Erectile dysfunction – an update of current practice and future strategies

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Introduction

Erectile dysfunction (ED) is defined as the inability to achieve and maintain a penile erection adequate for satisfactory sexual intercourse.1 Up to 150 million men worldwide suffer from ED and this figure is likely to double by the year 2025.2

A number of studies have attempted to characterise the true prevalence of ED. In a Danish study, Ventegodt reported that 5.4% of all patients had a decreased ability to achieve an erection.3 The prevalence was reported to be highest (18%) in those aged over 58 years. The Massachusetts Male Aging Study (MMAS)4 reported the results of a regional survey of 1709 men aged 40–69 years. In this study 52% reported some degree of ED, with 10% having complete ED. Moreover, the results suggest that the probability of complete ED at age 70 was threefold compared to that at age 40; the probability of moderate ED was two-fold.

Physiology of penile erection

Penile erection is a complex neurovascular event. The degree of contraction or relaxation of the cavernosal smooth muscle determines the degree of tumescence or detumescence.5 The balance between the contractile and relaxant factors is known to be controlled by both central and peripheral mechanisms and involves the interaction of three different systems:6 (a) the central nervous system (CNS); (b) the peripheral nervous system; and (c) the vascular and cavernosal smooth muscle in the penis.

The CNS

The CNS coordinates incoming sensory information from a variety of sources which may be visual, auditory, cognitive/imaginative, tactile or olfactory. The central pathways integrating these inputs and controlling erectile function are complex and only partially understood. However, there is strong evidence to support the involvement of the paraventricular nucleus (PVN) and the medial pre-optic area (MPOA) within the hypothalamus in the control of erectile function. The MPOA has been postulated to be an integrative centre that collects the input and redistributes to other structures within the CNS such as the PVN. The PVN in turn has been suggested to activate selective autonomic pathways resulting in an erection.7 The neurons from the PVN have been reported to project onto the spinal cord either directly or via the median forebrain bundle, pons and medulla. The descending pathways from the PVN to the spinal cord have been reported to contain a variety of neurotransmitters such as oxytocin, vasopressin, encephalin and dopamine.7

The peripheral nervous system

Within the spinal cord, there are various specific areas which contain integral components of the erectile system. These are known as the “erection centres”7 (Figure 1). The thoraco-lumbar erection centre is located between T1 and L2 and gives rise to the sympathetic outflow pathway. This connects to the urogenital tract via the pelvic, cavernosal and pudendal nerves. The sacral erection centre is located between the S2 and S4 segments of the spinal cord and gives rise to the parasympathetic outflow pathway. These fibres reach the penis via the pelvic, cavernosal and pudendal nerves. Furthermore, the penis receives dense somatic input from

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sensory branches of the dorsal nerve, a branch of the pudendal nerve. The individual nerves innervating the penis may contain a number of different neurotransmitters and as a result the nerves are categorised as either being adrenergic or cholinergic according to the predominant transmitter present. However, non-adrenergic non-cholinergic (NANC) neurotransmitters may be found and indeed be co-localised with either adrenergic or cholinergic nerves. Nitric oxide (NO) is one of the NANC neurotransmitters which has now been widely accepted to be the major mediator eliciting relaxation of the penile smooth muscle.8

During sexual arousal, NO has been reported to be released from sympathetic nerves causes contraction of the blood vessels and smooth muscle of the corpus cavernosum, thus leading to detumescence of the penis. Erection of the penis is therefore regulated by a balance between pro- and anti-erectile mediators (Figure 2). Studies with human corpus cavernosum suggest that when the two systems are simultaneously active, the nitrergic system is dominant over the sympathetic system.12

**Vascular and cavernosal smooth muscle in the penis**

The human penis is composed of paired corpora cavernosa and the single corpus spongiosum (Figure 3). The corpus cavernosum consists of a meshwork of sinusoidal spaces lined by endothelial cells.5 In order for an erection to occur, relaxation of penile smooth muscle is required to allow blood to flow into the penile structures. The resulting increase in intracavernosal pressure (ICP) leads to compression of the subtunical venules against the tunica albuginea.5 This process reduces venous drainage from the corpora cavernosa and increases pressure within the corpora, resulting in an erection. In full rigidity the ICP reaches values considerably higher than systemic (systolic) blood pressure with the contribution of the skeletal muscles of the pelvic floor.

