Erectile dysfunction (ED) has been defined as 'the inability to attain or maintain an erection sufficient for satisfactory intercourse'. Its prevalence is difficult to determine accurately, because of differences in definitions of ED among epidemiological studies. Also, there is widespread reluctance to discuss the condition, not only on the part of sufferers but also on the part of some health-care professionals.

Published estimates of the prevalence of ED in the UK are scarce, though anecdotal evidence suggests an overall UK prevalence of about 10%, and a review of 23 studies conducted in the US suggests that up to 9% of patients in the community have the condition.

The development of ED is related to age, and patients aged 70 are three times more likely to have complete ED than patients aged 40. However, ED is not necessarily a consequence of the ageing process itself; rather, it appears to develop in association with a number of other risk factors which are also more prevalent in older men, such as hypertension and cardiovascular disease.

The detection of ED in previously undiagnosed men may also result in the underlying causes of this condition, such as hypertension and cardiovascular disease, being detected and treated. This will have considerable health gain in these patients, who might otherwise have had their condition diagnosed at a later stage of the disease. An early diagnosis of ED in patients with cardiovascular disease may also aid the clinician in deciding which treatment to administer, as certain antihypertensives (including β-blockers and thiazide diuretics) may contribute to the development of the condition.

CARDIOVASCULAR DISEASE AND ED

ED may result from a dysfunction of any component of the muscular, vascular or nervous components of the erectile apparatus. Hypertension has frequently been cited as a risk factor for ED, although the results of epidemiological studies on the link between hypertension and ED are conflicting. However, it does appear that the quality of erections in hypertensive men with ED may be lower than in normotensive men with ED.

Vascular disease appears to be the most common aetiology of organic ED. Four studies reviewed by Bortolotti et al. involving a total of 1476 men with a history of heart disease, vascular surgery or myocardial infarction, revealed incidences of sexual dysfunction (described as mainly representing impotence or difficulty with erections) ranging from 39% to 64% for each patient group. ED may be among the first signs of cardiovascular disease, as the small vessels of the penis appear more sensitive to atherosclerotic occlusion than blood vessels in the heart or elsewhere. Indeed, the presence of vasculogenic ED has been suggested as a predictive factor for the presence of occult cardiovascular disease, and elevated cholesterol levels may be predictive of the development of ED.

In addition to reduced blood flow into the penis resulting from penile artery occlusion, vascular disease is also associated with structural damage to the smooth muscle in the corpora cavernosa, which may represent an important aetiological factor in vasculogenic ED. Interestingly, recent work has suggested that erectile function is correlated with the severity of cardiovascular disease, as patients with single-vessel ischaemic heart disease had firmer erections.

ADDRESS CORRESPONDENCE TO: Dr Graham Jackson, Cardiac Department, St Thomas' Hospital, Lambeth Palace Road, London SE1 7EH, UK
and less difficulty obtaining an erection than patients with two- or three-vessel disease (Figure 1).¹³

**Impact of ED**

ED is a deeply distressing condition and, given its impact on overall well-being, it is surprising that little focused research has been carried out in this area. In a recent survey of 1680 men, ED was found to have a negative effect on quality of life measurements, as assessed by a comprehensive questionnaire.¹⁴ In this study, a significant correlation was observed between impotence and all quality of life questions (p<0.001). Furthermore, a significant relationship was also established between impotence and age (p<0.001). A survey of patients with sexual dysfunction caused by radiotherapy also cited sexual dysfunction as a significant source of stress involved in the break-up of relationships.¹⁵

The successful treatment of ED is associated with psychological benefits that manifest as improvements in overall health status.¹⁶ In a recent two-year trial of 1511 men, patients who responded to transurethral alprostadil in the clinic were randomly assigned to home treatment with alprostadil (125-1000 mg) or placebo.¹⁷ These patients were also asked to complete a quality of life questionnaire before and after the study. The results show that 43% of all patients on active treatment had successful intercourse in the home setting compared with only 12% on placebo (p<0.001). There was also a significant improvement in the quality of life questionnaire relating to emotional well-being in responsive patients (p<0.004).

