British Society for Sexual Medicine Guidelines on the Management of Erectile Dysfunction

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This guidance has been supported by unrestricted educational grants from Ardana, Bayer, Ipsen, Lilly UK, Pfizer and Schering Health Care.
The development and content of this guidance has not been influenced in any way by the supporting companies.
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Introduction

The current UK primary care contract is largely driven by evidence-based medicine, but there is no current knowledge-based guidance for the management of erectile dysfunction (ED) specifically for the UK. The major resource for reference is Health Service Circular (HSC) 1999, a non-evidence based document defining guidance for good practice, largely on economic grounds, for those patients qualifying for treatment under the UK National Heath Service. Guidance by the National Institute for Health and Clinical Excellence (NICE) is the strongest influence, but NICE can only review issues identified by the Department of Health and not by clinicians. The guidelines presented here were developed by an expert panel of the Committee of the British Society for Sexual Medicine (BSSM). The principal aim of these guidelines is to enable physicians and other healthcare professionals to manage ED in line with recent evidence, modern research and clinical opinion, while adhering to the correct interpretation of current Department of Health regulations.

A Epidemiology

ED has been defined as the persistent inability to attain and/or maintain an erection sufficient for sexual performance. Although ED is not perceived as a life-threatening condition, it is closely associated with many important physical conditions and may affect psychosocial health. As such, ED has a significant impact on the quality of life of patients and their partners [1].

Several large epidemiological studies have shown a high prevalence and incidence of ED worldwide [1-3]. In the Massachusetts Male Aging Study (MMAS), the prevalence of ED was 52% in non-institutionalized 40 to 70-year-old men in the Boston area: 17.2%, 25.2% and 9.6% for minimal, moderate and complete ED, respectively [1]. The incidence of ED, calculated from longitudinal data in the MMAS, was 26 new cases per 1000 per year [4]. A large European study of men aged 30-80 reported a prevalence of 19% [3]. A UK study of men aged 18-75 showed a rate of 39% for lifetime ED with a current prevalence of 26% [5]. Both studies showed a steep age-related increase. These epidemiological studies provide different estimates of the prevalence of ED, which can be explained by the methodology design of the different surveys. In particular, the estimates were influenced by the development of the International Index of Erectile Function (IIEF) and similar assessment tools in 1998, and minor changes in the definition of the condition. The age and the socio-economic status of the populations also differed between the studies.

B Risk factors

Penile erection is a complex neurovascular phenomenon under hormonal control that includes arterial dilatation, trabecular smooth muscle relaxation and activation of the corporeal veno-occlusive mechanism [6]. The risk factors for ED (sedentary lifestyle, obesity, smoking, hypercholesterolaemia and the metabolic syndrome), are very similar to the risk factors for cardiovascular disease.

In addition to the risk factors for ED, ED itself is a cardiovascular risk factor conferring a risk equivalent to a current moderate level of smoking. ED confers a 1.46 increased risk for cardiovascular disease [7]. The authors of this finding suggested that ED be included in future cardiovascular risk calculations [7].

C The need for ED guidelines

The prescription of newer treatment options for ED are generally within the scope of primary care practice, and pharmacological agents for oral, intracavernosal and intraurethral use are widely available. As a result, treatment strategies have been significantly modified and fewer patients require referral to urological surgeons as operative intervention has a minor role in overall ED management.

The availability of effective and safe oral drugs for ED [8-10] has contributed to an upsurge of media interest, which has led to an increase in the number of men seeking help for ED. Many of these men are then diagnosed and treated by physicians who have limited background knowledge and clinical experience of ED. This can be a problem because the proper assessment of men presenting with ED can:

- Uncover diabetes (as ED may be the first symptom in up to 20% [11])
- Detect dyslipidaemia, which might not otherwise dictate treatment according to primary coronary prevention guidelines but may be the major reversible component in the patient's ED [12]
- Reveal the presence of hypogonadism, a reversible cause of ED, which can be sometimes managed without the need for specific ED therapy and which has other long-term health implications [13].
- Identify occult cardiac disease; ED in an otherwise asymptomatic man may be a marker for underlying coronary artery disease [7].

Despite the likely presence of such underlying conditions, many men with ED may undergo little or no evaluation before treatment, particularly if they seek help from sources such as the internet. The early diagnosis and management of such cardiovascular and endocrine conditions are fundamental to the GP's role under the 2002 General Medical Services (GMS) contract. Men do not readily visit their GP with medical problems and a consultation for ED may represent an important opportunity for health intervention.

All these factors have made the development of UK guidelines for the diagnosis and treatment of ED a necessity to improve men's health.

A Initial assessment

A.1 Case history

A detailed description of the problem, including the duration of symptoms and original precipitants, should be obtained [14]. Other factors that should be identified and recorded are:

- Original precipitating factor or factors (if identified) (Table 1)
- Predisposing factors (if identified) (Table 1)
- Maintaining factors (if identified) (Table 1)
- Any subsequent investigations
- Treatment interventions along with the response achieved
- An expression of tumescence and rigidity with quality of morning awakening erections, and spontaneous, masturbatory or partner-related activity erections
- Sexual desire, ejaculatory and orgasmic dysfunction
- Previous erectile capacity
- Issues around any sexual aversion or sexual pain
- Partner issues e.g. menopause or vaginal pain.

Concurrent medical, psychiatric and surgical history should also be recorded, as should the current relationship status (single, married, in a long-term relationship, etc) and a history of previous sexual partners and relationships. Issues of sexual orientation and gender identity should also be noted. Finally, the patient should be asked about alcohol, smoking and illicit drug misuse.

The use of validated questionnaires, particularly the International Index of Erectile Function (IIEF) or the validated shorter version of the SHIM (Sexual Health Inventory for Men) (see Appendix) may be helpful to assess sexual function domains as well as the impact of treatments and interventions, but they are not a replacement for a thorough history and medical examination.

A.2 Examination

All patients should have a focused physical examination. A genital examination is recommended, and this is essential if there is a history of rapid onset of pain, deviation of the penis during tumescence, the symptoms of hypogonadism or other urological symptoms (past or present). A digital rectal examination (DRE) of the prostate is not mandatory in ED but should be conducted in the presence of genito-urinary or protracted secondary ejaculatory symptoms. Blood pressure, heart rate, waist circumference and weight should be measured [15].

A.3 Investigations

The choice of investigations depends on the individual circumstances of the patient. ED is an independent marker for cardiovascular risk and can be the presenting feature of diabetes [16], so serum lipids and fasting plasma glucose should be measured in all patients.

Hypogonadism is a treatable cause of ED that may also make men less responsive, or even non-responsive to phosphodiesterase type 5 (PDE5) inhibitors [17, 18], therefore all men with ED should have serum testosterone measured on a blood sample taken in the morning between 08.00 and 11.00 (see Section Hormone Deficiencies and ED below). Serum free testosterone is a more reliable measure of androgen status but often only total testosterone estimation is available. A reasonable estimate of free and bioavailable testosterone levels can be calculated from total testosterone, sex hormone binding globulin (SHBG) and albumin levels, using one of the many free, on-line calculators that are currently available (for example, on the ISSAM website - http://www.issam.ch/freetesto.htm). If the serum testosterone level is borderline or low it should be repeated on a further morning blood sample, together with serum FSH, LH and prolactin. Discussion with, or referral to, a specialist clinic should be considered if the results are abnormal.

Serum prostate specific antigen (PSA) should be considered if clinically indicated. It should certainly be measured before commencing testosterone and at regular intervals during testosterone therapy.

B ED and the cardiovascular system

Coronary heart disease (CHD) is associated with many of the same risk factors as ED [3]. Coronary artery disease is often just one affected site in a generalised arteriopathy that is also likely to affect the arterial inflow to the corpora cavernosum of the penis. As the penile arteries are significantly smaller than the main coronary arteries, erectile dysfunction frequently pre-dates coronary artery disease [19]. ED in men with CHD is probably related to this generalised arteriopathy that contributes to both conditions simultaneously. Psychogenic factors may also affect men with CHD; they, and their partners, may be afraid that the exertion and excitement of intercourse could precipitate further coronary episodes.

The vast majority of men with coronary heart disease can safely resume sexual activity and use ED therapies [20]. Education and appropriate counselling about sex should be given to all men with coronary heart disease, so that the majority can continue to enjoy this important aspect of their relationship. Men with unstable heart disease, a history of recent myocardial infarction (MI), poorly-compensated heart failure or unstable dysrrhythmia are exceptions.

