

Treatment of erectile dysfunction in men with diabetes

William D Alexander

ARTICLE POINTS

1 ED is a common and important complication of diabetes, significantly affecting quality of life.

2 ED should be actively sought. It may be a marker for endothelial function and cardiovascular disease.

3 ED in diabetes is multifactorial in its causation.

4 PDE5 inhibitors are the treatment of first choice.

5 PDE5 inhibitors and other treatments are usually safe in men with coronary artery disease or other cardiovascular disease.

KEY WORDS

- Erectile dysfunction
- PDE5 inhibitors
- Cardiovascular disease
- Nitrates
- Surgery

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Introduction

Erectile dysfunction is a common and important complication of diabetes. It should be actively sought not only because of its importance to a man and his partner's quality of life but also because it may be a marker of underlying vascular disease. It is multifactorial in its causation and effective treatments are available. Oral PDE5 inhibitors are usually the treatment of first choice and there are now a variety available. They and other treatments are usually safe in men with overt cardiovascular disease except for those taking concurrent nitrate and/or nitric oxide donor drugs.

Male erectile dysfunction (ED) or impotence is a problem that becomes increasingly frequent with age (Feldman et al, 1994). It is particularly common in association with diabetes, other cardiovascular risk factors and overt cardiovascular disease. Under these circumstances ED is usually of an organic aetiology, although in most men there will be some psychological factors. It is an important problem to many men and despite having a significant negative effect on quality of life, men remain reluctant to mention the problem and many health care professionals are also reluctant to address it.

Much management can be carried out by primary and secondary care diabetes and cardiovascular services without the need of referral to more specialist departments. In fact, the increasingly recognised association with cardiovascular and other complications of diabetes make such services the most appropriate. ED may be the first manifestation of endothelial dysfunction and atherosclerosis; it is now considered important not only to screen men with diabetes and/or cardiovascular risk factors for ED, but also to screen men with ED for occult underlying cardiovascular risk factors and physical disease.

Causes of ED

The cause of ED in diabetes is often multifactorial (*Table 1*) and will vary according to the type of diabetes, its

Table 1. Factors leading to the high incidence of ED in diabetes

- Stress of living with a chronic disease.
- Metabolic effects of hyperglycaemia and excessive protein glycosylation.
- Penile disorders: balanitis, phimosis, Peyronie's disease.
- Premature ageing and degeneration of corpora cavernosal smooth muscle.
- Endothelial dysfunction.
- Microvascular complications and smooth muscle myopathy.
- Sensory and autonomic neuropathy.
- Macrovascular disease and its risk factors, treatments and consequences.
- Hypertension and its treatment.
- Psychosexual factors affecting the man and his partner.

complications and the individual man. ED is often severe and initial treatments can be disappointing, but there are now many options available and these are outlined in this review. Successful treatment produces a significant improvement in general and disease-specific quality of life.

Treatment of ED

Men should be made aware of all the treatment options. The choice will depend upon the man and his partner's preference, the clinician involved and the local availability. Treatment options are shown in *Table 2*.

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1 Erectile dysfunction is often associated with other conditions and particularly cardiovascular risk factors.

2 There is a strong direct association between hypertension and dyslipidaemia and ED.

3 It is essential that the man's relationship with his partner is discussed. The partner should be invited to attend with the man.

4 Many topical drug creams and pastes have been tried and continue to be developed. Such agents are not currently generally recommended in the UK

Table 2. Current available treatments for ED

- Lifestyle measures
- Psychosexual therapy
- Topical treatments
- Oral treatments
- Intraurethral treatment
- Intracavernosal injection treatment
- Vacuum tumescence devices
- Surgery

