64 Drugs Used in the Treatment of Erectile Dysfunction

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DRUG LIST

The term impotence has been used to indicate the inability of the male to attain and maintain erection of the penis sufficient to permit satisfactory sexual intercourse. Erectile dysfunction (ED) is the preferred term. ED is a common problem, especially among older men. Perhaps a more precise term for ED is that used to signify inability of the man to achieve an erect penis as part of the multifaceted process of male sexual function. Overall, the process encompasses a variety of physical aspects with significant psychological and behavioral components.

In the United States approximately 10 million men have ED. While erectile function may not be the most important indicator of sexual satisfaction, ED may contribute to mental stress that affects interactions with family and associates. While many advances have occurred in the diagnosis and treatment of ED, other aspects remain poorly understood by the general population and even health care professionals. ED is frequently assumed to be a physiological event associated with aging, but that is not entirely accurate.

The incidence of ED can be as high as 50% in men aged 40 to 70, with the percentage increasing with age. Other risk factors associated with ED include chronic illnesses, medications, cigarette smoking, heavy alcohol consumption, sedentary patterns, and obesity. ED can be due to vasculogenic, neurogenic, hormonal, and/or psychogenic factors. It can also be due to changes in the nitric acid–cyclic guanosine monophosphate (cGMP) biochemical pathway.

Most cases of secondary ED are related to arteriosclerosis. ED is also associated with hypertension, antihypertensive therapy, and diabetes mellitus, particularly in the older diabetic. Other chronic diseases, such as psychogenic disorders and Peyronie's disease, may be associated with ED.

Several therapeutic agents, especially those that affect neurotransmitter activity (both agonist and antagonist) are often associated with ED. Many such reports have been anecdotal, although 25% of ED may be drug-related. Several classes of drugs have been associated with ED (Table 64.1). The mechanism or mechanisms of

TABLE 64.1 Drugs That May Cause Erectile Dysfunction

Therapeutic Class	Drug or Drug Class
Antihypertensives	Thiazide diuretics, β-blockers, clonidine, methyldopa
Antidepressants	SSRIs, MAOIs
Antipsychotics	Phenothiazines, thioxanthenes
Antianxiety agents	Benzodiazepines
Hormones	Estrogens, antiandrogens
Miscellaneous	Alcohol, metoclopramide, opioids

SSRI, selective serotonin reuptake inhibitor; MAOI, monoamine oxidase inhibitor.

drug-induced ED may be neural, endocrine, or idiopathic. ED seems to be most frequently associated with antihypertensive medications, particularly β-blockers and thiazide diuretics. Estrogen therapy (see Chapter 61) and the use of antiandrogens (see Chapter 63) can lead to changes in the endocrine system resulting in ED. Paradoxically, selective serotonin reuptake inhibitors (SSRIs) can be associated with ED while also being useful be for the treatment of premature ejaculation.

Erection involves a coordinated action of the autonomic nervous system, and certain drugs may interfere with either the sympathetic division (e.g., α_1- receptors) or the parasympathetic division (e.g., noncholinergic neurotransmitters).

PHYSIOLOGY OF PENILE ERECTION

The physiology of penile erection involves an interplay of anatomical, hemodynamic, neurophysiological, and sex hormone interaction. Penile erection is the result of a complex interaction between the central nervous system and other local factors. This physical event also can be influenced by psychological factors.

The penis is mainly supplied by the internal pudendal artery, and three major sets of veins, superficial, intermediate, and deep veins, drain it. Drug-induced changes in neurotransmitter action can affect local blood flow. Vascular supply, intrinsic smooth muscles of the penis, and adjacent striated muscles are controlled by nerves arising from the thoracolumbar sympathetic, the lumbosacral parasympathetic, and the lumbosacral somatic systems. The pudendal nerve is the major somatic pathway innervating the male genitalia.

In addition to the integrated participation of the peripheral nerves, central neural pathways are involved in the process. These central mechanisms interact during normal sexual activity and require complex coordination between the autonomic nervous system and the somatic outflow at the level of the spinal cord.

