Erectile dysfunction in patients with diabetes

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Erectile dysfunction, which is common among men with diabetes, leads to significant reduction in quality of life, and as with other complications of diabetes deserves to be treated on the NHS. This article explores the problem of erectile dysfunction and diabetes and the role of sildenafil, which is likely to be the first choice treatment of patients presenting with erectile dysfunction.

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Erectile dysfunction (ED) is a distressing condition which may seriously impair quality of life, particularly with respect to emotional functioning (Litwin et al, 1998). The problem is also exacerbated by a lack of understanding among patients concerning the nature of ED and the treatments available for it (Cummings et al, 1997).

Until recently the medical options for the treatment of ED were often either inconvenient and/or ineffective. The recent development of sildenafil as an effective, orally active treatment for ED has raised awareness of ED as a potentially easily treatable condition. The cardiovascular and neurological complications commonly found in patients with diabetes markedly increase the risk of developing ED. The purpose of this review is to explore the extent of the problem of ED in diabetic men and the options for pharmacological management of the condition.

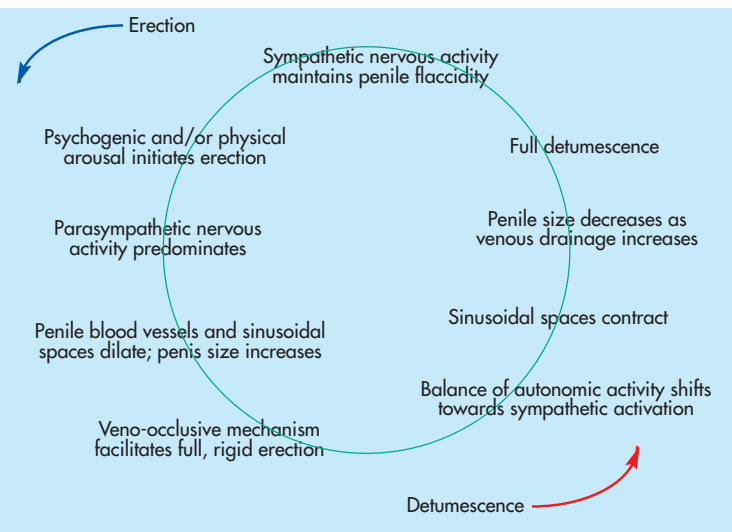

Figure 1. Physiological processes involved in erection and detumescence.

CLINICAL CHARACTERISTICS OF ED

Prevalence in men with diabetes

The precise prevalence of ED is difficult to establish accurately, and caution must be exercised in interpreting differences between epidemiological studies in the classification and definition of ED. However, it is clear that the prevalence of ED among diabetic subjects is higher than in the general population. It is estimated that within the general population approximately 28% of 40–70-year-olds have complete ED, and 23–35% under the age of 60 years have undefined ED in the UK (Feldman et al, 1994; Bortolotti et al, 1997). Additional evidence suggests that at least 40% of men with ED have diabetes (Zonszein, 1995). These figures therefore underline the public health challenge posed by diabetic ED in the UK.

Aetiology

Erection is a vascular event under autonomic nervous, hormonal and psychological control (*Figure 1*). The main erectile structures consist of the two corpora cavernosa, which run the length of the penis, containing a network of blood vessels and interconnected sinusoidal spaces. The penis is intensively innervated by autonomic nerves, which are in turn influenced by input from higher centres during sexual stimulation.

Neurotransmitters released by parasympathetic nerve terminals (principally acetylcholine and nitric oxide) induce smooth muscle relaxation, vasodilatation of penile arterioles and relaxation and expansion of the sinusoidal spaces. The net blood flow into the penis is thereby increased, and the penis increases in size. At this point, the veins draining the sinusoidal spaces become occluded as a result of pressure exerted by the

expanding corpora cavernosa, and blood flow out of the penile structures is inhibited. This event, the 'veno-occlusive mechanism', leads to a further net increase in pressure within the penis and the achievement of a full erection. Normally, after ejaculation the erection is terminated by increased sympathetic nervous activity, which constricts the sinusoidal spaces and allows blood to leave the erectile structures, restoring flaccidity.

