Oral agents for erectile dysfunction

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Erectile dysfunction is a common disease affecting the lives of millions of men worldwide. Sildenafil was the first oral treatment licensed for male erectile dysfunction. However, there are now a number of other options available. In this article the currently available oral treatments are reviewed.

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In 1992 the National Institute for Health defined erectile dysfunction (ED) as the inability to achieve and maintain a penile erection adequate for satisfactory sexual intercourse (National Institute for Health, 1992). It has since been recognized to be a significant male health problem affecting approximately 150 million men worldwide (Aytac et al, 1999). However, epidemiological studies may underestimate the problem because of the stigma associated with ED. In a primary care study approximately 34% of men reported ED, however, less than 12% of men with ED had been treated (Chew et al, 2000).

There is now an expanding range of options available for the management of ED. They include oral agents such as phosphodiesterase type 5 (PDE5) inhibitors, dopamine agonists and alpha-receptor blocking drugs (*Table 1*). Other options include intracavernosal injection (alprostadil, papaverine, phentolamine, prostaglandin E1), transurethral vasoactive agents (prostaglandin E1), vacuum erection devices and penile prostheses.

Oral therapy is used as the first-line therapy in the majority of cases and is generally the most acceptable form of treatment. The currently available oral preparations are briefly reviewed.

TABLE 1.
Current oral agents for male erectile dysfunction

Oral treatments	Mechanism of action
Sildenafil citrate (Viagra)	PDE5 inhibitor
Tadalafil (Cialis)	PDE5 inhibitor
Vardenafil hydrochloride (Levitra)	PDE5 inhibitor
Apomorphine sublingual (Uprima)	Dopamine agonist
Phentolamine (Vasomax)	Alpha adrenoceptor antagonist
Yohimbine	Alpha adrenoceptor antagonist
Prazosin and doxazosin	Alpha adrenoceptor antagonist

PDE5 = phosphodiesterase type 5

PDE5 INHIBITORS

The PDE5 inhibitors sildenafil, tadalafil and vardenafil share the same mechanism of action. However, they differ in their efficacy for the inhibition of the enzyme, in their selectivity for PDE5 over other isoenzymes such as PDE6 and their duration of action (*Table 2*).

Sildenafil

In 1998 sildenafil citrate (Viagra, Pfizer, Sandwich, UK) became the first oral treatment for ED to be approved by the Food and Drug Administration (FDA). Sildenafil improves erectile function in 82% of patients compared with 24% taking placebo (Goldstein et al, 1999). It ameliorates ED in a wide range of patient subtypes (*Figure 1*) (Dinsmore et al, 1999), with maintenance of efficacy regardless of age, aetiology of ED (organic, psychogenic or mixed) and baseline severity of the condition. Psychogenic patients respond the best (85%) whereas men who have undergone a radical prostatectomy demonstrate the lowest response rate (31%) (Blander et al, 2000).

TABLE 2.
Properties of the PDE5 inhibitors

		Sildenafil	Tadalafil	Vardenafil
Time to onset		60 min	45 min	25–40 min
Duration of action		4–8 hours	24–36 hours	Not known
IC_{50} PDE5 (nM)		3.5	0.9	0.7
Selectivity ratio	PDE1	80	>10 000	257
	PDE2	1000	>10 000	>10 000
	PDE3	1000	>10 000	>10 000
	PDE4	>10000	>10 000	>10 000
	PDE5	1	1	1
	PDE6	10	780	16

IC_{50} = concentration of drug required to achieve 50% inhibition of enzyme; the lower the value the more efficacious the drug. The selectivity ratio is represented for phosphodiesterase type 5 (PDE5) over the other PDE isoenzymes; the higher the value the more specific the drug is for PDE5 over the other isoenzymes

Figure 1. Percentage of patients with improved erections after treatment with sildenafil in a range of aetiologies. TURP = post transurethral resection of prostate for benign prostatic hyperplasia.

Sildenafil is effective when taken approximately 1 hour before sexual activity. Food intake, particularly fatty meals, decreases the rate of absorption, reduces the maximum plasma concentration and results in a decrease or delay of efficacy.

Side effects: Headache (16.3%), flushing (12.5%), dyspepsia (2.5%) and rhinitis (2.5) are the most common side effects seen. The incidence of side effects reduces as the duration of medication is increased. The dose of sildenafil should be adjusted in patients older than 65 years, those who have renal or hepatic insufficiency, or are taking medications that share the cytochrome P450 pathway (erythromycin, cimetidine or ketoconazole).

