

by Joshua M. Radl, Doctor of Pharmacy Candidate & Deborah B. Dunham, MA

Column Editor: Lee Vermeulen, M.S., R.Ph.,

Director, Center for Drug Policy, University of Wisconsin Hospital and Clinics

Recent Developments in the Treatment of Erectile Dysfunction

In this issue, Josh Radl and Deb Dunham present a summary of new treatment approaches for erectile dysfunction (ED). Previously referred to as “impotence,” ED (one type of male sexual dysfunction) is believed to be one of the most common genitourinary diseases. However, the social stigma associated with the disorder makes it nearly impossible to measure its prevalence accurately.

The treatment of erectile dysfunction (ED) has included both pharmacologic and non-pharmacologic approaches, but effective medications prescribed in the past (including intracavernosal injection of vasoactive agents and prostaglandin) were often unacceptable to patients. In recent weeks a new product, sildenafil (Viagra™, Pfizer Pharmaceuticals) has been approved for marketing in the United States. An oral agent used to produce erection, the product was dispensed nearly 150,000 times in the first two weeks of its availability. According to IMS America (a marketing firm involved in monitoring prescription drug trends), this level of sales more than doubles the previous record (set recently by atorvastatin, Pfizer’s entry into the lipid management market). The fact that these sales were made *prior to the start* of any direct-to-consumer advertising, and indeed, before the Pfizer sales force began marketing the product to physicians suggests that the number of men aware of their disorder and actively pursuing treatment alternatives is enormous.

Pharmacists can play an important role in both the prevention and the effective treatment of erectile dysfunction. In this issue, a summary of medications known to cause ED is presented. It is essential for pharmacists to consider this list when dispensing prescriptions for sildenafil and

other ED treatments. Pharmacists should approach ED patients with sensitivity and tact, and above all the understanding that the patient is seeking treatment to alleviate an illness.

But is erectile dysfunction a disease? Should the treatment be a covered benefit under prescription benefit programs provided by most insurance carriers? Clearly, some diseases such as diabetes and peripheral vascular disorders can be blamed as the underlying cause of ED. Therefore, the medical management of the ED itself may be considered “medically necessary” as it may restore function that would generally be expected to be present without that underlying disease. However, the etiology of ED is unknown in a large proportion of patients. Whether erectile dysfunction is a symptom of age-related disease, or is a consequence of aging per se, many men have exaggerated expectations of their own sexual function later in life. Ultimately, payers must decide if the alleviation of sexual dysfunction (beyond the age at which sexual function is physiologically less likely) should be a component of their covered benefits. It has been reported (also by IMS America) that 51 percent of all prescriptions for sildenafil were reimbursed by insurers during the first two weeks of the product marketing, while the overall prescription reimbursement rate (for all pharmaceuticals) was 76 percent.

As always, please contact me at lc.vermeulen@hosp.wisc.edu with comments on this article or suggestions for future issues.

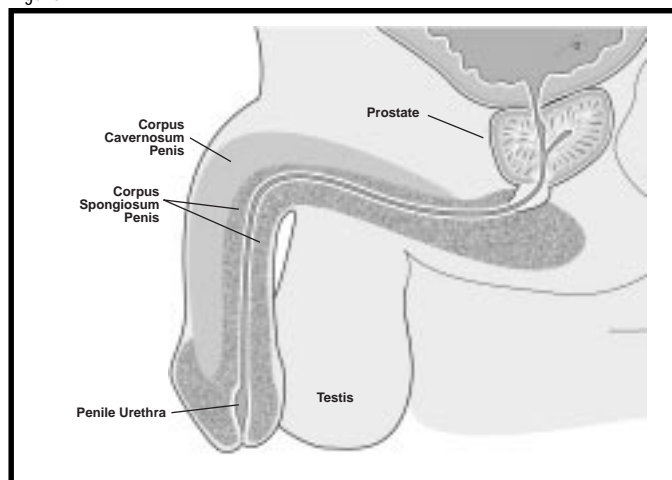
—Lee Vermeulen, M.S., R.Ph.
Column Editor

Introduction

Erectile dysfunction (ED) is defined as the inability to develop or maintain an erection sufficient for intercourse in 25% of attempts.^{1,2} Although precise figures are unavailable, erectile dysfunction is believed to affect 10 to 30 million American men.^{2,3} The incidence of ED appears to increase with increasing age; the prevalence of ED among 40 year old men is 40% and 70% among 70-year-old men. Erectile dysfunction is both an economic and a quality of life issue. In 1985, there were 400,000 outpatient visits and