ED may result from dysfunction of any physical or psychological component of the erectile process ('organic' and 'psychogenic' ED respectively). Until recently, the causes of organic ED were thought to relate primarily to vascular and neuropathic dysfunction, including defective blood flow into the penis (e.g. resulting from atherosclerosis), endocrine pathology, an inefficient veno-occlusive mechanism, or peripheral autonomic neuropathy. More recently, attention has focused on pathological changes in the structure and function of corporal smooth muscle and endothelium (Aydos et al, 1996). Also, advanced glycation products in diabetes may adversely affect nitric oxide signalling mechanisms within the corpora cavernosa (Seftel et al, 1997).

In practice, the aetiology of ED is often complex, with contributions from organic and psychogenic causes in many patients. Typically, the appearance of ED causes anxiety in the patient, which further diminishes erectile function, reinforcing ED as part of a negative interplay between the organic and psychogenic components of the condition.

The relationship between ED and diabetes

The risk of ED increases with both increasing duration of diabetes and metabolic indices of inadequate diabetes control, e.g. concentrations of blood glucose and glycated haemoglobin (Klein et al, 1996). Organic vasculogenic ED appears to be the most frequent cause of ED in diabetic men (Lee et al, 1994).

The degree of overlap between typical comorbidities of diabetes and risk factors for ED is striking (*Figure 2*). Vascular disease, treated or untreated hypertension, peripheral neuropathy and obesity are all significantly more common in diabetic subjects than in their normoglycaemic peers (Kannel et al, 1991; Bianchi et al, 1995; Greenstein et al, 1997). Recent epidemiological evidence has suggested that patients with type 2 diabetes (who represent approximately 80% of the overall diabetic population) require intensive management to improve their cardiovascular risk profile. Indeed, type 2 diabetic patients with no history of myocardial infarction are at the same increased risk of developing a myocardial infarction as non-diabetic patients who have had a previous myocardial infarction (Haffner et al, 1998). This observation suggests that cardiovascular risk factors in all type 2 diabetic patients should be treated as aggressively as in non-diabetic survivors of myocardial infarction (Haffner et al, 1998). Therefore, many diabetic patients are likely to receive long-term treatment with antihypertensive and lipid-lowering drugs, some of which may further adversely affect erectile function.

Thiazide diuretics are commonly associated with the development of ED, although their use may be restricted in diabetic subjects because of concerns over adverse metabolic effects. Reports of ED have also appeared following administration of other classes of antihypertensive drugs (e.g. β-blockers, Rosen and Weiner, 1997). The Treatment of Mild Hypertension Study (TOMHS) (Grimm et al, 1997), which examined the effects of five antihypertensives (acebutolol, amlodipine, chlorthalidone, doxazosin and enalapril) on sexual function, suggested that the only group in which the incidence of erectile problems was not increased was the doxazosin group.

As targets for reduced cardiovascular mortality in diabetes have become more aggressive, this is likely to lead to more intensive management of hypertension in diabetic patients. Drug contraindications are therefore an important consideration in these subjects, and it is essential for physicians to consider that while anti-

