

MANAGEMENT OF ERECTILE DYSFUNCTION

SUMMARY

- + **Erectile dysfunction is a common problem affecting 10% of the male population and may require pharmacological and/or non-pharmacological treatment.**
- + **Intracavernosal and intraurethral alprostadil are effective treatments but have poor patient acceptability.**
- + **Oral sildenafil, a phosphodiesterase inhibitor type 5, is well tolerated and approximately 50-70% more effective than placebo.**
- + **Sildenafil, is contra-indicated in patients on nitrate therapy. It should be used with caution in those with cardiovascular disease.**

INTRODUCTION

Erectile dysfunction (ED) may be defined as the consistent inability to attain or maintain penile erection for satisfactory sexual intercourse.^{1,2,3,4} It is recognised as a common problem, the prevalence of which increases with age. An overall prevalence of 10% has been reported.⁴ In Ireland this equates to 180,000 men.

AETIOLOGY

ED is a hidden condition with patients rarely volunteering information due to a variety of factors including embarrassment and a feeling that little can be done.^{1,2,4} It is associated with significant morbidity and can impair the patient's quality of life. Depression, increased anxiety and poor self-esteem may also be associated with this condition.⁴ Risk factors for ED are included in Table 1.

Table 1: Risk Factors For Erectile Dysfunction

Age
Diabetes Mellitus
Vascular disease e.g. hypertension
Hyperlipidaemia
Medication use e.g. beta-blockers
High alcohol intake
Depression
Smoking

The aetiology of ED may be categorised as follows:

- Organic
- Psychogenic
- Mixed causes

ED due to organic causes such as diabetes, drug therapy e.g. thiazides, antihypertensives, often has an insidious onset with progressive worsening until no erection is obtained. Initially, there is a loss of rigidity and/or difficulty sustaining an erection. Later, there is a complete inability to penetrate. Psychogenic ED is more likely to have an abrupt onset. Commonly there are good quality spontaneous/waking erections but early collapse of erection occurs. It is often related to a distinct precipitating event e.g. a psychologically traumatic episode of sexual failure.^{3,4}

DIAGNOSIS

Information on the history of the ED, in addition to a physical examination, may be valuable in the assessment of this condition. The onset and duration of the ED should be ascertained and information on concurrent diseases and medication should be elicited. Physical examination should focus on the genitalia, signs of vascular disease, and neurologic disease.^{5,6,7,8} Further investigations/specialist referral may be required in a minority of patients.

TREATMENT

The treatment options for ED must be patient guided in part. Interventions may be classified as non-pharmacological and pharmacological.

Non-Pharmacological

Non-pharmacological treatment options for ED consist of:

- **Psychosexual Counselling** The contribution of emotional factors should not be underestimated. May be useful for both organic and psychogenic ED even if a physical intervention is planned.²
- **Vacuum Devices** Composed of a plastic cylinder, a vacuum pump and elastic constriction band. Useful for ED due to a variety of aetiologies. May have low patient acceptability rate as they limit spontaneity. Have a low incidence of side effects.^{4,6,7}
- **Surgery** Venous surgery is now rarely performed and arterial surgery has a limited role. Insertion of a penile prostheses is usually only considered when all other options have failed.⁷

Pharmacological

The pharmacological modalities licensed in Ireland at present consist of intracavernosal or transurethral alprostadil and the oral agent sildenafil. Other treatment options that have been employed include oral phentolamine. It is anticipated that a proprietary preparation will be available in Europe in the near future.^{9,10} Sublingual administration of apomorphine for erectile dysfunction is currently in phase three trials in the USA.¹⁰

Alprostadil

Intracavernosal alprostadil (prostaglandin E₁) acts by relaxing cavernous and arteriolar smooth muscle while causing restriction of venous outflow.¹¹ Patient and/or partner motivation is required with 80% of men reported to achieve functional erections within ten minutes.⁷ The majority of patients will achieve a satisfactory response at a dose of 10-20 micrograms.^{12,13} The duration of erection is dose-dependent. Alprostadil should be injected no more than once a day and no more than three times a week.⁷ Doses should be titrated to achieve erectile rigidity sufficient for sexual intercourse with detumescence occurring within one hour after injection.^{2,7}

Systemic adverse reactions are rare. The most common adverse reaction reported is penile pain which has been reported in 75% of men using this treatment.⁶ Priapism, a problem with papaverine (no longer used), is less likely with alprostadil and may occur with an incidence of 1%.³ Patients should be instructed to seek medical attention if the duration of erection exceeds four hours.^{5,7,8} Intracavernosal administration should not be used in patients with conditions known to predispose them to priapism e.g. sickle cell anaemia, anatomical deformation of the penis.¹³ Concomitant use of smooth muscle relaxants such as alpha-blockers should be avoided due to the risk of prolongation of erection.¹²