5-Hydroxytryptamine (5-HT), dopamine, and norepinephrine play important roles as central neurotransmitters in the process of erection. Still other substances or hormones, such as endorphins, oxytocin, vasopressin, adrenocorticotropic hormone (ACTH) and related peptides, and prolactin, appear to participate in the complex and coordinated process of penile erection. Central nonadrenergic neurons also may influence male sexual behavior.

Nitric oxide (NO) released during nonadrenergic, noncholinergic (NANC) neurotransmission and from the vascular endothelium is most likely the major neurotransmitter mediating penile erection. NO is a mediator of relaxation of the corpus cavernosum in response to NANC neurotransmission. An endothelium-derived relaxing factor (EDRF) in the peripheral vasculature also can induce relaxation of vascular smooth muscles. NO functions as EDRF in many blood vessels, and its release from the endothelial cell relaxes vascular smooth muscle by activating soluble guanylate cyclase, thereby increasing the production of the intracellular messenger cGMP.

The role of NO in the physiology of male sexual function establishes its importance as the principal modulator of penile erection. An increase in cGMP activates specific protein kinases, which in turn phosphorylate certain proteins, activate ion channels, and through intermediary biochemical events lead to reduction in cytosolic calcium and relaxation of smooth muscles. Following an erection or the return to a flaccid state, cGMP is hydrolyzed to GMP by phosphodiesterase type 5 (PD-5). Although other types of phosphodiesterases are present in the corpus cavernosum, they do not appear to play a significant physiological role in erection.

Certain drugs (e.g., sildenafil, vardenafil, and cialis) exert their pharmacological actions by inhibiting the breakdown of cGMP. Sildenafil (*Viagra*) is a selective inhibitor of PD-5, an enzyme that inactivates cGMP. Vardenifil (*Levitra*) is a particularly effective inhibitor of PD-5. It has a shorter onset of action and can be used in smaller doses than sildenafil. Other drugs used in the treatment of ED exert their effects through other biochemical pathways, both central and peripheral.

INDIVIDUAL AGENTS

The pharmacological agents useful in this disorder may be grouped under five broad categories of treatment (Table 64.2). Such a classification system takes into account the mode of drug action, the route of administration, and the means by which target organ selectivity is achieved.

Oral medication for treatment of ED is relatively new. Earlier measures often employed the intracaver-

TABLE 64.2 Classification by Mode of Action for Treatments of Erectile Dysfunction

Class	Name	Definition
I	Central initiator	Compounds that have the main site of action in the CNS to activate neural events that result in coordinated signaling that results in the initiation of a penile erection (e.g. apomorphine)
II	Peripheral initiator	Compounds that have the main site of action in the periphery to activate events that result in a penile erection (e.g. PGE_1)
III	Central conditioner	Compounds that act mainly to improve the internal milieu of the CNS so that penile erection is enabled or enhanced, they do not on their own initiate an erection (e.g. trazodone)
IV	Peripheral conditioner (local or systemic)	Compounds that act mainly to improve the local or systemic internal milieu so that penile erection is enabled or enhanced (e.g. sildenafil)
V	Other	Other ways of promoting penile rigidity including devices and surgery (e.g. prostheses)

Reprinted with permission from Heaton JP, Adams MA, and Morales A. A therapeutic taxonomy of treatment for erectile dysfunction: An evolutional imperative. *Int J Impot Res* 1997;9:115–121. Dept of Urology, Queen's University, Kingston, Ontario.

nosal injection of a vasoactive agent or a systemic mode of drug administration. Local injections or dermal applications were frequently required for satisfactory pharmacological actions upon the vascular smooth muscles of the penis. Compounds with relatively short duration of action were found to be less than satisfactory in maintaining penile erections.

Combinations of drugs have sometimes been used to take advantage of the differing onset and duration of action of the individual compounds. A rapid onset of action and a sufficient duration are important characteristics of drugs used in the treatment of ED. Vasoactive agents that are orally effective have been available for about 20 years, but sildenafil and apomorphine (buccal) have significantly improved upon the therapeutic efficacy of orally active agents.