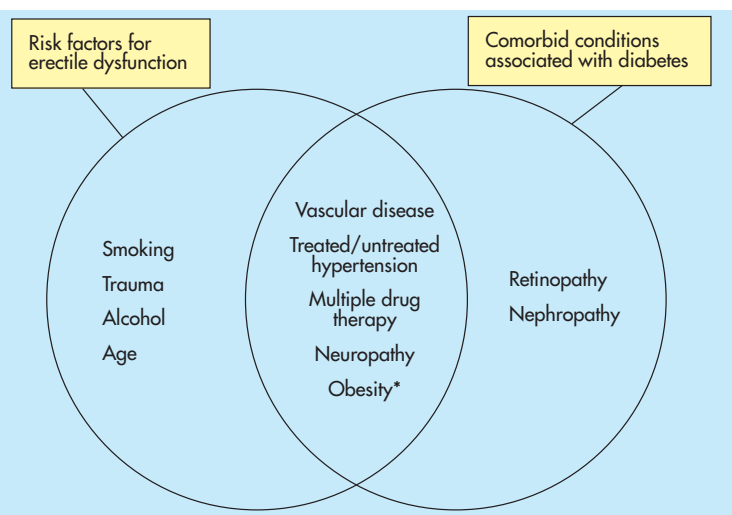

Figure 2. Risk factors for organic erectile dysfunction and comorbidities associated with diabetes. Text in each circle shows aetiological factors/comorbidities relevant to erectile dysfunction or diabetes, as indicated. Items in the area of overlap are relevant to both conditions. *Particularly relevant to type 2 diabetes.

hypertensives are not contraindicated with sildenafil, organic nitrates are a strict contraindication because sildenafil potentiates the hypotensive effects of nitrates. More diabetic men have also been placed on lipid-lowering drugs, of which the fibrate class, for example, is associated with the development of ED (Bruckert et al, 1996).

TREATING ED IN THE DIABETIC SUBJECT

The epidemiological evidence described above suggests that a high proportion of men with diabetes will develop ED at some stage during their lives, and this is likely to seriously affect their overall wellbeing. However, the additional problems of underdiagnosis of the condition and reluctance to discuss sexual matters with patients are significant barriers to effective treatment. Physicians treating patients with diabetes must therefore be alert to the likelihood of ED, and be prepared to sensitively elicit information to allow correct diagnosis and treatment of the condition, even where patients may be initially reluctant to discuss it. The overall health gains available from resolving ED render the management of ED in diabetic patients worthwhile and rewarding for both the patient and the physician.

Maintaining metabolic control in patients with diabetes is crucial, so pharmacological treatments for ED should not adversely affect glucose or lipid homeostasis. In addition, treatments must not interact with other medications that diabetic men frequently require, e.g. insulin, oral antidiabetic, antihypertensive or lipid-lowering drugs. A suggested practical approach to the medical management of ED is outlined in *Figure 3*.