In another study of 579 patients with ED, the quality of life effects of self-administered intracavernosal injections of alprostadil were assessed for up to six months.¹⁸ In this trial, improvements were recorded in the quality of life questions relating to depression, and global scores were found to significantly improve (p<0.001).

Other studies show a significant association between ED and psychological ill-health, but cause and effect are not clearly defined.¹⁹²⁰ These studies identify ED as a source of psychological as well as physical ill-health, but there is a clear need for research to quantify the distress seen by physicians treating the condition on a day-to-day basis. Improvements in quality of life, associated with the effective treatment of ED, may also result in these patients being compliant with other forms of medication. It therefore follows that patients with cardiovascular disease may have greater compliance with their drug regimens if they are no longer troubled with ED.

**DIAGNOSIS OF VASCULOGENIC ED**

ED, as with all matters relating to sexuality, is still surrounded by social taboos and a lack of knowledge concerning the available treatment options. Therefore, patients with ED secondary to vascular disease but who have presented with other symptoms may not readily volunteer the information that would lead to the correct diagnosis of ED. Such attitudes probably underlie a significant proportion of underdiagnosis of ED in the general population. In patient populations with higher than average incidences of ED, such as patients with vascular disease, it is particularly important to consider the possibility that ED may be present. Given the need to treat the whole patient, the potential distress caused by ED cannot be ignored and, where possible, health-care professionals should investigate the possibility of ED by appropriate and sensitive questioning during the consultation.

Where the presence of ED has been established, it is important to gain as much information as possible regarding any underlying pathologies before embarking on a treatment programme. In addition to vascular disease, there may also be other organic causes of ED, e.g. chronic illnesses in general, such as severe angina, heart failure, side-effects of drugs, alcohol abuse, benign prostatic hyperplasia, prostate or other cancer, thyroid dysfunction, diabetes or abnormal testosterone levels. When clinically relevant, levels of testosterone and prostate-specific antigen should be measured in patients with a view to possibly addressing the ED by treating the underlying condition, e.g. by administering testosterone supplements to a patient with hypogonadism. The ED may also have a psychogenic component that might respond to psychotherapeutic techniques. A suggested treatment algorithm for patients presenting with ED is shown in Figure 2.²¹

A wide variety of drugs has been associated with the development of ED, including antihypertensive agents, particularly β-blockers and thiazide diuretics.²² The importance of iatrogenic ED may increase in future, as more aggressive treatment of cardiovascular risk factors in patients with vascular disease could lead to a higher proportion of patients receiving treatment with pharmacological agents, which may interfere with their sexual function. Where there is a suspicion of ED arising as a side-effect of a pharmacological treatment, the drug in question may be withdrawn for 7-10 days, if clinically feasible. In a small number of patients, an improvement in erectile function may be seen, but generally most ED observed in cardiovascular disease is associated with psychological and social factors.
The drug most often used by intracavernosal injection is the prostaglandin derivative alprostadil, supplied as powder plus separate diluent in pre-loaded syringes; patients must be trained by a health-care professional to prepare and self-administer intracavernosal injections. A recent double-blind, multicentre study indicated that intracavernosal injection with alprostadil may be more effective than with moxisylyte, though it is associated with a greater risk of painful or prolonged erection. With either drug, pain or haematoma may occur at the injection site. Intracavernous injection is often inconvenient, and long-term compliance is generally low, with drop-out rates of approximately 40-70% during periods of treatment in excess of one year.

**Intraurethral administration**

An intraurethral formulation of alprostadil has been developed in order to avoid the need for intracavernous injection. Clinical trial evidence indicates that penile pain occurs in 7-8% of patients using intraurethral alprostadil and urethral bleeding in 5%. While intraurethral administration may represent a more acceptable formulation than intracavernous self-injection, it has been shown to be effective in only a quarter of a series of unselected patients who had previously failed on, or had refused, intracavernous injection therapy.

**Oral therapy**

Early attempts at oral therapy for ED largely involved administration of the non-selective α-adrenoceptor blocker phentolamine or the α1-adrenoceptor blocker yohimbine. The use of these drugs has been limited by poor efficacy and systemic tolerability, and they are not licensed for use in the UK.

