Erectile dysfunction: diagnosis and management with newer oral agents

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*Gladly I think of the days
When all my members were limber,
all except one.
Those days are certainly gone.
Now all my members are stiff,
all except one. —GOETHE*

For centuries, men have been dealing with the issue of impotence. In this article, I review the physiology of erections and the new medications available to treat erectile dysfunction (ED). A number of new drugs are in phase I, II, and III trials. Most of them are similar to the drugs reviewed in this article in that they stimulate the corpus cavernosum or the central nervous system (CNS). In the 1990s and now the 21st century, ED has been defined as the consistent inability to attain and maintain penile erection sufficient to permit satisfactory intercourse.

Based on data extrapolated from the Massachusetts Male Aging Study, ED affects some 20 million to 30 million American men today, most of them >50 years of age. The Massachusetts Male Aging Study is one of the best epidemiological studies ever done and it is ongoing, with some additional data from it published only recently (1). The original study looked at 1709 men in a suburban Boston community. Although the men studied were fairly homogeneous—mostly white and middle income—the Massachusetts Male Aging Study does provide insight into the incidence of ED among a community of noninstitutionalized men who are not under routine medical care. Overall, 52% of men aged 40 to 70 years had ED: 10% had complete ED; 25%, moderate; and 17%, minimal. The prevalence of ED increased with age (Figure 1). The percentages of ED were much higher—often double—in men who had risk factors such as taking cardiac, antihypertensive, or vasodilator drugs or using tobacco.

PHYSIOLOGY OF ERECTIONS

In the 1970s, erections were thought to occur when valvular structures on the arterial side and an active valve on the venous side worked in a coordinated and syncopated fashion to shunt blood into the penis. Scanning electron microscopy later allowed evaluation of this theory and showed that such valvular structures were not present in human baby cadavers. In fact, what were originally thought to be valvular structures in adult men were shown to be hypercholesterolemic atherosclerotic plaques.

Figure 1. Association between age and prevalence of erectile dysfunction. Adapted from reference 2.

As a result of electron microscopy, casting, and pharmacologic studies conducted in the past decade, a new theory for the mechanism of erections has become elucidated. When a healthy man receives psychological or physical stimulation of the penis, first nitric oxide is released from the nerve endings in the corpus cavernosum, which produces dilation of the cavernosal arteries. This in turn increases blood flow into the penis (3). The blood flow stimulates the endothelial cells that line the lacunar spaces to produce more nitric oxide, and the increased nitric oxide production causes relaxation of the corpus cavernosum smooth muscle tissue. The venous structures beneath the very rigid tunica albuginea are compressed, producing a rigid erection. In addition, the CNS stimulates the perineal musculature to contract, which further increases the pressure exerted in the penis and actually raises the pressure beyond that of the abdominal aorta. The erection persists until the stimulation is decreased and the nitric oxide disappears.

The smooth muscle relaxation is controlled with neurotransmitters, particularly nitric oxide (4). In the penis, nitric oxide is available from the nitrergic nerve and the endothelial cells that

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Figure 2. Nitric oxide–cyclic guanosine monophosphate mechanism of corpus cavernosal smooth muscle relaxation and penile erection. NO indicates nitric oxide; NANC, nonadrenergic-noncholinergic neurons; GTP, guanosine triphosphate; GMP, guanosine monophosphate; cGMP, cyclic guanosine monophosphate; and PDE5, phosphodiesterase type 5.

line the lacunar spaces. The neurotransmitter is derived from the precursor L-arginine and is changed to nitric oxide through the enzyme nitric oxide synthase. A variety of substances change nitric oxide synthase activity; one of them is the concentration of testosterone, or more specifically androgens, in the smooth muscle cells of the corpus cavernosum.

Through the guanylate cyclase system and through cyclic guanosine monophosphate (cGMP), nitric oxide produces an efflux of calcium from the cell, which then causes relaxation of the corpus cavernosum smooth muscle (Figure 2). cGMP is broken down by the enzyme phosphodiesterase (PDE), and PDE inhibitors such as sildenafil and papaverine prolong the presence of cGMP and in fact facilitate relaxation in the corpus cavernosum. The predominant PDE type in the corpus cavernosum is type 5 (PDE5). This type is also present to a small extent in the retina, and sildenafil actually has some PDE6 effect, which causes the occasional retinal and visual changes reported by some patients who take the drug.