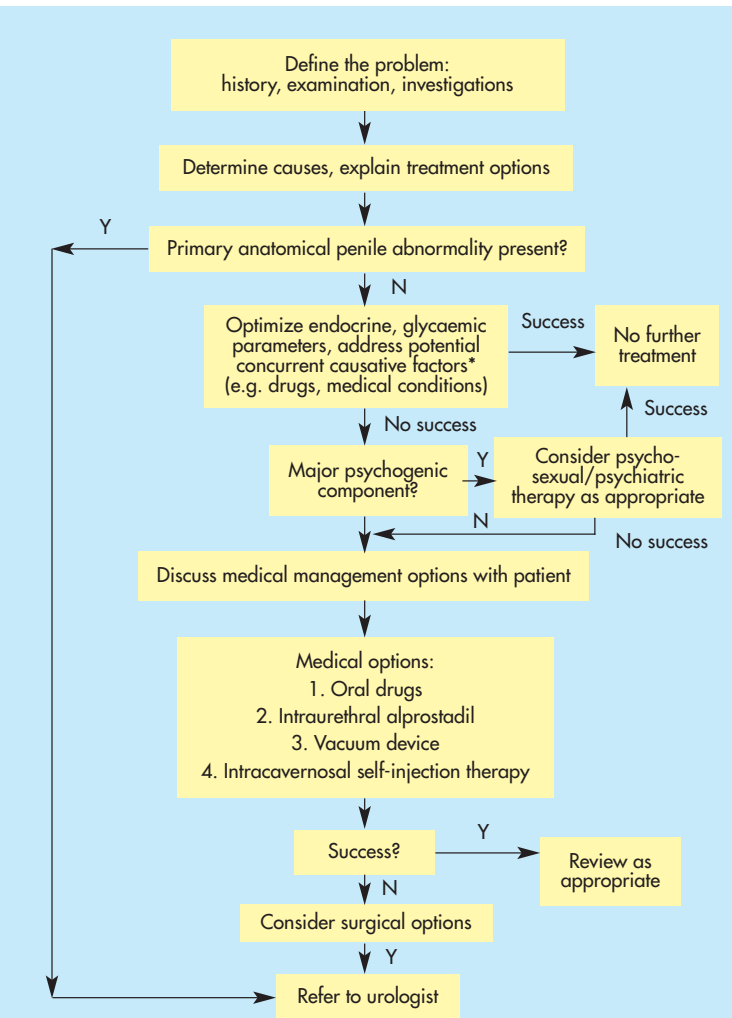

*Figure 3. Practical approach to the medical management of erectile dysfunction (ED). Adapted from Meeking et al (1995). *Patients who experience ED as a result of drug therapy (e.g. antihypertensive or lipid-lowering drugs) or poor glycaemic control demonstrate a clear temporal association. ED in these patients will resolve itself within 5–10 days once these patients have been taken off medication or achieve acceptable glycaemic control; however, this can only be achieved in the case of drug therapy if a suitable alternative therapy can be prescribed without an unacceptable loss of blood pressure or lipid level control.*

Injectable treatments

Some drugs may be injected directly into the corpora cavernosa to produce erection. These agents are frequently effective in improving erectile function, but training in their use is required, and some patients might find the injections difficult or stressful to perform. The most commonly used, licensed drug in injectable form is the prostaglandin E_1 alprostadil. Other injectable agents include combinations that contain papaverine and the non-selective α-adrenoceptor antagonist phentolamine. The combination of vasoactive intestinal peptide and phentolamine is used but its use is currently unlicensed in the UK.

Inappropriate doses of injected drugs may cause prolonged erections (priapism) in a proportion of patients. Recent attempts to avoid the need for intracavernosal injections by transurethral administration of alprostadil have proved disappointing because of poor clinical efficacy (Fulgham et al, 1998) compared with intracavernosal alprostadil.

Oral treatments

The potential for orally administered drugs in the treatment of ED has been explored in a number of studies. Yohimbine has been the most commonly used drug and phentolamine, apomorphine and others are under development. Unfortunately, these drugs are only likely to be effective in less than half of patients with ED at

best (Zorgniotti, 1994) and may be even less effective in patients with diabetes (Susset et al, 1989; Becker et al, 1998; Teloken et al, 1998). In addition, yohimbine may increase blood pressure, which may inhibit its use in patients at risk of hypertension and cardiovascular disease.

Sildenafil is a new, orally active drug for ED. The mechanism of action of sildenafil involves inhibition of phosphodiesterase (type 5) in the smooth muscle of the corpora cavernosa and penile resistance arteries (Rulten et al, 1998). This results in potentiation of the smooth muscle relaxation induced by nitric oxide released from autonomic nerve terminals during sexual stimulation. The action of sildenafil therefore directly addresses the impaired relaxation of smooth muscle in the corpora cavernosa, which has been identified as an important cause of ED, as described above.

Sildenafil is straightforward for patients to use, being taken orally approximately 1 hour before intercourse. Evidence to date shows that sildenafil is clinically effective, irrespective of the underlying aetiology of the ED, including diabetes. A study by Goldstein et al (1998) found that the percentage increase in score from baseline in patient's ability to achieve an erection suitable for penetration was 95% in the sildenafil treatment group compared to 10% in the placebo group ($P<0.001$). Sildenafil is also extremely effective in patients with severe ED, and a recent meta-analysis of sildenafil trials indicated that up to 73% of patients with ED responded to sildenafil treatment (Steers, 1998). In addition, sildenafil is similarly efficacious in older patients, which is important given the increasing prevalence of diabetes with advancing age (Wagner et al, 1998).

