The pharmacological management of erectile dysfunction

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Abstract

The inability to attain or maintain a penile erection sufficient for sexual intercourse is a common problem experienced by a third of men over the age of 40 years. Erectile dysfunction (ED) is a debilitating disease which can have profound psychological effects on personal relationships and the social well-being of the affected individual. The diagnosis and evaluation of sexual dysfunction has been well described, and several validated algorithms are available to quantify the classification and severity. The International Index of Erectile Function and the Sexual Health Inventory for Men questionnaires are commonly used in the initial assessment of ED. Several risk factors have been linked to the pathophysiology of ED. Endothelial damage has been the focus of many recent studies. An evaluation of cardiovascular status, in addition to the administration of questionnaires to men with ED, might reduce mortality and improve sexual quality of life.

Keywords: cardiovascular disease, erectile dysfunction, phosphodiesterase-5 inhibitors, prostaglandin, testosterone

Introduction

The inability to attain or maintain a penile erection sufficient for sexual intercourse is a common problem experienced by a third of men over the age of 40 years. Erectile dysfunction (ED) is a debilitating disease which can have profound psychological effects on personal relationships and the social well-being of the affected individual. The diagnosis and evaluation of sexual dysfunction has been well described, and several validated algorithms are available to quantify the classification and severity. The International Index of Erectile Function (IIEF) and the Sexual Health Inventory for Men questionnaires are commonly used in the initial assessment of ED.

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The mechanism of an erection

Penile tumescence and detumescence depend on the complex integration of various neurovascular signalling pathways. This includes autonomic neurotransmitters (noradrenaline and serotonin), nonadrenergic, noncholinergic neurotransmitters (neural nitric oxide and vasoactive intestinal polypeptide), and vasoactive agents produced by the vascular endothelium (prostacyclin and prostaglandin).

Tumescence

Sexual stimulation results in nitric oxide (NO) being released from the nerve endings in the corpus cavernosum. In turn, NO mediates the release of cyclic guanosine monophosphate (cGMP) via the activation of the enzyme, guanylate cyclase. cGMP triggers smooth muscle relaxation, allowing increased arterial inflow and filling of the sinusoids in the corpus cavernosum. The accumulation of blood increases the intracavernosal pressure, causing passive veno-occlusion and subsequent erection. Continuous smooth muscle relaxation and a sustainable erection is dependent on cGMP, including the release of NO, and prostaglandins and prostacyclins from the endothelium in response to the mechanical stretching caused by the initial increase in pressure.

Detumescence

Detumescence occurs when cGMP is degraded to the inactive form via specific hydrolysing phosphodiesterase-5 (PDE-5) enzyme, almost exclusively present in the corpus cavernosum. Ejaculation is mediated by the action of noradrenaline on the α1-adrenoceptors, followed by contraction of the vascular and trabecular smooth muscle. The intracavernosal pressure decreases and the veno-occlusion terminates. This physiological effect of smooth muscle contraction after ejaculation results in a refractory period whereby immediate restimulation does not result in subsequent vasodilation and arterial filling.
The effect of serotonin on erectile function involves sympathetic, parasympathetic and somatic outflow mechanisms, and is considered to exert a general inhibitory effect on male sexual behaviour.3

Causes of erectile dysfunction

As with most diseases, ED can be attributed to organic (physical) and non-organic (psychological) causes, but is often the result of a combination of both.4 Traditionally, physical causes refer to vasculogenic, neurogenic or endocrinological disorders (Table I) and should be differentiated from other male sexual dysfunctions, such as premature ejaculation, Peyronie's disease (anatomical causes) and disorders of orgasm. The absence of morning erections, muscle pain and cramps relieved by rest and numbness in the saddle area might indicate a physical cause and should be thoroughly investigated.