Tadalafil

Tadalafil (Cialis, Lilly-Icos, Indianapolis, USA) has been approved by the FDA in the United States with conditions attached and has been approved in the European Union. Tadalafil was commercially launched in the European Union and Australia in February 2003. Tadalafil is rapidly absorbed, predominantly eliminated by the liver and distributed widely in tissues. It has a half-life of 17.5 hours. Compared with placebo, tadalafil at doses from 5–20 mg significantly enhances erectile function (*Figure 2*) (Brock et al, 2002b). Treatment with 20 mg leads to successful intercourse even when attempted up to 36 hours after dosing (Brock et al, 2002b). Doses of 10 and 20 mg are effective in patients with diabetes mellitus-associated ED (Saenz de Tejada et al, 2001).

Side effects: Headache (11%) and dyspepsia (7%) are the commonest side effects, followed by back pain (4%), nasal congestion (4%), myalgia (4%) and flushing (4%). Side effects decrease in frequency with continued administration. Tadalafil exerts no significant effects on vision.

Vardenafil

Vardenafil (Livetra, Bayer, Newbury, UK) is a PDE5 inhibitor currently being evaluated for the treatment of ED. It is expected to be commercially launched in late 2003. Vardenafil reaches maximum plasma concentrations within 40 minutes and has a half-life of 4.4–4.8 hours. Treatment with vardenafil 5–20 mg significantly improves erectile function compared with placebo (*Figure 3*) (Porst et al, 2001). Vardenafil at 10 and 20 mg significantly improves both erectile func-

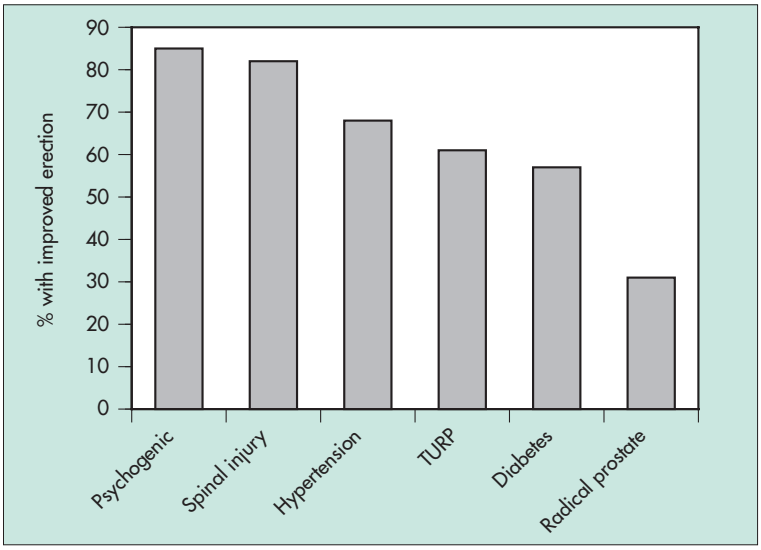
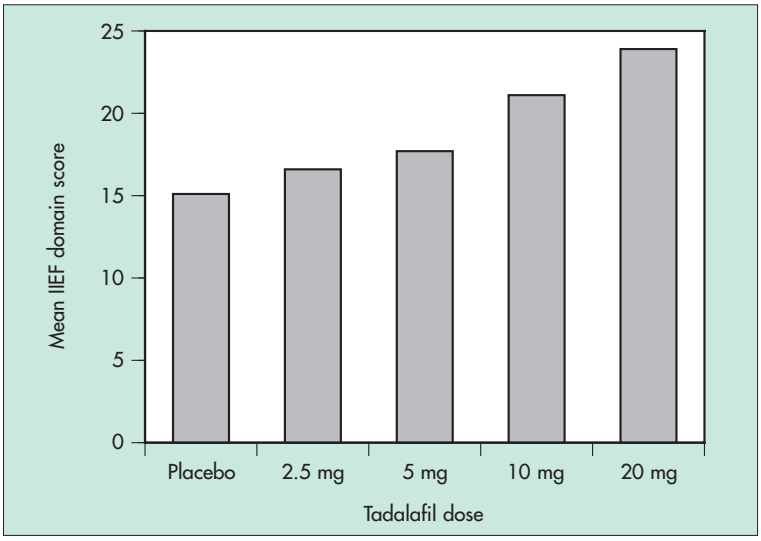


Figure 2. The effect of tadalafil on the International Index of Erectile Function (IIEF) domain scores (Brock et al, 2002b).