Alprostadil

Alprostadil (prostaglandin E_1 [PGE_1]; *Edex, Topiglan*) exerts a number of effects, including systemic vasodilation, inhibition of platelet aggregation, and stimulation of intestinal motility. PGE_1 relaxes isolated smooth muscle cells contracted by norepinephrine. It has become widely used in the treatment of ED. Alprostadil binds with PGE receptors and results in a cyclic adenosine monophosphate (cAMP) mediated smooth muscle relaxation. Little is known about the pharmacokinetics of PGE_1, but it is believed that as much as 80% is metabolized in one pass through the lungs. Such rapid degradation probably accounts for its lack of significant cardiovascular side effects when administered intracavernosally. PGE_1 can also be metabolized in the penis.

PGE_1 is not orally effective. Its therapeutic success depends on its being injected intracavernosally or administered transurethrally or intraurethrally. PGE_1 has also been used in combination with other agents, such as papaverine. The injection does not appear to produce any long-term side effects on penile smooth muscle. Transurethral therapy with alprostadil, such as MUSE (alprostadil urethral suppository or *m*edicated *u*rethral *s*ystem for *e*rection) is also an effective therapeutic technique, and there may be a role for this form of administration in selected patients with ED. The intracavernosal injection of alprostadil (e.g., alprostadil alfadex; *Edex, Viridal*) is safe and effective in patients with ED when sildenafil is ineffective. Both of these delivery systems have been used in the treatment of ED. MUSE can also be used in conjunction with a penile constrictor device (e.g., *ACTIS*).

Apomorphine

Apomorphine (*Uprima*) is a short-acting central and peripheral dopamine receptor agonist that can elicit male sexual responses. Dopamine appears to have an important role in normal erectile function. Apomorphine is a D_1-like, D_2-like dopamine receptor agonist. Apomorphine is not a new drug, and it has been used with limited success in ameliorating the symptoms of Parkinson's disease and to induce emesis. It is not orally active except for a special buccal formulation, but it can be given parenterally, usually subcutaneously. Apomorphine is rapidly cleared from the kidney because of its high lipid solubility, its large volume of distribution, and its rapid metabolism.

Aside from sildenafil, apomorphine is one of the few orally active (buccal route) pharmacological agents used in the treatment of ED. Apomorphine stimulates penile erection in both normal men and in men who are impotent. Apomorphine can be the drug of choice in patients with coexisting benign prostatic hyperplasia (BPH), coronary artery disease, and hypertension.

When formulated into a controlled release sublingual capsule, apomorphine becomes a very effective orally active drug representative of a new class of centrally acting drugs useful in the treatment of ED. It has a narrow range (2 to 6 mg) of effective doses for its erectogenic actions, with the higher doses being more effective in inducing erections. Apomorphine can cause nausea, emesis, drowsiness, and dizziness.

Androgens: Testosterone

Androgen deficiency can lead to decreases in nocturnal erections and libido. Hypogonadism is associated with impotence, yet erection in response to visual stimulation is preserved in men with hypogonadism, suggesting that androgens are not essential for erection. Although androgens can enhance male sexual function, testosterone therapy for the treatment of ED should be discouraged unless the cause is clearly related to hypogonadism. Androgen therapy in normal men may enhance sexual behavior but is without significant effect upon erectile function.

Usefulness of oral methyltestosterone is limited in men with hypogonadal impotence. Improvement following transdermal testosterone may require several months of therapy. Androgen replacement regimens for treating male hypogonadism include long-acting intramuscular injections (e.g., testosterone enanate, testosterone cypionate) and oral preparations (e.g. methyltestosterone, fluoxymesterone). Transdermal patches (*Testoderm, Androderm*) and topical testosterone gel (*Androgel*) are also available. Transdermal testosterone also may improve sexual function and psychological well-being in women who have undergone oophorectomy and hysterectomy. Transdermal delivery systems can provide a more constant serum testosterone level than do intramuscular injections, but they are more expensive.

Papaverine

Papaverine (*Pavabid*) is a nonspecific phosphodiesterase inhibitor that increases cAMP and cGMP levels in penile erectile tissue. Papaverine is particularly known as a smooth muscle relaxant and vasodilator. Its principal pharmacological action is as a nonspecific vasodilator of smooth muscles of the arterioles and capillaries. Various vascular beds and smooth muscle respond differently to papaverine administration both in intensity and duration. Papaverine decreases the resistance to arterial inflow and increases the resistance to venous outflow.

