

# Gavel

Evidence-Based Medicine *in practice*

## Management of erectile dysfunction

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- Male erectile dysfunction is common, with almost 10% of men aged under 70 suffering from total erectile failure.
- Around 65–70% of men with erectile dysfunction have an underlying organic cause for their problem. Less than 12% of cases result from purely psychological causes.
- Most men presenting to their GP with erectile dysfunction will need to be considered for active drug therapy.
- There are few direct comparisons of treatment alternatives so our conclusions are based on separate placebo-controlled trials.
- Of the licensed drug therapies, intracavernosal injection of alprostadil is associated with the greatest success rate, but requires specialist instruction before use.
- Oral sildenafil is slightly less effective than injected alprostadil, but is significantly cheaper and more practical for primary care use.
- Transurethral alprostadil is less effective than intracavernosal alprostadil or sildenafil, but may present an alternative where sildenafil is inappropriate or contraindicated and injection is unacceptable.
- Both transurethral alprostadil and oral sildenafil treatment may be initiated in primary care after appropriate patient assessment and basic investigations.
- Surgery is needed in a minority of patients, and should only be recommended after specialist investigation.

# Impotence therapy

Until relatively recently, the management of erectile dysfunction was not a subject that impinged greatly on the average GP's workload. The high profile launch of sildenafil (Viagra® Pfizer Limited, UK), however, has brought the issue to the forefront of the medical agenda. At the time of writing, the Department of Health is considering its position with regard to the availability of sildenafil within the NHS.

There is a substantial risk, however, that the media noise around this issue will drown out important questions about the clinical value of impotence therapy – not only sildenafil but also the other available treatments. There are a number of large, high-quality clinical trials in this area, and it is important for GPs to be aware of their conclusions if this disease area is to be managed responsibly. In this issue of *Gavel*, therefore, we will look in detail at each of these studies and draw together a rational, evidence-based strategy for the primary care management of erectile dysfunction.

## Epidemiological background

There are no published epidemiological surveys relating to the prevalence of erectile dysfunction in the UK, so we must be guided

by US studies. Probably the best constructed is the Massachusetts Male Aging Study (MMAS), which examined the health status of a representative sample of 1,709 men aged between 40 and 70.<sup>1</sup> Part of this assessment involved the completion of a detailed sexual questionnaire, including questions on potency; 91% of men with a current sexual partner completed the questionnaire.

Not surprisingly, some degree of erectile dysfunction was common, with about 50% of respondents reporting erectile problems. Severe impotence, on the other hand, was less commonly seen, although it was found to occur in 9.6% of men. Although it is clearly seen more frequently in older men, 5% of 40-year-olds none the less reported complete erectile impotence (Figure 1).

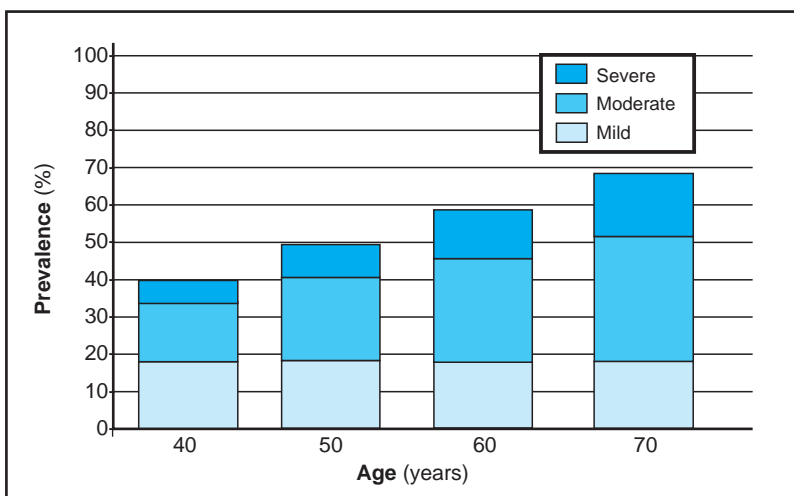
As 40- to 70-year-old men represent approximately 16.5% of the total population in the UK,<sup>2</sup> one would expect to find, in the average 8,000-patient general practice, approximately 1,300 men in this age group. If, as seems likely, the results of the MMAS are applicable to a UK population, 9.6% of these (approximately 125 men) might be expected to have total erectile failure.

