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REVIEW

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.[1] 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.[2]

Several risk factors have been linked to the pathophysiology of ED. Endothelial damage has been the focus of many recent studies. An evaluation of the cardiovascular status, in addition to the administration of questionnaires to men with ED, might reduce mortality and improve sexual quality of life.[3]

The mechanism of an erection

Penile tumescence and detumescence depend on the complex integration of various neurovascular signalling pathways. This includes autonomic neurotransmitters (noradrenalin 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.[4]

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 noradrenalin on the α1-adrenoreceptors, 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.[5]

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

Table I: Organic causes associated with erectile dysfunction

Vasculogenic causes	Neurogenic causes	Endocrinological causes
• Atherosclerosis • Hypertension • Hyperlipidaemia • Diabetes • Increased age • Sinusoidal fibrosis	• Multiple sclerosis • Epilepsy • Parkinson's disease • Alzheimer's disease • A stroke • Spinal cord injury • Pelvic surgery	• Testosterone deficiency syndrome • Hypogonadism • Hyperprolactinaemia

Table II: Drugs associated with erectile dysfunction

Antihypertensive drugs	Antiarrhythmic agents	Psychotropic drugs	GnRH agonists	Anti-androgen drugs and 5-alpha-reductase inhibitors	Recreational drugs
• Thiazide duiretics • β blockers • Calcium-channel blockers • Methyldopa • Reserpine • Doxazozin	• Digoxin • Amiodarone • Disopyramide	• TCAs • SSRIs • Phenothiazines • Butyrophenones	• Leuprolide • Goserelin	• Cyclophosphamide • Flutamide • Ketoconazole • Spirinolactone • Cimetidine • Cyproterone • Finasteride • Dutasteride	• Marijuana • Opiates • Cocaine • Nicotine • Alcohol

GnRH: gonadotropin-releasing hormone, SSRIs: selective serotonin reuptake inhibitors, TCAs: tricyclic antidepressants

of a combination of both.[6] 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 drugs[7] (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.[3,8] 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 reducing cardiovascular risk factors, which might start off by an undiagnosed patient presenting with ED.

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 buproprion 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 intraurethral 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 Zeanland 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 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.[16] 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]

Avanafil

Avanafil is the newest PDE-5 inhibitor. It exhibits enhanced PDE-5 selectivity compared to the other available PDE-5 inhibitors, thereby displaying a more favourable side-effect profile. It has a rapid onset of action, and is the only PDE-5 inhibitor specifically indicated for ED in men > 65years of age.[18]

Table III provides a comparative summary of currently available PDE-5 inhibitors.

Table III: A comparative summary of currently available phosphodiesterase-5 inhibitors

	Strength	SEP per 1 dose*	Maximum dose frequency	Time to clinical effect	Duration of clinical effect	Satisfaction on maximum dose	Effect with food	Incidence of common side-effects
Sildenafil Videna (Adcock Genesis)								
Avigra® (Pharmacia)	50 mg 100 mg	R42.55 R58.38	100 mg per 24 hours	12-37 minutes	4-5 hours	74% 82%	Must take on empty stomach Fat and alcohol reduces absorption	Headaches (4.1%) Flushing (1.7%) Dyspepsia (0.7%) Nasal congestion (0.5%)
Dynafil® (Pharmadynamics)	50 mg 100 mg	R36.04 R49.43		30-120 minutes	4 hours	N/A		
Viagra® (Pfizer)	25 mg 50 mg 100 mg	R71.67 R91.92 R120.01		12-37 minutes	4-5 hours	62% 74% 82%		
Tadalafil								
Cialis® (Eli Lilly)	20 mg 5 mg	R91.27 R27.38	20 mg per 24 hours	16-30 minutes	36 hours	81% 68%	No effect	Headaches (3.3%) Flushing (1.1%) Dyspepsia (0.7%) Nasal congestion (0.5%)
Ciavor® (Aspen)	20 mg	R82.10		16-30 minutes	36 hours	N/A		
Vardenafil								
Levitra® (Bayer)	5 mg 10 mg 20 mg	R27.54 R55.08 R110.13	20 mg per 24 hours	15-120 minutes	3-5 hours	56% 77% 81%	Must take on empty stomach Fat and alcohol reduces absorption	Headaches (6.3%) Flushing (1.7%) Dyspepsia (1.0%) Nasal congestion (1.0%)
	10 mg ODT	R59.86	10 mg per 24 hours	10-30 minutes	4-6 hours	79%	No effect with food, but should not be taken with liquid	
Avanafil**								
Stendra®/Spedra® (Vivus Inc)	50 mg 100 mg 200 mg	N/A N/A N/A	200 mg per 24 hours	10-20 minutes	6-17 hours	47% 58% 59%	No effect	N/A

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

Testosterone replacement therapy

Administering testosterone in the absence of low testosterone levels may be ineffective in treating ED and increases the risk of hepatic and prostate cancer. Testosterone replacement therapy should only be initiated in men with serum testosterone levels ≤ 12 nmol/l, indicative of testosterone deficiency syndrome.[19] Low levels of testosterone in the presence of raised prolactin, abnormal follicle-stimulating hormone or luteinising hormone, thyroid-stimulating hormone, thyroxine and cortisol should be evaluated by an endocrinologist for specialist care.

There is a strong association between metabolic syndrome and testosterone deficiency syndrome.[4] This necessitates the routine evaluation of testosterone levels in all patients with features of cardiovascular disease and diabetes mellitus, regardless of the presence or absence of ED.[20] Long-acting testosterone undecanoate 1 000 mg [Nebido®, Bayer HealthCare, single exit price (SEP) of R1 636.09 for 1 000 mg] may be injected 4-5 times per year, and shows a significant improvement in libido, morning erections, mood changes and depressive symptoms. Shorter-acting testosterone cypionate 200-400 mg (Depo-Testosterone®, Pfizer, SEP of R337.29 for 1 000 mg) can be injected every 3-4 weeks in patients where cost is an issue, but does not provide the favourable physiological profile associated with the long-acting agent.

Intracavernosal prostaglandin injections

Alprostadil (Caverject®, Pfizer, SEP of R166.17 for 20 µg) is indicated as the second-line treatment when PDE-5 inhibitors fail, or patients experience an unsatisfactory response.[7] Failure is regarded as the inability to attain or maintain an adequate erection on at least four successive occasions while on optimal PDE-5 inhibitor drug dosing. Alprostadil may be preferred in men with spinal cord injuries or post radical prostatectomy.

The intracavernosal injection of alprostadil blocks the inhibitory effect of the sympathetic nervous system, and acts as a direct smooth muscle vasodilator, causing an increase in blood flow to the penis. A predictable, sustainable erection is achieved within 10 minutes, and is independent of sexual stimulation. Compliance is the largest indicator for discontinuation, and patients need adequate counselling before commencing treatment. Side-effects include pain at the site of injection, hypotension and priapism, and penile fibrosis, if not administered correctly.

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.

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