ERECTILE DYSFUNCTION (ED) is a common problem affecting the quality of life for many thousands of men, their wives and partners. Whilst not life threatening, erectile dysfunction may alter relationships and interactions between the patient and his partner, thus affecting the whole family. Men often hide their problems from their partner, which leads to suspicion and mistrust. Once the problem is out in the open, improved communication between the couple can restore confidence and sympathy, which can help greatly with treatment and management.

Erectile dysfunction can be diagnosed as a persistent inability for more than six months to achieve and maintain an erection sufficient to permit satisfactory sexual performance. Erectile dysfunction increases with age as confirmed by numerous studies. In 1995 it was estimated that in the US about 30 million men were affected by erectile dysfunction and it is predicted that this number will rise to 45 million by 2025. Numerous smaller studies have confirmed similar results in other countries.

Normal erectile response

Obtaining and maintaining an erection is a complex process that is partly voluntary and partly involuntary. Erections can be classified as central (the normal erection involved in sexual activity), reflexogenic (such as may occur after a spinal injury), and nocturnal. The mechanism of action of these latter erections is poorly understood. They occur during REM sleep and start in utero and continue throughout life. One theory is that nocturnal erections act as an exercise mechanism, oxygenating the cavernosal tissue and maintaining its viability.

Causes of erectile dysfunction

Erectile dysfunction occurs when one or more mechanisms involved in the physiology of erection are interrupted. Vascular abnormalities, eg. atherosclerosis of the penile vasculature arising from diabetes, hypercholesterolaemia, or hypertension is believed to be the primary cause of ED in about 40% of men over 50 years of age.

Most other cases result from neurological, endocrine or psychological disorders.

Erectile dysfunction is a common complication of diabetes. This is usually in patients with longstanding disease who develop complications such as diabetic retinopathy, diabetic nephropathy or neuropathy. ED may be caused by vascular or neurological problems or a combination. ED in diabetic men is often more severe and more difficult to treat than in a ‘healthy’ population.

Diabetes aside, other endocrine problems can cause or contribute to erectile dysfunction. Hypogonadism can lead to loss of sex drive and libido. Supplementation with androgens (testosterone) can improve libido but does not have a clear-cut effect on erectile function. It does however facilitate the responses to phosphodiesterase type 5 inhibitors (PDE5) and should be considered in those men who do not initially respond to PDE5 inhibitors before moving to second line therapies. ED is also a well recognised complication of thyroid problems and hyperprolactinaemia.

Neurological problems are relatively common causes for ED, but the patient usually presents with the condition and ED is mentioned afterwards. Spinal injuries frequently affect young men and sexual dysfunction and fertility problems are a major source of distress.

CVAs and other central nervous system diseases such as multiple sclerosis and Parkinson’s disease affect mainly older age groups and with the exception of MS are relatively rare before the fifth decade. Again, the ED presents as a complication of the disease rather than as a presenting symptom. Other rare causes include lumbar disc prolapse and injury to the cavernous nerves during radical prostatectomy.

Psychosexual issues often play a key role in erectile dysfunction. Indeed, mild or minimal ED can be made much worse by performance anxiety. Anxiety leads to a heightened stress level with stimulation of the adrenergic system and release of adrenaline and noradrenaline, which activates alpha 1-adrenergic receptors and encourages detumescence. If this happens on one or two occasions, the anxiety worsens, and an erection is less likely to occur, thus becoming a self-perpetuating problem with no way out. Other aspects that can cause problems are a history of sexual abuse, leading to guilt and depression. Worries about sexual orientation in a young man can also be very traumatic and affect sexual function.
Chronic illness and erectile dysfunction

Chronic medical illnesses can lead to ED by reducing health, sense of well-being and as a complication of medical therapy. These diseases/conditions include:

- Diabetes
- Ischaemic heart disease
- Renal impairment
- Liver disease
- Hypertension
- Hyperlipidaemia
- Other rare conditions such as Peyronie’s disease and priapism can result in ED due to local factors
- Pelvic trauma can result in interruption to the vascular supply and damage the cavernous nerves
- Iatrogenic injury due mainly to radical prostatectomy for prostate cancer may cause temporary or permanent ED
- Polypharmacy.