## Causes of erectile dysfunction

Normal erectile function depends on an interaction of endocrine, vascular and neurological mechanisms, combined with a favourable psychological state. Although psychological factors may have a role to play in many patients, for the vast majority of men there is an underlying organic cause for their problem (Figure 2).<sup>3,4</sup>

Within the general category of organic causes, several clearly defined aetiologies exist:

- Atheromatous arterial disease (approximately 50% of cases).
- Neurological causes: peripheral neuropathy; spinal cord injury; stroke; multiple sclerosis.
- Iatrogenic: drugs (thiazides, anti-epileptics, beta-blockers, GnRH analogues,



**Figure 1. Prevalence of erectile dysfunction with age in the Massachusetts Male Aging Study<sup>1</sup>**

antidepressants, lipid-lowering drugs);  
post-prostatectomy.

- Venous insufficiency.
- Endocrine causes: hypogonadism; hyperprolactinaemia.
- Others (<5% of cases): physical injury; Peyronie's disease; and so on.

Several of these causes may act in conjunction, resulting in high rates of erectile dysfunction in patients with diabetes, renal disease and hypertension.

## Management options

Current options available in the UK for the treatment of erectile dysfunction include:

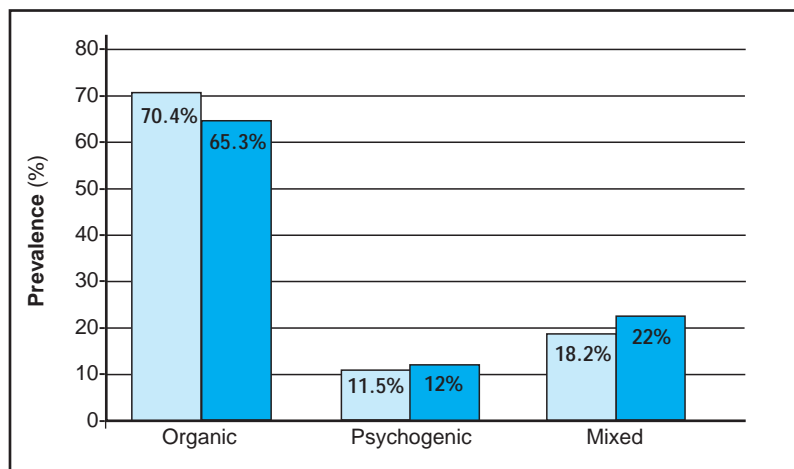
- Non-drug therapies
  - psychosexual counselling
  - vacuum devices
  - penile implants
  - reconstructive surgery
- Drug therapies
  - injected alprostadil
  - injected moxisylyte
  - transurethral alprostadil
  - oral sildenafil

### Non-drug treatments

Very little structured research has been carried out into the use of non-pharmaceutical measures. Most of our understanding of these methods is therefore based on retrospective studies and case series. Because this type of research cannot be randomised, a certain degree of caution should be exercised when applying the results to a general population.

#### *Psychosexual counselling*

Although widely recommended, there have been no controlled studies of the use of psychosexual counselling in erectile dysfunction. One questionnaire survey of 289 sex therapists suggested that they achieved a successful outcome in 25% of patients treated for impotence, although the nature of the patients referred is unclear.<sup>5</sup> In another study, 20 consecutive diabetic men with erectile dysfunction were referred for psychosexual assessment and treatment.<sup>6</sup> Three of these achieved long-term improvement in sexual function, although it proved impossible to identify these responders from their pre-treatment characteristics. A third study looked



**Figure 2. Underlying aetiology of erectile dysfunction (pooled data)<sup>3,4</sup>**

at a combination of treatment strategies in 145 men.<sup>7</sup> Twenty-one per cent of those studied were able to have intercourse after psychotherapy alone. Interestingly, those with clearly organic impotence benefited almost as much as those with psychogenic impotence (21% versus 32%).