Guidance on the assessment and management of ED in the cardiovascular patient has been published by a UK expert group [20]. The key points of this guidance are summarised below:

- The cardiac risk of sexual activity in patients diagnosed with cardiovascular disease is minimal in properly assessed and advised patients. Sexual activity is no more stressful to the heart than a number of other common daily activities (Table 2). Men in the low-risk group with stable but symptomatic cardiovascular disease should be advised that their risk of developing symptoms during sex should be equivalent to the risk when performing other routine tasks of daily living. Avoidance of vigorous sexual activity, particularly with an unfamiliar partner, may be advisable in some men.

ED in an otherwise asymptomatic man may be a marker for underlying coronary artery disease.

- All men with unexplained ED should have a thorough evaluation and any risk factors for CHD that are identified should be addressed. A man with ED and no cardiac symptoms is a cardiac patient until proven otherwise [21]
- The pro-active management of ED in the cardiovascular patient provides an ideal and effective opportunity to address other cardiovascular risk factors and improve treatment outcomes
- Men with previously-diagnosed CHD should be asked about ED as part of their routine surveillance and management; ED treatments should be offered to all who desire them
- Patients at *low cardiac risk*, as defined in Figure 1, should be managed in primary care
- Patients at *intermediate cardiac risk*, as defined in Figure 1, should be re-evaluated, in primary or secondary care as appropriate, and assigned to either the low- or high-risk group
- Patients that remain in the group defined as *high cardiac risk* should not be offered treatment for ED in primary care. Such treatment may not be absolutely contra-indicated but their assessment and management should be supervised by a specialist team, which will probably include a cardiologist
- There is no evidence that currently licensed treatments for ED add to the overall cardiovascular risk in patients with or without previously-diagnosed cardiovascular disease

C Specialised investigations

Most patients do not need further investigations unless specifically indicated (Table 3). However some patients wish to know the aetiology of their ED and should be investigated appropriately. Other indications for specialist investigations include:

- Young patients who have always had difficulty in obtaining and/or sustaining an erection
- Patients with a history of trauma
- Where an abnormality of the testes or penis is found on examination.
- Patients unresponsive to medical therapies that may desire surgical treatment for ED.

C.1 Nocturnal penile tumescence and rigidity (NPTR)

Nocturnal and early awakening erections are a normal physiological event in all men and are associated with the REM pattern of sleep. This test (see Table 4) measures a natural event, free from the confines of needles and a radiology department that may cause patient anxiety and a subsequent artificial result [22]. The disadvantage is that it often requires hospital admission.

C.2 Intracavernous injection test

This outpatient test involves the injection of prostaglandin E1 into the corpus cavernosum of the penis and to assess penile rigidity after 10 minutes [23]. Its use as a diagnostic test for ED is limited as a positive result can be found in patients with both normal and mild vascular disease [24]. The main use of this test is in the assessment of penile deformities to aid the surgical management.

C.3 Duplex ultrasound of penile arteries

This radiological investigation which measures blood flow will give an excellent assessment of the penile vasculature in response to an injection of a vasoactive agent (Table 5) [23].

C.4 Arteriography and dynamic infusion cavernosometry or cavernosography

These are highly specialised investigations that are only performed in specific circumstances as outlined in Table 6. Arteriography should only be performed when an arterial lesion has been found on Duplex Doppler evaluation. Cavernosometry is used to diagnose primary venous pathology in young men.

C.5 Penile abnormalities

Surgical problems that cause erectile dysfunction, for example, phimosis, tight frenulum and penile curvatures, should be diagnosed clinically and are usually simple to treat surgically, which results in a permanent cure of ED.

Peyronie's Disease is a disorder affecting the penis, characterised by

- A lump within the shaft of the penis
- Pain in the shaft of the penis
- Abnormal angulation of the erect penis ("bent" penis)

Not all of these features may be present; there is not usually any deformity of the flaccid penis. Peyronie's Disease can occur at any time from young adult life onwards, but most commonly occurs in men aged 40 to 60 years. It is uncommon and affects around 3% of the middle aged male population [3].

Peyronie's Disease causes variable degrees of deformity and inconvenience. Some men are barely troubled by it, whilst others may find that it makes sexual intercourse physically impossible. Many men will not require any active treatment, but all should be encouraged to seek medical advice.

The aetiology of Peyronie's disease is uncertain. In the early stages there is a painful inflammation of the tunica albuginea, which heals by forming a "plaque" that is often palpable. The plaque is usually situated on the dorsal surface of the penis and results in a dorsal penile deformity on erection. Erectile dysfunction due to Peyronie's disease can be psychogenic in nature due to embarrassment at the shape of the penis, the deformity itself may prevent sexual intercourse or in extensive disease there may be involvement of erectile tissue and an impaired erection. Medical therapy is often unhelpful and a minority of affected men undergo a surgical intervention. This involves an operation to straighten the penis either by excision of an ellipse of the tunic albuginea opposite the apex of the deformity – the Nesbit operation (however, the Nesbit operation does not improve ED) – or by an incision of the plaque and inserting a vein graft to lengthen the shorter side. Patients with significant penile deformity and an impaired erectile capacity often need a penile prosthesis inserted [25, 26].

Penile fibrosis of the cavernous muscle can occur following trauma, either direct or iatrogenic, and is also commonly found at the injection site of patients on a self-injection treatment programme. The most common cause of penile fibrosis is priapism (a painful persistent erection lasting more than four hours),

of which there are many causes (self-injection with a vasoactive agent or the use of psychiatric medications are the most frequent causes). It is important to stop the erection as soon as possible to prevent cavernous smooth muscle necrosis with subsequent healing by fibrosis [27].

D Patient/partner consultation and referral

The primary reason for referral to the clinician should be elicited. In particular, it is useful to know if the referral was initiated by the patient, the partner, both, or another health care professional. The motivating factors and expectations should be clarified as well as the intention, or otherwise, of the partner to accept any specific pharmacological, physical or psychological therapies. An understanding by the patient and partner of basic anatomy and physiology and the purpose of blood and specialist investigations is helpful. An explanation of the principles of the treatment options is valuable. Provision of information, initially by a leaflet and followed up by some other source of information (such as videos or internet pages) is valuable reinforcement for patients.

A Objectives of treatment

The primary goal of management of ED is to enable the individual or couple to enjoy a satisfactory sexual experience. This involves:

- Identifying and treating any curable causes of ED
- Initiating lifestyle change and risk factor modification
- Providing education and counselling to patients and their partners.

It is clear that ED may be associated with other causes of cardiovascular disease such as hypertension, dyslipidaemia and endothelial dysfunction. ED may be the first presentation of serious medical conditions such as diabetes or hypertension.

ED can be successfully treated, and cured in some cases, with current treatments. A management algorithm will need to not only take into account efficacy and safety of the various treatment modalities available, but also patient and partner preference and all of the factors which may influence this. In order to effectively manage patients with ED, physicians must be fully informed of all treatment options and also have these available within their clinical network.

B Lifestyle modifications

Investigations for ED should be aimed at identifying reversible risk factors. Modifications in lifestyle can greatly reduce the risk of ED and lifestyle changes and risk factor modification should accompany any specific pharmacotherapy or psychological therapy. However, pharmacotherapy should not be withheld on the basis that lifestyle changes have not been made. Lifestyle factors include psychosocial issues, adverse side effects of non-prescription drugs and the influence of any co-morbidities, including those in the partner. The potential advantages of lifestyle changes may be particularly pronounced in those with psychogenic ED, but patients with serious medical illnesses such as diabetes may also benefit from these changes, e.g., weight loss.

In MMAS, men who started physical activity in midlife had a 70% reduced risk for ED relative to those who remained sedentary, and regular exercise produced a significantly lower incidence of ED over an 8-year follow up period [28]. ED was also significantly improved in obese men in a multicentre, randomized, open-label study with 2 years of intensive exercise and weight loss (versus education only) [29]. These improvements were highly correlated with both weight loss and activity levels. Aggressive lipid lowering may also improve ED within 3 months and may significantly enhance the effects of ED therapy in patients who are failing to respond to oral therapies [30]. Despite this current evidence, further large-scale controlled prospective studies are needed to determine the effects of exercise or other lifestyle changes in prevention or treatment of ED as public awareness of such associations could be a major motivation for lifestyle alteration.

C Reversible causes of ED

C.1 Hormone deficiencies and ED

Endocrine disorders may have a significant effect on sexual function. Their resolution might also lead to the resolution of co-existing sexual dysfunction. Hypogonadism, hyperthyroidism and hyperprolactinaemia are examples of relevant disorders. The advice of an endocrinologist is necessary where there is doubt about the cause and appropriate management of the disorder.

Hypogonadism and testosterone replacement therapy

Androgen deficiency in the adult male becomes more common with increasing age [31] but its management remains controversial. As well as sexual dysfunction, androgen deficiency is associated with osteoporosis, dyslipidaemia, type 2 diabetes, metabolic syndrome and depression [32-34].

