

## Erectile Dysfunction in the Patient With Diabetes Mellitus

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Diabetes mellitus (DM) is strongly associated with an increased risk of erectile dysfunction (ED), the persistent inability to achieve or maintain an erection sufficient for satisfactory sexual performance, but this condition can be successfully treated in the majority of diabetes patients. ED is present in 32% of type 1 and 46% of type 2 DM patients. Several population-based studies of ED prevalence calculated the odds ratios for the association between ED and various chronic diseases. An odds ratio must be sufficiently greater than 1.0 to identify an increased risk. Diabetes has an odds ratio, ED risk multiplier of 4.1, compared with 1.7 for hyperlipidemia and 1.6 for hypertension. Erectile dysfunction in diabetes mellitus (EDDM) patients has been considered to have an organic etiology. Healthcare providers have long realized that ED can be the first symptom of DM.

In the first 75 years of the 20th century, very few treatment options were available for diabetic men with ED. Yohimbine, alone or in combination, empirically prescribed testosterone, or thyroid supplements were commonly used. These therapies were rarely efficacious. The EDDM patient had one option, implantation of a penile prosthesis.

In subsequent clinical studies, a surprisingly high percentage of EDDM patients—10% to 20%—claimed that the placebo “improved my erections,” thus indicating a psychological basis for their ED. In the latter half of the 1980s, objective means were developed that could help determine if a EDDM patient had organic or psychogenic ED. The absence of rigid sleep erections confirmed by penile monitors was one criterion for organic ED. The failure of vasoactive

agents (papaverine, Trimix, or prostaglandin E-1 [PGE-1]) injected into the corpora cavernosa to induce penile rigidity was another criterion for organic disease. Intracavernosal maintenance flow rates during pharmacocavernosometry and maximum cavernosal arterial flow during penile Doppler ultrasonography were additional determinants.

Based on this testing, EDDM patients were treated with behavioral therapy, intracavernosal (papaverine, PGE-1, or Trimix) or intraurethral PGE-1, a vacuum constriction device (VCD), or implantation of a penile prosthesis. Novel surgical procedures, ligation of incompetent cavernosal veins or penile revascularization, were seldom efficacious with EDDM and were soon abandoned. Although these nonsurgical therapies were efficacious, they were not widely requested because of their invasive or mechanical nature.

The discovery in 1992 of the second messenger of cavernosal smooth muscle relaxation was the critical step that led to the era of nonhormonal oral drug therapy for ED. In 1998, the multicenter trial of sildenafil in the treatment of ED was published in the *New England Journal of Medicine*, and the era of the phosphodiesterase type 5 (PDE-5) inhibitor began.<sup>1</sup> For 5 years, sildenafil was the primary therapy for men with EDDM. Recently, 2 new PDE-5 inhibitors, vardenafil and tadalafil, were introduced.

Preclinical and clinical trials of these oral agents have clearly demonstrated that they are well tolerated by most DM patients and have an efficacy rate superior to other oral agents. The ultimate result is an improved quality of life (QOL) in EDDM patients. With a greater willingness of DM patients to

discuss and seek treatment for ED, it is highly probable that the use of these oral agents will continue to increase. The goal of this article is to provide the physician and pharmacist with a background and working knowledge of these oral agents and their present-day alternatives.