30,000 operations for ED in the United States, at a cost of \$146 million.² For the individual patient, ED may result in depression, loss of self-esteem, poor self-image and disruption of interpersonal relationships.^{4,5} The last 2 decades have seen numerous advances in the treatment of ED beginning with the introduction of intracavernosal injections of vasoactive drugs, such as papaverine, phentolamine and prostaglandin E₁ and continuing with the introduction of sildenafil (Viagra™).⁶⁻⁸

Figure 1



Physiology

The penis contains a pair of long tubes (corpus cavernosum) which are filled with spongy sinusoidal tissue (corpus spongiosum, see Figure 1).^{1,3} The corpus cavernosum are encircled by an inelastic membrane (tunica albuginea). In the flaccid penis, the corporal smooth muscle and cavernosal arteries are contracted due to normal adrenergic tone. Smooth muscle contraction reduces blood flow into the sinusoids. Following reflexogenic or erotogenic stimulation, the smooth muscles relax allowing arterial blood to surge in and fill the cavernosa. Compression of the veins between the tunica and the corpus cavernosum restricts venous outflow and results in an erection. Nitric oxide, vasoactive intestinal polypeptide, acetylcholine and alpha-adrenergic blockade are believed to be the major controls of the erectile process.

A variety of etiologies exist for ED.^{1,3-5} Erectile dysfunction may occur as a result of vascular disease such as atherosclerotic occlusion or stenosis of the pudendal or cavernosa arteries, arterial damage from pelvic radiation leak or hypertension. Neurologic trauma, spinal cord injury or peripheral neuropathy may all impede the normal erectile process. In diabetics, the incidence of ED is estimated to range from 35% to 50%.⁵ Decreased testosterone levels from primary hypogonadism or hormonal drug therapy or elevated prolactin levels. Other causes of ED include drugs (see Table 1), alcohol consumption, high levels of cholesterol, low levels of high-density lipoprotein, prostate surgery, Peyronie's disease, priapism and depression.^{1,3} Treatment of ED should begin with identification and, if possible, correction of the underlying problem.⁸

Joshua M. Radl is a doctor of pharmacy candidate at the UW-Madison School of Pharmacy. Deborah B. Dunham, MA, is a clinical pharmacist in the Center for Drug Policy, University of Wisconsin Hospital and Clinics.

Pharmacologic Treatment

Pharmacologic treatment with vasoactive agents has proven effective in the treatment of erectile dysfunction.^{1,3,9-12} These agents can be administered by direct injection into the corpora cavernosum, and alprostadil can be successfully administered intra-urethrally.^{6,9,10} Doses depend on the route of administration and vary depending on the etiology of ED; therefore, a careful evaluation should be obtained prior to treatment.¹¹ Men with arterial insufficiency, neurological or psychological ED generally respond to lower doses than those with veno-occlusive disease.¹²

Intracavernosal injection

Intracavernosal injections of papaverine, phentolamine and prostaglandin E1 have all been used alone and in combination for the treatment of ED.⁹⁻¹² Papaverine, a smooth muscle relaxant, and phentolamine, an alpha-antagonist, have synergistic effects in relaxing the corporal smooth muscle, allowing for a significant decrease in their respective single doses. Prostaglandin E1 relaxes intracorporal smooth muscle and antagonizes the action of norepinephrine. These dual effects may explain its efficacy in inducing erections.¹⁰ Approximately 5 to 10 minutes after direct administration into the corpora cavernosum, these agents typically produce an erection that lasts 30 to 60 minutes.^{1,13}

Intracavernosal injection of vasoactive agents carries the risk of fibrosis, penile pain, prolonged erection, priapism and hematoma at the injection site. Fibrosis of the corpus cavernosum is a particular concern with papaverine. The rate of fibrosis is 4% after injection alone or in combination with other drugs. Fibrosis in the cavernosum occurs less frequently with alprostadil.^{13,14} The Alprostadil Study Group reported a 2% incidence of penile fibrosis.¹⁵ The risk of fibrosis may be reduced by careful injection technique and applying 3 to 5 minutes of compression at the injection site.¹⁶ Pain is the major problem associated with alprostadil injection, with an incidence of 16 to 40% and a clear dose dependency.¹³ Alprostadil has a higher rate of penile pain compared to papaverine.⁹ Penile pain was reported by 50% of men using intracavernosal alprostadil, but pain occurred after only 11% of all injections. In most cases, the pain was mild, but 6% discontinued use because of pain. Prolonged erection is a common adverse event of intracavernosal drug therapy and occurred in 5% of the men in the Alprostadil Study Group.¹⁵