Far from being a benign consequence of ageing, hypogonadism has important and unwanted metabolic consequences, and is a significant cause of increased cardiovascular risk. Androgens act at several sites in the sexual response system: within the CNS, peripheral nitrergic nerves and corpora cavernosa. Androgen deficiency may affect sexual interest, erections and responsiveness to PDE5 inhibitors [35].

Diagnosis of androgen deficiency is based upon the identification of its non-specific features through clinical assessment and blood testing. As there is a circadian variation in testosterone release, samples for testosterone assay should be drawn in the morning, 08.00 -11.00. The assay should be repeated after two or three weeks as testosterone is also released in a pulsatile manner and the result of a single assay may be misleading [36]. Levels vary depending on the local laboratory but, in general, men with a total serum testosterone that is consistently less than 11nmol/l might benefit from a trial of testosterone replacement therapy for ED and should be managed according to current guidelines (Figure 2) [37].

There is no evidence that giving testosterone to men with ED and normal androgen levels restores or improves their erectile function. Hypogonadal men restored to the eugonadal state with testosterone replacement may experience:

- A general improvement in sexual function
- Improved erection
- Restored or enhanced responsiveness to PDE5 inhibitors [13, 18].

The cause of hypogonadism should always be sought before treatment with testosterone is initiated, but this does not mean that treatment for ED should be deferred. Prior assessment and safety monitoring should be performed according to contemporary authoritative guidelines [38, 39].

A range of well-tolerated testosterone formulations is available including:

- Oral
- Transdermal gel (Testim®, Testogel®, Tostran®)
- Transdermal reservoir patch (Andropatch®)
- Buccal pellet (Striant®)
- Long-acting injection (3-monthly) (Nebido®)
- Traditional depot injection (3-weekly) (Sustanon®, etc)
- Implanted pellets

Long-acting (three-monthly) testosterone injection or daily application of a transdermal testosterone gel is acceptable to most men.

Hyperthyroidism/hypothyroidism

Hyperthyroidism may influence erectile function by increasing SHBG production, thereby reducing free testosterone levels. Effective treatment of hyperthyroidism may resolve coexisting ED. Provided that there is no other contraindication, ED treatment may be provided until the patient is rendered euthyroid through other treatments [40].

Hyperprolactinaemia

Hyperprolactinaemia is associated with ED, loss of sexual interest and anorgasmia. It is frequently accompanied by androgen deficiency, because high prolactin levels suppress LH production and, consequently, cause hypogonadism. Hyperprolactinaemia should be excluded by blood testing in all men with reduced sexual interest. Moderate elevation of prolactin levels (<1000 mU/l) is unlikely to cause ED [41].

Hyperprolactinaemia can have many causes:

- Medical and physical stress
- Drugs (notably major tranquilisers and anti-mimetics)
- A small proportion of men with hyperprolactinaemia will have a prolactin-secreting pituitary tumour – identification of these cases is important
- Chronic renal failure.

A misdiagnosis of hyperprolactinaemia can result from the presence of macroprolactin or 'big-big' prolactin. This is a heterogenous complex of prolactin and immunoglobulin and is the cause of apparent hyperprolactaemia in about 20% of cases [42]. It is measured by all commercial immunoassays to a greater or lesser extent and its presence should be considered in all cases of mild to moderate hyperprolactinaemia. It is diagnosed by re-assaying after precipitation with polyethylene glycol.

Patients with persistent and unexplained hyperprolactinaemia should be referred to an endocrinologist.

C.2 Post-traumatic arteriogenic ED in young patients

Penile revascularisation involves harvesting of the inferior epigastric artery and anastomosing it to either the dorsal vein or artery of the penis to increase arterial inflow to the corporal bodies. It is particularly useful in patients who have an isolated arterial lesion usually due to pelvic or perineal trauma which has been diagnosed on a selective arteriogram. These patients should be young and have no other arterial or neurological risk factors. With careful selection, success rates of 65% can be achieved [43].

Bicycle riding for more than 3 hours per week has been described as an independent risk factor for ED. The mechanism is postulated as related to the rider interaction with the saddle. This may produce a neurapraxia, which is occasionally persistent but usually reversible or vascular endothelial injury and vasculogenic ED. Questions about bike riding should be considered, especially in young men with no clear cause of ED [44].

There is no role for venous ligation unless an isolated venous anomaly can be demonstrated on cavernosography [45].

C.3 Drug-induced ED

A wide range of drugs has been implicated in ED (Table 7). In many cases, the evidence for drugs having a direct causal relationship with some form of sexual dysfunction is relatively poor (but the patients often blame the drugs). There are very few randomised, placebo-controlled studies looking specifically at the sexual side effects of drugs and most reports of adverse events arise from clinical trials, post-marketing surveillance, consumer surveys, isolated case reports and anecdote.

Cardiovascular drugs and ED

In patients with hypertension and CHD, their ED is usually caused by the medical condition [19]. Patients frequently blame the medication, particularly if there seems to be a temporal relationship. Stopping the offending drug is rarely effective, unless an early therapy switch is made when a definite relationship is found [46]. Thiazides and non selective beta-blockers have been shown in a number of studies to be associated with ED and the SPCs of both classes of drug state these warnings [47]. In a recent study, atenolol was associated with fewer sexual attempts, lower level of serum testosterone after 16 weeks and a rate of ED of 18% compared with 0% with the angiotensin II inhibitor valsartan [48]. ACE inhibitors and calcium channel blockers, in normal doses, are unlikely to be a major contributory factor to the development of ED [49]. Three trials suggest that angiotensin II inhibitors may actually improve sexual function [48, 50, 51] and may be the drug of choice in the ED patient newly diagnosed with hypertension [46]. Prescribing cheaper drugs is usually less cost effective if more expensive therapy is required to reverse the sexual adverse event. It is strongly recommended by this and other panels that physicians routinely ask about sexual function before initiating treatment for hypertension [46].

Drugs may affect sexual response in a number of ways:

- Those that cause sedation may affect sexual motivation and, indirectly, cause ED
- Those that affect cardiovascular function, such as antihypertensive agents, may act centrally and may also affect penile haemodynamics
- Some drugs affect endocrine parameters – anti-androgens and oestrogens may affect both sexual desire and erection
- Drugs that cause hyperprolactinaemia, such as phenothiazines, may also affect sexual desire and erection.

Physicians are often faced with a difficult decision; withdrawing or changing a drug suspected of causing sexual dysfunction may reduce ED, but can potentially compromise the treatment of another important condition. It is important to remember that the condition being treated, as well as the drugs being used to treat it, can often cause sexual dysfunction. There is little good-quality evidence that modifying drug therapy alleviates sexual dysfunction but expert opinion is that it helps sometimes. Where there is a strong temporal relationship between starting a drug and development of a sexual side effect, it seems more likely that there will be a causal relationship. If the patient has been on a drug for many years and the sexual problem has only recently developed, the causal relationship seems less likely. It is important not to compromise the effective management of other important conditions when attempting to identify or resolve suspected drug-induced ED. Physicians should be aware that some men may stop medication without telling them, particularly when pack labelling indicates that it may cause ED.

C.4 Partner sexual problems and ED

Men with ED should, ideally, be assessed with their partner so that co-existing sexual problems in the partner can be identified and addressed. Where this is not possible, enquiry should always be made about partner sexual health and satisfaction. It may be essential to address a partner sexual function problem in order to effectively treat ED [52].

Partners with aversion to sex, low desire [53], arousal problems and sexual pain disorders may not allow the man to have sex with them [54]. Some men may present this to their doctor as an erection problem, either from a genuine belief that this is the cause of their dissatisfaction and, almost certainly incorrectly, that improving their erection will resolve their partner's problem. Sometimes it is because it is less embarrassing for the man to blame his erection than to admit that their partner does not want to have sex with them.

Female partners with sexual function problems should be offered appropriate professional care. As in men with ED, there are often several factors contributing to their problem including biomedical or psycho-socio-cultural problems, or problems related to their interpersonal relationship. A relatively common problem experienced by females over 50 years of age whose partners have ED is oestrogen deficiency-related vaginal atrophy. This is usually straightforward to treat and highlights the importance of always considering partner issues when treating ED.

C.5 Psychosexual/relationship therapy

Psychosexual therapy either alone or alongside the couple's relationship therapy is indicated particularly where the patient and or partner identify significant psychological contribution to the problem or as perpetuating the problem.

