

Erectile Dysfunction and Diabetes Mellitus

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ABSTRACT

Background: Erectile dysfunction (ED) is highly prevalent, affecting $\geq 50\%$ of men with diabetes mellitus (DM) worldwide.

Objective: This article reviews current knowledge on the epidemiology and underlying pathophysiology of ED in men with DM, diagnostic modalities, and treatment options.

Methods: A MEDLINE literature search was conducted for articles published in English from inception of the database through November 2008, using the terms *erectile dysfunction, diabetes, epidemiology, pathophysiology, phosphodiesterase inhibitors, intracavernosal injection, and penile prosthesis*. Data on the epidemiology, diagnosis, and treatment of ED were extracted from all relevant articles.

Results: The literature search revealed 685 original articles and reviews, 67 of which were selected for inclusion in this review. DM may cause ED through a number of pathophysiologic changes, including neuropathy, endothelial dysfunction, cavernosal smooth muscle structural/functional changes, hormonal changes, and psychological effects. The diagnosis of ED in men with DM is based on their sexual and medical histories and results of validated questionnaires such as the International Index of Erectile Function. Laboratory examinations are usually limited to testosterone and prolactin levels that may independently contribute to ED because specialized examinations are not necessary in most diabetic men with ED. The first step in the treatment of ED in men with DM includes glyce-mic control and treatment of diabetic comorbidities. The associated hypogonadism must also be treated; otherwise, pharmacologic treatment may be less efficacious or not efficacious at all. Phosphodiesterase type-5 (PDE-5) inhibitors have revolutionized the treatment of ED, and they are considered first-line treatment, with a mean efficacy rate of 50% and a favorable safety profile. Intracavernous administration of vasoactive drugs is the second-line medical treatment when PDE-5 inhibitors have failed. Alprostadil is the most widely used drug for this condition, but the combination of papaverine, phentolamine, and alprostadil represents the most efficacious pharmacologic treatment option for patients whose ED does not respond to monotherapy. Excellent functional and safety results have been reported for penile prosthesis implantation, and this approach, along with proper counseling, can be considered for selected patients with treatment-refractory ED.

Conclusions: ED is common in men with DM, who represent one of the most difficult-to-treat subgroups of ED patients. PDE-5 inhibitors are the first-line treatment option, followed by intracavernosal injections and implantation of a penile prosthesis. (*Insulin*. 2009;4:114–122) © 2009 Excerpta Medica Inc.

Key words: erectile dysfunction, diabetes, epidemiology, pathophysiology, phosphodiesterase inhibitors.

INTRODUCTION

Erectile dysfunction (ED), defined as the persistent inability to achieve and maintain an erection for successful intercourse, is a major sexual concern for many men.¹ Risk factors for ED include cardiovascular disease, diabetes mellitus (DM), hyperlipidemia, smoking, and obesity.^{2,3} ED is associated with depression and has a profound negative impact on the quality of life of patients and their partners.⁴ The prevalence of ED is higher in men with DM than in those without DM (age-adjusted relative risk [RR], 1.32; 95% CI, 1.3–1.4).⁵ The pathophysiology of ED is multifactorial, and men with DM are one of the most difficult-to-treat subgroups of patients with ED. The aim of this

review was to provide an overview of the epidemiology and underlying pathophysiology of ED in men with DM, diagnostic modalities, and treatment options.

METHODS

A MEDLINE literature search was conducted for articles published in English from inception of the database through November 2008, using the terms *erectile dysfunction, diabetes, epidemiology, pathophysiology, phosphodiesterase inhibitors, intracavernosal injection, and penile prosthesis*. Data on the epidemiology, diagnosis, and treatment of ED were extracted from all relevant articles.

RESULTS

The literature search revealed 685 original articles and reviews, 67 of which were selected for inclusion in this review.

