Erectile dysfunction

Erectile dysfunction is a common but readily treated condition in the older man. Extensive investigation is usually unnecessary and treatment options straightforward and clearly defined. Management increasingly takes place in a non specialist or primary care setting and this is often a more satisfactory arrangement for the patient.

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Erectile dysfunction (ED) is defined as the persistent inability to achieve and maintain an erection adequate for penetrative intercourse. Disorders of ejaculation and orgasm are comparatively uncommon and should be referred directly to a specialist. Male sexual function has long been known to decline with age. Seminal studies by Kinsey in the 1940s showed that the frequency of coitus steadily decreased with age and that ED rates increased concomitantly over the age of 55 years.[1] The prevalence of ED symptoms was estimated in a recent American study at 10% in a population of 30–39 year old men and 59% in the age group of 70–79[2] whilst a four-centre European/Asian study[3] found self reported ED symptoms in 21% of a population aged 40–79 years with a linear increase with age. Complete ED rates were reported in a Welsh population aged 55–70 at 13·2%.[4] A decrease in libido parallels the age related increase in ED.

Diagnosis

Despite recent publicity regarding ED, many older men remain reluctant or embarrassed to seek medical attention with regard to erectile difficulties. Indeed ED is commonly brought up only as a secondary problem at consultation. The term "impotence" which is commonly used by patients has lay meanings ranging from varying degrees of ED, loss of libido, premature ejaculation, problems with orgasm or even dyspareunia, and it is important to establish early in the consultation the exact nature of the problem that the patient is having.

The aetiological causes of ED can be classified into vasculogenic, neurogenic, endocrine, drug related, iatrogenic and psychogenic categories. A further breakdown of disease associations may be found in Box 1.

When focusing on ED, important key points in the sexual history to consider include the duration of problems experienced and the rapidity of onset. A gradual onset points to an organic cause whereas sudden onset may suggest a psychosexual cause. The nature of the problem in terms of its psycho-social context (ie. when it happens and in what circumstances together with its severity and impact on the patient) are also key points to take in a patient's sexual history. The quality of the erection and any deformity (the latter suggesting Peyronie's disease) should be noted. It is often useful to enquire about the patient's relationship with his partner, focusing on the state of the relationship, stresses and the health of the partner. Finally patient expectations with regard to treatment should be established and previous treatments noted.

A general medical history should be taken with particular attention paid to cardiovascular risk factors, such as ischaemic heart disease, hypertension, diabetes and hyperlipidaemia. A full drug history is important taking note of recent changes to medication. The list of medication that is associated with ED is extensive. In the elderly, the most commonly encountered include antihypertensives, digoxin, anticonvulsants, psychotropic and anxiolytic drugs, and antidepressants. A breakdown of these is listed in Box 2. Pelvic surgery, particularly radical or transurethral prostatectomy, and colorectal resection may result in damage to the pelvic nerves resulting in ED. Irradiation to the pelvis is similarly associated with nerve damage and ED, although this may only be apparent several years after the radiation dose. On the other hand, surgery and trauma induced ED usually have an early presentation. Aorto-iliac vascular surgery may result in penile ischaemia and subsequent impotence secondary to damage to the vascular smooth muscle. Neurological conditions, including Alzheimer's disease, Parkinson's

Box 1: Aetiology of ED

Category	Specific conditions
Vasculogenic	Ischaemic heart disease Peripheral vascular disease Small vessel vasculitis
Neurogenic	CVA Parkinson's disease Alzheimer's disease MS
Endocrine	Diabetes mellitus Hypogonadism Hyperprolactinaemia
Drug related	See table 3
Iatrogenic	Pelvic surgery: radical prostatectomy, cystectomy, TURP
Psychogenic	

Box 2: Drugs associated with ED

Antihypertensives	Beta adrenergic blockers Diuretics (almost all are associated with ED except ACE inhibitors)
Psychotropic drugs	Antidepressants (SSRI, tricyclics, MAOI) Tranquillisers Anxiolytics and hypnotics
Antiepileptic drugs	Phenytoin Carbamazepine
Endocrine drugs	Steroidal antiandrogens (cyproterone) LHRH agonists Oestrogens
Anticholinergics	
Drugs for bladder outflow obstruction	Alpha adrenergic blockers 5 alpha reductase inhibitors
Alcohol	
Other	Digoxin Cimetidine Metoclopramide

disease and cerebrovascular accident (CVA), are a significant aetiological consideration in the older male.

