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# Erectile dysfunction

## When tablets don't work

### Background

Erectile dysfunction (ED) is a common clinical problem managed in the general practice setting. While the majority of men will find phosphodiesterase-5 (PDE-5) inhibitors effective, there is a subgroup of men who require second and third line therapies.

### Objective

This article provides an overview of ED and its management with particular focus on the group of patients in whom oral agents fail.

### Discussion

Erectile dysfunction is a multifactorial condition that affects approximately 40% of Australian men. The incidence of ED is age related however, it shares common risk factors with cardiovascular disease and metabolic disorders. The management of ED should begin with an assessment of cardiovascular risk factors, advice on lifestyle modification, and a trial of PDE-5 inhibitors. Second line therapies include intracavernosal injections and vacuum erection devices, while third line therapy entails penile implants. Factors that influence treatment success include partner inclusion, good patient selection, as well as ongoing support and education.

**Keywords:** erectile dysfunction; men's health



Erectile dysfunction (ED) is the persistent inability to attain and maintain an erection sufficient to permit satisfactory sexual performance.<sup>1</sup> The overall prevalence of ED in Australia is estimated at 40%.<sup>2,3</sup> The risk of developing ED is age related, occurring in approximately 26% of men aged 50–59 years, and approximately 40% of men aged 60–69 years.<sup>2,4</sup> With the advent of phosphodiesterase-5 PDE-5 inhibitors, the management of ED occurs predominantly in the primary care setting. Risk factors for ED are shown in *Table 1*. Guidelines for assessment and management of ED are available from *Andrology Australia*<sup>5</sup> (see *Resources*).

Erectile dysfunction is primarily an organic condition, sharing common risk factors

with cardiovascular disease including lack of exercise, obesity, smoking, hypercholesterolaemia and the metabolic syndrome.<sup>6,7</sup> This is an important consideration as ED may be an early marker of subclinical metabolic and vascular disease.<sup>8</sup> Many medications can potentiate ED including commonly used antihypertensives such as calcium channel blockers, angiotensin II receptor antagonists, angiotensin converting enzyme receptor antagonists, beta blockers and thiazides.

The physical symptoms of ED are often associated with depression, a loss of self confidence, loss of intimacy in a relationship, and a reduced quality of life.<sup>9</sup> Although public awareness of ED has improved in the past decade, less than half the men with the disorder seek treatment.<sup>10</sup> A delay often occurs between the onset of symptoms and attendance in the primary care setting, with a mean time of 1.0–3.5 years.<sup>10</sup> The goals of ED treatment are to restore quality of life and allow the patient and his partner to enjoy a satisfying sex life.

### Assessment

Consultations around the issue of erectile dysfunction should be conducted in a relaxed, reassuring, and nonjudgmental manner. The first step is to take a full medical, sexual, surgical and psychosocial history (*Table 2*). A focused physical examination includes:

- a genital examination
- assessment of secondary sexual characteristics
- a digital rectal examination to assess the prostate gland.

A cardiovascular risk assessment should be performed before commencing a patient on a PDE-5 inhibitor and advising the resumption of sexual activity.<sup>11,12</sup> Kostis et al, have developed

**Table 1. Risk factors associated with erectile dysfunction<sup>6,7</sup>**

- Hypertension
- Cardiovascular disease
- Diabetes mellitus
- Smoking
- Alcohol
- Prostate surgery
- Pelvic trauma
- Pelvic radiotherapy
- Medications
- Depression
- Penile abnormalities (eg. Peyronie disease)
- Obesity
- Sleep apnoea
- Hyperlipidaemia
- Spinal cord trauma
- Medical conditions such as multiple sclerosis

a cardiovascular risk stratification algorithm, to evaluate the degree of cardiovascular risk associated with sexual activity.<sup>13</sup> Men who have intermediate or high risk cardiovascular disease should obtain a cardiologist opinion before commencement.

It is important to establish the severity of ED. A validated questionnaire such as the Sexual Health Inventory for Men can accurately detect and quantify ED.<sup>14,15</sup> This brief questionnaire can be completed by the patient in the waiting room before the consultation or between the initial consultation and follow up (see *Resources*). Given that ED and lower urinary tract symptoms commonly coexist, it is advisable to screen patients for voiding symptoms using a screening tool such as the International Prostate Symptom Score Sheet<sup>7,16</sup> (see *Resources*).