**How do new oral therapies work?**

The development of sildenafill promises to revolutionise the treatment of ED. Sildenafil, taken one hour before intercourse, promotes erection by selective inhibition of the enzyme phosphodiesterase (type) 5 in the smooth muscle of the corpus cavernosum and penile resistance arteries. Sildenafil therefore facilitates the natural process of erection by augmenting the parasympathetically induced relaxation of smooth muscle within the corpora, and this enables the sinusoidal spaces to dilate, fill with blood and increase penile volume and length. Consistent with this mechanism, sildenafil is effective irrespective of the aetiology of ED, although it must be emphasised that it is not an aphrodisiac and sexual stimulation is still needed to augment this natural process.

The clinical efficacy of sildenafil has been studied extensively. The administration of sildenafil to 532 men for up to 24 weeks resulted in a significant increase in the percentage of men achieving erections suitable for sexual intercourse (72%, 80% and 85% for doses of 25, 50 and 100 mg sildenafil respectively, compared with 25% on placebo [p<0.001]). The percentage of men achieving successful sexual intercourse also increased (69% on sildenafil compared with 22% on placebo). Sildenafil is also effective in severe ED. In a meta-analysis of sildenafil trials in patients with
severe ED of various aetiologies, almost half of patients achieved penetration or maintained erections on every attempt, or on almost every attempt, versus 8% on placebo (p<0.0001) (Figure 3). In addition, almost three-quarters of men reported 'severe' adverse events (7% on sildenafil, 2% on placebo). Other adverse events were headache (16% on sildenafil, 4% on placebo), flushing (10% on sildenafil, 1% on placebo) and dyspepsia (7% on sildenafil, 2% on placebo). Other adverse events occurred sporadically with low frequency in either group. Similar proportions of patients receiving sildenafil and placebo reported 'severe' adverse events (7% vs 9%), or discontinued treatment (2.5% vs 2.3%).

The cardiovascular profile of sildenafil is of particular relevance to the administration of this drug in patients with vascular disease. As can be seen from Table 1, the overall incidence of cardiovascular adverse events on sildenafil (other than flushing), the incidence of severe adverse events, and the incidence of myocardial infarction were similar to the rates on placebo. Modest and transient decreases in blood pressure (mean changes of up to -8/-5 mmHg) have been observed in middle-aged or elderly subjects following oral administration of sildenafil in clinical trials. The maximum effect on blood pressure occurs approximately one hour post-dose, and blood pressure generally returns to pre-treatment values within four hours. In a recent study, sildenafil (20, 40 and 80 mg) was found to decrease the supine systolic and diastolic blood pressure (p<0.01). The mean decreases from baseline were 7.0/6.9 and 9.2/6.7 mmHg for the 40 mg and 80 mg doses of sildenafil respectively, although these changes were transient.

From a haemodynamic perspective, sildenafil appears to be suitable for administration to patients with ED secondary to vascular disease. Hypotension (BP less than 90/50 mmHg) and concurrent treatment with nitrates are strict contraindications for its use, as sildenafil may potentiate the hypotensive effects of nitrates, resulting in sudden blood pressure reductions.

A recent study that examined the effects of co-administering sildenafil with glyceryl trinitrate (GTN) showed that subjects were less tolerant of intravenously administered GTN during sildenafil treatment than placebo (p<0.01). This observation was based on the occurrence of a >25 mmHg reduction in blood pressure or the incidence of symptomatic hypotension. In contrast, no synergistic effects have been observed between sildenafil and the calcium channel blocker amloidipine in patients with hypertension.

Recent studies suggest that co-administration of sildenafil does not significantly affect the pharmacokinetics of amloidipine when compared with placebo (p=0.002). The concomitant use of sildenafil and other antihypertensives, including α-blockers, β-adrenoceptor blockers, diuretics, and angiotensin-converting enzyme inhibitors has not resulted in any increase in adverse events or episodes of hypotension in comparison to patients treated with sildenafil alone.

