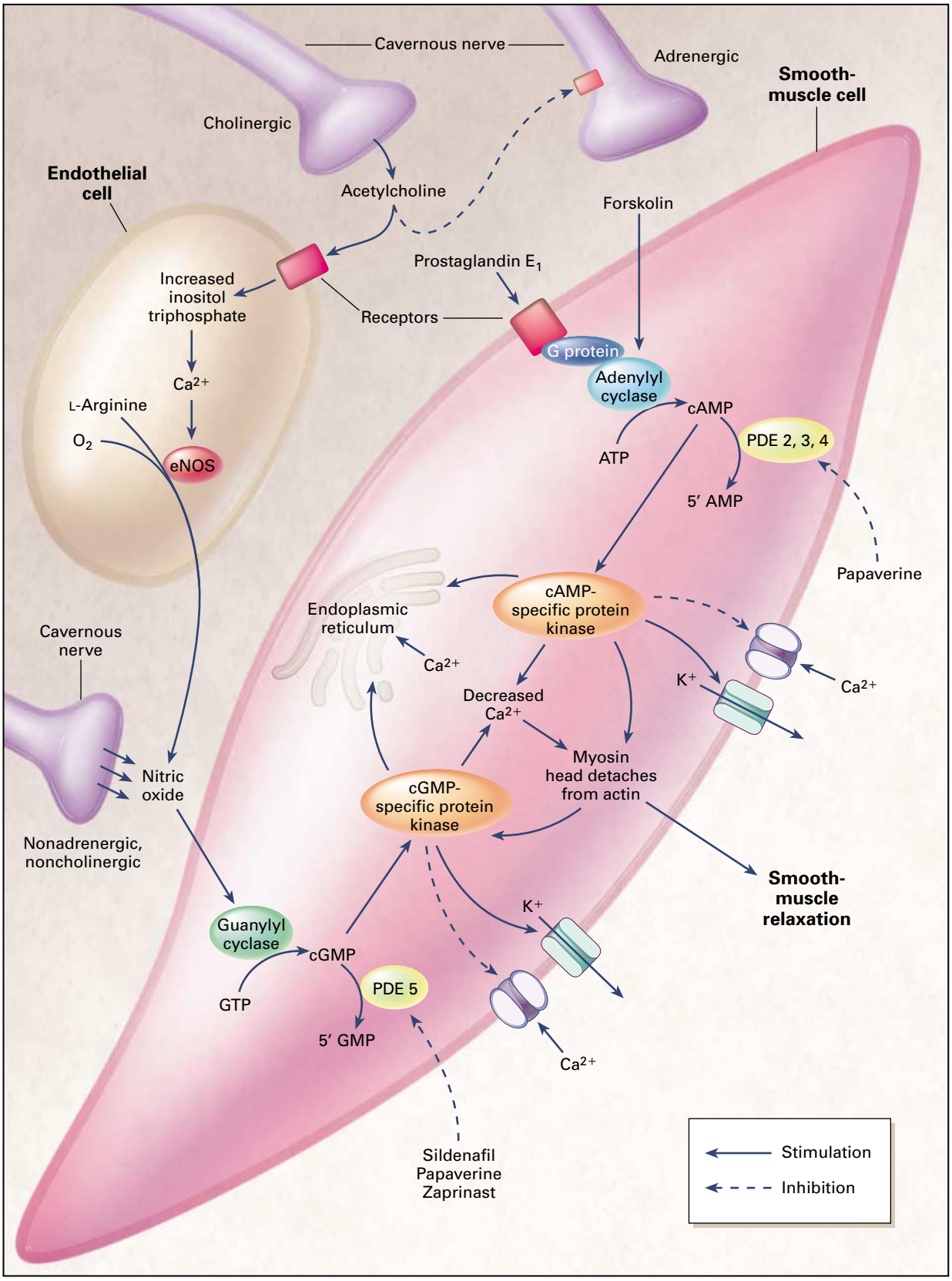

TABLE 1. CLASSIFICATION AND COMMON CAUSES OF ERECTILE DYSFUNCTION.