**Physiology of Erection and the Pathophysiology of EDDM**

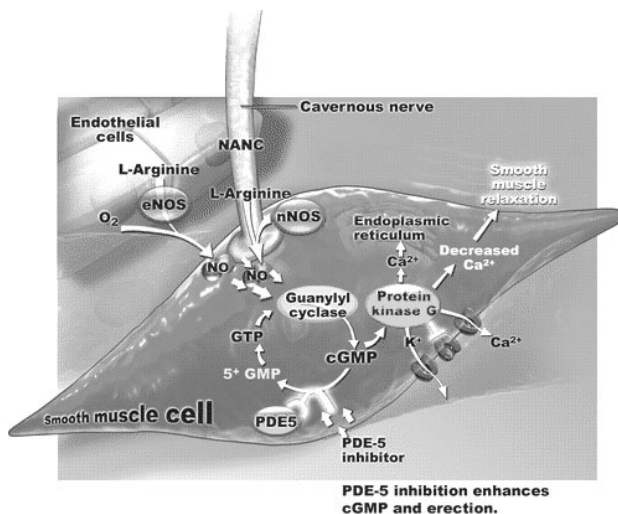
The initial event for normal erectile function is sexual stimulation. Subsequent to processing in the central nervous system neural impulses are conveyed along the spinal cord, exiting through the pelvic parasympathetic preganglionic nerves. These pelvic nerves form the pelvic plexus and send their message through first messenger, acetyl choline, to the cavernosal nerves. The cavernosal nerves enter erectile bodies (corpora cavernosa) (Figure 1). Here, their nerve endings release a second messenger, nitric oxide. Nitric oxide activates the enzyme guanylyl cyclase, which lyses guanosine triphosphate (GTP) to produce a third messenger, the intracellular cyclic guanosine monophosphate (cGMP). Ultimately, the result is a decrease of intracellular calcium and an opening of potassium channels with the resultant relaxation of vascular smooth muscle in the arteries, arterioles, and sinusoids of the corpora cavernosa. The sinusoids open and rapidly fill

with blood. Finally, the distended sinusoids compress their drainage pathways (venules) against the fibroelastic covering of the cavernosal bodies (tunica albuginea) and trap the blood in cavernosal bodies. The combination of an increased inflow of blood into the penis and coincident markedly diminished outflow results in rapidly increasing intracavernosal pressure that ultimately approximates systolic pressure. At this pressure the penis has sufficient axial rigidity to permit vaginal penetration.

Abnormalities in the vascular, neural, endocrine, muscular, or psychiatric systems can result in ED.<sup>2,3</sup> EDDM is due to multisystemic disease. Atrophy or apoptosis of cavernosal smooth muscle can occur due to loss of Bel-2 expression in cavernosal smooth muscle and lead to ED. Abnormal amounts of advanced glycation end products is a common occurrence. These chemicals may have an effect on potassium channels that facilitate intracellular calcium release and subsequent cavernosal smooth muscle relaxation. Connective tissue synthesis is increased due to transforming growth factor-beta. The decrease in smooth muscle and the increase in collagen decreases the compliance of the erectile tissue. Neuropathic damage to both the somatic and autonomic nerves has been clearly defined in DM. Partial occlusion of the pelvic or intracavernosal arteries, hypogonadotropic hypogonadism, and depression associated with a chronic illness (DM) can all play a primary or secondary role in the development of EDDM. On a molecular level, studies have demonstrated decreased levels of endothelial and neuronal nitric acid synthase (NS) and decreased cavernosal artery and sinusoidal response to nitric oxide. Abnormalities in nitric oxide rapidly render the functional syncytium of the corpora cavernosa unable to synchronously relax. As the patient with diabetes ages, the concentration of constrictors, including endothelin, prostanoids, and possibly angiotensin, increases as the production of the relaxants, including nitric oxide, vasointestinal peptide, and prostacyclin, decreases.

PDE-5 inhibitors amplify the intracavernosal production of cGMP in response to nitric oxide. This is achieved through the

**Figure 1.** Cellular Processes Involved in Normal Erectile Function



inhibition of cGMP's breakdown by the enzyme, PDE-5. If the predominant abnormality in the individual EDDM patient is molecular, the higher tissue levels of cGMP will overcome these inhibitory factors and the patient will regain erectile function. If the physical structure (eg, the compliance) of the cavernosal tissue has been significantly compromised by apoptosis of smooth muscle or increased collagen deposits, restoration of erectile function will not be achieved. These structural changes explain the lower efficacy rates of PDE-5 inhibitors in EDDM than in the general population.