A number of deaths among patients taking sildenafil have been reported, and these have been investigated by the US Food and Drug Administration (FDA). In a period of approximately four months, the FDA received 69 verifiable reports of patients who had died after taking sildenafil, from a total number of outpatient prescriptions in excess of
3.6 million. The deaths appear to be due to cardiovascular events, and it was observed that 51 (74%) of these patients had existing cardiovascular and cerebrovascular risk factors including hypertension, diabetes mellitus or a previous cardiac history. In 12 patients, sildenafil was co-administered with nitrate (a contraindication for sildenafil) and should not therefore have been given to these patients. Furthermore, given the large numbers of patients involved, a mortality rate of this magnitude is well within the expected rate of cardiovascular deaths over this period of time in the population as a whole.

**Does effective treatment of ED improve the quality of life in patients with cardiovascular disease?**

ED is highly prevalent in patients with cardiovascular diseases, including atherosclerosis and hypertension. An association between reduced quality of sexual functioning and ischaemic coronary disease has also been observed. ED will also affect the overall quality of life in patients with cardiovascular diseases, so it is essential to manage these patients effectively in order to improve overall well-being.

Clinical improvements in ED, via the use of alprostadil, were found to improve not only the sexual functioning of these patients but also the overall mental health status, as shown by the results from a sexual functioning questionnaire. Overall mental health was found to significantly improve as a result of treatment (p<0.01). Sildenafil was also found to improve the quality of life in 940 patients, 281 of whom had organic ED and 375 of whom had ED of mixed aetiology. Significant improvements were observed in 7/11 quality of life endpoints in the psychological general well-being index (p<0.05) used in this study. Sildenafil is therefore effective for improving quality of life parameters in men with broad-spectrum ED.

**Sexual dysfunction in women**

This review does not address the problem of female sexual dysfunction. Although reports of sildenafil being administered to women with sexual dysfunction are beginning to appear, we have no detailed information regarding the extent of the problem of sexual dysfunction in women, or of its management.

**DISCUSSION**

Organic ED is a relatively common complication of vascular disease, which may intrude into every aspect of the patient's life by damaging self-esteem in affected men and causing lasting damage to relationships. The situation is exacerbated by the social taboos that prevent full and open discussion of this condition, so that ED is probably seriously underdiagnosed and undertreated. Conversely, successful management of ED is associated with gains in psychological well-being of both patient and partner. This aim is entirely consistent with the UK government's public health strategy, in that the recent Green Paper *Our Healthier Nation* stresses the need to increase quantity and quality of life.

The inconvenience of intracavernous or intraurethral pharmacotherapy has inhibited the treatment of ED for many patients. However, the discovery of sildenafil, with its convenient oral formulation, has the potential to reach patients who are not prepared to undergo intracavernous injection, and thus may change fundamentally the way ED is treated. On the one hand, the publicity surrounding the introduction of sildenafil has provided a great service to patients with ED and their physicians; the realisation that treatment is achievable has broken down the social taboos regarding acknowledgement and discussion of the condition. On the other hand, media speculation for apparently high levels of demand for sildenafil has provoked the UK government into a defensive stance concerning its provision on the grounds of cost.

The true cost of sildenafil provision in the long term is unclear and requires further study. A rigorous analysis of the cost of treating ED is hampered by the probable under-diagnosis and undertreatment of the condition. Furthermore, anecdotal evidence suggests the demand for sildenafil may have declined markedly in the US following the intense media interest surrounding its launch. In the meantime, the costs of treatment of ED secondary to vascular disease with sildenafil should be considered in the context of the overall costs of treating vascular disease and its complications, and the probable cost offset from preventing psychological health problems in impotent men and their partners. It should also be remembered that, in the UK, doctors have not been prevented from prescribing treatments for ED based on moxisylyte and alprostadil, both of which are more expensive than sildenafil at effective dosage.

**CONCLUSIONS**

Organic ED should be recognised as one of a number of clinically important and distressing sequelae of cardiovascular disease and should be treated accordingly. The introduction of sildenafil promises the first effective and well-tolerated orally active treatment for ED. Patients with ED arising from cardiovascular disease represent a well-defined patient population with a clear need for therapeutic intervention, and sildenafil should be available as a treatment option for these patients.

