Erectile dysfunction
update on oral therapies

Erectile dysfunction is an important medical problem because of its association with cardiovascular risk factors and heart disease. After medically assessment, patients seeking to re-establish sexual intercourse should be counselled about the available treatments. PDE5 inhibitors (sildenafil, tadalafil and vardenafil) are safe, effective drugs and will be first line treatment for most men with erectile dysfunction.

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Erectile dysfunction is defined as the persistent inability to attain and/or maintain an erection adequate for satisfactory sexual intercourse. It is a common problem affecting about one-third of men over the age of 40 years, increasing with age.[1]

In recent years, the medical importance of erectile dysfunction has been recognised because:

- epidemiological studies have confirmed strong associations between erectile dysfunction and diabetes, hypertension, lipid disorders and cigarette use – all risk factors for vascular disease[2]
- quality of life studies have shown significant morbidity for affected couples who desire sexual activity, and there is a strong association with depression
- simple to take, safe and effective oral treatments are available, ensuring that most of the men can be easily and successfully treated.

Pathophysiological considerations

Within the corpora of the penis, trabecular and vascular smooth muscle relaxation is required for penile erection. Nitric oxide from nerves and endothelial cells stimulates the production of cyclic guanosine monophosphate (cGMP), which is the intracellular messenger that facilitates relaxation. Cyclic guanosine monophosphate is enzymatically degraded by phosphodiesterase type 5 (PDE5). Inhibitors of PDE5 enhance the erectile effect.

The understanding of this mechanism has led to therapeutic opportunities, most importantly the development of PDE5 inhibitors such as sildenafil (Viagra), tadalafil (Cialis) and vardenafil (Levitra).

Intracerebral control of the initiation of erection also involves complex neurological connections. Dopamine plays an important role in the hypothalamus, acting through D2 dopaminergic

IN SUMMARY

- **Erectile dysfunction is an important medical problem because of its association with cardiovascular risk factors and heart disease and a psychosocial problem for affected couples desiring sexual intercourse.**
- **It is necessary to do a full clinical assessment to establish the diagnosis and plan treatment, and to take the opportunity to treat any potentially reversible underlying conditions.**
- **The PDE5 inhibitors are safe, effective drugs and will be first line treatment for most men with erectile dysfunction.**
- **All three PDE5 inhibitors are contraindicated in men who are using nitrates.**
- **If in doubt about the patient's cardiac fitness, seek specialist advice.**

Table 1. Causes of erectile dysfunction

Psychogenic
Performance anxiety
Sexual upbringing and experiences
Relationship issues
Work and financial pressures
Depression
Psychiatric illness

Metabolic/vascular
Endothelial dysfunction:
– diabetes
– hypertension
– hyperlipidaemia
– cigarette smoking
Macrovascular disease:
– internal iliac artery disease
– pudendal artery disease

Neurogenic
Parkinson's disease
Alzheimer's disease
Spinal cord lesions
Multiple sclerosis
Diabetic neuropathy
Pelvic surgery (prostate, bowel)
Pelvic injuries

Pharmacological
Antihypertensives
Statins
Antidepressants
Antipsychotics
Antiandrogens
Alcohol and drug abuse

Hormonal
Hypogonadism
Hyperprolactinaemia
Hyper- and hypothyroidism

Miscellaneous
Peyronie's disease
Injection-related fibrosis

STONE

Both the man and his partner may suffer as a result of erectile dysfunction. There is a strong association with depression.

receptors, and dopamine agonists such as sublingual apomorphine facilitate erection.

Clinical assessment

All men presenting with erectile dysfunction should be properly assessed. For many, this may be their first thorough medical assessment. In general practice, this will create an opportunity to undertake a broader health check. Table 1 lists the common causes of erectile dysfunction, and the box on page 60 lists important clinical tips essential for adequate assessment.

The metabolic factors that ultimately cause overt vascular disease also cause endothelial dysfunction (which, because of the impact on nitric oxide release, may be the major cause of erectile

dysfunction) and vascular smooth muscle fibrosis. It is vitally important to realise that erectile dysfunction may be a forerunner of significant cardiovascular disease.