### Treatment Options for EDDM

The EDDM patient has a variety of first-line options. The risk factors for vascular disease are the risk factors for ED. First-line therapy begins with attempts to minimize or eliminate these factors. These include smoking cessation, regular exercise, tighter glycemic control by attention to dietary restrictions, addition of statin drugs to correct dyslipidemia, and moderation of alcohol ingestion. Although there is very limited evidence that these modifications will dramatically reverse ED, they certainly will sponsor improved general health.<sup>4</sup>

A number of drugs are known to cause ED in patients with DM (Table 1). For example, many EDDM patients are on antihypertensive medications. Replacement of thiazides or beta-blockers with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers may be sufficient to regain erectile ability.<sup>5</sup> Furthermore, discontinuation of selective serotonin reuptake inhibitors, if these drugs are not essential for patient well-being, may be therapeutic. Careful monitoring following drug discontinuation will help to determine if ED is due to the medication or other underlying disorders. The benefits of continued drug therapy with these drugs should always be weighed against the likelihood of causing ED and impacting on the patient's QOL.

Although DM patients often correctly assume that their ED is of organic origin, a psychogenic component should be considered, especially in the younger patient. If this is the case, the patient may benefit from psychosocial therapy that includes anxiety

**Table 1.** Drugs Known to Cause ED in Patients With DM

#### Antihypertensives

Beta-blockers, methyl dopa, clonidine, reserpine, thiazide diuretics, spironolactone

#### Central Nervous System Agents

Phenothiazines, butyrophenones, tricyclic antidepressants, atypical antidepressants, antipsychotics, selective serotonin reuptake inhibitors

#### Drugs Acting on Endocrine System

Estrogens, antiandrogens, gonadotropin-releasing hormone agonists and antagonists, cimetidine, metoclopramide, alcohol, marijuana

ED indicates erectile dysfunction; DM, diabetes mellitus. Adapted from Richardson D, Vinik A. Etiology and treatment of erectile failure in diabetes mellitus. *Cur Diab Rep.* 2002;2:501-509.

reduction and desensitization, cognitive-behavioral intervention, sexual stimulation techniques, and interpersonal assertiveness with couples communication training.<sup>6</sup> Not all healthcare providers offer these options. Freudian-based psychotherapy for EDDM has not been proved to be efficacious.

In DM patients with a documented androgen deficiency, testosterone replacement may correct or facilitate the treatment of ED.<sup>7</sup> A transdermal testosterone gel or patch, or intramuscular testosterone cypionate are the alternatives. Oral testosterone is contraindicated in the United States due to hepatotoxicity, but a new product has been developed that allows for buccal absorption of testosterone. Thyroid supplements rarely alleviate EDDM.

If the cause is believed to be organic but not hormonal, or if the patient defers psychological intervention, he can be offered the VCD or oral drug therapy. EDDM patients on organic nitrates or who have experienced or are concerned about potential adverse reaction to PDE-5 inhibitors are suitable candidates for the VCD. The VCD induces functional rigidity in 75% of patients with diabetes with autonomic neuropathy. Some patients or their partners may reject or discontinue the use of the VCD because it induces an unnatural erection, causes bruising and numbness of the penis, and or inhibits antegrade ejaculation.<sup>8</sup>

**Phosphodiesterase Inhibitors.** The cornerstone of first-line therapy is the PDE-5 inhibitor. No other class of oral agents approaches the efficacy of PDE-5 inhibitors. Yohimbine, trazodone, phentolamine, L-arginine, and OTC herbal remedies have been used with very limited success. The superiority of yohimbine over placebo in the treatment of organic ED is a matter of dispute.<sup>9</sup> A recent trazodone study failed to detect any difference between trazodone and placebo on sexual function.<sup>10</sup> Oral phentolamine, although available in Mexico, has not been approved by the US FDA for the treatment of ED. Apomorphine, a central dopaminergic receptor drug, has recently been voluntarily withdrawn from FDA consideration for the treatment of ED. The efficacy of ginkgo biloba and Korean red ginseng has yet to be demonstrated by randomized, placebo-controlled trials.

The treatment of EDDM with PDE-5 inhibitors is based on amplification of the natural release of intracavernosal endothelial and neuronal nitric oxide in response to sexual stimulation. Suberectile levels of cGMP are increased to critical erectile levels by delaying the degradation of this molecule by the enzyme PDE-5 (Figure 1). PDE-5 inhibitors help the sexually excited patient achieve functional rigidity. Unlike Trimix and alprostadil, PDE-5 inhibitors cannot induce rigidity without sexual excitement.