Papaverine is highly effective in men with psychogenic and neurogenic ED but less effective in men with vasculogenic ED. Papaverine–phentolamine combinations have been used in self-injection procedures. Papaverine doses may range from 15 to 60 mg. Papaverine treatment in patients with severe arterial or venous incompetence is usually unsuccessful, but autoinjections using low doses sufficient to achieve an erection are safe and efficient.

Major side effects associated with papaverine therapy include priapism, corporeal fibrosis, and occasional increases in serum aminotransferases. Intracorporeal scarring may be related to the low pH of the vehicle that is necessary to solubilize papaverine. Attempts to buffer papaverine to render it more suitable for intracavernosal injection have not been entirely satisfactory, and such delivery may still lead to intracorporeal scarring.

Phentolamine

Human erectile tissue has a population of membrane receptors that are predominantly of the α-adrenoceptor subtype. Phentolamine (*Vasomax*) is a nonselective α-adrenoceptor blocking agent (see Chapter 11), and like other such agents, it has been used to treat ED. Nonselective adrenoceptor antagonists may provoke a reflex that increases both sympathetic outflow and the release of norepinephrine.

Phentolamine has been used orally and intracavernosally in the treatment of ED. Following oral administration, phentolamine has a plasma half-life of about 30 minutes and a duration of action of 2 to 4 hours. An intracavernosal injection of phentolamine results in the drug reaching maximum serum levels in about 20 to 30 minutes. It is rapidly metabolized.

Phentolamine has been used in combination with papaverine, chlorpromazine, and vasoactive peptides in the treatment of ED.

Side effects of phentolamine are dose related. It may cause orthostatic hypotension, reflex tachycardia, cardiac arrhythmias, and rarely, myocardial infarction. Phentolamine also may reduce sperm motility in vitro.

Other α-adrenoceptor receptor antagonists include yohimbine, phenoxybenzamine, and thymoxamine. Yohimbine is an α_2-adrenoceptor antagonist, and thymoxamine is a competitive and relatively selective blocking agent for α_1- adrenoceptors. Phenoxybenzamine blocks both α_1- and α_2-adrenoreceptors, although it has a greater affinity for the α_1-subtype. All three of these α-receptor blocking drugs can induce penile erection, but their effects are generally less consistent and less effective than those of phentolamine. Yohimbine is only moderately effective in treating patients with organic impotence, and side effects may include postural hypotension, heart palpitations, fine tremors, and cavernosal fibrosis, especially following intracavernosal injections.

Sildenafil

Sildenafil (*Viagra*) was developed more than 10 years ago as an antihypertensive and antianginal drug. It

proved ineffective in these applications but was shown to affect the smooth muscles of the penis.

Sildenafil is a selective inhibitor of cGMP-specific PD-5 and therefore inhibits the degradation of cGMP. PD-5, the predominant type in the corpus cavernosum, also is present in other tissues (e.g., lungs, platelets, and eye). The selective inhibition of this enzyme facilitates the release of nitric oxide and smooth muscle relaxation of the corpus cavernosa. Sildenafil enhances erection by augmenting nitric oxide–mediated relaxation pathways. It has been suggested that sildenafil's mechanism of action is due to cross-talk between cGMP- and cAMP-dependent transduction pathways within the cavernous muscles.

Sildenafil is readily absorbed after oral administration and reaches peak plasma levels after about an hour. It undergoes hepatic metabolism and has a terminal half-life of about 4 hours. An initial dose of 50 mg is taken about an hour prior to sexual activity to induce penile erection.

Orally administered sildenafil is an effective and well-tolerated treatment for men with ED, including those with diabetes mellitus. It has also been used for so-called salvage therapy in men who do not respond to intracorporeal injections of other agents.

Headache is a common side effect, as are flushing and rhinitis. More serious side effects include definite or suspected myocardial infarctions and cardiac arrest.