Epidemiology

ED has been reported to occur in $\geq 50\%$ of men with DM worldwide.^{3,6} ED is usually present within 10 years of diagnosis of DM. The incidence of ED was reported to be higher at each decade of life for men with DM than for men without DM, and up to 12% of men who present with ED were found to have previously undiagnosed DM.³ ED occurs at a younger age in men with type 1 DM than in the general population, and the incidence of insulin resistance is 3 times higher in men with ED.⁷

In the Health Professionals Follow-Up Study cohort reported by Bacon et al,⁵ men with DM had an age-adjusted RR of 1.32 (95% CI, 1.3–1.4) for having ED compared with their nondiabetic counterparts. Men with type 1 DM were at a significantly higher risk for ED (RR, 3.0; 95% CI, 1.5–5.9) compared with men with type 2 DM (RR, 1.3; 95% CI, 1.1–1.5). Furthermore, men with type 2 DM had an increasingly greater risk of ED with increased duration since diagnosis, particularly for men whose DM was diagnosed >20 years previously. Fedele et al⁸ reported a 35.8% prevalence rate for ED in a cross-sectional study, ranging from 4.6% for men 20 to 29 years of age to 45.5% for men 60 to 69 years of age. Fedele et al⁹ also reported a crude incidence rate of 68 cases per 1000 person-years (95% CI, 59–77) in a subset of 1010 men without ED at baseline who were followed prospectively for 2.8 years. Grover et al¹⁰ reported a 49.4% prevalence of ED in a cross-sectional sample of 3921 Canadian men aged 40 to 88 years who were seen by primary care physicians.

The RR for ED in men with DM increases with coexisting cardiovascular disease, renal disease, diabetic foot, and retinal disease.^{8,10} The prevalence of ED differs across subsets of patients with coronary artery disease (CAD) and is an early marker of vascular disease. In patients with established CAD, ED may precede the clinical diagnosis of CAD by an average of 2 to 3 years.¹¹ Furthermore, several studies suggested that phosphodiesterase type-5 (PDE-5) inhibitors can improve endothelial function in addition to saving the patient's life.¹² ED is present in almost all men with DM-related neuropathy, and it is correlated with glycemic control (based on measurement of glycosylated hemoglobin [A1C] levels).¹³

DM is a major component of the metabolic syndrome, and results of several studies revealed that a high percentage of men with ED also had metabolic syndrome.¹⁴ Esposito et al¹⁵ reported a 26.7% prevalence of ED in patients with metabolic syndrome compared with 13.0% in the control group. In addition to ED, the presence of DM at baseline was significantly associated with all aspects of sexual dysfunction, including sexual drive, ejaculatory function, and sexual satisfaction (all, $P < 0.001$).¹⁶

