

Erectile dysfunction

Erectile dysfunction can have a devastating effect on a relationship. Safe and effective treatment is available.

SUNIL SINHA, FCS (Urol) (SA), FRCS (Glasg), HDip (Surg) (SA), MS (Gen Surg) (India), MB BS (India)
Senior Specialist, Department of Urology, Groote Schuur Hospital, Cape Town

Sunil Sinha is a Senior Specialist in the Department of Urology at Groote Schuur Hospital, where he co-ordinates postgraduate academic teaching. His special interest is in uro-oncology.

Erectile dysfunction (ED) is defined as the consistent or recurrent inability of a man to attain and /or maintain a penile erection sufficient for sexual activity.

Sexual health and function are important determinants of quality of life (QoL). ED and female sexual dysfunction (FSD) are increasingly becoming more important because of an ageing population and newer therapies.

As this subject is discussed widely in the media, men and women are seeking guidance. Successful treatment of ED has been demonstrated to improve intimacy, satisfaction, and the sexual aspect of QoL, and relieve symptoms of depression.

While in the past ED was a disease treated exclusively by specialists, it has now become a common problem seen by most general practitioners. The rapid developments in the treatment of ED have emphasised the importance of continuing medical education. This concise update on the topic is designed to meet this challenge.

Although this article focuses primarily on ED in men, one must remember that one's sexual partner plays an integral role; hence discussion of any intervention should include both partners.

Incidence

Sexual dysfunction is highly prevalent in men and women.

In the Massachusetts Male Aging Study (MMAS), a community-based survey of 1 209 men aged 40 - 70 years, 52% of the responders reported some degree of erectile difficulty (Fig. 1). Seventeen per cent had mild, 25% moderate and 10% severe ED, with no nocturnal erection and total inability to obtain or maintain an erection during sexual stimulation.

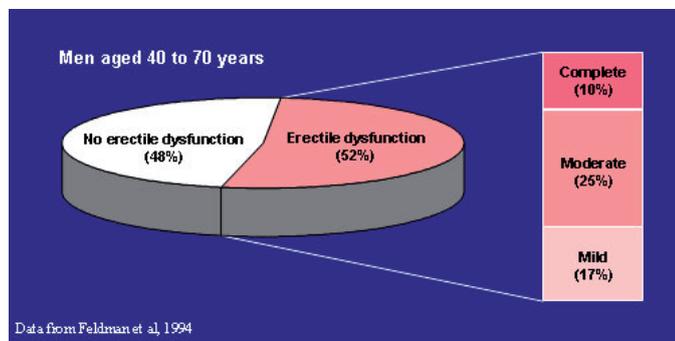


Fig. 1. Prevalence of ED in the MMAS – a community-based survey.

In the National Health and Social Life Survey, a nationally representative probability sample of men and women aged 18 - 59 years, 10.4% of men reported complete ED (similar to the MMAS result (Fig. 2)). Both studies noted a strong correlation between ED and advancing age.

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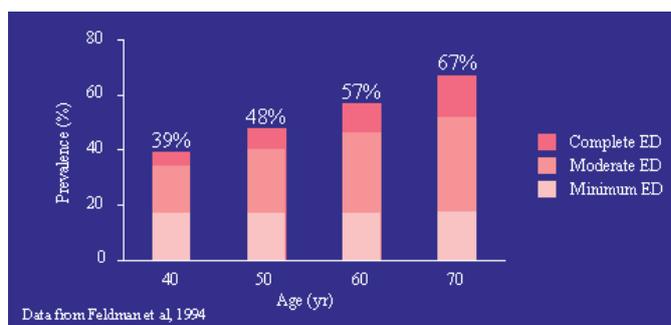


Fig. 2. Association between age and prevalence of ED – MMAS (N = 1 209).

Other male sexual dysfunctions, such as premature ejaculation (28.5%) and hypoactive sexual desire (15.8%), were reported in the National Health and Social Life Survey. An additional 17% reported anxiety about sexual performance, and 8% had a lack of pleasure in sex. Long-term predictions based on an ageing population and an increase in risk factors suggest a large increase in the number of men with ED. Also, the prevalence of ED is underestimated because physicians frequently do not question their patients about this disorder.

