Erectile dysfunction

Part 1: Patient assessment and treatment options

CHRIS G. McMAHON MB BS, FAChSHM
CHELSEA N. McMAHON MB BS, BSc(Hons), FRACP

Erectile dysfunction (ED) may be an early manifestation of generalised endothelial dysfunction and a predictor of other forms of cardiovascular disease, suggesting a need for screening. ED treatments include oral medications, intracavernous injection pharmacotherapy, vacuum constriction devices and penile prostheses, alone or in combination with graded levels of psychosexual counselling.

KEY POINTS

- Erectile dysfunction (ED) is common and can be treated pharmacologically in most men.
- ED may be a predictor and a precursor of other forms of cardiovascular disease morbidity and mortality.
- The patient's cardiovascular status and overall fitness for renewed sexual activity should be assessed before initiation of ED treatment.
- Oral phosphodiesterase-5 (PDE5) inhibitors are effective in 65 to 70% of men with ED; their efficacy is significantly reduced in patients with severe vasculogenic ED, diabetic ED and ED after radical prostatectomy.
- Alprostadil is the drug of first choice for self-administered intracavernous injections and is effective in 70% of men with ED, with a low risk of priapism and penile fibrosis.
- Intrapenile prostheses are effective treatments in men with ED unresponsive to pharmacotherapy.

Erectile dysfunction (ED) is a common male sexual dysfunction that is associated with a reduced quality of life for men and their partners. In the past three decades, advances in our understanding of the physiology of erection have resulted in parallel changes in the approach to evaluation and treatment of men with ED. The ED treatment paradigm has evolved from the previous psychosexual model to a new integrated treatment model that incorporates oral and intracavernous injection pharmacotherapy, devices and prostheses, alone or in combination with graded levels of psychosexual counselling. The link between coronary artery disease and vasculogenic ED is now well established, with implications for cardiovascular screening of men with ED.

In this first of a series of two articles on ED, we discuss assessment of men with ED and treatment options, including oral phosphodiesterase-5 (PDE5) inhibitors, intracavernous alprostadil injections, devices and prostheses. In Part 2 of the series, in the April issue of *Medicine Today*, we will discuss management of men with ED that is unresponsive to PDE5 inhibitor therapy.

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Dr Chris McMahon Is a Sexual Health Physician and Director of the Australian Centre for Sexual Health, Sydney, NSW. Dr Chelsea McMahon is an Endocrinologist at St Vincent's Private Hospital, Lismore, NSW.

1. CAUSES OF ERECTILE DYSFUNCTION

Psychogenic: Performance anxiety, depression, relationship and psychosocial factors

Vasculogenic: Atherosclerotic penile arterial disease, corporal venous leakage, traumatic arterial stenosis or occlusion

Endocrine or metabolic: Diabetes, hypogonadism, hyperprolactinaemia, subthyroidism, end-stage renal failure

Neurogenic: Spinal cord injury, multiple sclerosis, major pelvic cancer surgery (e.g. radical prostatectomy)

End-organ disease: Peyronie's disease, pelvic or genital radiotherapy

Medications: Selective serotonin reuptake inhibitors, thiazide diuretics, nonselective alpha blockers and beta-2 blockers

Epidemiology

A range of definitions of ED have been proposed by different expert bodies.[1-3] The most commonly quoted National Institutes of Health (NIH) definition of ED is the inability to get or keep an erection firm enough for satisfactory sexual intercourse.[1]

Epidemiological data from Australian, US and UK observational studies estimate the prevalence of complete ED as about 5% among 40-year-olds, 10% among men in their 60s, 15% among men in their 70s and 30 to 40% among men in their 80s. However, only half of the men who self-report ED are concerned about it. Prevalence studies show that, when controlling for other factors, ED is associated with increasing age, depression, obesity, lack of exercise, diabetes, hypertension, dyslipidaemia, cardiovascular disease and lower urinary tract symptoms (LUTS) or benign prostatic hyperplasia (BPH).[4,5] The Multinational Survey on the Aging Male (MSAM-7) study reported that men with LUTS had an overall prevalence of ED of 49%, complete erectile failure in 10% and an overall prevalence of ejaculatory disorders of 46%.[6]

Pathophysiology

Penile erection is a neurovascular phenomenon that requires relaxation of arterial and corporal smooth muscle, dilation of penile vasculature and corporal lacunar spaces, increased intracavernosal blood flow and normal veno-occlusive function. Penile vascular disease is the most common cause of organic ED and may involve several pathophysiological mechanisms including impaired arterial inflow, impaired smooth muscle cavernosal relaxation, chronic ischaemia-induced increased cavernosal smooth muscle contraction, cavernosal fibrosis, veno-occlusive dysfunction and chronic or episodic hypoxaemia. Endothelial dysfunction appears to be the final common pathway for many cases of ED.[7] ED may be an early manifestation of generalised endothelial dysfunction and a predictor and precursor of other forms of cardiovascular disease.[8] More than half of men with ED who have no cardiac symptoms have abnormal results on stress testing, and 40% have significant coronary artery disease when studied.[9]

Apart from age, the main risk factors for ED are those for vascular disease: smoking, diabetes mellitus, hypertension, abnormal lipid profile, obesity and lack of exercise. Other factors include depression and endocrine disorders (Box 1).