CATEGORY OF ERECTILE DYSFUNCTION	COMMON DISORDERS	PATHOPHYSIOLOGY
Psychogenic	Performance anxiety Relationship problems Psychological stress Depression	Loss of libido, overinhibition, or impaired nitric oxide release
Neurogenic	Stroke or Alzheimer's disease Spinal cord injury Radical pelvic surgery Diabetic neuropathy Pelvic injury	Failure to initiate nerve impulse or interrupted neural transmission
Hormonal	Hypogonadism Hyperprolactinemia	Loss of libido and inadequate nitric oxide release
Vasculogenic (arterial or cavernosal)	Atherosclerosis Hypertension Diabetes mellitus Trauma Peyronie's disease	Inadequate arterial flow or impaired veno-occlusion
Drug-induced	Antihypertensive and antidepressant drugs Antiandrogens Alcohol abuse Cigarette smoking	Central suppression Decreased libido Alcoholic neuropathy Vascular insufficiency
Caused by other systemic diseases and aging	Old age Diabetes mellitus Chronic renal failure Coronary heart disease	Usually multifactorial, resulting in neural and vascular dysfunction

pends largely on the nature, location, and extent of the lesion. Sensory involvement of the genitalia is essential to achieve and maintain reflexogenic erection, and this becomes more important as the effect of psychological stimuli abates with age.

Hormonal Causes of Erectile Dysfunction

Androgen deficiency decreases nocturnal erections and libido. However, erection in response to visual sexual stimulation is preserved in men with hypogonadism, demonstrating that androgen is not essential for erection.[17] Hyperprolactinemia from any cause results in both reproductive and sexual dysfunction because prolactin inhibits central dopaminergic activity and therefore the secretion of gonadotropin-releasing hormone, resulting in hypogonadotropic hypogonadism.

Vascular Causes of Erectile Dysfunction

Common risk factors associated with generalized penile arterial insufficiency include hypertension, hyperlipidemia, cigarette smoking, diabetes mellitus, and pelvic irradiation.[18,19] Focal stenosis of the common penile artery most often occurs in men who have sustained blunt pelvic or perineal trauma (e.g., from bicycling accidents).[18] In men with hypertension, erectile function is impaired not by the increased blood pressure itself but by the associated arterial stenotic lesions.[20]

Failure of the veins to close during an erection (veno-occlusive dysfunction) can cause erectile dysfunction.[21] Veno-occlusive dysfunction may be caused by the formation of large venous channels draining the corpora cavernosa, degenerative changes to the tunica albuginea (due to Peyronie's disease, old age, or diabetes mellitus) or traumatic injury (penile fracture), structural alterations of the cavernous smooth muscle and endothelium, poor relaxation of trabecular smooth muscle (in anxious men with excessive adrenergic tone[22]), and shunts acquired as a result of operative correction of priapism.

Drug-Induced Erectile Dysfunction

Many drugs have been reported to cause erectile dysfunction. Central neurotransmitter pathways, including serotonergic, noradrenergic, and dopaminergic pathways involved in sexual function, may be disturbed by antipsychotic, antidepressant, and centrally acting antihypertensive drugs.

β-Adrenergic–blocking drugs may cause erectile dysfunction by potentiating α_1-adrenergic activity in the penis. Thiazide diuretics have been reported to produce erectile dysfunction, but the cause is unknown. Spironolactone can cause erectile failure as well as gynecomastia and a decrease in libido.

Cigarette smoking may induce vasoconstriction and penile venous leakage because of its contractile effect on the cavernous smooth muscle.[23] Alcohol in small amounts improves erection and increases libido because of its vasodilatory effect and the suppression of anxiety; however, large amounts can cause central sedation, decreased libido, and transient erectile dysfunction. Chronic alcoholism may cause hypogonadism and polyneuropathy, which may affect penile nerve function.[24] Cimetidine, a histamine H_2-receptor antagonist, has been reported to decrease libido and cause erectile failure; it acts as an antiandrogen and can cause hyperprolactinemia.[25] Other drugs known to cause erectile dysfunction are estrogens and drugs with antiandrogenic action, such as ketoconazole and cyproterone acetate.