Physiology

It is worthwhile first considering the underlying mechanism of normal erection and the pathophysiology of ED.

Erection involves the nervous system, vascular system and hormones. The nervous system involves the central, peripheral, sympathetic and parasympathetic nervous systems. Higher centres in the brain, such as the hypothalamus and the limbic system, play an important role in the integration and control of reproductive and sexual functions.

Erection occurs in response to tactile, olfactory and audiovisual stimuli. The afferent information is assessed in the forebrain and relayed to the hypothalamus. The efferent pathways from the hypothalamus enter the medial forebrain bundle and project caudally near the lateral part of the substantia nigra into the midbrain tegmental region. It is then conveyed through the

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dorsal spinal columns to thoracolumbar (sympathetic T11, 12; L1, 2) and sacral autonomic (parasympathetic S2, 3, 4) nuclei.

The primary nerve fibres to the penis originate in the dorsal nerve of the penis – a branch of the pudendal nerve. This nerve originates from the Onuf nucleus (S2, 3, 4), and forms part of the somatic peripheral nervous system primarily responsible for the sensation from the genitalia and the contraction of bulbocavernosus and ischiocavernosus muscles necessary for a rigid erection.

The cavernous nerve of the penis is the other nerve that carries both the nerve of erection (parasympathetic) and the nerve of detumescence (sympathetic).

They travel posterolaterally along the prostate and enter the corpora cavernosa and corpus spongiosum by piercing the urogenital diaphragm about 5 mm lateral to the urethral sphincter. They can be damaged during any pelvic or perineal surgery.

Sexual stimulation causes the release of neurotransmitters from the cavernous nerve endings and sinusoidal endothelial cells that lead to relaxation of penile smooth muscles and cause erection.

The neurotransmitter involved in erection is called nitric oxide (NO) and is formed by the non-adrenergic non-cholinergic (NANC) nerve and endothelial cells.

The cholinergic nerve stimulates endothelial cells to form NO and contribute to erection.

NO is produced from arginine with the help of the enzyme nitric oxide synthetase (NOS). This, in turn, produces other muscle-relaxing chemicals such as cGMP, which results in the relaxation of smooth muscle of the erectile tissue, producing a dramatic increase in penile blood flow and thus erection (Fig. 3).

Erection is maintained as penile venous leak is markedly reduced. This occurs as the venules beneath the rigid tunica albuginea

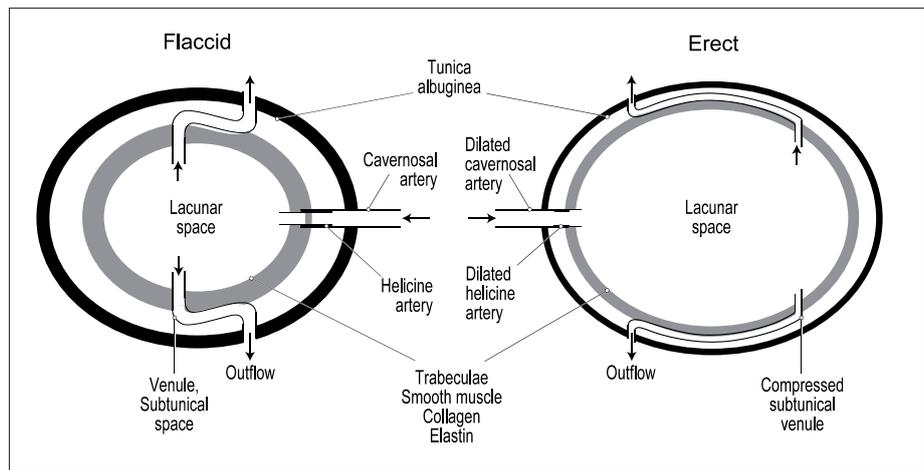


Fig. 4. Mechanism of venous occlusion leading to erection.

are compressed, resulting in near-total occlusion of venous outflow (Fig. 4).

Additional sexual stimulation initiates the bulbocavernosus reflex where ischiocavernosus muscles forcefully compress the base of the blood-filled corpora cavernosa. At this pressure both the inflow and outflow of blood temporarily cease, causing further rigid erection.