The use of validated questionnaires provide a rapid self assessment of ED and are a useful diagnostic tool. The International Index of Erectile Function (IIEF)–15 and its abbreviated five question form are the most utilised and provide information on erectile function over the past one and six months respectively.[5] Other commonly used questionnaires include EDITS (Erectile Dysfunction Inventory For Treatment Satisfaction) and BMFSI (Brief Male Sexual Function Inventory).

A full examination is not required. However, an examination of the genital region looking for abnormalities of the prepuce, penis or testes is recommended. Although rare in the older male, it is always worth noting the presence of male secondary sexual characteristics. Digital rectal examination to look for prostate abnormalities, particularly cancer, should be carried out in men over the age of 50 years especially if testosterone therapy is being considered. A neurological examination may be carried out if a neurogenic aetiology is suspected.

Numerous guidelines and consensus statements on ED have been published. Both the European Association of Urology and American Urological Association have freely accessible contemporary and detailed guidelines on the investigation and management of ED.[6,7] Blood pressure measurement is mandatory. Serum total testosterone should be measured as should serum lipids and a fasting blood glucose. The reason for this is the strong association between cardiovascular disease and ED. Indeed one study showed a 49% prevalence of ED in men with angiogram confirmed coronary vessel disease who had presented with acute chest pain.[8] Serum testosterone is subject to diurnal variation and should be measured in the morning when it is maximal. Serum HbA1c is measured in known diabetics. Further endocrinological investigations in the form of free serum testosterone, gonadotrophins and prolactin are only required where there is an abnormality in total serum testosterone levels or a clinical suspicion of hypogonadism or hyperprolactinaemia. The latter should be suspected in the presence of gynaecomastia or galactorrhoea. A prolactinoma of the anterior

Box 3: Evaluation of the patient with ED

History	Examination	Investigation
Sexual history	Secondary sexual characteristics	Blood pressure
General medical history esp. cardiovascular, neurological, endocrine	Genitalia	Serum lipids, fasting blood glucose
Drug history	Gynaecomastia	Total serum testosterone
Validated questionnaires	(prostate DRE)	(bioavailable testosterone, prolactin, FSH,LH)

pituitary is the most important aetiology of raised serum prolactin and is classically associated with headache and a bitemporal hemianopia. The evaluation of the patient with ED is summarised in table 3.

Management

The use of phosphodiesterase 5 (PDE5) inhibitors has revolutionised the management of ED. There are three commercially available PDE5 inhibitors: sildenafil, which was the first to market, vardenafil, and tadalafil. Goldstein et al[9] published the seminal paper on the use of sildenafil in 1998. This was a randomised, placebo controlled 24 week study involving 532 patients with mixed cause ED. A second dose escalation study over 12 weeks of 329 men with an additional 32 week extension period was also carried out. Outcome measures included IIEF scores particularly focusing on the ability to penetrate and maintenance of erection after penetration. By the end of the study, 69% of attempts at intercourse in patients taking sildenafil were successful versus 22% for placebo. Patients taking sildenafil reported significant improvements in IIEF overall erectile function scores, intercourse and overall satisfaction scores though not sexual desire versus placebo. Dose escalation studies showed a small but significant dose escalation response (85% erections hard enough for intercourse on 100mg versus 80% for 50mg and 72% for 25mg). Similar phase 3 studies have demonstrated the efficacy of vardenafil[10] and tadalafil[11] over placebo for mixed cause ED with successful intercourse rates of 67 and 70% respectively. It is worth noting that ED in patients with diabetes have a lower rate of treatment success compared with the general population.

