Erectile dysfunction
Part 1: investigation and management

Effective treatment of erectile dysfunction involves early diagnosis and prompt management. With early intervention, erectile function can be improved by treating comorbid disease, identifying and correcting risk factors, counselling patients on psychosocial issues and using several effective medical and surgical therapies.

CHRIS G. McMAHON
MB BS, FAChSHM

CHELSEA N. McMAHON
MB BS, BSc(Hons)

Associate Professor Chris McMahon is an Associate Professor at the University of Sydney, Australian Centre for Sexual Health, St Leonards, Sydney. Dr Chelsea McMahon is a Medical Registrar at St Vincent's Hospital, Darlinghurst, Sydney, NSW.

Erectile dysfunction (ED) is the inability to achieve and maintain an erection of sufficient rigidity for satisfactory sexual intercourse.[1] Community-based epidemiological studies suggest that sexual dysfunction, particularly ED, is a common disorder in men and is associated with a reduced quality of life (Figure 1).[2,3] Over the past 15 years, our understanding of ED has evolved from the initial premise that most men with ED were experiencing psychogenic impotence to a new understanding that the majority of men have a physical basis to their impotence. In parallel with this new understanding of the mechanisms of ED, a greater insight into the factors that can disrupt normal function, new diagnostic tests and new treatments for ED have been developed. One of the most significant advances has been a recognition that blood flow into the corpora cavernosa is regulated by smooth muscle tone and that this mechanism can be pharmacologically altered.

In the first of this two-part article, the assessment and management of men with ED are described. The management of men with ED that is unresponsive to phosphodiesterase-5 (PDE5) inhibitors is discussed in the second part of this article, to be published in the November issue of *Medicine Today*.

IN SUMMARY

- **Erectile dysfunction (ED) is a common condition and can usually be managed pharmacologically with oral phosphodiesterase-5 (PDE5) inhibitor drugs or self-administered intracorporal injections.**
- **The cardiovascular status of the patient and his overall fitness for renewed sexual activity should be assessed before initiation of treatment for ED.**
- **PDE5 inhibitor drugs are effective in 65 to 70% of men with ED.**
- **The efficacy of PDE5 inhibitor drugs is related to the extent and severity of ED, with significantly reduced efficacy shown in patients with severe vasculogenic ED, diabetic ED and ED after radical prostatectomy.**
- **Alprostadil is the first choice of drug in patients treated with intracorporal injections. It is effective in 70% of men with ED and is associated with a low risk of priapism and penile fibrosis.**

Physiology and pathophysiology

A penile erection is a neurovascular event that requires dilation of the penile vasculature, relaxation of smooth muscle, increased intracorporal blood flow and normal veno-occlusive function (Figure 2). With sexual stimulation, the helicine arteries and cavernous smooth muscle relax, allowing markedly increased arterial blood inflow to the lacunar spaces. The systemic blood pressure, transmitted through the dilated helicine arteries, expands the trabeculae against the tunica albuginea. Compression of the subtunical plexus of venules, reduction of lacunar venous outflow and elevation of intracorporal pressure combine to make the penis rigid.

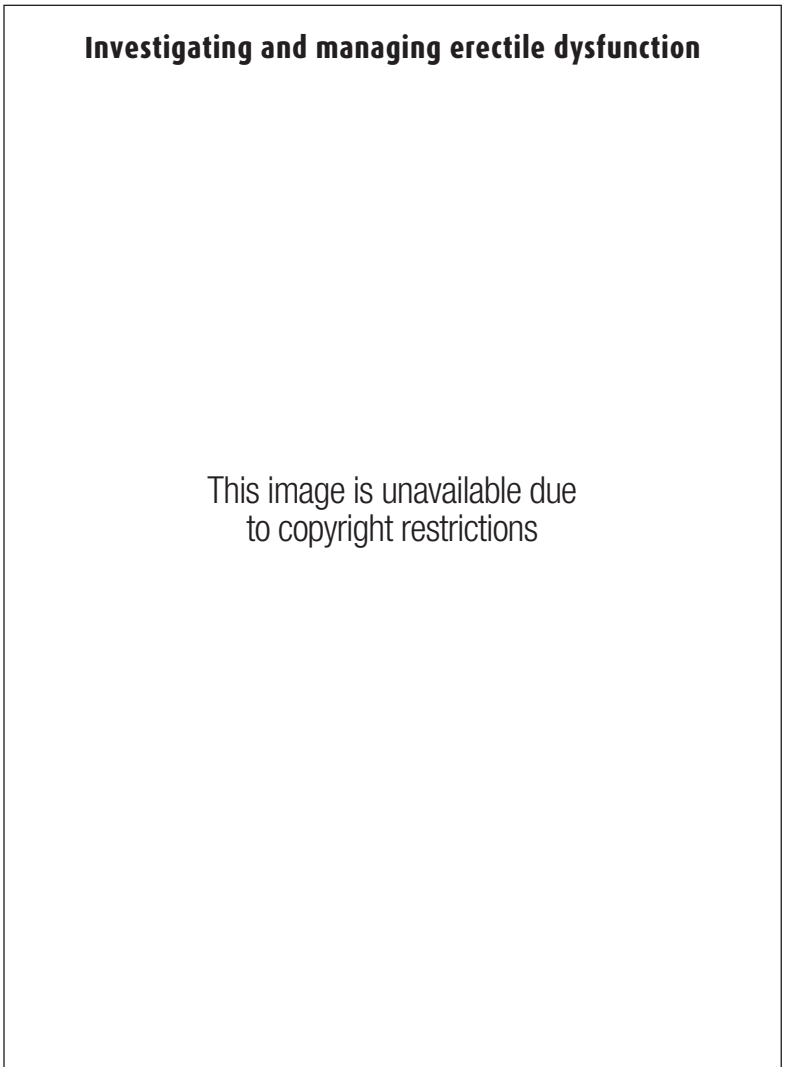
It is now well established that endothelial dysfunction related to diabetes, hypertension, hypercholesterolaemia and cigarette smoking is the precursor of atherosclerotic penile vascular occlusive disease. This can interfere with the intricate vascular mechanisms underlying a normal erection.[4-7] The incidence of ED increases with the presence of concomitant conditions, such as diabetes, hypertension, coronary artery disease, peripheral vascular disease, hyperlipidaemia, neurological injury or disease, and endocrine disorders.