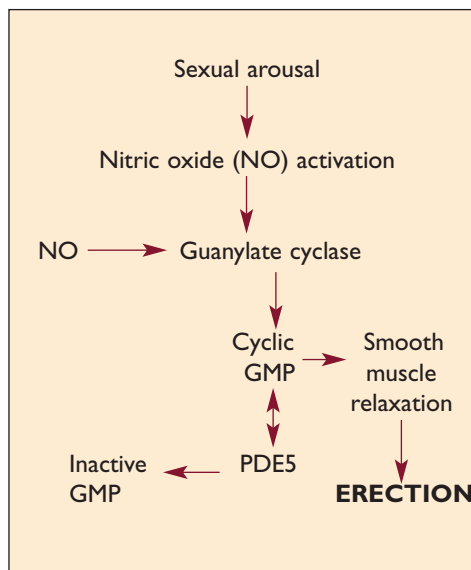


Figure 1. Mechanism of action of PDE5 inhibition

Table 3. Comparison of current PDE5 inhibitors

	Vardenafil	Sildenafil	Tadalafil
Doses (mg)	5, 10, 20	25, 50, 100	10, 20
Onset (min)	15–60	30–60	30–60
*WOO factor (h)	4	4	24+
Efficacy (%)	60–80	60–80	60–80
**Cost (£/tab max)	6	6	5

Adapted from MIMS, 2003.
 * WOO=window of opportunity
 ** Cost per maximum tablet dose

Lifestyle issues

Erectile dysfunction is often associated with other conditions and particularly cardiovascular risk factors. General advice should be given about smoking, alcohol, weight and general fitness. Such advice should not be a substitute for other treatment but given in conjunction.

Concomitant medications

Consideration should be given to concomitant medications particularly when men are convinced there is a definite temporal association. Antidepressants, antihypertensive drugs and lipid soluble statins are often considered the most relevant in this respect. There is, however, a strong direct association between hypertension and dyslipidaemia and ED, and many patients with diabetes are now on multiple antihypertensive and other drug regimens that are difficult to change. In practice, altering these regimens is usually disappointing but practitioners should be sensitive to this issue.

Relationship issues

It is essential that the man's relationship with his partner is discussed. The partner should be invited to attend with the man. Simply restoring erectile function may not resolve all issues and lead to adequate sexual satisfaction. It may be helpful, particularly if there is performance anxiety, to discuss techniques such as the Masters and Johnson sensate-focusing techniques (Masters and Johnson, 1970). This may improve communication and understanding between partners.

Men with general psychological problems and/or severely dysfunctional relationships should be referred for specialist counselling.

Topical treatments

Many topical drug creams and pastes have been tried and continue to be developed. They include smooth muscle relaxants and/or vasodilators with or without transdermal permeation enhancers.

Such agents include nitroglycerine, alprostadil, minoxidil and mixtures of various drugs, but they have had only limited success except perhaps in less severe degrees of ED. They are not currently generally recommended in the UK

Oral therapy

Current oral therapy includes the peripherally active phosphodiesterase 5 (PDE5) inhibitors sildenafil, tadalafil, and vardenafil, and the centrally active apomorphine.

PDE5 inhibitors

PDE5 inhibitors are currently the first line choice of treatment. PDE5 inhibitors act peripherally on the penile erectile smooth muscle. Inhibition of PDE5 leads to an increase in cyclic-guanosine monophosphate (GMP). This in turn potentiates the action of nitric oxide and thereby enhances cavernosal smooth muscle relaxation and penile erection during sexual stimulation (*Figure 1*). PDE5 inhibitors are only effective in conjunction with sexual arousal. There are currently three available PDE5 inhibitors: sildenafil (Viagra), tadalafil (Cialis) and vardenafil (Levitra). Some comparisons are shown in *Table 3*.

Dosing should be started with the lower doses and increased as necessary. Most men with severe ED will require the higher doses. Effectiveness depends upon an adequate trial of treatment. Men failing to respond initially should be encouraged to use the drug in association with some sexual activity to stimulate erection on a weekly basis for 2–3 months before abandoning it as ineffective.