As sex is a subjective experience, it is inevitable that all couples affected by sexual dysfunction have at least some psychological component to their problem. Almost all couples will benefit from simple sex education, and clinicians treating ED should be able to provide this. Helping men to achieve an understanding of their physiological sexual response, the effects of ageing, concurrent disease and medication may also be important. An improved understanding of the similarities and differences in sexual interest and response in men and women may be beneficial. The clinician should be able to provide simple behavioural advice regarding foreplay, sexual activity and on the integration of medication into the couple's sexual behaviour.

Formal cognitive-behavioural interventions should be provided by appropriately trained and experienced therapists. They may be of some benefit in all men but are probably best used in men with a predominantly psychogenic component in ED. Such interventions are less likely to be beneficial in men with complete ED of predominantly organic aetiology. Concurrent use of medication, such as PDE5 inhibitors, is not precluded in men engaged in cognitive-behavioural therapy, and a combined pharmacotherapeutic-psychotherapeutic approach may be more effective than using these interventions individually or consecutively [55].

C.6 Treatment of ED after radical prostatectomy

A very high proportion of men develop acute ED after radical prostatectomy. This is thought to be predominantly due to neural damage incurred during surgery. The cavernous nerves that modulate penile vascular smooth muscle tone are found in the neurovascular bundles adjacent to the prostate gland and, even if not transected, are susceptible to trauma during radical prostate surgery. Where a nerve-sparing procedure has been performed, there is often a gradual improvement in neural function, but this improvement may take up to two years.

Consequently, men with probable neurogenic ED following radical prostatectomy have, initially at least, healthy cavernosal vascular smooth muscle and structural integrity. Provided that this is maintained, they should recover erectile function concurrently with their cavernous nerve function. However, in men who develop persistent ED after surgery, cavernosal smooth muscle is gradually replaced by collagenous tissue [56]. This change in cavernosal structure may be what leads to persistent ED in some men, even though they have had nerve-sparing surgery. In these men, there is inadequate healthy cavernosal smooth muscle to facilitate erection.

Early introduction of pharmacotherapy may improve the rate of recovery of normal erectile function after nerve-sparing surgery. One study of such an 'erection rehabilitation programme' required men to routinely attain erections three times a week by using drug therapy – 18 months after surgery, 52% of men participating in the programme had normal erections (not requiring the use of any ED therapy), compared with only 19% of men not participating in the programme [57]. Another study used nightly sildenafil versus placebo for 26 weeks with 27% compared with 4% regaining normal spontaneous erections [58]. Rehabilitation programmes for men after radical prostatectomy may offer the prospect of a 'cure' for ED, but at present the efficacy of such programmes are unproven.

D First-line treatment

D.1 Oral pharmacotherapy – PDE5 inhibitors

Drugs that inhibit PDE5 increase arterial blood flow, which leads to smooth muscle relaxation, vasodilation and penile erection [59]. Three potent selective PDE5 inhibitors have been approved by the European Medicines Agency (EMEA) and the US Food and Drug Administration (FDA) – sildenafil (Viagra®), tadalafil (Cialis®) and vardenafil (Levitra®). These medications have proven efficacy and safety both in non-selected populations of men with ED and in specific sub-groups of patients (for example, men with diabetes and those who have had a prostatectomy) [60-62]. The major difference in these drugs is that sildenafil and vardenafil are relatively short-acting drugs, having a half life of approximately 4 hours, whereas tadalafil has a significantly longer half life of 17.5 hours. PDE5 inhibitors are not initiators of erection but require sexual stimulation in order to facilitate an erection [60-62]. It is currently recommended that patients should receive 8 doses of a PDE5 inhibitor with sexual stimulation at maximum dose before classifying a patient as a non-responder.

Published studies on all three PDE5 inhibitors suggest that 75% of sexual attempts result in successful intercourse (SEP 3 – the ability to maintain an erection for successful intercourse). Data from the Global Assessment Question (GAQ) are usually higher than this 75% figure but these values should be viewed with caution, as improved erection does not necessarily mean successful intercourse. Quoted efficacy rates are lower for patients with diabetes (50-55%) and after nerve-sparing radical prostatectomy (37-41%) for all three drugs [63-66]. Differences between the selection criteria in studies of the three drugs (particularly in the way patients previously treated with sildenafil were included or excluded) prevent direct comparison of the efficacy of the three drugs.

Interaction of PDE5 inhibitors and food, particularly fatty food, is greatest with sildenafil and least with tadalafil [60-62]. No interaction with alcohol, up to concentrations of 0.5 to 0.6mg/kg, has been observed with any of the three drugs [60-62]. Recent media reports have linked PDE5 inhibitor use to a small increase in the incidence of non-arteritic anterior ischaemic optic neuropathy (NAION) currently all three PDE5 inhibitors mention NAION as a warning on their SPCs [60-62, 67]. However, as risk factors for NAION include age over 50, heart disease, diabetes, hypertension, dyslipidaemia, nicotine use and a congenital predisposition, patients at risk of NAION would be the patients more likely to suffer from ED and require a PDE5 inhibitor [67].

Non-responders to PDE5 inhibitors

Approximately 25% of patients do not respond to PDE5 inhibitors. Patients should be exposed to a minimum of 4 (preferably 8) of the highest tolerated dose of at least two drugs (taken sequentially, not concurrently) with adequate sexual stimulation. Patients should be followed up, ideally within 6 weeks of commencing therapy. So-called failure may be due to suboptimal counselling at the initial consultation, which should aim to ensure that the patient understands how to take the tablets properly and to return to the doctor if they are dissatisfied. Cost of drug therapy and reluctance of the partner are frequent reasons for unsatisfactory response [68]. Several measures are described in the literature to salvage patients, clearly identified as non responders:

- Re-counselling on proper use
- Optimal treatment of concurrent diseases and frequent re-evaluation for new risk factors
- Treatment of concurrent hypogonadism. It is well established that testosterone regulates the expression of PDE5 and the responsiveness of PDE5 inhibitors in the corpus cavernosum [69, 70] and several studies have shown that patients can be salvaged by treating low or low-normal levels of testosterone [71, 72]
- Occasionally patients may respond to one drug when another has failed [73]
- More frequent dosing regimes [73, 74]. In clinical trials, patients were allowed up to daily dosing whereas in clinical practice medication is often restricted.

Choice or preference between the different PDE5 inhibitors

The availability of three PDE5 inhibitors has led to several preference studies, most of which had questionable designs and methodology. Ideally such studies should be conducted on treatment naïve patients, with adequate treatment periods, suitable washout periods, robust outcome measures and statistics, and preferably be double blinded. Double blinding is a problem when all three drugs are well recognised, and one has a half life of 17.5 hours and the other two 4 hours.

Three recent studies are worthy of mention. Eardley et al [75] showed a patient preference for tadalafil (71%) versus sildenafil (29%) in an open-label cross-over study of naïve patients with 8 weeks of dose optimisation followed by 4 weeks of assessment. The major reason for preference was the ability to get an erection long after taking the drug. Efficacy of both drugs was very similar. Rubio-Aurioles et al [76] compared vardenafil with sildenafil in a double-blind, cross-over study with fixed doses of 20mg versus 100mg in non-naïve patients. Despite finding a 38.9% versus 34.5% preference in favour of vardenafil with 26.6% expressing no preference, efficacy was similar for both drugs. Tolra et al [77] compared all three PDE5 inhibitors in an open-label study in treatment-naïve patients and found 52% favoured tadalafil, 28% sildenafil and 20% vardenafil, with the possibility of an erection well after taking the drug being the main reason for preference. Once again efficacy rates were similar for all three drugs.

Safety of PDE5 inhibitors and drug interactions

Over 30 million men have taken sildenafil since 1998, with experience of the two newer PDE5 inhibitors reaching 8 million and 5 million. There is no evidence that PDE5 inhibitors significantly increase the rate of myocardial infarction. PDE5 inhibitors do not adversely affect total exercise time or time to ischaemia during exercise testing in men with stable angina. In fact, all three PDE5 inhibitors may improve the time to ST elevation [20, 21, 60-62].

Organic nitrates (e.g., nitroglycerine, isosorbide mononitrate, isosorbide dinitrate), other nitrate preparations used to treat angina such as nicorandil and recreational drugs such as amyl nitrate (poppers) are absolute contraindications with PDE5 inhibitors. Combined use could result in cGMP accumulation and unpredictable falls in blood pressure and, potentially, catastrophic hypotension [60-62]. Interactions between organic nitrates and PDE5 inhibitors vary with different drugs. For example, if sildenafil or vardenafil are taken and the patient develops chest pain, nitroglycerine must be withheld for at least 24 hours; if this happens with tadalafil then nitroglycerine must be withheld for at least 48 hours. If the patient develops angina while taking a PDE5 inhibitor, nitroglycerine should only be administered under close medical observation. Nitrates are usually prescribed for the treatment of angina; unlike calcium channel blockers and beta-blockers, they convey no prognostic benefit with regard to the prevention of further coronary episodes [20]. As such, it is often appropriate for the physician to review their use in an affected individual and consider their replacement with other anti-anginal agents [78]. In addition, some men may have been given a supply of glyceryl trinitrate tablets or spray upon their discharge from hospital following a coronary event, even though they do not have angina. They will often have been told to carry it with them at all times and will have dutifully obeyed these instructions for many years, regularly refilling their prescription from their family physician, even though they never use the drug. Men who never use this medication should be reviewed by their cardiologist or GP and, if appropriate, be advised that they do not need to carry nitrate therapy, thus enabling them to have PDE5 inhibitors as an ED treatment option [78].