ETIOLOGY OF ED

ED has both organic and psychogenic etiologies. When Masters and Johnson published their sentinel work on sexual dysfunction, they felt that organic causes accounted for approximately 10% of the incidence of ED in American men and psychogenic causes accounted for 90% (5). Now we know that about 60% of patients have organic ED, which we define as a vasculogenic, neurologic, hormonal, or smooth muscle abnormality; <40% have truly psychogenic ED. In fact, we may be labeling some cases as psychogenic simply because we cannot yet identify an organic cause. We do know that patients with psychogenic causes, specifically stress disorders and depression, have an overactivity of alpha-agonists in their corpus cavernosum smooth muscle tissue, so a chemical imbalance may be to blame.

RISK FACTORS FOR ED

When completing a history of a patient with ED, an important issue to ask about is libido. Physicians used to think that if a patient had a low libido, he had low levels of testosterone. In fact, that's not the case. Several studies have shown that libido

Table. Medications associated with erectile dysfunction

Major tranquilizers

- Phenothiazines (e.g., fluphenazine, chlorpromazine, promazine, mesoridazine)
- Butyrophenones (e.g., haloperidol)
- Thioxanthines (e.g., thiothixene, chlorprothixene)

Anticholinergics

- Atropine
- Propantheline
- Benztropine
- Dimenhydrinate
- Diphenhydramine

Luteinizing hormone-releasing hormones

Hormone analogues

Antiandrogens

Antihypertensives

- Diuretics (e.g., thiazides, spironolactone)
- Vasodilators (e.g., hydralazine)
- Central sympatholytics (e.g., methyldopa, clonidine, reserpine)
- Ganglion blockers (e.g., guanethidine, bethanidine)
- Beta-blockers (e.g., propranolol, metoprolol, atenolol)
- Angiotensin-converting enzyme inhibitors (e.g., enalapril)
- Calcium channel blockers (e.g., nifedipine)

Antidepressants

- Tricyclics (e.g., nortriptyline, amitriptyline, desipramine, doxepin)
- Monoamine oxidase inhibitors (e.g., isocarboazide, phenelzine, tranylcypromine, pargyline, procarbazine)

Anxiolytics

- Benzodiazepines (e.g., chlordiazepoxide, diazepam, chlorazepate)

Psychotropic drugs

- Alcohol
- Marijuana
- Amphetamines
- Barbiturates
- Nicotine
- Opiates

Miscellaneous

- Cimetidine
- Clofibrate
- Digoxin
- Estrogens
- Indomethacin

level is a better marker for depression and stress than it is for hypogonadism. Less than 50% of patients who were truly hypogonadal—meaning testosterone levels <100—had a measurable low libido, whereas >80% of patients who were depressed had a low libido (6). So while the physician should ask about libido, the patient's response cannot eliminate the need for a testosterone determination.

It is also important to determine what medications patients are taking (Table). Medications most often associated with ED are the antihypertensives, although antidepressants, particularly the selective serotonin reuptake inhibitors, are also culprits. Smoking is also among the most common risk factors for ED.

The Treatment of Mild Hypertension Study looked at a group of people with mild to moderate hypertension who had not been

previously treated. The researchers compared representatives from each of the most commonly used families of drugs with placebo and followed the subjects for 2 years, asking questions related to lifestyle as well as the control of hypertension. Among the male members of the study, erectile function was one of the variables studied. Placebo was associated with some ED; the incidence of ED in patients taking analapril was similar to that in the placebo group. The alpha-blockers, represented by doxazosin, were better than placebo in preserving erectile function (7).

Our laboratory studies confirmed this finding. When we reviewed the effect of antihypertensive agents on relaxation of the corpus cavernosum smooth muscle in vitro, we found that the classes of agents most likely to preserve or be hospitable to erectile function are the alpha-blockers, angiotensin-converting enzyme inhibitors, and calcium channel blockers, in that order (8). This is an important message to share with cardiologists, internists, and family practitioners prescribing antihypertensive drugs.

Diabetes is another major culprit for ED. While we know that ED increases as patients age, diabetes pushes that age curve to the left. A patient who has been diabetic, especially insulin-dependent, for >10 years has about a 50% chance of having significant and substantial ED.