Trazodone

Trazodone (*Apothecon*) is also classified as an antidepressant agent. It is a selective serotonin reuptake inhibitor (SSRI), partial agonist at postsynaptic 5-HT_{1A} receptors, and exhibits α-adrenoceptor blocking actions.

Trazodone may cause priapism and enhance libido, and it prolongs nocturnal erections. This drug has been used both orally and by intracavernosal injection. It can be used alone or in combination with yohimbine. Overall, trazodone has not been as effective in treating ED as other available agents. However, it may be an option for selected patients, particularly those with performance anxiety or low libido.

Other Agents

Many other drugs and herbals exhibit varying degrees of potency with respect to penile erection. Some have undergone limited clinical trials, while others are associated with anecdotal reports. Generally, these agents are not particularly effective and are not widely used among mainstream therapeutic options for ED.

Linsidomine (SIN-1) is an active metabolite of the antianginal drug molsidomine. Its mechanism of action upon the corpus cavernosum involves the release of nitric oxide. Injected intracavernosally it can produce penile erections, but its clinical usefulness has not been fully established.

Nitroglycerin (also isosorbide nitrate) relaxes isolated strips of human corpus cavernosum. Its mechanism involves the stimulation of guanylate cyclase. Clinically, nitroglycerin has been of limited use in the treatment of ED.

Minoxidil, an antihypertensive agent, produces arteriolar vasodilation by an unknown mechanism. In limited clinical studies, minoxidil increases penile rigidity and has been used in the long-term treatment of organic impotence.

Naltrexone, an orally active opioid receptor antagonist, restores erectile function in some patients with idiopathic ED.

Calcitonin gene–related peptide (CGRP) induces a dose-related increase in penile arterial inflow, cavernous smooth muscle relaxation, cavernous outflow occlusion, and an erectile response. CGRP plus PGE_1 may be an alternative to penile implants in selected patients.

Forskolin, an herbal, relaxes smooth muscle. Injected intracavernosally, forskolin has been of limited use in the treatment of vasculogenic impotence.

Other herbal remedies or so-called natural products purportedly can enhance male sexual activity. Some may contain yohimbine. Natural prosexual agents of herbal origin include *Epidemicum sagthatum, Tribulas terrestris,* and *Murira puama.* Their use in folk medicine in China and other countries is likely due to their sexual stimulating properties and their aphrodisiac effects. *Ginkgo biloba* extract also has been used in the therapy of ED and sexual dysfunction.

Drug Interactions

Orally active agents used in the treatment of ED are more affected by aging and disease processes than are those injected intracavernosally. In addition, alterations in hepatic metabolism and/or renal clearance in the elderly man (see Chapter 6) influence the frequency of appearance of adverse reactions between several coadministered drugs in the treatment of ED. For example, the concomitant use of sildenafil and nitroglycerin is contraindicated by cardiovascular complications. Also, the use of testosterone in the presence of androgen-dependent tumors may promote tumor growth.

Sildenafil has other minor adverse effects, such as headache, nasal congestion, and flushing. There are no clinically significant drug interactions between sildenafil and apomorphine. Apomorphine, like sildenafil, is orally active. However, unlike sildenafil, it exerts its action through the central nervous system. Apomorphine can produce dizziness, nausea, pallor, and hypotension, and in the presence of ethanol, it purportedly increases

the incidence of these side effects. Such a synergy caused by ethanol and apomorphine coadministration is not unique and would likely be present with other agents that induce mild hypotension.

The concomitant intake of grapefruit juice increases the concentration of many drugs (e.g., testosterone, sildenafil) in humans. Such actions appear to be mediated mainly by the suppression of the cytochrome P450 enzyme CYP3A4 in the small intestine. The resultant diminished first-pass metabolism and increased bioavailability can lead to increased drug levels in the blood. Because sildenafil is metabolized by CYP3A and to a lesser extent by CYP2C9, grapefruit juice can reduce the clearance of this drug. Other drugs can either increase or decrease serum levels of sildenafil. Administration of cimetidine, erythromycin, or ritonavir can lead to increases in serum concentrations of sildenafil, while rifampin diminishes blood levels of sildenafil.