**Relaxant factors: the NO-soluble guanylate cyclase (sGC)-cyclic guanosine monophosphate (cGMP) pathway**

In 1990 Ignarro et al.13 reported that electrical field stimulation (EFS) of isolated strips of rabbit corpus cavernosum resulted in the endogenous generation and release of NO,
nitrite and cGMP. These were the first published results to suggest that penile erection is mediated by NO generated in response to NANC stimulation.

Immuno-histochemical studies have demonstrated that the enzyme neuronal nitric oxide synthase (nNOS) is present in the nerve fibres of the pelvic plexus, corpus cavernosum and around blood vessels.\(^\text{14}\)

NO may be released from both the endothelium via eNOS and the nitrergic nerves via nNOS. Nitrergic-derived NO may be functionally more important, as nitrergic relaxation of the corpus cavernosum has been reported to not require a functional endothelium after removal by either physical\(^\text{15}\) or chemical means.\(^\text{15,16}\)

Once released, NO exerts its action on smooth muscle cells by activating the enzyme sGC. The activation of sGC results in an increase in intracellular cGMP concentrations (Figure 4).\(^\text{17}\) This in turn activates a number of second messenger systems which ultimately result in smooth muscle relaxation.

Pathophysiology of erectile dysfunction

ED can be caused by either psychogenic or organic factors; however, in many patients the disorder is of mixed aetiology with both factors contributing. The psychogenic component of ED is reported to be especially important in younger men (aged less than 35 years)\(^\text{18}\) and in elderly men who start a relationship with a new partner. Diseases which become more prevalent with age such as diabetes and vascular disease are major risk factors in the ageing male. It has been reported that in patients older than 50, up to 50% may have ED secondary to vascular disease. The presence of ED of any aetiology is itself associated with psychological distress. This of course may in turn reduce the probability of achieving satisfactory erectile function.

Endothelial dysfunction

As ED and coronary artery disease share common risk factors, the concept of endothelial dysfunction has developed. Here ED is considered another manifestation of vascular disease specific to small vessels. ED can be considered to be an early manifestation of systemic endothelial dysfunction.\(^\text{19}\)

It is now well established that ED often precedes and predisposes subsequent atherosclerosis. Moreover, endothelial dysfunction is a reflection of the loss of NO activity or biosynthesis at the endothelial level. This is associated with vasoconstriction, coagulation, leucocyte adhesion and smooth muscle cell hyperplasia, which is central to the process of atherosclerosis. The inhibition of eNOS (via impaired hydrolysis of dimethyl arginine) and the uncoupling of eNOS activity increase the oxidative stress in the endothelial cells. This in turn results in further oxidative catabolism of NO and formation of peroxynitrite.

In diabetes-associated endothelial dysfunction, elevated free fatty acids which are seen in patients with insulin resistance may induce endothelial dysfunction through the activation of protein kinase C (PKC), the increased production of reactive oxygen species (ROS), elevation in triglyceride and low-density lipoprotein (LDL), and decrease in high-density lipoprotein (HDL) levels.\(^\text{20}\) More recent evidence suggests that the effects of hyperglycaemia and insulin resistance on endothelial cells are additive, since defects in both glucose and lipid metabolism produce similar effects with the resultant decrease in endothelial NO availability.\(^\text{21}\) The association between metabolic syndrome, insulin resistance and obesity and ED in men are now well characterised and understood.\(^\text{22}\)
**Diabetes mellitus**

Many epidemiologic studies have reported an increased risk of ED in diabetic men. The prevalence of ED has been reported to affect between 35% to 50% of diabetic patients. Furthermore, a positive relationship was demonstrated between ED, poor metabolic control and age. These results indicate that diabetes is a significant risk factor for the development of ED.