The first reported study on the effects of sildenafil in patients with ED and diabetes was undertaken by Price et al (1998). They examined the effects of two doses of sildenafil (25 mg and 50 mg) *vs* placebo in a randomized, double-blind, three-way crossover trial. The duration of penile rigidity during visual sexual stimulation was increased by sildenafil in a dose-dependent manner, with the effects of the higher dose reaching statistical significance relative to placebo. Sildenafil was also effective in the home setting, where significant increases in the mean number of erections suitable for intercourse occurred at both doses studied (*Figure 4*). In these patients, improved erections were reported by 50% and 52% of those treated with 25 mg and 50 mg of sildenafil respectively, compared with 10% of those receiving placebo ($P<0.05$). The drug was well tolerated, with no withdrawals resulting from treatment-related adverse events. More recently, the effects of sildenafil *vs* placebo were evaluated in a randomized, double-blind trial of 268 patients with ED and diabetes, and with a mean age of 57 years. Patients were randomized to treatment with either placebo or sildenafil, at an initial dose of 50 mg which could be reduced to 25 mg or increased to 100 mg based on tolerability and efficacy (Rendell et al, 1999). The investigators reported improved erectile function in 56% of sildenafil-treated patients compared to only 10% in the placebo group ($P<0.001$). The drug was well tolerated and no patient discontinued treatment because of adverse events. These findings are extremely encouraging, given that diabetic patients are likely to present with multiple risk factors for ED.

An analysis of data from 940 patients in three double-blind, placebo-controlled clinical trials has evaluated the effect of treatment of ED with sildenafil on quality of life, measured using standard questionnaire techniques (Quirk et al, 1998). Compared with placebo, treatment with sildenafil improved quality of life in 7 out of 11 dimensions; conversely, only a single dimension was significantly improved in patients receiving placebo compared with sildenafil (*Table 1*). These results confirm that successful treatment of ED is associated with significant benefits in overall wellbeing.

The tolerability of sildenafil has been evaluated in more than 3700 patients, with a total exposure to the drug of more than 1600

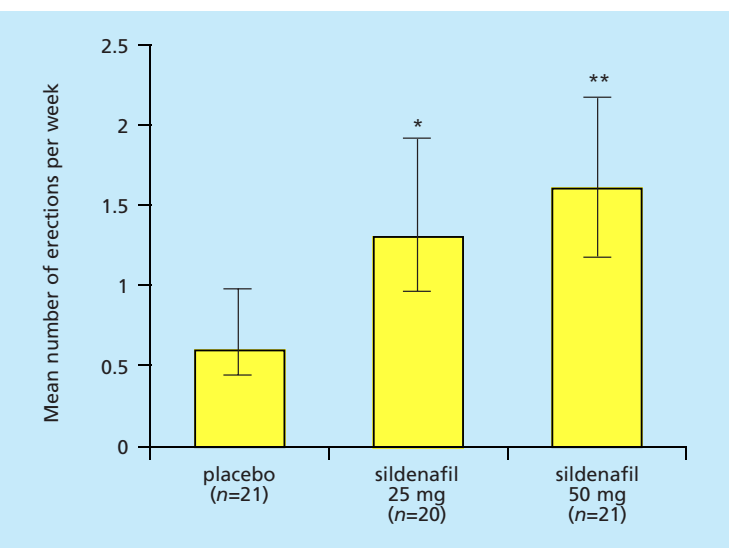

Figure 4. Efficacy of sildenafil in patients with erectile dysfunction secondary to diabetes. Columns represent mean number of erections/week attained during treatments shown. Bars represent 95% confidence interval. *P=0.0025, **P=0.0002 vs placebo. Adapted from Price et al (1998).

TABLE 1.
Effects of treatment of erectile dysfunction with sildenafil on quality of life (*n*=940)

Quality of life dimension		Significant difference in favour of
Psychological General Wellbeing Index	General health *vs* 3 months previously	S
	Positive wellbeing	S
	Self-control	S
	Depression	S
	Anxiety	NS
SF-12 Questionnaire	Mental health summary	S
	Physical health summary	P
Impact of Erectile Problems Scale		S
Satisfaction With Relationship With Partner		S
Rosenberg Self Esteem Scale		NS
Medical Outcomes Study Family Interaction Survey		NS

Adapted from Quirk et al (1998). Significant differences were determined using analysis of covariance and the level of significance was set at $P<0.05$. S = sildenafil; P = placebo; NS = not significant.

patient-years (Morales et al, 1998). The adverse events encountered more frequently on sildenafil treatment than placebo were headache (16% *vs* 4%), flushing (10% *vs* 1%), dyspepsia (7% *vs* 2%), nasal congestion (4% *vs* 2%), abnormal vision (3% *vs* 0%) and diarrhoea (3% *vs* 1%). These adverse events reflect the pharmacological mechanism of action of sildenafil, were usually transient and were mostly mild or moderate in severity. All-cause treatment withdrawals occurred in sildenafil and placebo groups with an almost identical frequency (2.5% *vs* 2.3%). There were no cases of priapism.