Depression affects erectile function to a similar degree. The Massachusetts Male Aging Study looked at classes of depression, with 1 being minimally depressed and 5 being maximally depressed. In class 5, 60% of the men aged 61 to 70 had ED. In contrast, ED incidence is <10% if a patient is not depressed and is in the 40- to 50-year age group (1).

LABORATORY STUDIES

Several studies have proposed a list of laboratory studies to be done for initial evaluation of ED (9). In addition, the American Urological Association with the International Society of Impotence Research convened a guidelines panel to address this issue (10). The following tests are recommended: 1) a glucose or hemoglobin A_{1c} (to evaluate patients for diabetes), 2) a lipid profile, and 3) testosterone, with morning level preferable (some groups suggest 1 test and others suggest 2). If the testosterone level is abnormal, it should be repeated with a morning level. The addition of a free testosterone and a prolactin, perhaps a luteinizing hormone and follicle-stimulating hormone, may elucidate the androgen deficiency.

Testosterone levels change substantially with age. Beginning at about age 50, testosterone begins to fall off, and during that same time period, there is an increase in sex hormone binding globulin, which results in a substantial decrease in free testosterone and bioavailable testosterone. Since nitric oxide synthase activity decreases substantially with a decrease in testosterone level, androgen levels are critical for erectile function.

In animal studies, Chamness showed that nitric oxide synthase decreased almost 50% in castrated rats. Such a decrease was prevented or reversed by testosterone replacement (11). Similar studies by Baba and Alcorn have demonstrated changes in smooth muscle relaxation in the hypogonadal laboratory animal (12, 13). Clearly, then, normal nitric oxide production requires adequate levels of testosterone.

ORAL MEDICATION FOR TREATMENT OF ED

Over the past decade, basic laboratory investigation has improved the understanding of the fundamental physiology and pharmacology of the corpus cavernosum, as well as the neurophysiology and vascular physiology of erectile function and dysfunction. Similarly, the mechanism of erection and its dependence upon neurogenic, arterial, venous, and androgenic systems to produce erectile rigidity continues to be elucidated. These advances have led to substantial changes in the diagnosis and treatment of men who experience ED. Investigation into smooth muscle physiology, endothelial cell function, and CNS control, as well as identification of neurotransmitters in the corpus cavernosum such as nitric oxide and vasoactive intestinal polypeptide, have led to the design, development, and use of pharmacologic agents, both systemically and locally, to recreate the normal physiology of erectile function in men previously referred to as "impotent."

A safe, effective oral agent for the treatment of men with ED has long been sought. Early agents such as yohimbine, often considered an aphrodisiac in men, produces its effect on erectile function by blocking alpha-2 adrenergic receptors (14, 15). In vitro yohimbine produces significant corpus cavernosum smooth muscle relaxation. However, the adrenoreceptors in the penile erectile tissue are primarily alpha-1 type (16). The effectiveness of selective alpha-2 blockade in vivo, therefore, is likely due to central rather than peripheral effects. In animal models, blockade of alpha-2 receptors resulted in increased sexual arousal and activity. Nevertheless, direct intracavernous infusion of yohimbine in normal volunteers does not produce significant penile tumescence. Clinical trials involving yohimbine alone have shown only minimal improvement in erectile function compared with placebo (15).

Delaquamine, a new, more potent and selective alpha-2 adrenoceptor antagonist, is approximately 100 times more potent than yohimbine. It has good bioavailability and a half-life of 5 to 8 hours. Clinical studies have revealed some restoration in erectile function compared with placebo using this selective alpha-2 agonist (17).

Trazodone, an older but well-established antidepressant which does not work through the selective serotonin reuptake inhibitor mechanism, has been demonstrated to cause priapism and may restore erectile function in some patients (18, 19). Trazodone selectively inhibits CNS serotonin uptake, increases dopamine, and also has some peripheral alpha-adrenergic blocking activity. While this agent is not designed for treatment of ED, its combined central and peripheral activity does improve erectile function in men with mild ED. Trazodone combined with yohimbine has likewise been used with limited success (20).

L-Arginine has been used to treat patients with ED (21, 22). This precursor of nitric oxide has been suggested as an oral supplement for patients with ED. In a small group of patients, a placebo-controlled trial of two 800-mg tablets given daily for 2 weeks improved erectile function compared with placebo (22). Most patients in this small study had minimal ED. The use of L-arginine, both alone and in combination with yohimbine, is being studied in European trials.

