Effective treatment of erectile dysfunction in men with diabetes

Michael Cummings

ARTICLE POINTS

1 Many factors can trigger erectile dysfunction (ED), and men with diabetes are at greater risk of developing ED.

2 Patients presenting with ED should be screened for diabetes, as up to 40% may have underlying diabetes.

3 Several ED treatment options are available for patients with diabetes and ED, with oral PDE-5 inhibitors considered to be the first-line choice.

4 The PDE-5 inhibitors have similar efficacy and tolerability profiles, and all are effective in the treatment of men with diabetes and ED.

5 Tadalafil, a new long-acting PDE-5 inhibitor, is unique in providing a broad window of responsiveness of up to 36 hours and lack of food effect.

KEY WORDS

- Diabetes
- Erectile dysfunction
- Treatment
- PDE-5 inhibitors

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Introduction

Erectile dysfunction (ED) is a common disorder that can be caused by numerous factors, including lifestyle (e.g. obesity), drug treatment, and chronic diseases such as hypertension, cardiovascular disease and diabetes mellitus (Hood and Kirby, 2004). This review describes the scale, impact and underlying causes of ED in patients with diabetes and provides an overview of the available management options. Particular attention is paid to the clinical profile of the phosphodiesterase type 5 (PDE-5) inhibitors – sildenafil, vardenafil and tadalafil.

Erectile dysfunction (ED), an inability to achieve or sustain an erection of sufficient rigidity for sexual intercourse, is estimated to affect 150 million men worldwide. The extent of the problem is increasing, and this figure is expected to rise to more than 320 million by 2025 (Aytac et al, 1999). As the frequency of ED increases with age, the increase in incidence is partly due to an increasing ageing population. ED is reported to affect more than 50% of men between 40 and 70 years of age (Feldman et al, 1994).

ED and diabetes

Men who have diabetes are more likely to develop ED than men without diabetes. As a result, ED is perhaps the most common complication in men with diabetes, with an estimated incidence of 27–75% (Bacon et al, 2002). Men with diabetes also develop ED at an earlier age than men in the general population. Few studies have segregated findings in type 1 and 2 subjects; however, results to date suggest that the type of diabetes does not influence the incidence or age of onset of ED (Pointel et al, 1989; Sarica et al, 1994).

Many men, whether they have diabetes or not, feel uncomfortable about discussing sexual health with their doctor (Cummings et al, 1997). This is a significant barrier to effective treatment. Healthcare professionals who treat patients with diabetes must, therefore, be alert to the possibility of ED. Sensitive questioning, even in patients who are initially very reluctant to discuss sexual matters, can elicit the information that will allow correct diagnosis and treatment of the condition.

In many cases, ED and the vascular complications of diabetes share the same pathological processes. Studies have shown that as many as 40% of men with ED may also have underlying diabetes. Healthcare professionals should therefore be aware that ED might indicate the presence of diabetes or cardiovascular disease. Consequently, patients with ED should be screened for diabetes in accordance with the National Service Framework for diabetes (Department of Health, 2001).

Normal erectile function

Penile erection results from vasodilation of the vascular bed of the sinuses of the two corpora cavernosa, which are adjacent cylindrical bodies of vascular tissue that run throughout the penis (Andersson, 2001). The mechanism of penile erection is outlined in *Figure 1*.

Following sexual arousal, nerve impulses cause the release of neurotransmitters from nerve endings and endothelial cells of the penis. The release of several neurotransmitters, particularly nitric oxide (NO), affects the degree of contraction of the penile smooth muscles. NO promotes penile erection by stimulating the formation of cyclic guanosine monophosphate (cGMP), leading to smooth muscle relaxation and vasodilation in the arteries and arterioles

supplying the erectile tissue. Net blood flow is increased, causing the penis to become engorged with blood. The pressure exerted by the expanding corpora cavernosa causes the veins that drain the sinusoidal spaces to become occluded; this inhibits blood flow out of the penile structures, thereby maintaining the erection.