Co-administration of PDE5 inhibitors with antihypertensive agents may result in a small additive drop in the blood pressure, which does not usually cause significant orthostatic hypotension. The reduction in blood pressure is 8.4/5.5 mmHg for sildenafil, 7/8 mmHg for vardenafil and 1.6/0.8 mmHg for tadalafil, when the drugs are taken on an on-demand basis [60-62]. Generally, the adverse event profile of PDE5 inhibitors is not worsened by the concomitant use of antihypertensive medicines [60-62].

Alpha-blockers have some interaction with PDE5 inhibitors. Under some conditions, this interaction may result in orthostatic hypotension, and PDE5 inhibitors should be used with caution in patients receiving alpha-blockers. According to the drug SPCs, the use of tadalafil with alpha-blockers is not recommended. Vardenafil should only be initiated at the lowest dose, only if the patient is stabilised on alpha-blocker therapy, and dosing of the two drugs should be separated by at least 6 hours (vardenafil can be used at any time with tamsulosin). Sildenafil should only be initiated at the lowest dose, only if the patient is stabilised on alpha-blocker therapy, and dosing of the two drugs should be separated by at least 4 hours. These interactions are more pronounced when PDE5 inhibitors are given to healthy volunteers not previously taking alpha blockers and are rarely of clinical significance when the drugs are not started simultaneously [60-62]. The SPCs for alpha-blocking drugs do not carry warnings for use with PDE5 inhibitors.

Adverse events

Safety data for PDE5 inhibitors are shown in Table 8.

D.2 Vacuum erection devices

The principle of vacuum erection devices is simple. A cylinder is placed over the penis, air is pumped out with an attached pump and the resulting tumescence is maintained by a constriction ring around the base of the penis.

- Vacuum devices are highly effective in inducing erections regardless of the aetiology of the ED [79, 80]
- Reported satisfaction rates vary considerably from 35% [81] to 84% [82]
- Long term usage of vacuum devices also varies but is considerably higher than for self-injection therapy
- Most men who are satisfied with vacuum devices continue to use them long term [81]
- Adverse effects include bruising, local pain, and failure to ejaculate. Partners sometimes report the penis feels cold
- Serious adverse events are very rare but skin necrosis has been reported

Vacuum devices are contraindicated in men with bleeding disorders or those taking anticoagulant therapy. They work best if the man and his partner have a positive attitude to them and sufficient time has been spent demonstrating their use. They can be prescribed under Schedule 2 and represent a very cost-effective way of treating ED, even though initial costs are high.

E Second-line treatment

E.1 Intracavernous injection therapy

Intracavernous injection therapy is the most effective form of pharmacotherapy for ED and has been used for more than 20 years [83]. Providing the blood supply is good, an excellent result can be achieved in most men. It does not require an intact nerve supply and can therefore be highly effective after spinal cord injuries and after major pelvic surgery such as after radical prostatectomy. However, because of the invasive nature of the procedure it is not acceptable to some patients and their partners, and this may result in poor long-term compliance in those who do try it [83, 84]. Compliance may be a particular problem if the procedure is not explained clearly and fully at first consultation and if adequate support and follow-up visits are not provided.

Alprostadil

Alprostadil (Caverject™, Viridal™) was the first and until recently was the only licensed drug approved for intracavernous ED treatment.

Alprostadil can be used in doses from 5-40 µg. The erection occurs typically 5-15 minutes after penile injection and frequently last 30-40 minutes, although the duration can be dose dependent. Two or three visits are usually required to ascertain the correct dosage and teach the patient the technique. In patients with limited manual dexterity and in some other groups, the partner may be taught the technique. Partner participation in the consultation and training programme can be valuable and improve long-term compliance. Some patients prefer to use an automatic injection pen that avoids a view of the needle and can help with the fear of penile puncture.

Efficacy and safety of alprostadil is summarised below:

- Efficacy rates are high – around 70-80% in the general ED population and higher in those without vascular disease [85]
- Once properly taught the procedure has a high reproducibility and high satisfaction rate for both patients and their partners
- Long-term compliance rates however can be low with as many as 50% of patients stopping in the first 2-3 months [83, 84]
- Careful counselling in the early stages with an easy availability of advice in the first few weeks can improve compliance
- Adverse effects of intracavernous alprostadil include post-injection penile pain (in up to half patients after at least some of their injections) [83, 84]
- Other complications include priapism (1%) and fibrosis (2%) [83, 84]

- Systemic side effects are uncommon; the most common being mild hypotension when using higher doses
- Contraindications are few but include a history of hypersensitivity to alprostadil, a risk of priapism and bleeding disorders (for management of priapism, see section E.2).

Combination therapy

Papaverine (20-80 mg) was the first drug to be used widely for intracavernous injection therapy. It is still used 'off-license' in some patients as monotherapy but it has more complications than alprostadil (more fibrosis and priapism but less pain) [86]. However, it may be possible to use papaverine in combination with alprostadil due to their different modes of action – this may reduce side effects by using a lower dose of each drug.

Phentolamine (0.25-2mg) [87] is another drug that is effective in combination with alprostadil but has weak efficacy if used alone. Triple therapy (with phentolamine, papaverine and alprostadil) has been described as effective in some patients but it is not approved for the treatment of ED [88, 89]. Fibrosis is more common with the addition of papaverine to alprostadil regimens but penile pain is reduced by the lower dose of alprostadil.

The combination of alprostadil mentioned above or combination injections with oral PDE5 inhibitors, whilst not approved, can be effective in men not responding to injection therapy alone. This can be discussed with patients before consideration of penile prosthesis surgery in carefully selected patients.

Aviptadil and phentolamine injection

Recently a combination of aviptadil (formerly known as vaso-intestinal polypeptide) and phentolamine (Invicorp™) was approved and licensed in several European countries for ED. Phentolamine mesilate is a short-acting alpha-adrenoreceptor antagonist that also has a direct effect on smooth muscle, causing relaxation [90]. Aviptadil has been shown to have a role in local nervous control of smooth muscle activity in the genito-urinary tract and is a possible neurotransmitter in penile erection [90]. The fact that normal erections require an adequate arterial inflow and an efficient veno-occlusive mechanism provides the rationale for using aviptadil/phentolamine combination. Key facts about aviptadil/phentolamine are:

- Clinical trials have shown its effectiveness in ED from a variety of causes with a notably low incidence of post-injection pain [91]
- A direct comparator, crossover trial has shown similar efficacy to alprostadil [92]
  This study also showed that compared with alprostadil, significantly fewer aviptadil/phentolamine injections were associated with pain
- Unlike alprostadil, the aviptadil/phentolamine combination usually needs to be accompanied by some form of sexual stimulation in order to produce an optimal erection, which may be preferred by some patients
- Adverse events include mild or moderate facial flushing and rare cardiovascular events such as dizziness, tachycardia and palpitations [91].

E.2 Treatment of prolonged erection and priapism

Patients are advised to consult their doctor or in most circumstances the emergency department of a hospital if they have an erection that lasts longer than 4 hours [93]. This is to avoid damage to the intracavernous muscle and blood vessels which could result in permanent ED. Patients should be advised initially to take light exercise such as going up and down stairs but if the prolonged erection persists, a 19-gauge butterfly needle should be inserted into the corpora cavernosa to aspirate blood and thereby decrease intracavernous pressure [93]. This simple method can be effective in many cases, particularly if done early enough. Further improvements can be gained by 'washing out' the corpora by injecting in saline and then withdrawing the saline and blood together. If this is not effective or if the penis becomes rigid again, phenylephrine or adrenaline injection may be effective, but requires very close monitoring of blood pressure and is best performed in the Urology Department of a hospital. Appropriate doses are adrenaline 10-20 µg or phenylephrine 250-500 µg. Dilution (1:10) of this in N.Saline and then using this as a cavernosal washout can be safer than direct injection. A lower dose of alprostadil should be used for any subsequent injections [94].