Erectile Dysfunction Due to Other Systemic Diseases and Aging

Sexual function progressively declines in healthy aging men. For example, the latent period between sexual stimulation and erection increases, erections are less turgid, ejaculation is less forceful, the ejaculatory volume decreases, and the refractory period between erections lengthens.[26] There is also a decrease in penile sensitivity to tactile stimulation,[27] a decrease in the serum testosterone concentrations,[28] and an increase in cavernous muscle tone.[22]

About 50 percent of men with chronic diabetes mellitus have erectile dysfunction. In addition to affecting small vessels, diabetes may affect the cavernous

nerve terminals and endothelial cells, resulting in a deficiency of neurotransmitters.[11] Chronic renal failure has frequently been associated with diminished erectile function, impaired libido, and infertility. The mechanism is probably multifactorial, involving low serum testosterone concentrations, vascular insufficiency, use of multiple medications, autonomic and somatic neuropathy,[29] and psychological stress. Men with angina, myocardial infarction, or heart failure may have erectile dysfunction due to anxiety, depression, or concomitant penile arterial insufficiency.

DIAGNOSIS OF ERECTILE DYSFUNCTION

Erectile dysfunction is occasionally the presenting symptom of a variety of diseases, such as diabetes mellitus, coronary artery disease, hyperlipidemia, hypertension, spinal cord compression, and pituitary tumor. Therefore, when a patient presents with erectile dysfunction, a thorough history (medical, sexual, and psychosocial) should be taken, the patient should undergo physical examination, and appropriate laboratory tests aimed at detecting these diseases should be performed (Fig. 4). A detailed psychosocial history may reveal deep-seated psychological problems or relationship conflicts that can be successfully treated only by mental health professionals. The physical examination should include evaluation of the breasts, hair distribution, penis, and testes; palpation of the femoral and pedal pulses; and testing of genital and perineal sensation. Recommended laboratory tests include urinalysis, a complete blood count, and measurements of serum glucose, creatinine, cholesterol, triglycerides, and testosterone while the patient is fasting. If the man's serum testosterone concentration is low, serum free (or bioavailable) testosterone, prolactin, and luteinizing hormone should be measured.

The physician should then assess the findings, inquire about the goals and preferences of the man (and his partner), discuss further diagnostic tests (Table 2) and therapeutic options (Table 3), and provide information on sexual physiology and pathophysiology so that the man's participation and that of his partner in the decision-making process will be well informed. Some men may benefit from referral for further testing and treatment. The indications for referral to a specialist include complex gonadal or other endocrine disorders, a neurologic deficit suggestive of brain or spinal cord disease, deep-seated psychological or psychiatric problems, Peyronie's disease, post-traumatic or primary erectile dysfunction, and active cardiovascular disease, especially if the man wishes to take sildenafil. If the man is taking recrea-