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Pathophysiology

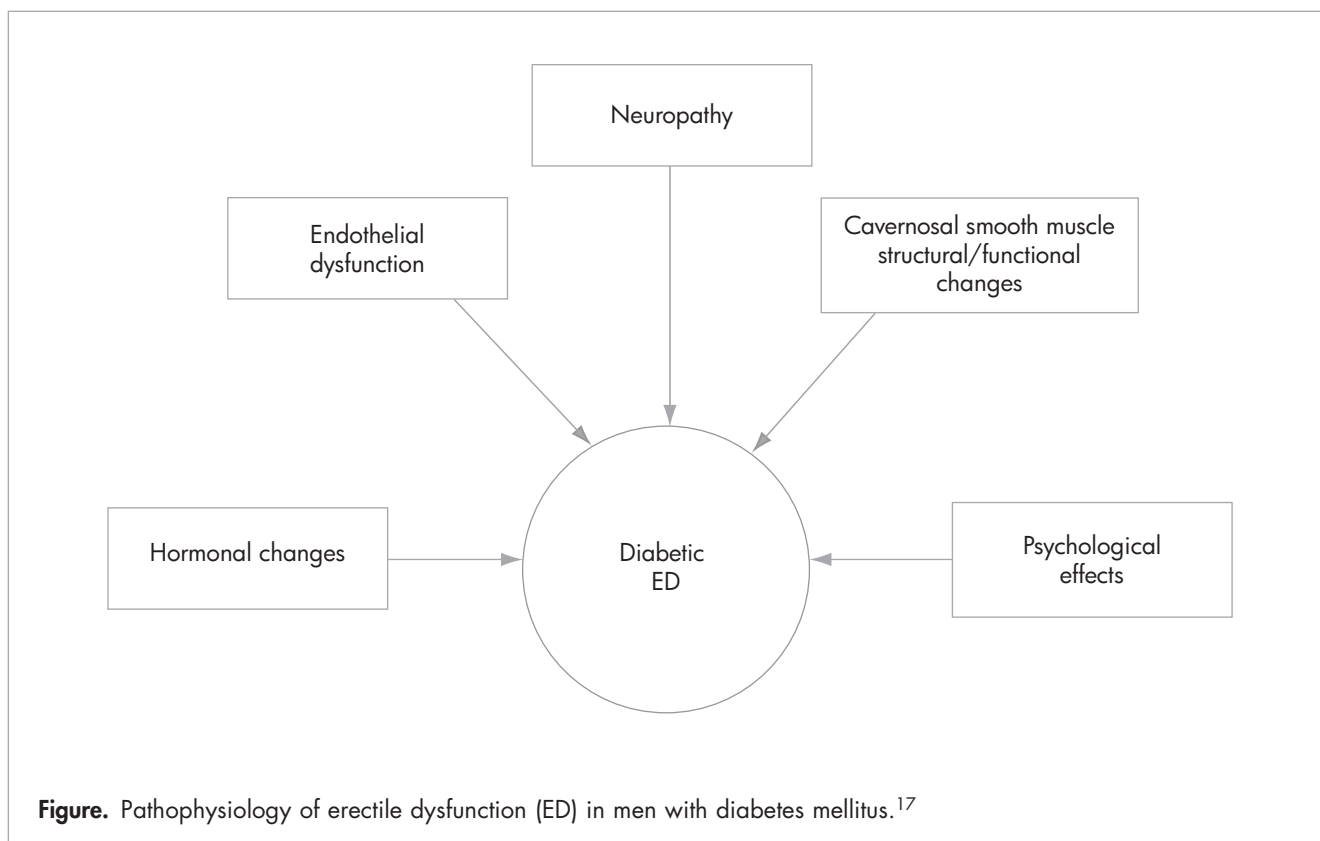
DM may cause ED through a number of pathophysiologic changes, including neuropathy, endothelial dysfunction, cavernosal smooth muscle structural/functional changes, hormonal changes, and psychological effects (Figure).¹⁷ Although pathophysiologic changes may be more pronounced in type 1 DM than in type 2 DM, functional studies failed to document any differences between the 2 types of DM.¹⁸

Diabetic neuropathy may be linked to selective neurodegeneration that results in decreased neuronal nitric oxide (NO) synthase activity and diminished NO associated with impaired nitregic relaxation in the corpus cavernosum.¹⁹ In addition, oxidative damage through the formation of oxygen free radicals may contribute to the neurodegeneration, suggesting that it is an NO-dependent process.^{20,21}

Endothelial dysfunction is a major cause of diabetic ED.²² Hyperglycemia reduces activity of endothelial NO synthase, diminishes the effect of released NO, and decreases oxygen free radicals, including advanced glycosylation end products (AGEs).²³ The ultrastructural changes in the endothelium result in increased penile vasoconstriction due to increased levels of endothelin-1 (ET-1) and upregulation of the endothelin receptors (ETA and ETB) in the corpus cavernosum.²⁴ ET-1-induced vasoconstriction is linked to the RhoA/Rho-kinase pathway that mediates ED through decreased production of NO in the corpora cavernosa.^{25,26}

Structural changes include reduction in smooth muscle content, increased collagen deposition, thickening of the basal lamina, and loss of endothelial cells.²⁷ Several studies have consistently found a reduction in the relaxation responses mediated by endothelial and neurogenic NO in the corpus cavernosum.^{20,28} These findings may be explained by the presence of AGEs, which decrease compliance in the corpora cavernosa and impair smooth muscle relaxation by generating free radicals or reactive oxygen species that react with NO.^{29,30}