Recent years have witnessed the introduction of new oral agents for the treatment of ED, including sildenafil and sublin-

Figure 3. Efficacy of sildenafil citrate (Viagra) in improving erections. Overall treatment: $P < 0.0001$ sildenafil vs placebo. Adapted from references 23–27.

gual apomorphine. Sildenafil (Viagra), already approved for clinical use, has revolutionized the evaluation and treatment of ED (23). Sildenafil was originally conceived as an anti-anginal agent because of its vasodilatory affects. It is a selective inhibitor of PDE5, the enzyme that breaks down cGMP in the corpus cavernosum and enhances a guanosine monophosphate duration, facilitating erections. Sildenafil has few side effects and significantly enhances vasodilation of the corpus cavernosum. It is available in 25-, 50-, and 100-mg tablets and is taken 1 hour before sexual activity because optimal tissue levels occur approximately 60 minutes after administration.

Placebo-controlled clinical trials of >3000 patients followed for >3 years have demonstrated statistically significant improvement and durable effectiveness compared with placebo (Figure 3). More than 70% of men taking sildenafil reported improved erections compared with 10% to 30% of men receiving placebo. Clinical trials have demonstrated improved erectile function in patients with a cross-section of etiologies of ED, including men with diabetes (57%), spinal cord injury (60%), hypertension (70%), radical prostatectomy (60%), and mild depression (80%).

Sildenafil is also safe and effective in patients taking a variety of other medications. Adverse effects may include mild headache, facial flushing, dyspepsia, nasal congestion, and muscle aches. In clinical studies, discontinuation due to adverse events was no higher in men taking the active drug than in those receiving placebo.

The most important contraindication of sildenafil is in patients with cardiac disease who are taking nitrates such as nitroglycerin. Even patients with satisfactory cardiac status and exercise tolerance who may require an occasional short-acting nitroglycerin may not take PDE5 inhibitors such as sildenafil. Because sildenafil is metabolized in the liver through the cytochrome P450 isoenzyme pathway, agents that inhibit cytochrome P450 such as cimetidine, erythromycin, and ketoconazole may reduce metabolism and clearance of sildenafil, substantially increasing serum levels. Newer PDE5 inhibitors including vardenafil and cialis (IC351) are currently in phase III clinical trials.

Apomorphine, which was reviewed by the Food and Drug Administration panel and found to be “approvable,” has long been known as an erectogenic agent in both animals and men. Its use

as a subcutaneous agent was demonstrated more than a decade ago. Unfortunately, direct injection of apomorphine results in severe nausea and vomiting. The development of a sublingual formulation of apomorphine, now known as Uprima, has maintained the erectogenic function while decreasing adverse events (28). Apomorphine stimulates postsynaptic dopamine receptors (D1 and D2) in the hypothalamus and is effective as a precoital oral agent. In phase III pivotal trials, >60% of patients had durable erections 20 to 40 minutes after sublingual administration of apomorphine (29). Adverse events of sublingual apomorphine include nausea, hypotension, occasional vomiting, and rare syncope. In clinical trials, few patients required antiemetics from taking apomorphine for sexual activity, and there was a significant first-dose effect associated with nausea and syncope, such that few patients reported subsequent nausea, vomiting, or syncope after initial trials of medication.

While currently available and approved oral erectogenic therapeutic agents include only sildenafil, and possibly apomorphine, the mechanisms of action currently manipulated by these agents are limited. Early agents such as trazodone, yohimbine, and delaquamine that depend on alpha blockade appear to demonstrate clinical effectiveness in generating erectile function (17). Both selective alpha-1 blockers (doxazosin) and alpha-2 blockers (yohimbine) produce improved erectile function in clinical trials and clinical practice. Kaplan et al have demonstrated the effectiveness of doxazosin as an oral treatment for some men with mild to moderate ED (30). Similarly, the Treatment of Mild Hypertension Study has documented the improvement in erectile function in men with mild hypertension compared with placebo (31). This salutary effect is not found with any other antihypertensive agent. Oral phentolamine, a nonselective alpha-blocker, has been used successfully for facilitating erections and treating men with ED (32–35).

Future treatment of ED with oral agents requires that agents be available for stimulation of erectile function from a variety of pharmacologic pathways. Peripheral stimulators and facilitators using various methods for producing erections must be available to begin therapy, and CNS stimulators and facilitators should be available to supplement these peripherally acting agents (36).

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