ABSTRACT

Background: This is an update of the 2008 British Society for Sexual Medicine (BSSM) guidelines.

Aim: To provide up-to-date guidance for U.K. (and international) health care professionals managing male sexual dysfunction.

Methods: Source information was obtained from peer-reviewed articles, meetings, and presentations. A search of Embase, MEDLINE, and Cochrane Reviews was performed, covering the search terms “hypogonadism,” “eugonadal or hypogonadism or hypogonadal or gonadal,” and “low or lower testosterone,” starting from 2009 with a cut-off date of September 2017.

Outcomes: We offer evidence-based statements and recommendations for clinicians.

Results: Expert guidance for health care professionals managing male sexual dysfunction is included.

Clinical Translation: Current U.K. management has been largely influenced by non-evidence guidance from National Health Service departments, largely based on providing access to care limited by resources. The 2008 BSSM guidelines to date have been widely quoted in U.K. policy decision making.

Conclusions: There is now overwhelming evidence that erectile dysfunction 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. Measurement of fasting serum glucose, lipid profile, and morning total testosterone should be considered mandatory in all newly presenting patients. 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.


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Key Words: Erectile Dysfunction; Epidemiology; Risk Factors; Hypogonadism; Diagnosis; Therapy; Coronary Heart Disease; Cardiovascular Disease; Type 2 Diabetes; Color Duplex Ultrasound; Summary of Product Characteristics
here were developed by a multidisciplinary expert panel from the Committee of the BSSM. The principal aim of these guidelines is to enable physicians and other health care 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. Source information was obtained from peer-reviewed articles, meetings, and presentations. A search was performed, covering the search terms “hypogonadism,” “eugonadal or hypogonadism or hypogonadal or gonadal,” and “low or lower testosterone,” starting from 2009 with a cut-off date of September 2017. Embase, MEDLINE, and the Cochrane Central Register of Controlled Trials databases were searched, with a limitation to reviews, meta-analyses, or meta-analysis of randomized controlled trials. A total of 4,202 records were identified and screened for relevance, of which 71 publications were selected for inclusion.

ED BACKGROUND

Epidemiology

ED has been defined as the persistent inability to attain and/or maintain an erection sufficient for sexual performance. Although ED is not usually 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.

Several large epidemiological studies have shown a high prevalence and incidence of ED worldwide. In the Massachusetts Male Aging Study, 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. The incidence of ED, calculated from longitudinal data in the Massachusetts Male Aging Study, was 26 new cases per 1,000 per year. A large European study of men aged 30–80 years reported a prevalence of 19%. In the Men’s Attitude to Life Events and Sexuality Study, which included 20- to 75-year-old men from 8 countries (United States, United Kingdom, Germany, France, Italy, Spain, Mexico, and Brazil), the ED prevalence, assessed by International Index of Erectile Function (IIEF), ranged from 22% in the United States to 10% in Spain. All studies showed a steep age-related increase. These epidemiological studies provide different estimates of the prevalence of ED, which can be explained by the methodological designs in the different surveys. In particular, the estimates were influenced by the development of the 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.

Risk Factors

Penile erection is a complex neurovascular phenomenon under hormonal control that includes arterial dilatation, trabecular smooth-muscle relaxation, and activation of the corporal venoocclusive mechanism. The development of ED is attributable to neuronal, vascular, hormonal, and metabolic factors, mediated through endothelial and smooth-muscle dysfunction. The risk factors for ED (age, sedentary lifestyle, obesity, smoking, dyslipidemia, and the metabolic syndrome), are very similar to the established 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. The fact that ED is found more commonly in men with hypertension, dyslipidemia, acute coronary syndrome, diabetes mellitus (DM), metabolic syndrome, and lower urinary tract symptoms (LUTS)/benign prostatic hyperplasia (BPH) led to the recognition that ED is an important marker of future cardiovascular risk. ED is associated with the severity of ischemic heart disease, in terms of plaque burden, and number of coronary arteries affected. ED is believed to be a sentinel marker for future cardiovascular events, occurring 3–5 years before an event, based on the arterial size hypothesis.

The predictive value of ED and coronary artery disease is most impressive in younger men aged 40–49 years, where traditional risk assessment tools are unhelpful. Data from the Olmsted County Study suggested a 50-fold relative risk with incident ED in younger men. These findings were supported by a long-term study from Western Australia where men with incident ED had 7 times the cardiovascular risk compared with men without ED. In men with DM, incident ED was a better predictor of cardiovascular events than hypertension, dyslipidemia, and microalbuminuria.

ED confers a 1.46 increased risk for cardiovascular disease. A recent meta-analysis of 12 prospective studies involving 36,744 men found ED to be an independent marker of cardiovascular events such as hospitalization and mortality, in addition to conventional risk factors (age, weight, hypertension, DM, dyslipidemia, and smoking). The authors of this finding suggested that ED should be included in future cardiovascular risk calculations.

Long-term follow-up from the European Males Aging Study concluded that ED and low testosterone independently predicted early death and that early detection of these 2 conditions represented an opportunity to detect a small number of men at high risk of early death. We endorse recent evidence suggesting that the practical predictive value of ED now merits re-classification of ED as an independent risk factor for cardiovascular disease (especially in men younger than 45 years) with modification of established risk calculators.

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, intra-cavernosal, and intra-urethral 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 until the condition is deemed end stage. The important links with cardiometabolic disease and the importance of relationship and psychological issues strongly suggest that primary care or specialist men’s health physicians are best placed to manage ED.12

The availability of effective and safe oral drugs for ED19–21 has contributed to an upsurge in media interest, which has led to an increase in the number of men seeking help for ED, creating an opportunity to:

- Uncover diabetes (as ED may be the first symptom in up to 20%8,15).
- Detect dyslipidemia, which might not otherwise dictate treatment according to primary coronary prevention guidelines but may be the major reversible component in the patient’s ED.15
- Reveal the presence of hypogonadism, a reversible cause of ED, which can be sometimes managed without the need for specific ED therapy and has other long-term health implications.17
- Identify occult cardiac disease; ED in an otherwise asymptomatic man may be a marker for underlying coronary artery disease.15,16
- Identify associated LUTS/BPH, as severity of LUTS is closely related to ED severity and therapies for one condition may beneficially or adversely affect the other.8,22

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 general practitioner (GP)’s role under the quality outcome framework. Men do not readily visit their GP with medical problems and a consultation for ED may represent an important opportunity for health intervention.15,23

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

ED DIAGNOSIS
Initial Assessment
Case History
A detailed description of the problem, including the duration of symptoms and original precipitants, should be obtained.17 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 timing, control, and orgasmic dysfunction.
- Previous erectile capacity.
- Issues around any sexual aversion or sexual pain.
- Partner issues, eg, low sexual desire, menopause, or gynecological pain.

Table 1. Pathophysiological causes of erectile dysfunction115

<table>
<thead>
<tr>
<th>Predisposing</th>
<th>Precipitating</th>
<th>Maintaining</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lack of sexual knowledge</td>
<td>New relationship</td>
<td>Relationship problems</td>
</tr>
<tr>
<td>Poor past sexual experience</td>
<td>Acute relationship problems</td>
<td>Poor communication between partners</td>
</tr>
<tr>
<td>Relationship problems</td>
<td>Family or social pressures</td>
<td>Lack of knowledge about treatment options</td>
</tr>
<tr>
<td>Religious or cultural beliefs</td>
<td>Pregnancy and childbirth</td>
<td>Ongoing physical or mental health problems</td>
</tr>
<tr>
<td>Restrictive upbringing</td>
<td>Other major life events</td>
<td>Other sexual problems in the man or his partner</td>
</tr>
<tr>
<td>Unclear sexual or gender preference</td>
<td>Partner’s menopause</td>
<td>Drugs</td>
</tr>
<tr>
<td>Previous sexual abuse</td>
<td>Acute physical or mental health problems</td>
<td></td>
</tr>
<tr>
<td>Physical or mental health problems</td>
<td>Lack of knowledge about normal changes of aging</td>
<td></td>
</tr>
<tr>
<td>Other sexual problems in the man or his partner</td>
<td>Other sexual problems in the man or his partner</td>
<td></td>
</tr>
<tr>
<td>Drugs</td>
<td>Drugs</td>
<td></td>
</tr>
</tbody>
</table>
Concurrent medical, psychiatric, and surgical history should also be recorded, as should the current relationship status (eg, single, married, in a long-term relationship; and age of partner) and a history of 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 recreational drug misuse.