Penile vascular occlusive disease is the most common cause of organic ED. There are several pathophysiological mechanisms of vasculogenic ED, including impaired arterial inflow, impaired smooth muscle cavernosal relaxation, increased cavernosal smooth muscle contraction induced by chronic ischaemia, penile fibrosis, veno-occlusive dysfunction and chronic or episodic hypoxaemia. Therapeutic approaches to treating vasculogenic ED need to address these mechanisms.

Diabetes

Diabetes is a leading cause of ED. Between 25 and 75% of men with type 2 diabetes will complain of ED. Treatment of diabetes-induced ED is often difficult, with patients with diabetes having lower response rates of pharmacological therapies than those seen in patients without diabetes. To diagnose and treat diabetes-induced ED effectively, a multilevel treatment approach must be taken early in the disease process and encompass improving diabetic glycaemic control and a variety of treatment strategies.

Investigating and managing erectile dysfunction



Erectile dysfunction is a common disorder in men and is associated with a reduced quality of life. The condition can usually be managed pharmacologically with phosphodiesterase-5 inhibitors, effective in 65 to 70% of cases, or intracorporal injections, effective in 70% of cases.

Coronary artery disease

It is well known that ED is associated with numerous risk factors for coronary artery disease, including lipid abnormalities, hypertension, smoking, diabetes, obesity and lack of physical activity. However, most physicians do not routinely ask patients with coronary artery disease about ED, and these patients are often reluctant or embarrassed to discuss this subject. In addition, there is a paucity of studies examining the effect on ED of controlling

continued

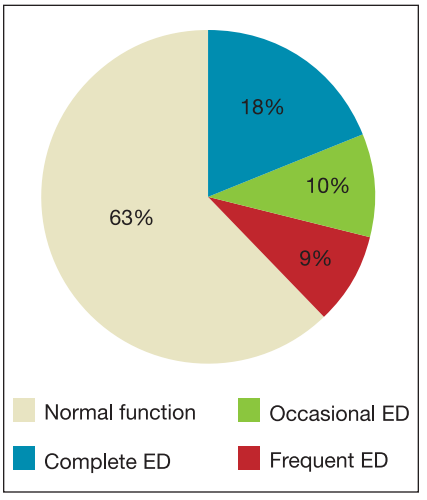


Figure 1. Prevalence of erectile dysfunction (ED) in 1240 men attending their GPs in Western Australia.

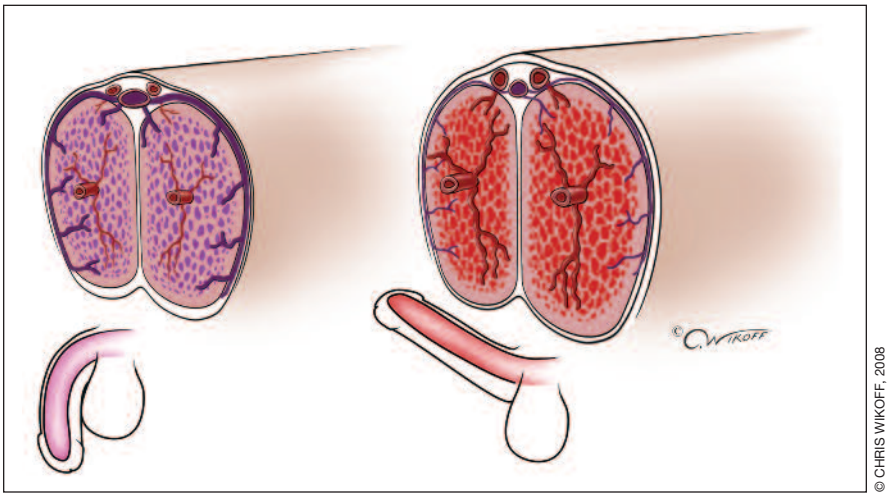


Figure 2. Penile erection is a neurovascular phenomenon that requires dilation of penile vasculature, relaxation of smooth muscle, increased intracorporal blood flow and normal veno-occlusive function.

risk factors after the diagnosis of ED has been made. The results of the few studies that have been performed indicate that the only lifestyle modification that may make a difference to the incidence of ED is continuation or initiation of physical activity.[8-10] Midlife changes in lifestyle other than physical activity may not have a beneficial effect on ED because it is simply too late. Some studies have suggested that smoking cessation may improve erectile function, which other studies have refuted.[11-14] In addition, use of some antihypertensive and lipid-lowering drugs may actually exacerbate ED. Future studies are needed to examine the effect of controlling cardiovascular risk factors on ED.

Neurological diseases

Many neurological disorders, including spinal cord injury, multiple sclerosis and cavernous nerve damage after major pelvic cancer surgery such as radical prostatectomy, commonly lead to ED.

Endocrine disorders

Endocrine disorders, such as hypogonadism, androgenic abnormalities, abnormal growth hormone levels and thyroid disease, also play a significant role in ED physiology. Although, androgens profoundly affect overall male sexual function and erectile physiology, a testosterone deficiency is a relatively uncommon cause of ED. Diagnosis of a testosterone deficiency involves demonstration of significant and persistent subnormal early morning total testosterone levels on at least two to three occasions. Further qualification of androgen status may require determination of pituitary gonadotrophin and prolactin levels. Treatment of hypogonadism includes oral tablets, topical gels, transdermal patches, intramuscular injections and implantable pellets.

