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SPECIAL REPORT

Investigating the underlying cause of erectile dysfunction

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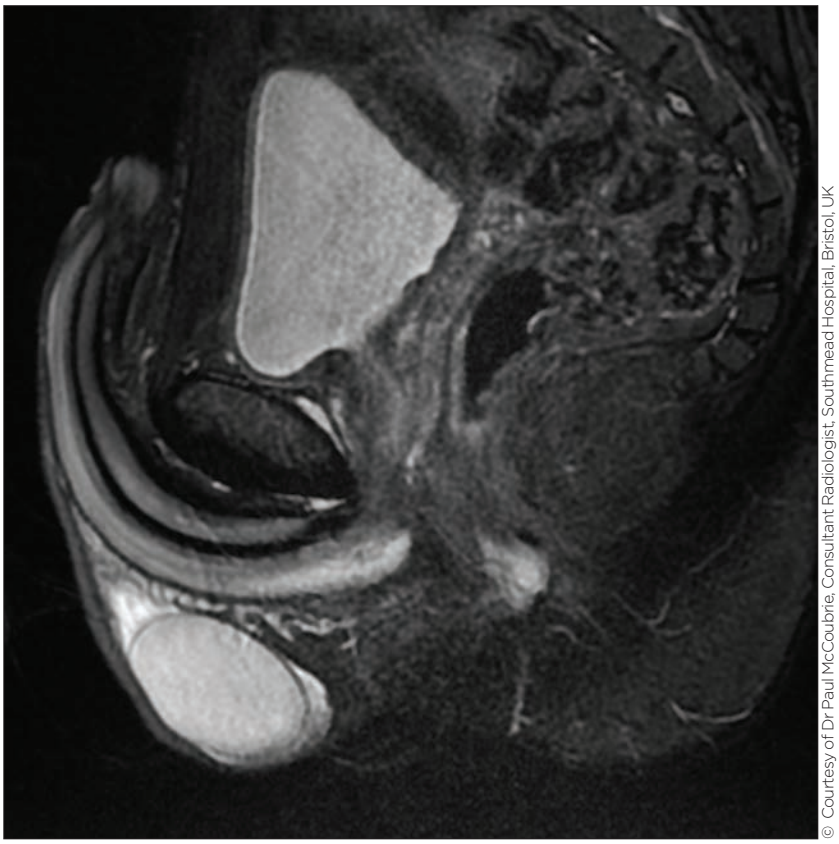

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FIGURE
MRI penis

How should patients be assessed?

What are the management approaches?

Which patients should be referred?

ERECTILE DYSFUNCTION (ED) IS THE PERSISTENT INABILITY TO ACHIEVE AND MAINTAIN AN ERECTION sufficient to permit satisfactory sexual performance. The term 'impotence' may also be used to describe ED.

ED has several possible organic and/or psychogenic causes. Common associations with ED are detailed in table 1, p24.[1] Rates of ED increase with age, with an estimated 70% of men aged 70 affected to some extent.[2]

Men may attend primary care with ED as a main presenting complaint or mention it during a consultation for unrelated concerns. Although increased awareness has destigmatised talking about ED, men can still feel embarrassed about discussing this complaint. A sensitive and nonjudgmental approach is essential to draw out important factors during history taking.

ED has been shown to be a significant predictor of underlying cardiovascular disease (CVD) which requires further investigation and as such ED should not be regarded as a condition which just impacts on quality of life.[3] All men should routinely be asked about ED during any assessment of cardiovascular risk. Men with established diagnoses of CVD, diabetes or lower urinary tract symptoms (LUTS) should be specifically questioned about ED.[4]

ASSESSMENT

A thorough history is essential to identify the most likely underlying ED aetiology and inform further investigations and management strategy. In addition to the onset and duration of symptoms important points in the history to clarify are:

- How does the patient define their ED? First clarify that the patient is actually complaining of an erection problem (sometimes men may use the term incorrectly) and ask the patient to quantify the loss of rigidity. Is there any ejaculatory or orgasmic dysfunction?
- Has the patient ever had erectile function?
- Are morning erections preserved or lost?
- Is the ED related to all sexual encounters or only in specific circumstances?
- Does the man have a partner and has there been any recent change in partner or behaviour?