Diabetes

Erectile dysfunction is reported to occur in 35 to 70% of men with type 2 diabetes.[10] Erectile dysfunction occurs at an earlier age in men with diabetes compared with men without diabetes, and the age-adjusted probability of complete ED is nearly three times higher in the former.[4,10] More than 50% of men develop ED within 10 years of being diagnosed with diabetes. The prevalence of ED increases with diabetes duration, poor glycaemic control and diabetes complications such as vascular and microvascular disease and neuropathies.[11] Studies have found prevalence rates for ED of 49% in patients with type 1 diabetes and 34% and 24% for severe and mild to moderate ED, respectively, in patients with type 2 diabetes.[12,13]

Neurological disease

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

Endocrine disorders

Endocrine disorders such as hypogonadism, hyperprolactinaemia and thyroid disease play a significant role in ED physiology. Testosterone regulates cavernosal nerve structure and function, nitric oxide (NO) synthase expression and activity, phosphodiesterase type 5 and corporal smooth muscle cell growth and differentiation.

Benign prostatic hyperplasia

Men with BPH have a high prevalence of ED. The reason for this association is unclear. The quality of life of men with BPH is reduced by its effects on sexual function.[14]

Iatrogenic ED

Antihypertensive and antidepressant drugs may cause ED as an adverse drug reaction, and discontinuation does not always result in the recovery of erectile function. Antihypertensive agents such as thiazide diuretics, nonselective alpha blockers, and beta-2 blockers may cause ED. ACE inhibitors, calcium channel blockers, alpha-1 blockers and angiotensin receptor blockers are known to have a low risk of ED.[15]

Psychogenic contributors

Although most men with ED have an underlying vascular cause, usually related to endothelial dysfunction, there is always a contributing, sometimes substantial, psychogenic component related to

performance anxiety. Treatment of this component alone may be sufficient to restore normal erections.

Sexuality in the ageing male

Ageing is a risk factor for ED because of the common pathological conditions in the ageing male, such as atherosclerosis, hypogonadism, chronic diseases associated with organic ED and their treatments which can interfere with sexual function at a central and peripheral level. Ageing is associated with impaired endothelial function and atherosclerosis.[16] It is well recognised that androgen decline in ageing men is associated with a reduction in the number and quality of erections, and that testosterone has a central role in endothelial function.[17,18]

Many older men and their partners are interested in maintaining an active sexual life, often into their 90s. Although the incidence of ED rises significantly with increasing age, recent studies indicate that 55 to 70% of men aged 77 to 79 years are sexually active. It is important not to discriminate against older people wishing to continue or reinstate sexual activity. Older patients may feel especially reluctant to discuss sex and the possibility 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 when sexual function is disrupted.

Older men are less capable of achieving an erection solely through 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 when younger. Erections in older men are often less stable, with many men experiencing some softening of their erection during sexual activity. The refractory period, or time after ejaculation before a man can develop a subsequent erection, increases progressively as men age. Many potent older men 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 postmenopausal 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.

Evaluation of patients with ED

A full medical and personally and culturally sensitive sexual history and a thorough clinical examination of the patient are needed to:

- confirm that the patient is experiencing ED or another sexual dysfunction such as hypoactive desire or premature ejaculation
- assess the onset, severity and duration of the condition and its impact on the man's partner
- identify the presence and contribution of potentially reversible causes (medications, drug or alcohol abuse), risk factors, comorbid disease or psychosocial factors
- determine whether the cause of ED is psychogenic, organic (e.g. vasculogenic, endocrine, neurological or end organ disease such as penile deformity due to Peyronie's disease) or mixed (Box 1)
- assess the fitness of the patient to resume sexual activity.

Any relationship between anxiety and ED should be explored. Psychogenic ED is likely in younger men with no vascular risk factors who report an abrupt onset of ED and persistent early morning or nocturnal erections. The causes of psychogenic ED are manifold and include sexual performance anxiety, global anxiety, relationship problems, depression, guilt and fear. Careful enquiry should be made about current medications, such as thiazide diuretics, nonselective alpha blockers, beta-2 blockers and antidepressants, as well as the use of recreational drugs.

Several patient self-administered questionnaires have been validated to objectively score erectile function. The short five-question form of the International Index of Erectile Function (IIEF) – the IIEF-5 or Sexual Health Inventory for Men (SHIM) – is useful for both diagnosis and assessment of response to treatment (Box 2).[19]

Physical examination

A focused physical examination in men with ED includes general body habitus and genital anatomy and should identify any related genital abnormalities (e.g. Peyronie's plaques), endocrine signs and possible comorbidities (neurological, vascular and possible life-threatening conditions).[20] The gently stretched flaccid penis should be carefully palpated to identify any fibrous Peyronie's plaques or phimosis. The presence, size and consistency of testes and adnexa should be determined to evaluate the presence of atrophy and androgen status. Screening for prostate adenocarcinoma with a digital rectal examination and measurement of prostate-specific antigen (PSA) in men over the age of 50 years is prudent but not mandatory, except in men with an increased risk of prostate adenocarcinoma or LUTS suggesting BPH.

Clinical investigations

Laboratory investigations

The degree to which men should undergo clinical investigation depends on the history and examination findings.[21-28] General investigations include measurement of serum concentrations of total testosterone (before 10 am), fasting glucose, fasting lipids and PSA in men over 50 years of age and selected high-risk or LUTS-symptomatic patients.[21,23,24,27,29]

There is a general consensus that screening for low testosterone levels with a morning total testosterone assay (8.00 am to 11.00 am) is the investigation of choice

2. SEXUAL HEALTH INVENTORY FOR MEN*[19]

The Sexual Health Inventory for Men (SHIM) questionnaire (also known as the IIEF-5) is a condensed five-item version of the 15-item International Index of Erectile Function (IIEF), designed for easy use by clinicians to diagnose the presence and severity of erectile dysfunction (ED) in clinical settings. It is intended to complement physical examination and history taking.
Men are asked to rate their answers to five questions on a scale of 1 to 5.

