Practice pointer

Treating erectile dysfunction when PDE5 inhibitors fail

Chelsea N McMahon, Christopher J Smith, Ridwan Shabsigh

New oral drugs, especially phosphodiesterase type 5 (PDE5) inhibitors, have revolutionalised the treatment of erectile dysfunction by decreasing reliance on more invasive options. These inhibitors compete with cyclic GMP (guanosine monophosphate) for the PDE5 receptor site. Sexual arousal activates the nitric oxide-cyclic GMP pathway, leading to relaxation of cavernosal smooth muscle cells, engorgement of lacunar spaces, and erection. PDE5 hydrolyses cyclic GMP to 5-GMP, which terminates the pathway and produces detumescence, so that PDE5 inhibitors result in increased intracellular concentrations of cyclic GMP and erection.

Three potent selective PDE5 inhibitors (sildenafil (Viagra; Pfizer), tadalafil (Cialis; Lilly), and vardenafil (Levitra; Bayer)) are currently available. Although large multicentre clinical trials have shown the efficacy and tolerability of these drugs in erectile dysfunction with various aetiologies and a broad range of severity, 30-35% of patients fail to respond. The reported 62% prescription renewal rate at three to four months of follow-up, which dropped to around 30% by 6-12 months, suggests that patients stop taking the drug for reasons other than failure of treatment.[1]

The reasons for acute or delayed failure include severe erectile dysfunction at presentation, worsening of endothelial dysfunction and progression of penile atherosclerosis, erectile dysfunction after radical prostatectomy, unrecognised hypogonadism, inadequate patient education and incorrect drug usage, the development of tachyphylaxis (drug tolerance), and psychosocial factors. Alternative treatment methods, education on the use of the drug, androgen replacement, lifestyle changes, correction of risk factors, and relationship or psychosexual counselling have been reported.

We searched PubMed and Medline for papers published from January 1980 to May 2005, using the term "erectile dysfunction". We selected papers (published in English) on the management of erectile dysfunction and erectile dysfunction that does not respond to oral drugs. We review the treatment options available to primary care doctors and specialists who treat sexual dysfunction and propose a scheme for managing the failure of oral drugs (figure).

St Vincent's Hospital, Darlinghurst, NSW 2010, Australia
Chelsea N McMahon *medical officer*
Princess Alexandra Hospital, Woolloongabba QLD 4102, Australia
Christopher J Smith *medical officer*
Department of Urology, Columbia University, New York, NY, USA
Ridwan Shabsigh *associate professor*
Correspondence to: R Shabsigh rs66@columbia.edu

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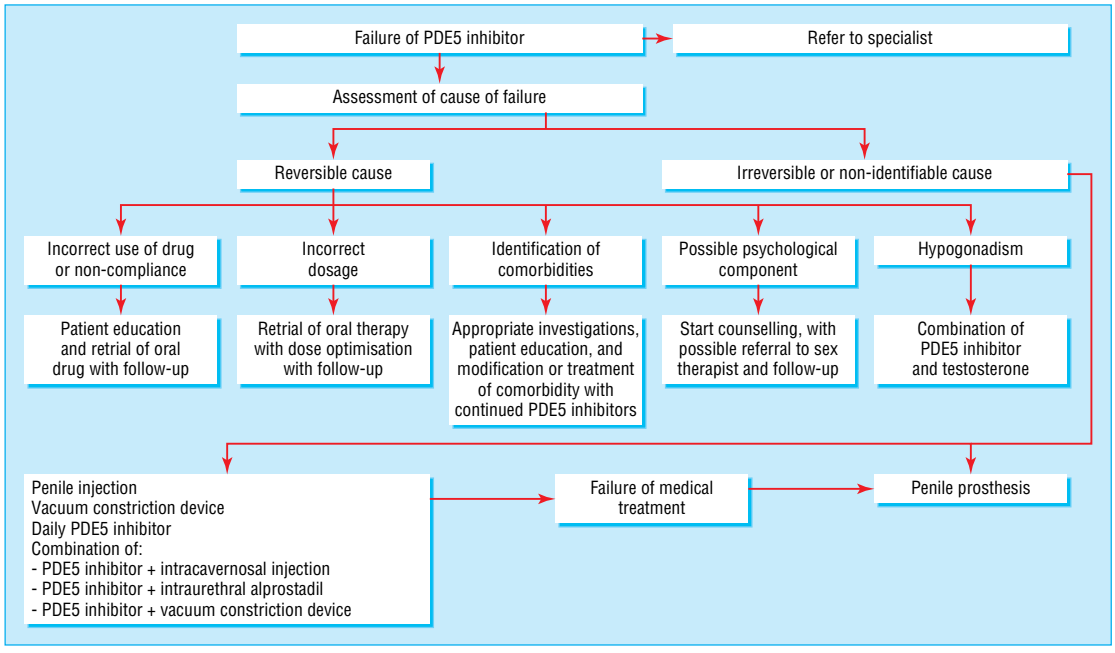