Levels of total, free, and bioavailable testosterone are frequently low in men with type 2 DM; most of these men have clinical symptoms of hypogonadism, including ED and decreased libido.^{31,32} Obesity and age are associated with low testosterone levels in men with DM. Hypogonadism has been associated with metabolic syndrome and insulin resistance. Guay and Jacobson⁷ reported a 79% prevalence of insulin resistance in men with ED. Several studies confirmed that men with high testosterone values were more likely than men with low testosterone values to have <3 components of the metabolic syndrome. The reverse association



was also found. Testosterone modulates insulin sensitivity directly. Patients with lower testosterone levels had elevated insulin values. This association is bidirectional; insulin is capable of stimulating testosterone production and simultaneously reducing sex hormone-binding globulin concentrations in both normal-weight and obese men.³³ Androgen deficiency plays a central role in the pathology of metabolic syndrome, type 2 DM, and insulin resistance, and contributes significantly to the processes of adipogenesis. Visceral fat serves as an endocrine organ, which produces proinflammatory cytokines, thereby affecting multiple tissues and organs and further increasing the risk for insulin resistance, metabolic syndrome, type 2 DM, and endothelial dysfunction leading to ED.^{34,35} Early detection and treatment of the metabolic syndrome and the associated improvement of endothelial function are important in the treatment of ED.³⁶

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Psychological effects are another important factor in the pathophysiology of DM-associated ED. Depression, anxiety, and stress are common factors in diabetic men that may be

associated with ED through an excessive sympathetic outflow that results in inhibition of erection. Other psychological factors contributing to ED, although not specific to men with DM, include relationship issues and performance anxiety.³⁷

Diagnosis

The diagnosis of ED is based on the patient's sexual and medical histories, as well as the results of validated questionnaires such as the International Index of Erectile Function (IIEF).³⁸ Several medications have been associated with ED (Table I),¹⁸ and these agents need to be identified through the patient's medical history. Physical examination is focused on signs of cardiovascular disease and associated neuropathy, whereas penile examination is focused on identification of other comorbidities such as Peyronie disease. Laboratory examinations are limited to testosterone and prolactin levels, which may independently contribute to ED. These abnormalities occur significantly more often in men with DM than in the general ED population (all, $P < 0.001$), and they have implications for treatment.³¹ Specialized examinations are not necessary for most diabetic men with ED.³⁹

Treatment

No curative treatment for ED is yet available. However, the current treatment of ED in men with DM requires a multimodal approach. Important, but often neglected, aspects are the control of hyperglycemia and the treatment of diabetic comorbidities. Uncontrolled DM will exacerbate the

Table I. Frequently used medications that are associated with erectile dysfunction.¹⁸

Antihypertensives (eg, thiazide diuretics, β -blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors)
Antidepressants (eg, tricyclic antidepressants, selective serotonin reuptake inhibitors)
Antiarrhythmics (eg, digoxin)
Antiandrogens
Histamine ₂ -receptor antagonists (eg, cimetidine)
Recreational drugs/agents of abuse (eg, cocaine, marijuana)

previously described pathophysiologic changes, and ED will worsen. Moreover, a responder to a pharmacologic treatment for ED may become a nonresponder if DM is left untreated. Testosterone therapy in patients with hypogonadism may provide protective effects against the onset of DM or may ameliorate the pathology of diabetic complications. Thus, testosterone plays an important role in maintaining glycemic control and improving insulin resistance, avoiding the onset of metabolic syndrome and its vascular consequences, including ED. Lifestyle changes are highly recommended in the treatment of ED. Weight loss, increased physical activity, and a Mediterranean diet have been shown to improve sexual function through improvement of endothelial function.^{40,41} The associated hypogonadism must also be treated; otherwise, pharmacologic treatment may be less efficacious or not efficacious at all.