Understanding patient needs

One of the initial steps in linking pathophysiology with optimal ED treatment outcomes is to understand the needs and objectives of the patient and his partner. The central issue in understanding the patient with ED is not only understanding ED as a medical condition, but also understanding patient and partner behaviours, attitudes and responses to sexual dysfunction. Physicians must consider sexual dysfunction in a broader context by focusing on the genital response and the psychosocial consequences and obstacles of ED. Further research in this field is necessary, particularly in the areas of patient behaviour, treatment seeking motivators and barriers, the effect of ED on the quality of life of the patient and his partner, the impact of successful treatment of ED on men with hypertension or diabetes, and patient education needs.

Taking a sexual history

Many men are reluctant to openly discuss their sexual problems with their doctor and elect to 'suffer in silence'. Many doctors fail to include a specific enquiry about sexual function when taking a general medical history. Doctors often rationalise the omission of the sexual history component of the medical history as the result of a lack of training or knowledge, feeling uncomfortable or a lack of sufficient time. Reasons for GPs' reluctance to openly discuss sexual health issues with their patients include a lack of appreciation of the importance of sexual health to general health, and a lack of specific knowledge, clinical skills and experience in this area. We often experience difficulty in finding the appropriate words and expressions when discussing sexuality which may be

due to discomfort with our own sexuality. In addition, resources and referral options may be limited or unavailable.

Doctors can utilise the general counselling skills they employ in the management of depression and anxiety when taking a sexual history and in sexual counselling. The PLISSIT counselling model represents a simple graded approach to sexual counselling (see the box on the PLISSIT model of counselling on this page). This model allows us to provide counselling up to the level of our expertise and comfort before referring patients for more specialised advice. To feel competent to perform sexual counselling, we often only need reassurance that we already have or can readily acquire the relevant counselling skills.

The PLISSIT model of counselling

The PLISSIT model of counselling is a simple graded approach that can readily be used in everyday clinical practice.

- P = permission. This is permission to talk about sex, permission to be anxious, permission to be ignorant, permission to ask questions and permission to be sexually active or not.
- LI = limited information. This is basic information about normal sexual functioning that serves to reassure patients that their experience is normal and to explain the basis of common sexual problems – in other words adult sex education.
- SS = specific suggestions. This might be something as simple as a lifestyle change; losing weight; giving up smoking; reducing alcohol intake; taking a holiday or spending more time with the partner; making more time available for foreplay; or perhaps changing a prescribed medication or stopping recreational drug use.
- IT = intensive therapy. This involves more in-depth counselling for sexual and relationship problems.

Sexuality in the ageing male

Many elderly men and their partners remain interested in maintaining an active sexual life often into their 90s. It is important not to discriminate against older people wishing to continue or reinstate sexual activity. Elderly patients may feel especially reluctant to discuss the subject of sex and that their partner may also be experiencing sexual dysfunction requiring specific treatment. Assessment of the severity, extent and aetiology of sexual dysfunction, the approach to diagnosis and the rationale for treatment must be underpinned by a thorough understanding of the changes that occur in the normal male sexual response as men age and what occurs when sexual function is disrupted.

Elderly men are less capable of achieving an erection solely with the use of sexual fantasy and usually require prolonged and more intense physical stimulation. The erectile response will generally take longer and the erection may not be as rigid as it was in the younger years. Erections in elderly men are often less stable with many men experiencing some softening of their erection during sexual activity. The refractory period, the time after ejaculation before a man can develop a subsequent erection, will increase progressively as men age. Many potent elderly men may have a refractory period of several days. Both the intensity of ejaculation and the volume of ejaculate may be less in older men. These men may also experience some delay in ejaculation due to an age-related degenerative reduction in penile skin sensitivity coupled with some post-menopausal loss of pelvic floor muscle tone in their often multiparous partners. All of these changes are a normal part of the male ageing process. Patients need to understand the nature of these changes so that they do not become anxious and concerned as their sexual responses alter.

Investigations

All men with ED require a careful general physical examination with specific attention to their external genitals, androgen status, lower limb pulses and prostate. Fasting lipids, glucose, morning total testosterone and, where indicated, prostate specific antigen (PSA) levels should always be determined. Further detailed investigations such as penile duplex Doppler ultrasonography may be indicated in patients refractory to initial drug treatment. (See the second part of this article, Erectile dysfunction Part 2: Managing men unresponsive to PDE5 inhibitors, in the November issue of *Medicine Today*.)

Treatment

Treatment of ED should include a structured approach to diagnosis, identification and correction of risk factors and treatment (see the box on managing erectile dysfunction on page 20).

Phosphodiesterase-5 inhibitor drugs

The potent, competitive PDE5 inhibitor drugs sildenafil (Viagra), tadalafil (Cialis) and vardenafil (Levitra) have been shown to be efficacious, safe and well tolerated in the treatment of ED (see the box on the PDE5 inhibitor drug profile on page 22).[15-17] Following activation of the nitric oxide/cyclic guanosine monophosphate (cGMP) pathway by sexual arousal, inhibition of PDE5 iso-enzyme results in increased corporal levels of cGMP and an augmented penile erection in men with ED (Figure 3). Data indicate that there are differences among sildenafil, tadalafil and vardenafil in pharmacokinetic properties, efficacy, potency, half-life and adverse effect profiles. Well-designed

continued

Managing erectile dysfunction

Step 1: Diagnosis of erectile dysfunction
- Sexual, medical and psychological history
- Physical examination
- Laboratory tests

Step 2: Patient assessment and education
- Review test findings
- Identify patient and partner needs and preferences
- Refer if needed or requested

Step 3: Modify reversible causes
- Medication change
- Hormonal replacement
- Lifestyle modification

Step 4: Treatment

First-line treatment
- Phosphodiesterase-5 inhibitors
- Vacuum constriction devices
- Sex therapy

Second-line treatment
- Penile injections

Third-line treatment
- Combination therapy

Fourth-line treatment
- Penile prosthesis

Step 5: Erectile dysfunction resolution with follow up or erectile dysfunction resolved

studies are needed to compare these products.