Complex and invasive investigations have little role in the routine management of erectile dysfunction and should be instigated only by doctors who are specialising in the field, and only in specific circumstances.

Treatment principles

The underlying cause of erectile dysfunction should be determined. If there is a specifically treatable component, which will be infrequent, appropriate management should be started (Table 2). When vascular risk factors are identified, they should be treated – although it is not expected that this will restore erectile function. Psychosexual support is always appropriate.

Mostly, treatment will involve educating the patient, and his partner if possible, about the medications that can stimulate an erection in a nonspecific manner (that is, regardless of the cause of the dysfunction). Although recovery of natural erectile function does sometimes follow these treatments, they are not considered curative in themselves. A common treatment algorithm is shown in the box on page 63.

The development of PDE5 inhibitors has dramatically changed clinical practice and puts the initial work up and first line management firmly in the domain of general practice.

Clinical tips for erectile dysfunction assessment

- Allow enough time to talk with the patient about his problem; reschedule if necessary.
- Differentiate erectile dysfunction from other sexual dysfunctions: premature ejaculation, low libido, failure of orgasm.
- Document cardiac risk factors; measure glucose and lipids if not known.
- Measure total serum testosterone and other tests if clinically indicated.
- Bear in mind that radiological investigations are rarely indicated because they do not influence treatment.
- Assume a psychosexual element is present (even if it is obvious that there is a physical cause); offer appropriate support.
- Aim to interview the partner, particularly if psychosexual factors are important.
- Make a working diagnosis based on simple assessment, noting that some men will have multiple factors while others may have no identifiable factors.

Table 2. Treatment for underlying causes

Cause	Treatment
Testosterone deficiency	Determine cause and replace testosterone
Acute psychogenic effect	Psychosexual counselling
Pharmacological	Withdraw the causative drug if the effect is clear cut and recent
Acute pelvic trauma	Consider referral for investigation and surgical correction
Peyronie's disease	Straighten the penis if there is severe curvature

PDE5 inhibitors

Three years of open label experience with sildenafil (Viagra) in a wide range of clinical settings has confirmed the safety and efficacy predicted in clinical trials.[3,4] Tadalafil (Cialis)[5] and vardenafil (Levitra)[6] have shown similar clinical value in trials, and their availability enhances options for men with erectile dysfunction.

In summary, a PDE5 inhibitor will be the treatment of first choice in most men with erectile dysfunction and will frequently be successful. It may take up to six tries before achieving success, so men should be encouraged to persevere. With sildenafil, it has become common practice to start at 50 mg and increase to 100 mg after a few doses if required. With tadalafil and vardenafil, the starting dose will usually be 20 mg.

Many men and their partners continue to harbour significant misgivings about cardiac safety, or are overanxious about the use of these drugs, and suffer significant anxiety when taking PDE5 inhibitors. Review and reassurance are essential to maximise success.

When these drugs are prescribed the following factors need to be considered.

Efficacy

There have been no head-to-head studies showing one PDE5 inhibitor superior to another. In general, these drugs improve erections sufficient to allow intercourse in more than 60% of all patients, being effective at all ages and in a wide range of aetiologies. They are less effective in patients with diabetes and even less so after radical prostatectomy, but are still indicated in those conditions.

These drugs are effective in younger men with psychogenic erectile dysfunction and, although not well studied, early intervention in this group may reduce the incidence of persistent erectile dysfunction.

Duration of action

Sildenafil and vardenafil have similar half-lives of around four hours and the

clinical effect may last for up to 12 hours, although it is generally recommended that intercourse be attempted between 30 minutes and four hours after dosing. Tadalafil has a significantly longer half-life of about 17 hours, and it has been shown in one trial that about 60% of men can achieve an erection at 24 hours or longer after dosing. While this offers a potential advantage, the effects of longer term PDE5 inhibition are uncertain, and as yet there are no studies to show patient preference.

Food and alcohol interaction

Fatty meals have been shown to slow the absorption of sildenafil and this may need to be taken into account when using this drug. Alcohol may have obvious effects on sexual function, which may interfere with the efficacy of these drugs but does not have a significant direct effect.