Intracavernosal alprostadil, available as Caverject® and EDEX™, are the only injectable forms of alprostadil with FDA approval for the treatment of ED. Caverject® is

available as 5, 10 or 20 mcg disposable syringes (lyophilized powder and diluent). EDEX™ is marketed in a similar manner, in 5, 10, 20 or 40 mcg strengths. Although convenient, these products are costly, with an average wholesale price of approximately \$18 per 20 mcg dose.

Extemporaneously compounded injectable formulations containing alprostadil plus papaverine and/or phentolamine are not FDA approved specifically for ED. The two formulations commonly used in clinical practice are (1) alprostadil 2.5 to 7.5 mcg with phentolamine 10 to 75 mcg and (2) alprostadil 2.5 to 30 mcg, phentolamine 10 to 75 mcg and papaverine 150 to 450 mcg combined. Based on reviewed literature the efficacy of the three-drug combination in inducing full erection ranges from 73% to 85%.¹⁰ It has been suggested that the three-drug combination produces a better response in vascular ED, while the two-drug combination is preferred in men with purely neurogenic or psychologic ED, which usually requires smaller doses.¹² The cost of the combination formulations is approximately \$5 per injection.

Intra-urethral administration

A device for the intra-urethral administration of prostaglandin E1 is now available, circumventing the need for patients to use intracavernosal injections. The Medicated Urethral System for Erection (MUSE) is a small, disposable applicator that delivers alprostadil by a novel transurethral delivery system.^{4,5} The polypropylene applicator consists of a hollow stem (3.2 cm in length and 3.5 mm in diameter) with the tip containing a semisolid pellet of alprostadil. Men are instructed to urinate immediately before application, then to insert the stem of the applicator fully into the urethra, depress a button to deposit the pellet and remove the applicator. The MUSE Study Group reported on the results of a large, double-blind, placebo-controlled study that included 1500 men affected by organic ED.⁶ In this trial, intra-urethral alprostadil was administered initially in the physician's office in 4 doses (125, 250, 500, and 1000 mcg) to determine the dose for the "at-home" phase of the study. Sixty-six percent of the patients had responses sufficient to enter the "at-home" phase. Of these men, 65% using alprostadil had intercourse successfully at least once compared to 19% who received placebo. The most common side effect was mild penile pain (10.8%), but the pain rarely resulted in refusal to continue in the study. Hypotension occurred in 3.3% of the men receiving alprostadil during the clinic testing. Priapism and fibrosis were not observed with intra-urethral alprostadil administration.

Intra-urethral alprostadil has shown to be an effective option in the treatment of organic ED before considering the use of intracavernosal injections. However, preliminary

clinical observations indicate that MUSE therapy may be ineffective in patients previously treated with intracavernosal injections of combination pharmacotherapy.¹⁷ In 100 of these patients that used MUSE, only 7% had well-sustained, rigid erections, while 30% had full erection with partial rigidity. Sixty-three percent of patients reported erections inadequate for intercourse. Penile pain (24%), syncope (3%) and urethral bleeding (3%) occurred at higher rates than in the MUSE Study Group. When these patients retried intracavernosal injections, 49% had sustained rigid erections, 40% had full erections with partial rigidity and only 11% reported an erection inadequate for penetration.

Follow-up studies have shown that a surprisingly high proportion of men are dissatisfied with present ED treatments and do not persist with the use of vacuum devices or intracavernosal injections, despite good initial response.¹⁵⁻¹⁶ At a mean follow-up of 5.4 years, only 41% of patients were still using intracavernosal injection. The most common reasons for discontinuing intracavernosal injection were inadequate erection (14%), lack of spontaneity (12%), side effects (10%), lack of partner (9%) and loss of sexual interest (5%).^{18,19} The cost of intracavernosal injection therapy is also an important factor in discontinuation. Half of the patients who discontinued due to inadequate erectile response, did not seek further medical help.²⁰

Oral Drug Therapy

On March 27, 1998, the Food and Drug Administration approved sildenafil (Viagra™), the first oral medication for the treatment of ED, in less than 6 months after submission.²¹ The demand for sildenafil has been overwhelming; the drug generated over 36,000 new prescriptions in its first week alone and almost 150,000 by week 2. Sildenafil is approved for the treatment of men who have difficulty obtaining and maintaining an erection. Sildenafil is contraindicated in patients taking organic nitrates such as nitroglycerin, isosorbide dinitrate or isosorbide mononitrate, because of potentiation of the hypotensive effects of the nitrates.