PDE5 inhibitor drugs are effective in restoring erectile function and improving intercourse success rates in a wide range of patients, including those with hypertension, diabetes, spinal cord injury or other concomitant medical conditions, and in those patients taking a wide variety of concomitant medications. Their efficacy is related to the extent and severity of ED, with significantly reduced efficacy demonstrated in patients with severe vasculogenic

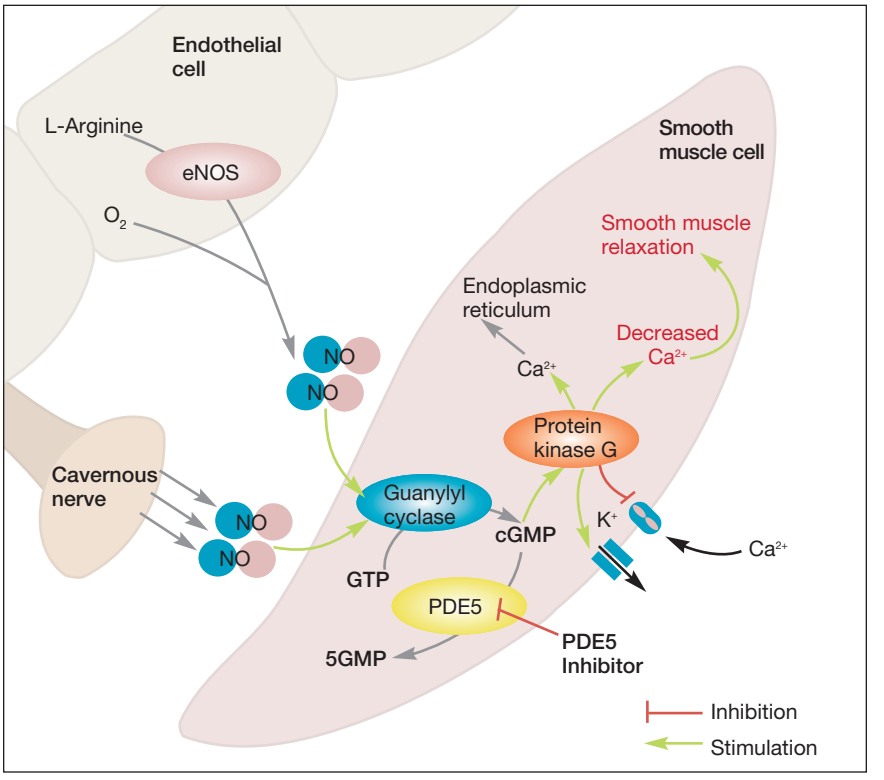


Figure 3. Following activation of the nitric oxide (NO)/cyclic guanosine monophosphate pathway by sexual arousal, inhibition of phosphodiesterase-5 (PDE5) iso-enzyme results in increased corporal levels of cGMP and an augmented penile erection in men with erectile dysfunction.

ED, diabetic ED and ED after radical prostatectomy.

Treatment with PDE5 inhibitor drugs is generally well tolerated and the adverse effects reported are usually transient, mild to moderate in nature and dose dependent. The most commonly reported adverse effects are headache, flushing, dyspepsia, muscle or back ache and nasal congestion. PDE5 inhibitors are contraindicated in patients taking aerosol, tablet or topical short- or long-acting organic nitrates, such as glyceryl trinitrate or isosorbide dinitrate. PDE5 inhibitors have been shown to cause greater decreases in blood pressure in some patients on organic nitrates. The frequency of discontinuation of treatment because of adverse events is low and in clinical trials was comparable with that with placebo.[15-17] No cases of priapism, a persistent painful erection of the penis, have been reported with normal clinical use (see the box on the PDE5 inhibitor drug profile on page 22).

Intracorporal injection therapy

Treatment with self-administered intracorporal injection therapy using vasodilator drugs such as alprostadil (Caverject Impulse) or papaverine, which relax the arterial and trabecular smooth muscle, is an effective therapy for ED.

Alprostadil

The mechanism of the vasodilating action of alprostadil remains incompletely understood. Alprostadil increases intracellular cyclic adenosine monophosphate (cAMP) via modulation of the enzyme adenyl

continued

Phosphodiesterase-5 (PDE5) inhibitor drug profile*

Action
- Sexual arousal activates the nitric oxide/cGMP pathway. Inhibition of PDE5 results in increased corporal levels of cGMP, relaxation of penile vascular smooth muscle, increased corporal blood flow and augmented penile tumescence/erection

Drugs
- Sildenafil (Viagra), tadalafil (Cialis) and vardenafil (Levitra)

Onset
- Sexual arousal is essential for a response
- An erection occurs as early as 15 minutes after administration
- High-fat meals limit speed and extent of absorption of sildenafil and vardenafil but not tadalafil
- Detumescence occurs immediately after ejaculation or cessation of sexual arousal

Duration of response
- Sildenafil: four to six hours
- Vardenafil: four to five hours
- Tadalafil: up to 36 hours

Dosage
- Assess patient fitness for renewed sexual activity before initiating treatment
- Refer to the Table below for recommended dosages