Drug interactions

The most important drug interaction is between the PDE5 inhibitors and nitrates, with some men having a catastrophic fall in blood pressure with concomitant use. All three PDE5 inhibitors are contraindicated in men who are using nitrates. (Nitrate use usually relates to angina and ischaemic heart disease, but some patients may be using amyl nitrate as a recreational drug.)

Inhibitors of the cytochrome P450 enzymes 3A4 and 2C9, such as ketaconazole, cimetidine, erythromycin and the protease inhibitors, will reduce the metabolism of PDE5 inhibitors. The starting dose of the PDE5 inhibitor should be halved in patients taking these drugs.

Recently it has been shown that alpha blocking drugs may cause a fall in blood pressure when coadministered with PDE5 inhibitors. Coadministration is not recommended.

There has been no significant interaction demonstrated with warfarin, other antihypertensive agents or the statins.

Special patient groups

In elderly patients and those with severe renal impairment or liver disease, the recommended starting dose of PDE5 inhibitor is half the usual dose.

Adverse events

Effect on the heart

After sildenafil was launched, a number of cardiac events, including deaths, were reported to the US Food and Drug

Algorithm for treatment of erectile dysfunction

1. Carry out a full clinical assessment to establish diagnosis and treatment plan.
2. Treat potentially reversible conditions (Table 2).
3. Initiate 'nonspecific' treatment to restore erectile capacity – usually commencing with a first line treatment (see below).

First line: noninvasive options

- Vacuum constriction device
- Oral therapy – choose an appropriate PDE5 inhibitor unless contraindicated, or consider sublingual apomorphine (if available)

Second line: minimally invasive options

- Intracavernosal injection of prostaglandin E1 (PGE1) and drug mixtures
- Urethral applications

Third line: surgical options

- Penile implant
- Invasive vascular intervention (including venous ligation surgery)

Important cardiac considerations

- Document the patient's cardiac history and findings of examination.
- Check his blood pressure, glucose and lipids.
- Ask any patient with a history of heart disease about nitrate use, and document it.
- Assess the patient's exercise capacity, to judge whether sex is safe.
- Investigate unexplained cardiac symptoms, including chest pain, before treating erectile dysfunction.
- Do not prescribe PDE5 inhibitors in men with 'high risk' conditions without specialist assessment (see Table A).
- Ensure that PDE5 users know what adverse effects are likely to occur.
- Counsel about the risk of concomitant nitrate use.
- Give specific advice regarding what to do should chest pain occur during intercourse – usually cease activity, rest, and call an ambulance if pain persists.
- If in doubt about the patient's cardiac fitness, seek specialist advice.

Table A. Examples of 'high risk' conditions

Unstable angina
Uncontrolled hypertension
Symptomatic cardiac failure
Myocardial infarction or stroke within six weeks
Poorly controlled arrhythmias
Severe valvular disease

Administration and in case reports. Clinical trials had not demonstrated problems but did exclude men with some types of heart disease. Subsequently there have been many studies in men with various forms of heart disease confirming the safety of PDE5 inhibitors. The box on page 63 lists the major aspects to consider in practice.

Specificity of PDE5 inhibition

PDE5 inhibitors can inhibit other PDE enzymes,[7] and if the degree of inhibition is significant it may cause unwanted effects. There are two areas where this may be clinically relevant.

- **PDE6 and the eye.** Inhibition of PDE6 in the retina is responsible for the visual side effects seen mainly with sildenafil. This includes changes in colour hue (blue vision) and exaggeration of brightness. These symptoms rarely cause a problem in practice.
- **PDE11 effects.** Compared with the other two PDE5 inhibitors, tadalafil is a much more potent inhibitor of PDE11, which is found in the pituitary, testes and skeletal and cardiac muscle. There has been no demonstration that this action causes any clinical problems in men using tadalafil.

Common side effects

Headache, facial flushing, nasal congestion, myalgia and dyspepsia are the most frequently reported side effects, but they rarely lead to cessation of the PDE5 inhibitor. Backache has been more frequently reported with tadalafil. All these side effects are usually mild and transient, and headaches often lessen with continuing use. These effects are detailed in Table 3. Dizziness, faintness and lightheadedness, which may relate to minor blood pressure falls, are uncommon.