Medications that are frequently used by men with DM (eg, antihypertensives, antidepressants) must be taken into account and replaced (if appropriate) by medications with the least adverse impact on sexual function (eg, changing diuretics or β -blockers to calcium channel antagonists). Furthermore, angiotensin receptor antagonists can be used relatively safely.⁴² These drugs may even enhance sexual function by increasing intracavernosal pressure through reduction of oxidative stress in endothelial and other vascular cells.⁴³ Proper counseling of patients and their partners is important because it maximizes treatment efficacy and may even salvage treatment.⁴⁴ Gruenwald et al⁴⁴ reported that, of the 220 patients studied, 23.6% did not respond to sildenafil initially, but did respond later when they were given comprehensive oral and written instructions on the pharmacologic actions and correct usage of sildenafil.

ED treatment follows a stepwise approach, from the least to the most invasive options.³⁹ However, the selection of treatment options should be based on the needs and expectations of the patient and his partner for their sexual life. Regardless of the treatment selection, clinical follow-up is fundamental. Physicians should assess the therapeutic out-

come (efficacy and adverse effects), assess patient and partner satisfaction, and provide new instructions and counseling or an alternative therapy in case of suboptimal satisfaction. Internists should be able to provide basic consultation and treatment and then refer to specialists those patients who do not respond to drug therapy and patients who are complex clinical cases. Penile prosthesis implantation is a surgical option offered only by specialized urologists.

The panel of the Second Princeton Consensus on Sexual Dysfunction and Cardiac Risk provided instructions on ED treatment in patients with cardiac risk.⁴⁵ Briefly, patients were assigned to 3 risk categories: low, intermediate, and high. Patients in the low-risk category (<3 risk factors for CAD; mild, stable angina; uncomplicated previous myocardial infarction; successful coronary revascularization) can be offered ED treatment without any specific cardiac evaluation. Patients in the intermediate category (≥ 3 risk factors for CAD; moderate, stable angina; myocardial infarction within the previous 6 weeks) should be referred to a cardiologist for further evaluation. Patients in the high-risk category (high-risk arrhythmias, unstable or refractory angina, myocardial infarction within the previous 2 weeks) should not be offered any form of ED treatment because sexual intercourse is contraindicated.

Primary care physicians or internists should be able to provide treatment with oral drugs for most patients with ED. They should provide proper instructions for use of these drugs, including titration to the maximum tolerated dose for at least 4 sexual attempts, and provide follow-up, including assessment of efficacy and tolerability. Nonresponders to oral drugs and patients who cannot tolerate treatment with these agents should be referred to a specialist (urologist/andrologist). Any patient with a complex ED history, including hormonal disorders, psychosexual problems, or anatomical problems (penile deviation), should also be referred to a specialist.

Phosphodiesterase Type-5 Inhibitors

PDE-5 inhibitors have revolutionized ED treatment with their high efficacy rates and favorable safety profiles; they are currently considered first-line treatment by most physicians. This class of drugs currently includes sildenafil,* tadalafil,[†] and vardenafil.[‡] However, the efficacy of these agents (ie, ability to maintain erections long enough for successful intercourse) is considerably lower in men with DM than in the general ED population.⁴⁶ The efficacy of the PDE-5 inhibitors is presented in **Table II**.⁴⁷⁻⁵¹ In men with DM who were treated with sildenafil, 66.6% reported improved erections (using the General Assessment Question) and 63% reported successful intercourse attempts compared with

*Trademark: Viagra[®] (Pfizer Labs, a division of Pfizer Inc, New York, New York).

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[‡]Trademark: Levitra[®] (Bayer HealthCare Pharmaceuticals, Wayne, New Jersey).

Table II. Efficacy of phosphodiesterase type-5 inhibitors in men with diabetes mellitus.