Managing failure of phosphodiesterase 5 (PDE5) inhibitors in treatment of erectile dysfunction

Referral

A busy primary care doctor may decide to refer patients with erectile dysfunction that does not respond to PDE5 inhibitors to a urologist, sexual health specialist, or other specialist.

Patient education

Educating patients on the correct use of the drug can be effective. One study found that 81% of patients initially took sildenafil incorrectly, and education solved the problem in 40% of men who did not respond previously.[2] Another study reported a similar response rate of 55% after education in men who had previously not responded.[3] Initial education, focusing on the following points, will optimise treatment outcomes.

- Adequate sexual stimulation, ideally with a partner, is required.
- Sildenafil and vardenafil should be taken 30-60 minutes before intercourse, and food and excessive amounts of alcohol should be avoided, as both may reduce the speed and extent of drug absorption.[4 5] The absorption of tadalafil is unaffected by food and alcohol, but the drug does not reach maximum plasma concentrations until two hours after dosing.[6] Although about half of men respond by 30 minutes, patients are advised to take tadalafil several hours before sexual activity and take advantage of the long duration of its effects (up to 36 hours).
- Sildenafil and vardenafil are active for four to six hours and are rapidly cleared from the body. Tadalafil, with a half life of 17.5 hours, is active for up to 36 hours.[6]
- Although most men will respond after one or two doses, some men may need six to eight doses before an optimal response occurs.[3]

Dose optimisation

PDE5 inhibitors may fail because of inadequate dosage. Sildenafil should be started at 50 mg (25 mg for elderly patients and patients with hepatic cirrhosis or renal impairment) and titrated to a maximum dose of 100 mg to achieve maximum response. Doses higher than 100 mg may be effective, but they have a significantly higher risk of side effects and 31% of men discontinue treatment.[7] Vardenafil and tadalafil should be started at 10 mg with dose titration to achieve either an optimal response or a maximum dose of 20 mg.[4 5]

Another consideration is the possibility of tachyphylaxis (decreased responsiveness after repeated doses). One study reported a 17% rate of discontinuation for sildenafil owing to loss of efficacy after two years.[8] Another study reported that high concentrations of sildenafil increase PDE5 expression in cultures of cavernosal smooth muscle cells; these findings provide a molecular basis for tachyphylaxis.[9] However, this study used higher concentrations than those approved for patients. Tachyphylaxis has not been confirmed clinically, and further long term studies are required. A more plausible explanation of decreased efficacy is progressive worsening of the underlying cause of erectile dysfunction—for example, worsening atherosclerosis or diabetes.

Switching oral agents

Although no study directly compares the efficacy of the three PDE5 inhibitors, efficacy and tolerability are probably similar for the three drugs. Most patients will try another PDE5 inhibitor before they consider more invasive options.

Daily dosing with PDE5 inhibitors

In patients who were unresponsive to on-demand tadalafil, treatment with daily tadalafil significantly improved all treatment outcomes.[10] Successful intercourse increased from a mean of 21% with on-demand 20 mg tadalafil to 58% with daily 10 mg tadalafil. This improvement is probably related to improved endothelial function.