Currently available PDE-5 inhibitors include sildenafil, vardenafil, and tadalafil. Phase 3 trials for sildenafil, tadalafil, and vardenafil in people with diabetes have been published in peer-reviewed journals.<sup>11-21</sup> Class-specific pharmacologic properties of PDE-5 inhibitors can be gleaned from a review of these trials. However, it is not feasible to draw conclusions based on simple comparison of these studies, because the inclusion and exclusion criteria, the number of study patients, the drop-out rate, the dosing methodology, and the format for presentation of results vary from study to study.<sup>2</sup> No head-to-head comparative trials have been published.

Before providing an overview of the principal PDE-5 inhibitor clinical studies, an examination of the meaning of efficacy when applied to these drugs is important. Because

these drug trials were essentially home trials, not office trials as in the intracavernosal PGE-1 or MUSE (medicated urethral system for erection), investigators developed questionnaires to determine efficacy. The 3 most commonly used questionnaires are (1) the International Index of Erectile Function (IIEF), a 15-question validated, multidimensional, self-administered questionnaire; (2) the response (yes or no) to a global efficacy question (Did the treatment improve your erections?); and (3) an event log of sexual encounters.<sup>22</sup> In the event log, the date and dose of medications taken, the presence of sexual stimulation, the hardness of the erection, and whether sexual intercourse was successful were entered. The collection of these data was straightforward, but then each trial interpreted and reported its data in a different format. For one study, the final mean score for a question (IIEF) was compared to placebo and reported, for another the change in mean score for subgroups of the study group (based on HbA1c) was compared to placebo and then reported, for another the change in mean score for subgroups (based on degree of ED) was compared to placebo and then reported. This variance in data presentation makes a comparative analysis less tempting.

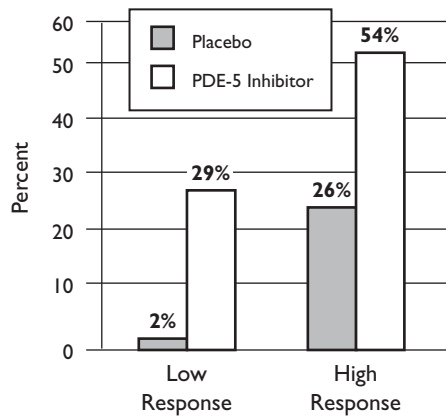
Another important point to recognize is the fact that a PDE-5 inhibitor drug can be determined by placebo-controlled drug trials to be efficacious, yet not aid in the ultimate achievement of a rigid, functional erection and intercourse. For example, in a vardenafil trial, the questionnaires demonstrate a difference between placebo and inhibitor with  $P < .001$  in patients with mild-to-severe ED. In fact, this drug restored erectile function to 71% of men with mild ED, 51% of men with mild-to-moderate ED, 47% of men with moderate ED, and 39% of men with severe ED to "normal erectile function." Similar dissociation between efficacy and sexual intercourse and patient satisfaction were observed in the sildenafil and tadalafil trials.

Many patients have unrealistic expectations due to the publicity associated with the release of a new ED drug. Even when the patient with the aid of the PDE-5 inhibitor is able to have intercourse, psychological barriers may remain with his partner. These

will need to be addressed before the patient will be satisfied with the drug. The failure to meet patient expectations and to recapture normal function are likely the main reasons for PDE-5 inhibitor discontinuation rates of as high as 50%, as observed in postmarketing data.<sup>23</sup>

With the disclaimer of the analysis in mind, it can be confidently stated that PDE-5 inhibitors will help many EDDM patients.<sup>2</sup> Approximately 56% to 72% of EDDM patients in the PDE-5 inhibitor safety and efficacy trials reported "Yes, the treatment improved my erections." The percent of successful intercourse attempts was significantly higher in the sildenafil group with twice as many patients answering in the affirmative compared with placebo, irrespective of ED severity. The mean ability of each man in the diabetic study population to maintain erections until completion of intercourse was 54% with 20 mg of vardenafil compared with 23% with placebo. Even patients with severe ED had up to a 40% probability of having successful intercourse (Figure 2). The efficacy of the 3 PDE-5 inhibitors was maintained in patients with poorly controlled diabetes irrespective of the type or treatment, in patients who smoked, in

**Figure 2.** PDE-5 Inhibitor Response Versus Placebo in EDDM Patients Achieving Erections Hard Enough for Sexual Intercourse (Diary Records)



PDE-5 inhibitor indicates phosphodiesterase type 5 inhibitor; EDDM, erectile dysfunction in diabetes mellitus.