E.3 Intraurethral alprostadil

A formulation of alprostadil in a medicated pellet (MUSE™) is approved for the treatment of ED [94]. Patients are told to void to make sure the urethra is moist, the pellet is inserted into the urethra via a small applicator and the penis massaged. Alprostadil is delivered into the penile urethra and is absorbed through the epithelium into the venous channels of the corpus spongiosum. It reaches the vascular smooth muscle of the corpora cavernosum by retrograde flow through emissary veins, encouraged by penile massage at the time of administration. Use of MUSE results in erections in approximately 30-60% of patients [95-97].

- In clinical practice only the higher dosages of 500 µg and 1000 µg are effective [98]
- Application of a constriction ring at the base of the penis may help in some patients, but currently this is not available in the UK
- Side effects include penile pain (30-40%) and dizziness (2-10%)
- Penile fibrosis and priapism are rare (<1%)
- Urethral bleeding and urinary infection may result from faulty technique [83]

This is a less invasive but also less effective treatment than intracavernosal injection therapy.

F Third-line treatment

F.1 Penile prosthesis

Penile prostheses should be offered to all patients who are unwilling to consider, failing to respond to, or unable to continue with medical therapy or external devices. All patients and their partners should be counselled pre-operatively, see and handle all the available devices and if possible speak to other patients who have had surgery.

Penile prostheses are particularly suitable for those with severe organic ED, especially if the cause is Peyronie's disease or post priapism. All patients should be given a choice of either a malleable or inflatable prosthesis. Satisfaction rates of 89% were shown in one series of 434 implants. High rates are mainly due to the improved mechanical reliability of the new devices [99, 100]. Five-year survival of these devices is 93% but a revision rate of 7% per year can be expected [99, 100].

The advantages of penile prosthesis include:

- Long-term efficacy with a high satisfaction rate
- No need for medication
- Improved ability to lead a normal sexual life.

However, patients must be medically fit for surgery and accept potential complications of infection, erosion and mechanical failure which may need re-operation. The initial cost is high but manufacturers do offer a lifetime guarantee.

G Other therapies

Efficacy rates with apomorphine (Uprima®) are lower than those reported for PDE5 inhibitors, ranging from 26 to 55% [101-104] and this product has now been discontinued in the UK. A number of other agents have been used for ED, with varying degrees of success. None of the following products is licensed for the treatment of ED and they should not be used routinely:

- Yohombine
- Delaquamine
- Trazodone
- L-arginine
- Red Korea
- Ginseng
- Oral limaprost
- Oral phentolamine and nitroglycerine
- Papaverine
- Minoxidil topically.

Health Service Circulars: HSC/115 [105], HSC/148 [106] and HSC/177 [107] from 1999 explain the Secretary of State for Health's decisions about the availability of "impotence" treatments from GPs on NHS prescriptions and these came into place on 1 July 1999. ED associated with the following medical conditions were deemed to qualify for prescription at NHS expense (which shall be endorsed SLS). The regulations do not state that these conditions must cause the ED:

■ Diabetes ■ Multiple sclerosis ■ Parkinson's disease ■ Poliomyelitis ■ Prostate cancer ■ Prostatectomy (including TURP) ■ Radical pelvic surgery ■ Renal failure treated by dialysis or transplant ■ Severe pelvic injury ■ Single gene neurological disease ■ Spinal cord injury ■ Spina bifida

There are two qualifiers:

1. In addition, a patient qualifies if they were receiving a course of NHS drug treatment on 14th September 1998.
2. The other qualifier is if patients are suffering "severe distress" on account of their ED.

The decision about referral for specialist services is a matter of the clinical judgement of the GP. The Department of Health recommends referral when the GP is satisfied that the man is suffering from impotence and that this impotence is causing him (there is no mention of the partner) severe distress. To determine a diagnosis of severe distress it is recommended that the following should be taken into account:

■ Significant disruption to normal social and occupational activity

■ Marked effect on mood, behaviour, social and environmental awareness

■ Marked effect on interpersonal relationships.

It could be argued that most ED patients, by definition, suffer a marked effect on interpersonal relationships by being unable to have a satisfactory sexual relationship, and many men (if questioned) state that they perceive their relationship or marriage to be threatened. It would be difficult to argue that such a perception did not constitute a marked effect on the central interpersonal relationship in that man's life [108]. For example, Fugl-Meyer et al reviewed 662 Swedish men referred to a specialist clinic with ED using the LISAT 11 checklist and found manifest distress in 88%, compared with 5% of men in an age-matched control group without ED [109]. After treatment 36% had no distress, 40% remained mildly affected and 24% unchanged.

Document HSC/177 is the only document that makes reference to the concept of 'severe distress' and there is no other resource for information. If the wording of these documents is literally interpreted, many more than those who currently receive ED treatment on the NHS would be entitled to this treatment.

The ongoing prescribing of medication for severe distress is the responsibility of the secondary care provider delivered by service agreements that are commissioned by Health Authorities and Primary Care Groups. Local agreements will be necessary to determine treatment and referral pathways. The wording of HSC/177 has been interpreted differently across the UK. The strict interpretation involves the hospital continuing ongoing prescribing for life, with no additional financial resources and the need to institute repeat prescribing structures. Many trusts have decided that they simply cannot absorb these costs and have declined to provide a service.

It is difficult to see how these standards of care can be applied as new drugs become available for other sexual problems, particularly for women.

Frequency of treatment

HSC/148 states that the department advises doctors *that one treatment per week will be appropriate for most patients*. If the GP, in exercising their clinical judgement, considers more than one treatment a week is appropriate, they should prescribe that amount on the NHS. The GP must not charge for private scripts or mix private and NHS scripts.

The reference for once per week treatment was the 1990 sexual attitudes and lifestyle study [110]. It is of interest that this and other studies showed that the frequency of sexual activity was higher in younger patients [111], and that if patients with ED are excluded then the frequency for 'non-ED couples' is twice per week. In clinical trials, patients were given significantly more medication to produce the reported responses, and therefore, restrictive prescribing would probably result in lower efficacy rates and lower levels of patient and partner satisfaction.

CONCLUSION

There is now overwhelming evidence that ED is strongly associated with cardiovascular disease, such that newly presenting patients should be thoroughly evaluated for cardiovascular and endocrine risk factors, which should be managed accordingly. Patients attending their primary care physician with chronic cardiovascular disease should be asked about erectile problems. There can no longer be an excuse for avoiding discussions about sexual activity due to embarrassment.

Sexual activity is associated with benefits to cardiovascular health and improved well being. A certain degree of cardiovascular fitness is required for sexual activity, irrespective of the type of treatment required to make intercourse possible. The major risk in sexual activity is therefore from the disease not the treatment. Many cardiac patients may be attempting intercourse without the necessary fitness and yet this is rarely discussed with the physician.

The availability of effective oral medication has revolutionised the treatment of ED but patients are still not being diagnosed and treated. These drugs need to be prescribed with appropriate advice and support, and with adequate doses being given for the appropriate duration.

Oral therapies are effective in approximately 75% of patients, and for non-responders second and third line therapies can be offered.

There is considerable evidence that adequate levels of testosterone are required for ED therapies, especially PDE5 inhibitors, to achieve maximal response and in many cases normalisation of testosterone levels can restore erectile function.

Current Department of Health guidance on good practice restricts access to patients with certain medical conditions and restricts the frequency of medication frequently compromising optimal management.

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APPENDIX

Table 1. Pathophysiological causes of ED (from [112])

Predisposing	Precipitating	Maintaining
Lack of sexual knowledge	New relationship	Relationship problems
Poor past sexual experience	Acute relationship problems	Poor communication between partners
Relationship problems	Family or social pressures	Lack of knowledge about treatment options
Religious or cultural beliefs	Pregnancy & childbirth	Ongoing physical or mental health problems
Restrictive upbringing	Other major life events	Other sexual problems in the man or his partner
Unclear sexual or gender preference	Partner's menopause	Drugs
Previous sexual abuse	Acute physical or mental health problems	
Physical or mental health problems	Lack of knowledge about normal changes of ageing	
Other sexual problems in the man or his partner	Other sexual problems in the man or his partner	
Drugs	Drugs	

Table 2. MET equivalents to sexual activity

Daily activity	METs
Sexual intercourse with established partner	
lower range ('normal')	2-3
upper range (vigorous activity)	5-6
Lifting and carrying objects (9-20 kg)	4-5
Walking one mile in 20 minutes on the level	3-4
Golf	4-5
Gardening (digging)	3-5
DIY, wallpapering, etc	4-5
Light housework, e.g. ironing, polishing	2-4
Heavy housework, e.g. making beds, scrubbing floors	3-6

