**Treatment of male sexual dysfunction**

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Male sexual dysfunction is a prevalent condition in the population, is a major health problem and has previously been both under diagnosed and under treated. There are now a number of treatments available that are safe and easy to use which provide an effective solution for most presenting patients. Oral drugs have recently become the first-line option for many men with about 60–70% of new presentations achieving success. Those who fail a trial of oral treatments have a number of other options available, which are able to provide erections sufficient for intercourse in many of the oral drug failures. All these options, their indications, side-effects and complications are outlined in this chapter.

Sexual dysfunction is a very common disorder in the adult population of this country. Prevalence studies suggest that as many as 31% of men and 43% of women between the ages of 18 and 59 years suffer from some form of sexual dysfunction. The two commonest problems encountered in men are premature ejaculation and erectile dysfunction.

**Premature ejaculation**

There is no clear or universally accepted definition of premature ejaculation, but it is generally regarded as the inability to delay ejaculation to either partner’s satisfaction. The prevalence of the condition is unknown, but it is certainly more common in younger, more inexperienced men. The cause is mostly psychogenic, though there is some evidence that sufferers have increased sensitivities in their penile skin and glans; it may be a failure to learn how to delay climax. Treatment has usually relied on sexual therapy for the couple but more recently drug therapies have been tried. Clomipramine (25 mg daily) has been shown to delay ejaculation in those with the condition and paroxetine (20 mg each evening) has also been shown to be effective in clinical trials.

**Erectile dysfunction**

Defined as the inability to get an erection sufficient for sexual activity, erectile dysfunction is a prevalent disorder within the population. There are few good epidemiological studies in existence but the most often quoted...
work is the Massachusetts Male Ageing Study which suggested that 9.6% of men between the ages of 40 and 70 years suffered from complete erectile dysfunction and a further 25% admitted moderate dysfunction. Another meta-analysis review of 23 studies also suggested the prevalence of complete erectile dysfunction amongst men to be up to 10%. One factor that is common to all these studies, and previous observations, is that the incidence of erectile dysfunction increases with age. Complete erectile dysfunction is uncommon before the age of 40 years, but occurs in over 15% of men by the age of 70 years. Despite the increased publicity surrounding the condition and the greater diversity of treatment options that now exist, only a very small proportion of men with erectile dysfunction have currently presented themselves for treatment.

Views regarding the aetiology of erectile dysfunction have changed a little over the last 30 years. Freud, Kinsey and other early observers of sexual function believed that nearly all men had an underlying psychological cause to their problem. More recently, as treatment options became available and patients underwent more detailed investigation, it was thought that physical causes predominated. In fact, it is probable that the majority of men have a combination of both psychogenic and organic causes, the former often resulting from the latter. An erection is a haemodynamic event under neurological control and, therefore, the organic causes of erectile dysfunction are usually related to a problem in one of these systems. The main aetiologies are listed in Table 1.

### Treatments for erectile dysfunction

There now exists a wide range of treatment options available for men with erectile dysfunction. These have mostly evolved as a result of the

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**Table 1** Diseases associated with erectile dysfunction

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<thead>
<tr>
<th>Cardiovascular disease</th>
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<tr>
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<td>Heart disease</td>
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<td>Peripheral vascular disease</td>
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<td>Cigarette smoking</td>
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<th>Neurological disease</th>
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<td>Spinal injury</td>
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<td>Surgical damage</td>
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<td>Disseminating disease</td>
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<th>Systemic disease</th>
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<td>Renal failure</td>
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<td></td>
<td>Liver failure</td>
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<td>Malignant disease</td>
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<tr>
<th>Endocrine disease</th>
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<td></td>
<td>Thyroid disease</td>
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<td>Hyperprolactinaemia</td>
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improved understanding of the physiology and pharmacology of the erectile mechanism and, in particular, the control of smooth muscle function and the neurotransmitters that mediate this control.