Although these studies do not confirm a significant benefit from psychosexual counselling, it seems likely that, for a minority of patients, there is improvement to be had from counselling alone, regardless of the aetiology of their erectile dysfunction.

#### *Vacuum devices*

Vacuum devices rely on first drawing blood into the penis, by means of an externally applied suction pump, and then retaining the resultant erection by means of an elastic ring applied to the base of the penis. Provided it is used properly, the failure rate is very low and serious adverse effects are rare, although many patients find the method cumbersome. The band may only be kept on for 30 minutes and ejaculation may be obstructed. One small retrospective study shows that 81% of men stopped using the device over a one-year period.<sup>8</sup> A second study of 50 men suggested that only 27% preferred the vacuum device over intracavernosal injection therapy.<sup>9</sup>

#### *Surgical options*

Where all other treatment strategies fail, surgery may be a viable option. This will generally take the form of an implanted penile rod, or a hydraulically operated prosthesis. Anecdotal evidence suggests that these are well tolerated, with a low risk of infection or

expulsion. In one case series of 65 patients, followed up for an average of five years, 70% of patients were found still to be sexually active with their prosthesis, compared with only 41% of patients on intracavernosal injection.<sup>10</sup> It should be borne in mind, however, that this was a highly selected group of patients, who would already have tried all other available treatments, and would have been aware that no other options existed.

In some patients, it may prove possible to improve the arterial supply to the penis or to restore normal venous function. This is, perhaps, a preferable surgical option to start with, as failure does not preclude subsequent insertion of a penile implant. The procedure, however, is not widely available and is only associated with a 30% success rate.<sup>11</sup>

#### Drug treatments

Perhaps inevitably, given the relatively poor success rates of the above treatments, most erectile dysfunction patients will be treated with some form of drug therapy. A wide range of approaches has been tried over the years, whether by the oral, topical or injectable routes, with varying degrees of success. We currently have four products licensed in the UK – injected alprostadil, injected moxisylyte, transurethral alprostadil and oral sildenafil. Moxisylyte will be withdrawn from the UK market early in 1999, but the data relating to

this drug have been included for the sake of completeness. In addition, various unlicensed products, including injected papaverine and oral yohimbine, have been used. Unless the doctor is comfortable to accept clinical responsibility for such use, these are probably best avoided. The use of each of the licensed treatments is supported by at least one substantial controlled trial, and that enables us to make comparisons.

#### The trials

Although superficially similar, these studies have important differences that may influence prescribing decisions. The following criteria are important to bear in mind:

- What is the setting? Preliminary dose finding is usually carried out in an outpatient setting, with objective measurement of erectile response. Success rates tend to be lower than in subsequent, home-based studies.
- How are the patients selected? In some studies, the patients are recruited randomly, subject to defined exclusions. In others, their response to the test treatment is first evaluated, with progression to extended use only if this is successful.
- How is the end-point determined? Degree of erectile function may be determined by means of clinical assessment, electronic measurement, questionnaire response or reported ability to have intercourse. As the

## Box 1. How to calculate NNTs

In order to compare clinical trials in a meaningful fashion, some measure of statistical comparison is required. A review of published papers reveals a bewildering range of statistical techniques, but these are generally difficult for the non-specialist to interpret. For this reason, *Gavel*, where possible, expresses trial results in terms of Number-Needed-to-Treat (NNT). The NNT, as the name implies, is an estimate of the number of patients that would need to be given a therapy, in order to achieve the desired result.

For an outcome such as improved sexual function, it is calculated very simply:

$$\text{NNT} = \frac{1}{\text{Proportion of men on active treatment having an adequate erection} - \text{Proportion of men on placebo having an adequate erection}}$$

As an example, in the last four weeks of the dose response arm of the sildenafil study, described in this issue of *Gavel*, the following results are described:

- Fifty percent of men on placebo achieved erections sufficient for intercourse.
- Eighty-five percent of men on 100 mg sildenafil achieved erections sufficient for intercourse.

$$\text{NNT} = \frac{1}{0.85 - 0.5} = 2.86$$

This means that, for every three patients treated with sildenafil, one will achieve intercourse who would otherwise not have done.