In diabetes, the severity of ED has been demonstrated to be related to both the severity and duration of diabetes. However, it is likely that the etiology of ED in diabetes is multifactorial. It is now well established that there is a higher incidence of peripheral neuropathy, autonomic neuropathy, microangiopathy and arterial insufficiency in diabetic patients with ED than in potent diabetic patients.

The proposed mechanisms of ED in diabetics include: elevated advanced glycation end-products (AGEs) and increased levels of oxygen free radicals, impaired (NO elevation) and NO dependent nitric oxide synthase (NOS), increased endothelin B (ETB) receptor binding sites and ultrastructural changes, upregulated RhoA/Rho-kinase pathway, increased endothelin 1, acting as an inhibitor of nNOS and NO-dependent selective nitricergic nerve degeneration.

**Therapeutic options for ED**

**Lifestyle modifications**

The identification of specific risk factors associated with ED provides an opportunity for conservative measures in patients with mild to moderate ED. Cessation of smoking, weight loss and exercise are associated with an improvement in erectile function, as well as improving endothelial function and reducing long-term cardiovascular risk.

**Pharmacological treatments for ED**

There are a number of options available for the management of ED. They include oral agents, intracavernosal injection (papaverine, phentolamine, prostaglandin E1, vasoactive intestinal polypeptide (VIP)), transurethral vasoactive agents (prostaglandin E1), vacuum erection devices, penile revascularisation surgery and insertion of a penile prosthesis.

Oral agents are the least invasive option and are the most accepted form of first-line treatment (Table 1).

**PDE5 inhibitors**

The second messenger cGMP is metabolised to GMP by a superfamily of enzymes called phosphodiesterases (PDEs). Among all of the PDEs, PDE5, 6 and 9 are specific for cGMP, and PDE5 is the predominant PDE found in the corpus cavernosum.

Sildenafil (Viagra™), vardenafil (Levitra™) and tadalafil (Cialis™) are the currently available PDE5 inhibitors. Vardenafil is now also available as an orodispersible tablet (ODT).

<table>
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<tr>
<th>Oral treatments</th>
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<td>Yohimbine</td>
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<td>Apomorphine (Uprima™, Ixense™ and Taluvian™)</td>
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Table 1. Oral agents for the treatment of male erectile dysfunction.

Vardenafil is now also available as an orodispersible tablet (ODT).

Newer PDE5 inhibitors avanafil (Stendra™) and udenafil have recently been approved by the Food and Drug Administration (FDA) in the United States (US). Tadalafil (once daily 5mg) has also recently been licensed for the treatment of both ED and symptoms related to benign prostatic hyperplasia (BPH) by the FDA in the US. Udenafil, unlike the other PDE5 inhibitors, may also have a second mechanism of action. In animal models it has been found to increase ICP whilst reducing levels of the pro-contractile mediator endothelin 1, acting as an inhibitor of nNOS (asymmetric dimethylarginine (ADMA)).

All of the PDE5 inhibitors have the same mechanism of action. However, they differ in their efficacy for the inhibition of the enzyme, in their selectivity for PDE5 over other isoenzymes such as PDE6 and in their pharmacological properties.

**Potency and selectivity.** The potency of the PDE5 inhibitors can be measured in vitro by assessing the IC50 value (concentration at which the enzyme activity is 50% inhibited). Using these values, vardenafil exhibits a PDE5 inhibitory potential approximately five times higher than that of sildenafil (Table 2). PDE6 plays an important role in the conversion of light impulses into nerve impulses in the retina. For PDE6, sildenafil and vardenafil show a lower selectivity than tadalafil. With respect to PDE11, tadalafil shows only five times greater selectivity than does PDE5. PDE11 has been detected in a variety of human tissues, e.g. in the heart, pituitary gland, brain and testes. The physiological significance of PDE11 and the possible consequences of its inhibition have not yet been fully established.