**Table 2. History taking in patients with erectile dysfunction**

Sexual	Medical	Urological
Nature of problem	Medical history	History of lower urinary tract symptoms
Mode of onset	Psychological history	Penile complaints (eg. pain, curvature)
Degree of disability	Surgical history	
Precipitating factors	Medications	
	Recreational drug use	
	Alcohol use	
	Smoking history	

## Management

The management of ED should follow a stepwise approach as outlined in *Table 3*. Importantly, partners play a key role in supporting the patient, allaying anxiety and achieving treatment compliance; a couples based approach should be encouraged.

### First line: PDE-5 inhibitors

There are currently three PDE-5 inhibitors on the market: sildenafil (Viagra™), vardenafil (Levitra™) and tadalafil (Cialis™), which is available as a daily dose. Features of these medications are described in *Table 4*. The efficacy of this class of medication is well established for the general population, as well as in men following radical prostatectomy and radiotherapy for prostate cancer and those with diabetes mellitus, spinal cord injury, multiple sclerosis, and depression.<sup>11,17,18</sup> PDE-5s are contraindicated following a recent myocardial infarction, concurrent nitrate therapy, and high risk cardiovascular disease.

The success rate of PDE-5 inhibitors is dependent upon the aetiology of the ED and can range from approximately 43–89%.<sup>19</sup> A poorer response to PDE-5 inhibitors is seen in the context of adverse factors such as following prostate surgery (43%), diabetes with neuropathy (50%) and peripheral vascular disease (63%).<sup>19</sup> A better response is seen in an otherwise healthy male whose ED is secondary to depression (89%), neurological disease (85%) and smoking (80%).<sup>19</sup>

Other factors contributing to the failure of PDE-5s include incorrect usage, worsening corporal endothelial dysfunction, poor tolerance to side effects, and hypoandrogenism.<sup>19</sup> For initial nonresponders, education alone can improve the response by 40–55%.<sup>19</sup> The probability of

**Table 3. Stepwise approach to management of erectile dysfunction**

#### First line

- Lifestyle modifications (eg. quitting smoking, exercise, weight loss)
- Management of cardiovascular risk factors
- Trial of PDE-5 inhibitors (at least four attempts with two different PDE-5 inhibitors) in the absence of contraindications

#### Second line

- Self intracavernosal injections
- Vacuum erection devices
- Hormonal therapies (eg. testosterone replacement)
- Combination therapy

#### Third line

- Penile prostheses

successful intercourse increases with each treatment attempt, therefore patients should be encouraged to persevere with a trial of at least two PDE-5 inhibitors for up to four attempts of each, and at the maximum dosage.<sup>19</sup> Information regarding the need for sexual stimulation and the onset and duration of action of PDE-5 inhibitors can also increase success rates.

### Second line: vacuum devices, intercavernosal injections and testosterone therapy

Following a complete trial with PDE-5 inhibitors, second line therapies can be used in combination with PDE-5 inhibitors to improve response, or as a single therapy when PDE-5s are contraindicated. The advantages and disadvantages of vacuum erection devices (VEDs) and intercavernosal injections are shown in *Table 5*.

#### Vacuum erection devices

Vacuum erection devices provide a safe, cost effective, and noninvasive alternative for men who have failed oral pharmacotherapy. Negative pressure is applied to the penis, producing passive engorgement of the corpora cavernosa, resulting in an erection that can be maintained by an elastic band at the base of the penis for 30 minutes (*Figure 1*). Successful vaginal penetration is as high as 90%, however device satisfaction

**Table 4. PDE-5 inhibitors**

Drug	Onset of action	Half life	Adverse effects
Sildenafil	Tmax* 30–120 minutes Median 60 minutes	2–5 hours	<ul style="list-style-type: none"> <li>• Headache</li> <li>• Flushing</li> <li>• Dyspepsia</li> </ul>
Vardenafil	Tmax 30–120 minutes Median 60 minutes	4.5 hours	<ul style="list-style-type: none"> <li>• Headache</li> <li>• Flushing</li> <li>• Dyspepsia</li> </ul>
Tadalafil	Tmax 30–120 minutes Median 120 minutes	15.5 hours	<ul style="list-style-type: none"> <li>• Headache</li> <li>• Flushing</li> <li>• Dyspepsia</li> </ul>