Men should be asked about symptoms of hypogonadism such as loss of libido or low energy levels in addition to questions regarding their lifestyle. A brief assessment of exercise routines and capacity as well as a medication history may give an insight into the man's cardiovascular risk status.

However, we would recommend that all men presenting with ED should have their cardiovascular risk status formally evaluated using the QRISK prediction tool. ED has been shown to be an independent risk factor for CVD, »

Table 1

Potential causes of erectile dysfunction and associated underlying diseases of erectile dysfunction[6]

Vascular	Coronary artery disease Peripheral arterial disease Hypertension Hyperlipidaemia
Neurological	Post pelvic surgery or radiotherapy Peripheral neuropathy Parkinson's disease Multiple sclerosis Alzheimer's disease Spinal cord injury Autonomic neuropathy
Endocrine	Diabetes mellitus Metabolic syndrome Low testosterone (primary or secondary hypogonadism) Hypothyroidism/hyperthyroidism Cushing's syndrome
Drug induced	Antihypertensives Antidepressants Antipsychotics Antiandrogens Recreational drug use Anabolic steroids Alcohol
Psychosexual	Generalised Situational
Anatomical abnormalities	Peyronie's disease Post priapism Foreskin abnormalities

Table 2

Cardiac risk stratification, adapted from the European Association of Urology guidelines[6]

Low risk	Intermediate risk	High risk
Asymptomatic, < 3 risk factors for CAD (excluding sex)	≥ 3 risk factors for CAD (excluding sex)	High-risk arrhythmias
Mild, stable angina (evaluated and/or being treated)	Moderate, stable angina	Unstable or refractory angina
Uncomplicated previous MI	Recent MI (> 2, < 6 weeks)	Recent MI (< 2 weeks)
LVD/CHF (NYHA class I or II)	LVD/CHF (NYHA class III)	LVD/CHF (NYHA class IV)
Following successful coronary revascularisation	Non-cardiac sequelae of atherosclerotic disease (e.g. stroke, peripheral vascular disease)	Hypertrophic obstructive and other cardiomyopathies
Controlled hypertension		Uncontrolled hypertension
Mild valvular disease		Moderate to severe valvular disease

Key: CAD = coronary artery disease; CHF = congestive heart failure; LVD = left ventricular dysfunction; MI = myocardial infarction; NYHA = New York Heart Association

associated with a 25% increased risk of CVD. Consequently, ED has been included as a clinical variable in the most recent version of QRISK (QRISK 3), a validated algorithm to identify those at risk of heart disease and stroke.[5]

Other validated questionnaires such as the International Index of Erectile Function (IIEF) or Shorter Sexual Health Inventory for Men (SHIM) may facilitate history taking and establish a baseline against which responses to treatment can be assessed.[4,7]

It is important to look for signs of hypogonadism such as gynaecomastia or loss of body hair and examine the external genitalia for any penile or testicular deformity. Examining lower limb pulses may also highlight evidence of peripheral vascular disease.

Population-based studies have previously demonstrated an association between LUTS and sexual dysfunction.[8] If LUTS are elicited during the patient's history a digital rectal examination (DRE) should be performed as part of the man's assessment. Current NICE guidance also recommends performing a DRE in men with a history of prostate cancer and in men over 50 years of age.[6,9]

BMI, heart rate and blood pressure should be recorded for all patients, and if indicated by the history a cardiovascular or neurological examination may be performed.

Although the clinical history forms the bedrock of assessment in men with ED, further investigations in the form of blood tests may be appropriate. The European Association of Urology (EAU) guidelines recommend that initial blood tests include an HbA_{1c} or fasting glucose and lipid profile (if not recorded in the past 12 months). Early morning total testosterone levels should be measured in all patients.[6]

The Endocrine Society recommends that optimally clinicians investigating hypogonadism should measure fasting total testosterone concentrations on two separate mornings to confirm a low testosterone diagnosis. This is because testosterone concentrations may be subject to diurnal variations and can be suppressed by food or glucose intake.[10] If total fasting testosterone levels are low then repeat with FSH, LH and prolactin levels included.[9]

A PSA test is only indicated during the diagnostic work up of ED: if the DRE is abnormal or the man is over 50 years old and after counselling wishes to have a PSA test having weighed up the benefits and risks of the test, or if he is considering testosterone replacement

Table 3

Pharmacokinetics of PDE-5 inhibitors - adapted from NICE guidance[9]