Study, Year	Drug/ Dose	Diabetes Type (No. of Patients)	Outcome Measure	Efficacy
Stuckey et al, ⁴⁷ 2003	Sildenafil* 25–100 mg	Type I (188)	IIEF-4	Placebo, 2.2%; sildenafil, 3.2%; mean scores, $P \leq 0.001$
Safarinejad, ⁴⁸ 2004	Sildenafil* 100 mg	Type I (48), type II (234)	IIEF-4	Placebo, 2.9%; sildenafil, 2.0%; mean scores, $P < 0.002$
Fonseca et al, ⁴⁹ 2004	Tadalafil† 10 or 20 mg	Type I (210), type II (427)	SEP-3	Placebo, 21.5%; tadalafil 10 mg, 48.6%; tadalafil 20 mg, 52.8%; $P < 0.001$ for both 10 and 20 mg
Hatzichristou et al, ⁵⁰ 2008	Tadalafil† 2.5 or 5 mg	Type I (33), type II (265)	SEP-3	Placebo, 28.2%; tadalafil 2.5 mg, 46.0%; tadalafil 5 mg, 41.1%; $P \leq 0.005$ for both 2.5 and 5 mg
Goldstein et al, ⁵¹ 2003	Vardenafil‡ 10 or 20 mg	Type I (51), type II (387)	SEP-3	Placebo, 23.0%; vardenafil 10 mg, 49.0%; vardenafil 20 mg, 54.0%; $P < 0.001$ for both 10 and 20 mg

IIEF-4 = International Index of Erectile Function question 4 ("During sexual intercourse, how often were you able to maintain your erection to completion of intercourse?" Scale, 0–5); SEP-3 = Sexual Encounter Profile question 3 ("Did your erection last long enough for you to have successful intercourse?" Yes/no response).

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28.6% and 33.0%, respectively, for those taking placebo.⁴⁷ Two other randomized, placebo-controlled studies confirmed these findings.^{46,48}

PDE-5 inhibitors have revolutionized ED treatment with their high efficacy rates and favorable safety profiles; they are currently considered first-line treatment by most physicians.

In a retrospective analysis of 12 placebo-controlled trials of tadalafil in men with type 1 or type 2 DM, tadalafil improved all primary efficacy outcomes in both patient groups (10 and 20 mg) compared with placebo.⁴⁹ Men with

DM who received tadalafil 20 mg experienced a mean improvement of 7.4 in their IIEF erectile function domain score (relative to baseline) compared with a score of 0.9 for men in the placebo group. Men in the tadalafil group reported that, on average, 53% of their attempts at intercourse were successful, compared with 22% for those in the placebo group. Baseline IIEF erectile function domain scores correlated inversely with baseline A1C levels. In a recent randomized, double-blind, placebo-controlled study,⁵⁰ patients who received tadalafil 2.5 or 5 mg daily had statistically significant improvements in IIEF erectile function domain score, in mean success rates for vaginal penetration, completion of intercourse, and overall treatment satisfaction (all, $P < 0.005$).

In men with DM who were treated with vardenafil (10 or 20 mg), the mean IIEF erectile function domain scores were 17.1 and 19.0, respectively, compared with 12.6 in the placebo group.⁵¹ Success rates based on Sexual Encounter

Profile (SEP) question 2 (“Were you able to insert your penis into your partner’s vagina?”) were 64% with vardenafil 20 mg compared with 36% in the placebo group, whereas success rates based on SEP question 3 (“Did your erection last long enough for you to have successful intercourse?”) were 54% with vardenafil 20 mg and 23% with placebo. With vardenafil 10 mg, success rates for SEP-2 and SEP-3 were 61% and 49%, respectively (both, $P < 0.001$). Success rates were independent of both the severity of ED at baseline and the level of glycemic control and irrespective of whether patients had type 1 or type 2 DM.

In a review of treatment options for ED,⁵² the most frequently reported adverse events were headache, flushing, and rhinitis, which are consistent with the vasodilatory properties of PDE-5 inhibitors. Treatment-emergent adverse events were generally mild to moderate in severity and rapidly decreased during long-term treatment. Serious adverse events and dropouts because of adverse events were infrequent (<3% of patients).