**Pharmacokinetics.** All four drugs are rapidly absorbed from the gastrointestinal tract, with peak plasma levels being attained within one hour in the case of sildenafil and vardenafil and after two hours in the case of tadalafil. For avanafil, it has been reported that peak levels are achieved within 33 minutes. Food intake causes no delay or reduction in tadalafil absorption, whereas it is known to reduce and delay absorption of sildenafil. The mean half-lives (t1/2) of...
sildenafil and vardenafil are three to four hours; for avanafil it is five to 10 hours whereas that of tadalafil is approximately 18 hours. The elimination of sildenafil, vardenafil and tadalafil takes place predominantly via cytochrome enzyme P450 (CYP3A4) in the liver.

Clinical efficacy. Results from clinical trials suggest that all three currently available PDE5 inhibitors are effective in a wide range of patient groups. Treatment with vardenafil at a dose of 20 mg produced an improvement in the ability to achieve an erection in 80% of ED patients. In a comparable study of sildenafil (100 mg dose), 84% of ED patients were successfully treated. Treatment with tadalafil 20 mg produced an improvement in the ability to achieve an erection in 81% of ED patients. Comparative studies between vardenafil and sildenafil suggest that patients do not have a significant preference among the PDE5 inhibitors.

Adverse effects. The most common side effects seen with sildenafil include headache, flushing, dyspepsia and rhinitis. The adverse effects with tadalafil and vardenafil are similar to sildenafil; however, tadalafil is associated with a higher incidence of back pain (4%–9%) and myalgia (1%–7%).

Difficult treatment groups

Diabetes mellitus

The sildenafil Diabetes Study Group reported that 56% of men with ED and diabetes who received sildenafil (25–100 mg) for 12 weeks reported improved erections (Global Assessment Questionnaire (GAQ)). With placebo only 10% reported better erections. In a more recent double-blind, placebo-controlled, flexible-dose study patients were randomised to receive sildenafil or placebo for 12 weeks. The erectile function domain of the International Index of Erectile Function (IIEF) showed only a six-point increase in the mean score over placebo (Figure 5). However, men with mild/moderate ED achieved a higher overall score compared with men with severe ED.

In a multicentre, double-blind, placebo-controlled, fixed-dose trial, patients with diabetes and ED were randomized to take vardenafil or placebo as needed for 12 weeks. With respect to the erectile function domain, the dose-dependent final scores for the 10- and 20-mg dose were 17.1 and 19.0 compared with 12.6 for placebo. Similar results have been reported in a prospective, randomised study in PDE5 inhibitor-naive patients with type 1 diabetes. Vardenafil treatment significantly improved the erectile function domain score of the IIEF (from 13 to 20) (Figure 5).

For tadalafil, at doses of 10 mg or 20 mg, the erectile function domain score was improved by 6.4 and 7.3, respectively, regardless of baseline HbA1c levels (Figure 5).
For the newly launched PDE5 inhibitor avanafil, the results of the REVIVE ED study were recently presented. These results suggest that erections sufficient for penetration (SEP2) were found in 63% of patients versus 42% with placebo, and successful intercourse was possible (SEP3) in 40% (versus 20% for placebo). Moreover, it was reported that over 70% of participants were able to achieve an erection within 15 minutes.

**Testosterone replacement therapy**

Androgens are known to be involved in both the central and peripheral pathways associated with penile erection. Testosterone is required for NOS expression in the corpus cavernosum and also for the maintenance of the neural pathway. Although controversial, testosterone supplementation is an option in patients with erectile dysfunction who are non-responders to PDE5 inhibitors and have a low serum testosterone level.54,55 Studies have suggested that up to 60% of non-responders may be converted to responders following combination treatment.56

**Alternative oral treatment options**

**Apomorphine**

The PVN in the hypothalamus is involved in initiating the erectile response. Apomorphine hydrochloride is a dopaminergic receptor agonist (D1 and D2 receptors) that has been developed as a sublingual agent to activate oxytocinergic neurons in the PVN. The median onset to action is 19 minutes and the half-life is one hour. An open-label, randomised, flexible-dose comparison of apomorphine and sildenafil demonstrated the superior efficacy of sildenafil to apomorphine (75% versus 35%, respectively). The side effect profile – nausea (7%), dizziness (6.5%) and yawning (8.1%) – combined with a high non-responder rate has limited the therapeutic acceptance of this drug and has led to its withdrawal from the market.