**Psychotherapy**

Erections are often stimulated by audiovisual stimuli or fantasy but can likewise be inhibited by other negative CNS signals. This psychogenic erectile dysfunction can be brought on by a number of factors such as performance anxiety, guilt, depression and relationship problems, but all would appear to have the common effect of increasing general anxiety levels. This will lead to an increase in sympathetic outflow and release of systemic catecholamines which promote smooth muscle contraction and thus flaccidity. For patients with a predominantly psychogenic erectile dysfunction, psychotherapy can offer a solution that does not involve the use of drugs in any way. However, treatment can be expensive in terms of time and money and initially involves participation of both the patient and his partner. The form of therapy depends on the exact nature of the problem and varies from simple advice about improvement in a couple’s communication skills to behaviourally orientated psychotherapy. This latter treatment aims to reduce the performance anxiety through a programmed relearning of sexual contact and activity by gradually increasing the repertoire of sexual activities that do not depend on maintaining an erection until full confidence is restored. Successful treatment can result in long-term improvement in up to 70% of couples using this modality.

**Testosterone supplementation**

The role of testosterone in the treatment of erectile dysfunction remains controversial. A normal serum testosterone level is not absolutely necessary for erectile function as demonstrated by the observation that about 20% of castrate males are sexually active. Sexual desire or libido is the sexual function determined by testosterone levels. However, some men with documented hypogonadism will get restoration of sexual function on testosterone replacement though there are few men presenting with erectile dysfunction who are found to have significantly low testosterone levels. Testosterone replacement can be achieved by oral tablets, intramuscular injections, depot subcutaneous injections or cutaneous skin patches. The skin patches provide the most physiological form of replacement and will probably become the treatment of choice for most men. Transdermal delivery of testosterone requires quite high
doses and thus large surface areas of the patches. This means that these patches can be difficult to hide, they may be visible through clothes and can cause skin irritation and allergy. A newer transdermal delivery system uses the skin of the scrotum which allows a very rapid absorption of testosterone and thus a smaller surface area of patch. Patients with very low testosterone levels can expect to benefit from this treatment, but evidence has suggested that those men with borderline low levels rarely obtain restoration of erectile function with this treatment alone. Hypogonadal men report improvement in mood, energy levels libido and sexual function on these forms of treatment.

**Oral drug therapy**

Most patients and doctors would select an oral drug as their favoured selection as a treatment for erectile dysfunction, assuming it to be safe and effective. Until recently this has not been realised, but there are now a number of oral agents that have been described which appear to go some way to realising this ambition. One of these, Sildenafil (Viagra), has entered clinical practice with initial encouraging results and thus has become the most popular choice as first treatment option. These drugs have a different mode of action to the other options and should be regarded as enhancers of the normal erectile response rather than initiators. In other words, they are only effective when accompanied by normal sexual desire and sexual stimulation; an erection does not just appear after their use, as occurs with many of the other alternatives.

**Sildenafil**

There are a number of potential mechanisms of action of oral drugs acting either in the central nervous system or peripherally within the penis itself. Sildenafil, the only oral drug currently licensed, acts peripherally. It is a potent inhibitor of an enzyme, phosphodiesterase type 5 (PDE5), and prevents the breakdown of cyclic guanosine monophosphate (cGMP) which is the intracellular messenger that brings about smooth muscle relaxation. The erectile response is thus enhanced. The production of cGMP is stimulated by the neurotransmitter nitric oxide, released from parasympathetic nerve endings in the corpora (Fig. 1).

**Efficacy**

Clinical studies using Sildenafil have confirmed its efficacy in a wide range of patients with erectile dysfunction. Large, multi-centred, randomised, placebo-controlled studies have shown that about 70% of men with erectile dysfunction of all aetiologies will respond to the drug with
Nitric oxide

\[ \text{GTP} \rightarrow \text{cGMP} \rightarrow \text{Smooth muscle relaxation} \leftarrow \text{cAMP} \]

Smooth muscle contraction

Adrenergic stimulation

Fig. 1 Intracellular control of smooth muscle tone

Improvement in the quality and frequency of erections. In these studies, most attempts at intercourse (70%) were successful compared to placebo (22%). More recent studies on specific patient subgroups with erectile dysfunction have also shown the efficacy of Sildenafil, such as diabetic patients (50%), patients with psychogenic erectile dysfunction (90%), ischaemic heart disease sufferers (70%) and neurological disease (64%).