**Table 1. Efficacy of treatment versus placebo**

Treatment	Response (%)*		NNT	Comment
	Placebo	Active		
Intracavernosal alprostadil (dose response study) <sup>3</sup>	0	50	2	At 20 µg dosage
Intracavernosal moxisylyte <sup>13</sup>	3	21	5	At 10 mg dosage
Transurethral alprostadil (US study) <sup>15</sup>	19	45	3.8	Figure includes all patients given active treatment, whether or not entered into randomised part of trial
Transurethral alprostadil (EU study) <sup>16</sup>	11	47	2.8	Figure includes all patients given active treatment, whether or not entered into randomised part of trial
Oral sildenafil (final four weeks of dose response study) <sup>4</sup>	50	85	2.9	At 100 mg dosage

\*Percentage response is determined by the number of men experiencing an erection judged sufficient for intercourse

ultimate objective is to improve the patient's sex life, we shall try, where possible, to stick to the latter outcome in this review.

● How is the result expressed? Ideally, we would like to define the proportion of men who benefited from a given treatment. In some cases, however, only the proportion of successful *treatments* is reported. Thus, a patient who finds the treatment acceptable and uses it successfully on nine out of 10 occasions, will have a much greater impact on the result than the man who uses it once, fails and does not use it again. The result is a bias in favour of the treatment that makes statistical interpretation difficult. Specifically, a meaningful NNT (Box 1) cannot be calculated in this situation.

#### Studies of intracavernosal alprostadil (with at least 150 patients participating)

There is one paper, reporting three separate prospective studies<sup>3</sup> (an additional paper reporting on the European Alprostadil Study<sup>12</sup> did not have a placebo arm and has therefore been excluded from this analysis):

- 296 men were assessed in a hospital setting after receiving various doses of alprostadil or placebo.
- Outcomes were graded according to clinical and objective measurements as to whether they had attained an erection sufficient for intercourse.

- 201 men (including 12 from the first trial) were given successively higher doses of alprostadil to assess dose response, according to an objective measure.

- 683 men (including 40 from the first trial) were given alprostadil to use at home, after its efficacy and dose had first been established for each individual. There was no placebo arm.

- Assessment was by means of sexual diaries. Results are reported in Tables 1 and 2.

#### Studies of intracavernosal moxisylyte (with at least 150 patients participating)

There are two papers, reporting one placebo-controlled study and one prospective comparison with alprostadil:<sup>13,14</sup>

- 307 patients were assessed clinically and objectively in a hospital setting after receiving either moxisylyte or placebo.

- Those who had a successful outcome then continued treatment at home. There was no placebo arm at this stage.

- Assessment was by means of sexual diary.

- 156 patients were assessed objectively in a hospital setting after receiving either moxisylyte or alprostadil.

- 129 of these then went on to evaluate the two treatments at home.

- Assessment was by means of sexual diary. Results are reported in Tables 1 and 2.

**Table 2. Best home efficacy rate**

Treatment	Best response (%)*	Comment
Intracavernosal alprostadil** (flexible dose study) <sup>3</sup>	87	683 men were entered in the study; 487 completed three months' evaluation. Outcomes are recorded for 13,762 treatments
Intracavernosal moxisylyte** <sup>13</sup>	62	307 men were entered in the study; 225 completed 3–11 months' evaluation. Outcomes are recorded for 4,487 treatments
Transurethral alprostadil** (US study) <sup>15</sup>	50	1,511 men were entered in the study; 873 completed three months' evaluation. Outcomes are recorded for 4,933 treatments
Oral sildenafil (dose escalation study) <sup>4</sup>	69	329 men were entered in the study; 307 completed three months' evaluation. Total number of treatments used is not reported

\* Percentage response is the proportion of doses that resulted in sexual activity  
\*\* Selected population of treatment responders

**Studies of transurethral alprostadil (with at least 150 patients participating)**  
There are two papers, describing two separate placebo-controlled trials:<sup>15,16</sup>

- 1,511 patients with organic erectile dysfunction were given transurethral alprostadil in a hospital setting to clinically assess responsiveness. No placebo arm.
- The 996 who responded to treatment were then given either alprostadil or placebo to use at home. Assessment was by sexual diary.
- In the second study, 249 patients with organic erectile dysfunction were given transurethral alprostadil in a hospital setting to assess responsiveness. No placebo arm.
- The 159 who responded to treatment were then given either alprostadil or placebo to use at home. Assessment was by sexual diary. Results are reported in Tables 1 and 2.