Detumescence results from the cessation of neurotransmitter release, breakdown of second messengers (cGMP, cAMP) by PDE-5 (phosphodiesterases), and sympathetic nerve excitation during ejaculation. Contraction of the trabecular smooth muscle reopens the venous channels, allowing the blood to be expelled, which results in flaccidity or detumescence.

Pathophysiology and causes of ED

ED is essentially a vascular disease, although the aetiology is usually multifactorial.

It can be stratified into organic and psychogenic impotence, but most men with organic ED usually have an associated psychogenic component.

Many diseases may affect erectile function by altering the nervous, vascular or hormonal systems. Various diseases may produce

changes in the smooth muscle tissue of the corpora cavernosa or influence the patient's psychological mood and behaviour.

Pure psychogenic ED is an uncommon disorder, although most cases of ED were previously attributed to psychological factors. It is characterised objectively by the presence of good nocturnal and morning erections and negative findings from all other tests. Such men have a history of highly variable erections that can be totally absent on one day but virtually normal on the next day.

Diseases associated with ED are summarised in Table I.

Evaluation of ED

Highly recommended

- History directed at aetiology
- International Index of Erectile Function (IIEF) (to measure the degree of ED – see Table II)
- Physical examination directed at aetiology
- Focused neurological examination for S2, 3, 4 reflex arc (anal tone, peri-anal sensation, bulbocavernosus reflex)

Recommended

- Fasting glucose/HbA1c
- Lipid profile
- Testosterone if clinically indicated (decreased libido, atrophic testes)

Optional

- Psychological/psychiatric consultation
- Laboratory tests (prolactin, LH, TSH, FBC, urinalysis)

Specialised

- In-depth psychosexual and relationship evaluation
- Psychiatric evaluation
- Nocturnal penile tumescence and rigidity tests

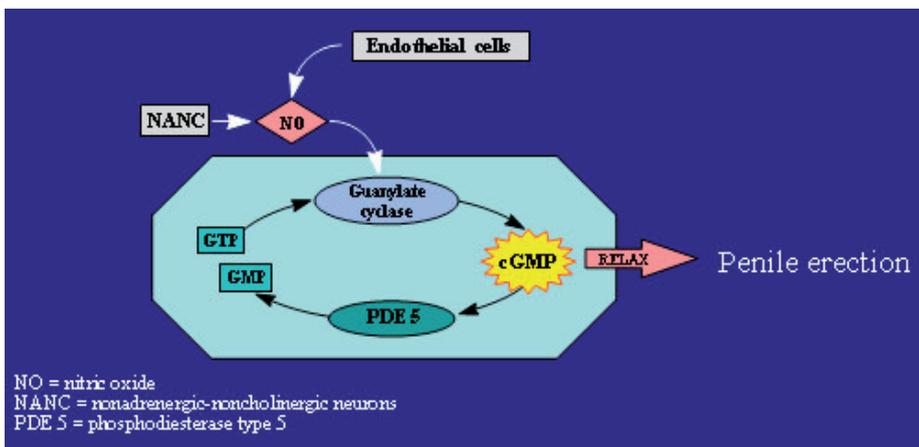


Fig. 3. Nitric oxide-cGMP mechanism of corpus cavernosal smooth-muscle relaxation and penile erection.

- Vascular imaging (arterial and venous)
- Endocrine
- Neurophysiological assessment.

The IIEF-5 score is the sum of questions 1 - 5. The lowest score is 5 and the highest score 25, 22 - 25 (no ED), 17 - 21 (mild ED), 12 - 16 (mild-moderate ED), 8 - 11 (moderate ED) and 5 - 7 (severe ED).

Management

After all the information regarding the patient's status has been gathered, the various options can be discussed. This is best done in the presence of his partner. There are enough options available for every man who wants to be sexually active.

Psychogenic ED

Patients with obvious psychogenic ED are referred for psychotherapy.

Organic ED

The diagnosis and treatment of these patients must be goal directed and based on the expectations of the patient and his sexual partner.