\* Tmax = median time to peak plasma concentration of drug

**Table 5. Advantages and disadvantages of VEDs and intracavernosal injections**

Therapy	Advantage	Disadvantage	Contraindications
Vacuum erection devices	<ul style="list-style-type: none"> <li>• Effective in all aetiological groups</li> <li>• Do not require erectile reserve</li> <li>• Noninvasive</li> <li>• Low complication rates</li> <li>• No restriction on frequency of use</li> </ul>	<ul style="list-style-type: none"> <li>• Bruising</li> <li>• Interference of ejaculation due to constriction ring</li> <li>• Loss of acute angle of erection</li> <li>• Pain</li> <li>• 'Nonphysiological' erection</li> <li>• Requires the use of bulky equipment</li> </ul>	<ul style="list-style-type: none"> <li>• Bleeding disorders</li> <li>• Anticoagulation therapy</li> </ul>
Intracavernosal injections	<ul style="list-style-type: none"> <li>• Suitable for all causes of ED</li> </ul>	<ul style="list-style-type: none"> <li>• Risk of priapism</li> <li>• Fibrosis of tunica albuginea</li> <li>• Painful erections</li> <li>• Tolerance</li> <li>• Urethral bleeding</li> <li>• Hypotension</li> <li>• Low compliance rates</li> </ul>	<ul style="list-style-type: none"> <li>• Conditions that predispose to priapism</li> <li>• Sickle cell anaemia</li> <li>• Leukaemia</li> </ul>

ranges from 26–94%, and long term use reduces satisfaction to 50–64% after 2 years.<sup>11,20</sup> Proper instruction and manual dexterity are crucial to the success of, and compliance with, VEDs. Quality devices with an instructional DVD and technical support can be obtained from medical aid sources.

### Self intracavernosal injections

Injectable agents effective in treating ED where PDE-5 inhibitors have failed include papaverine, phentolamine and alprostadil (PGE1).<sup>20,21</sup> Men must receive education on the risk of priapism,

injection technique, and dosing, before beginning home injections (*Figure 2*). Discontinuation rates with intracavernosal therapy range from 40.7–68.0%.<sup>11</sup> A return of spontaneous erections has been reported in men undergoing intracavernosal injections.<sup>22</sup>

Alprostadil (Caverject Impulse<sup>®</sup>) is a vasoactive mediator that acts primarily on cavernosal smooth muscle receptors.<sup>20</sup> Erection usually occurs within 5–20 minutes of injection and can last up to 2–3 hours after ejaculation.<sup>20</sup> A meta-analysis of four randomised controlled



Figure 1. Second line treatment: vacuum erection device

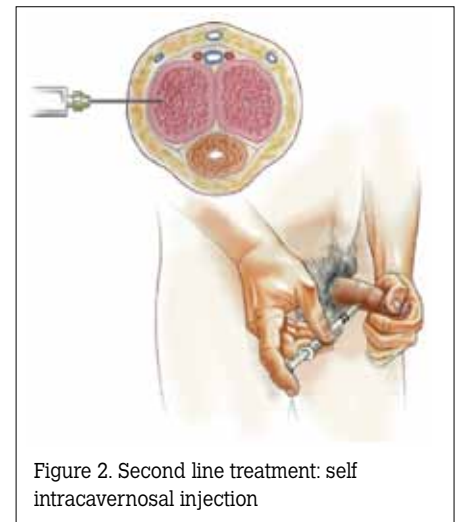


Figure 2. Second line treatment: self intracavernosal injection

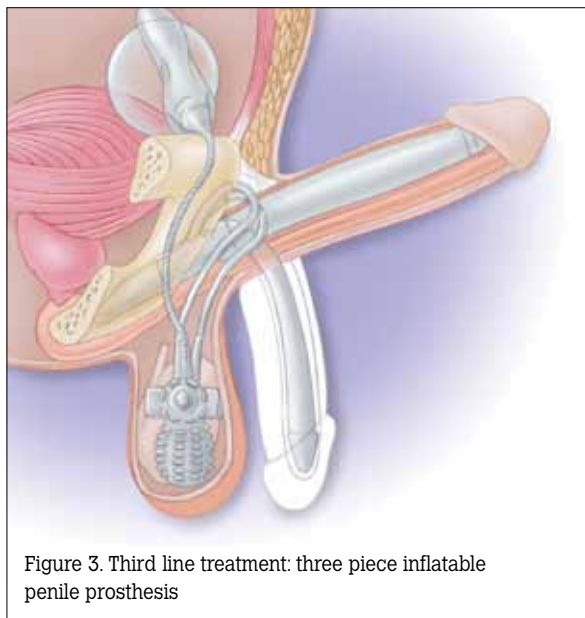
trials comparing PGE1 to placebo demonstrated a 63.6% success rate of alprostadil, with a relatively low incidence of priapism (0.35–4.0%) and tunica albuginea fibrosis (1–23%).<sup>21,23</sup>