Table 3. Further investigations

Investigation	Rationale	Indication
Intracavernous injection test		Assessment of penile deformities
Colour Doppler ultrasound	Assesses vascular integrity	Young patients being considered for surgical intervention
Phalloarteriography	To clarify vascular abnormality	Arterial abnormality found on Doppler ultrasound
Cavernosometry/ cavernosography	Assesses venous occlusive mechanism	When primary venous leakage suspected in young man
Nocturnal penile tumescence	Assesses nocturnal erections when smooth muscle relaxed. Reduces false positive investigation rate	When other investigations inconclusive or prior to surgery

Table 4. Nocturnal penile tumescence

Method	Rigiscan with 2 circular strain gauges applied to penis – 1 base, 1 tip
	2 nights recording
	Single room, quiet surroundings
Normal values	>70% rigidity
	3-4 erections lasting >10 minutes
Uses	To confirm neurogenic ED
	For medico-legal cases
	To exclude false-positive results from other investigations
	To confirm normal erectile function

Table 5. Colour Doppler Duplex Ultrasound

Method	Inject 20 ug PGE_1	
	Monitor vascular response between 2–10 minutes	
Normal values	✦ max (maximum systolic velocity) > 25-30 cm/s	
	✦ min (end diastolic velocity) < 5 cm/s	
	Arteriogenic insufficiency	✦ max < 25 – 30 cm/s
	Veno-occlusive dysfunction	✦ max > 30 cm/s
		✦ min > 5 cm/s
Uses	Assesses arterial integrity	
	Assesses veno-occlusive mechanism	
	Vascular anomalies e.g., fistulae	
	Priapism	
	Peyronie's plaque	

Table 6. Arteriography and cavernosometry/cavernosography

Phalloarteriogram		
Method	Femoral artery puncture	
	Selective arteriography of pudendal vessels	
Uses	To confirm arterial lesion diagnosed by Doppler	
	As part of embolisation in high flow priapism	
	When penile revascularisation considered	
Cavernosometry/cavernosography		
Method	19G butterfly needle in each corpus cavernosus	
	Inject 20 ug PGE_1	
	Infuse with NaCl via infusion pump	
	Monitor intracavernosal pressure at known infusion rate	
Values	Normal intracavernosal pressure >90 mmHg	
	Normal infusion to maintain erection < 20 ml/min	
	Flow to maintain >20 ml/min = veno occlusive dysfunction	
Uses	To confirm VOD	
	Cavernosography:	✦ Identify sites of venous leakage
		✦ Assess degree of corporal fibrosis

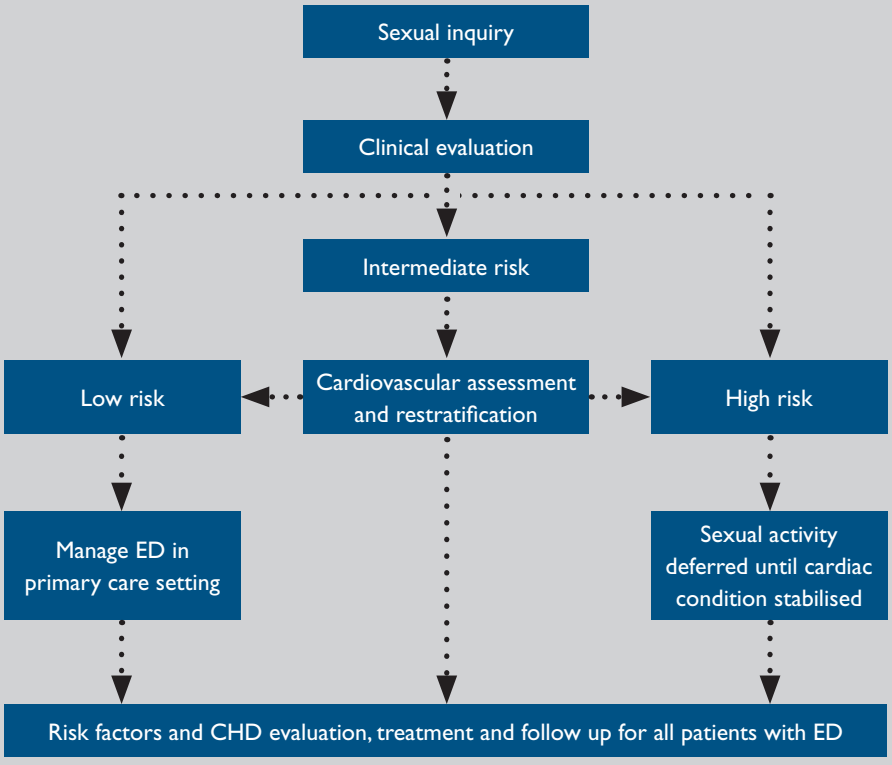
Table 7. Drugs that may contribute to ED [20, 115]

Class	Individual agents
Diuretics	Thiazides Spironolactone
Antihypertensives	Methyldopa Clonidine Reserpine Beta-blockers Guanethidine Verapamil
Cardiac/circulatory	Clofibrate Gemfibrozil Digoxin
Tranquilisers	Phenothiazines Butyrophenones
Antidepressants	Tricyclic antidepressants MAOIs Lithium SSRIs
H_2 antagonists	Cimetidine Ranitidine
Hormones	Oestrogens/progesterone Corticosteroids Cyproterone acetate 5-Alpha reductase inhibitors LHRH agonists
Cytotoxic agents	Cyclophosphamide Methotraxate Roferon-A
Anticholinergics	Disopyramide Anticonvulsants

Table 8. Adverse events reported with PDE5 inhibitor use

	Incidence (%)		
Adverse event	**Sildenafil (n=5918) [113]**	**Vardenafil (n=2203) [114]**	**Tadalafil (n=804) [8]**
Headache	14.6	14.5	14
Flushing	14.1	11.1	4
Dyspepsia	6.2	3.7	10
Rhinitis	2.6	9.2	5
Back pain	0	0	6
Visual disturbance	5.2	0	0

Figure 1. Management algorithm according to graded risk (adapted from [20] and [115])