Sildenafil was the first of the PDE5 inhibitors and has been hugely successful, being effective in greater than 70% of men with ED of mixed aetiologies. Lower success rates of approximately 60% are found in conditions associated with particularly severe ED, such as diabetes and cardiovascular disease.

Tadalafil and vardenafil are equally effective. Vardenafil is similar in structure and action to sildenafil. Tadalafil has a longer half-life and has the potential advantage of a longer window of opportunity, remaining active for up to 24 or even 36h. This may help to improve spontaneity.

The choice will depend upon the pattern of the man's sexual activity and needs. Longer drug activity suiting some men and short action being sufficient for many. It may be wise, at least for the moment, to avoid the longer acting tadalafil in men with overt symptomatic cardiac disease. Side-effects of PDE5 inhibitors are shown in *Table 4*. Full details of drug interactions can be found in the British National Formulary (BNF, 2003). The most commonly

Table 4. Side-effects of PDE5 inhibitors

- Side-effects**
- Headache
 - Dizziness
 - Flushing
 - Dyspepsia
 - Visual disturbance (sildenafil, vardenafil)
 - Myalgia, backpain (tadalafil)

Table 5. Effects of using PDE5 inhibitors in patients with CVD

- Well tolerated
- Similar effect to nitrates (Jackson, 1999)
- Effective in 60–80% of patients
- No effect on heart rate and echocardiogram
- Modest fall in blood pressure (8–10 units systolic blood pressure; 4–6 units diastolic blood pressure over 6 h)
- No increase in death, myocardial infarction or cerebrovascular accident.

encountered contraindication is in men taking nitrate drugs or other nitric oxide donors such as nicorandil.

Coronary artery disease and PDE5 inhibitors

Men can be reassured that coronary artery disease is not a contraindication to any of the treatments for ED and this includes PDE5 inhibitors. They are safe provided the man is able to tolerate mild to moderate everyday activities such as walking on the level for 20 minutes. This equates to the likely energy requirement of routine sexual intercourse. Consensus specialist statements have been published in both the UK and USA and are reassuring (DeBusk et al, 2000; Jackson et al, 1999). *Table 5* outlines effects of PDE5 inhibitors in men with cardiovascular disease (CVD).

Men taking nitrates:

Nitrates are not of prognostic significance in patients with coronary artery disease but are a symptomatic treatment. In many instances, therefore, they can be discontinued or an alternative antianginal

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4 PDE5 inhibitors are well tolerated and are effective in 60–80% of patients.

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1 Short-acting nitrates should not be used within 12 h of a PDE5 inhibitor or vice versa. Long-acting nitrates should not be used within 1 week of a PDE5 inhibitor or vice versa.

2 Apomorphine can be used safely in patients with cardiovascular disease and is generally safe if used with caution in combination with nitrates and other nitric oxide donors such as nicorandil.

3 Apomorphine can have the following side-effects: nausea, yawning, dizziness, somnolence, headache and vasodilation.

4 Intraurethral alprostadil is available as MUSE (Medicated Urethral System for Erection).

Table 6. Use of PDE5 inhibitors in men taking nitrates

- Angina troublesome:**
- Consider calcium antagonist and/or β -blocker.
 - Investigate with exercise test and echocardiogram. Refer to cardiology.
 - Defer ED treatment.
- No angina:**
- Stop long-acting nitrate for 1 week.
 - Encourage exercise.
 - Advise regarding short-acting nitrates.
- If no angina, prescribe PDE5 inhibitor. Ban use of short-acting nitrate.*
- Angina recurs:**
- Prescribe calcium channel blocker and/or β -blocker.
 - Refer to cardiology if no response.
 - Start PDE5 inhibitor when/if angina-free.