Drug selection
- Choice of drug should be individualised to patient's needs
- No 'head to head' comparative studies are available
- The extended period of responsiveness of tadalafil may suit some patients

Metabolism
- Rapidly absorbed after oral administration
- Maximum plasma concentrations are reached within 30 to 120 minutes in the fasted state
- Pharmacokinetics are dose proportional over the recommended dose range
- Extensively metabolised by cytochrome P450 (CYP) 3A4 (major route) and CYP2C9 (minor route) hepatic microsomal iso-enzymes

Adverse effects
- Adverse effects are dose related and are usually of mild-to-moderate severity
- Most common adverse effects are headache, flushing, dyspepsia, muscle or back ache and nasal congestion
- Mild transient alteration in colour vision may occur with sildenafil and vardenafil
- No cases of priapism have been reported in routine clinical use

Drug interactions
- Concomitant use of potent CYP3A4 inhibitors (e.g. erythromycin, ketoconazole, itraconazole, protease inhibitors) as well as the nonspecific CYP inhibitor, cimetidine, is associated with increased plasma levels
- Concomitant administration of CYP3A4 inducers, such as rifampin, will decrease plasma levels
- Potentiation of the hypotensive effects of nitrates and administration in patients who use nitric oxide donors or nitrates in any form is therefore contraindicated

Table. Recommended dosages of PDE5 inhibitors*

Drug	Doses available	Starting dose	Timing of dose before sexual activity	Maximum dose	Comments
Sildenafil	25, 50 and 100 mg	50 mg	60 minutes	100 mg	Reduce dose in the elderly, or in men with renal or liver failure
Tadalafil	10 and 20 mg	20 mg	60 to 120 minutes or more	20 mg	–
Vardenafil	5, 10 and 20 mg	10 mg	25 to 60 minutes	20 mg	Reduce dose in the elderly

* Please refer to full product information before prescribing.

cyclase, leading to a decrease in the free calcium concentration and, subsequently, to smooth muscle relaxation. Alprostadil has a short duration of action, is extensively metabolised by corporal dehydrogenase and reductase enzymes, and has a plasma half-life of less than one minute because of rapid pulmonary clearance of up to 80% after the first pass through the lungs (see the box on the alprostadil drug profile on page 23). About 30% of the drug is metabolised within the corpora cavernosa.

Alprostadil has shown superior efficacy and reduced risk of priapism and penile fibrosis compared with papaverine alone or in combination with phentolamine.[19] Alprostadil resulted in an erection of sufficient rigidity for sexual intercourse in 72.6% of men with ED. The principal side effect of intracorporal injection of alprostadil is pain at the site of injection, which occurs in up to 30% of patients. Prolonged erections seem to be a rare complication. Although early experience suggested that fibrosis was uncommon with alprostadil intracorporal injections, recent long-term studies document a much higher incidence of fibrosis and scar formation of 9 to 23.3% in mid-term and long-term users suggesting that patients be specifically warned of the possibility of penile fibrosis before starting treatment.[19] Penile fibrosis may be associated with the development of painful penile nodules, penile deformity including curvature of the erect penis sufficient to preclude intercourse or the development of more severe ED (see the box on the alprostadil drug profile on this page).

Papaverine

Papaverine is a potent nonspecific smooth muscle relaxant that causes vasodilation of penile vascular and sinusoidal smooth muscle by its action at multiple levels but primarily by its action as a nonselective cAMP PDE5 inhibitor. Papaverine has a relatively short plasma half-life of one to two hours and is extensively metabolised in the liver.

A meta-analysis of the largest published studies on the therapeutic use of papaverine reported an efficacy of 53% in men with ED.[19] When combined with phentolamine, a competitive alpha-adrenoceptor antagonist, 68% of users responded with a rigid erection. The efficacy of intracorporal injections of papaverine is limited by frequent reports of local adverse effects, principally priapism and penile fibrosis. As such, papaverine use should be restricted to informed patients

Alprostadil drug profile*

Action

- Relaxation of trabecular smooth muscle and dilation of cavernosal arteries, expansion of lacunae and entrapment of blood by compression of the drainage venules against the tunica albuginea
- Administered by direct intracorporal injection

Onset

- Five to 20 minutes after intracorporal injection
- Arousal is usually required to produce a maximal response
- With correct dosing, detumescence should commence within 10 to 20 minutes of ejaculation but a fully flaccid penis may not occur for a further one to two hours

Dosage

- Assess patient fitness for renewed sexual activity
- Administer five to 20 minutes before planned sexual activity
- Individualise dose by initial in-office physician supervised dosage titration using the lowest possible effective dose
- Available as Caverject Impulse 10 (10 µg) or Caverject Impulse 20 (20 µg)
- Instruct patient on sterile injection technique, used needle disposal and the management of prolonged erections
- Maximum frequency of use is no more than three times a week with at least 24 hours between each dose
- Start with 5 µg and titrate in 5 µg increments to a maximum of 20 µg in patients with organic ED
- Start with 1.25 µg and titrate in 1.25 µg increments in patients with spinal cord injuries

Management of prolonged erection[18]

- Patient should use lowest possible effective dose
- If still rigid:
  - two hours after administration, the patient should take pseudoephedrine 120 mg
  - four hours after administration, the patient should take pseudoephedrine 120 mg and walk briskly for 10 to 15 minutes
  - six hours after administration, the patient should contact his treating doctor or hospital emergency department
- Some patients may require aspiration of corpora, irrigation with dilute vasoconstrictors or surgical drainage

Metabolism

- Short duration of action and a brief plasma half-life
- Thirty percent of the drug is metabolised within the corpora cavernosa and/or urethral mucosa and up to 80% after the first pass through the lungs to inactive metabolites

Adverse effects

- Mild penile pain (15 to 20%), priapism (0.25%) and penile fibrosis (5 to 10%) with long-term use[19]
- About 30% of users discontinue intracorporal injections each year

Drug interactions

- Systemic drug-drug interactions are unlikely because of low or undetectable levels of alprostadil in the peripheral venous circulation

* Please refer to full product information before prescribing.

refractory to alprostadil. A meta-analysis of the published literature reports priapism in 7.1% of patients. In one study, penile fibrosis, presenting as penile nodules or curvature, was reported in 95% of long-term users.[19] Penile fibrosis is related to poor injection technique, frequent injections and long-term use. Papaverine hepatotoxicity is rarely a clinical problem and may manifest either as an increase in liver transaminases, which is relatively common (occurring in more than one in 100 treated patients), or as drug-induced hepatitis, which is rare (occurring in less than one in 1000 treated patients).