Complications and side-effects

Sildenafil is an inhibitor of PDE5. Although this enzyme is found mostly in cavernosal smooth muscle, it is present in other tissues and, therefore, has effects on other body tissues. The commonest side-effects are related to the presence of PDE5 in vascular smooth muscle cells and are headache (16%) and facial flushing (10%). Other possible adverse events include dyspepsia (as PDE5 is present in the gastro-oesophageal junction muscle cells) and in alterations in colour vision. The effects on colour vision are related to the limited inhibition of PDE type 6 by Sildenafil, which is found in the retina and is responsible for the conversion of photon energy to a neuronal signal. It is a rare side-effect (3% of patients in trials) and is transient, reversible and not associated with any long-term complications.

The drug is well tolerated by patients with over 90% of men still taking the drug one year after initiation. Serious side-effects such as myocardial infarction or significant cardiovascular events were no more common in men taking Sildenafil than placebo in all the large patient trials. Sudden death has been reported in men using this drug, but it is believed that the risk was related to the exercise involved in sexual activity rather than the drug itself that led to the deaths. There is no
doubt that sexual activity carries a risk of sudden death (albeit very small), but men with mild or moderate cardiovascular disease should be able to use this drug without concern. The one major concern and absolute contra-indication to the use of Sildenafil is when a patient is taking any form of nitrate drug. Concurrent use with any nitrate drug (or nitric oxide donor drug) can result in a precipitous drop in blood pressure (due to their synergistic action) and, therefore, be potentially dangerous. Patients commencing therapy should be questioned about their drug history and warned of this possible drug interaction.

**Phentolamine**

Phentolamine is an alpha receptor antagonist and produces smooth muscle relaxation. Used as an oral form that leads to rapid high serum levels (either as a 40 mg or 80 mg tablet), it has been established in clinical trials\(^1\) as a potential agent for men with erectile dysfunction. Producing an erection sufficient for intercourse in 53% of men compared to 38% for placebo this drug may be faster acting than Sildenafil and can be used in those using nitrate medications. The side-effects reported from these trials included rhinitis, dizziness and tachycardia, but at a low incidence. The true clinical position of this drug remains to be seen but it is expected to gain regulatory approval in the near future.

**Other agents**

A number of other agents have been proposed and investigated for their potential in the treatment of male erectile dysfunction. Apomorphine is a dopaminergic agonist that acts centrally and may enhance the erectile response. A placebo controlled study suggested that 53–60% of men obtained erections after its use compared to 35% using the placebo\(^2\). Side-effects included yawning, nausea and vomiting and 8% of men required the concomitant use of anti-emetic medication.

**Self-injection therapy**

The observation that some drugs injected directly into the corpora cavernosa cause an erection was made in the early 1980s. This provided both the first treatment option and sparked much of the interest and research into the physiology of the erectile mechanism. This research has subsequently led to the variety of treatment options that are now available. The first drug that was used to any great extent clinically was papaverine, which is a general phosphodiesterase inhibitor and causes
smooth muscle relaxation. Although initially gaining widespread use as an intracorporeal drug, it is now rarely used as a single agent. It is probably less effective than newer agents and certainly has a higher side-effect profile and no licence status for use as a treatment for erectile dysfunction. Prostaglandin E₁ (PGE₁ or the synthetic analogue alprostadil) is now the most commonly used agent for intracorporeal injection. It acts via specific receptors on the surface of smooth muscle cells via the adenylate cyclase system to induce relaxation and hence opening of both the vascular spaces of the erectile tissue and the feeding vascular arterioles. The drug is marketed as both Caverject™ and Viridal™ and is available in a wide range of doses (5–40 μg) to accommodate most patients’ needs. Other, newer injectable agents are currently being investigated as potential therapeutic options: the combination of vasoactive intestinal polypeptide (VIP) and phentolamine has completed some promising clinical trials where it appeared to be effective, safe with a low side-effect profile.