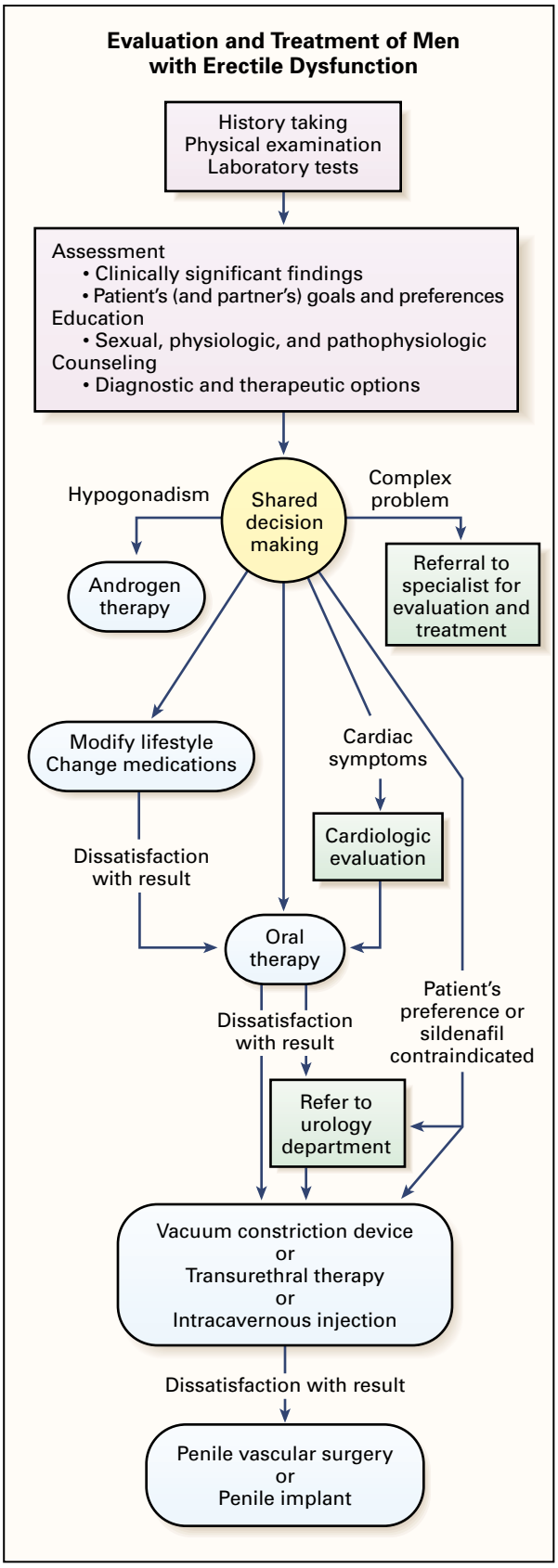

Figure 4. Approach to the Diagnosis and Treatment of Erectile Dysfunction.

TABLE 2. SPECIALIZED UROLOGIC AND RADIOLOGIC TESTS FOR MEN WITH ERECTILE DYSFUNCTION.

TEST	INDICATIONS
Combined penile injection of a vasodilator and sexual stimulation	Assess penile vascular function Therapeutic test in men who choose intracavernous therapy
Duplex (color) ultrasonography	Assess vascular function and evaluate for Peyronie's disease
Cavernosography	Young men with congenital or traumatic venous leakage
Pelvic arteriography	Young men with traumatic arterial insufficiency
Nocturnal penile monitoring (RigiScan Ambulatory Rigidity and Tumescence System, Timm Medical, Minneapolis)	Differentiate psychogenic from organic erectile dysfunction

tional drugs or a drug known to cause erectile dysfunction or has vascular risk factors, a change in drug use or lifestyle may be helpful. If primary hypogonadism is detected, androgen therapy is the treatment of choice. This approach to the diagnosis and treatment of erectile dysfunction,[30] tailored to the individual man's health status and goals, is outlined in Figure 4.

DRUG THERAPY FOR ERECTILE DYSFUNCTION

Androgens

Historically, androgens were touted as enhancing male sexual function. Today, more effective treatments are available, and testosterone therapy should be discouraged in men in whom erectile dysfunction is not associated with hypogonadism. In a study of 12 men with normal gonadal function who had erectile dysfunction, androgen therapy appeared to activate sexual behavior without enhancing erectile capacity, and had no effect on mood and psychological symptoms.[31]

In men with hypogonadism, oral testosterone preparations are less effective than intramuscular and transdermal testosterone preparations[32,33] and may be hepatotoxic (causing cholestasis, hepatitis, and benign or malignant tumors). Testosterone cypionate and testosterone enanthate are often used for replacement therapy; the usual dosage is 200 mg intramuscularly every two to three weeks. Their chief drawback is their roller-coaster effect: they have high activity the first week after injection, with a decrease thereafter. Two transdermal testosterone preparations are now available. Daily application of these preparations raises serum testosterone concentrations to within the normal range in over 90 percent of men. The most common adverse effects are skin irritation and contact

TABLE 3. TREATMENT OPTIONS FOR MEN WITH ERECTILE DYSFUNCTION.