The use of validated questionnaires, particularly the IIEF or the validated shorter version of the Sexual Health Inventory for Men, International Prostate Symptom Score, and Aging Male Symptom Score 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.

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, symptoms of hypogonadism, or other urological symptoms (past or present). A digital rectal examination 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

Investigations

The choice of investigations depends on the individual circumstances of the patient. ED is now regarded as an independent risk factor for cardiovascular disease and can be the presenting feature of diabetes,11,15 so serum lipids and fasting plasma glucose and/or glycated hemoglobin 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 (PDE5Is),15,24 therefore all men with ED should have serum testosterone measured on a blood fasting sample taken in the morning between 8–11 AM (see “Hormone Deficiencies and ED” section below). Serum-free testosterone is a more reliable measure of androgen status, having a greater correlation with clinical symptoms, but often only total testosterone estimation is available.25 A reasonable estimate of free and bioavailable testosterone levels can be calculated from total testosterone, sex hormone-binding globulin, and albumin levels, using one of the many free, online calculators that are currently available (eg, on the International Society for the Study of the Aging Male [http://www.issam.ch/freetesto.htm] or Primary Care Testosterone Advisory Group [www.pctag.uk] websites). If the serum testosterone level is borderline or low it should be repeated on a further morning blood sample, together with serum, luteinising hormone, and prolactin (total testosterone less than 8 nmol/L).25 Discussion with, or referral to, a specialist clinic should be considered if the results are abnormal.

Serum prostate-specific antigen should be considered if clinically indicated. It should certainly be measured before commencing testosterone and at 3–6 months and then annually after commencing testosterone therapy.26

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Level of Evidence</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. A comprehensive medical, sexual, and relationship history is required in all cases.</td>
<td>3</td>
<td>B</td>
</tr>
<tr>
<td>2. Clinically validated questionnaires to assess ED are recommended to assess sexual function domains and response to therapies.</td>
<td>3</td>
<td>B</td>
</tr>
<tr>
<td>3. Physical examination is recommended in all cases to detect potentially reversible causes of ED.</td>
<td>4</td>
<td>B</td>
</tr>
<tr>
<td>4. Routine laboratory testing for ED includes fasting glucose and/or glycated hemoglobin, lipid profile, and fasting testosterone level in all cases.</td>
<td>4</td>
<td>A</td>
</tr>
</tbody>
</table>

ED and the Cardiovascular System

Coronary heart disease (CHD) is associated with many of the same risk factors as ED.11,15 Coronary artery disease is often just one affected site in a generalized arteriopathy that is also likely to affect the arterial inflow to the corpora cavernosa of the penis. As the penile arteries are significantly smaller than the main coronary arteries, ED frequently pre-dates coronary artery disease by 3–5 years.26 ED in men with CHD is probably related to this generalized 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.27

The majority of men with CHD can safely resume sexual activity and use ED therapies.15 Education and appropriate counseling about sex should be given to all men with CHD, so

Table 2. Metabolic equivalent to sexual activity

<table>
<thead>
<tr>
<th>Daily activity</th>
<th>METs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sexual intercourse with established partner</td>
<td></td>
</tr>
<tr>
<td>Lower range (normal)</td>
<td>2–3</td>
</tr>
<tr>
<td>Upper range (vigorous activity)</td>
<td>5–6</td>
</tr>
<tr>
<td>Lifting and carrying objects (9–20 kg)</td>
<td>4–5</td>
</tr>
<tr>
<td>Walking 1 mile in 20 min on the level</td>
<td>3–4</td>
</tr>
<tr>
<td>Golf</td>
<td>4–5</td>
</tr>
<tr>
<td>Gardening (digging)</td>
<td>3–5</td>
</tr>
<tr>
<td>Do-it-yourself, wallpapering, etc</td>
<td>4–5</td>
</tr>
<tr>
<td>Light housework, eg, ironing, polishing</td>
<td>2–4</td>
</tr>
<tr>
<td>Heavy housework, eg, making beds, scrubbing floors</td>
<td>3–6</td>
</tr>
</tbody>
</table>

MET = metabolic equivalent.
that the majority can continue to enjoy this important aspect of their relationship. This is particularly relevant to the prescribing of nitrates, which are contraindicated with oral PDE5Is, where effective alternatives can be readily substituted.\(^\text{15}\) Men should be considered sexually active unless clearly established otherwise. Men with unstable heart disease, a history of recent myocardial infarction (MI), poorly compensated heart failure, or unstable dysrhythmia are exceptions.\(^\text{15}\)

Guidance on the assessment and management of ED in the cardiovascular patient has been published by an international expert group.\(^\text{28}\) The key points of this guidance are summarized 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 many 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.\(^\text{28}\)

- 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 who 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 contraindicated 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.

### ED and LUTS/BPH

Regarding the known link between ED and LUTS, some of the larger studies that have evaluated relative risk or odds ratios (OR) of the probability of a link clearly highlight the association between the 2 conditions.\(^\text{9}\) Multivariate analysis showed that severity of LUTS was a strong predictor of sexual dysfunction, with an OR for erection problems of 8.90 (95% CI 6.85–11.55) in those with severe LUTS. Indeed, results from this important study essentially showed that going from mild to moderate, or moderate to severe, LUTS had a greater impact on ED than aging by 10 years. Similarly, in a study involving patients in the United Kingdom, general practices OR for ED in patients with both storage and voidance LUTS were calculated to be 4.0 (95% CI 3.3–4.9).

### Table 3. Further investigations

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Rationale</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intra-cavernous injection test</td>
<td>Assessment of penile deformities</td>
<td>Assessments of penile deformities</td>
</tr>
<tr>
<td>Color Doppler ultrasound</td>
<td>Assesses vascular integrity</td>
<td>Young patients with primary cardiovascular</td>
</tr>
<tr>
<td></td>
<td></td>
<td>abnormality and those being considered for</td>
</tr>
<tr>
<td></td>
<td></td>
<td>surgical intervention</td>
</tr>
<tr>
<td>Phalloarteriography</td>
<td>To clarify vascular abnormality</td>
<td>Arterial abnormality found on Doppler ultrasound</td>
</tr>
<tr>
<td>Cavernosometry/cavernosography</td>
<td>Assesses venous occlusive mechanism</td>
<td>Currently very limited indication such as primary venous leakage suspected in a young man</td>
</tr>
<tr>
<td>Nocturnal penile tumescence</td>
<td>Assesses nocturnal erections when smooth muscle relaxed—reduces false-positive investigation rate</td>
<td>When other investigations inconclusive or prior to surgery</td>
</tr>
</tbody>
</table>

ED = erectile dysfunction.
From the ED perspective, a study in Finland involving over 1,000 men calculated the relative risk of LUTS in patients with severe ED as 2.3 (95% CI 1.4–3.8). In addition to these individual studies, a recent systematic review of available epidemiological data has concluded that most men seeking treatment for either LUTS or ED have both conditions. Taken together, these results provide overwhelming evidence of the independent association between LUTS and ED, and highlight the importance of awareness of this link for the practicing physician.31,32

Recognition of these links can be important because:
- They improve understanding of the etiology of the conditions.
- They enable patients to connect conditions and risk factors.
- They can inform case finding and screening strategies.
- They can identify comorbidities.
- They can affect the choice of appropriate treatment.

### Depression and ED

Many studies have shown a consistent bi-directional association between ED and symptoms of depression but a recent 8-year study found that depression at baseline failed to predict incident ED, suggesting that depression is a likely consequence of ED.34

### Acute Stress and Performance Anxiety

ED can be triggered or maintained by performance anxiety, a process involving interplay among the cognitive, affective, behavioral, and physiological responses throughout a sexual situation. It can be triggered by any sexual stimulus that a man associates with his sexual inadequacy. The excessive sympathetic stimulation that results can counteract the onset and maintenance of erection and diminish the response to therapies.35 Continuous erectile failure can lead to sexual avoidance and decreased sexual arousal.

### Specialized Investigations

Most patients do not need further investigations unless specifically indicated (Table 3). However, some patients wish to know the etiology 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 testicles or penis is found on examination.
- Patients unresponsive to medical therapies who may desire surgical treatment for ED.