Sildenafil, a phosphodiesterase type 5 (PDE5) inhibitor, does not cause penile erections directly, but augments the response to sexual stimulation by enhancing the smooth muscle relaxant effects of nitric oxide (NO).²² Nitric oxide activates the enzyme guanylate cyclase, which results in increased levels of cGMP, producing smooth muscle relaxation in the corpus cavernosum and allowing inflow of blood into the corpus cavernosum of the penis.⁷ At recommended doses, sildenafil has no effect in the absence of sexual stimulation.

In clinical studies, sildenafil was administered to more than 3,000 patients (ages 19 to 87 years) with ED of various causes (organic, psychogenic and mixed) with a mean dura-

tion of 5 years. The patients had a wide range of concomitant illnesses, including coronary artery disease, hypertension, diabetes, depression and spinal cord injury. The drug was evaluated at doses of 25 mg, 50 mg and 100 mg in twenty-one double-blind, placebo-controlled trials of up to 6 months duration. The primary measure of efficacy was a sexual function questionnaire which addressed two issues: (1) the ability to achieve erections sufficient for sexual intercourse and (2) the maintenance of erections after penetration. An improvement in their erections was reported by 63%, 74%, 82%, 24% of the patients on 25 mg, 50 mg, and 100 mg of sildenafil, and placebo, respectively. Per patient weekly attempted intercourse success rates averaged 1.3 on 50 to 100 mg sildenafil versus 0.4 on placebo. Men with erectile dysfunction attributed to diabetes mellitus and radical prostatectomy reported somewhat less improvement in erections than did other groups (57% vs 10% placebo and 43% vs 15% placebo, respectively).²³⁻²⁸

Sildenafil has a low incidence of adverse effects, and these side effects are generally transient and mild to moderate in nature. In clinical trials the most common side effects were headache (16%), flushing (10%) and dyspepsia (7%).^{7,21,22} Some patients (about 3%) also reported changes in vision, predominantly color tinge to vision, but also increased sensitivity to light or blurred vision. No cases of priapism were reported.²² The discontinuation rate due to adverse events among the treated patients was not significantly different from those receiving placebo (2.5% vs 2.3%).⁷

Sildenafil is extensively metabolized by cytochrome P450 3A4 and 2C9.⁷ Drugs which inhibit these isoenzymes may increase sildenafil plasma levels. Erythromycin, a CYP3A4 inhibitor, has been shown to increase plasma sildenafil concentrations by 182%. Other potent inhibitors of this isoenzyme, such as ketoconazole, itraconazole or mibefradil, would be expected to have a similar effect.²²

The recommended dose is 50 mg taken one hour (range 0.5 to 4 hours) before sexual activity, and the maximum recommended dosing frequency is once per day.²² Based on patient response, the dose may be increased to a maximum of 100 mg or decreased to 25 mg. In patients with hepatic or renal impairment or who are taking cytochrome P450 3A4 inhibitors, the starting dose should be reduced to 25 mg. Sildenafil is available as 25 mg, 50 mg and 100 mg strengths in bottles of 30 oral tablets, at a cost of approximately \$9 for a single 50 mg tablet. Since most prescription insurance plans classify ED as a cosmetic problem, there inevitably will be some hard choices for purchasers.