TREATMENT	COST	ADVANTAGES	DISADVANTAGES	RECOMMENDATION
Psychosexual therapy	$50–$150/session	Noninvasive Partner involved Curative	Time-consuming Patient resistance	First-line treatment May be combined with other treatments
Oral sildenafil	$10/dose	Oral dosage Effective	Cardiovascular disease a contraindication in some men 1-Hr wait	First-line treatment Contraindicated with nitrates
Transurethral alprostadil	$25/dose	Local therapy Few systemic side effects	Moderately effective (43–60% with Actis*) Requires office training Causes penile pain	Second-line treatment
Intracavernous alprostadil or drug mixtures†	$5–$25/dose	Highly effective (up to 90%) Few systemic side effects	Requires injection High dropout rate Can cause priapism or fibrosis Causes penile pain	Second-line treatment
Vacuum constriction device	$150–$450/device	Least expensive No systemic side effects	Unnatural erection Causes petechiae Causes numbness (20%) Trapped ejaculation	Second-line treatment
Surgical treatment				
Prosthesis (all types)	$8,000–$15,000	Highly effective	Unnatural erection (semirigid device) Infection Requires replacement in 5–10 yr Requires anesthesia and surgery	For men not satisfied with medical treatment
Vascular surgery	$10,000–$15,000	Curative	Poor results in older men with generalized disease Requires anesthesia and surgery	For young men with congenital or traumatic erectile dysfunction

*Actis is an adjustable penile-constriction device.

†Drug mixtures contain two or three of the following drugs: papaverine, phentolamine, and alprostadil.

dermatitis. Because it stimulates growth of the prostate, androgen therapy is contraindicated in men with prostate cancer or obstruction of the bladder neck caused by prostatic hypertrophy. In men receiving long-term testosterone therapy, the hematocrit and serum testosterone, lipids, and prostate-specific antigen should be measured every six months.

Sildenafil

Sildenafil is a selective inhibitor of phosphodiesterase type 5, which inactivates cyclic GMP. Since its release in March 1998, it has become the drug of choice for most men with erectile dysfunction. When sexual stimulation releases nitric oxide into the penile smooth muscle, inhibition of phosphodiesterase type 5 by sildenafil causes a marked elevation of cyclic GMP concentrations in the glans penis, corpus cavernosum, and corpus spongiosum, resulting in increased smooth-muscle relaxation and better erection. Sildenafil has no effect on the penis in the absence of sexual stimulation, when the concentrations of nitric oxide and cyclic GMP are low.

Sildenafil has been evaluated in 21 clinical trials of up to six months' duration in over 3000 men and in 10 open-label extension studies. In most of the men in these studies, erectile dysfunction was caused by organic or combined organic and psychogenic factors. The results were based mainly on the reports of the men (and sometimes the partners) and scores on the International Index of Erectile Function. This index is a validated questionnaire with five domains: erectile function (six questions), orgasmic function (two questions), sexual desire (two questions), satisfaction with intercourse (three questions), and overall sexual satisfaction (two questions).[34] In these studies, the number of erections and the rates of penile rigidity (Table 4), orgasmic function, and overall sexual satisfaction were significantly higher with sildenafil than with placebo.[35-37] However, sildenafil had little effect on libido.

Among more than 3700 men with 1631 patient-years of exposure to sildenafil, most adverse events were mild to moderate and self-limited in duration.[37] Among men taking 25 to 100 mg of sildenafil, 16 percent reported headache, 10 percent flushing, 7 percent dyspepsia, 4 percent nasal congestion, and 3 percent abnormal vision (described as a mild and transient color tinge or increased sensitivity to light). These rates were twice as high among men taking 100 mg of sildenafil as among men who were taking lower doses. The visual effect is probably related to inhibition of phosphodiesterase type 6 in the retina. No chronic visual impairment has been reported, and the incidence of visual side effects was similar in diabetic and nondiabetic men.[38] Nevertheless, because of the short duration of the clinical trials and the difficulty in detecting subtle retinal changes, the long-term safety of sildenafil treatment is still unknown. In men with retinal diseases, an ophthalmologic consultation may be warranted before sildenafil treatment is initiated.

Adverse cardiovascular events (nasal congestion, headache, and flushing) were mild and transient in the majority of men. The rate of serious cardiovascular events (angina and coronary-artery disorder) was 4.1 per 100 man-years of treatment among those taking sildenafil and 5.7 per 100 man-years for those taking placebo. The rates of myocardial infarction were 1.7 and 1.4 per 100 man-years for the sildenafil and placebo groups, respectively.[37] However, because most of the studies excluded men taking nitrates and those with concomitant medical conditions, the incidence of serious cardiovascular events could be expected to be higher in the general population. From late March to mid-November 1998, more than 6 million outpatient prescriptions of sildenafil were dispensed