**Efficacy**

Self-injection therapies are effective treatments with the majority of men using this technique achieving erections sufficient for intercourse. A meta-analysis of 25,000 patients showed that 75–80% of patients achieved success using PGE₁, 80% with the combination of VIP and phentolamine and 50% for papaverine alone. Erections occur about 5–10 min after injection and last from 15 min to 2 h.

Long-term studies suggest that there is a high drop-out rate from patients using the injection technique (about 50% within 3–4 years). There are many reasons for this, including reappearance of spontaneous erections, patients or partner’s dissatisfaction with the treatment and if the therapy becomes ineffective.

**Complications and side-effects**

The commonest side-effect after use of any injectable agent is failure of response. This is usually due to a failure in the injection technique, either in the preparation of the agent or in the correct injection of the drug into the corpora cavernosa. Immediate local problems include penile pain, urethral bleeding, bruising and corporal fibrosis and are related to the actual injection technique and the frequency of use. The complication that seems to cause most concern is that of prolonged erection or priapism. An erection that lasts more than 4 h is regarded as prolonged and patients who experience these should seek medical help. All patients who use self-injection should thus be informed of this potential complication and be provided with written instructions of how to obtain suitable assistance. The incidence of prolonged erection is related to the drug injected and is higher with papaverine than the other agents. When it does occur, simple aspiration will usually resolve the problem.
Table 2 Complications of self-injection therapy

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<tr>
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<th>Papaverine (%)</th>
<th>PGE$_1$ (%)</th>
<th>VIP and phentolamine (%)</th>
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<tbody>
<tr>
<td>Pain</td>
<td>6</td>
<td>17-50%</td>
<td>1</td>
</tr>
<tr>
<td>Prolonged erection</td>
<td>2-3-5%</td>
<td>0.5-1.3%</td>
<td>0.4%</td>
</tr>
<tr>
<td>Haematoma</td>
<td>3</td>
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especially if combined with some mild physical activity by the patient. For those who fail to respond, injection of an alpha agonist such as phenylepherine into the corpora will usually work; surgical drainage is reserved for those patients who fail to respond to these treatments and usually necessary for those who present with an erection of 12 h duration or more.

Penile pain occurs most commonly after use of PGE$_1$ (up to 30% of patients)\textsuperscript{15} and may be due to stimulation of pain nerve endings by the prostaglandin. Penile bruising can occur with any of the injectable agents and often arises if the needle passes through a superficial penile vein (Table 2). The risk is increased if the patient has any form of coagulopathy and these should be regarded as a relative contra-indication to their use.

**Technique of self-injection**

All of the injectable agents require education of the patient in the techniques of drug storage, use and self-administration by injection. The prescribing physician must be confident that the patient can use the drug safely and effectively and that he has an appropriate dose. The majority of patients can be taught the technique if they are well-motivated and have reasonable manual dexterity, especially if they use one of the auto-injectable devices that are now available for self-injection therapy. Selection of an appropriate dose is made by the physician and needs to be made by careful titration prior to prescription. The dose selected is a balance between the efficacy of the treatment and the risk of possible side-effects. Patients with a major psychogenic aetiology to their problem will require a lower dose than those with a vasculogenic cause, though in all cases titration upwards from a low dose is necessary.

**Intra-urethral therapy**

The efficacy of PGE$_1$, as a drug that can induce an erectile response has been established for some years. Use of the urethral mucosa for delivery of this drug to the erectile tissues is a more recent innovation, now available as a pellet, which dissolves across the mucosa into the cavernosal smooth muscle. Marketed as MUSE\textsuperscript{TM} (Medicated Urethral System for Erection) the PGE$_1$ is administered as a pellet through a specific delivery
device, used by the patient prior to intercourse. The patient voids urine before use, inserts the device, releases the pellet and then massages the penis to promote dissolution until efficacy is achieved. There are 4 doses of the PGE, available with this system with the majority of patients (41%) requiring the highest dose of 1000 μg. These comparatively high doses suggest that much of the drug never reaches the corpora cavernosa following this form of administration. Clinical studies of its use have shown variable success with between 66% and 43% of patients achieving erections satisfactory for intercourse. Side-effects are quite common, but mostly mild and include penile pain (33%), though this rarely led to discontinuation of use, and mild urethral trauma (5%). Priapism is a very rarely reported adverse event.