SHIM QUESTIONNAIRE				
Over the past six months				
1. How do you rate your confidence that you could keep an erection?				
1 (very low)	2 (low)	3 (moderate)	4 (high)	5 (very high)
2. When you had erections with sexual stimulation, how often were your erections hard enough for penetration (entering your partner)?				
1 (almost never or never)	2 (a few times [much less than half the time])	3 (sometimes [about half the time])	4 (most times [more than half the time])	5 (almost always or always)
3. During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?				
1 (almost never or never)	2 (a few times [much less than half the time])	3 (sometimes [about half the time])	4 (most times [more than half the time])	5 (almost always or always)
4. During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?				
1 (extremely difficult)	2 (very difficult)	3 (difficult)	4 (slightly difficult)	5 (not difficult)
5. When you attempted sexual intercourse, how often was it satisfactory for you?				
1 (almost never or never)	2 (a few times [much less than half the time])	3 (sometimes [about half the time])	4 (most times [more than half the time])	5 (almost always or always)

Scoring
22 to 25: no significant ED; 17 to 21: mild ED; 12 to 16: mild-to-moderate ED; 8 to 11: moderate ED; 5 to 7: severe ED.
A total score of 21 or less suggests ED that needs to be addressed.

* Adapted from: Rosen RC, et al. Int J Impot Res 1999; 11; 319-326.[19]

and is appropriate in men with ED and hypoactive sexual desire, an incomplete response to PDE5-inhibitor treatment or delayed ejaculation and in all men with known diabetes.[21-28,30-32] The prevalence of low total testosterone levels in men with ED varies widely across studies, ranging from 12.5 to 35%.[30] The threshold of testosterone level to maintain an erection is low (less than 5.5 nmol/L), and ED is usually a symptom of more severe cases of hypogonadism.[21] If the total testosterone level is 12 nmol/L or higher, testosterone deficiency is unlikely.[31]

If the total testosterone level is less than 12 nmol/L then proceed to a second morning venous blood sample drawn after an interval of at least one week, together with serum measurement of luteinising hormone (LH) and prolactin levels. Serum LH measurement is essential to identify the subtype of testosterone deficiency as primary or secondary. Measurement of sex hormone binding globulin (SHBG) may be useful in older and obese men or men with liver cirrhosis, with chronic, suspicious symptoms and a borderline total testosterone level. Hyperprolactinaemia has a causal association with hypogonadotrophic (secondary) hypogonadism. Haemochromatosis has a causal association with both hypergonadotrophic (primary) and hypogonadotrophic (secondary) hypogonadism.

Undiagnosed type 2 diabetes has been reported in 5 to 12% of men with ED.[33] Measurement of the fasting plasma glucose (FPG) level and HbA_{1c} will identify occult impaired glucose tolerance or impaired fasting glucose (FPG 5.6 to 6.9 nmol/L; HbA_{1c} ≥39 mmol/mol [≥5.7%]) or type 2 diabetes (FPG ≥7.0 nmol/L; HbA_{1c} ≥48 mmol/mol [≥6.5%]). A 75 g oral 2-hour glucose tolerance test may be required.[34]

Further optional and complementary investigations may be indicated based on the history, examination findings and results of these initial investigations. These may include iron studies, measurement of thyroid stimulating hormone (TSH) and other pituitary hormone levels, pituitary imaging studies, chromosome analysis, full blood count and urinalysis.[20,21,26]

Specialised testing

Most patients do not need further investigations unless specifically indicated.

3. TREATMENT OPTIONS FOR ERECTILE DYSFUNCTION

- Oral PDE5 inhibitors: on-demand or daily (patient re-education may salvage initial treatment failures)
- Testosterone replacement therapy: topical or intramuscular (alone or in combination with PDE5 inhibitors)
- Psychosexual counselling
- Penile injection therapy with alprostadil
- Vacuum constriction device
- Surgery
  - Penile implant
  - Peyronie's surgical repair
  - Vascular reconstructive surgery (usually reserved for young men with arterial trauma)

Abbreviation: PDE5 = phosphodiesterase-5.

Indications for the following specialised investigations include:[35]

- patients who wish to know the aetiology of their ED
- young patients with lifelong ED
- patients with a history of pelvic, perineal or genital trauma
- patients with an abnormality of the testes or penis found on examination
- patients unresponsive to medical therapies who may desire surgical treatment for ED.

Psychological assessment

Psychological assessment of men with ED may provide information on the contribution of relationships, cultural and religious factors, depression and other psychological factors.[21-28] Patients with comorbid psychiatric disorders or younger men with lifelong primary ED should be referred to a psychiatrist or psychologist with an interest in sexual health.[21,36]

Intracavernous injection test

The intracavernous injection test is an office test that involves a physician-administered intracavernous injection of a vasoactive drug such as alprostadil followed by assessment of penile rigidity after 10 minutes.[37] The development of a rigid erection within 10 minutes that lasts for 30 minutes suggests psychogenic ED.[38] However, the use of intracavernous injection as a diagnostic test is limited as a positive result can also be found in patients with mild vascular disease.[28] The main use of this test is in the assessment of penile deformities to aid surgical management.[35]

Vascular testing

Colour duplex Doppler imaging may be indicated in young men with lifelong (primary) ED or Peyronie's disease, men unresponsive to ED pharmacotherapy or men wishing to know the cause of their ED.