**α-adrenoceptor antagonists**

The aim of these agents is to reduce the corpus cavernosum smooth muscle tone by inhibiting the innervation of the sympathetic nervous system. These agents are not routinely used in clinical practice as we now know that the NO-cGMP signalling system is the predominant pathway in achieving smooth muscle relaxation.

Yohimbine is an orally administered indolalquinolonic alkaloid agent with both peripheral α2 adrenergic receptor blockade and central noradrenergic agonist activity. Phentolamine is a non-selective α-adrenoceptor antagonist, but has not gained acceptance – partly because of the associated systemic effects. The selective α1 antagonists doxazosin and terazosin are routinely utilised for patients with bladder outflow obstruction and can improve erectile function in patients with very mild symptoms.

**Intracavernosal and intraurethral prostaglandins**

The synthetic PGE1 analogue alprostadil can be administered as a second-line therapy in patients failing oral pharmacotherapies or who have a specific contraindication to treatment with oral agents. PGE1 increases the intracellular concentrations of the second messenger cAMP, resulting in corpus cavernosum smooth muscle relaxation. Currently, two methods of administration are available: direct intracavernosal injection (80% response rate) or intraurethral application of a small pellet (MUSE® dose 250–1000 μg, 65% response rate). This second-line treatment is useful in patients with long-standing diabetes or ED secondary to pelvic surgery, who have a higher incidence of ED refractory to oral pharmacotherapies.

A recent study suggests that a poor response to intracavernosal alprostadil is associated with small vessel disease and a higher risk of cardiovascular events.57

**Mechanical interventions**

**Vacuum devices**

These devices are useful in patients with psychogenic or organic ED and can be used alone or in combination with other therapies. An external cylinder is utilised to create a negative pressure and penile tumescence is maintained by means of a constriction ring at the base of the penis. The reported patient satisfaction rate is 50%–70%.58

**Penile prosthesis surgery**

The insertion of a penile prosthesis is suitable for patients with severe organic ED. Two main subtypes of prosthesis are available: malleable (or semi-rigid) and inflatable. The malleable devices have the advantages of decreased mechanical breakdown, easier placement and lower cost. Inflatable devices are available as two- (Ambicor, American Medical Systems) or three-piece devices (AMS 700CX or Coloplast Titan, Titan Zero Degree). The two- and three-piece devices have a pump placed in the scrotum that controls the inflation and deflation of the device and therefore requires an element of patient dexterity.

Complications include infection rates of up to 2%–3% and re-operation rates for mechanical failure of 15% by 10 years. The overall satisfaction rates have been reported as over 90% from the patients and partners, respectively.59 Using a minimal handling approach and antibiotic-coated implants, infection rates have fallen to less than 1%60 (Figure 6).
Future therapeutic options

Rho-kinase inhibitors

Rho-A is a small monomeric G protein that activates rho-kinase and is involved in the sensitisation of the smooth muscle contractile elements to Ca\(^{2+}\). Therefore, smooth muscle relaxation can be modulated without a change in the intracellular Ca\(^{2+}\) levels. Rho-kinase inhibitors provide an alternative pathway to produce smooth muscle relaxation, and in vitro studies have shown that specific inhibitors of rho-kinase such as Y-27632 can cause a concentration-dependent relaxation of the corpus cavernosum.\(^6\)