TABLE 4. EFFICACY OF SILDENAFIL IN MEN WITH ERECTILE DYSFUNCTION.*

RESPONSE	CAUSE OF ERECTILE DYSFUNCTION				
	DIABETES MELLITUS (N=268)	SPINAL CORD INJURY (N=178)	RADICAL PROSTATECTOMY (N=198)	PSYCHOGENIC CAUSE (N=179)	DEPRESSION (N=151)
	percentage of patients				
Improved erection					
Placebo	10	12	15	26	18
Sildenafil	57	83	43	84	76
Successful intercourse					
Placebo	12	13	NA	29	Not measured
Sildenafil	48	59	26 (at 0–6 mo), 60 (at 18–24 mo)†	70	Not measured

*Most data are from the sildenafil package insert (Viagra, Pfizer, New York, 1998). The dose is 50 to 100 mg. NA denotes not applicable.

†The data are from a non–placebo-controlled trial.[35] The rate of satisfaction with treatment was higher in men who underwent bilateral nerve-sparing prostatectomy.

(about 50 million tablets) to more than 3 million men. During the same period, 130 deaths associated with sildenafil therapy were reported to the Food and Drug Administration (FDA) (Table 5).

Sexual activity was thought to be a likely contributor to myocardial infarction in only 0.9 percent of 858 men in one study.[39] Thus, the absolute increase in risk caused by sexual activity is low (one chance in a million for a healthy man). According to data from the National Center for Health Statistics and the Framingham Heart Study, the rate of death from myocardial infarction or stroke for men in the age range in which erectile dysfunction is common is approximately 170 per million men per week. Therefore, it appears that sildenafil therapy is safe for most men. Nevertheless, given that most of the men who died had underlying cardiovascular disease, cardiovascular status should be carefully assessed before treatment. The combination of nitrates and sildenafil has resulted in severe hypotension and 16 deaths in the United States. Therefore, nitrate therapy is an absolute contraindication to sildenafil therapy. In response to the concern of physicians, the American Heart Association has published a guideline for sildenafil therapy (Table 6).[40]

Sildenafil is absorbed well during fasting, and the plasma concentrations are maximal within 30 to 120 minutes (mean, 60). It is eliminated predominantly by hepatic metabolism, and the terminal half-life is about four hours. The recommended starting dose is 50 mg taken one hour before sexual activity. The maximal recommended frequency is once per day. On the basis of effectiveness and side effects, the dose may be increased to 100 mg or decreased to 25 mg.

Table 5. Deaths Associated with Sildenafil Therapy in the United States.*

Cause of Death	No. of Patients†
Definite or suspected myocardial infarction	41
Cardiac arrest	27
Cardiac symptoms	6
Coronary artery disease	3
Stroke	3
Homicide or drowning	2
Unknown	48
Total	130

*Deaths were reported by the Food and Drug Administration from late March to mid-November 1998. During this period, 6 million outpatient prescriptions were dispensed, in doses ranging from 25 to 100 mg.

†The average age of the patients was 64 years (range, 29 to 87). Sixteen patients who died were using nitroglycerin or other nitrates. Forty-four patients died less than four hours after taking sildenafil; 27 of these died during sexual intercourse or immediately thereafter.

Table 6. Recommendations for Use of Sildenafil by Men with Cardiac Disease.*

1. Sildenafil is absolutely contraindicated in men taking long-acting or short-acting nitrate drugs.
2. If the man has stable coronary disease and does not need nitrates regularly, the risks of sildenafil should be carefully discussed with him. If the man requires nitrates because of mild-to-moderate exercise limitation due to coronary disease, sildenafil should not be given.
3. All men taking an organic nitrate (including amyl nitrate) should be informed about the nitrate–sildenafil hypotensive interaction.
4. Men must be warned of the danger of taking sildenafil 24 hours before or after taking a nitrate preparation.
5. Before sildenafil is prescribed, treadmill testing may be indicated in some men with cardiac disease to assess the risk of cardiac ischemia during sexual intercourse.
6. Initial monitoring of blood pressure after the administration of sildenafil may be indicated in men with congestive heart failure who have borderline low blood pressure and low volume status and men being treated with complicated, multidrug antihypertensive regimens.