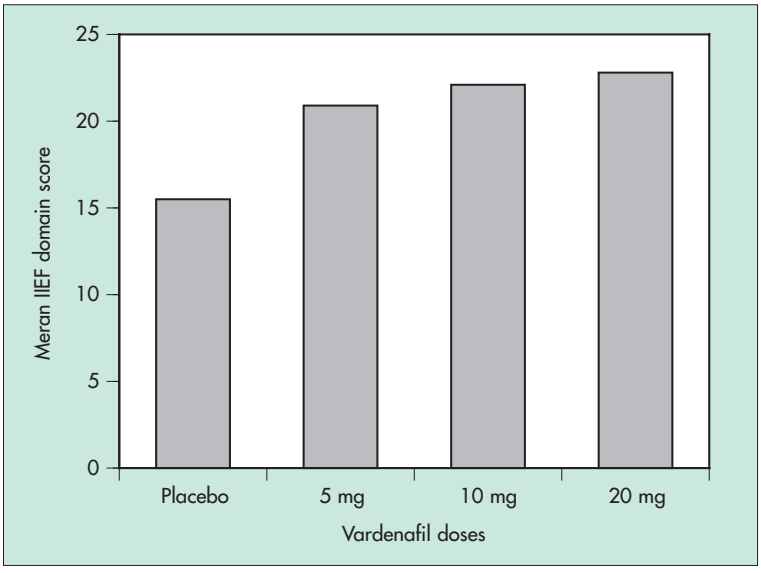


Figure 3. The effect of vardenafil on International Index of Erectile Function (IIEF) domain score (Porst et al, 2001).

tion and erection quality following nerve-sparing radical prostatectomy (Brock et al, 2002a) and ED associated with diabetes (Goldstein et al, 2003).

Side effects: The side-effect profile for vardenafil is similar to that of sildenafil, with headache, flushing, dyspepsia and rhinitis the commonest reported adverse symptoms in 6.8%, 10.2%, 0.7% and 4.8% of patients respectively. There have been no reports of altered vision or serious cardiovascular events (Porst et al, 2001).

PDE5 inhibitors may be safely used to treat ED in patients with stable angina who are not taking nitrates. *Table 3* shows the cautions and contraindications for use of PDE5 inhibitors.

ALPHA-ADRENOCEPTOR ANTAGONISTS

Alpha-adrenoceptor antagonists act by reducing the anti-erectile forces during the initiation and maintenance of erection.

Phentolamine

Phentolamine is a non-selective α-adrenoceptor antagonist. Peak plasma concentrations are achieved in 30–60 minutes, and the half-life is 5–7 hours. Food decreases the rate of absorption but not the bioavailability. At 40 and 80 mg phentolamine significantly improves erectile function over placebo (Goldstein, 2000; Goldstein et al, 2001), and 55 and 59% of men respectively are able to achieve penetration. The commonest side effects are nasal congestion (10%), headache (3%), dizziness (3%) and tachycardia (3%) (Goldstein, 2000; Goldstein et al, 2001).

Phentolamine is contraindicated in patients with known coronary artery disease (CAD) and hypotension. Unfortunately, there have been no clinical trials looking at the comparative efficacy of phentolamine *vs* other oral medications for ED.

Yohimbine

Yohimbine is an indolalquinolonic alkaloid derived from the bark of the African Yohimbine tree. It is a potent selective α2-adrenoceptor antagonist with weaker α1-antagonist activity.

TABLE 3.
Cautions and contraindications with PDE5 inhibitors

Contraindications	Concomitant use of nitrates
	Hereditary degenerative retinal disorders
	Hypotension (systolic pressure less than 90 mmHg)
	Recent cerebrovascular accident
Cautions	Significant coronary artery disease (e.g. myocardial infarction, unstable angina)
	Congestive heart failure

PDE5 = phosphodiesterase type 5

Yohimbine shows a marginal improvement in erectile function over placebo in organic, psychogenic and mixed aetiology ED (Riley et al, 1989; Morales, 2000). The best results are seen in psychogenic ED. Side effects include tachycardia, hypertension, postural hypotension, anxiety and agitation (>5%) (Riley et al, 1989; Morales, 2000). It is contraindicated in patients with hypercalcaemia, glaucoma and ischaemic heart disease.

Doxazosin

Doxazosin is a selective α1-adrenoceptor antagonist with a half-life of 16 hours, which permits once-daily administration. Because it is metabolized in the liver, it should be used with caution in patients with impaired hepatic function. Doxazosin significantly improves erectile function in patients with benign prostatic hyperplasia (De Rose et al, 2002a). It has also been successfully combined with sildenafil to treat ED refractory to sildenafil alone (De Rose et al, 2002b).

DOPAMINE AGONISTS

Apomorphine

Sublingual apomorphine (Uprima, Abbott, Maidenhead, UK) is a centrally acting agent licensed for the treatment of ED in most European and South American countries, but not currently in the United States. It has been reported to exert much of its pro-erectile activity by acting upon the paraventricular nucleus of the hypothalamus. A sublingual preparation minimizes side effects while maintaining efficacy.