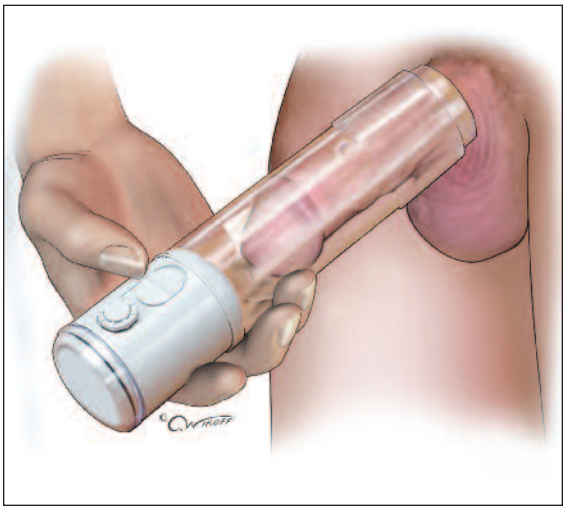


Figure 4. Vacuum constriction devices comprise a clear plastic cylinder, either an integrated or separate battery or hand vacuum pump, and a collection of different sized rings. They work by creating a vacuum negative pressure, which increases the blood flow into the corpora cavernosa. The resulting engorgement is maintained by trapping the blood in the penis using a constriction ring at the base, cutting off the venous outflow.

Polyagent intracorporal injection therapy

The use of polyagent intracorporal injections containing alprostadil combined with other agents such as papaverine, phentolamine and atropine may be effective in patients refractory to maximum dose alprostadil monotherapy. In a comparative study, a 91.6% response rate to a combination of alprostadil, papaverine and phentolamine was reported.[20] Polyagent intracorporal injections appear effective as 'salvage therapy' when treating patients with severe vasculogenic ED. However, despite its proven efficacy, a significant number of patients remain refractory to intracorporal injection therapy.

Vacuum constriction devices

Vacuum constriction devices work by creating a vacuum negative pressure that increases blood flow into the corpora cavernosa. The erection is maintained by trapping the blood in the penis using a constriction ring at the base, which reduces venous outflow. Vacuum constriction devices comprise of a clear plastic cylinder, either an integrated or separate battery or hand vacuum pump, and a collection of different sized rings (Figure 4).

Vacuum constriction devices require enthusiasm on the part of the patient and a sympathetic partner. They are more popular in middle-aged and older-aged couples and are an uncommon treatment choice in single younger men. The patient requires manual dexterity and repeated practice because this technique is not necessarily successful in the first few attempts. Patient satisfaction varies enormously and is related to effectiveness. About 60 to 70% of men find the device straightforward. Satisfaction rates, both short and long term, vary considerably from as low as 27% in the short term, to as high as 69% with two-year follow up. Complications include petechiae, pain at the site of the ring, ejaculatory changes including pain on ejaculation and blocked ejaculation, numbness and pivoting of the penis at the base. The ring should not be left on the penis for more than 30 minutes and the use of vacuum constriction devices is relatively contraindicated in men taking warfarin and in those with an increased risk of intravascular thrombosis due to myeloproliferative diseases and sickle cell anaemia.

Penile implants

Penile implants are the last resort of treatment despite the fact that this type of treatment is associated with a high satisfaction rate. Malleable penile implants have the advantage of being implanted with simple surgery and at low cost but are limited by the presence of a permanent erection and poor cosmetic appearance. Multicomponent inflatable penile implants are more expensive but produce a more natural erection because of the voluntary control over the erection (Figure 5). Device failure and prosthetic infection are uncommon, although infection is the most problematic complication after surgery and often requires removal of the prosthesis and either immediate replacement or staged re-implantation at a later time.

Alternative and unproven therapies

Herbal and unproven drugs and medical device treatments with no evidence basis to support their efficacy and safety are now commonly advertised to the public. These advertisements often make unsubstantiated statements about global efficacy and absent adverse effects. Furthermore, these treatments are often unjustifiably expensive. Patients should be advised to avoid these types of treatment and consult their GPs with any problems.

Erectile dysfunction in patients with coronary artery disease

Although sexual intercourse is associated with an increased relative risk of acute myocardial infarction in patients with coronary artery disease, the absolute risk is actually low. There is a finite chance of developing myocardial ischaemia with sexual activity in patients with coronary