#### Nocturnal Penile Tumescence and Rigidity

Nocturnal and early awakening erections are a normal physiological event in all men and are associated with the rapid eye movement pattern of sleep. This test (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.36 The disadvantage is that it often requires an overnight hospital admission.

#### Intra-cavernous Injection Test

This outpatient test involves an intra-cavernosal injection (usually prostaglandin E1) to assess penile rigidity after 10 minutes. 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.37 The main use of this test is in the assessment of penile deformities to aid and plan surgical management.

### Table 4. Nocturnal penile tumescence

<table>
<thead>
<tr>
<th>Method</th>
<th>Nocturnal penile tumescence with 2 circular strain gauges applied to penis—1 base, 1 tip</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overnight recording</td>
<td>Single room, quiet surroundings</td>
</tr>
<tr>
<td>Normal values</td>
<td>&gt;70% Rigidity</td>
</tr>
<tr>
<td></td>
<td>3–4 Erections lasting &gt;10 min</td>
</tr>
<tr>
<td>Uses</td>
<td>To confirm neurogenic ED</td>
</tr>
<tr>
<td></td>
<td>For medico-legal cases</td>
</tr>
<tr>
<td></td>
<td>To exclude false-positive results from other investigations</td>
</tr>
<tr>
<td></td>
<td>To confirm normal erectile potency</td>
</tr>
</tbody>
</table>

ED = erectile dysfunction.

### Table 5. Color Doppler duplex ultrasound

| Method | Inject 10–20 μg prostaglandin E1 |
|--------| Monitor vascular response between 2–10 min |
| 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, eg, fistulae |
| | Priapism |
| | Peyronie plaque |
Duplex Ultrasound of Penile Arteries

This radiological investigation that measures blood flow will give an excellent assessment of the penile vasculature in response to an injection of a vasoactive agent (Table 5). There is evidence that findings of duplex ultrasound of penile arteries predict generalized endothelial dysfunction.

Arteriography and Dynamic Infusion Cavernosometry or Cavernosography

These are highly specialized investigations that are only performed in specific circumstances as outlined in Table 6. Arteriography should only be performed when there is evidence of arterial insufficiency on a duplex Doppler evaluation and there is an indication for penile revascularization surgery. Cavernosometry is rarely used nowadays. The sole indication is probably the investigation of primary venous pathology in young men.

Penile Abnormalities

Surgical problems that cause ED, for example, phimosis, tight frenulum, and penile curvatures, should be diagnosed clinically and are amenable to surgical intervention.

Peyronie disease is a benign disorder affecting the penis, characterized 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 simultaneously and there is no noticeable deformity of the flaccid penis. Peyronie disease can occur at any time from young adult life onward, but most commonly occurs in men aged 40–60 years. It is not an uncommon disorder, affecting around 3% of the population of middle-aged men.

Patients with significant penile deformity and impaired erections that are unresponsive to oral or intra-cavernosal pharmacotherapy may need a penile prosthesis inserted that can straighten the penis as well as providing rigidity to the penis to allow penetration.

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 program. The most common cause of penile fibrosis is priapism (a painful persistent erection lasting more than 4 hours), of which there are many causes (sickle cell disease, self-injection with a vasoactive agent, or the use of anti-psychotic medications are the most frequent causes). It is important to ensure detumescence is achieved as soon as possible to prevent cavernous smooth-muscle necrosis with subsequent cavernosal fibrosis that manifests as ED.

Table 6. Arteriography and cavernosometry/cavernosography

<table>
<thead>
<tr>
<th>Subheading</th>
<th>Method</th>
<th>Values</th>
<th>Uses</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Phalloarteriogram</strong></td>
<td>Femoral artery puncture</td>
<td>Normal intra-cavernosal pressure &gt;90 mm Hg</td>
<td>To confirm arterial lesion diagnosed by Doppler</td>
</tr>
<tr>
<td></td>
<td>Selective arteriography of pudendal vessels</td>
<td>Normal infusion to maintain erection &lt;20 mL/min</td>
<td>As part of embolization in high-flow priapism</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Flow to maintain &gt;20 mL/min = veno-occlusive dysfunction</td>
<td>When penile revascularization considered</td>
</tr>
<tr>
<td><strong>Cavernosometry/cavernosography</strong></td>
<td>19G butterfly needle in each corpus cavernous</td>
<td></td>
<td>To confirm VOD</td>
</tr>
<tr>
<td></td>
<td>Inject 20 µg prostaglandin E1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Infuse with NaCl via infusion pump</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Monitor intra-cavernosal pressure at known infusion rate</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Values</strong></td>
<td>Normal intra-cavernosal pressure &gt;90 mm Hg</td>
<td>Normal infusion to maintain erection &lt;20 mL/min</td>
<td></td>
</tr>
<tr>
<td><strong>Uses</strong></td>
<td>To confirm arterial lesion diagnosed by Doppler</td>
<td>Flow to maintain &gt;20 mL/min = veno-occlusive dysfunction</td>
<td></td>
</tr>
<tr>
<td><strong>Cavernosography:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>✷ Identify sites of venous leakage</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>✷ Assess degree of corporal fibrosis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

5. Specific diagnostic tests are only required in rare cases.

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
TREATMENT

Objectives of Treatment

The primary goal in the 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 counseling to patients and their partners.

ED may be associated with other causes of cardiovascular disease such as hypertension, dyslipidemia, 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 that 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.

Lifestyle Modifications

Investigations for ED should be aimed at identifying reversible risk factors. Modifications in lifestyle can reduce the risk of ED and lifestyle changes and risk-factor modification should accompany any specific pharmacotherapy or psychological therapy (level of evidence 1b, recommendation A).42 However, pharmacotherapy should not be withheld on the basis that lifestyle changes have not been made. Lifestyle interventions have been shown to produce moderate improvement in ED and markers of cardiovascular risk after.43,44 A meta-analysis showed that intense lifestyle modification with exercise and a Mediterranean diet improved ED after 2 years in 4 out of 5 studies,43 but one study in men with DM showed minimal benefit.45

Lifestyle factors include psychosocial issues, adverse side effects of non-prescription drugs, and the influence of any comorbidity, including those in the partner. The potential advantages of lifestyle changes may be particularly pronounced in those with psychogenic ED,44 but not in men with severe cardiovascular disease or DM.45

A meta-analysis of exercise and ED associated moderate and high-level exercise with lower risk of ED (OR 0.63 and 0.42).46 In a prospective study with a 14-year follow-up, exercise was found to be preventative against ED.42 An 8-week intervention study of exercise in a hypertensive population corrected ED compared with a matched control group.47 A study in middle-aged men improved ED and endothelial function.48 A randomized open-label study of 60 men with ED demonstrated that intensive aerobic exercise combined with PDE5Is improved erectile function (EF) score and restored EF in 77.8% vs 39.5% (P = .004).49

Smoking cessation has been shown to decrease incident ED and cardiovascular risk by 36%.50

Alcohol has long been considered a risk factor for ED, but repeated studies have shown low to moderate alcohol consumption beneficial for sexual function.51,52 The OR were lowest for those drinking within the level recommended by the Medical Research Council of less than 14 U per day for men.53 The evidence suggests no evidence for advising men with ED who drink within this range to cease or decrease their consumption to improve ED.52

There is evidence that pelvic floor exercises improve ED in an observational study of 122 men participating in supervised 30-minute sessions.54 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.55,56 Despite this current evidence, further large-scale controlled prospective studies are needed to determine the effects of exercise or other lifestyle changes in the prevention or treatment of ED as public awareness of such associations could be a major motivation for lifestyle alterations.

Because improvements in sexual function are modest in men with established risk factors and may take many months, we strongly recommend that lifestyle advice should be combined with pharmacological or relationship therapy.

| 6. Lifestyle change and risk-factor management should accompany all ED treatment regimens. | 1a | A |
| 7. Lifestyle change and risk-factor management is unlikely to be successful as sole therapy in moderate or severe ED. | 1a | A |

Treatment for Reversible Causes of ED

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 hyperprolactinemia may significantly affect sexual function. The advice of an endocrinologist may be necessary where there is doubt about the cause and appropriate management of the disorder.
Hypogonadism and Testosterone Replacement Therapy

Androgen deficiency in men becomes more common with increasing age but is primarily related to obesity, type 2 DM (T2DM), and metabolic syndrome. As well as sexual dysfunction, androgen deficiency is associated with osteoporosis and depression.