Effect of diabetes on erectile function

Cardiovascular, neurological and endocrine complications of diabetes can impact on erectile function, resulting in a higher prevalence of ED. Abnormalities within the parasympathetic nervous system can interrupt signal transmission, interfering with penile erection. Indeed, peripheral neuropathy, a co-morbidity of diabetes, is a risk factor for ED. One study showed that diabetic neuropathies were associated with the development of ED in approximately 80% of men with ED and diabetes (Ellenberg, 1971).

Vascular disease and hypertension are more common in patients with diabetes than in the general population. The pathological vascular effects of diabetes damage small arteries and arterioles, leading to cavernosal artery insufficiency. Indeed, reduced blood flow to the penis has been reported in approximately 95% of men with diabetes and ED (Jevtich et al, 1982). Abnormalities within the corpora cavernosa can also predispose men with diabetes to develop ED. Chronic dysglycaemia may be associated with impaired NO-induced smooth muscle relaxation (Cartledge et al, 2000). There is also evidence to show that neurogenic and endothelium-mediated relaxation of penile smooth muscle is impaired in men with diabetes and ED (Saenz de Tejada et al, 1989).

Management options for ED in diabetes

Optimal management of patients with diabetes involves prevention of complications, such as ED, through effective glycaemic control. However, following the diagnosis of ED, specific treatment is necessary to restore adequate erectile function.

Treatments should not impede the metabolic control of diabetes or interact with existing medications, such as insulin or oral hypoglycaemic drugs. As in the general population, treatment should also be effective and convenient. Some patients also want a treatment with a broad window of responsiveness, so that they can be free to choose when to have sex. Currently available treatments include vacuum devices, injectable drugs or transurethral therapy, psychosexual therapy, and oral medications. Penile prostheses are also available, but should only be considered as a last resort (Dinsmore et al, 2004; Montague, 2002).

The most widely prescribed treatment option, and the first-line treatment recommended by the World Health Organization, is the oral phosphodiesterase type 5 (PDE-5) inhibitors – sildenafil, vardenafil, and tadalafil (Jardin et al, 2000). The PDE-5 inhibitors are effective, non-invasive and convenient.

PAGE POINTS

1 Treatments for ED should not impede the metabolic control of diabetes or interact with existing medications.

2 The most widely prescribed treatment option, and the first-line treatment recommended by the WHO, is the oral phosphodiesterase type-5 (PDE-5) inhibitors.