Other areas to consider are lifestyle changes such as regular exercise, no smoking, healthy diet, moderate alcohol consumption, etc.

The patient's medication also needs to be reviewed and changed if it contributes to ED.

Patients with organic ED have options, including:

- Oral drugs
- Vacuum device
- Intracavernosal injection
- Prosthesis
- Reconstruction surgery.

Oral drugs

5-phosphodiesterase inhibitors (PDE-5)

Sildenafil (Viagra). This is the first oral agent to be well documented as an effective form of treatment. Since its introduction in March 1998, no other therapy for ED has achieved such prominent public recognition.

The efficacy of sildenafil has been demonstrated by 21 randomised, double-blind, placebo-controlled studies of up to 6 months' duration, involving more than 3 000 men aged 20 - 87 years. The long-term efficacy has been shown in a 48-month, open-label, non-controlled, flexible-dose study.

Sildenafil is a potent inhibitor of PDE-5, the enzyme that acts in the corpora to break down cGMP mediated by the secondary neurotransmitter NO, which is primarily

Table I. Classification of ED

A.	Psychogenic: Depression, widower syndrome, performance anxiety, post-traumatic stress disorder
B.	Organic
I.	Vascular diseases: Atherosclerosis, peripheral vascular disease (PVD), myocardial infarction, hypertension, post-radiotherapy of pelvis, long-distance bicycle riders (perineal blood vessel and nerve trauma), drugs related to treatment of vascular disease
II.	Systemic disease: Diabetes mellitus, hypertension, dyslipidaemia, malignancy and its treatment, idiopathic haemochromatosis, scleroderma, renal failure, cirrhosis
III.	Neurological disease: Trauma, multiple sclerosis, Guillain-Barré syndrome, stroke, epilepsy, Alzheimer's disease
IV.	Endocrine disease: Hypogonadism, hypothyroidism, hyperthyroidism, hyperprolactinaemia
V.	Penile conditions: Peyronie's disease, priapism, epispadias, micropenis, trauma
VI.	Drugs: Antidepressants (tricyclic antidepressants, tranquillisers), antipsychotics, antihypertensives (thiazide diuretics, beta blockers, calcium-channel blockers, ACE inhibitors, alpha blockers - seldom), antiarrhythmics (digoxin), H ₂ blockers (cimetidine), antiandrogens (GnRH agonist, ketoconazole, spironolactone) 5-alpha reductase (finasteride), anticholesterol agents, recreational drugs (alcohol, marijuana, cocaine, heroine)
VII.	Surgery: Brain and spinal cord surgery, aortic surgery, abdomino-perineal resection of the rectum (APR), rectal surgery, prostatectomy
VIII.	Trauma: Fracture of the pelvis due to nerve and/or vascular damage
IX.	Radiotherapy

Table II. International Index of Erectile Function-5 (IIEF-5)*

Over the past 6 months	1	2	3	4	5
How do you rate your confidence that you could get and keep an erection?	Very low	Low	Moderate	High	Very high
When you had erections with sexual stimulation, how often were your erections hard enough for penetration ?	Almost never or never	Much less than half the time	About half the time	Much more than half the time	Almost always or always
During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?	Almost never or never	Much less than half the time	About half the time	Much more than half the time	Almost always or always
During sexual intercourse how difficult was it to maintain your erection to the completion of intercourse?	Extremely difficult	Very difficult	Difficult	Slightly difficult	Not difficult
When you attempted sexual intercourse, how often was it satisfactory for you?	Almost never or never	Much less than half the time	About half the time	Much more than half the time	Almost always or always

* IIEF-5 is an abridged and slightly modified 5-item version of a 15-item IIEF designed for easy use by clinicians.

responsible for smooth muscle relaxation. This permits the development of an improved and sustainable erection. It has been demonstrated to improve erectile function in diabetic, hypertensive, post-prostatectomy,

post-irradiation, spinal cord injury, geriatric and depressive patients.

Safety concerns and adverse effects have been studied carefully. The most common

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are mild headache and upper GI distress which are self-limiting. It is a mild inhibitor of PDE-6 found in the retina, causing blue haze at the periphery of the field of vision, but is not dangerous. Anterior ischaemic optic neuropathy (unilateral blurred vision) has been reported.

