Erectile Dysfunction

Plan of treatment
Regardless of the aetiology of the ED, most men will benefit from oral therapy. If oral therapy fails, then more invasive options are indicated, progressing if necessary to penile implants for severe cases, providing that the patient is willing to have them inserted.

In addition to oral therapy, it is clear that risk factors as diabetes, depression and hypertension should be treated. Not only will treatment of these conditions help the ED, but it may also prevent further clinically related problems arising in the future.

There are certain groups of men in whom specific therapy is indicated because there is a possibility of cure. Patients in whom cure is possible include:

- Patients with predominantly psychosexual ED
- Patients with endocrine disease
- Patients with localised vascular disease such as those who have developed ED following pelvic or perineal trauma

General measures for the man with ED

General measures that are valuable in all men with ED include:

Control of concurrent risk factors
This includes control of diabetes, hypertension and hyperlipidaemia. Better control often helps the ED, and may resolve the problem altogether. Similarly, treatment of depression often results in improved sexual function.

Change of medication
If the onset of the ED appears to be related to the onset of the ED, then a change of medication to a drug with less risk of causing ED might be beneficial.

Change of lifestyle
- For the middle-aged man with undue stress, at home, at work or with respect to money, sexual function may be improved by a change in lifestyle, with more exercise, more relaxation and decreased responsibilities.
- Advice to reduce any excessive alcohol intake together with cessation of smoking is helpful. Although the evidence that stopping smoking actually helps is somewhat limited, prevention of subsequent cardiovascular and cerebrovascular disease is important. Other recreational drugs can also affect sexual function, and advice in this respect is also helpful, where relevant.

Oral therapy for Erectile dysfunction

Phosphodiesterase inhibitors (Sildenafil, Tadalafil, Vardenafil)
Nitric oxide is released within the corpus cavernosum by parasympathetic nerve endings and by the vascular endothelium. When it enters the smooth muscle cell it stimulates the enzyme guanylate cyclase to produce cyclic GMP, its’ active second messenger. Cyclic GMP (cGMP) produces smooth muscle relaxation which in turn leads to increased arterial inflow, cavernosal expansion and reduced venous outflow.
The action of cyclic GMP is terminated by the enzyme Phosphodiesterase type 5 (PDE5) and inhibition of PDE5 will potentiate the pro-erectile effects of cGMP.

![Diagram of cyclic GMP action](image)

**Potency and selectivity**

Eleven different groups of phosphodiesterase enzymes have been identified within the body. These are called isoenzymes and are numbered PDE1 to PDE11. An ideal PDE5 inhibitor would inhibit only PDE5 and none of the other isoenzymes.

All three drugs are potent inhibitors of PDE5. None of the three drugs has any significant activity against PDE’s 1, 2, 3 and 4 and PDE’s 7, 8, 9 and 10 and the only differences in selectivity is in their activity against PDE6 and PDE11.

PDE6 is found in the retina and is involved in phototransduction. At high doses, sildenafil inhibits it, resulting in the occasional transient visual changes seen with sildenafil treatment. There is no evidence that there are any permanent visual changes. Vardenafil has less activity against PDE6 and tadalafil has no significant activity at all.

PDE11 is the newest isoenzyme to be identified, and is found in a number of tissues, including the testis and the heart. Its’ physiological function is as yet, unknown. Sildenafil and vardenafil have no significant activity against it, but at high doses, tadalafil does. At present there is no evidence of any deleterious effect due to this inhibition.

**Clinical results of the PDE5 inhibitors**

PDE5 inhibitors need to be taken in conjunction with sexual stimulation, when they will facilitate a return to normal erectile function. In responders, upon sexual stimulation the man will get a normal erection that usually persists until orgasm and ejaculation, following which detumescence will occur. Repeated sexual activity is possible while the drug is still present in the body.

**Efficacy**

- Treatment of men with ED of mixed aetiology results in around 70-75% of men achieving normal erections with rigidity adequate for penetration and which is maintained to ejaculation.
• The aetiology of the ED has an effect on the outcome of therapy, with particularly high response rates in men with psychogenic ED, and men with ED secondary to depression or hypertension.
• Lower efficacy rates are seen in diabetics (when around 50-60% of men get adequate erections) and in men who have undergone radical pelvic surgery for prostate cancer, where response rates as low as 30-40% are seen.

Side effects
• Side effects seen with all drugs include headache, flushing, indigestion and nasal congestion.
• The commonest of these is the headache that is seen in around 15% of patients.
• The side effects become more frequent with increasing doses of the drugs, and reflect inhibition of PDE5 in other tissues within the body.
• All the side effects are transient and well tolerated.

Safety of the medication
• Although there were initial concerns about the cardiac safety of this class of drugs, these concerns have proven unfounded.
• There is no evidence of any increased risk of either sudden death or myocardial infarction when these drugs are used in men with ED.
• Concurrent use of nitrate medication is a contraindication for this class of drugs, since they potentiate the vascular smooth muscle relaxation produced by nitrates, and considerable falls in blood pressure have been seen when both are taken together.