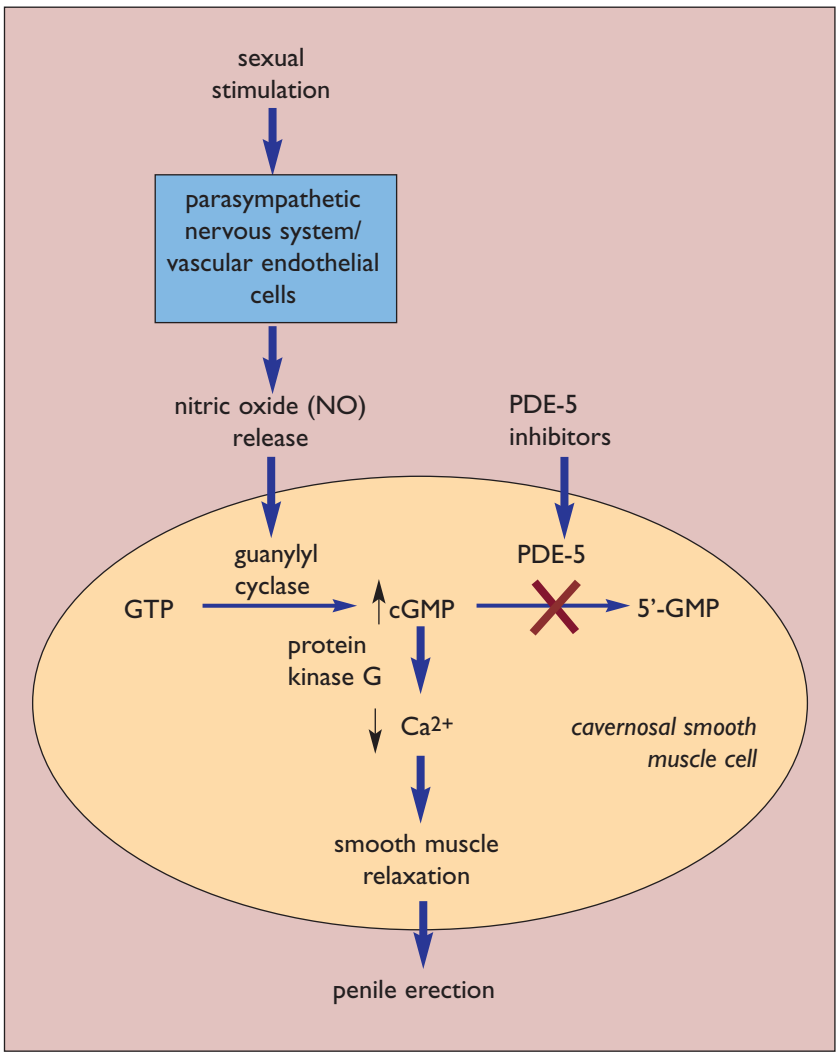
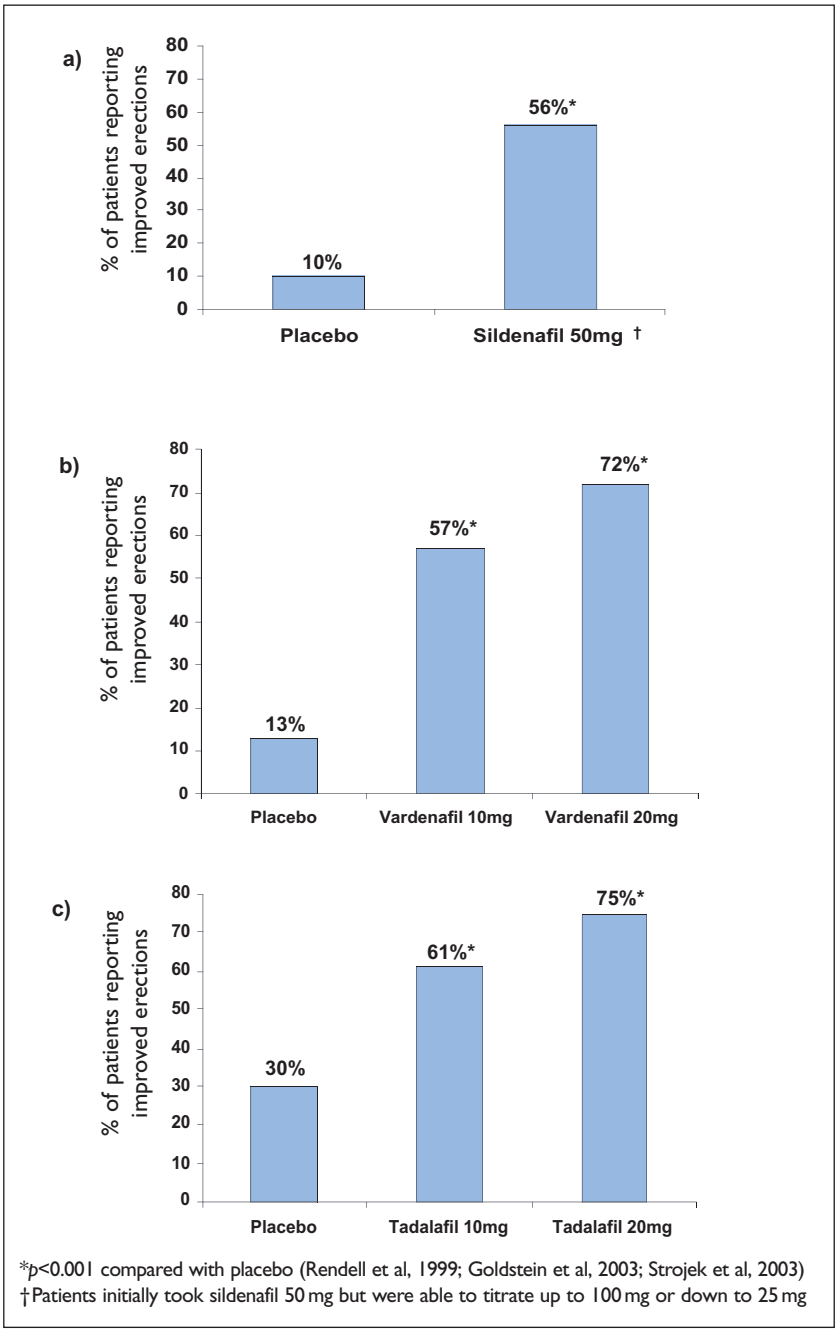