Sildenafil is absolutely contraindicated in patients taking nitrates (nitroglycerine or isosorbide) as it can potentiate the vasodilatory effect to dangerously low blood pressure levels. Exertion associated with sexual activity has been documented to increase the chances of ischaemic events in patients on nitrates.

Co-administration of ketoconazole, erythromycin or cimetidine (CYP4503A4 inhibitor) increases its plasma concentration and rifampicin decreases it; therefore sildenafil requires dose adjustments. This is, however, a feature of all PDE-5 inhibitors.

It is available in 3 doses: 25 mg, 50 mg and 100 mg. The starting dose depends on the severity of ED. The dose can be modified after at least 3 tries, although 5 - 6 tries are advised. It is recommended to take it on an empty stomach 30 - 60 minutes before sexual intercourse. Sexual stimulation (foreplay and/or audiovisual) is necessary to produce an erection. The half-life of sildenafil is 6 - 8 hours but the ability to obtain an erection may last up to 24 hours.

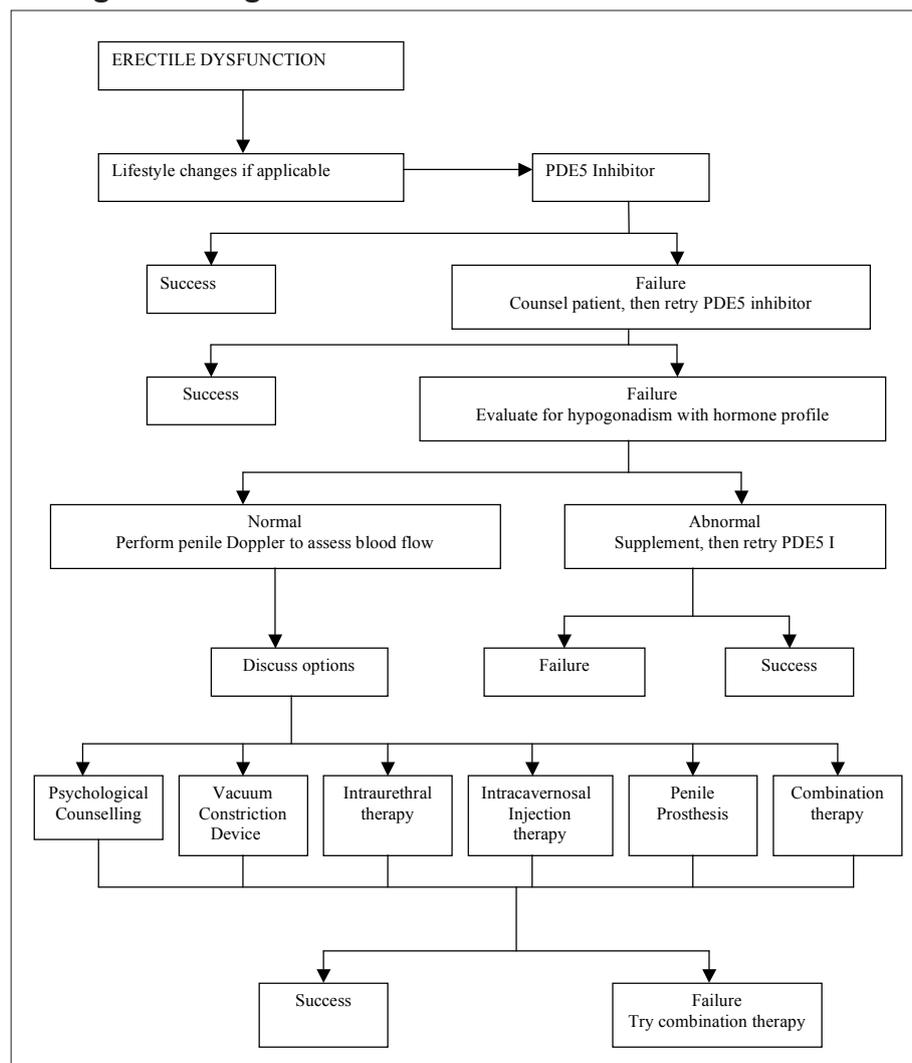
To refractory patients (after 6 tries), benefit may be obtained by another PDE-5 inhibitor or combination with intracorporeal injection.