Issues specific to Sildenafil
• In fasted patients, it is effective within 30 minutes, but food delays it’s absorption, and it is usually best to tell patients to leave an hour after dosing before attempting sexual intercourse.
• The half-life of the drug is around 4 hours, giving a duration of action of 6-8 hours.
• Side effects are as above, but in addition, occasional visual side effects are seen, such as bluish vision or blurred vision.
• The usual starting dose is 50mg, which can be titrated up to 100mg or down to 25mg. The lower dose is recommended in older patients and in those with renal or hepatic impairment.

Issues specific to Tadalafil
• Following administration, it reaches maximal plasma levels in around 2 hours, but it is active before that time and because of this, there is only marginal food interaction.
• It has a significantly greater half life than sildenafil at around 17 hours, and there is data to confirm it’s efficacy at 36 hours.
• Accordingly, it is probably best administered several hours before sex is attempted, thereby reducing any anxiety that might be associated with using a drug to treat ED.
• The side effect profile is broadly similar to sildenafil with a few exceptions. Visual side effects are not seen, the frequency of flushing appears to be reduced and some patients (around 10%) complain of muscular discomfort or backache.
• The usual starting dose is 10mg, which can be increased to 20mg if necessary. The lower dose is recommended for men with hepatic or renal impairment.
Issues specific to Vardenafil

- It reaches maximal plasma levels more rapidly than sildenafil, and may well be more rapidly acting in fasted patients and in patients who have eaten lightly. Absorption is delayed by heavy meals containing fatty food, and again, it is sensible to allow around an hour between dosing and attempting sexual activity.
- Its half-life is around 4 hours, giving 6-8 hours of clinical benefit.
- Side effects are similar to sildenafil, but there are few (if any) visual side effects, and none of the muscular cramps seen with tadalafil.
- The usual starting dose is 10mg, which can be raised to 20mg or reduced to 5mg as required. The lower dose is recommended for men with hepatic or renal impairment.

Comparative trials of PDE5 inhibitors

- While many trials have sought to compare the efficacy and safety of the PDE5 inhibitors, most have suffered from poor design making interpretation of the results impossible. However, more recently, some trials have been published with reasonable (if not perfect design) which suggest the following:
  - Efficacy and safety of the PDE5 inhibitors is approximately equal.
  - Some patients prefer to use one or the other drug, based upon characteristics such as speed of action of the drug, duration of action, and perceived ability to provide a rigid erection.

Using PDE5 inhibitors: practical considerations

- When commencing a man on a PDE5 inhibitor, he will take some time to become adjusted to the use of a tablet to treat his erectile dysfunction. There may well be anxiety, both on his part and on the part of his partner.
- Accordingly, it is important to carefully explain the importance of sexual stimulation and of leaving an adequate period between taking the drug and attempting sex.
- In addition it is important to provide the patient with an adequate number of tablets (usually four at least), and to be prepared to increase dosage up to the maximum, again providing tablets for at least four attempts.
- The use of nitrates for angina is a contraindication to the use of any PDE5 inhibitor. Co-administration can lead to significant hypotension.
- Other drugs that interfere with the metabolism of these drugs include ketoconazole, erythromycin and the protease inhibitors used in AIDS patients, which inhibit the hepatic enzymes which metabolise these drugs. In the patients the lowest starting dose of the drug should be used. On the other hand, in patients taking rifampicin, which stimulates the metabolism of these drugs, the maximal dose is advisable.

Treatment of non responders to PDE5 Inhibitors

When a patient apparently fails to respond to a PDE5 inhibitor a number of approaches are possible to “rescue” the situation;

- Issues such as the need for appropriate sexual stimulation, awareness of the appropriate time window for the medication, and avoidance of any food interactions are vitally important to maximise success.
- An adequate trial of therapy must include at least 6-8 attempts with the top dose of the drug used since it has been clearly shown that that several attempts are required to maximise the response rate to PDE5 inhibitors.
- Continuous dosing of the PDE5 inhibitor may be helpful. The mechanism whereby regular dosing with a PDE5 inhibitor can be effective, when intermittent use has...
been ineffective is that there may be some more generalised improvement in endothelial function that is modulating this improved response.

- It has been demonstrated that testosterone levels may modulate PDE5 expression and activity and there is a suggestion that in men whose testosterone levels are low or even in the lower end of the “normal” range, that testosterone supplementation might be effective as a means of salvaging men who have failed to respond to a PDE5 inhibitor.

**Hormonal therapy for erectile dysfunction**
- Testosterone is vital for normal sexual functioning in man. Reduced levels of testosterone affect sexual function significantly, with changes in sexual drive and erectile function.
- For men with ED who have clear evidence of reduced testosterone levels, testosterone replacement is usually beneficial.
- Options for therapeutic replacement include oral, transdermal (patches and gels), intramuscular or implanted testosterone.
- Side effects of testosterone treatment in general include oedema, raised haematocrit, gynaecomastia, acne, hirsutism. Hepatotoxicity has been reported especially with oral preparations.
- Patients on testosterone therapy need regular monitoring of lipid levels and PSA.

**References**