Improvement in comorbid conditions

Many men have underlying comorbidities that are risk factors for erectile dysfunction: diabetes, hypertension, cardiovascular disease, depression, prostatic hypertrophy, smoking, drug treatment, a sedentary lifestyle, drug and alcohol misuse, etc. Control of these risk factors is an essential part of first line treatment for erectile dysfunction, to improve erectile function and the patient's response to treatment. One study showed that modifying associated risk factors before sildenafil was started improved the overall success rate to 82%, and 77% of patients had success at every attempt at intercourse.[3] The success rate varied with different comorbidities and was lower in patients with more than one risk factor. Another study obtained similar results.[11] These findings indicate that modification of risk factors has an important role in the success of oral PDE5 inhibitors.

Psychosexual therapy

To be effective, the treatment of erectile dysfunction must go beyond just restoring erectile function,[12] and some cases require integrated treatment using psychosexual therapy and pharmacotherapy. Many psychological factors adversely influence the efficacy of sildenafil and result in non-compliance with treatment.[13]

Treatment may be perceived as temporary, unnatural, or unacceptable. Expectations may be unrealistic or the patient may worry about side effects and complications. Regaining potency does not necessarily translate into resuming sexual intercourse, and the resistance of partners may result in the failure of pharmacotherapy. Contributing factors include the duration of sexual abstinence before seeking treatment; the man's approach to resuming sexual contact; the partner's physical and emotional readiness to resume sexual contact; and the quality of the non-sexual relationship.[12]

Sex therapists are trained to deal with these issues and can also remotivate patients in whom treatment with oral PDE5 inhibitors failed, making these patients more likely to try again or seek further options.[13] Although data from controlled trials on the efficacy of this integrated approach are lacking, clinical experi-

ence indicates that it may be effective in patients with psychosocial issues.

Testosterone for hypogonadal men

Endocrine abnormalities are an uncommon cause of erectile dysfunction. Androgen deficiencies are often associated with reduced libido and frequency of intercourse and less often with decreased frequency and quality of erections.[14]

However, testosterone is being investigated as a treatment for erectile dysfunction. Animal studies have shown that testosterone reverses apoptosis of cavernosal smooth muscle cells and reduced expression of the genes encoding nitric oxide synthase and PDE5 which occur after castration.[15 16] Consistent with these findings, testosterone improves sexual function in hypogonadal men with erectile dysfunction.[17]

Recent studies show that men with symptoms of hypogonadism have a reduced response to PDE5 inhibitors. Treatment with testosterone significantly improved the response to sildenafil in men with erectile dysfunction who initially had low initial serum concentrations of testosterone.[14] Treatment with a 1% testosterone gel improved erectile function in hypogonadal men who did not initially respond to sildenafil.[18] In another study, men who did not initially respond to sildenafil but whose response to the drug improved after testosterone replacement had lower serum concentrations of testosterone at baseline than age matched controls who had responded to sildenafil.[19] Larger randomised controlled trials will help clarify the evolving role of treatment combining PDE5 inhibitors with testosterone.

Combination treatments

Men who do not respond to oral PDE5 inhibitors alone may respond to treatments that combine agents that act synergistically. This approach may also allow lower drug doses and reduce the incidence of adverse effects.

Sildenafil and alprostadil

Alprostadil modulates the action of the enzyme adenyl cyclase, increases intracellular cyclic AMP, and leads to the relaxation of cavernosal smooth muscle cells and erection. Cyclic AMP may also exert positive feedback on the nitric oxide-cyclic GMP pathway and further increase cyclic GMP concentrations. Sildenafil can be combined with either intracavernosal or intraurethral alprostadil.

In one study, 29 of 61 men (48%) who failed to respond to either intracavernosal injection of alprostadil or oral sildenafil responded to a combination of these treatments.[20] However 33% of patients reported adverse events (including a 20% overall incidence of dizziness), which were largely mild to moderate in severity and responsible for the discontinuation of treatment in 14% of patients who responded to combined treatment.