Oral administration of phentolamine, yohimbine,

delaquamine, apomorphine, trazadone and testosterone have all been studied in the treatment of ED.^{2,4,8} Yohimbine and delaquamine have failed to demonstrate beneficial effects on erectile dysfunction compared with placebo.² While apomorphine has shown some benefits, it has too many adverse effects, including persistent yawning, nausea, vomiting and hypotension, to be clinically useful. Phentolamine and trazadone have shown modest improvements in patients with psychogenic and mild vascular ED compared to placebo. Testosterone therapy for ED is indicated only in confirmed cases of documented hypogonadism.^{2,3} Intramuscular testosterone preparations (200-300 mg IM every 2-3 weeks) are preferable to oral preparations because the latter are associated with relatively unpredictable serum levels, a risk of liver toxicity and elevated lipid levels.³

Topical Drug Therapy

Topically acting vasodilators have long been tried in treating ED. Many agents have shown variable success, probably due to variable ability in penetrating the cutaneous tissues. Papaverine, nitroglycerin (glyceryl trinitrate), minoxidil, and testosterone have all been studied for topical use in the management of ED.² Most studies have found nitroglycerin not clinically useful; it induced headache at all concentrations used. Transdermal testosterone patches have shown success in the management of erectile difficulties resulting from hypogonadism.⁵ Papaverine gel applied topically may be of benefit in augmenting reflex erections in men with spinal cord injuries.²⁹ In pilot studies, topical minoxidil, nitroglycerin and prostaglandin E1 failed to induce rigid erections.²

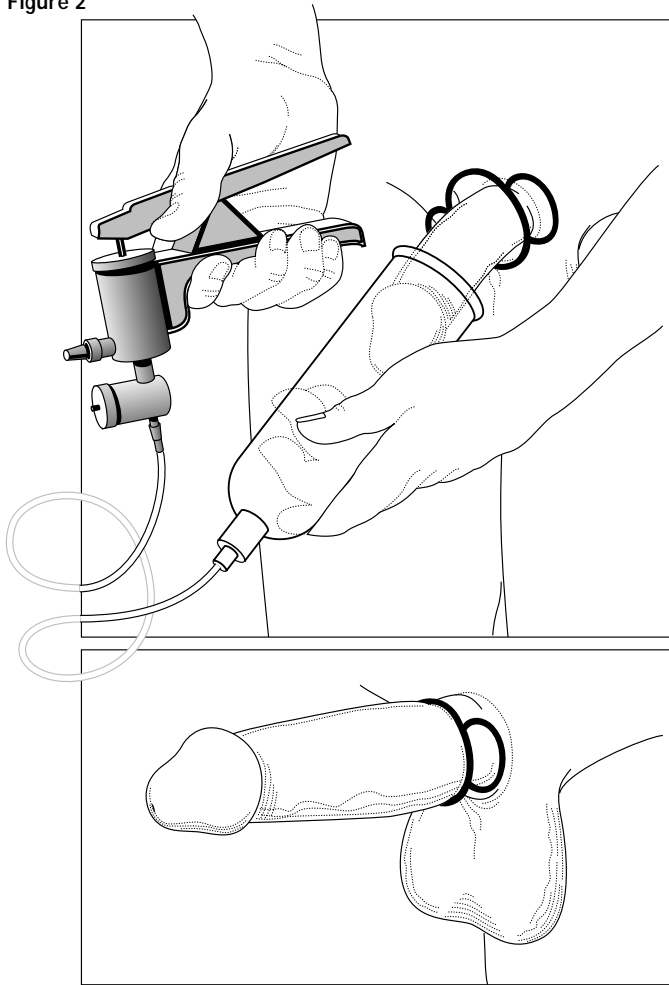
Most recently, a topical treatment using a cream containing aminophylline 3%, isosorbide dinitrate 0.25% and codergocrine mesylate 0.05% was studied in 36 men with ED.³⁰ Twenty-one patients reported full erection and satisfactory intercourse with the active cream; however, only 4 of 8 men with neurogenic impotence and 2 of 7 men with arterial insufficiency achieved a full erection.

Nonpharmacologic Treatment

Vacuum Devices

When used properly, the vacuum constriction devices that are available by prescription are noninvasive, safe and effective treatments for erectile dysfunction.⁸ The typical device consists of an elastic band on a cylinder attached to a vacuum pump (see Figure 2). The plastic cylinder is placed over the flaccid penis and the air in the cylinder is pumped out, either manually or with a battery operated pump. Negative pressure created in the cylinder draws blood into the corpora cavernosa, resulting in an erection. The constriction

Figure 2



band is then pulled off the cylinder and placed at the base of the penis, which traps the blood and maintains the erection.^{5,12} Penile rigidity is reportedly improved by using a double pumping technique (apply vacuum for 1 to 2 minutes, release for 1 minute and reapply vacuum for 3 to 4 minutes). The constriction band should not be left on longer than 30 minutes. Patient complaints with vacuum devices include the lack of spontaneity, using a mechanical device, the time involved in using the device, coldness of the penis and difficulty and discomfort with ejaculation.¹² The AUA recommends only devices that are available by prescription be used (battery operated devices retailing \$500-\$700).⁸