Tachyphylaxis

The possibility of tachyphylaxis has been raised; however, there is no evidence that the potency of PDE5 inhibitors wanes with prolonged use. Some men do find that the clinical usefulness diminishes. This will include men with an initial placebo response (about 20% of men in trials respond to placebo) or where a new factor is influencing erectile dysfunction. Men with erectile dysfunction associated with vascular disease or its risk factors may have progression of the underlying problem.

Cost and packaging

For all but a few patients, the PDE5 inhibitors will be on private prescription. Therefore cost will be an important issue for many patients – precluding some men from being treated. At the time of preparing this article, cost and packaging details are available for sildenafil and tadalafil but not for vardenafil.

Table 3. Adverse effects of PDE5 inhibitors*

	Sildenafil 100 mg	Tadalafil 20 mg	Vardenafil 20 mg
Headache	30% (6%)	21% (6%)	21% (4%)
Dyspepsia	16% (1%)	17% (2%)	6% (<1%)
Flushing	20% (1%)	5% (2%)	13% (0)
Nasal effect/rhinitis	11% (2%)	5% (4%)	17% (5%)
Myalgia	<2%	7% (2%)†	2% (1%)†
Back pain	No reports	9% (5%)†	No reports
Visual effect	9% (<1%)	No effect	<2%
Discontinuation of drug	2% (<1%)	2.1% (1.3%)	Low

* Adapted from references 3, 5 and 6. Data presented as % of subjects receiving active drug compared with % of those receiving placebo (shown in brackets) .
† Reporting of musculoskeletal effects varies in the different studies. In addition to myalgia, 9% of men on tadalafil (5% on placebo) reported back pain, which is not documented separately in the other studies. In the vardenafil study, the classification 'flu syndrome' is used, and is taken to reflect myalgic symptoms.

Apomorphine

Sublingual apomorphine (Uprima) is available in some countries for erectile dysfunction, following evaluation in clinical trials where efficacy has been demonstrated. However, it is not yet available in Australia. The drug appears to be less efficacious than PDE5 inhibitors; however, it can be used in men who are taking nitrates, provided other cardiac issues are taken into account. Whether apomorphine will work in men who have failed to respond to PDE5 inhibitors has not been reported. Similarly it is unknown whether combining this drug with a PDE5 inhibitor will improve responsiveness.

The percentages of men experiencing adverse effects with a 3 mg dose of apomorphine (compared with placebo) are: nausea 7% (1.1%), yawning 8.1% (0.6%), dizziness 6.5% (3.4%) and somnolence 4.9% (1.7%). Headache and flushing are not problems at this dose.[8]

Related issues regarding other treatments

Self-injection treatment

A substantial number of men with erectile dysfunction are treated with intracavernosal injections of prostaglandin

E1 (Caverject). The usual indications have been ineffectiveness or contraindication of available oral agents, lower cost (but now reimbursable only within the Repatriation Pharmaceutical Benefits Scheme) and superior efficacy. Self-injection will remain an important modality, although the cost differential has been lost except for veterans.

Whereas the assessment of men with erectile dysfunction and the initiation and follow up of treatment with oral agents must by necessity be the responsibility of primary care physicians, the teaching and supervision of men self-injecting largely falls within the domain of the specialist.

Testosterone replacement

Only a small number of men presenting with erectile dysfunction will have clear-cut hypogonadism. However, this diagnosis is important not to miss because of the possibility of pituitary disease, infertility, osteoporosis and general health issues that may arise in association with testosterone deficiency. It is important to define the cause of hypogonadism before testosterone replacement is commenced.

Many older men will have borderline low testosterone levels, and it remains unclear whether they will benefit from replacement. Men with low testosterone levels may respond significantly better to PDE5 inhibitors if they are made testosterone replete. There are clear guidelines for prescribing testosterone through the PBS.

A digital rectal examination and prostate specific antigen measurement are recommended before commencing testosterone replacement.

Conclusion

Erectile dysfunction is an important medical condition, and the link with heart disease demands attention. Men should be encouraged to have a health check if they have erectile dysfunction. For those who desire restoration of sexual function, there are many options, including the PDE5 inhibitors. Primary care doctors should be familiar with these drugs so that they can prescribe them safely and with confidence. MT

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