Figure 1. The physiological mechanisms leading to penile erection. PDE-5 = phosphodiesterase type 5; Ca^{2+} = calcium ions

(29% and 33%, respectively; Stuckey et al, 2003).

Vardenafil

Significant improvement in erectile function was also seen with vardenafil (Goldstein et al, 2003). In a phase III trial of 452 men with ED and type 1 or type 2 diabetes, improved erections were reported after 12 weeks with both 10mg and 20mg vardenafil



*p<0.001 compared with placebo (Rendell et al, 1999; Goldstein et al, 2003; Strojek et al, 2003)
†Patients initially took sildenafil 50 mg but were able to titrate up to 100 mg or down to 25 mg

Figure 2. Improvements in erections with the PDE-5 inhibitors: (a) sildenafil, (b) vardenafil and (c) tadalafil in patients with diabetes and erectile dysfunction. Data expressed as the percentage of patients with a positive response to the question (General Assessment Questionnaire, Question 1): Has the treatment you have been taking improved your erections? (Yes/No).

The PDE-5 inhibitors

The PDE-5 inhibitors potentiate the smooth muscle relaxation triggered by NO by blocking the hydrolysis of cGMP (*Figure 1*). All three currently available PDE-5 inhibitors have been shown to be effective in the general population. However, clinical trials that have assessed the efficacy of individual PDE-5 inhibitors have used different study designs and efficacy measures, and there is a lack of head-to-head comparative data.

When assessing the utility of the PDE-5 inhibitors in patients with diabetes, several factors must be taken into account, including the clinical characteristics of the patient, the severity of ED and underlying diabetes, as well as the pharmacological profiles of the different PDE-5 inhibitors. Nevertheless, sildenafil, vardenafil and tadalafil have all been shown to be effective and well-tolerated treatments for ED in men with diabetes (Vickers and Satyanarayana, 2002).

Sildenafil

The efficacy of sildenafil in men with diabetes was examined in an analysis of 11 randomised, double-blind, placebo-controlled trials. Improved erections were reported in 59% of patients with type 1 diabetes and 63% of patients with type 2 diabetes receiving sildenafil, compared with 18% and 17% of patients receiving placebo respectively (Blonde et al, 2000).

In a placebo-controlled study examining the efficacy and tolerability of sildenafil in patients with diabetes and ED, a significantly greater percentage of the 131 patients taking sildenafil had improved erections, compared with the 127 patients taking placebo (*Figure 2a*) (Rendell et al, 1999).

Significant improvements were also seen in a study of 219 patients with type 2 diabetes. Men taking sildenafil showed an increased ability to achieve and maintain an erection compared with those taking placebo (64.6% vs 10.5%, Boulton et al, 2001).

In a separate study of 188 men with type 1 diabetes, the sildenafil group had a significantly greater percentage of improved erections (67%) and successful attempts at intercourse (63%) than the placebo group

compared with placebo (*Figure 2b*) (Goldstein et al, 2003). The number of men who successfully completed intercourse was also significantly higher in those receiving vardenafil than in those taking placebo (10 mg vardenafil 49%, 20 mg vardenafil 54%, compared with placebo 23%).