	Sildenafil	Tadalafil	Vardenafil	Avanafil
Time taken before sexual activity	1 hour	At least 30 minutes	25–60 minutes	15–30 minutes
Duration of action	4–5 hours	Up to 36 hours	4–5 hours	Up to 6 hours
Effect of food intake	Rate of absorption reduced by 60 minutes when taken with food	None	Rate of absorption reduced by 60 minutes when taken with high-fat meals	Rate of absorption reduced by 75 minutes when taken with high-fat meals

therapy.[4] Any additional laboratory tests should be performed only if indicated, guided by clinical findings. It is worth considering carrying out a resting ECG in men with suspected CVD risk factors.

MANAGEMENT

ED is associated with an increased risk of future cardiovascular events including after sexual activity, even in men without cardiovascular symptoms at presentation.[11] The EAU guidelines recommend cardiac risk stratification at diagnosis in men seeking treatment.[6] Men with high CVD risk should be referred to a cardiologist for a review before considering any treatment other than lifestyle adaptations (see table 2, opposite).

All men with ED should be advised to review their lifestyle and improve their health; weight loss, smoking cessation, increasing exercise and reducing alcohol consumption are examples of factors which should be optimised.

Any reversible causes of ED should also be addressed. [6] If there is a clear drug-related cause consider the risk versus benefit to the patient's perceived quality of life and seek an alternative therapy, if appropriate, after shared decision making.

REFERRAL

The following groups of men should be referred directly for specialist management in secondary care after their ED diagnosis:

- Men with psychosexual dysfunction should be referred for psychosexual counselling, men with severe distress or a suspected underlying psychogenic cause may need to be referred to their local mental health services team[9]
- Men with hypogonadism should be referred to the secondary care endocrinology team for assessment and consideration of testosterone replacement[9]
- Men with severe or unstable CVD that would make sexual activity unsafe should be referred to cardiology[9]
- Young men who have always had ED, men who suffer ED after priapism (a persistent and painful erection lasting more than four hours) or ED as a consequence of trauma to the penis, genitals or spine should be referred to urology[9]

For men not referred directly to specialist services phosphodiesterase type-5 (PDE-5) inhibitors form the mainstay of oral treatment and can be started in the community. It is important to tell men prescribed PDE-5 inhibitors that sexual stimulation is necessary to enable an erection.

Common PDE-5 inhibitors and their time interval to efficacy are described in table 3, above. A trial period of six weeks is recommended to assess efficacy.[12] All men should be followed up after starting treatment as approximately 35% of patients may fail first-line treatment. Most commonly this is due to a lack of patient education regarding correct usage. If the first PDE-5 inhibitor is not effective at maximum dosage a change to one of the other PDE-5 inhibitors would be appropriate for a further six-week trial with counselling regarding usage.[12] It is important to check that patients are not taking versions of PDE-5 inhibitors that are sourced from the internet from non pharmacologically approved sources.

Commonly recognised side effects of PDE-5 inhibitors are headaches, flushing, indigestion, nasal congestion, blue vision and back pain.[9] Absolute contraindications and cautions for PDE-5 inhibitors are listed in table 4, above. This list is not exhaustive and prescribing information should be reviewed before administration.

Men with ED that has not responded to PDE-5 inhibitors should be referred for specialist review as further treatment options are available for those who wish to pursue them. The specialist expertise to deliver this service may be present within community facilities or secondary care depending on regional networks, competencies and protocols.

Vacuum erection devices, are a non pharmacological treatment option which may enable erections sufficient for intercourse in motivated patients and are an alternative first-line option in men in whom PDE-5 inhibitors are contraindicated or the elderly when clinicians are concerned about potential side effects or drug interactions.[6] »

Table 4

Generic contraindications and cautions for PDE-5 inhibitor use[6]

Contraindications	Cautions
● MI/stroke/arrhythmia in past 6 months ● Untreated hypotension or hypertension ● Unstable angina OR angina on sexual intercourse OR NYHA IV heart failure ● Concurrent use of nitrates ● Non anterior ischaemic neuropathy	● Adjust dose if used with an alpha-blocker ● Predisposition to priapism e.g. sickle cell disease, myeloma, leukaemia ● Anatomical penile deformity ● Active peptic ulcer ● Left ventricular outflow obstruction ● Vardenafil in elderly men

This list is not exhaustive and prescribing information should be reviewed before administration

key points

SELECTED BY

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Erectile dysfunction (ED) is the persistent inability to achieve and maintain an erection sufficient to permit satisfactory sexual performance. Rates of ED increase with age, with an estimated 70% of men aged 70 affected to some extent. ED is a significant predictor of underlying cardiovascular disease and is included in QRISK3.