Far from being a benign consequence of aging, 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 central nervous system, peripheral nitricergic nerves, and corpora cavernosa. Androgen deficiency may affect sexual interest, erections, and responsiveness to PDE5Is.

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, fasting, in the morning, 8–11 AM. The assay should be repeated after 2 or 3 weeks as testosterone is also released in a pulsatile manner and the result of a single assay may be misleading. Total testosterone levels vary depending on the local laboratory but, in general, men with a total serum testosterone that is consistently less than 8 nmol/L (free testosterone <0.18 nmol/L) usually require treatment and total testosterone <12 nmol/L (free testosterone <0.225 nmol/L) might benefit from a 6-month trial of testosterone replacement therapy according to 2017 BSSM guidelines (Figure 2).

Patients with additional comorbidities will usually require a PDE5I as well as testosterone therapy. Low testosterone is a frequent reason for failure to respond to PDE5I and correction of low testosterone has been shown in multiple studies to restore the response to PDE5Is. In one study this was significant for total testosterone levels below 10.4 nmol/L and below 8 nmol/L in men with T2DM, but improvement in sexual desire was seen up to 12 nmol/L in men with T2DM. Because sexual desire is important in motivating men to take both PDE5Is on demand (and particularly to self-inject with alprostadil), we recommend a cut-off of 12 nmol/L for initiating testosterone therapy for PDE5I failures. We also recommend that a trial of testosterone therapy is required for a minimum of 6 months, based on several trials and meta-analyses and that daily dosing of PDE5Is might be considered for men with low sexual desire as restoration of spontaneous and morning erections are likely to increase motivation to make sexual attempts after a sustained period of failure. Now that generic PDE5Is are widely available, the rationale for salvaging PDE5I failures by correcting low or borderline testosterone levels often has considerable cost saving for patients and health care systems. The recent evidence for independent reduction in cardiovascular events associated with long-term PDE5I use and testosterone therapy makes this a logical approach compared with previous advice on progression to second- and third-line therapies.
There is no evidence that giving testosterone to men with ED and normal androgen levels restores or improves their erectile function. There is evidence that hypogonadal men restored to the eugonadal state with testosterone replacement for at least 6 months experience:

- A general improvement in sexual function.
- Improved sexual desire.
- Improved energy, mood, and motivation.
- Improved orgasm and ejaculation.
- Improved spontaneous and nocturnal erection.
- Restored or enhanced responsiveness to PDE5Is.
- Metabolic benefits such as loss of visceral fat mass and increased lean muscle mass.
- Increased insulin sensitivity.
- Reduced risk of osteoporosis, especially lumbar spine.

These important clinical issues should be discussed with the patient, along with possible treatment side effects, rather than considering a patient purely as a case of ED.

The cause of hypogonadism should always be sought, but this does not mean that treatment for ED should be deferred. The treatment for symptomatic primary hypogonadism is testosterone replacement. In secondary hypogonadism, the treatment is either testosterone replacement therapy or human chorionic gonadotrophin (HCG). Off-label clomiphene citrate or tamoxifen in men with an intact hypothalamic-pituitary-testicular axis, in conjunction with lifestyle advice. Recent meta-analyses show response to testosterone therapy is unrelated to the cause of hypogonadism. We, therefore, disagree with the traditional view that only classical hypogonadism merits treatment. A recent study by Ng Tang Fui et al. clearly showed that, in obese men with clearly hypogonadal testosterone levels, testosterone therapy in addition to strict diet was superior to strict diet alone, after 12 months, but not 10 weeks, in terms of sexual function, sexual desire, and mood, in addition to visceral fat reduction and preservation of lean muscle mass. We believe that there is insufficient evidence that lifestyle alone produces significant symptomatic resolution within a relevant period to recommend lifestyle therapy alone as sole treatment in men with severe symptoms and proven low testosterone levels.

Prior assessment and safety monitoring should be performed according to contemporary authoritative guidelines.

A range of well-tolerated testosterone formulations (Table 7) is available including:

- Oral.
- Transdermal gel.
- Transdermal axillary solution.
- Long-acting injection 1,000 mg/4 mL deep intra-muscular injection (3 monthly).
- Traditional depot injection 100/250 mg (2–3 weekly).
- Implanted pellets.

Long-acting (3 monthly) testosterone injection or daily application of a transdermal testosterone gel is acceptable to most men, according to patient preference. External testosterone replacement should be avoided in men actively wishing to father children currently or within the near future. We suggest that this issue should be actively asked rather than physicians making subjective conclusions.

A separate BSSM 2017 guideline covers the management of primary and secondary hypogonadism.

Hyperthyroidism/Hypothyroidism

Hyperthyroidism may influence erectile function by increasing sex hormone-binding globulin 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. Hyperthyroidism may be associated with ED and premature ejaculation. Resolution usually follows normalization of thyroid function.

Hyperprolactinemia

Hyperprolactinemia 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. Serum prolactin levels should be measured in all men with low testosterone as men with raised prolactin levels are often resistant to testosterone therapy.

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Table 7. Pharmacokinetics of the 4 currently approved phosphodiesterase type 5 inhibitors

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Sildenafil 100 mg</th>
<th>Tadalafil 20 mg</th>
<th>Vardenafil 20 mg</th>
<th>Avanafil 200 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>C_max</td>
<td>560 µg/L</td>
<td>378 µg/L</td>
<td>18.7 µg/L</td>
<td>5.2 µg/L</td>
</tr>
<tr>
<td>T_max (median)</td>
<td>0.8–1 h</td>
<td>2 h</td>
<td>0.9 h</td>
<td>0.5–0.75 h</td>
</tr>
<tr>
<td>T1/2</td>
<td>2.6–3.7 h</td>
<td>17.5 h</td>
<td>3.9 h</td>
<td>6–17 h</td>
</tr>
<tr>
<td>AUC</td>
<td>1685 µg·h/L</td>
<td>8066 µg·h/L</td>
<td>56.8 µg·h/L</td>
<td>11.6 µg·h/L</td>
</tr>
<tr>
<td>Protein binding</td>
<td>96%</td>
<td>94%</td>
<td>94%</td>
<td>99%</td>
</tr>
<tr>
<td>Bioavailability</td>
<td>41%</td>
<td>NA</td>
<td>15%</td>
<td>8–10%</td>
</tr>
</tbody>
</table>

Data adapted from European Medicines Agency statements on product characteristics.

AUC = area under curve or serum concentration time curve; C_max = maximal concentration; NA = not available; T_max = time-to-maximum plasma concentration; T1/2 = plasma elimination half-time.

*Fasted state, higher recommended dose.
Hyperprolactinemia should be excluded by blood testing in all men with reduced sexual interest. Men with prolactin >735 µU/mL have an increased risk of ED and low libido. However, the association with ED usually disappeared after adjustment for testosterone levels.87

Hyperprolactinemia can have many causes (Table 8):
- Medical and physical stress.
- Drugs (notably major tranquilizers and anti-emetics).
- A small proportion of men with hyperprolactinemia will have a prolactin-secreting pituitary tumor—identification of these cases is important.
- Chronic renal failure.

A misdiagnosis of hyperprolactinemia can result from the presence of macro-prolactin or “big-big” prolactin. This is a heterogenous complex of prolactin and immunoglobulin and is the cause of apparent hyperprolactinemia in about 20% of cases.85 It is measured by commercial immunoassays to a greater or lesser extent and its presence should be considered in all cases of mild to moderate hyperprolactinemia. It is diagnosed by re-assaying after precipitation with polyethylene glycol.

Treatment of hyperprolactinemia is with the dopamine agonist, cabergoline 500 µg twice weekly, in preference to bromocriptine. Therapy is usually effective in restoring testosterone levels, and improving ED and ejaculatory function. Treatment may need to be long term for idiopathic hyperprolactinemia. ED therapy with PDE5Is may be required for associated comorbidities.88 Patients with persistent and unexplained hyperprolactinemia should be referred to an endocrinologist.