Contemporary management of ED rarely includes penile pharmacoangiography, dynamic intracavernous cavernosometry and cavernosography (DICC), nocturnal penile tumescence and rigidity (NPTR), neurophysiological testing, vascular reconstructive surgery or venous ligation surgery.[22]

Impact of an ED diagnosis

It is increasingly recognised that a diagnosis of ED can have a profound impact on the quality of life of patients and their partners.[39] ED can lead to withdrawal from intimacy, avoidance of all physical contact with a partner and an increase in emotional stress, which itself can perpetuate any psychogenic component of the ED. The condition can affect a man's self-esteem and self-image and lead to anxiety and depression. Treatment of ED has been shown to lead to resolution of depression, restoration of self-esteem and improvement in quality of life.[40]

Treatment options

Treatment of ED usually requires initial lifestyle modification to reduce the impact of comorbid vascular risk factors and treatment of organic or psychosexual dysfunction with either pharmacotherapy alone or in combination with psychosexual therapy. The efficacy, benefits, appropriateness and risks of treatment should be discussed with patients and their partners so that their treatment expectations are realistic.

The treatment options for men with ED are effective, safe and well tolerated (Box 3). Treatment selection depends on the severity and aetiology of ED, the patient's overall health and comorbid disease and the patient's and their partner's choice. Progression from first-line oral agents through second- and third-line therapies is indicated in treatment failures.

Coronary artery disease and risk

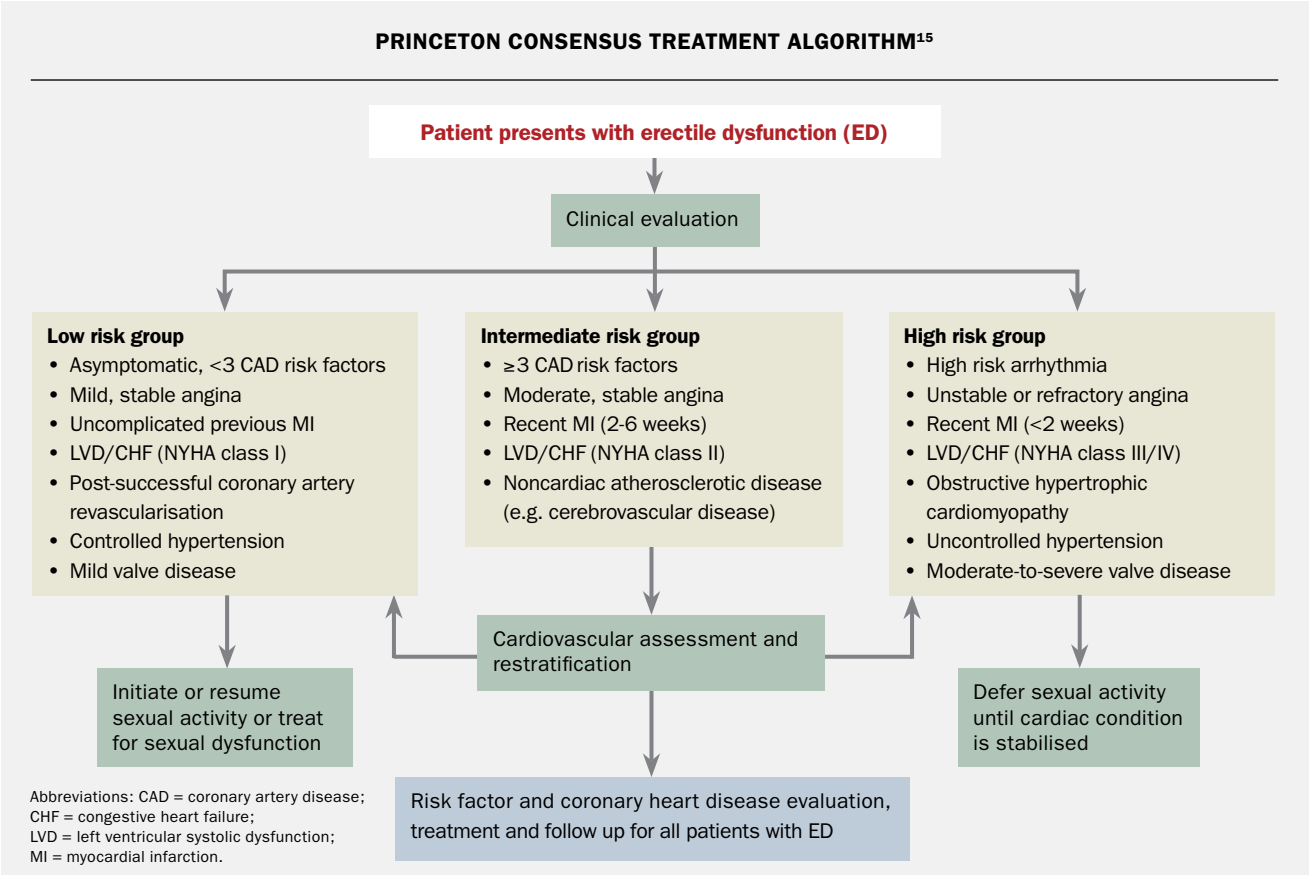
ED and coronary artery disease share the risk factors of dyslipidaemia, hypertension, smoking, diabetes, obesity, lack of physical activity and a family history of early onset coronary artery disease. Erectile dysfunction may be a predictor and a precursor of other forms of cardiovascular disease morbidity and mortality.[8] ED confers a 1.46-fold increased risk for cardiovascular disease.[41] Men with proven or suspected vasculogenic ED or multiple vascular risk factors, especially diabetes, should be screened for silent myocardial ischaemia with a treadmill stress ECG, CT coronary artery calcium scoring or CT coronary angiography.[41]