In addition to the onset and duration of symptoms, important points in the history to clarify are: how the patient defines their ED, whether they have ever had erectile function, whether morning erections are preserved, the context of ED and recent sexual history. Men should be asked about symptoms of hypogonadism such as loss of libido or low energy levels. Cardiovascular risk should be evaluated.

GPs should look for signs of hypogonadism and examine the external genitalia for any penile or testicular deformity. Examination of lower limb pulses may provide evidence of peripheral vascular disease. If LUTS are elicited during the patient's history a digital rectal examination (DRE) should be performed as part of the man's assessment. NICE guidance also recommends performing a DRE in men with a history of prostate cancer and in men over 50 years of age. BMI, heart rate and BP should be recorded for all patients, and if indicated by the history a cardiovascular or neurological examination may be performed. Initial blood tests should include HbA_{1c} or fasting glucose, a lipid profile and fasting early morning total testosterone.

Patients should be stratified into cardiovascular risk categories. Those at high risk should be referred to cardiology before considering any treatment other than lifestyle adaptations. Men with suspected hypogonadism should be referred to endocrinology and counselling should be considered for men with psychosexual dysfunction. Medications known to cause ED should be reviewed and alternative therapy offered if appropriate. Lifestyle advice should include weight loss, smoking cessation, increased exercise and reduced alcohol intake.

Phosphodiesterase type-5 (PDE-5) inhibitors are first-line treatment and a trial period of 6 weeks is recommended to assess efficacy. Treatment failure is most commonly due to patients not being educated regarding correct usage. If the first PDE-5 inhibitor is not effective at maximum dosage a change to one of the other PDE-5 inhibitors would be appropriate for a further 6-week trial.

Men with ED that has not responded to PDE-5 inhibitors should be referred to a specialist. Vacuum erection devices are an option when PDE-5 inhibitors are ineffective or contraindicated, and in elderly patients where there are concerns about potential side effects or drug interactions. Unless there is a clear reversible organic or psychological cause, men with treatment-refractory ED should be referred to a urologist specialising in andrology, as should those with associated structural penile abnormalities such as Peyronie's disease and all those who develop ED after priapism or genital trauma.

Intracavernosal injections describe treatments for ED where vasoactive drugs are injected directly into the corpus cavernosum to increase blood flow into the penis and enable an erection. Alprostadil is currently the most common formulation used for this purpose. Patients started on this treatment (and if appropriate their partners) are taught how to prepare and administer the injection. Intracavernosal alprostadil is a highly efficacious treatment for ED.[13]

Men considering the treatment should be fully informed regarding potential complications, which include: penile pain, prolonged erections, priapism and penile fibrosis at injection sites. Penile pain is usually self-limiting after prolonged use but local anaesthetic can be considered to alleviate the pain from injections. Systemic side effects from intracavernosal injections are rare. Intracavernosal injections are contraindicated in men with bleeding disorders, a history of priapism or known hypersensitivity to alprostadil.[14]

Alprostadil may also be administered as either intraurethral or topical preparations. While such preparations are associated with lower rates of efficacy they offer reasonably well tolerated slightly less invasive alternatives.

The urology secondary care team have access to a full range of ED treatment options, including specialist expertise in whether combining treatments is appropriate and if necessary access to penile prostheses.

Men with ED refractory to treatment or complicated by concerns regarding structural abnormalities such as Peyronie's disease should always be referred to a urologist with a special interest in andrology.

Competing interests: None

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Useful information

British Association of Urological Surgeons
www.baus.org.uk/professionals/sections/erectile_dysfunction.aspx

NICE. Clinical Knowledge Summaries
https://cks.nice.org.uk/erectile-dysfunction#!scenario

British Society for Sexual Medicine Guidelines on the Management of Erectile Dysfunction in Men-2017
https://www.jsm.jsexmed.org/article/S1743-6095(18)30077-8/fulltext

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