Direct sGC activators

Patients with significant endothelial dysfunction or nitric-ergic nerve impairment are unable to produce adequate endogenous NO. Therefore, direct NO-independent activation of sGC provides a novel approach. The benzylindazole derivative YC-1 has been investigated as a potential sGC activator, but has been found to have non-specific phosphodiesterase inhibitory activity – although alternative compounds based on this prototype have been developed and are under investigation.\(^6\)

NO-releasing PDE5 inhibitors

Sildenafil nitrate is an NO-releasing derivative of sildenafil citrate that can release NO spontaneously and can also inhibit PDE5. This compound is more potent than sildenafil citrate and can release NO in the absence of endogenous NO. Further research is required before any clinical application is proposed.\(^6\)

Further strategies for the treatment of ED

ED is invariably the result of a number of pathophysiological events which result in a reduction in the bioavailability of NO. We believe that future strategies for the treatment of ED should be aimed at correcting or treating the underlying mechanisms involved in the pathogenesis of ED as well as finding more specific and effective sGC activators and NO-releasing compounds.

Novel research areas include gene therapy with neurotrophic factors, eNOS, nNOS and superoxide dismutase. Through the use of an appropriate vector, diabetic animals have already been successfully transfected with these agents. Direct injections into the cavernous sheath of diabetic rats with neurotrophin-3 (NT3) using the herpes simplex virus as the vector have been performed. Subsequent immunoreactive strains have demonstrated a significant increase in nNOS neurons in the major pelvic ganglia. Moreover, this was associated with significant increases in the ICP following cavernous nerve stimulation.\(^6\)

Moreover, diabetic rats injected with adenoviruses containing eNOS into the corpus cavernosum have produced significant rises in ICP secondary to cavernous nerve stimulation. This was further associated with a rise in eNOS (measured by Western blot analysis) and an increase in NOS biosynthesis (measured by an increase in cavernous nitrate and nitrite formation).\(^6\)

Further studies have examined the intracavernous injection of adenoviruses containing superoxide dismutase into diabetic rats. The results indicate a decrease in superoxide anion levels, an increase in NO bioavailability and an increase in cGMP levels.\(^2\)

More recently, the effects of gene transfer on erectile function and sexual behaviour have evaluated in male cynomolgus monkeys with ED and an ageing rat model. The animals were injected intracavernously with a smooth-muscle-specific gene transfer vector (pSMAA-hSlo) encoding the pore-forming subunit of the human large-conductance, calcium-sensitive potassium channels (Maxi-K). The results have shown a significant improvement in erectile function and sexual behaviour or increased ICP responses to cavernous nerve stimulation after the intracorporeal gene transfer. These results support the concept that intracorporeal Maxi-K-channel gene transfer may be a novel way of improving erectile function.

Conclusion

Despite major advances in the understanding of the physiology of penile erection and the pathophysiology of ED, together with an increase in the available pharmacotherapies, ED remains a significant global male health problem. This condition has an impact on the patients’ and partners’ quality of life and self-esteem.
Oral tablets, in particular PDE5 inhibitors, have revolutionised the treatment of ED by decreasing reliance on more invasive options. Three potent selective PDE5 inhibitors, sildenafil (Viagra; Pfizer), tadalafil (Cialis; Lilly) and vardenafil (Levitra; Bayer) are currently available in the United Kingdom. Although large multicentre clinical trials have shown the efficacy and tolerability of these drugs in ED with various aetiologies and a broad range of severity, 30%–35% of patients fail to respond to oral pharmacotherapies, especially in difficult treatment groups such as diabetic patients. The possible reasons for failure include severe ED at presentation, worsening of endothelial dysfunction, ED after radical prostatectomy or diabetes, unrecognised or untreated hypogonadism, inadequate patient education or incorrect drug usage or the development of drug tolerance. However, end-stage surgical treatment using penile prosthesis surgery is still associated with a high patient and partner satisfaction rate of over 80%. The continued refinement of penile prostheses has resulted in reduced infection and mechanical failure rates.

Conflict of interest
None declared.

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