When treating diabetic patients, it is important to establish that adverse effects related to metabolic function, which could exacerbate diabetes, do not occur. There is no indication from clinical trial data that sildenafil affects blood glucose levels in diabetic patients (Pfizer Ltd, unpublished data, 1997). Furthermore, the study in 21 diabetic men, described above, did not reveal any clinically significant changes in laboratory test results, suggesting that sildenafil did not impair metabolic control (Price et al, 1998). Additional evidence comes from a pooled analysis of placebo-controlled UK trials, in which 30% of 449 patients who received sildenafil were diabetic, and there were no treatment withdrawals caused by laboratory abnormalities (Pfizer Ltd, unpublished data, 1997). Thus, in diabetic men there does not appear to be an adverse effect on blood glucose levels. Sildenafil therefore appears to be highly suitable for administration to diabetic patients.

All approved drugs are subject to post-marketing surveillance through the spontaneous adverse event reporting system. In this system, all reports received are recorded regardless of the source, data quality or causality assessment.

Much media attention worldwide has focused on deaths of patients taking sildenafil. A United States Food and Drug Administration inquiry in 1998 has concluded that 130 deaths occurred in the USA among patients verified to have taken sildenafil between late March 1998 and the end of November 1998, following the issuing of more than 6 million outpatient prescriptions of the drug (www.fda.gov/cder/consumerinfo/viagra/default.htm). All reported deaths have not been assessed as being causally related to sildenafil and the number of deaths observed is well within what would be expected in this population.

Blinded, placebo-controlled trials are considered the gold standard in terms of evaluating treatment effects. Within the phase II and phase III sildenafil trials, no significant differences have been found regarding the incidence of myocardial infarction or other serious cardiovascular events between sildenafil and placebo. Morales et al (1998) found that the incidence of cardiovascular-related adverse events (other than flushing) in a general population with ED was 3% in the sildenafil-treatment group compared to 3.5% in the placebo group. Rendell et al (1999) reported that, for patients with ED and diabetes, the incidence of cardiovascular adverse events was also comparable (3% in the sildenafil group compared to 5% in the placebo group).

Because of the correlation between vascular disease and ED, the cardiovascular implications of any therapy for ED must be considered carefully before initiating treatment. Erectile failure may be the first sign of previously occult cardiovascular disease and older men with diabetes

have a high prevalence of cardiovascular risk factors and, often, overt disease. It is therefore important to consider such concomitant diseases before commencing treatment for ED.

DISCUSSION

ED should be viewed as a common complication of diabetes. Furthermore, the large number of patients with ED, and the profound distress which ED may cause (Litwin et al, 1998), makes imperative the management of ED in diabetic patients. Despite the increased morbidity associated with ED, the condition remains widely under-diagnosed and inadequately treated. There are also wider implications for the management of diabetes; anecdotal evidence suggests that the loss of self-esteem associated with ED may reduce the motivation of patients to manage their diabetes adequately on a day-to-day basis. Given the clear link between the quality of blood glucose control and the risk of diabetic complications (Diabetes Control and Complications Trial Group, 1995), removing barriers to psychological wellbeing in diabetic patients, including those with ED, should be viewed as a priority. In addition, by emphasizing the importance of intensive regimens aimed at reducing cardiovascular risk in diabetic patients, the findings of the UK Prospective Diabetes Study (UKPDS) Group have the potential to reduce the prevalence of ED (UKPDS, 1998a).