Reprinted with permission from Vickers M, Satyanarayana R. Phosphodiesterase type 5 inhibitors for the treatment of erectile dysfunction in patients with diabetes mellitus. *Int J Impot Res.* 2002;14:466-471.

**Table 2.** Comparison of Adverse Events Experienced by General Patient Population and Type 1 and Type 2 Diabetes Mellitus Study Population

	Placebo/Sildenafil Placebo/25-50-100 mg		Placebo/Tadalafil Placebo/5-10-25 mg		Placebo/Vardenafil Placebo/5-10-20 mg	
	General Population	Type 1 and 2 Diabetes Mellitus	General Population	Type 1 and 2 Diabetes Mellitus	General Population	Type 1 and 2 Diabetes Mellitus
Headache	6/14-21-30	2/11	6/3-17-14	1/8-6	4/7-9-15	2/9-10
Flushing	1/13-27-20	0/4	NR	NR	1/10-11-11	1/9-10
Dyspepsia	1/3-11-16	0/9	0/8-3-8	0/11-8	0/1-3-7	NR
Rhinitis	2/1-3-11	0/4	NR	NR	3/5-3-7	0/3-6
Visual disturbance	1/2-6-9	1/4	NR	NR	NR	NR
Myalgia	NR	NR	0/0-8-3	NR	NR	NR
Respiratory tract disorder (sinus congestion or drainage)	NR	2/6	NR	NR	NR	NR

NR indicates none reported.

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**Table 3.** Dosing and Pharmacokinetics of PDE-5 Inhibitors

Drug	Dosing	T <sub>max</sub> (hr)	T <sub>1/2</sub> (hr)	CYP3A4
Sildenafil	25-100 mg*	0.7-0.9	3-5	Yes
Vardenafil	2.5-20 mg*	1	3-5	Yes
Tadalafil	5-20 mg*	2	18	Yes

PDE-5 indicates phosphodiesterase type 5.

\*Dosing is reduced for patients >65 years of age, those with hepatic impairment, those with creatinine clearance <30 mL/min, or those taking CYP3A4 inhibitors.

patients with cardiovascular complications, on antihypertensive medications, or with microvascular complications. No patient characteristic has been found that will predict absolute failure of sildenafil therapy.<sup>24</sup>

Several trends are apparent in these trials. The higher the dose of the various PDE-5 inhibitors, the greater the percentage of study patients who were able to achieve vaginal penetration. The more severe the degree of ED, based on the total score of questions 1 through 5 and 15 of the IIEF questionnaire, the less likely that there will be a functional response. Studies in non-DM patients have demonstrated that success increases with the number of doses taken up to 8 doses. In non-DM patients, 67% of men who took 20 mg of tadalafil experienced successful intercourse after the first dose. After the first 4 doses, 86% achieved successful intercourse for the first time compared to 48% of men on placebo.<sup>24</sup> This finding will very likely be mirrored in the EDDM population.

**Table 2** lists the adverse events experienced by the EDDM study patients.<sup>2</sup> Again, comparative analysis of these trials would be erroneous, although certain trends are evident. Headache (10%-20%) and dyspepsia are associated with all 3 PDE-5 inhibitors. Visual disturbances were noted in sildenafil and vardenafil trials due to their inhibitory effects on the ocular isoenzyme PDE-6 (blue/green color impairment and increased brightness). Rhinitis is noted in the vardenafil trials but not in the sildenafil and tadalafil trials. Back pain and myalgias are noted in the tadalafil trials, explained by the activity of tadalafil on the PDE-2 isoenzyme, but not in the sildenafil and vardenafil trials.