Tadalafil

An integrated analysis of 12 multicentre, randomised, double-blind, placebo-controlled studies showed that tadalafil was significantly more effective than placebo (Brock et al, 2002). Data obtained in these studies for 637 men with diabetes and ED showed that tadalafil 10 mg and 20 mg were significantly more effective than placebo, according to all efficacy outcomes measured (Strojek et al, 2003) (*Figure 2c*).

In a study that exclusively enrolled patients with diabetes (type 1 or type 2) and ED, 56% and 64% of the 216 participants reported improved erections with tadalafil 10 mg and 20 mg respectively (Saenz de Tejada et al, 2002a). Similar improvements were also seen in the ability to engage in sexual activity (placebo 30%; tadalafil 10 mg 51% and tadalafil 20 mg 58%). Tadalafil was effective irrespective of severity of ED, diabetes type or initial level of glycaemic control (Saenz de Tejada et al, 2002a).

Duration of action of PDE-5 inhibitors

The duration of action of sildenafil and vardenafil is approximately four hours, whereas tadalafil has a considerably longer duration of efficacy of up to 36 hours (Stark et al, 2001; Eardley et al, 2002; Eardley, 2003). Shorter-acting drugs, such as sildenafil and vardenafil, are suitable for patients who wish to have sexual intercourse soon after taking the drug (i.e. in the four hours after dosing). However, for couples who want more freedom to choose when they have sex, the broader therapeutic window provided by tadalafil may be more appropriate.

Interactions and tolerability

PDE-5 inhibitors are contraindicated in patients taking nitrates, owing to their synergistic action on the NO/cGMP pathway, which can lead to excessive vasodilation and significant hypotension.

The absorption of sildenafil is slowed by food, reducing the maximal plasma concentration (C_{max}) and delaying the mean time to C_{max} by about an hour (Nichols et al, 2002). Similarly, a high-fat meal may alter the vardenafil C_{max} and delay its absorption by up to one hour (Rajagopalan et al, 2003). In contrast, tadalafil has no food interaction (Patterson et al, 2001).

Alcohol does not affect the pharmacokinetics of the three PDE-5 inhibitors.

All three currently available PDE-5 inhibitors are well tolerated and their use is generally associated with only mild class-specific side-effects. These include headache, rhinitis, sinusitis, flushing, myalgia and back pain (Goldstein et al, 1998; Guay et al, 2000; Saenz de Tejada et al, 2002a; Goldstein et al, 2003). The use of sildenafil and vardenafil is also associated with visual disturbances, which are thought to be due to inhibition of PDE-6 (Goldstein et al, 1998; Hellstrom et al, 2003). Visual disturbances have also been reported with tadalafil, but are very rare (incidence <0.1%; Padma-Nathan, 2003).

Tadalafil has been shown to cause some inhibition of PDE-11 (Saenz de Tejada et al, 2002b), but the physiological role of this isozyme has yet to be established and so the potential impact of any PDE-11 inhibition is unknown.

Case study

Case history

A 59-year-old man presented with a six-month history of progressively worsening ED. He had a history of hypertension, for which he had been receiving atenolol 50 mg daily for the last three years. He had no history of diabetes mellitus or cardiac disease. He was a non-smoker and drank 10 units of alcohol a week. Examination revealed normal secondary sexual characteristics with no evidence of any hormonal imbalance. Cardiovascular and neurological examinations were unremarkable, and his blood pressure was 130/75 mmHg.

Baseline investigations revealed that the patient's levels of testosterone, luteinising hormone (LH), follicle-stimulating hormone (FSH), prolactin and thyroid hormone were

PAGE POINTS

1 Sildenafil and vardenafil have a duration of action of about four hours, and tadalafil up to 36 hours.

2 Sildenafil and vardenafil are thus suitable for patients who wish to have sexual intercourse soon after taking the drug, whereas tadalafil is better suited to couples who want more freedom to choose when they have sex.