Until recently, current therapy for ED requiring intracavernosal injection, although efficacious, has proven in practice to be unacceptable to some patients. Our own experience with intracavernosal injection treatment suggests that about half of patients cease using the treatment very early on because of lack of acceptability. There is evidence to suggest that diabetic patients with ED would actively seek treatment if they knew it were available, and if it was convenient to use (Cummings et al, 1997). The availability of sildenafil, an effective, well-tolerated and orally active agent for ED, promises to meet this need by improving the treatment of ED in those countries where it is made available.

Are new oral therapies cost-effective?

The potential cost of providing sildenafil has been raised as an argument against making it available via NHS prescription. In light of such controversy, a careful evaluation of the cost–benefit of sildenafil is undoubtedly required to resolve this issue. It remains unclear as to why sildenafil has been targeted by the government, despite clear evidence that it is as least as effective as treatments for ED currently available on the NHS, improves the quality of life of patients, and is less expensive than available alternatives.

The financial cost of sildenafil must be considered in context of the wider health costs associated with the care of diabetic complications in general, and in particular the broader consequences to society of ED. The costs of treating diabetes have recently been reviewed (Alberti, 1997). Even excluding primary care and community costs, 4–5% of total health-care costs in the UK are accounted for by the management of diabetes. Furthermore, almost 10% of inpatient days may be attributable to diabetes, and treating diabetes accounts for at least 10% of the total health-care budget.

The total cost of sildenafil treatment for diabetic men with ED would be at least partially offset by savings in other treatments, and also perhaps by benefits in terms of improved diabetic care and reduced diabetic morbidity leading to lower health-care costs and improved wellbeing for these patients. It could be that if patients are less troubled by ED they are more likely to be compliant with other forms of medication, and this will have considerable health gains. Intensive blood pressure and blood glucose control in patients with type 2 diabetes has been shown to substantially reduce both micro- and macrovascular complications in the UKPDS. Cost-effectiveness analysis of the UKPDS data suggests that intensive regimens will therefore reduce the long-term costs of treating problems associated with diabetic complications (UKPDS, 1998b).

Who should provide treatment for diabetic men with ED? In the UK, patients seeking treatment for ED are likely to discuss the problem with their general practitioner initially. With adequate training, selecting the most appropriate treatment option at the primary care level would provide a rational and efficient management strategy, as long as providers of care (e.g. general practitioners and/or nurse specialists) are suitably trained and competent in the management of ED. However, for this strategy to work efficiently and cost-effectively, a full range of treatment options, including sildenafil, should be available on NHS prescription by all practitioners adequately trained to treat this condition. Such training in primary and secondary care could increase availability of treatment and relieve excessive workload on urology practices.

CONCLUSION

ED is common in diabetic men, and is a serious condition which may adversely affect relationships, and impair quality of life and psychologi-

cal health. This in turn may lead to diminished motivation to maintain optimal control of the metabolic syndrome, thereby increasing the risk of diabetic complications. Conversely, successful management of ED is associated with significant gains in quality of life and overall health status. Until recently, treatments for ED were effective, but often inconvenient. In the UK, sildenafil promises to revolutionize the management of this condition, but only if available for use on NHS prescription. HM

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KEY POINTS

- Between 30 and 50% of diabetic patients in the UK have erectile dysfunction (ED), as a result of the higher incidence of vascular disease, smooth muscle pathology and neuropathy in this population.
- ED is a deeply distressing condition which affects both patients and partners.
- Until recently, pharmacological treatments have been ineffective, inconvenient or both. The introduction of sildenafil promises effective and well tolerated therapy for ED of any aetiology.
- It is important to consider the cost of treating ED in context with the overall cost of treating diabetes and its complications, and the costs to society associated with ED itself.
- Emerging evidence suggests that psychological benefits resulting from successful treatment of ED result in improved overall health status in diabetic patients, which may in turn lead to enhanced self-esteem, better glycaemic management and reduced risk of diabetic complications.
- We propose that a full range of treatment options, including sildenafil, should be available on NHS prescription to all practitioners adequately trained to treat ED.