Post-Traumatic Arteriogenic ED in Young Patients
Penile revascularization involves harvesting of the inferior epigastric artery and anastomosing it to either the deep dorsal vein or artery of the penis to increase arterial inflow to the corpus cavernosum. 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 angiogram. These patients should be young and have no other arterial or neurological risk factors. With careful selection, success rates of 65% can be achieved.89

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 neuropaxia, 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.91,92

There is no role for venous ligation unless an isolated venous anomaly can be demonstrated on cavernosography.93

Drug-Induced ED
A wide range of drugs has been implicated in ED (Table 9). 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 randomized, 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.

Drugs may affect sexual response in a number of ways:94
- Those causing sedation may affect sexual motivation and, indirectly, cause ED.
- Those that affect cardiovascular function, such as anti-hypertensive agents, may act centrally and may also affect penile hemodynamics.
- Some drugs affect endocrine parameters—anti-androgens and estrogens may affect both sexual desire and erection.
- Drugs that cause hyperprolactinemia, such as phenothiazines, may also affect sexual desire and erection.87

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.

### Table 8. Commonly reported adverse events from the 4 European Medicines Agency–licensed phosphodiesterase type 5 inhibitors (highest recommended dose)

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Sildenafil</th>
<th>Tadalafil</th>
<th>Vardenafil</th>
<th>Avanafil</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>12.8%</td>
<td>14.5%</td>
<td>16%</td>
<td>9.3%</td>
</tr>
<tr>
<td>Flushing</td>
<td>10.4%</td>
<td>4.3%</td>
<td>12%</td>
<td>3.7%</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>4.6%</td>
<td>12.3%</td>
<td>4%</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>1.1%</td>
<td>4.3%</td>
<td>10%</td>
<td>1.9%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1.2%</td>
<td>2.3%</td>
<td>2%</td>
<td>0.6%</td>
</tr>
<tr>
<td>Abnormal vision</td>
<td>1.9%</td>
<td>&lt;2%</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Back pain</td>
<td>6.5%</td>
<td></td>
<td>&lt;2%</td>
<td></td>
</tr>
<tr>
<td>Myalgia</td>
<td>5.7%</td>
<td></td>
<td>&lt;2%</td>
<td></td>
</tr>
</tbody>
</table>

*Adapted from European Medicines Agency statements on product characteristics.*
Table 9. Drugs that may contribute to erectile dysfunction

<table>
<thead>
<tr>
<th>Class</th>
<th>Individual agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuretics</td>
<td>Thiazides, Spironolactone</td>
</tr>
<tr>
<td>Anti-hypertensives</td>
<td>Methyldopa, Clonidine, Reserpine, Beta-blockers, Guanethidin, Verapamil</td>
</tr>
<tr>
<td>Cardiac/circulatory</td>
<td>Clofibrate, Gemfibrozil, Digoxin</td>
</tr>
<tr>
<td>Tranquilizers</td>
<td>Phenothiazines, Butyrophenones</td>
</tr>
<tr>
<td>Anti-depressants</td>
<td>Tetracyclic anti-depressants, MAOIs, Lithium, SSRIs</td>
</tr>
<tr>
<td>H₂ antagonists</td>
<td>Cimetidine, Ranitidine</td>
</tr>
<tr>
<td>Hormones</td>
<td>Estrogens/progesterone, Corticosteroids, Cyproterone acetate, 5-Alpha reductase inhibitors, LHRH agonists</td>
</tr>
<tr>
<td>Cytotoxic agents</td>
<td>Cyclophosphamide, Methotrexate, Roferon-A</td>
</tr>
<tr>
<td>Anti-cholinergics</td>
<td>Disopyramide, Anti-convulsants, Pregabalin, Gabapentin, Duloxetine</td>
</tr>
</tbody>
</table>

LHRH = luteinizing hormone; MAOIs = monoamine oxidase inhibitor; SSRIs = selective serotonin reuptake inhibitors.

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 package labeling indicates that it may cause ED.

Cardiovascular Drugs and ED

In patients with hypertension and CHD, their ED is usually caused by the medical condition. 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. Thiazides and non-selective beta-blockers have been shown in a number of studies to be associated with ED and the summary of product characteristics (SPCs) of both classes of drug state these warnings. Nebivolol is a beta-blocker with nitric oxide donor properties that may improve ED. In one 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. Angiotensin-converting-enzyme inhibitors and calcium channel blockers, in normal doses, are unlikely to be a major contributory factor to the development of ED. Trials suggest that angiotensin receptor blockers may actually improve sexual function and may be the drug of choice in the ED patient newly diagnosed with hypertension. 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.

The clinical importance is likely to be seen in men with mild ED, where a change in therapy might result in the minor improvement required to concert them to normal function. Likewise, in men at high risk of ED, the drug least likely to contribute in ED should be considered. In men with sub-optimal response to oral therapy, a medication change may convert them to responders. In men with severe or non-responsive ED, therapy changes are likely to be of minimal benefit.

Neurological Drugs and ED

Depression and ED often co-exist. Successful therapy for depression might improve ED, but selective serotonin reuptake inhibitor anti-depressants have been reported to cause sexual adverse events (ED, delayed ejaculation, anorgasmia, and reduced desire), in up to 70% of patients. Some anti-depressants with less serotoninergic side effects (mirtazapine, moclobemide, agomelatine, buspirone, and trazadone) have been shown to have minimal sexual side effect but may not be considered optimum therapy. Phenothiazines cause ED by a combination of anti-cholinergic effects and elevation of prolactin levels. Newer agents have fewer side effects. Frequently psychiatrists are reluctant to change medications to risk compromising the mental status.

Pregabalin and gabapentin are frequently prescribed for neuropathic pain, especially in T2DM. They have been shown to cause dose-related ED in patients with difficult-to-treat ED.

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, inquiry 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.

Partners with aversion to sex, low desire, arousal problems, and sexual pain disorders may not allow the man to have sex with
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 his partner does not want to have sex with him.

Women 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 women older than 50 years whose partners have ED is estrogen deficiency–related vaginal atrophy. This is usually straightforward to treat with vaginal estrogen or lubricants and highlights the importance of always considering partner issues when treating ED.

**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 aging, 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 behavioral advice regarding foreplay, sexual activity, and integration of medication into the couple’s sexual behavior.

Formal cognitive-behavioral 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 etiology. Psychotherapeutic methods integrating cognitive, behavioral, systemic, psychodynamic, and interpersonal approaches still lack adequate evidence-based outcome studies, but literature suggests positive outcomes from a synthesis of these approaches. Concurrent use of medication, such as PDE5Is, is not precluded in men engaged in cognitive-behavioral therapy, and a combined pharmaco-psychotherapeutic approach may be more effective than using these interventions individually or consecutively.

**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 (diathermy, traction, or compression) 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 2 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. A change in cavernosal structure may be what leads to persistent ED in some men, even though they have had nerve-sparing surgery. In men who develop ED after radical prostatectomy the smooth muscle is gradually replaced by collagen. This alteration in smooth muscle to collagen ratio is thought to account for persisting ED.

Response rates to on-demand PDE5Is post-radical prostatectomy are poor. Response rates to sildenafil treatment post-radical prostatectomy has ranged from 35%–75% among those who underwent nerve-sparing radical prostatectomy and from 0–15% among those who underwent non-nerve-sparing radical prostatectomy.

Early use of high-dose sildenafil after radical prostatectomy was thought to be associated with preservation of cavernosal smooth muscle. Daily sildenafil also results in a greater return of spontaneous normal erectile function after radical prostatectomy compared to placebo following bi-lateral nerve-sparing radical prostatectomy in patients who were fully potent before surgery. Many men have pre-operative ED due to associated comorbidities and ideally this should be treated prior to surgery.

A randomized, double-blind multicenter study in men with normal pre-operative erectile function who underwent nerve-sparing radical prostatectomy compared tadalafil once daily with placebo. Data suggested a potential role for tadalafil once daily—provided early after surgery—in contributing to the recovery of post-operative erectile function and possibly protecting penile structural changes. Multiple erection rehabilitation programs have been described that required men to routinely attain erections 3 times a week by using escalating drug therapy, initially with daily PDE5I and progressing with injection therapy to achieve erectile response. 18 Months after surgery, 52% of men participating in the program had normal erections (not requiring the use of any ED therapy), compared with only 19% of men not participating in the program. Another study used nightly sildenafil vs placebo for 26 weeks with 27% compared with 4% regaining normal spontaneous erections. Another study showed no difference between daily vardenafil vs on-demand post-radical prostatectomy causing many to doubt the cost-effectiveness of daily dosing regimens.