Penile Prostheses

For men with ED refractory to other treatment options, prosthetic devices may be beneficial. Penile prosthesis implantation should not be performed in men with psychogenic ED unless a psychiatrist or psychologist concurs with the need for prosthesis implantation.⁸ The prosthetic penis consists of a semi-rigid or self-contained inflatable prosthesis with a built-in cylinder pump which is surgically implanted. One outcome analysis performed from January

1984 to December 1993 evaluated 246 implants on the basis of adverse effects and function. The infection rate for primary implants was 4.3% and 10.8% for secondary implants. Depending on the prosthetic type, 82 to 92% of patients reported satisfactory prosthetic function, but overall satisfaction was only 71%.³³ The patient considering prosthesis implantation should be informed of the possibilities of infection and erosion, mechanical failure and migration of the device that usually require reoperation. Both the appearance of the flaccid penis and the erection produced by prostheses are different than normal.^{6,12}

Vascular Interventions

Young men with normal corporeal venous function who have arteriogenic ED secondary to pelvic or perineal trauma may be effectively treated with arterial revascularization.⁸ In young men with veno-occlusive disease, venous surgery, with extensive ligation of the veins that drain the corpora cavernosa, is sometimes used as a last resort before the implantation of a penile prosthesis. However, only 30% of patients report long term improvement.³⁴ The American Urologic Association's position on venous surgery is that "penile venous surgery, and arterial reconstructive and dorsal vein arterialization procedures in men with arteriosclerotic disease are investigational and should be performed only in a research setting with long-term follow-up available."⁸

Priapism

Priapism has become a more common complication with intracavernous injections of vasoactive drugs; however, it remains an infrequent adverse event. The Alprostadil Study Group reported a 1% incidence of priapism in a six-month study of intracavernosal alprostadil.¹⁵ The papaverine plus phentolamine combination reportedly carries a somewhat higher risk of priapism (2.5%) than alprostadil.¹³ The trans-urethral route of administration of alprostadil may reduce the risk of priapism. No cases of priapism either in the clinic or at home were reported by the Medicated Urethral System for Erection (MUSE) Study Group after 3 months in 996 men.⁶ To date, no cases of priapism have been reported with oral sildenafil.²²

Because priapism can result in corporal scarring and irreversible hypoxic damage, all patients should be instructed to seek immediate medical attention for a painful erection lasting longer than 4 hours.¹² Prolonged erections of less than 24 hours duration may be reversed by intermittent injections of phenylephrine 200-500 mcg, administered to the side of the shaft every 10 minutes until the erection has subsided (maximum of 10 injections).^{31,32} Increases in blood pressure and heart rate should be monitored after phenyleph-

rine administration. For priapism of greater than 24 hours duration, corporal irrigation and aspiration are indicated.³³ For prolonged erections of 3 ½ to 4 hours duration, Saulie and Campbell have recommended putting a cold washcloth on the erect penis, or having the patient ejaculate an additional time and do mild exercise by walking around the block once or twice.¹²

AUA Guidelines

The American Urological Association (AUA) has released guidelines for the treatment of organic erectile dysfunction.⁹ Based on an extensive review of the medical literature published from January 1979 through December 1994, the AUA recommends three treatment options for organic erectile dysfunction: (1) intracavernous vasoactive drug injection therapy, (2) vacuum constriction devices and (3) penile prosthesis implantation. The AUA recommends against the use of yohimbine, which in controlled studies has not proven significantly more effective than placebo. Sildenafil is not included in the guidelines since they were written prior to the approval of the drug. With the introduction of sildenafil, the guidelines will need to be rewritten to include sildenafil and to establish its place in the management of ED. All of the recommended therapies are considered to be effective options; however, the patient and partner should be fully informed in an unbiased manner about the relative risks and benefits of each, so they can make an educated treatment decision.