3 PDE-5 inhibitors are contraindicated in patients taking nitrates.

4 Alcohol does not affect the pharmacokinetics of the three PDE-5 inhibitors.

5 All three PDE-5 inhibitors are well tolerated and their use is generally associated with only mild side-effects, e.g. headache, rhinitis, sinusitis, flushing, myalgia and back pain.

PAGE POINTS

1 Hypertension is an aetiological factor in the development of ED.

2 So too are many antihypertensive drugs, e.g. beta-blockers are commonly associated with the development of ED.

3 Where there is a clear temporal relationship between introduction of medication and onset of ED (e.g. within two weeks of starting the drug), stopping the drug has sometimes proven effective.

4 However, where a patient has received a beta-blocker for many years, for example, stopping it is unlikely to improve erectile function.

5 Also, in many cases, causative drugs cannot be discontinued for clinical reasons.

6 Differences in PDE-5 inhibitors' pharmacokinetic profiles allow the choice of ED treatment to be tailored to the needs of the individual patient.

all within normal limits and there was evidence of glycosuria. During assessment of the most appropriate course of action and consideration of the treatment options, the patient also mentioned vague chest pains.

Points to consider

This case illustrates a number of important issues:

- Upon further evaluation, repeated measurements of fasting plasma glucose confirmed an underlying diagnosis of diabetes mellitus. Urine testing for diabetes has a high rate of false negatives and cannot be relied upon to screen for diabetes mellitus (Sairam et al, 2001). Approximately 40% of patients presenting with ED are likely to have underlying diabetes, and in 11–12% of patients this represents a new diagnosis of diabetes (Bacon et al, 2002; Foresta et al, 2004). Given these observations, it would be prudent to check for diabetes by plasma sampling in all patients who present with ED that have not been previously diagnosed with diabetes.
- Hypertension is recognised as an underlying aetiological factor in the development of ED, as are many antihypertensive drugs (Hood and Kirby, 2004). For instance, beta-blockers are commonly associated with the development of ED. Where a clear temporal relationship exists between the introduction of medication and the onset of ED (usually within two weeks of starting the drug), discontinuing medication has proven to be effective. However, in this patient (who had received atenolol for three years), stopping the beta-blocker would have been unlikely to result in an improvement in erectile function. Furthermore, in many instances, causative drugs cannot be discontinued for clinical reasons.
- The patient reported vague chest pains. Given the frequent association between ED, diabetes and coronary artery disease, it was important to have a clear understanding of the nature of this pain. Upon further evaluation, this patient was found to have coronary ischaemia. A coronary angiogram revealed single vessel disease, which was then managed by angioplasty.
- Sexual intercourse is associated with a modest increase in cardiac output, which can be critical in patients with significant abnormalities of coronary perfusion and can precipitate cardiac events. It is therefore important to assess the patient for the presence and severity of coronary ischaemia. However, in patients with stable coronary artery disease who present with ED, it is perfectly reasonable to support them in practising sexual activity.

Patient outcome

In this patient, ED heralded the diagnosis of underlying concomitant diabetes mellitus and coronary artery disease. Coronary angioplasty resolved his chest pain and he required no anti-anginal agent or sublingual nitrate spray. A PDE-5 inhibitor was successful in restoring sexual activity.

Conclusions

Several treatment options are available for patients with diabetes and ED, with oral PDE-5 inhibitors considered the first-line choice. All PDE-5 inhibitors have similar efficacy and tolerability profiles but show differences in their pharmacokinetic profiles. Such characteristics allow the choice of ED treatment to be tailored to the needs of the individual patient.

Sildenafil, the first member of the class, has the most comprehensive research and literature base. Vardenafil is similar in structure to sildenafil and therefore has similar pharmacokinetics and a comparable side-effect profile. Tadalafil, a new long-acting PDE-5 inhibitor, provides a broad window of responsiveness, which offers patients the freedom to choose when to have sex. ■

CONFLICTS OF INTEREST: *Dr Cummings has received honoraria for lectures and attended advisory boards, and sponsorship to educational meetings, from Pfizer and Lilly-ICOS. He has also received lecture honoraria from Bayer.*

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