Intraurethral alprostadil is delivered by application of a microsuppository into the distal urethra. The drug is rapidly absorbed across the mucosa, initially into the corpus spongiosum and then into the corpora. Studies that combined intraurethral alprostadil with oral sildenafil reported a response in 92-100% patients who did not respond to oral sildenafil alone.[21 22]

Sildenafil and doxazosin

Doxazosin, an α adrenergic antagonist, is a weak erectogenic agent. In a group of men with psychogenic erectile dysfunction, doxazosin and sildenafil produced a 79% response rate compared with a 7% response to sildenafil and placebo.[23] Patients experienced few adverse effects and no appreciable alteration in blood pressure

Sildenafil and apomorphine

Apomorphine is a D1/D2 dopamine receptor agonist and is the first centrally acting treatment for erectile dysfunction. The drug is given sublingually, acts rapidly (within 15-20 minutes), has a small effect in men with mild erectile dysfunction, and is unlikely to be effective in men who do not respond to sildenafil.[24]

Although the combination of a centrally acting treatment with one that acts peripherally is appealing, controlled clinical trials are lacking and the potential risk of precipitant and severe hypotension is worrying.

Conclusions on combination treatments

Despite the growing evidence that combination treatment may be successful in men for whom monotherapy fails, double blind randomised controlled trials are needed to establish the benefits, optimal dosage, possible adverse effects, and acceptability to patients of these treatments.

Alternative treatments

Vacuum constriction devices

Vacuum constrictor devices are the least invasive and cheapest option for men who are not interested in or are unsuitable for pharmacotherapy. They apply negative pressure to the penis, producing an erection that is maintained by an elastic band at the base of the penis for up to 30 minutes. The device can be used daily and the reported rates of success range between 70% and 94%.[25] The associated side effects include penile pain, numbness, bruising, and obstructed ejaculation.

Intracavernosal injection

Intracavernosal injection involves self administration of vasodilator drugs, which act by relaxing arterial and trabecular smooth muscle and result in an erection. It is regarded as a second line treatment for erectile dysfunction and should be considered when oral treatment with PDE5 inhibitors fails. The most commonly used intracavernosal drugs are alprostadil and "trimix," a combination of papaverine, phentolamine, and alprostadil.

Alprostadil has a response rate of more than 70% and a lower risk of complications than other intracavernosal drugs.[26] This treatment is effective and safe in patients who do not respond to initial treatment with sildenafil: 88% of patients reported a response.[27] The most commonly reported adverse effects include penile pain, fibrosis, and priapism.

Trimix may be an effective treatment for patients who do not respond to monotherapy with alprostadil. One study reported a 92% response rate for this combination of drugs.[28]

Summary points

Although oral phosphodiesterase type 5 (PDE5) inhibitors have improved the treatment of erectile dysfunction, 30-35% of men do not respond to these drugs

In patients who do not initially respond to PDE5 inhibitors, the response may be improved by educating patients on the correct use of the drug, optimising the dose, daily dosing of the drug (rather than on-demand), improving comorbid conditions, treating hypogonadal men with testosterone

PDE5 inhibitors can also be combined with other classes of drug

Alternative treatments include injecting drugs intracavernosally, and providing psychosexual therapy, vacuum constriction devices, and penile prostheses

Penile prosthesis

Implanting a penile prosthesis is often the best treatment for patients with severe erectile dysfunction that does not respond to pharmacotherapy. Pharmacotherapy often fails in patients with diabetes, radical prostatectomy, Peyronie's disease, and severe penile fibrosis. Penile prosthetic surgery has high long term mechanical reliability and patient satisfaction rates of more than 85%.[29] One of the most serious complications is infection, although infection has decreased greatly since the introduction of antibiotic coated penile prostheses.[30]

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Interactive case report

A 28 year old postpartum woman with right sided chest discomfort

This case was described on 18 and 25 February (*BMJ* 2006;332:406, 471). Debate on the patient's management continues on bmj.com/cgi/content/full/332/7539/471. On 11 March we will publish the case outcome together with commentaries on the issues raised by the management and online discussion from relevant experts and the patient.