There is no doubt that a healthy lifestyle contributes to good sexual health and performance. Cigarette smoking contributes to multiple medical problems as well as leading to vasospasm, which further restricts penile arterial blood flow in patients at high risk for atherosclerosis. Obesity, lack of exercise and poor diet contribute to hypertension, type 2 diabetes and hypercholesterolaemia. Men presenting with ED represent a group at high risk for other medical problems and evaluation of lifestyle should be a routine part of their assessment.

Atherosclerosis is a systemic disorder uniformly affecting the vascular tree. Clinical manifestations depend on the degree of vascular obstruction and the size of the artery affected and its supply territory. A >50% lumen obstruction leads to a haemodynamically significant fall in blood flow resulting in symptoms. Penile arteries (2mm-3mm) will be affected before the coronary arteries (3mm-4mm), the carotids (5mm-7mm), and the major peripheral vessels (6mm-8mm). This would suggest that in theory ED should present before angina, which should present before TIAs or embolic CVA from the carotids, or intermittent claudication. In life this is often true. Men with ED often have asymptomatic coronary artery disease and the ED often predates the onset of ischaemic cardiac symptoms by a number of years, allowing a window of opportunity to encourage alteration of lifestyle and prevention of further progression of the underlying atherosclerosis.

There is no doubt that ED and coronary disease are part of the disease process. Patients presenting with ED should be evaluated for risk factors and asymptomatic coronary and carotid disease. Likewise, men presenting with cardiac symptoms should be asked about erectile and sexual function.

Diagnosis, investigation and management

Erectile dysfunction is such a common disorder that ideally symptoms should be routinely elicited in elderly patients and in those men with diabetes, hypertension, neurological disorders, prostate problems, obesity, smokers, alcohol abusers and in those with signs and symptoms of cardiovascular disease.

ED treatment summary

- Most patients with erectile dysfunction can be helped with PDE5 inhibitors
- Patients with ED should be screened for manifestations of cardiovascular disease and given appropriate lifestyle advice
- Sexual intercourse should be considered vigorous exercise and cardiac fitness considered before treatment
- Future work may concentrate on prevention of ED and the development of oral therapies with greater efficacy and fewer side effects

Diagnosis is relatively easy but many patients are embarrassed and reluctant to bring up the subject. Therefore, the doctor or physician must ask the patient. This needs to be done in a relaxed, open and unhurried fashion. It is necessary to get a detailed evaluation of the problem.

Having ascertained the extent and bother the problem is causing, it is important to complete a full history, including past medical events, co-morbidities, list of medications, a social history especially concentrating on relationships with his partner and his perceptions about how she feels about the problem (this may actually be very different from how he thinks she feels).

It is essential to perform a focused physical examination. This should concentrate on the endocrine, neurological, vascular and genitourinary system. Evidence of hypothyroidism, peripheral neuropathy, diminished pedal pulses or hypertension may all be relevant. A large prostate with urinary symptoms may also be significant.

Often the diagnosis is clear-cut, physical examination normal and treatment with oral therapy appropriate. In such cases further investigation would appear unnecessary. However, because of ED’s links with atherosclerosis and diabetes, all patients should at least have a fasting glucose and lipid profile. A hormone profile is appropriate in those patients complaining of diminished libido or exhibiting signs of hypogonadism; for example, atrophic testes. In such cases it is appropriate to measure serum testosterone, sex hormone binding globulin (SHBG), free androgen index, FSH and prolactin. Thyroid function tests may also be appropriate.

There are a number of other investigations that may be appropriate in complicated cases of ED such as those failing to respond to phosphodiesterase inhibitors. A trial of 10 mg intracavernosal alprostadil may be helpful to determine if the erectile mechanism is intact in men who are complaining of complete ED.

A normal erection achieved in this way excludes venous leakage as a cause and shows that the erectile mechanism is intact. A duplex scan of the penile arteries can determine the increase in arterial flow and velocity confirming an adequate arterial supply. Arteriography and cavernosography can be helpful in venous leakage cases and in trauma cases to determine if the penile arteries are intact. Rarely, pudendal nerve latency studies can be used to determine if there
is a neurological problem. Lastly, nocturnal penile tumescence and rigidity studies can be helpful in patients with psychogenic ED. Normal nocturnal erections and rigidity strongly suggest a psychogenic problem, as the erectile mechanism is intact.