### Combination therapy

Combination intracavernosal injections such as Trimix (phentolamine, papaverine, and PGE1) and Quadmix (phentolamine, papaverine, prostaglandin E1 and atropine) can be initiated after an unsuccessful trial of alprostadil. Although data is limited, the reported rate of full erection is more than 90%.<sup>22,24</sup> There is, however, a higher incidence of priapism with combination therapy, and these need to be prepared by a compound chemist and generally warrant urologist referral for monitoring.

### Testosterone therapy

Testosterone supplementation can be considered for all men who have signs and symptoms of



'Penile rehabilitation' is indicated postoperatively and is usually initiated by the urologist. This often includes injectables or PDE-5s from several weeks postoperation. If erections are failing despite rehabilitation, the clinician should ensure that a complete trial of first and second line therapies has occurred. A man motivated to resume sexual activity who fails these therapies will most likely benefit from a penile implant. This decision needs careful consideration, ideally with partner involvement. A urologist with an interest in prosthetic surgery should be consulted.

guide: [www.andrologyaustralia.org](http://www.andrologyaustralia.org)

- The Sexual Health Inventory for Men (SHIM): [www.rohbaltimore.com/SHIM.pdf](http://www.rohbaltimore.com/SHIM.pdf)
- The International Prostate Symptom Score Sheet (IPSS): [www.gp-training.net/protocol/docs/ipss.doc](http://www.gp-training.net/protocol/docs/ipss.doc).

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low testosterone confirmed by two low morning serum testosterone levels. This will include the subgroup of men suffering from late onset hypoandrogenism.<sup>25</sup> The management of these patients is complex and should be comanaged with an endocrinologist and/or urologist.

### Third line: penile prosthesis

A penile prosthesis is indicated when there is a lack of efficacy, or dissatisfaction with first and second line treatments. Currently, three classes of penile implants are available: semirigid malleable rod devices and two piece, and three piece inflatable hydraulic implants.

The three piece inflatable devices, composed of paired cylinders, a scrotal pump, and a reservoir are considered the gold standard of inflatable implants (Figure 3). Satisfaction with this device is approximately 90% and device durability at 10 years is 75%.<sup>26,27</sup> Complications include corporal/urethral erosion (1–11%), infection (0.68–1.06%) and mechanical failure (0.8–10.3%).<sup>26</sup> In a man comfortable with having an implant, they are well tolerated.

### Erectile dysfunction following radical prostatectomy

The pathophysiology of ED following radical prostatectomy is multifactorial and is related to cavernous nerve injury and fibrosis of cavernosal smooth muscle due to poor oxygenation and venous leak.<sup>28</sup>

### Summary of important points

- Erectile dysfunction is a significant clinical problem largely undertreated in the community; the issue should be explored in any man who is over 40 years of age or has cardiovascular disease.
- Erectile dysfunction may be an early marker of subclinical metabolic and vascular disease.
- The physical symptoms of ED are often associated with depression, a loss of self confidence, loss of intimacy in a relationship, and a reduced quality of life.
- The severity of ED should be evaluated with a self assessment questionnaire.
- Partner inclusion will improve success of treatment and increase treatment compliance.
- Treatment of ED should follow a stepwise approach, including ongoing education and support.
- PDE-5s are first line treatment. They are contraindicated in the context of recent myocardial infarction, concurrent nitrate therapy, and high risk cardiovascular disease.
- Second line treatments for ED can be offered in conjunction with PDE-5 inhibitors to increase success rates.
- Penile implants are well tolerated and have high success rates in well selected patients.

### Resources

- Andrology Australia. Erectile dysfunction: diagnosis and management. GP summary

Conflict of interest: Prem Rashid has been a visitor to the American Medical Systems (AMS) USA manufacturing facility undertaking a cadaveric dissection clinic and observing operative procedures by high volume implant urologists affiliated with AMS during that time. He also has acted as a consultant for Coloplast, AstraZeneca, Hospira & Abbott Pharmaceuticals. No commercial organisation initiated or contributed to the writing of this article apart from granting permission to use diagrams of their respective devices.

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