The Second Princeton Consensus Panel Guidelines for managing ED in patients with cardiovascular disease recommend assigning patients according to their risk factors to one of three risk levels: low, intermediate or high (Flowchart).[15] These cardiovascular risk categories can form the basis for a treatment decision for initiating or resuming sexual activity.

Most men with coronary artery disease can safely resume sexual activity and undergo treatment for ED after appropriate education and counselling.[42] The cardiac risk of sexual activity in men with cardiovascular disease is minimal in properly assessed and advised patients. There is no evidence that currently approved ED treatments add to the overall cardiovascular risk in patients with or without previously diagnosed cardiovascular disease.

Lifestyle changes and risk factor modification

Lifestyle changes and risk factor modification must precede or accompany any



pharmacological or psychological ED treatment.[21-28] Lifestyle changes in men with comorbid cardiovascular or metabolic disorders, such as diabetes or hypertension, or psychosocial issues may achieve major clinical benefits.[43] Cessation of smoking, maintaining an ideal body weight, engaging in regular exercise and optimal management of these diseases may prevent the development of ED.[44-47]

In the Massachusetts Male Aging Study, men who started physical activity in midlife had a 70% reduced risk for ED relative to those who remained sedentary, and regular exercise produced a significantly lower incidence of ED over an 8-year follow-up period.[46] Similarly, in a multicentre, randomised, open-label study of obese men, intensive exercise and weight loss significantly improved erectile function.[45] Correction of dyslipidaemia may improve ED within three months and significantly augment the response to ED pharmacotherapy in patients with unresponsive or refractory ED.[47] However, data conflict on the benefit of smoking cessation to improve erectile function.

Psychosexual therapy

Psychosexual therapy for ED is not standardised, as the foundation of anxiety varies between patients.[48] Relationship difficulties, depression, guilt, previous sexual abuse, lack of sexual experience and problems with intimacy may all increase anxiety and conflict, which may then manifest as ED. Psychosexual treatments range from simple sex coaching and education through improved partner communication to cognitive behavioural therapy and are often combined with ED pharmacotherapy.

A large proportion of patients experience negative psychological consequences of organic ED, which may result in progressively worsening performance anxiety and further deterioration of erectile function.[49] Collaboration between the physician and psychosexual counsellor is often required to develop and implement an integrated pharmacotherapy/psychotherapy treatment program.

Oral PDE5 inhibitor therapy

Overall, 60 to 65% of men with ED, including those with hypertension, diabetes, spinal cord injury and other comorbid medical conditions, can successfully complete intercourse in response to a PDE5 inhibitor such as sildenafil, tadalafil, vardenafil or avanafil.[50-52] The PDE5 inhibitors selectively inhibit the PDE5 isoenzyme, increasing the amount of cyclic GMP available for smooth muscle relaxation, and induce vasodilatation, increased corporal blood flow and erection (Figure 1). The efficacy of the different PDE5 inhibitors appears similar and is related to the severity of ED, with significantly reduced efficacy in patients with severe vasculogenic ED,

diabetic ED and ED after radical prostatectomy.[50-52] Sildenafil, tadalafil, vardenafil and avanafil have differing pharmacokinetic properties (Table).

Daily dosing with tadalafil has similar efficacy and side effect rates to on-demand PDE5 inhibitors and is often selected as first-line treatment by men who engage in frequent intercourse or regard sexual intercourse spontaneity as a key treatment goal.[53] Daily dosing may improve endothelial function and improve or restore erectile function. Salvage of on-demand tadalafil failures with daily or alternate-day high-dose tadalafil (10 to 20 mg) has been reported but is limited by the relatively high cost of treatment.[54]

Adverse effects of PDE5 inhibitors are usually transient, mild to moderate in nature and dose dependent. They often attenuate or disappear within four to six weeks of continued use.[50-52] The most commonly reported adverse effects are:

- headache (11 to 16%)
- facial flushing (2 to 11%)
- dyspepsia (4 to 10%)
- muscle or backache (0 to 4%)
- nasal congestion (2 to 9%).

Nonarteritic ischaemic optic neuropathy (NAION) has been linked to PDE5 inhibitors, although a causal relationship has not been established. In a population of four million veterans aged over 50 years with ED treated with PDE5 inhibitors, there was no increased risk for NAION.[55] However, loss of vision or reduced vision requires urgent ophthalmological assessment and immediate cessation of PDE5 inhibitor use.

PDE5 inhibitors may exacerbate the hypotensive effects of aerosol, tablet or topical short- or long-acting organic nitrates, such as glyceryl trinitrate or isosorbide dinitrate. Coadministration is contraindicated.