Prior to the development of PDE5 inhibitors, the mainstay of therapy was intracavernosal therapy initially using papaverine with or without phentolamine. The prostaglandin inhibitor alprostadil was then licensed (1996) for use intracavernously and was successfully launched. With the onset of oral phosphodiesterase inhibitors, intracavernosal therapy has been relegated to second line therapy.

**Sildenafil**

In 1998 sildenafil (Viagra) was licensed for use in the UK and brought about an explosion in interest in ED. Sildenafil is effective after 30-60 minutes with sexual stimulation and its efficacy is reduced by a fatty meal. Its half-life is four hours. Doses start at 50mg and can be increased to 100mg. The 25mg dose is rarely used. Whilst it is recommended to start with the 50mg dose, I frequently start with the 100mg dose especially in the younger patient with psychosexual problems. This frequently encourages a very good erection and gives the patient great confidence from the beginning. Problems. This frequently encourages a very good erection and brings about an explosion in interest in ED. Sildenafil has been relegated to second line therapy.

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**Tadalafil**

The third PDE5 inhibitor on the market is tadalafil (Cialis). This has a number of distinct differences from the previous two agents. Like them, it too is effective after about 30 minutes however, its absorption is not affected by fatty food or a meal. Its half-life is 17.5 hours, giving it a window of efficacy of about 36 hours. It is for this reason the French refer to it as ‘le weekend’ pill. A tablet taken on Friday night can often contribute to successful intercourse on Sunday morning. It comes in 10mg and 20mg tablets with the lower dose being the recommended starting dose.

A number of comparative studies have suggested that tadalafil is as effective as the other agents but its long half-life improves the spontaneity of lovemaking, in that there is no pressure to have intercourse just because ‘I have taken the tablet and don’t want to waste it’. This is particularly helpful in men with performance anxiety where it is important for the patient to be calm and relaxed and not stressed. One side effect of tadalafil is back pain, believed to be due to pelvic blood pooling. This occurs in about 9% of patients and is self-limiting after the tablet wears off. There is also an increased incidence of dyspepsia compared with other PDE5 inhibitors.

Lastly, men taking tadalafil often report the return of spontaneous nocturnal erections due to its long half-life. This is often very reassuring for men and gives them confidence. Perhaps more important, however, is that it ‘exercises’ the penis thus facilitating erectile activity. It may be speculative now but regular dosing with tadalafil may help preserve erectile activity in men at high risk of developing erectile dysfunction, such as diabetics. Unfortunately there is, as yet, no studies confirming this theory.

**Vardenafil**

More recently, two newer PDE5 inhibitors have arrived on the market. Vardenafil (Levitra) is more specific than sildenafil for PDE5 and avoids the co-inhibition of PDE6 seen with that agent. It is effective after 30 minutes with sexual stimulation but like sildenafil, absorption is affected by a fatty meal. It is 10-fold more potent than sildenafil, hence the doses are lower. The starting dose is 10 mg but it also comes in 5mg and 20mg tablets. Its half-life is four hours. It is specifically contraindicated in patients with long QT syndromes and on alpha-blockers, as well as the other agents contraindicated in sildenafil.

The reason for this is that alpha-blockade can cause postural hypotension. This may be aggravated by a PDE5 inhibitor resulting in significant hypotension. It should be noted that tamsulosin and perhaps alfuzosin do not significantly drop blood pressure compared with indoramin, terazosin, and doxazosin and it may be reasonable to allow vardenafil if the former two drugs are prescribed. There is no doubt that men with ED are often the same men suffering from LUTS from BPH and it seems harsh to deny them the chance of restoring potency. Indeed, recent work has correlated the severity of LUTS with increasing erectile problems. Improvement in prostatic symptoms also improves sexual function. A recent study (the PROVEN study) has demonstrated that it is reasonable to try another PDE5 inhibitor before confirming the patient is a true non-responder and moving to second line therapy.
**Sublingual apomorphine**

Sublingual apomorphine (Uprima) is the fourth oral agent on the market for erectile dysfunction. Apomorphine is a dopamine agonist that acts centrally by enhancing pro-erectile activity through hypothalamic neural pathways. It is administered sub-lingually to avoid first pass metabolism. It has a rapid onset of activity of <20 minutes. It does not appear to be as effective as the PDE5 inhibitors but results confirm a response rate of 47% vs 32% for placebo for the 3mg dose.