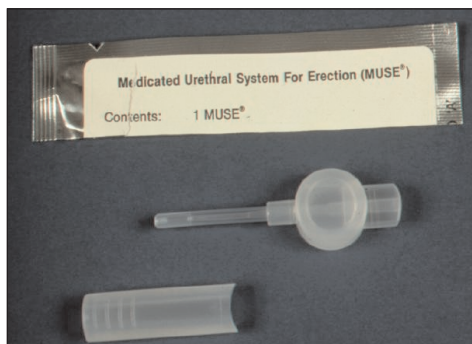


Figure 2. A MUSE applicator

agent such as a calcium channel blocker or β -blocker substituted.

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Apomorphine

Apomorphine (Uprima) is a sublingual preparation. It is a dopamine receptor agonist and exerts its effect centrally by stimulating the dopamine receptors in the paraventricular nucleus of the brain and the spinal cord and releasing proerectile neurotransmitters. It may also have a positive effect on libido. Its onset of action is within 20 minutes.

Dosage should start with 2mg and be



Figure 3. Intracavernosal injection treatment; a patient injecting



Figure 4. Caverject dual chamber

increased to 3 mg or more, if necessary and if tolerated. Efficacy is best in mild or psychogenic ED. It is less effective in severe cases and the response in men with diabetes has been disappointing.

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Intraurethral therapy

Intraurethral alprostadil is available as MUSE (Medicated Urethral System for Erection; see *Figure 2*). It consists of a polypropylene applicator containing, at its tip, a pellet of alprostadil. MUSE is available in pellet doses of 125, 250, 500 and 1000 μ g. Most men need to use the higher doses; continued use has been limited by side-effects, particularly penile and lower extremity pain. A constriction ring (Actis) can be used in conjunction to reduce

Table 7. Cautions about treatment with intracavernosal self-injection

Contraindications or caution should be exercised if there is:

- Haemoglobinopathy or bleeding diathesis
- Severe Peyronie's disease
- Poor manual dexterity
- Inadequate visual acuity
- Large abdomen, small penis preventing safe technique
- Needle-phobia or tendency to syncope
- Serious psychiatric disorders
- Likely abuse.



Figure 6. Some examples of VTDs

proximal absorption and help sustain the erection. Patient studies have shown men to prefer self-injection therapy.

Use of a condom is recommended to prevent transfer of prostaglandin to the partner; this is particularly important if the partner is pregnant.

Intracavernosal injection therapy

Prostaglandin E1 – alprostadil is now the drug most commonly used in the UK but various mixtures of alprostadil, phentolamine, papaverine, and vasoactive intestinal polypeptides are favoured by practitioners in some other European countries and the USA.

Intracavernosal injection therapy is simple and relatively painless to administer, effective and safe. Men need to be taught the technique carefully. Figure 3 shows a patient injecting treatment.

In the UK, alprostadil is available either in packs with syringes, needles and separate vials of powder and diluent for mixing (Caverject or Viridal) or with a simple

injector device Caverject Dual Chamber or Viridal Duo. Currently the Caverject Dual Chamber preparation is the easiest to use. Figure 4 shows a Caverject dual chamber.

Most men will be suitable for injection treatment though caution should be exercised under certain circumstances (Table 7).

Method of administration

Intracavernosal injection treatment involves the injection of a small volume (less than 1 ml) of the vasoactive drug into one of the corpora cavernosa. Men should be carefully instructed on its use to be sure they are going to be competent, safe and confident in its use.

Painful erection is a not uncommon problem. Recent studies have suggested that the use of prophylactic or therapeutic glyceryl trinitrate (sublingual or transdermal) can prevent and/or treat this problem successfully.

Dosage should be determined by the man in his normal home environment rather than in clinic/surgery. He should be given written instructions to start with a small dose and gradually increase on separate occasions until the lowest effective dose is found. Written instructions on incremental dose increases should be provided.

Vacuum tumescence devices (VTDs)

Vacuum pumps for the treatment of ED have been around for many years. The design was first patented in 1917 by Otto Lederer. The basic principle remains unchanged but there are now a variety of designs available (Figure 7). VTDs consist of a cylinder and vacuum pump to produce an erection and a constriction ring to maintain it.