*The recommendations were prepared by the American Heart Association.[40]

Adrenergic-Receptor Antagonists

Yohimbine

Yohimbine is an α_2-adrenergic–receptor antagonist produced in the bark of yohim trees. It presumably acts at the adrenergic receptors in brain centers associated with libido and penile erection. A meta-analysis of seven randomized, placebo-controlled studies of 419 men with erectile dysfunction from various causes found that yohimbine was better than placebo for all types of erectile dysfunction combined, and its effects were most noticeable with respect to nonorganic erectile dysfunction.[41] The most frequently reported side effects are palpitation, fine tremor, elevation of blood pressure, and anxiety. Yohimbine is not recommended for men with organic erectile dysfunction because its effect is marginal in such cases.

Phentolamine

Oral phentolamine has been reported to improve erectile function.[42,43] In a clinical trial of 459 men with mild-to-moderate erectile dysfunction, improved erections occurred in 37 percent of the men treated with 40 mg of phentolamine, 45 percent of those treated with 80 mg, and 16 percent of those given placebo.[44] Side effects include headache, facial flushing, and nasal congestion. Oral phentolamine has not been approved by the FDA, although it is available in several South American countries.

Apomorphine

Apomorphine is a potent emetic that acts on central dopaminergic (D1 or D2) receptors. When injected subcutaneously, it induces erections in rats and humans,[45] but the side effects, notably nausea, seriously limit its clinical usefulness. A sublingual

formulation of apomorphine is now undergoing clinical trials. In one study of 457 men with erectile dysfunction that had no major organic component, 52 percent of those taking a 4-mg dose attained erection, as compared with 35 percent of those in the placebo group. Furthermore, 43 percent of those in the treated group were able to engage in sexual intercourse, as compared with 27 percent of those in the placebo group. However, 17 percent of the treated men reported nausea, and 4 percent needed an antiemetic drug.[46] Sublingual apomorphine has not received FDA approval.

Trazodone

Trazodone is a serotonin antagonist and reuptake inhibitor, used as a sedative and antidepressant, which causes priapism in rare cases. Its effect on erection is thought to be the result of serotonergic and α-adrenolytic activity. Although trazodone alone or in combination with yohimbine has been reported to improve erectile function in some men,[47,48] its beneficial effects have not been substantiated in a double-blind, placebo-controlled, multicenter trial.[49]

Transurethral Therapy

Prostaglandin E_1 is an endogenous unsaturated 20-carbon fatty-acid derivative of arachidonic acid, and alprostadil is a more stable, synthetic form of prostaglandin E_1. In two large, multicenter, double-blind, placebo-controlled clinical trials conducted in the United States[50] and Europe,[51] transurethral alprostadil was effective in 43 percent of men with erectile dysfunction from various organic causes. The most common side effects were penile pain (32 percent) and urethral pain or burning (12 percent).

The advantages of transurethral therapy include local application, minimal systemic effects, and the rarity of drug interactions. The major drawbacks are moderate-to-severe penile pain, a low response rate, and inconsistent efficacy.[52,53] In one study of 51 men, use of an adjustable constriction device (Actis, Vivus, Mountain View, Calif.) placed at the base of the penis after the transurethral administration of alprostadil resulted in successful sexual intercourse in 69 percent.[54]

The first application (usually a 500-μg dose) should be undertaken in the physician's office because of the potential complications of urethral bleeding, vasovagal reflex, hypotension, and priapism. Depending on the erectile response, the man can then be instructed to increase or decrease the dose (up to 1000 μg or down to 250 μg).

Intracavernous Therapy

The most commonly used intracavernous drugs in the United States are alprostadil and a combination of papaverine, phentolamine, and alprostadil (trimix).

Papaverine

Papaverine is a nonspecific phosphodiesterase inhibitor that increases cyclic AMP and cyclic GMP concentrations in penile erectile tissue.[55] The usual dose ranges from 15 to 60 mg. It is highly effective (up to 80 percent) in men with psychogenic and neurogenic erectile dysfunction, but it is less effective in men with vasculogenic erectile dysfunction (36 to 50 percent). Its advantages include its low cost and stability at room temperature. Its major disadvantages are priapism (in up to 35 percent of cases), corporal fibrosis (in up to 33 percent of cases), and occasional increases in serum aminotransferase concentrations.