Its main side effect is nausea in about 7% of patients. It also has typical vasodilatory side effects and transient vaso-vagal reactions have been reported. While combination therapy would appear to be attractive in PDE5 failures, this is not recommended.

Its main benefit is that it has no interaction with medications, food or alcohol. Unlike PDE5 inhibitors, it can be used in patients taking nitrates, although it should not be prescribed to men who lack sufficient cardiac reserve, for whom intercourse would be dangerous. Although it comes in a 2mg and 3mg tablet, the latter would appear to be more effective. It should not be repeated for eight hours.

**Alternative non-invasive therapies**

A vacuum device - may be very helpful in helping a man achieve and maintain a rigid erection.

A cylinder - placed over the penis and a seal created at the bottom. A pump then draws air out of the cylinder causing a partial vacuum and encouraging blood flow into the penis. When the penis is erect, a constriction band is applied to the base of the penis to maintain the erection.

**Androgens and erectile dysfunction**

Androgen deficiency has long been associated with erectile dysfunction. It leads to loss of libido and sexual motivation. Androgen deficiency and ED frequently co-exist in the aging male but may not be causally related. The MMAS study noted no relationship between testosterone and ED however ED was noted to be related to low dehydroepiandrosterone (DHEA) levels.

It is important that middle-aged men are screened for prostate cancer prior to starting androgen supplements. The absolute risk would appear to be low, particularly if levels of testosterone are raised to the normal eugonadal level rather than supraphysiological levels.

It would be difficult to defend prescribing testosterone supplements for a 60 year old man without first making sure his PSA was within the normal age-related range. If in doubt refer to a urologist.

**Psychosexual problems**

Many men have genuine physical reasons for developing erectile dysfunction. However, psychosexual problems are also common. These may vary from mild inhibition due to performance anxiety to complete erectile failure. First line treatment with PDE5 inhibitors restores potency to many by restoring confidence and spontaneous erectile activity resumes. Some men however, have deeper-rooted psycho-logical problems, perhaps stemming from feelings of inadequacy, poor self-confidence, and depression. A history of sexual abuse may be elicited or there may be issues of sexual orientation. Counselling may be of great benefit to the general as well as the sexual well-being of the patient.

**Failed oral therapy**

Many men do not respond initially to PDE5 inhibitors prescribed for them. It is important to identify the true and false non-responders in this group. It is estimated that up to 40% of non-responders can be converted to responders by further review in the clinic and reinforcing a patient’s knowledge about the correct way to use the drug. Issues that arise include the timing of the attempted intercourse, not taking the right (or maximal) dose, inadequate sexual stimulation – ‘waiting for things to happen’, less than four attempts, and food and drug interactions. Addressing these issues can result in successful therapy in many patients. Psychosexual counselling should also be considered at this stage in some men and their partners.

Once these parameters have been addressed, a patient should be given a further trial of the same or another PDE5 inhibitor for four more attempts. If he fails at this stage then he should be considered for second line therapies.

**Second-line therapy**

Alprostadil is prostaglandin E1. It can be used intracavernously (Caverject or Viridal Duo) or intraurethrally as a pellet (MUSE). PGE1 causes smooth muscle relaxation, and vasodilatation mediated through an increase in CAMP. When injected directly into the penile vasculature it causes an erection. It can be used as a diagnostic test to ensure that the erectile mechanism is intact. MUSE (Medicated Urethral System for Erection) is a semi-solid pellet of PGE1 with a claimed 70% success rate. It may cause urethral burning and hypotension. It is less successful than the intracavernous approach but has the advantage of not needing an injection, which not surprisingly, many patients are keen to avoid.

**Third-line therapy**

For those patients in which a pharmacological approach fails, a penile prosthesis offers the possibility of achieving sexual fulfilment. These patients are frequently younger and other therapies fail due to poor arterial supply, as in diabetics or following pelvic trauma, due to a major venous leak or a failed revascularisation procedure. Prostheses may be semi-rigid and malleable or inflatable. The former are relatively simple prostheses and the penis can be placed in an erect position by straightening the device manually or placed point down. The inflatable devices are more expensive, and have more working parts that can malfunction.

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The 4th World Congress on Men’s Health and Gender, held under the auspices of WONCA, will take place in Vienna from Sept 30-Oct 1. Topics include: men’s health around Europe, sexual disorders, health and lifestyle and erectile dysfunction. Details are available at www.wcmh.info