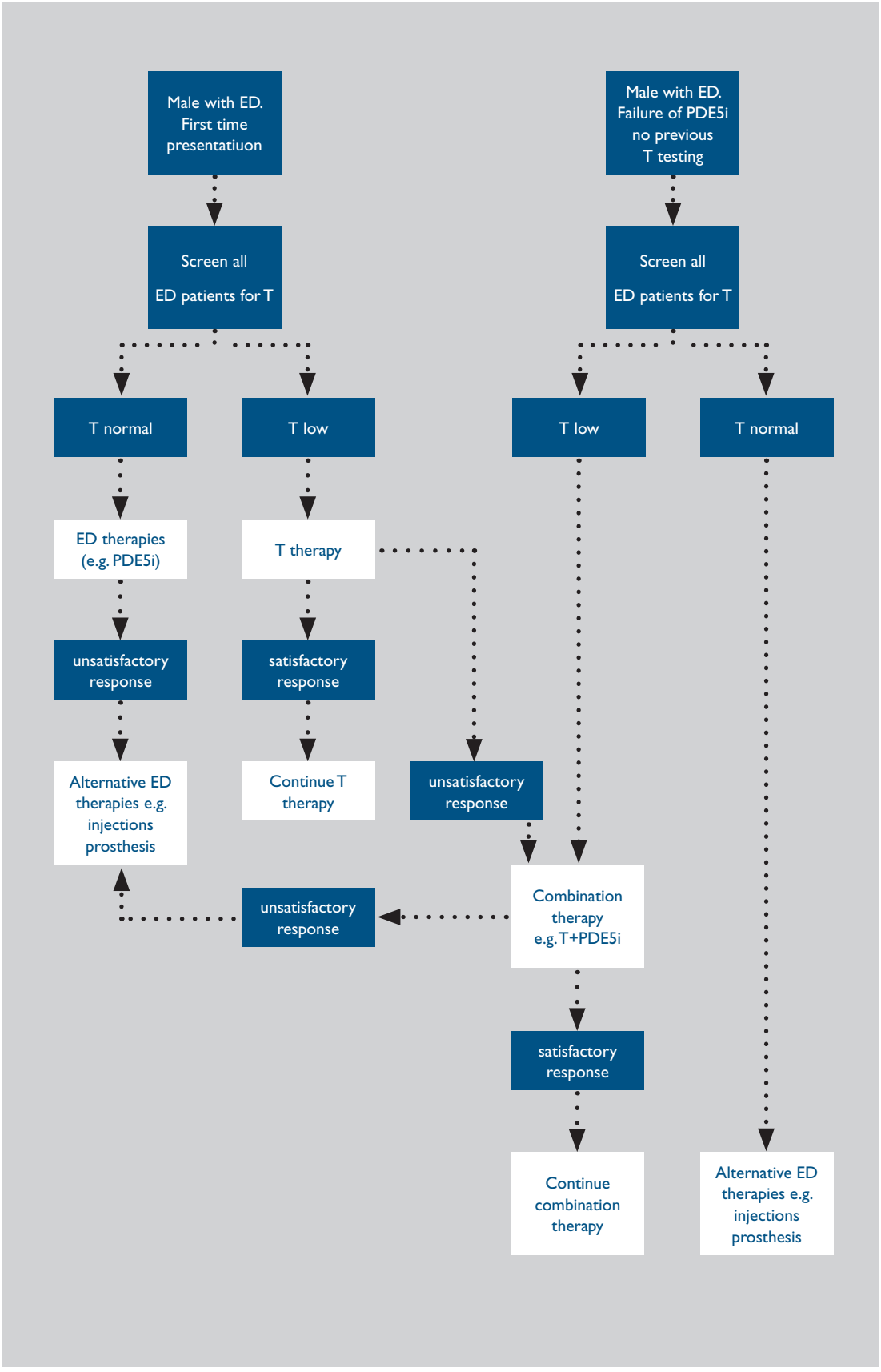


Grading of risk	Cardiovascular status upon presentation	ED management recommendations for the primary care physician
Low risk	• Controlled hypertension • Asymptomatic ≤3 risk factors for CAD - excluding age and gender • Mild valvular disease • Minimal/mild stable angina • Post successful revascularisation • CHF (I)	• Manage within the primary care setting • Review treatment options with patient and his partner (where possible)
Intermediate risk	• Recent MI or CVA (i.e., within last 6 weeks) • Asymptomatic but >3 risk factors for CAD – excluding age and gender • LVD/CHF (II) • Murmur of unknown cause • Moderate stable angina • Heart transplant • Recurrent TIAs	• Specialised evaluation recommended (e.g., exercise test for angina, Echo for murmur) • Patient to be placed in high or low risk category, depending upon outcome of testing
High risk	• Severe or unstable or refractory angina • Uncontrolled hypertension (SBP>180 mmHg) • CHF (III, IV) • Recent MI or CVA (i.e. within last 14 days) • High risk arrhythmias • Hypertrophic cardiomyopathy • Moderate/severe valve disease	• Refer for specialised cardiac evaluation and management • Treatment for ED to be deferred until cardiac condition established and/or specialist evaluation completed

CAD, coronary artery disease; MI, myocardial infarction; CVA, cerebral vascular accident; CHF, congestive heart failure, LVD, left ventricular dysfunction; SBP, systolic blood pressure; ED, erectile dysfunction; TIA, Transient Ischaemic Attack

Key considerations	New York Heart Association classification of congestive heart failure	
• A myocardial infarction or stroke can be triggered by exertion, anger, emotion or, more rarely, sexual activity but in many cases the trigger is unknown. No guarantees can be given that a person with pre-existing cardiovascular disease is 100% risk-free from suffering further cardiovascular adverse events in the short or long term, even with a normal exercise test or ECG. However, the objective is to minimise this risk, through appropriate risk assessment. • It is recognised that an exercise ECG is likely to have been conducted as part of the standard management process for many post-MI or angina patients, while under specialist care. If the MI is recent (less than 6 weeks) or if the GP is uncertain about symptom limitations, consideration should be given to further exercise testing.	Class I	Patients with cardiac disease but with no limitation during ordinary physical activity
	Class II	Slight limitations caused by cardiac disease. Activity such as walking causes dyspnoea
	Class III	Marked limitation; symptoms are provoked easily, e.g., by walking on the flat
	Class IV	Breathlessness at rest

Figure 2. Algorithm for androgen therapy in a man presenting with ED (adapted from [37])



The Sexual Health Inventory for Men (SHIM; from http://www.ucof.com/files/SHIM.pdf)

Patient Name: Today's Date:

Patient Instructions

Sexual health is an important part of an individual's overall physical and emotional well-being. Erectile dysfunction, also known as impotence, is one type of very common medical condition affecting sexual health. Fortunately, there are many different treatment options for erectile dysfunction. This questionnaire is designed to help you and your doctor identify if you may be experiencing erectile dysfunction. If you are, you may choose to discuss treatment options with your doctor.

Each question has several possible responses. Circle the number of the response that **best describes** your own situation. Please be sure that you select one and only one response for **each question.**

Over the past 6 months:

1. How do you rate your confidence that you could get and keep an erection?		Very low	Low	Moderate	High	Very high
		1	2	3	4	5
2. When you had erections with sexual stimulation, how often were your erections hard enough for penetration (entering your partner)?	No sexual activity	Almost never/ never	A few times (much less than half the time)	Sometimes (about half the time)	Most times (much more than half the time)	Almost always/ always
	0	1	2	3	4	5
3. During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?	Did not attempt intercourse	Almost never/ never	A few times (much less than half the time)	Sometimes (about half the time)	Most times (much more than half the time)	Almost always/ always
	0	1	2	3	4	5
4. During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?	Did not attempt intercourse	Extremely difficult	Very difficult	Difficult	Slightly difficult	Not difficult
	0	1	2	3	4	5
5. When you attempted sexual intercourse, how often was it satisfactory for you?	Did not attempt intercourse	Almost never/ never	A few times (much less than half the time)	Sometimes (about half the time)	Most times (much more than half the time)	Almost always/ always
	0	1	2	3	4	5

Add the numbers corresponding to questions 1-5. TOTAL:

The Sexual Health Inventory for Men further classifies ED severity with the following breakpoints: 1–7 Severe ED; 8-11 Moderate ED; 12–16 Mild to Moderate ED; 17–21 Mild ED.

The International Index of Erectile Function (IIEF) [116]

Over the past 4 weeks:

Question	Response options
Q1. How often were you able to get an erection during sexual activity? **Q2.** When you had erections with sexual stimulation, how often were your erections hard enough for penetration?	0 = No sexual activity 1 = Almost never/never 2 = A few times (much less than half the time) 3 = Sometimes (about half the time) 4 = Most times (much more than half the time) 5 = Almost always/always
Q3. When you attempted sexual intercourse, how often were you able to penetrate (enter) your partner? **Q4.** During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?	0 = Did not attempt intercourse 1 = Almost never/never 2 = A few times (much less than half the time) 3 = Sometimes (about half the time) 4 = Most times (much more than half the time) 5 = Almost always/always
Q5. During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?	0 = Did not attempt intercourse 1 = Extremely difficult 2 = Very difficult 3 = Difficult 4 = Slightly difficult 5 = Not difficult
Q6. How many times have you attempted sexual intercourse?	0 = No attempts 1 = One to two attempts 2 = Three to four attempts 3 = Five to six attempts 4 = Seven to 10 attempts 5 = More than 11 attempts
Q7. When you attempted sexual intercourse, how often was it satisfactory to you?	0 = Did not attempt intercourse 1 = Almost never/never 2 = A few times (much less than half the time) 3 = Sometimes (about half the time) 4 = Most times (much more than half the time) 5 = Almost always/always
Q8. How much have you enjoyed sexual intercourse?	0 = No intercourse 1 = No enjoyment 2 = Not very enjoyable 3 = Fairly enjoyable 4 = Highly enjoyable 5 = Very highly enjoyable
Q9. When you had sexual stimulation or intercourse, how often did you ejaculate? **Q10.** When you had sexual stimulation or intercourse, how often did you have the feeling of orgasm or climax?	0 = No sexual stimulation/intercourse 1 = Almost never/never 2 = A few times (much less than half the time) 3 = Sometimes (about half the time) 4 = Most times (much more than half the time) 5 = Almost always/always
Q11. How often have you felt sexual desire?	1 = Almost never 2 = A few times (much less than half the time) 3 = Sometimes (about half the time) 4 = Most times (much more than half the time) 5 = Almost always/always
Q12. How would you rate your level of sexual desire?	1 = Very low/none at all 2 = Low 3 = Moderate 4 = High 5 = Very high
Q13. How satisfied have you been with your overall sex life? **Q14.** How satisfied have you been with your sexual relationship with your partner?	1 = Very dissatisfied 2 = Moderately dissatisfied 3 = About equally satisfied and dissatisfied 4 = Moderately satisfied 5 = Very satisfied
Q15. How do you rate your confidence that you could get and keep an erection?	1 = Very low 2 = Low 3 = Moderate 4 = High 5 = Very high

Six questions (1-5, 15) are related to erectile function, three (6-8) to satisfaction with intercourse, two (9, 10) to orgasm, two (11, 12) to sexual desire, and two (13, 14) to overall satisfaction.