Phentolamine

Phentolamine is a competitive α-adrenergic–receptor antagonist. When used alone, phentolamine does not produce rigid erections[56]; when it is combined with papaverine, success rates range from 63 to 87 percent.[56-58] Most urologists prescribe a combination of 30 mg of papaverine and 0.5 to 1 mg of phentolamine, and the usual dose ranges from 0.1 to 1 ml. The side effects of phentolamine include hypotension and reflex tachycardia.

Alprostadil

Three formulations of alprostadil have been used for intracavernous injection: Prostin VR (Pharmacia & Upjohn), a pediatric formulation; Caverject (Pharmacia & Upjohn), a lyophilized powder; and Edex (Schwarz Pharma), which contains alprostadil in complex with α-cyclodextrin.

Alprostadil is the only intracavernous drug approved in the United States. Its efficacy is superior to that of papaverine and the combination of papaverine and phentolamine; it results in erections in more than 70 percent of men.[59-61] In addition, alprostadil is associated with a relatively low incidence of priapism (0.35 to 4 percent) and fibrosis (1 to 23 percent).[61-64]

The usual dose ranges from 5 to 20 μg. The most frequent side effect is painful erections (17 to 34 percent of men).[61,62] The hyperalgesic effect is more prominent in men with partial nerve injury, such as those with diabetic neuropathy and those who have undergone radical pelvic surgery.

Vasoactive Intestinal Polypeptide

Vasoactive intestinal polypeptide is a potent smooth-muscle relaxant originally isolated from the small intestine. Injection of vasoactive intestinal polypeptide alone does not cause a rigid erection,[65] but when it was combined with phentolamine, 67 percent of 70 men had erections sufficient for sexual intercourse.[66] Common side effects include transient facial flushing (53 percent), bruising (20 percent), pain at the injection site (11 percent), and truncal flushing (9 per-

cent). The combination is available in several European countries, but not in the United States.

Drug Combinations

Combinations such as papaverine and alprostadil,[67] ketanserin and alprostadil,[68] and phentolamine and alprostadil[69] have proved superior to alprostadil alone. The most effective intracavernous therapy used in the United States is a three-drug mixture containing papaverine, phentolamine, and alprostadil (trimix). The usual dose of trimix solution ranges from 0.1 to 0.5 ml. The rate of response to this solution is as high as 90 percent.[70] Although it has not been approved by the FDA, it is widely used in the United States.

Other Aspects of Intracavernous Injection Therapy

Men must receive appropriate training and education by medical personnel before beginning home injections. The goal is to achieve an erection that is adequate for sexual intercourse but does not last for more than one hour. The two major side effects of intracavernous injection are priapism and fibrosis (which can lead to penile deviation, nodules, or plaque). Priapism is preventable through careful dose adjustment. To prevent fibrosis, we routinely instruct men to compress the injection site for 5 minutes (up to 10 minutes in men taking an anticoagulant drug). Intracavernous injection therapy is contraindicated in men with sickle cell anemia, schizophrenia or other severe psychiatric disorders, or severe venous leakage.

Although the response rate is high, in long-term studies 38 to 80 percent of men ceased therapy.[71,72] Some men alternate injection therapy with sildenafil or transurethral alprostadil, preferring injection when an erection of longer duration is desired.

Transdermal Medications

No transdermal medication has been approved by the FDA for erectile dysfunction, and none is available for clinical use. Nitroglycerin cream or paste, alprostadil cream, and a cream containing aminophylline, isosorbide dinitrate, and co-dergocrine mesylate have been used in pilot studies in men with erectile dysfunction; the results have been mixed.[73]

CONCLUSIONS

The past three decades have witnessed a dramatic change in the treatment of men with erectile dysfunction. Treatment options have progressed from psychosexual therapy and penile prostheses (1970s), through revascularization, vacuum constriction devices, and intracavernous injection therapy (1980s), to transurethral and oral drug therapy (1990s). The elucidation of the nitric oxide–cyclic GMP pathway for erectile function and the development of sildenafil have been only the most recent advances.

Dr. Lue has received grants from Pfizer, Tap, and Vivus and has served as a consultant to Osbon, Pentech, Pfizer, Roche, Syntex, Tap, Upjohn, and Vivus.

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