Longer follow-up with all 3 PDE-5 inhibitors has shown that the rate and severity of adverse events decline over time. The frequency of adverse events in clinical practice appears to be much lower than reported in these trials. Many adverse reactions will respond to symptomatic care. For example, acetaminophen will relieve back pain associated with tadalafil. Although it may be tempting to recommend switching from one PDE-5 inhibitor to another based on adverse events, the value of this has yet to be proved.

**Table 3** lists the pharmacokinetics of the PDE-5 inhibitors. All of the PDE-5 inhibitors have an onset of action within 15 to 30 minutes after ingestion. High-fat meals slow the absorption of sildenafil and vardenafil, with a delay in the T<sub>max</sub> of about 60 minutes and a slight drop in the C<sub>max</sub>. Tadalafil absorption is not affected by food. Despite effects of food on absorption, all agents may be taken with or without food. If a satisfactory erection is not obtained when sildenafil or vardenafil is taken shortly after a fatty meal, the patient may achieve this goal if he takes these medications on an empty stomach. Elimination of the PDE-5 inhibitors takes place predominantly by the CYP3A4 enzyme system. Therefore, patients with significant liver disease or those who are taking CYP3A4 inhibitors (eg, indinavir, erythromycin, ketoconazole) should begin treatment at lower doses. The most significant difference between the PDE-5 inhibitors is the half-life: The 17.5-hour half-life of tadalafil allows a duration of action up to 36 hours versus 3 to 5 hours for sildenafil and vardenafil. This longer duration may possibly encourage greater spontaneity and

relieve performance anxiety for both the patient and his partner. This is as yet a theoretic advantage and unproven by clinical trials. Special education may be beneficial to reassure the patient, and possibly the couple, that tadalafil might allow their special relationship to develop beyond 4 hours.

Several drug interactions exist with the PDE-5 inhibitors. Most notably, PDE-5 inhibitors potentiate the hypotensive effects of nitrates used either on a scheduled or an as-needed basis, which can result in myocardial ischemia. Hence, nitrates in any form are contraindicated with the use of PDE-5 inhibitors. Caution should also be used with other antihypertensive agents as additional reductions in blood pressure are likely with combined use. Specifically, patients taking alpha-blockers both specific and nonspecific (including tamsulosin) should not take vardenafil, and lower dosages of sildenafil (25 mg) are suggested due to the potential for hypotension. Tadalafil may be taken with tamsulosin, but not with any other alpha-blocker. Potent CYP3A4 inhibitors such as erythromycin, ketoconazole, itraconazole, indinavir, and ritonavir will affect the elimination of all 3 PDE-5 inhibitors, and lower starting doses are recommended.

**Second-Line Therapy.** A majority of patients are candidates for MUSE, intracavernosal injections (ICI) with PGE-1 (alprostadil), or a mixture of papaverine, phentolamine, and PGE-1 (Trimix). The following factors suggest second-line therapy:

- Conditions that contraindicate the use of PDE-5 inhibitors, such as unstable angina, uncontrolled hypertension, a recent myocardial infarction, congestive heart failure, ventricular arrhythmias
- Regular or intermittent use of nitrates in any form
- Lack of a functional response or the occurrence of an intolerable adverse reaction to PDE-5 inhibitors
- A preference not to use a VCD

Initial in-office trial with these options is mandatory to determine patient responsiveness and to minimize the incidence of pri-

apism. Hyperviscosity syndrome (multiple myeloma, polycythemia, sickle cell disease or trait) is a contraindication to ICI, but anticoagulant therapy is not. MUSE is less threatening to most patients than ICI, but it is significantly less effective. In addition, 6% of female partners of men using MUSE reported vaginal burning or itching versus only 0.8% using an intraurethral placebo pellet. Unless a condom barrier is used, MUSE is contraindicated in patients with pregnant sexual partners because of its potential to relax the cervix and ultimately precipitate uterine contractions.<sup>25</sup> Many patients who do not benefit from PGE-1 MUSE will achieve functional rigidity with alprostadil or Trimix. ICI patients must have office follow-up visits several times a year to titrate dosage and to monitor for the potential development of penile nodules or hepatic toxicity. In one study, 94% of patients with diabetes responded with either a full or partial erection to at least 1 dose of alprostadil during the office titration phase.<sup>26</sup> The median effective dose was 20 mg. Full erection was reported after 83% of home injections, and the response rate was similar in the type 1 and type 2 diabetic men. However, 24% of the study group reported penile pain and/or injection-site pain, and 6% (21/336) discontinued treatment because of this symptom. The incidence of penile pain may be slightly less frequent with intraurethral application. Older diabetic men ( $\geq 60$  years) are less likely to have a functional response to ICI.