Psychogenic causes are mostly the result of depression, low self-image, relationship conflict and a stressful lifestyle, which, in turn, lead to performance anxiety and a reduction in the desire to be intimate. ED is known to be associated with certain drugs5 (Table II). Identifying the cause and assessing the risk factors may be beneficial in reducing the mortality as a result of other medical conditions, and in particular, cardiovascular disease, where endothelial cell damage is the first event in the atherosclerotic process.6,7 The famous phrase “ED equals endothelial damage, which equals early death” is taught to medical students around the world in an attempt to emphasise the importance of identifying the cause.8

Treatment options

Several treatment options for ED are available. They consist of mechanical devices (vacuum pumps and constriction rings), surgical interventions (prosthetic penile implants, arterial reconstruction and venous blocking procedures), and pharmacological management (PDE-5 inhibitors, testosterone replacement therapy and invasive prostaglandin administration).9 The current approach to management aims to identify the underlying cause. Lifestyle interventions and limiting cardiovascular risk factors, such as smoking, hypertension, dyslipidaemia and obesity, should be advocated. Psychotherapy alone, or in combination with psychoactive drugs and PDE-5 inhibitors, should be prescribed when depression or anxiety is the primary cause.10 When a selective serotonin reuptake inhibitor is implicated as a possible cause, the appropriate addition of bupropion could be considered.11

First-line medical therapy with a PDE-5 inhibitor is recommended because of its efficacy, favourable side-effect profile and ease of use. Men with low serum testosterone levels should additionally receive hormonal replacement therapy, unless there are contraindications.12 Second-line treatment is reserved for men who do not respond to PDE-5 inhibitors. Available options include noninvasive vacuum devices and invasive alprostadil administration (intracavernosal injection or intrarethral suppository).13 Surgical interventions, such as prosthetic penile implantations and revascularisation procedures, are mainly reserved for failed first- and second-line responses.14

Phosphodiesterase-5 inhibitors

Currently, there are four available registered PDE-5 inhibitors, i.e. sildenafil, vardenafil, tadalafil and avanafil. The latter was only approved for registration and prescription in the USA from 2012, and in Europe, Australia and New Zealand from 2013. South African registration was still pending at the time of submission of this article.

PDE-5 inhibitors share a similar mechanism of action and general side-effect profile. However, individual agents have distinct pharmacokinetic and pharmacodynamic properties, which facilitate the tailoring of sexual therapy according to patients’ needs.15 These agents do not cause tumescence in the absence of sexual stimulation.
of sufficient sexual arousal and stimulation, but cause a marked reduction in the post-ejaculatory refractory time. However, a decrease in detumescence is achieved by inhibiting the PDE-5 enzyme, thereby effectively increasing the intracavernosal cGMP responsible for NO-induced smooth muscle relaxation and expansion in blood flow. The result is an increase in the number, strength and duration of erections. PDE-5 inhibitors are contraindicated in men receiving nitrate therapy, and should be used cautiously in combination with alpha-adrenergic blockers because of the risk of life-threatening hypotension. Common side-effects include headaches, flushing, dyspepsia and nasal congestion. In general, PDE-5 inhibitors appears to be safe in men > 65 years of age, although not specifically indicated as such.

**Sildenafil**

Sildenafil is the prototype PDE-5 inhibitor, and remains effective in treating mild ED, or men who do not complain of ED, but display risk factors and low IIEF scores, including ED-associated with Parkinson’s disease.11

**Vardenafil**

Vardenafil is comparable to sildenafil, but more effective in treating ED associated with diabetes or nerve-sparing radical prostatectomy. Orally disintegrating tablet formulations have a more rapid onset of action and higher systemic exposure than conventional film-coated tablets. Vardenafil is not influenced by the presence of food, making it preferable in some patients who require an immediate effect.17

**Tadalafil**

Tadalafil has the same efficacy as that of sildenafil and vardenafil, but a much longer duration of action. Lower doses can be used daily, but it still appears to be less effective than high-dose, on-demand administration.3

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<tr>
<th>Table III: A comparative summary of currently available phosphodiesterase-5 inhibitors</th>
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<td><strong>Strength SEP per 1 dose</strong></td>
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<td>Avigra® (Pharmacia)</td>
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<td>Avanafil**</td>
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*ODT: orally disintegrating tablet, SEP: single exit price

**Single exit price, as listed in the Monthly Index of Medical Specialities. 2015;55(4)

**Not available in South Africa
Conclusion

ED is a common condition and is vastly undertreated. Healthcare providers need to be familiar with all of the currently available treatment options. Association with an increased risk of cardiovascular disease and mortality should make physicians more vigilant and proactive with regard to the management of ED. Serum testosterone levels should be regularly checked in men with features of metabolic syndrome and ED. Stigma around the condition should be eliminated by proper education. Patients should be encouraged to report any symptoms to their healthcare provider, including primary care workers and pharmacists, who are in a position to adequately refer them to a physician. Mass media campaigns and government initiatives may improve cardiovascular mortality by creating public awareness concerning the health risks associated with ED.

References