Radical prostatectomy is associated with ED rates of 25-60%.[12,13] There has been much interest in daily dosing of PDE5 inhibitors as part of a penile rehabilitation programme. Animal studies support this and there are sound physiological bases for this. However, no large scale randomised studies in humans have confirmed a benefit and so daily dosing post radical prostatectomy cannot be considered standard practice at this stage.[14] However PDE5 inhibitors are efficacious for ED on an as required basis post radical prostatectomy, albeit at a lower response rate than the general population.[15,16]

The absorption of the PDE5 inhibitors sildenafil and vardenafil are delayed by the intake of fatty food prior to administration and so should be avoided. Tadalafil is not affected in this way. Alcohol does not appear to affect the pharmacokinetics of PDE5 inhibitors. There is very little head to head data between PDE5 inhibitors and no meaningful large scale randomised controlled trials. Small scale studies have yielded inconsistent results and prescribing seems largely down to physician and individual preference.[17,18,19] A randomised crossover study[20] seemed to indicate a patient preference for tadalafil over sildenafil, although this was open label and the methodology has been questioned, particularly as response rates were reported to be similar for both drugs. Certainly studies have all shown the benefit of dose escalation for all three drugs.[9,10,11] The trial of different PDE5 inhibitors is commonly practiced although no evidence supports this.

All PDE5 inhibitors work by inhibiting the breakdown of cyclic GMP to GMP. Cyclic GMP via its action on protein kinase G causes the closure of membrane L-type calcium channels and opening of potassium channels in corpus cavernosal smooth

muscle. The net effect is the relaxation of vascular smooth muscle and the engorgement of the cavernosal sinusoidal spaces resulting in erection. However, the pharmacokinetics of the three PDE5 inhibitors are different. Sidenafil and vardenafil have similar structures and both have a half-life of between three and five hours and an onset of action typically between 15 minutes to one hour. Tadalafil has a different structure and has a far longer half life of 17·5 hours although the time taken to reach peak plasma concentrations is around two hours compared with 0·8 hours for the other PDE5 inhibitors and this is reflected in both its longer duration of activity and its slower onset of activity.

The side effects of PDE5 sildenafil are headache (16%), flushing (10%), dyspepsia (7%), rhinitis (4%) and transient abnormalities of vision,[9] particularly the perception of a "blue tinge" due to cross activity on PDE6. The other PDE5 inhibitors have a similar side effect profile[10] although tadalafil is associated with backache in up to 6% of patients and myalgia in up to 4%.[11]

The safety of PDE5 inhibitors particularly in patients with myocardial disease has been widely discussed in the medical and lay press. Sexual activity in itself is associated with significant rises in heart rate, systolic blood pressure and a rise in mean oxygen consumption from around 4ml/kg/min to 11·7ml/kg/min.[1] A study has demonstrated that there is a 2·1 times increased risk of myocardial infarction (MI) in men if sexual activity has taken place in the preceding one hour[21] although the absolute risk of MI remains tiny. Although sudden deaths from MI post administration of PDE5 inhibitors have been reported, analysis of mortality in large multiple trials have not shown any excess deaths in subjects taking PDE5 inhibitors versus placebo.[22,23] The only absolute contraindication for PDE5 administration in patients with ischaemic heart disease remains the concomitant use of sublingual or oral nitrates as animal studies have shown that significant hypotension and potential myocardial ischaemia can result. Nitrates are not to be taken for 24 hours post PDE5 dosing if chest pain develops. It is worth noting that vardenafil has a caution issued if used with Type 1a (procainamide) and 3a (sotalol, amiodarone) antiarrhythmics due to potential prolongation of QT interval. PDE5 inhibitors should not be taken in patients who have had an MI in the past 90 days, CVA in the preceding six months or who have angina precipitated by sexual activity.[24]