Therapy with phentolamine may result in reflex tachycardia, arrhythmias, and hypotension; the latter effect can be exacerbated by other vasodilatory drugs and by the simultaneous ingestion of ethanol. The pharmacological actions of trazodone can be reduced by paroxetine and possibly other SSRIs.

Study Questions

1. Sildenafil's mechanism of action can best be described as
   (A) Selective inhibitor of phosphodiesterase type 5
   (B) Selective serotonin uptake inhibitor
   (C) Nonselective inhibitor of phosphodiesterase
   (D) β-Adrenoceptor blocking agent
2. Apomorphine
   (A) Has dopamine receptor antagonist properties
   (B) Efficacy depends upon a special buccal formulation
   (C) Actions are mediated only centrally
   (D) Action is contraindicated in patients with BPH
3. All of the following agents possess erectogenic properties EXCEPT
   (A) Papaverine
   (B) Phentolamine
   (C) Trazodone
   (D) Alcohol
4. All of the following classes of agents may produce erectile dysfunction EXCEPT
   (A) β-Adrenoceptor blocking agents
   (B) Oral hypoglycemic agents
   (C) Phenothiazines
   (D) Thiazide diuretics
   (E) α-Adrenoceptor blocking agents
5. Testosterone therapy may be indicated for the treatment of erectile dysfunction in which of the following situations?
   (A) Aged patient
   (B) Hypogonadism
   (C) Alcoholism
   (D) Depression

ANSWERS

1. **A.** The principal action of sildenafil is selective inhibition of the enzyme phosphodiesterase type 5. This is the enzyme that inactivates cGMP. Sildenafil does not appear to inhibit other forms of the enzyme. Sildenafil has no actions on either serotonin receptors or β-adrenoceptors.
2. **B.** Apomorphine is an older drug with dopamine receptor agonist properties. It acts both centrally and peripherally. It is not contraindicated in cases of BPH but rather may be the drug of choice in this instance.
3. **D.** Heavy use of alcohol is associated with impotence. The other choices are agents that possess erectogenic properties.
4. **E.** The first four choices all are associated with erectile dysfunction. Although α-adrenoceptor blocking agents are not approved for the treatment of erectile dysfunction, they have been shown to have some effectiveness.
5. **B.** The only time testosterone is indicated for the treatment of erectile dysfunction is if the cause is clearly related to hypogonadism. In other situations, the adverse effects related to testosterone and its limited effectiveness preclude its use.

SUPPLEMENTAL READING

Andersson KE. Pharmacology of erectile function and dysfunction. Urol Clin North Am 2001;28:233–248.

Keene LC and Davies PH. Drug-related erectile dysfunction. Adverse Drug React Toxicol Rev 1999;18:5–24.

Lue T. Erectile dysfunction. N Engl J Med 2000;348:1802–1813.

Melman A and Gingell JC. The epidemiology and pathophysiology of erectile dysfunction. J Urol 1999;161:5–11.

Padma-Nathan H and Giuliano F. Oral drug therapy for erectile dysfunction. Urol Clin North Am 2001;28:321–334.

CASE Study Diabetes and Erectile Dysfunction

A 48-year-old white man went to the local urology clinic with the chief complaint of sexual incompatibility associated with failure to attain an erection. He states that he has a family history of diabetes mellitus but is not receiving any insulin or oral hypoglycemic drugs. He is married and has fathered two children, aged 12 and 15. Blood chemistries and hormone levels are as follows: total insulin (free and bound), 15 microunits/mL; T_4 (thyroxine), 10 μg/dL; testosterone (total), 200 ng/dL; fasting blood glucose, 210 mg/dL; dihydrotestosterone, 10 ng/dL. Based on this medical history and the hormone levels, what treatment would you initiate?

ANSWER: This patient has possible diabetes mellitus with hypogonadism. Both testosterone and DHT levels lower than normal suggests hypogonadism. Whether or not there is a vasculogenic problem from the diabetes mellitus cannot be determined. The blood glucose is elevated, and a workup for diabetes may be pursued (blood insulin is normal). Initial therapy is administration of testosterone.