Apomorphine dissolves in the buccal mucosa within 5–10 minutes and has a median onset of action of 19 minutes; 71% of erections occur within the first 20 minutes of taking apomorphine (Dula et al, 2001). In clinical studies apomorphine 2 and 3 mg is statistically superior to placebo at inducing an erection sufficient for intercourse in up to 53% of patients (Dula et al, 2001; Heaton, 2001). It is more effective than placebo in patients with CAD, benign prostatic hyperplasia, hypertension and diabetes (*Figure 4*).

Increasing the dose above 3 mg can improve efficacy further, but it also increases the incidence of nausea from 3.3 to 14.1% (Dula et al, 2001). Moreover, efficacy is increased with increased duration of use (Mirone and Stieff, 2001).

Side effects: The commonest side effects include nausea (7%), dizziness (6.5%), yawning (8.1%), somnolence (4.9%) and headache (2.2%) (Dula et al, 2001; Heaton, 2001). No serious adverse cardiovascular events have been reported.

Cautions: Apomorphine use is not contraindicated in patients on nitrate therapy. However, these patients should inform their physician that they are

taking nitrates and be carefully monitored. Its use is contraindicated in severe cardiac failure, severe hypotension, unstable angina and in patients who have recently had a myocardial infarction.

CONCLUSIONS

The introduction of sildenafil has resulted in greater awareness of the epidemiology and treatment of ED. The newer, potentially more efficacious PDE5 inhibitors (tadalafil, vardenafil) will treat a greater number of patients, allowing once daily and more convenient dosing. However, they should be used with caution in patients with CAD.

Apomorphine has considerable efficacy in men with a broad range of ED aetiologies, severities and co-morbidities, although clearly inferior to PDE5 inhibitors. It is useful when a rapid reliable response is required and can be used in patients with CAD on nitrate therapy. It may be particularly useful for patients intolerant of or contraindicated to using PDE5 inhibitors.

Alpha adrenoceptors antagonists (e.g. doxazosin) are particularly useful in treating ED where there are also symptoms related to benign prostatic hyperplasia.

With an expanding armamentarium of treatment options it is even more important for the physician to treat each patient as an individual to achieve optimum results. HM

Conflict of interest: none.

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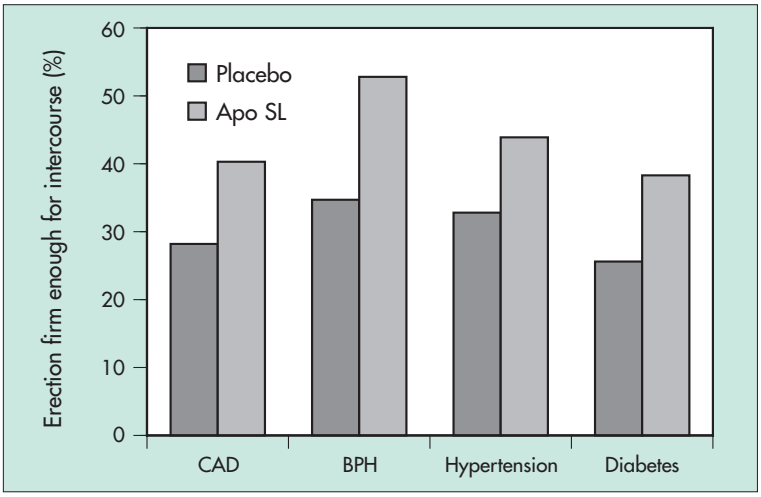
Figure 4. The pro-erectile effects of sublingual apomorphine (Apo SL) in patients with co-morbidities commonly found in patients with erectile dysfunction. BPH = benign prostatic hyperplasia; CAD = coronary artery disease. From Heaton (2001).



KEY POINTS

- Erectile dysfunction affects approximately 150 million men worldwide.
- Oral agents include phosphodiesterase type 5 (PDE5) inhibitors, dopamine agonists and alpha-receptor blocking drugs.
- Sildenafil was the first approved oral treatment for erectile dysfunction.
- Sildenafil improves erectile function in a wide range of patient subtypes.
- The newer PDE5 inhibitors (tadalafil, vardenafil) have greater efficacy in inhibiting the PDE5 enzyme.
- Tadalafil improves erections for 24–36 hours post dose.
- PDE5 inhibitors are safe in patients with stable coronary artery disease not on nitrates.
- The dopamine agonist apomorphine improves erectile function in many patient aetiologies and may be used by patients on nitrate therapy.
- The alpha adrenoceptor agonists may be used where there are also symptoms of benign prostatic hyperplasia.