**Studies of sildenafil (with at least 150 patients participating)**  
There is one paper describing two separate placebo-controlled trials:<sup>4</sup>

- 532 men were treated at home with various fixed doses of sildenafil or placebo.
- Response was assessed by means of structured questionnaire and sexual diary.
- 329 different men were then randomised to receive either sildenafil or placebo at home, with dosage determined by response.
- Assessment was by means of structured questionnaire and sexual diary. Results are reported in Tables 1 and 2.

### Comparative studies

There are a number of small studies directly comparing two alternative therapies. The conclusions that they draw are generally consistent with the above findings:

- Intracavernosal alprostadil is more effective than moxisylyte (70–80% response rate versus 45–50%).<sup>14</sup>
- Intracavernosal alprostadil is more effective than transurethral alprostadil (70% response rate versus 43%).<sup>17</sup>
- Patients who fail to respond to one form of alprostadil may find treatment with the other formulation successful.<sup>18,19</sup>

There are currently no published studies comparing sildenafil with other forms of treatment for erectile dysfunction.

### Adverse events

Minor adverse events are common with all treatments. Depending on the method used, these may include: penile pain; penile bruising; penile fibrosis; urethral trauma; prolonged erection; priapism; dizziness/flushing; hypotension; dyspepsia; headache.

Two of these events may be of further clinical significance – hypotension and priapism. Although mild dizziness and hypotension have been associated with the use of alprostadil, this is not usually a major problem. If, however, sildenafil is taken with organic nitrates, there may be a profound hypotension. This combination must, therefore, be avoided.

There have been several anecdotal reports of sudden death occurring in patients on sildenafil. It is, as yet, unclear whether this is due to the drug itself or simply reflects the underlying arteriopathic nature of the patients. The cardiovascular status of any patient being considered for erectile dysfunction treatment should be assessed.

Priapism is another potentially serious side-effect. If erection is maintained for long periods (greater than six hours), there is a risk that permanent vascular damage will ensue.

Treatment is therefore urgent and consists of:

- Penile aspiration to remove 20–50 ml blood.
- Intracavernosal injection of alpha-sympathomimetic agent.
- Surgical intervention.

The risk of priapism varies:

- Intracavernosal alprostadil – 1–4%.<sup>3,12,20</sup>
- Intracavernosal moxisylyte – <1%.<sup>13,14</sup>
- Transurethral alprostadil – <1%.<sup>15,16,21</sup>
- Oral sildenafil – few case reports.<sup>22</sup>

### Costs

The costs of single treatments with the available methods are shown in Table 3.

### Conclusions

- Although differing study methodology makes direct comparisons difficult, it appears that intracavernosal injection of alprostadil is the most effective treatment for erectile dysfunction, with intracavernosal moxisylyte lagging some way behind.
- The transurethral route of alprostadil administration is less effective, but in patients for whom injection is unacceptable this route may be a useful alternative. Unlike the intracavernosal route, this method does not require referral for specialist instruction.
- The evidence behind sildenafil suggests high levels of efficacy, in combination with an acceptable mode of administration, provided it is used in appropriate patients.
- The costs of treatment with alprostadil and moxisylyte are broadly comparable, regardless of the route of administration. Sildenafil is significantly cheaper, although its NHS status remains unclear at the time of writing.

## An evidence-based management strategy

These recommendations draw on the conclusions described above and place them in a practical context. This requires the reconciliation of crude efficacy data against issues of access and appropriateness. A stepped-care approach has therefore been adopted, with early treatment options being biased in favour of less invasive therapies.