Intracavernous injection therapy

Patient-administered intracavernous injection therapy using vasodilator drugs such as alprostadil is an effective treatment for ED (Box 4).[56] It is particularly useful in men who fail to respond to oral pharmacological agents.[57] Alprostadil resulted in an erection of sufficient rigidity for sexual intercourse in 72.6% of men with ED.[56]

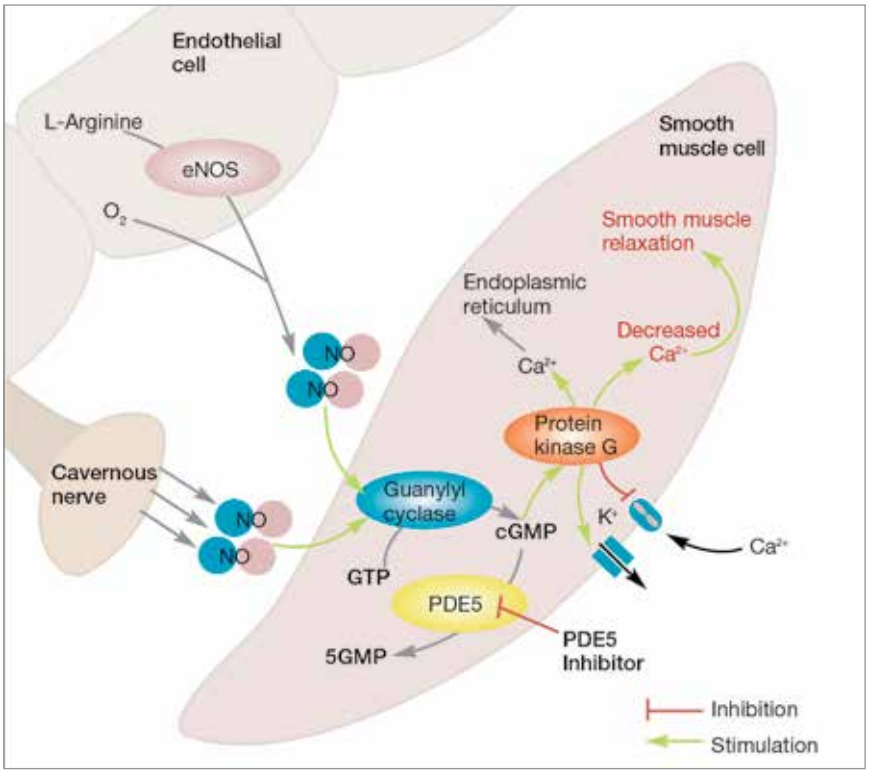


Figure 1. Mechanism of action of phosphodiesterase-5 (PDE5) inhibitors. After activation of the nitric oxide (NO)/cyclic guanosine monophosphate pathway by sexual arousal, inhibition of PDE5 isoenzyme results in increased corporal levels of cGMP and augmented penile erection in men with erectile dysfunction.

The principal side effects of intracavernous injection of alprostadil are pain at the site of injection (up to 30% of patients) and corporal fibrosis resulting in the development of penile nodules and curvature (9 to 23.3% of mid and long-term users).[56] Priapism is a rare complication that can cause irreversible ischaemic damage to the corpora cavernosa with subsequent fibrotic damage and permanent loss of erectile function.

Polyagent pharmacotherapy of alprostadil combined with other agents such as papaverine or phentolamine (available through accredited and licensed compounding pharmacists) is effective in 91.6% of patients and appears effective as 'salvage therapy' in treating patients with severe vasculogenic ED unresponsive to oral pharmacotherapy.[56] Intracavernous injection therapy combined with on-demand PDE5 inhibitors has also been reported as effective salvage therapy and potentially allows lower drug doses with a reduced incidence of adverse effects.[58]

Relative contraindications to intracavernous injection therapy include anticoagulation, previous poor compliance and a history of priapism.

Vacuum constriction devices

Vacuum constriction devices involve insertion of the flaccid penis into a vacuum cylinder and creation of a vacuum using an integrated hand- or battery-operated vacuum pump to create marked tumescence or rigidity, which is maintained with a constricting ring at the base of the penis.[59] A vacuum constriction erection differs from a physiological erection as trabecular smooth-muscle relaxation does not occur and blood is merely trapped within the

TABLE. COMPARISON OF PHOSPHODIESTERASE-5 INHIBITORS*

Property	Sildenafil	Tadalafil	Vardenafil	Avanafil
Tmax (minutes)	30 to 120 (median 60)	30 to 360 (median 120)	30 to 120 (median 60)	Median 30 to 45
Half life (hours)	4	17.5	4	6 to 17
Absorption	Fatty meals delay Tmax by a mean of 60 minutes	Not affected by food	Fatty meals reduce Cmax	Fatty meals cause a minimal reduction in Cmax
Available doses	25 mg, 50 mg, 100 mg as required	2.5 mg, 5 mg daily; 5 mg, 10 mg, 20 mg as required	2.5 mg, 5 mg, 10 mg, 20 mg as required	50 mg, 100 mg, 200 mg
Maximum dose	100 mg once daily	5 mg (daily dosing); 20 mg once daily (as-required dosing)	20 mg once daily	200 mg once daily
Efficacy	Each of the PDE5 inhibitors offers similar efficacy			
Dose adjustments may be needed	• Patients aged over 65 years • Hepatic impairment • Renal impairment • Concomitant use of potent cytochrome P450 3A4 inhibitors (e.g. ritonavir, cobicistat and erythromycin) • Concomitant use of cimetidine (sildenafil only)			
Contraindications	• Any patient using organic nitrates either regularly or intermittently • Any patient regarded as unfit for renewed sexual activity			
Use with alpha blockers	• Concomitant use of selective alpha blockers does not present a risk of significant hypotension • There is a potential risk of significant hypotension with use of nonselective alpha blockers			
Side effects (five most common in order of frequency compared with placebo)	• Headache • Flushing • Dyspepsia • Nasal congestion • Alteration in colour vision	• Headache • Dyspepsia • Back pain • Myalgia • Nasal congestion	• Headache • Flushing • Rhinitis • Dyspepsia • Sinusitis	• Headache • Flushing • Rhinitis • Dyspepsia • Sinusitis

Abbreviations: Cmax = maximum concentration; PDE5 = phosphodiesterase-5; Tmax = time to maximum concentration.
* Additional information can be found in the individual product information monographs.

corpora cavernosa distal to the constricting ring (Figure 2).