Another concern of PDE5 inhibitors relates to the reporting of the rare but devastating complication of nonarteritic anterior ischaemic optic neuropathy (NAION). Some 43 cases have been reported worldwide to 2005 with 38 of these in patients taking sildenafil.[25] Given the estimated 30 million users of the medication, the odds remain tiny and several reviews have failed to establish any causal or epidemiological association between NAION and the use of PDE5 inhibitors. It should be emphasised that vascular risk factors, which are associated with NAION are prevalent in the ED population. However, any history of visual loss in patients taking PDE5 inhibitors should prompt immediate discontinuation of the drug and referral to an ophthalmologist.

Dosing should be halved in patients with significant renal impairment CKD3 or above. The concomitant administration of drugs such as ketoconazole, erythromycin or the presence of significant hepatic impairment inhibit the CYP3A4 system and should result in PDE5 dose reduction.[24]

The rules for the NHS prescribing of PDE5 inhibitors allow for a doctor to prescribe in the following patients who:[24]

- Have diabetes, multiple sclerosis, Parkinson's disease, poliomyelitis, prostate cancer, severe pelvic injury, single gene neurological disease, spina bifida, or spinal cord injury
- Are receiving dialysis for renal failure
- Have had radical pelvic surgery, prostatectomy (including transurethral resection of the prostate), or kidney transplant
- Were receiving Caverject®, Erecnos®, MUSE®, Viagra®, or Viridal® for erectile dysfunction, at the expense of the NHS, on 14 September 1998
- Are suffering severe distress as a result of impotence (prescribed in specialist centres only).

Apart from the indication "severe distress", prescription can be made by any medical practitioner as long as "SLS" is clearly indicated on the prescription and that the dosing is given no more than once per week.

Other ED treatments have been somewhat overshadowed by the advent of PDE5 inhibitors, particularly injectable therapies. The latter are particularly useful in cases refractory to oral therapy or where oral treatment is contraindicated. Prostaglandin E1 (Alprostadil), a potent stimulator of adenylate cyclase is the most commonly used agent and is generally used on its own or sometimes in combination

with papaverine (a non specific phosphodiesterase inhibitor). Injection is into the corpus cavernosa laterally and is usually taught at a specialist clinic where the partner is encouraged to attend. Efficacy rates in terms of erection sufficient for intercourse are approximately 75% for PGE1 monotherapy rising to 80% for triple agent injection.[26] A combination of vasoactive intestinal peptide and phentolamine has been associated with a success rate of 80%.[26] Up to 69% of patients who have failed oral therapy will respond to intracavernosal injection.[26] Erections last for between 15 minutes and three hours. Side effects include penile pain in 15% of patients, bruising and priapism in 1% (up to 7·7% for PGE1/papaverine/phentolamine combination therapy). Intracavernocal fibrosis is a long term complication of all the above agents with a reported incidence of 4% for PGE1.[27] The intra-urethral route in the form of a PGE1 pellet (MUSE) can be utilised albeit with lower response rates of around 60%.[26] Penile pain and hypotension are the most commonly reported adverse events.

Mechanical devices to sustain erection consist of a vacuum device with a constriction ring used at the base of the penis in order to sustain an erection. These are reliable and safe in achieving an erection and efficacy is reported to be as high as 75–100%. However, there are drawbacks associated with these devices. In particular the penis proximal to the constriction ring remains flaccid so the penis does not adopt the acute angle of a normal erection. The penis appears cyanosed and normal antegrade ejaculation may fail.

Psychosexual therapy for the treatment of ED is out of the scope of this review, but has its role particularly where there is an inorganic component to the patient's disease.