No significant differences were noted between the PDE-5 inhibitors in terms of efficacy or tolerability. In terms of pharmacokinetic differences, absorption was more rapid for sildenafil and vardenafil than for tadalafil, which in clinical practice allowed erections hard enough for intercourse within an hour after administration, and the erections were maintained for 10 to 12 hours. Tadalafil had a more delayed onset of action (although erections sufficient for intercourse were attained within the first hour), but efficacy was maintained for at least 36 hours.⁵²

Vacuum Erection Devices

Vacuum erection devices have been used successfully by men with DM; in one report,⁵³ >70% of erections were sufficient for intercourse. However, the major problem is that these devices offer passive penile engorgement that requires placement of a ring at the base of the penis. Therefore, up to 30% of these patients discontinued use of the devices because of inadequate rigidity, penile pain, or failure to ejaculate.^{53,54}

Intraurethral Alprostadil

Intraurethral alprostadil* is another treatment option.⁵⁵ However, no studies of this agent in men with DM have yet been published. The efficacy rate for intraurethral alprostadil was considerably lower than that for intracavernosal alprostadil, but the intraurethral approach may be a viable treatment option for selected patients.⁵²

Intracavernosal Injections

Intracavernosal administration of vasoactive drugs is the second-line medical treatment when PDE-5 inhibitors have failed. Papaverine (20–80 mg) and alprostadil (prostaglandin E₁ 10–40 µg) are the main drugs for intracavernosal treatment. Alprostadil represents the most efficacious, and the

only approved, monotherapy.⁵² In an open-label, flexible, dose-escalating study in 336 men,⁵⁶ an effective dose was established with titration at the clinic before enrollment into the 6-month self-treatment home phase. An effective home dose was established with titration for 94% of men during the home phase, and a satisfactory erectile response was achieved after 99% of injections. Efficacy was usually maintained long term, although some dose adjustments were necessary.⁵⁷ Papaverine (7.5–45 mg) and phentolamine (0.25–1.5 mg), as well as combinations of papaverine (8–16 mg), phentolamine (0.2–0.4 mg), and alprostadil (10–20 µg) (bimixed and trimixed, respectively), have been widely used and resulted in higher efficacy rates (especially with the trimixed combination) in difficult-to-treat cases. Complications of intracavernosal pharmacotherapy included penile pain (50% of patients, after 11% of injections), prolonged erections (5%), priapism (1%), and fibrosis (5%–10%).^{58,59} However, no controlled studies have been conducted to define the actual incidence of fibrotic complications after intracavernosal injections.⁶⁰ Dropout rates of 41% to 68% have been reported because of the desire for a permanent treatment modality, lack of a suitable partner, poor response (especially among the early dropouts), fear of needles, fear of complications, and lack of spontaneity.⁵²

Intracavernosal administration of vasoactive drugs is the second-line medical treatment when PDE-5 inhibitors have failed.

Penile Prosthesis

Penile prosthesis implantation is a surgical treatment option that is usually offered to the patients when all other treatments have failed.⁶¹ Most patients prefer the 3-piece inflatable devices due to the more “natural” erections. Efficacy rates are not an issue with penile prostheses; all patients will achieve an erection sufficient for intercourse, assuming device reliability and proper implantation.⁶² However, fibrosis of the corpora cavernosa may be a major problem in men with DM, and implantation may be difficult or even impossible.^{63,64} Satisfaction rates for patients and their partners and improvements in quality-of-life issues ranged from 70% to 87%.^{65,66} Infection rates after penile prosthesis implantation were 1.8% to 6.5%, but careful surgical technique with proper antibiotic prophylaxis and use of antibiotic-coated prostheses reduced infection rates to 2% to 3%.⁶⁶ Although it is commonly believed that infection rates are higher in men with DM than in the general ED population, studies failed to confirm a disparity.^{66,67} Thus, patients with DM should be instructed that the risk of infection for men who undergo penile prosthesis implantation is similar to that for men with ED who do not undergo implantation.

*Trademark: MUSE® (Vivus, Inc., Mountain View, California).

CONCLUSIONS

ED is highly prevalent in men with DM because of the detrimental effects of DM in the nervous system, the endothelium, and the corpora cavernosa. The diagnosis of ED is based on the patient's sexual and medical histories and results of validated questionnaires; no specific laboratory evaluation is usually needed other than assessment of testosterone levels. PDE-5 inhibitors are considered first-line treatment, although the efficacy of these agents is lower in men with DM than in the general ED population. When

these agents fail, intracavernosal injections represent a viable treatment option. Penile prosthesis implantation, along with proper counseling, can be considered in treatment-refractory cases.

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