Vardenafil (Levitra). Its mechanism of action is similar but 9 times more selective than that of sildenafil; it therefore needs a low dose. It is available in 5 mg, 10 mg and 20 mg. It has similar efficacy, side-effects and limitations as sildenafil but is less affected by food; however, a high-fat meal can inhibit absorption.

Avoid co-administration with antiarrhythmic drugs that prolong the QT interval (quinidine, procainamide, amiodarone and sotalol). Caution is advised in hepatic impairment, as these patients may develop priapism.

Tadalafil (Cialis). This is available in 5 mg, 10 mg and 20 mg doses. Tadalafil, even though chemically unrelated to sildenafil and vardenafil, has a similar mechanism of action, efficacy and side-effects. It has an extended period of responsiveness that can last 36 hours or longer in some men. It can also be ingested without food restriction. It has a PDE-11 effect and can cause back pain. Studies have shown that a single, small daily dose (2.5 mg) has a similar effect to an intermittent dose, which can eliminate the need for careful timing before intercourse.

Management algorithm for ED



Yohimbine has been available for many years. It acts both centrally and peripherally, but its efficacy has been questioned as it has only done slightly better than placebo, even in well-controlled trials. There is renewed interest in combination therapy with sildenafil or some of the other oral agents. It is safe, with few adverse effects. The dosage is 1 tablet (6 mg) 3 times daily. However, it has limited effectiveness, with a success rate of only 20 - 25%.

Fluoxetine (an SSRI) is effective in psychogenic ED and also helps in cases of premature ejaculatory disorder. The dosage is 20 mg 3 times daily for 4 - 6 weeks.

Androgens

This is an option in cases of severe hypogonadism. It improves the libido and overall sense of well-being. It is available in oral, injectable, gel and transdermal preparations. Oral therapy is the least effective, with a small risk of hepatotoxicity. Parenteral therapy will most likely restore testosterone levels, but it has to be injected periodically and is known to have symptomatic trough plasma levels and supernormal peak levels. To manage this, weekly lower doses are recommended.

Skin patches deliver a sustained dose and are generally accepted by patients. Androgen creams (AndroGel and Testim) are now available for daily topical use, minimising the peaks and trough side-effects of injectables. However, they need daily dosing and are relatively expensive.

An elevated serum androgen level has the potential to stimulate prostate growth and there is a risk of activating latent cancer. Therefore periodic prostate examinations and follow-up PSA levels are recommended in all patients.

Possible side-effects are fluid retention and liver damage.

Others

Apomorphine (Uprima), phentolamine (Vasomax), vasodilators (nitroglycerine), pentoxifylline (Trental), trazodone (Desyrel) and others have been tried alone and in combinations, with limited success.

Injection therapy

This is indicated if oral agents fail or are contraindicated.

In 1993 alpha blockers, like papaverine, showed that an erection could be achieved

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when they were injected directly into the corpora cavernosa. Soon other vasodilators like prostaglandin E₁ and phentolamine were introduced. Self injection of these agents, either alone or in combination, achieve erection in a wide variety of ED if the vasculature of the corpus cavernosa is healthy. These agents were available before the introduction of sildenafil and are still used by a select group of men.

Alprostadil or Caverject (synthetic PGE₁) is most commonly used in doses of 5 - 40 µg. Papaverine (15 - 60 mg) and phentolamine (Regitine - mostly used in the combination Trimix preparation - dose of 0.2 mg) are also used. The main adverse effect is priapism or scarring at the injection site. Alprostadil is now available in a gel and a patch and cannot be used in patients on monoamine oxidase inhibitors (MAOIs). The injection technique is important.

Vacuum constriction device (VCD)

This is another option if first-line therapy fails.

Negative pressure is created around the penis with the aid of a cylindrical appliance. This draws blood into the penis, which is trapped with the aid of a constriction ring. It is safe, painless and effective but needs manual dexterity. Adverse effects are mild and well tolerated.