Androgen replacement therapy

The main indication for testosterone supplementation is low libido in a hypogonadal man. The replacement of testosterone for ED remains controversial.[28] The incidence of hypogonadism in patients with ED varies with the cut off figure applied. Buvat et al[29] reported a figure of 15% in the over 50 age group and 4% in the under 50 group when a cut off figure of 3nmol/l (approx 85ng/dl) was used, whilst Kohler[30] found a prevalence of 7% when a cutoff figure of <200ng/dl was applied rising to 23% for a cutoff of 300ng/dl and 47% for <400ng/dl total serum testosterone. Normal testosterone levels fall with age and there is little agreement about what constitutes a normal value. This is compounded by the marked circadian rhythm in testosterone secretion (more marked in younger men) and so a second morning testosterone level should always be checked if the first sample shows low testosterone levels. There are significant variations in laboratory assay techniques and reference ranges. The majority of serum testosterone is bound and bioavailable testosterone may not reflect total plasma levels.

Recently some small scale studies have shown improvement of erectile function in hypogonadal men with testosterone monotherapy, allbeit with response rates of around 50%, which may not be sustained long term.[31,32] Supplementation of testosterone with PDE5 inhibitors in hypogonadal men who have failed PDE5 treatment monotherapy has been shown in a small placebo controlled study of 82 men to improve erectile function although no correlation was found between IIEF score and androgen levels.[33] A separate contemporary study confirmed the above finding but found that testosterone monotherapy in hypogonadic patients was ineffective for the treatment of ED.[34] In summary, testosterone supplementation has not been shown by large randomised controlled trial to be an effective treatment for ED and should therefore only be prescribed in limited circumstances by a urologist or endocrinologist.

Testosterone supplementation in old age has received some publicity recently as epidemiological studies point to an association between low testosterone levels and the so called "metabolic syndrome" and its links with cardiovascular risks. There is no evidence to suggest that restoring testosterone levels results in any reduction in cardiovascular events yet modest reductions in risk factors particularly LDL (low density lipoproteins) have been reported.[35] The risk of promoting prostate cancer with testosterone treatment is unproven although theoretically correct. In six of 22 reported trials, testosterone treatment did raise PSA velocity by a mean of 0·52ng/ml/year, but no data exists to show either a rise in new prostate cancers detected or a more rapid progression of existing tumours.[36] The diagnosis of hypogonadism, however, should prompt further endocrinological investigation and the checking of bioavailable testosterone, prolactin and gonadotrophin levels.

Conclusion

ED is a common complaint in the ageing male and may be due to a variety of organic and inorganic causes. Vasculogenic, neurogenic, endocrine and drug related causes are the most important in this age group. Evaluation of this patient involves taking a medical, sexual and drug history with the use of self reported validated questionnaires being a helpful tool.

Investigations in the older ED patient centre largely around the identification of associated cardiovascular risk factors, diabetes and serum total testosterone levels.

Current treatment is based largely around PDE5 inhibitors, which have a proven safety and efficacy record for all causes of ED. The use of these drugs is contraindicated in patients taking nitrate therapy and in those with recent MI, cerebrovascular accident or unstable angina. Injectable therapy continues to have its role particularly in difficult to treat cases and in those who are unable to take oral therapy. Androgen replacement therapy for ED is unproven and has a limited role in specialist practice. The prescribing of drugs for ED is limited by the NHS with clearly defined criteria.

In summary, ED is a common but readily treated condition in the older man. Extensive investigation is usually unnecessary and treatment options straightforward and clearly defined. Management increasingly takes place in non specialist or primary care and this is often a more satisfactory arrangement for the patient. Referral to a specialist centre is indicated where initial treatment has failed, endocrine abnormalities discovered, or in patients where anatomical abnormalities of the genitalia or prostate are found at initial investigation. The association between ED, hypogonadism and cardiovascular risk factors should be taken into consideration and baseline checking of blood pressure, serum lipids, glucose and testosterone is considered mandatory.

We have no conflict of interest

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