continued

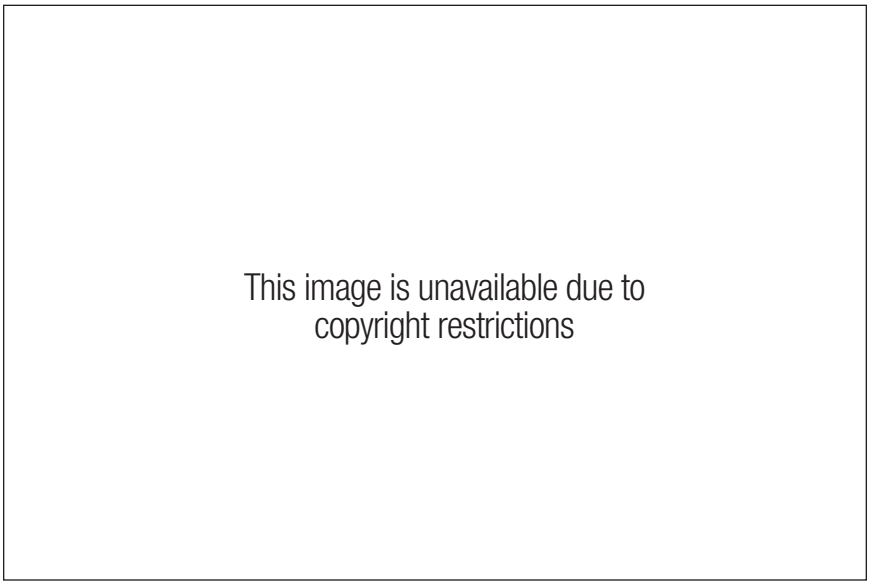


IMAGE COURTESY OF AMERICAN MEDICAL SYSTEMS

Figure 5. The AMS-700 MS inflatable penile implant. The three piece inflatable implant consists of a scrotal pump, a reservoir implanted in the abdomen and a pair of cylinders implanted in the penile.

artery disease. Sexual intercourse is associated with a certain physiological cost to the heart. Heart rate and blood pressure increase and anywhere from three to six metabolic equivalents (METs) are expended, depending on the vigour of the physical activity. If a patient can achieve this degree of physical exertion on an exercise test without angina or ST-segment depression of the electrocardiogram, or without perfusion or wall motion abnormalities, then the chance of myocardial ischaemia developing during sexual activity is low.

It is also important to remember that before and during sexual activity there may be anticipatory stimulation of the sympathetic nervous system, which could also contribute to ischaemia, arrhythmias and possible cardiac events independent of the energy expenditure associated with the sexual act. The American College of Cardiology and the Princeton Consensus Panel have issued guidelines for the treatment of sexual dysfunction of the cardiac patient.[21,22]

Because PDE5 is found not only in the smooth muscle cells within the corpus cavernosum, but also in the smooth muscle cells of the systemic arteries and veins throughout the body, PDE5 inhibitors have the potential to interact with the cardiovascular system. Sildenafil, tadalafil and vardenafil cause small decreases in arterial pressure. All PDE5 inhibitors are contraindicated in patients taking aerosol, tablet or topical short- or long-acting organic nitrates, such as glyceryl trinitrate or isosorbide dinitrate. PDE5 inhibitors have been shown to cause greater decreases in blood pressure in some patients on organic nitrates. Other than that contraindication, both of these drugs appear relatively safe in stable cardiac and stable hypertensive patients. Large controlled studies have not shown an increase in cardiovascular adverse events such as MI or cardiac death.[23]

PDE5 inhibitors may have small additive effects on decreasing blood pressure when given to patients on antihypertensives. However, the incidence of adverse events with the oral PDE5 inhibitor sildenafil was found to be no greater in patients taking antihypertensive medicines compared with those not taking antihypertensive medicines.[24] Sildenafil was shown to have no adverse effects on coronary artery

Important messages for patients

- The speed and extent of the male and female sexual responses reduce as men and women age – patient treatment expectations should be appropriate for the couple's ages.
- Erectile dysfunction is associated with cigarette smoking, hypertension, peripheral vascular disease, diabetes and depression – the presence of erectile dysfunction may indicate the presence of other underlying unrecognised physical disease.
- There is always a contributing psychological component, the resolution of which by psychosexual therapy may, despite the presence of a contributing physical cause, result in restoration of potency – not all men require treatment with medication.
- Most men can be successfully treated with a combination of sexual education, changes in lifestyle and oral medication.
- Many couples experience a fulfilling sexual relationship without penetrative sexual intercourse – not all men need to have potency restored.
- Men with long-term erectile dysfunction and chronic medical illness, for example, coronary artery disease or chronic obstructive pulmonary disease, must have their fitness for renewed sexual activity assessed before initiation of treatment.
- Men with angina who take prescribed nitrates should not take sildenafil.

diameter or flow and, in fact, improved coronary vasodilator reserve. Sildenafil, tadalafil and vardenafil were shown to have no deleterious effects on exercise tolerance or time to ischaemia during exercise testing. Thus, oral PDE5 inhibitors appear to be safe and effective for most stable cardiac patients.

There is increasing evidence to suggest that men with ED, especially those who also have diabetes, metabolic syndrome or testosterone deficiency syndrome, are at an increased risk of silent myocardial ischaemia and subsequent cardiac events. Screening for coronary artery disease with exercise electrocardiography and, if indicated, coronary angiography and/or other cardiac imaging techniques should be regarded as an important part of the evaluation of these 'at-risk' men.

Conclusion

Community-based epidemiological studies suggest that ED is common and is associated with a reduced quality of life. Oral PDE5 inhibitor drugs have changed the ED treatment paradigm and decreased the use of more invasive options.

The treatment of ED rests clearly within the domain of the primary care physician. Most couples with ED can be successfully managed by treatment of comorbid disease, correction of risk factors and modification of lifestyle, simple psychosexual education and counselling, and treatment with a PDE5 inhibitor drug (see the box on page 26 for some important messages for patients).

The busy GP may elect to refer patients with ED who are refractory to PDE5 inhibitor therapy to a urologist, sexual health physician or other interested specialists. GPs with an interest in male sexual health and specialists who manage sexual dysfunction are likely to help most patients with ED who are refractory to PDE5 inhibitors using one or a combination of approaches. This will consequently improve both the overall and sexual quality of life of the patient and his partner. These approaches are the subject of the second part of this article, Erectile dysfunction Part 2: Managing men unresponsive to PDE5 inhibitors, to be published in the November issue of *Medicine Today*. MT

A list of references is available on request to the editorial office.