**Table 3. Single treatment costs (NHS)**

Treatment	Brand name	Cost (£)
Intracavernosal alprostadil (5, 10, 20 µg)	Caverject® (Pharmacia & Upjohn Ltd, UK)	6.74–9.95
	Viridal® (Schwarz Pharma Ltd, UK)	6.74–9.95
Intracavernosal moxisylyte	Erecnos® (Fournier Pharmaceuticals Ltd, UK)	7.70–9.95*
Transurethral alprostadil	MUSE® (Astra Pharmaceuticals Ltd, UK)	9.14–10.18
Oral sildenafil	Viagra® (Pfizer Limited, UK)	4.15–5.88

\* To be withdrawn April 1999

(Source: MIMS September 1998 and press release from Pfizer Limited)

### Investigation before treatment

Although most patients with erectile dysfunction will not require specialist investigation, a basic assessment is essential in all patients in order to identify the ideal management strategy.

It should be remembered that the studies on which the above conclusions are based excluded certain groups of patients.<sup>3,4,13–16</sup>

Exclusions included:

- Patients with recent acute severe illness.
- Patients with anatomical penile disease.
- Patients with endocrine causes.
- Patients with poorly controlled diabetes.
- Patients with urethral stricture (transurethral alprostadil).
- Patients with severe dyspepsia (sildenafil).
- Heavy smokers (>40 cigarettes per day) (intracavernosal alprostadil).

Caution should therefore be exercised when treating these groups and the appropriate data sheet consulted.

### History

Full medical and sexual histories should be taken, including details of:

- Prescribed drugs.
- Alcohol consumption.
- Tobacco consumption.
- Indicators of vascular disease.
- Preservation of nocturnal erections (effectively excludes an organic cause).

### Examination

Particular attention should be focused on:

- Blood pressure.
- Peripheral pulses.
- Testicular size.
- Secondary sex characteristics.
- Anatomical defects of the penis.

## Investigations

These will be dictated by clinical findings, but should generally include measurement of:

- Free testosterone.
- Prolactin.
- Blood glucose.
- Lipids.

## Treatment choice

The precise treatment selection will depend on the individual patient and the local prescribing policies. A general approach can, none the less, be adopted in most cases:

**Step 1:** Stabilise general clinical condition:

- Ensure that blood pressure is below 160/90 mmHg.
- In diabetics, ensure that HbA1 is within normal range.
- Address any lipid abnormalities.

**Step 2:** Treat correctable causes:

- Adjust drug regimens where appropriate.
- Correct proven hypogonadism with testosterone replacement.
- Correct hyperprolactinaemia with dopamine agonist therapy (after appropriate investigation).
- Refer for psychotherapy where appropriate.

**Step 3:** Initiate specific therapy for erectile dysfunction:

- First line – oral sildenafil.
- Second line – transurethral alprostadil.
- Third line – refer for injectable alprostadil.
- At any stage consider use of vacuum devices (not generally available on NHS).

This prescribing strategy is based on the philosophy of minimum intervention. Injectable alprostadil is the most effective of the three approaches, but it requires specialist instruction before use and is associated with the highest risk of priapism. It should therefore be reserved for patients who fail to respond to simpler methods and are sufficiently motivated to use an invasive method.

Whichever method is chosen, it is important to bear in mind its risks and limitations and to consult the relevant data sheet. Key precautions to remember include:

- In a patient with unstable diabetes, or who is recovering from a myocardial infarction or stroke, any treatment for erectile dysfunction is contraindicated.
- All these agents must be used with caution where there are anatomical abnormalities of the penis.

- Alprostadil, by either route, is contraindicated in Peyronie's disease.
- Conditions predisposing to priapism (sickle cell disease, myeloma, leukaemia) are all relative contraindications, although sildenafil is likely to present fewer problems in this respect.
- Sildenafil must never be used in patients receiving any form of treatment with nitrates, as it may result in profound hypotension.

**Step 4:** In the exceptional cases that fail to respond to the preceding steps, onward referral may be required for detailed investigation and consideration of:

- Penile implants.
- Vascular reconstruction.

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