Penile implants

At one time this was the only option available, but currently it is the last option even though 90% of men who have had the procedure would recommend the procedure to their friends and relatives. It is now considered in those in whom all therapies have failed.

Two types, a semi-rigid and a multi-component inflatable system, are available.

The semi-rigid prosthesis has two matching cylinders that are implanted into the corpora cavernosa, providing enough rigidity for penetration, and it rarely breaks. The disadvantages are that it stays semi-rigid all the time, requires surgery and the natural erectile mechanism is tampered with to implant the prosthesis.

The inflatable devices consist of two silastic or bioflex cylinders inserted into the corpora cavernosa, a pump placed in the scrotum to inflate the cylinders, and a reservoir that is contained either within the cylinders or in a separate reservoir placed beneath the fascia of the lower abdomen.

It stays functional for 7 - 10 years before replacement is necessary. Complications include infection, erosion and painful erection (very low incidences). The newer antibiotic-coated implants have a reduced infection rate. Patient acceptance of these devices is very high, with nearly 100% of patients expressing satisfaction.

Reconstructive surgery

A penile abnormality - like Peyronie's disease - can be referred for surgical correction. Vascular reconstruction restores natural erection when successful, but it is technically the most difficult surgery and only 50% of patients are potential candidates, e.g. those suffering from trauma and patients less than 30 years of age.

Future

The development of future medical options will emphasise the restoration of physiological function due to better understanding of the molecular biology of ED.

Research involving gene therapy is already showing promise.

Vascular endothelial growth factor (VEGF) is produced by vascular smooth muscle, and endothelial and inflammatory cells. It increases the production of NO, which improves endothelial function and blood flow in chronic ischaemic disorders.

In animal models, direct intracavernosal injection of recombinant VEGF protein or adenoviral VEGF that contains plasmids has shown dramatic results based on cavernosography.

Burchardt *et al.* identified VEGF 165 as the predominant isoform of the corpora cavernosa.

Conclusion

While oral PDE-5 inhibitors continue to be the first-line therapy for patients with ED, a significant number do not respond satisfactorily to these agents. Change of PDE-5 inhibitors, evaluation of hormone status, and patient counselling are the first efforts to salvage non-responders. Failure of these measures can be followed by combination pharmacological therapy, intracavernosal injection, a vacuum constriction device, or ultimately penile prosthesis implantation. By following a stepwise approach (see algorithm), the clinician can offer a satisfactory, effective, and safe treatment plan for the majority of men with ED.

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In a nutshell

- Sexual health and function are important determinants of QOL.
- The attractiveness of oral therapy with the PDE5-Is and widespread publicity have made ED a household concept and hence a common problem seen by most GPs and no longer a condition exclusively treated by specialists.
- Due to an ageing population and increase in risk factors the prevalence of ED in the community has risen.
- True prevalence will be reflected if patients are encouraged to speak about their disorder and are asked about it.
- ED is essentially a vascular disease, although the aetiology is usually multifactorial.
- ED may be the first presentation of more generalised cerebrovascular disease and hence further investigations are recommended.
- IIEF-5 score is a helpful guide to assess the degree of ED.
- Various treatment options are available.
- Treatment options should be based on patient expectations and must be discussed together with the partners.
- PDE5-Is should not be used together with nitrates.
- In the case of non-responders, hypogonadism must be ruled out and replacement must be considered if clinically indicated.

Single suture

Genetically engineered pig organs could 'save our bacon'

Organs that are invisible to our immune system that won't be rejected when transplanted could be ready within 10 years, according to Robert Winston of Hammersmith Hospital and Carol Redhead of the California Institute of Technology. This is thanks to progress in faster ways of genetically engineering pigs, leading to 'xenotransplants'. Progress has so far been stalled by problems with funding and with the cloning technique used to engineer the pigs.

There is now a simpler technique that will alter the DNA in a boar's sperm cells, and therefore in any future offspring, by injecting a virus into its testicles that carries the desired genes. These genes can be used to 'disguise' pig organs, fooling the body into thinking that these are 'self'. When these boars breed naturally, they should pass on the genetic changes to their offspring.

New Scientist, 15 November 2008.