The erection produced is not physiologically normal. The penis becomes engorged and distended distal to the constricting ring but will tend to pivot proximal to the ring. The penis will appear rather cyanosed and cold and may become painful with time. The ring should not be left on for more than 30 minutes.

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1 VTDs are effective in approximately 70–80% of patients but this is dependent upon patient acceptability.

2 Occasionally men with severe proximal pelvic or aortoiliac disease and ED can be improved by corrective surgery and it is important to identify such men.

3 The mainstay of surgical treatment is the insertion of penile prostheses. Such treatment can be very successful.

4 Surgery should be considered as an important option in younger men with severe ED and others who fail to respond to less invasive treatments.

upon patient acceptability. Couples with a good and open general and sexual relationship are most likely to be suitable for this form of therapy. Long-term use appears to be as good if not better than self-injection therapy. Others may find VTDs to be rather intrusive and contrived.

VTDs may also appear expensive, involving a capital outlay of £90–300 depending upon the type. In the long-term, this is cost-effective compared with oral or self-injection therapy. VTDs are now, like other treatments, available on a National Health Service prescription in the UK for certain categories of patient.

Vacuum devices are usually used alone but can be used in conjunction with other treatments to augment the effect. The choice of device will depend upon availability, price, and personal preference.

Surgery

Vascular surgery

Microvascular surgical techniques remain largely experimental. Occasionally men with severe proximal pelvic or aortoiliac disease and ED can be improved by corrective surgery and it is important to identify such men.

Penile prostheses

The mainstay of surgical treatment is the insertion of penile prostheses. These may be either of the semi-rigid or inflatable type. Such treatment can be very successful.

The following might be considered factors warranting referral:

- Congenital or acquired anatomical abnormalities.
- Severe corpora-cavernosal fibrosis: post-injection therapy, Peyronie’s disease, etc.
- Failure of other treatments.
- Patient preference and unwillingness to try or persevere with other treatments.

Penile prosthetic surgery should also be considered in younger men with irreversible ED and longstanding diabetes, particularly if, as is so commonly the case, they have significant Peyronie’s disease. Referral to an experienced surgeon should be considered in such men if they have failed to respond to oral agents.

Conclusion

- High risk men should be screened for ED. It effects quality of life and is treatable.
- Men with ED are at high risk of cardiovascular disease and must be screened for this.
- PDE5 inhibitors are the first line treatment of choice. Newer PDE5 inhibitors have a different “window of opportunity” (up to 36 h with tadalafil).
- PDE5 inhibitors are safe in men with multiple cardiovascular risk factors, overt cardiovascular disease and men on multiple antihypertensive drugs.
- Intracavernosal injection therapy and vacuum pumps remain a second line option. Vacuum pumps are now available on prescription.
- Surgery should be considered as an important option in younger men with severe ED and others who fail to respond to less invasive treatments. ■

Feldman HA, Goldstein I, Hatzichristou DG et al. Impotence and its medical and psychosocial correlates: results of the Massachusetts Male Ageing Study (1994). *Journal of Urology* **151**: 54–61

Masters WH, Johnson VE (1970) Human sexual inadequacy. Churchill: London

Monthly Index of Medical Specialities (2003). *MIMS – April 2003*. Haymarket Medical Publications Ltd, London

DeBusk R, Drory Y, Goldstein I et al (2000) Management of sexual dysfunction in patients with cardiovascular disease: recommendations of the Princeton consensus panel. *American Journal of Cardiology* **86**(2): 175–81

Jackson G, Betteridge J, Dean J et al (1999) A systematic approach to erectile dysfunction in the cardiovascular patient: a consensus statement. *International Journal of Clinical Practice* **53**(6): 445–51

British National Formulary (2003) BNF 45 March 2003. British Medical Association, Royal Pharmaceutical Society of Great Britain: London