In the Recovery of Erectile Function After bilateral nerve-sparing Radical Prostatectomy A randomised placebo Controlled...
Trial of Tadalafil (REACTT) study, daily tadalafil for 9 months post-radical prostatectomy has been shown to maintain penile size but does not necessarily improve the time to regain erection. There was no difference in end-of-treatment erectile function, but men treated with daily tadalafil showed improved quality-of-life scores and were more likely to be PDE5I responsive after 9 months of daily tadalafil.116

Mulhall et al13 assessed the outcome of intra-cavernous injection test treatment in patients who were non-responders to postoperative sildenafil and had been treated with bi-lateral nerve-sparing, unilateral nerve-sparing, or non-nerve-sparing radical prostatectomy. Patients treated with a tri-mix formulation (papaverine, phentolamine, and prostaglandin E1) had higher response rates than those who received no treatment after radical prostatectomy, thus supporting the role of intra-cavernous injection tests in the U.K. rehabilitation flow-chart of non-responders to PDE5Is.117

In addition to pharmacological treatments, the effects of vacuum erection devices (VEDs) on penile rehabilitation after radical prostatectomy has been evaluated. Indeed, one study has demonstrated that VED therapy was responsible for the preservation of endothelial and smooth-muscle integrity due to a transient increase in arterial flow and oxygenation in the corpora cavernosa.118 However, a large study assessing the effect of VEDs in the post-radical prostatectomy setting have shown contradictory results.119

The importance of sexual counseling should not be under-valued in the postoperative setting. In this regard, it was previously demonstrated that up to 49% of patients not adequately counseled throughout an 18-month post-operative period decided not to begin any ED treatment, although before surgery they were highly motivated to preserve EF.119 Therefore, these and other findings support the proposal that, just as in the pre-operative setting, patients must be carefully counseled post-operatively regarding the need to find the optimal rehabilitation treatment to increase the possibility of re-gaining adequate EF.

Because of the lack of good-quality evidence and confusion regarding the management of men with sexual difficulties following both radical surgery and radical radiotherapy, U.K. guidance was published to achieve consensus on management117 (Table 7).

First-Line Treatment

Oral Pharmacotherapy—PDE5Is

Drugs that inhibit PDE5 increase arterial blood flow, which leads to smooth-muscle relaxation, vasodilation, and penile erection.120 4 Potent selective PDE5Is have been approved by the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA): sildenafil, tadalafil, vardenafil, and avanafil. These medications have proven efficacy and safety both in non-selected populations of men with ED and in specific subgroups of patients (eg, men with diabetes and those who have had a prostatectomy).121–124 The major difference in these drugs is that sildenafil, vardenafil, and avanafil 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. PDE5Is are not initiators of erection but require sexual stimulation in order to facilitate an erection.120 It is currently recommended that patients should receive 8 doses of a PDE5I with sexual stimulation at maximum dose before classifying a patient as a non-responder.67 Avanafil is reported to have the fastest onset of action and a lower rate of side effects, especially flushing.125 However, the reported side effects need to be viewed with caution as there are no head-to-head comparisons and recruitment criteria and studies differ in terms of exclusion of previous non-responders, which may be influenced by previous adverse events.126

Efficacy of PDE5Is in Different ED Populations

Published studies on all 4 PDE5Is suggest that 75% of sexual attempts result in successful intercourse (sexual encounter profile 3—the ability to maintain an erection for successful intercourse).127 Data from the Global Assessment Question 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 4 drugs.127 As men with treated low testosterone were excluded in studies, everyday clinical practice with restricted medication usually results in lower responses. In men with T2DM, response is related to duration and control of diabetes and the number of complications. Low levels of sexual desire are associated with lower response.128–130 Differences between the selection criteria in studies of the PDE5Is (particularly in the way patients previously treated with sildenafil were included or excluded) influence direct comparison of the efficacy of the drugs.126

A trade-off meta-analysis concluded that, for individuals, sildenafil 50 mg had highest efficacy and highest rate of adverse events, while tadalafil 10 mg had intermediate efficacy. Vardenafil 10 mg and avanafil had similar adverse events as sildenafil but lower efficacy.131 A systemic network meta-analysis comparison of 118 trials involving 31,195 individuals concluded that, based on IIEF score and after adjusting for dose, tadalafil was most efficacious, followed by vardenafil, and that all PDE5Is were generally well tolerated.132

Interaction of PDE5Is and food, particularly fatty food, is greatest with sildenafil133 and least with tadalafil. No interaction with alcohol, up to concentrations of 0.5–0.6 mg/kg, has been observed with any of the PDE5Is.127

Adverse Events

Pharmaco-kinetics and safety data for PDE5Is are shown in Table 10.
Contraindications to PDE5Is

Absolute contraindications are regular or intermittent use of nitrates in any form, including amyl nitrate “poppers,” nicorandil, and guanyl cyclase stimulators such as riociguat.

Dose adjustments of all PDE5Is may be needed in:
- Patients >65 years old.
- Hepatic impairment.
- Renal impairment.
- Concomitant use of potent cytochrome P450 3A4 inhibitors, such as ritonavir, erythromycin, and cimetidine.

Reports have linked PDE5I use to a small increase in the incidence of non-arteritic anterior ischemic optic neuropathy (NAION). Currently all 3 PDE5Is mention NAION as a warning on their SPCs. However, as risk factors for NAION include age over 50 years, heart disease, diabetes, hypertension, dyslipidemia, nicotine use, and a congenital predisposition, patients at risk of NAION would be the patients more likely to experience ED and require a PDE5I.

Non-Responders to PDE5Is

Approximately 25–50% of patients do not respond to PDE5Is within 12 months. Over 50% of men with T2DM...
and 70% of those post-radical prostatectomy also failed to respond in clinical trials.127 Response rates are likely to be even lower in clinical practice where access to drugs is restricted.

Patients should be exposed to a minimum of 4 (preferably 8) of the highest tolerated dose of at least 2 drugs (taken sequentially, not concurrently) with adequate sexual stimulation.127 Patients should be followed up, ideally within 6 weeks of commencing therapy. So-called failure may be due to sub-optimal counseling 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.127 Several measures are described in the literature to salvage patients, clearly identified as non-responders:

- Re-counseling 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 PDE5Is in the corpus cavernosum and several studies have shown that patients can be salvaged by treating low or low-normal levels of testosterone up to 10.4 nmol/L.67 Where reduced sexual desire is present then levels up to 12 nmol/L may salvage non-responders.73
- Occasionally patients may respond to one drug when another has failed. Evidence suggests that 8–12% of treatment failures respond to a second or third PDE5I.127,134 Those patients with minimal response to 1 drug will be unlikely to respond to drug switches. Repeated failure is likely to cause considerable lack of confidence.
- More frequent dosing regimens. In clinical trials, patients were allowed up to daily dosing whereas in clinical practice medication is often restricted. The European Society for Sexual Medicine (ESSM) syllabus suggests that daily dosing might salvage as many as 50% of non-responders to a first drug.127 Buvat et al67 confirmed earlier findings that up to 57% of PDE5I failures could be salvaged with up to 12 weeks of tadalafil 10 mg daily.135 Tadalafil 5 mg daily is licensed for this indication but sildenafil, vardenafil, and avanafil and tadalafil 10 mg and 20 mg can be used in this way within the product licence,121–124 which is for anticipated sexual activity (not intercourse). Many couples find on-demand therapy totally unacceptable. Daily dosing is likely to restore spontaneous and nocturnal erections, increasing the chance of spontaneous success.127 In men without a partner, chance of success can be enhanced by early attempts with masturbation.127 This is limited evidence that prolonged use of daily tadalafil might result in a progressive improvement in EF scores, not seen with on-demand dosing.136

- Combining a long-acting daily PDE5I with a short-acting on-demand PDE5I. One trial suggested that treatment failures with severe ED could be salvaged by adding in sildenafil 50–100 mg on demand to tadalafil 5 mg daily.137 Although not advised on the SPC of either drug, this practical solution may be more acceptable than moving to second-line therapy and, with generic PDE5Is, may have considerable cost savings.