Future Treatment

Research continues in the understanding and manipulation of the cellular mechanisms that mediate corporal smooth muscle relaxation and penile erection. Newer intracavernosal agents, including moxislyte (a new alpha-blocker), vasoactive intestinal peptide (VIP), calcitonin gene-related peptide (CGRP), linsidomine (a nitric oxide donor), and colforsin (a naturally occurring plant alkaloid) are all currently under investigation.² Newer transdermal delivery techniques are also being investigated. Finally, more oral phosphodiesterase type 5 inhibitors are in development. ■

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Table 1: Drugs Associated with Male Erectile Dysfunction

| | |
|---|--|
| alcohol | guanethidine (<i>Ismelin</i>) |
| amiloride (<i>Midamor</i> , etc.) | guanfacine (<i>Tenex</i> , etc.) |
| aminocaproic acid (<i>Amicar</i>) | hydralazine (<i>Apresoline</i> , etc.) |
| amiodarone (<i>Cordarone</i>) | H2 Receptor Antagonists |
| Amphetamines | indapamide (<i>Lozol</i> , etc.) |
| Angiotensin-Converting Enzyme Inhibitors | indomethacin (<i>Indocin</i> , etc.) |
| Anorexiant | interferon alfa (<i>Roferon-A</i> , <i>Intron A</i>) |
| Anticholinergics | itraconazole (<i>Sporanox</i>) |
| Antidepressants | ketoconazole (<i>Nizoral</i>) |
| Antihistamines | lansoprazole (<i>Prevacid</i>) |
| atropine (component of <i>Lomotil</i> , <i>Domnamal</i> , etc.) | leuprolide (<i>Leupron</i>) |
| baclofen (<i>Lioresal</i> , etc.) | lithium (<i>Eskalith</i> , etc.) |
| Barbiturates | losartan (<i>Cozaar</i> , <i>Hyzaar</i>) |
| Beta-Adrenergic Blockers | MAO Inhibitors |
| biperiden (<i>Akineton</i>) | mecamylamine (<i>Inversine</i>) |
| bromocriptine (<i>Parlodel</i> , etc.) | methyl dopa (<i>Aldomet</i> , etc.) |
| Calcium Channel Blockers | methysergide (<i>Sansert</i>) |
| carbamazepine (<i>Tegretol</i> , etc.) | metoclopramide (<i>Reglan</i> , etc.) |
| Carbonic anhydrase inhibitors | metyrosine (<i>Demser</i>) |
| chlorthalidone (<i>Hygroton</i> , etc.) | mexiletine (<i>Mexitil</i> , etc.) |
| clofibrate (<i>Atromid</i> , etc.) | minoxidil (<i>Loniten</i> , etc.) |
| clomipramine (<i>Anafranil</i>) | naproxen (<i>Naprosyn</i> , etc.) |
| clonidine (<i>Catapres</i> , etc.) | Nitrites/Nitrates |
| CNS Depressants | omeprazole (<i>Prilosec</i>) |
| cocaine | Opiate Narcotics |
| cyclobenzaprine (<i>Flexeril</i> , etc.) | orphenadrine (<i>Norflex</i> , <i>Norgesic</i>) |
| dichlorphenamide (<i>Daranide</i>) | Phenothiazines |
| digoxin (<i>Lanoxin</i> , etc.) | phentolamine (<i>Regitine</i>) |
| disopyramide (<i>Norpace</i> , etc.) | phenytoin (<i>Dilantin</i> , etc.) |
| disulfiram (<i>Antabuse</i> , etc.) | pimozide (<i>Orap</i>) |
| droperidol (<i>Inapsine</i> , etc.) | prazosin (<i>Minipress</i> , etc.) |
| Estrogens | primidone (<i>Mysoline</i>) |
| ethionamide (<i>Treacator-SC</i>) | procyclidine (<i>Kemadrim</i>) |
| etretinate (<i>Tegison</i>) | reserpine (component of <i>Ser-Ap-Es</i> , etc.) |
| finasteride (<i>Proscar</i>) | risperdone (<i>Risperdal</i>) |
| flutamide (<i>Eulexin</i>) | ritonavir (<i>Norvir</i>) |
| fluvastatin (<i>Lescol</i>) | Sedative-Hypnotics |
| furazolidine (<i>Furoxone</i>) | spironolactone (<i>Aldactone</i> , etc.) |
| gemfibrozil (<i>Lopid</i> , etc.) | terazosin (<i>Hytrin</i>) |
| guanabenz (<i>Wytensin</i> , etc.) | thiabendazole (<i>Mintezol</i>) |
| guanadrel (<i>Hylorel</i>) | Thiazide Diuretics |