Vacuum erection devices

Vacuum devices have been around since 1917 when the first device for the treatment of erectile dysfunction was patented. There is now a variety of devices available though all have the same combination of a plastic chamber, a vacuum inducing pump and a constriction ring to prevent loss of the erection. They operate by inducing a vacuum in the plastic chamber which draws and traps blood into both the corpora cavernosa and the extracorporeal compartment of the penis until erection occurs; then the constriction ring is placed around the base of the penis. This method is effective in that over 85% of all men presenting to an erectile dysfunction clinic will achieve an erection sufficient for intercourse. The drawbacks are several and include lack of spontaneity of the treatment, venous stasis and hence numbness in the penis, loss of ejaculation, discomfort at orgasm and pivoting of the penis from the level of the constriction ring. Despite all these, the method remains popular with some men as it avoids the use of both drugs and needles.

Surgery

The continued use of surgery for men with erectile dysfunction is uncertain. With more men coming forward for treatment of this condition, it may be that those who remain resistant to all the mechanical and drug remedies will elect to consider surgical means to restore potency. However, it may be that one or a combination of the non-surgical options will provide a solution to the vast majority of men and the role of surgery will diminish. It remains true though that men should only be considered for surgical treatment if they have failed other options. The surgery involves insertion of synthetic prostheses into the
corpora cavernosa of the penis and thus, by definition, removal of all existing erectile tissue.

**Patient selection**
The majority of patients are those who have failed all other treatment options. They are usually younger than the average erectile dysfunction patient and have chronic conditions such as diabetes mellitus or some neurological disease. The other group of patients suitable for these devices are those with Peyronnie's disease, where erectile dysfunction is associated with penile curvature. The prostheses will overcome both problems. Patients must all be carefully counselled about the implications of surgery and potential complications.

**Types of penile prostheses**
There are two main types of prostheses, the semi-rigid and inflatable. The semi-rigid devices are the most commonly used, consisting of two flexible rods surrounded by silicone rubber. Once they are inserted the patient simply points the penis into the upward or downward position by bending the rods. The inflatable devices have a simple hydraulic system that allows inflation of the prostheses leading to an increase in the length and girth of the penis on activation. This is controlled using a small pump placed in the scrotum, which leads to filling and distension of the penile cylinders. There are possible complications from insertion of any of these devices. Infection at the time of insertion occurs in about 5% of operations and almost inevitably leads to removal of the whole device; it is more commonly seen in diabetic patients. Erosion of the prosthesis through the skin or urethra is usually due to inappropriate size selection of the device and again leads to removal. Persistent pain and mechanical failure of the prostheses are less frequent complaints, but add up to a significant overall risk that the patient should be aware of.

**Conclusions**
Erectile dysfunction is a prevalent condition in the population and there is no doubt that it can have a major impact on the quality of life of men and their partners. Treatment advances, however, now offer a very realistic prospect of successful management with a wide range of therapeutic options available. Patients should be encouraged to present and be provided with an accurate diagnosis and sympathetic explanation of their problem.

Oral treatments offer a safe and effective first line therapy for many men. The debate about whether this option (and other erectile dysfunction products) should be available to patients on the NHS system will continue and will probably expand as other ‘life-style’ drugs become available in the
future. Injectable and trans-urethral agents and vacuum devices are suitable for many of the men who fail to respond to oral drugs and the option of surgery remains for those with more complex aetiologies. There are more products currently under investigation and hopefully further safe and simple solutions will be provided for this distressing disorder.

References

12. Hackett, unpublished data