**REFERENCES**

1. National Institutes of Health Consensus Statement. *Impotence.* December 7, 1992.
2. Haffer R. National guidance is needed for Viagra. *BMJ* 1998; 317: 165.
3. Spector IP, Carey MP. Incidence and prevalence of the sexual dysfunctions: a critical review of the empirical literature. *Arch Sex Behav* 1990; 19: 389-408.
4. Feldman HA, Goldstein I, Hatzichristou DG et al. *Impotence and its medical and psychosocial correlates: results of the Massachusetts Male Aging Study.* *J Urol* 1994; 151: 54-61.
5. McCarron DA. Diuretic therapy for mild hypertension: the 'real' cost of treatment. *Am J Cardiol* 1984; 53: 9A-11A.
6. Rosen RC, Weist DN. Cardiovascular disease and sleep-related erections. *J Psychosom Res* 1997; 42: 517-530.
7. Newman HF, Marcus H. Erectile dysfunction in diabetes and hypertension. *Urology* 1985; 26: 135-137.
8. Bortolotti A, Parazzini F, Colli E, Landoni M. The epidemiology of erectile dysfunction and its risk factors. *Int J Androl* 1997; 20: 323-334.
9. Hirshkowitz M, Karanac I, Gurakar A, Williams RL. Hypertension, erectile dysfunction and obstructive sleep apnoea. *Sleep* 1989; 12: 223-232.
10. Anderson M, Nicholson B, Louie E, Mulhall JP. An analysis of urological erectile dysfunction as a potential predictor of occult cardiac disease. *J Urol* 1998; 159(suppl 5): 115 (abstract).
11. Wei M, Macera CA, Davis DR et al. Total cholesterol and high density lipoprotein cholesterol as important predictors of erectile dysfunction. *Am J Epidemiol* 1994; 140: 930-937.
12. Basar MM, Sargon MF, Basar H et al. Comparative study between corpus cavernosum electromyography findings and electron microscopy of cavernosal muscle biopsies in erectile dysfunction patients. *Int J Urol* 1998; 5: 252-255.
13. Greenstein A, Chen J, Miller H et al. Does severity of ischemic coronary disease correlate with erectile function? *Int J Impot Res* 1997; 9: 123-126.
14. Jonler M, Moon T, Brannan W et al. The effect of age, ethnicity and geographical location on impotence and quality of life. *Br J Hosp Med* 1995; 75: 651-655.
15. Schover LR, von Eschenbach AC. Sexual and marital relationships after treatment for nonseminomatous testicular cancer. *Urology* 1985; 25: 251-255.
16. Gheorghiu S, Godschalk M, Gentili A, Mulligan T. Quality of life in patients using self-administered intracavernous injections of prostaglandin E1 for erectile dysfunction. *J Urol* 1996; 156: 80-81.
17. Kaiser FE. Transurethral alprostadil studies: efficacy, safety and quality of life results. *Asian Pacif Soc Impot Res* 1997; 9: 518 (abstract).
18. Wilkie RJ, Glick HA, McCarron TJ et al. Quality of life effects of alprostadil therapy for erectile dysfunction. *J Urol* 1997; 157: 2124-2128.
19. Bancroft J. Impact of environment stress occupational and other hazards on sexuality and sexual behaviour. *Environ Health Perspect Suppl* 1993; 101: 101-107.
20. Meeking D, Cummings M, Shaw KM, Alexander WD. Practical guidelines for the management of erectile dysfunction. *Practical Diabetes Int* 1995; 12: 211-214.
21. Brindle GS. Pilot experiments on the actions of drugs injected into the human corpus cavernosum penis. *Br J Pharmacol* 1986; 87: 495-500.
22. Crowe M, Jones M. Sex therapy: the successes, the failures, the future. *Br J Hosp Med* 1992; 48: 474-479.
23. Buvat J, Costa P, Morlier D et al. Double-blind multicenter study comparing alprostadil alpha-cyclodextrin with moxisylyte chlorhydrate in patients with chronic erectile dysfunction. *J Urol* 1998; 159: 116-119.
24. Irwin MB, Kata EJ. High attrition rate with intracavernous injection of prostaglandin E1 for impotency. *Urology* 1994; 43: 84-87.