**Third-Line Therapy.** When all less invasive options have failed, have been associated with intolerable side effects, or are contraindicated due to comorbid conditions, implantation of a penile prosthesis is an option.<sup>27</sup> This relatively rare situation is usually the result of permanent, extensive damage of the cavernosal smooth muscle with replacement by fibrous tissue. The intracavernosal bodies' spongy tissue has become noncompliant and nonresponsive to mechanical or pharmacologic stimulation. Priapism, Peyronie's disease, and penile trauma are the most common causes. Infrequently, ICI can be responsible. Both the malleable and inflatable penile prostheses are mechanically reliable. About 91% of patients reported

that the inflatable device permitted sexual intercourse, and 87% of patients would undergo implantation of the device again. Preoperative psychiatric screening can be helpful in avoiding the patient who will not tolerate the device.

Penile revascularization and/or ligation of incompetent penile veins has been performed in EDDM patients but is no longer believed to be efficacious and has been abandoned.<sup>28</sup>

**Combination Therapy.** The ability to attain and maintain a penile erection sufficient for sexual performance may be accompanied by the partner's expectations of mutual pleasuring. Previous interpersonal conflicts and misunderstandings may present barriers to the pleasuring process. Psychological counseling—couples therapy—is an invaluable adjunct to ED therapy and may permit the ultimate improvement of the sexual relationship.<sup>29</sup>

**Managing the Patient With EDDM**

Physicians and pharmacists are integrally involved in the treatment of diseases including ED. Below is a list of roles that the physicians and pharmacists may be involved in:

- Assess if current drug therapy could be contributing to ED
- Emphasize the importance of compliance with nonpharmacologic and pharmacologic treatments of ED and associated disorders
- Identify appropriate candidates for ED treatment
- Assess patients for contraindication to drug therapy
- Assess for significant drug interaction with PDE-5 inhibitor use
- Counsel patients on the use of drug therapy for ED

Counseling patients on the use of oral drug therapy is relatively simple. Patients should be counseled to take the medication about 30 to 60 minutes before anticipated sexual encounter and on an empty stomach for best results (sildenafil and vardenafil). Only 1 tablet per day is recommended. Patients should be instructed to talk to their physician if they experience dizziness, light-

headedness, unusual chest pain, palpitations, or visual changes. Counseling should also set realistic goals for the patient. Many patients have unrealistic expectations due to the publicity associated with the release of a new ED drug. Even when the patient with the aid of the drug is able to have intercourse, a psychological barrier may remain between the patient and his partner. These will need to be addressed before the patient will be satisfied with the drug. The failure to meet patient expectations and to recapture normal function are likely the main reasons for the discontinuation rates—as high as 50% in postmarketing data. In addition, healthcare providers should keep in mind that effectiveness is dose-dependent and time-dependent, and should counsel patients to be patient with identifying response. Healthcare providers who identify patients' lack of satisfaction should suggest continued lifestyle changes, reestablishment of patient expectations, and consultation with their primary care provider, pharmacist, urologist, or other provider.

**Conclusion**

DM is a significant risk factor for ED. Erectile function in the patient with diabetes can be restored. In many EDDM patients, PDE-5 inhibitors offer superior first-line therapy that can be taken orally, is well tolerated, has an efficacy rate that is far superior to other oral agents, and can restore normal erectile function. Unrealistic patient expectations and psychological barriers may be contributing factors to the lack of some patients' satisfaction with these drugs. Patient education by the provider is essential to maximize their efficacy.

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