Although 60 to 70% of men can eventually master the use of a vacuum constriction device and manage sexual intercourse, satisfaction rates vary considerably from as low as 27% in the short term, to as high as 69% with two-year follow-up.[59] Vacuum constriction devices are more popular in older age group couples but require substantial enthusiasm and understanding partners.[59] Adverse effects include bruising, obstructed and occasionally painful ejaculation, pain at the site of the ring and penile instability due to pivoting of the base of the penis.

Surgical treatment

Surgical treatment of ED is usually limited to patients with major penile arterial or venous disease, corporal fibrosis or Peyronie's disease, who are either unresponsive to or are not candidates for ED pharmacotherapy.

Multicomponent inflatable penile implants are associated with high satisfaction rates.[60,61] Device failure and prosthetic infection are uncommon. Infection requires removal of the prosthesis and either immediate replacement or delayed staged reimplantation.

Penile arterial revascularisation and venous ligation surgery are associated with relatively poor outcomes in men with penile atherosclerotic disease or corporal veno-occlusive dysfunction.[59] They are rarely required, with the exception of young men with traumatic occlusion or stenosis of the internal pudendal or common penile artery due to an anterior open-book type pelvic fracture.

Emerging treatments

There are several potential therapeutic targets with emerging treatments and novel drug delivery systems for ED. These include guanylate cyclase activators, which increase NO levels and promote vasodilation. They also include RhoA/Rho-kinase inhibitors, which prevent the development of vasculogenic ED, with a mechanism often independent of endothelial NO activity.[62] Orodispersible formulations of both vardenafil and sildenafil offer improved biocompatibility, biodegradability, ease of scalability and enhanced solubility release patterns.[63,64]

Regenerative medicine using tissue engineering and molecular biology to replace, engineer or regenerate corporal tissue has the potential to improve penile haemodynamics and renew cavernosal

4. INTRACAVERNOUS INJECTION THERAPY WITH ALPROSTADIL

Action of alprostadil
- Alprostadil acts by relaxing trabecular smooth muscle and dilating cavernosal arteries, expanding lacunae and entrapping blood by compression of the drainage venules against the tunica albuginea
- Administered by direct intracavernous injection
- Onset of action is 5 to 15 minutes after intracavernous injection
- Arousal is usually required to produce a maximal response
- With correct dosing, detumescence should commence within 10 to 20 minutes of ejaculation, but penis may not be fully flaccid for a further 1 to 2 hours

Prescribing
- Assess patient fitness for renewed sexual activity
- Instruct patient in sterile injection technique, used needle disposal, management of prolonged erections
- Individualise dose by initial in-office physician supervised dose titration using the lowest possible effective dose
- Available in two dosages: 10 mcg and 20 mcg
- Start with 5 mcg dose and titrate in 5 mcg increments to a maximum of 20 mcg (in patients with spinal cord injury, start with 1.25 mcg dose and titrate in 1.25 mcg increments)
- Patient to administer 5 to 15 minutes before planned sexual activity
- Maximum frequency of use is no more than three times a week with at least 24 hours between each dose

Management of prolonged erection
- Use lowest possible effective dose
- Treatment if penis still rigid
  - 2 hours after administration: 120 mg pseudoephedrine
  - 4 hours after administration: 120 mg pseudoephedrine and patient to walk briskly for 10 to 15 minutes
  - 6 hours after administration: patient to contact 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 brief plasma half life
- 30% of the drug is metabolised within the corpora cavernosa and urethral mucosa and up to 80% after the first pass through the lung to inactive metabolites

Adverse effects
- Mild penile pain (15 to 20%), priapism (0.25%), corporal fibrosis (5 to 10%) with long term use
- About 30% of users discontinue use each year

Drug interactions
- Interactions with systemic drugs are unlikely because of low or undetectable levels of alprostadil in the peripheral venous circulation

smooth muscle function, thereby preventing or reversing ED. However, convincing supportive human clinical trial data are lacking. There is emerging evidence to support the use of low-intensity extracorporeal shock wave therapy (LIESWT), especially in men with vasculogenic ED, but most clinical trials are small, single centre studies with poor study methodology.[65] Furthermore, the attempt to rapidly commercialise LIESWT without adequate supportive data is a concern. Gene therapy, stem cell therapy using autologous adipose tissue-derived stem cells enhanced by vascular endothelial growth factor or LIESWT, platelet-rich plasma and autologous tissue engineering remain experimental and have no place currently in the management of ED.[66-69]

Unproven treatments

Herbal and unproven drugs and medical device treatments with no evidence base 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 and are often unjustifiably expensive. Patients should be advised to avoid these types of treatment and to consult their GPs with any problems.