Choice or Preference Between the Different PDE5Is

The availability of 4 PDE5Is 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, and robust outcome measures and statistics, and preferably be double blinded. Double blinding is a problem when all 4 drugs are well recognized, and 1 has a half-life of 17.5 hours and the other 3 have a half-life of 4–6 hours. The optimal dosing instructions for the 4 drugs are also different.131,132

Safety of PDE5Is and Drug Interactions

PDE5Is have an extensive safety record over 20 years of use. There is no evidence that PDE5Is significantly increase the rate of MI.139 3 Studies in men with T2DM70,71,140 and previous MI72 suggest a 30–40% reduction on all-cause and cardiovascular mortality, in addition to reduced incidence and hospitalization for heart failure after MI.72 PDE5Is do not adversely affect total exercise time or time to ischemia during exercise testing in men with stable angina. In fact, PDE5Is may improve the time to ST elevation and recovery after myocardial ischemia.141,142

These findings suggest there may be long-term cardiovascular benefits from PDE5Is.

8. Where a potentially curable cause for ED is found, it should be treated in conjunction with ED-specific therapy.
9. PDE5Is are first-line therapy for ED.1a A
10. Inadequate prescribing or instruction is the major cause of PDE5I failure.3 A
11. Daily or frequent dosing regimens frequently salvage men who have failed with on-demand therapy.3 A
12. Correction of testosterone levels below 10.4 nmol/L may salvage non-responders to PDE5Is.2 A
13. Salvaging patients from failure with PDE5Is is a cost-effective strategy.4 A
14. For men with ED and bothersome LUTS, daily tadalafil should be considered as first-line therapy.1 A

Organic nitrates (eg, nitroglycerine, isosorbide mononitrate, isosorbide dinitrate), other nitrate preparations used to treat angina such as nicorandil, and recreational drugs such as amyl nitrite (poppers) are absolute contraindications with PDE5Is. Combined use could result in cyclic guanosine monophosphate accumulation and unpredictable falls in blood pressure and, potentially, catastrophic hypotension.143 Interactions between
organic nitrates and PDE5Is 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 PDE5I, nitroglycerine should only be administered under close medical observation. Nitrates are third-line drugs 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. 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 that may confer cardiovascular benefit. 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 PDE5Is as an ED treatment option. Recent studies suggesting cardiovascular benefit from PDE5Is confirm the importance of discussing sexual activity in all men with cardiovascular disease and avoiding nitrates wherever possible as all men should be considered as potentially sexual active until clearly proven otherwise.

Co-administration of PDE5Is with anti-hypertensive 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 mm Hg for sildenafil, 7.8 mm Hg for vardenafil, and 1.6/0.8 mm Hg for tadalafil, when the drugs are taken on an on-demand basis. Generally, the adverse event profile of PDE5Is is not worsened by the concomitant use of anti-hypertensive medicines.

Alpha-blockers have some interaction with PDE5Is. Under some conditions, this interaction may result in orthostatic hypotension, and PDE5Is should be used with caution in patients receiving alpha-blockers. Vardenafil should only be initiated at the lowest dose, only if the patient is stabilized on alpha-blocker therapy, and dosing of the 2 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 stabilized on alpha-blocker therapy, and dosing of the 2 drugs should be separated by at least 4 hours. These interactions are more pronounced when PDE5Is are given to healthy volunteers not previously taking alpha-blockers and are rarely of clinical significance when the drugs are not started simultaneously. As up to 70% of men with severe LUTS will have ED, studies reporting the rates of pre-treatment ED with alpha-blockers are misleading. Ejaculatory problems (anejaculation and retrograde ejaculation) are common with alpha-blockers and often become bothersome only after the ED has been treated.

Tadalafil 5 mg daily has been licensed and European Urology Association guidelines suggest that it is equal first-choice therapy for LUTS/BPH based on efficacy and preferred treatment where coincidental ED is present. As LUTS/BPH is strongly associated with T2DM and metabolic syndrome, recent studies proposing cardiovascular benefit from PDE5Is suggest that they should now be first-line therapy in such patients, especially with the patent expirations in 2017.

Adverse Events
Pharmaco-kinetics and safety data for PDE5Is are shown in Tables 7 and 8.

Vacuum Erection Devices
The principle of VEDs is simple but men do better after initial one-to-one supervised instruction. A cylinder is placed over the penis, air is pumped out with an attached manual or battery-powered pump, and the resulting penile tumescence is maintained by a constriction ring around the base of the penis. The tight restriction ring may interfere with ejaculation unless released.

- VEDs are highly effective in inducing erections regardless of the etiology of the ED.
- They may be useful combined with PDE5Is and injection therapy post-radical prostatectomy and to salvage treatment failures.
- VEDs, combined with viable sized insert tubes can be helpful in correcting penile curvature.
- Reported satisfaction rates vary considerably from 35–84%.
- Long-term usage of VEDs also varies but is considerably higher than for self-injection therapy.
- Most men who are satisfied with VEDs continue to use them long term.
- 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.

VEDs are contraindicated in men with bleeding disorders or those taking anti-coagulant 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.
Second-Line Treatment

Intra-cavernous Injection Therapy

Intra-cavernous injection therapy is the most effective form of pharmacotherapy for ED and has been used for more than 20 years. 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. 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 intra-cavernous 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. 2 or 3 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 program can be valuable and improve long-term compliance.

Efficacy and safety of alprostadil is summarized below:

- Efficacy rates are high—around 70—80% in the general ED population and higher in those without vascular disease.
- 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.
- Careful counseling in the early stages with an easy availability of advice in the first few weeks can improve compliance.
- Adverse effects of intra-cavernous alprostadil include post-injection penile pain (in up to half patients after at least some of their injections).
- Other complications include priapism (1%) and fibrosis (2%).
- 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 “Treatment of Prolonged Erection and Priapism” section).

Combination Therapy

Papaverine (20—80 mg) was the first drug to be used widely for intra-cavernous 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). 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—2 mg) 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. 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 PDE5Is, while 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 mesylate is a short-acting alpha-adrenoreceptor antagonist that also has a direct effect on smooth muscle, causing relaxation. 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. 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.
- A direct comparator, crossover trial has shown similar efficacy to alprostadil. 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.
- The ESSM syllabus suggests that, based on expert opinion, vasoactive intestinal polypeptide-phentolamine may be more effective in men with prostate cancer following radical prostatectomy or radiotherapy and in those with anti-androgens, as the effect is not thought to be androgen dependent.

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. This is to avoid damage to the intra-cavernous muscle and blood vessels that could result in smooth-muscle necrosis and the development of 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 ischemic blood and thereby promote detumescence. This simple method can be effective in many cases, particularly if performed early enough. Further improvements can be gained by washing out the corpora with saline and then withdrawing the saline and blood together. If this is not effective or if the penis becomes rigid again, a sympathomimetic drug such as phenylephrine or adrenaline may be effective but requires very close monitoring of blood pressure and is best performed within a hospital setting. Appropriate doses are adrenaline 10–20 μg or phenylephrine in 250- to 500-μg aliquots repeated every 10–15 minutes. A lower dose of alprostadil should be used for any subsequent injections.

Intra-Urethral Alprostadil

A formulation of alprostadil in a medicated pellet (medicated urethral system for erection) was approved for the treatment of ED in 1997. 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 cavernosa by retrograde ow through emissary veins, encouraged by penile massage at the time of administration. Use of MUSE results in erections in approximately 30–60% of patients.

- In clinical practice, only the higher dosages of 500 μg and 1,000 μg are effective.
- Application of a constriction ring at the base of the penis may help in some patients, but currently this is not available in the United Kingdom.
- 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.

This is a less invasive but also less effective treatment than intra-cavernosal injection therapy.

There is a more recent formulation of alprostadil cream (Vitaros). This is administered at a dose of 300 μg as a topical gel into the urethra followed by massage of the glans. In phase III trials 74% of men reported improved erections. NICE evaluated 2 randomized controlled trials (n = 1732) where a 300-μg dose produced a 2.5 increase in IIEF and a 15% increase in successful intercourse attempts. Side effects are usually related to the local effect of topical gel, mainly genital pain, tenderness, and local erythema. However, 0.4% reported priapism from an integrated analysis of multicenter studies. Improved tumescence of the glans with topical alprostadil may be useful in men post-penile prosthesis.