25. Hanash KA. Comparative results of goal oriented therapy for erectile dysfunction. *J Urol* 1997; 157: 2135-2138.
26. Gupta R, Kirschner J, Barrow RC II, Eid JF. Predictors of success and risk factors for attrition in the use of intracavernous injection. *J Urol* 1997; 157: 1681-1686.
27. Lundberg I, Olsson JO, Kihl B. Long-term experience of self-injection therapy with prostaglandin E1 for erectile dysfunction. *Scand J Urol Nephrol* 1996; 30: 395-397.
28. Porst H. Transurethral alprostadil with MUSE (medicated urethral system for erection) vs intracavernous alprostadil: a comparative study in 103 patients with erectile dysfunction. *Int J Impot Res* 1997; 9: 187-192.
29. Engel JD, McVary KT. Transurethral alprostadil as therapy for patients who withdrew from or failed prior intracavernous injection therapy. *Urology* 1998; 51: 687-692.
30. Williams G, Abbou CC, Amar E et al. Efficacy and safety of transurethral alprostadil therapy in men with erectile dysfunction. MUSE Study Group. *Br J Urol* 1998; 81: 889-894.
31. Galca G, Britanico J, Vapnek JM. Disappointing results for transurethral alprostadil in a VA impotence clinic. *J Urol* 1998; 159(suppl 5): 236 (abstract).
32. Zorgniotti AW. Experience with buccal phentolamine mesylate for impotence. *Int J Impot Res* 1994; 6: 37-41.
33. Saenz de Tejada I, Cuevas P et al. Sildenafil potentiates nitric oxide mediated relaxation of human penile resistance arteries. *J Urol* 1998; 159(suppl): 100 (abstract).
34. Goldstein I, Lue TF, Padma-Nathan H et al. Oral sildenafil in the treatment of erectile dysfunction. *New Engl J Med* 1998; 338(20): 1397-1404.
35. Steers WD. Meta-analysis of the efficacy of sildenafil (Viagra™) in the treatment of severe erectile dysfunction. *J Urol* 1998; 159(suppl 5): 238 (abstract).
36. Padma-Nathan H. A 24-week, fixed dose study to assess the efficacy and safety of sildenafil (Viagra™) in men with erectile dysfunction. *J Urol* 1998; 159(suppl 5): 238 (abstract).
37. Wagner G, Maytum M, Smith MD. Analysis of the efficacy of sildenafil (Viagra™) in the treatment of male erectile dysfunction in elderly patients. *J Urol* 1998; 159(suppl 5): 238 (abstract).
38. Morales A, Gingell C, Collins M et al. Clinical safety of oral sildenafil citrate (Viagra™) in the treatment of erectile dysfunction. *Int J Impot Res* 1998; 10: 69-74.
39. Jackson G, Benjamin N, Jackson N, Allen MJ. Effects of sildenafil citrate on human hemodynamics. *Am J Cardiol* 1999; 83(5A): 13C-20C.
40. Webb DJ, Freeston S, Allen MJ, Muirhead GI. Sildenafil citrate and blood-pressure-lowering drugs: results of drug interaction studies with an organic nitrate and a calcium channel blocker. *Am J Cardiol* 1999; 83(5A): 21C-28C.
41. Zuzman RM, Morales A, Glasser DB, Osterloh IH. Overall cardiovascular profile of sildenafil citrate. *Am J Cardiol* 1999; 83(5A): 35C-44C.
42. United States Food and Drug Administration. Postmarketing safety of sildenafil citrate (Viagra): summary of reports of death in Viagra users received from marketing (late March) through July 1998.
43. Quirk F, Giuliano F, Pena B et al. Effect of sildenafil (Viagra™) on quality-of-life parameters in men with broad spectrum erectile dysfunction. *J Urol* 1998; 159(suppl 5): 260.
44. Fava M, Rankin MA, Alpert JE et al. An open trial of oral sildenafilcitrate andropedient-induced sexual dysfunction. *Psychosom Psychosem* 1998; 67: 328-331.
45. UK Department of Health. *Our Healthier Nation: a contract for health*, London: The Stationery Office, 1998.
46. Coles J. Patients overestimated sexual appetite, say US doctors. *Guardian*, July 23 1998.