COMPETING INTERESTS: Associate Professor Chris McMahon is a consultant, investigator and/or a member of a speakers panel for Pfizer and Bayer Schering. Dr Chelsea McMahon: None.

Medicine Today 2008; 9(10): 16-28

Erectile dysfunction

Part 1: investigation and management

CHRIS G. McMAHON MB BS, FAChSHM **CHELSEA N. McMAHON** MB BS, BSc

References

1. NIH Consensus Conference. Impotence. NIH Consensus Development Panel on Impotence. JAMA 1993; 270: 83-90.
2. Laumann, EO, Paik A, Rosen RC. Sexual dysfunction in the United States: prevalence and predictors. JAMA 1999; 281: 537-544.
3. Chew KK, Earle CM, Stuckey BG, Jamrozik K, Keogh EJ. Erectile dysfunction in general medicine practice: prevalence and clinical correlates. Int J Impot Res 2000; 12: 41-45.
4. Desouza C, Parulkar A, Lumpkin D, Akers D, Fonseca VA. Acute and prolonged effects of sildenafil on brachial artery flow-mediated dilatation in type 2 diabetes. Diabetes Care 2002; 25: 1336-1339.
5. Halcox JP, Nour KR, Zalos G, et al. The effect of sildenafil on human vascular function, platelet activation, and myocardial ischemia. J Am Coll Cardiol 2002; 40: 1232-1240.
6. Katz SD, Balidemaj K, Homma S, Wu H, Wang J, Maybaum S. Acute type 5 phosphodiesterase inhibition with sildenafil enhances flow-mediated vasodilation in patients with chronic heart failure. J Am Coll Cardiol 2000; 36: 845-851.
7. Kimura M, Higashi Y, Hara K, et al. PDE5 inhibitor sildenafil citrate augments endothelium-dependent vasodilation in smokers. Hypertension 2003; 41: 1106-1110.
8. Feldman HA, Johannes CB, Derby CA, et al. Erectile dysfunction and coronary risk factors: prospective results from the Massachusetts male aging study. Prev Med 2000; 30: 328-338.
9. Feldman HA, Goldstein I, Hatzichristou DG, Krane RJ, McKinlay JB. Impotence and its medical and psychosocial correlates: results of the Massachusetts Male Aging Study. J Urol 1994; 151: 54-61.
10. Derby CA, Mohr BA, Goldstein I, Feldman HA, Johannes CB, McKinlay JB. Modifiable risk factors and erectile dysfunction: can lifestyle changes modify risk? Urology 2000; 56: 302-306.
11. Chew KK, Bremner A, Stuckey B, Earle C, Jamrozik K. Is the relationship between cigarette smoking and male erectile dysfunction independent of cardiovascular disease? Findings from a population-based cross-sectional study. J Sex Med 2008; online.
12. Kupelian V, Link CL, McKinlay JB. Association between smoking, passive smoking, and erectile dysfunction: results from the Boston Area Community Health (BACH) Survey. Eur Urol 2007; 52: 416-422.
13. Millett C, Wen LM, Rissel C, et al. Smoking and erectile dysfunction: findings from a representative sample of Australian men. Tob Control 2006; 15: 136-139.
14. Shiri R, Hakama M, Hakkinen J, Tammela TL, Auvinen A, Koskimaki J. Relationship between smoking and erectile dysfunction. Int J Impot Res 2005; 17: 164-169.
15. Goldstein I, Lue TF, Padma-Nathan H, Rosen RC, Steers WD, Wicker PA. Oral sildenafil in the treatment of erectile dysfunction. Sildenafil Study Group. N Engl J Med 1998; 338: 1397-1404.
16. Brock GB, McMahon CG, Chen KK, et al. Efficacy and safety of tadalafil for the treatment of erectile dysfunction: results of integrated analyses. J Urol 2002; 168: 1332-1336.
17. Porst H, Rosen R, Padma-Nathan H, et al. The efficacy and tolerability of vardenafil, a new, oral, selective phosphodiesterase type 5 inhibitor, in patients with erectile dysfunction: the first at-home clinical trial. Int J Impot Res 2001; 13: 192-199.
18. Nehra A. Priapism-pathophysiology and non-surgical management. In: Porst H, Buvat J, eds. Standard practice in sexual medicine. Oxford: Blackwell Publishing; 2006. p. 174-180.
19. Porst H. The rationale for prostaglandin E1 in erectile failure: a survey of worldwide experience. J Urol 1996; 155: 802-815.
20. Padma-Nathan H. The efficacy and synergy of polypharmacotherapy in primary and salvage therapy of vasculogenic erectile failure. Int J Impot Res 1990; 2: 257-258.
21. Jackson G, Rosen RC, Kloner RA, Kostis JB. The second Princeton consensus on sexual dysfunction and cardiac risk: new guidelines for sexual medicine. J Sex Med 2006; 3: 28-36.
22. Cheitlin MD, Hutter Jr AM, Brindis RG, et al. ACC/AHA expert consensus document. Use of sildenafil (Viagra) in patients with cardiovascular disease. American College of Cardiology/American Heart Association. J Am Coll Cardiol 1999; 33: 273-282.
23. Kontaras K, Varnavas V, Kyriakides ZS. Does sildenafil cause myocardial infarction or sudden cardiac death? Am J Cardiovasc Drugs 2008; 8: 1-7.
24. Bohm M, Burkart M, Baumann G. Sildenafil is well tolerated by erectile dysfunction patients taking antihypertensive medications, including those on multidrug regimens. Curr Drug Saf 2007; 2: 5-8.