Erectile dysfunction in special populations

Benign prostatic hyperplasia with lower urinary tract symptoms

Recent studies have shown a clear association between ED and benign prostatic hyperplasia with LUTS.[14] The association is independent of age, but the more severe the LUTS the more severe the ED. Recent data have not only confirmed this association but also demonstrated a moderate effect of tadalafil on patients with LUTS.

Prostate cancer

ED is a common consequence of treatment of prostate adenocarcinoma with radical retropubic prostatectomy, external beam radiotherapy, brachytherapy or androgen deprivation therapy.[70,71] The aetiology of ED after radical retropubic prostatectomy includes operative injury to the cavernous nerves and subsequent increased hypoxia-induced production of transforming growth factor in the corpora cavernosa, leading to increased extracellular matrix deposition, inhibition of smooth muscle growth, apoptosis of corporal smooth muscle, fibrosis and eventually structurally based corporal veno-occlusive dysfunction.[70]

Almost all men with postprostatectomy ED fail to respond initially to PDE5 inhibitors, but treatment with self-administered intracavernous injection therapy has a high response rate and increases the subsequent response to PDE5 inhibitors and the likelihood of eventual restoration of spontaneous erections.[72] Recovery of cavernous nerve function is more likely in men younger than 60 years who have normal preoperative erectile function and undergo

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Figure 2. Use of a vacuum constriction device.

nerve-sparing surgery. However, recovery may be protracted and incomplete, resulting in a failure to respond to PDE5 inhibitors for as long as 24 to 36 months or the need for long-term penile injection therapy or the insertion of a penile prosthesis.[73] There is early evidence to support a potential rehabilitative role for daily PDE5 inhibitors as an adjunct to initial treatment with intracavernous injection therapy in promoting the return of erectile function in men who undergo nerve-sparing radical retropubic prostatectomy.[74]

Erectile dysfunction after external beam radiotherapy or brachytherapy is insidious and progressive and is due to radiation-induced microvascular endarteritis of the penile arteries, possible acceleration of pre-existing atherosclerosis or proximal corporal fibrosis. The response rate to PDE5 inhibitors is similar to that of age-matched men with ED with other causes.[75]

Androgen blockade with androgen receptor blocking drugs (cyproterone acetate, flutamide, bicalutamide) or luteinising hormone-releasing hormone agonists (goserelin, leuprorelin) is often associated with hypoactive sexual desire, ED, delayed ejaculation, anejaculation and anorgasmia.[76] Erectile dysfunction due to androgen blockade can be a challenge to treat, although treatment is often not requested because of hypoactive sexual desire. The response to PDE5 inhibitors is reduced as the low testosterone levels reduce expression of both the NO synthase gene and the PDE5 gene and downregulate PDE5 enzyme. Similarly the response to self-administered intracavernous injection therapy is also reduced.

Peyronie's disease

Peyronie's disease is curvature of the penis caused by localised fibrosis within the tunica albuginea. The affected corpora cavernosa cannot lengthen on erection, leading to curvature. The condition is most common in middle-aged men who are sexually active. Its exact aetiology remains unknown, but it may result from trauma and bleeding into the tunica, followed by activation of the inflammatory process and fibrosis. It is regarded as a disorder of wound healing, is associated with similar conditions such as Dupuytren's contracture and Ledderhose disease and may have an inherited basis.[77]

ED occurs in 30 to 40% of men with Peyronie's disease. Although the mechanism of ED in this group is not clearly understood, most appear to have a vascular problem such as arterial insufficiency, where the fibrosis distorts the vessels, or failure of the veno-occlusive mechanism.

Treatment is influenced by whether the man with Peyronie's disease also has ED. Men with both conditions may be best advised to undergo insertion of a penile implant, as surgical straightening of the penis alone is unlikely to overcome the ED. If penile curvature alone is the factor that precludes intercourse, medical or surgical treatment may be indicated. Medical treatment is limited to noncalcified plaques and curvatures less than 70 degrees. It is usually multimodal and may include antifibrotic agents such as pentoxifylline (oxpentifylline) and intraplaque infiltrations with collagenase clostridium histolyticum or verapamil.[78,79] Surgical correction of the curvature by Nesbit type plication or plaque excision and grafting is indicated for severe or complex curvature. This surgery may be associated with penile shortening and the onset of ED.

Renal failure

Chronic renal impairment is associated with a high incidence of ED, with the incidence increasing with the level of creatinine. Erectile dysfunction is present in about 50% of patients by the time they require dialysis and is associated with anaemia, autonomic neuropathy, reduced testosterone levels with elevated prolactin, accelerated arterial disease, other drug therapies and psychological stress. Erythropoietin treatment and transplantation with normalisation of renal function often restore or improve the patient's overall quality of life and erectile function.

Conclusion

ED is common and is associated with a reduced quality of life for both affected men and their partners. ED is linked with risk factors that include obesity, lack of exercise, diabetes, hypertension, dyslipidaemia, cardiovascular disease and cigarette smoking. ED may be the initial sign of generalised endothelial dysfunction and is a predictor of cardiovascular health and silent myocardial ischaemia. Treatment with ED pharmacotherapy alone or in combination with graded psychosexual therapy is effective in improving or restoring sexual function in most men. MT

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A list of references is included in the online version of this article (www.medicinetoday.com.au).

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Erectile dysfunction

Part 1: Patient assessment and treatment options

CHRIS G. McMAHON MB BS, FAChSHM; **CHELSEA N. McMAHON** MB BS, BSc(Hons), FRACP

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