Low-Intensity Extracorporeal Shock Wave Therapy

Low-intensity extracorporeal shock wave treatment for ED has used the concept of neovascularization through mesenchyme stem/progenitor cells in the penile smooth muscle. Initially, small studies suggested a 6.7- vs 3.0-point improvement in IIEF compared with sham therapy. More recently 60% of PDE5I failures were salvaged by 4 treatments with improvement maintained at 12 months in those patients who continued on PDE5Is. 2 Recent meta-analyses suggest that there might be a place for low-intensity extracorporeal shock wave treatment in men with mild ED wishing to avoid medical therapy and as a salvage therapy for PDE5I non-responders. Although the initial outlay in equipment might be expensive, costs are likely to fall with increased patient numbers. As low-intensity extracorporeal shock wave treatment is well tolerated and safe, this might be a preferred option for patients failing oral therapy but reluctant to move to injection therapy. Further studies are required to confirm efficacy in a broad range of patients to establish the place of low-intensity extracorporeal shock wave treatment.

Third-Line Treatment

Penile Prosthesis

Penile prostheses should be offered to all patients who fail to respond to, or are unable to continue with, oral or intra-cavernosal/intra-urethral therapy or external devices. All patients and their partners should be counselled pre-operatively, see and handle the penile prostheses, and if possible speak to other patients who have already undergone surgery. The malleable prostheses are easier to insert but are less concealable compared to the 3-piece inflatable penile prostheses that consists of 2 inflatable cylinders with a reservoir placed in the abdomen and a pump that inflates and deflates the device and is located within the scrotum.

Penile prostheses are particularly suitable for those with severe organic ED, especially if the cause is diabetes, pelvic cancer, Peyronie disease, or post-priapism. All patients should be given a choice of either a malleable or an inflatable penile prosthesis and ensure that they have the adequate manual dexterity to manipulate the pump for the prosthesis otherwise a malleable implant is more suitable. Patient expectations are also addressed to ensure that they understand that this is an irreversible procedure as the corpus cavernosum smooth muscle is disrupted to make space for the cylinders. The prosthesis itself will provide girth and rigidity to the penis but no additional penile length. The majority of cases can be performed under a general anesthetic and an overnight hospital stay.
Satisfaction rates of 89% were shown in one series of 434 implants.\textsuperscript{173} High satisfaction rates are mainly due to the improved mechanical reliability of the new devices.\textsuperscript{173,174} 5-Year survival of these devices is 93% but a revision rate of 7% per year can be expected.\textsuperscript{175} The use of anti-biotic coatings on the prostheses has dramatically reduced the infection rates down to between 2–4% in large-volume centers.\textsuperscript{176}

The advantages of a penile prosthesis include:

- Long-term efficacy with a high satisfaction rate.
- No need for further medication.
- Improved ability to lead a normal sexual life.\textsuperscript{175}

In order to undergo the surgery, patients must be medically fit for surgery including cessation of smoking, body mass index less than 30, and acceptable control of diabetes in accordance with the NHS Clinical Commissioning Policy for End-Stage ED (NHS England 16059/P175). Patients should be aware of potential complications related to the surgery that include infection, erosion, and mechanical failure that may require revision surgery. Although the initial cost of the inflatable penile prosthesis and the surgery is high, the manufacturers offer a lifetime guarantee for mechanical failure.

New and Future Therapies

Gene Therapy

The first clinical paper on gene therapy in men with ED was presented in 2017.\textsuperscript{176} 21 Men with ED post-radical prostatectomy using autologous adipose-derived regenerative cells injected intra-cavernosally after concentration from liposuction samples. 8 Out of 14 (57%) urinary continent men who had failed to respond to oral or intra-cavernosal injection regained erectile function after 6 months, which was maintained at 12 months. There were minimal side effects, largely related to the liposuction. This therapy is based primarily on basic science studies but without FDA or EMA endorsement, private clinics are already making extravagant claims based on injections of so-called platelet-rich plasma.

Other Therapies

Efficacy rates with apomorphine (Uprima) are lower than those reported for PDE5Is, ranging from 26–55% and this product has now been discontinued throughout Europe.

A number of other agents have been used for ED, with varying degrees of success. None of the following products are licensed for the treatment of ED and they should not be used routinely:

- Yohimbine.
- Delaquamine.
- Trazodon.
- L-arginine.\textsuperscript{177}
- Red Korea.
- Ginseng.
- Oral limaprost.
- Oral phenolamine and nitroglycerine.
- Papaverine.
- Minoxidil topically.

ECONOMICS OF ED MANAGEMENT—SCHEDULE 2

Health Service Circulars

HSC/115,\textsuperscript{1} HSC/148,\textsuperscript{2} and HSC/177\textsuperscript{3} from 1999 explain the Secretary of State for Health decisions about the availability of impotence treatments from GPs on NHS prescriptions and these came into place on July 1, 1999.

In 2012, with the patent expiration, sildenafil was removed from schedule 2, meaning that no restrictions now apply. This means that sildenafil can be prescribed irrespective of the associated medical comorbidities and with no restriction to frequency of use.\textsuperscript{178} The SPC of sildenafil allows for up to 100 mg in any 24-hour period, prior to anticipated sexual activity (not intercourse). With the patent expiration of tadalafil and vardenal in November 2017, they are likely to be removed from the restrictions, with considerable reduction in price.

In contrast, intra-cavernosal and intra-urethral formulations remain under schedule-2 regulation. The lack of generic equivalents is largely due to manufacturing issues with the products themselves and the need for devices, which are subject to separate patents. Therefore, generic formulations of PDE5Is will be 3–5% of the cost of second-line therapies. This effectively means that any intervention allowing patients to continue with oral therapy will be highly cost-effective, whether the health care system or the patients are self-funding. This is a fundamental issue for clinicians and patients.

Schedule-2 regulations\textsuperscript{2,3,178} still exist for non-generic PDE5Is, alprostadil formulations, and VEDs and the restrictions are as below:

ED associated with the following medical conditions were deemed to qualify for prescription at NHS expense (which shall be endorsed by selected list scheme). The regulations do not state that these conditions must cause the ED:

- Diabetes.
- Multiple sclerosis.
- Parkinson disease.
- Poliomyelitis.
- Prostate cancer.
- Prostatectomy (including transurethral resection of the prostate).
- Radical pelvic surgery.
• Renal failure treated by dialysis or transplant.
• Severe pelvic injury.
• Single-gene neurological disease.
• Spinal cord injury.
• Spina bifida.

There are 2 qualifiers:

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

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 United Kingdom. The strict interpretation involves the hospital continuing ongoing prescribing for life, with no additional financial resources and the need to institute repeated prescribing structures. Many trusts have decided that they simply cannot absorb these costs and have declined to provide a service.

Frequency of Treatment
HSC/148 states that the department advises doctors that 1 treatment per week will be appropriate for most patients. If the GP, in exercising their clinical judgement, considers more than 1 treatment a week is appropriate, they should prescribe that amount on the National Health Service (NHS) prescription. The GP must not charge for private prescriptions or mix private and NHS prescriptions.

The reference for once-per-week treatment was the 1993 Sexual Attitudes and Lifestyle Study. It is of interest that this and other studies showed that the frequency of sexual activity was higher in younger patients 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.

Over-the-Counter Sildenafil (Viagra Connect 50 mg)
In November 2017, the Medicines and Healthcare Products Regulatory Agency approved the sale of sildenafil direct to consumers by pharmacists, to commence from 2018. Clearly defined questions must be asked by the pharmacist to ensure safe practice. If important comorbidities are detected, then referral to a physician is suggested. The BSSM support this initiative as a way for men who do not currently seek help through normal health care routes to access assistance. We hope that this initiative will aid in the detection of important comorbidities and prevent patients from accessing counterfeit medication via the Internet with all the associated risks.

CONCLUSIONS
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. Measurement of fasting serum glucose and/or glycated hemoglobin, lipid profile, and morning total testosterone should be considered mandatory in all newly presenting patients, even where the cause of their ED may appear obvious. 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 revolutionized the treatment of ED, but patients are still not being assessed and treated. Medications 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 PDE5Is, to achieve maximal response and in many cases normalization of testosterone levels can restore erectile function.

The availability of generic PDE5Is with no restriction on frequency of use, and evidence of possible reduction in cardiovascular risk, has radically changed the way in which ED will be managed in future.

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