Intracavernosal alprostadil in placebo-controlled studies produced higher response rates, with 87% of men rating sexual activity as satisfactory.¹⁴ While an effective therapy, a high dropout rate exists (40-50%) due to reasons including spontaneous recovery of erectile function, perceived unnaturalness of the injections or development of complications.^{4,15}

Alprostadil has also been administered as an intraurethral pellet in the management of ED. The MUSE (Medicated Urethral System for Erections) device has recently been licensed in Ireland. This non-injectable treatment delivers a tiny pellet of alprostadil into the urethra by means of a single dose applicator.¹⁶ In a study involving 1511 men with ED from various causes, 996 (65.9%) were found to have an erection sufficient for intercourse.¹⁷ The most common adverse effect reported was penile pain (32.7%).¹⁷ Transurethral administration of alprostadil does not appear to be as effective as intracavernosal administration but may potentially have greater patient acceptance.^{14,18}

Sildenafil

Sildenafil, an oral preparation for the management of ED was licensed in Ireland in September 1998. It is currently the only oral treatment for this indication. Sildenafil is a competitive inhibitor of phosphodiesterase type 5. Inhibition of this enzyme prevents the hydrolysis of cyclic guanosine monophosphate (cGMP) thus resulting in relaxation of the smooth muscle of the corpus cavernosum. Sildenafil is not an aphrodisiac, relaxation is mediated by the nitric oxide pathway leading to cGMP release, activated only during sexual stimulation.^{2,19,20,21} Sildenafil may be a useful therapy in patients who do not persist with the use of vacuum devices or intracavernosal injections.²²

Safety and tolerability data on sildenafil in over 4,000 patients are available from the manufacturer.²³ Sildenafil to date has generally been well tolerated with side effects of headache and flushing being the most commonly reported. An unusual and temporary effect of blue colouration of vision has been reported, most commonly at

higher doses. This adverse effect has been attributed to a degree of selectivity by sildenafil, for phosphodiesterase 6 which is involved in phototransduction. The long term effects on the retina are unknown.^{20,23,24,25} The Food and Drug Administration (FDA) in the USA has received reports from March 1998-mid November 1998 of 130 deaths in patients who were taking sildenafil. At present it is not possible to determine whether the cardiovascular events are directly related to sildenafil, to sexual activity, to the patient's underlying disease, or to a combination of these factors.²⁶

Sildenafil may potentiate the hypotensive effect of nitrates and its use is contraindicated in patients taking concurrent nitrate preparations.^{20,24} Sildenafil is metabolised via the cytochrome P450 enzyme system, predominantly involving the isozyme CYP3A4. Caution is required when CYP3A4 inhibitors e.g. cimetidine, erythromycin, ketoconazole are administered concomitantly as increases in sildenafil serum concentrations have been reported. In these patients a starting dose of 25mg is recommended.^{20,24}

Sildenafil has been shown to be approximately 50-70% more effective than placebo in several double blind, dose response and dose escalation studies.^{27,28} Two of these studies involved a total of 861 men with ED due to several causes (70% organic, 11% psychogenic, 18% mixed).²⁷ Few studies undertaken however have used objective methods e.g. penile plethysmography to assess the efficacy of sildenafil.²⁹

Cardiovascular Disorders

Experience in this patient population is limited. A long list of exclusion criteria has been applied to studies including poorly controlled diabetes, stroke or myocardial infarction within six months and history of alcohol or substance misuse.³⁰ Sildenafil should not be prescribed where sexual activity is inadvisable because of cardiovascular status including transient decreases in blood pressure. Caution should be exercised in patients with unstable angina, heart failure, hypertension (> 170/110mmHg), hypotension or a myocardial infarction, life threatening arrhythmia or stroke in the previous six months.^{26,31}

Prescribing Sildenafil

It is recommended that an initial dose of 50mg is taken one hour before sexual stimulation. The dose may be titrated to 25mg or 100mg depending on efficacy and tolerability. The maximum frequency of administration is once a day.²⁴ An initial dose of 25mg is recommended in elderly patients.²⁴

Sildenafil does offer advantages in the treatment of ED in terms of cost and ease of administration. There is no evidence that sildenafil will produce beneficial effects in men without ED. It has been suggested that prescribing initially in doses that provide for intercourse four times a month (i.e. similar to the average frequency reported in clinical trials) would be advisable.^{25,28,32} An initial prescription of four tablets per month could be reviewed according to patient experience and tolerability.

Table 2 : Treatment Costs of Preparations Licensed For Erectile Dysfunction (GMS May 1999)

Preparation	Price per dose
Caverject® - 10 microgram (Intracavernosal alprostadil)	£7.65
Viridal® - 10 microgram (Intracavernosal alprostadil)	£7.65
MUSE - 250 microgram (Intraurethral alprostadil)	£10.27
Viagra® - 50mg (Sildenafil)	£5.65 (from 1/7/99)

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