REVIEW ARTICLE

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Erectile Dysfunction

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Abstract

Inability to sustain a penile erection to ensure successful vaginal intercourse during sexual activity constitutes erectile dysfunction. It greatly impacts the psychosocial health of a patient, along with his interpersonal relationships, their outlook, attitude and quality of life. The mechanisms involved in erection may be psychogenic, originating in the limbic system of the central nervous system, or in the peripheral nervous system and lower areas of the spinal cord, that is cause a reflex erection in response to touch of the penile shaft. Earlier, psychogenic causes were thought to be the commonest cause; however, that is not the case as a large percentage of these patients have been found to have an organic cause. There has been a better understanding of the pathophysiology of erectile dysfunction leading to evolution of better and effective therapies, both medical and surgical.

Introduction

Erectile dysfunction (ED) prevalence is more in older men above 40 years of age. The aetiology is multifactorial and may be associated with endocrine or non-endocrine causes. Non-endocrine causes may be vasogenic, involving abnormalities of arterial inflow or venous outflow, neurogenic or iatrogenic. Reduced testosterone levels have been implicated in endocrine causes. The importance of ED is now paramount, as its role is not limited to sexual satisfaction alone; it has now been implicated as a measure of systemic endothelial dysfunction. It's presence in a patient is a sign of advent of cardiovascular diseases and associated with major cardiovascular events, therefore these patients should be thoroughly investigated for organic causes and followed up closely for cardiovascular monitoring. A number of lifestyle diseases are associated with ED, such as hypertension, diabetes mellitus, dyslipidaemia, neurological disorders, morbid obesity, stress, depression, anxiety, chronic kidney disease, chronic liver disease, substance abuse and smoking. Various cultural and socio-economic factors also contribute to the problem. It is imperative to completely comprehend the physiology of erection and the various mechanisms playing a part in this process in order to diagnose accurately and manage the problem. A detailed history, a thorough clinical examination can guide us in determining the line of diagnostics that need to be undertaken to guide management of the individual patient. With time, there have been several breakthroughs in management, including pharmaco-therapeutics, lifestyle modifications, devices, prostheses and surgical interventions. The discovery of the role of nitric oxide (NO) system in signalling smooth muscle relaxation has fuelled an expansive research, focussing on sexual dysfunction in men.

Epidemiology

It has been seen in various studies that the prevalence of ED is higher in the United States, Eastern and Southeast Asian countries as compared to South American and European nations. It also has a strong association with patients presenting with lower urinary tract symptoms in benign prostatic hyperplasia (BPH). Both ED and lower urinary tract symptoms due to BPH are more frequently seen in aging men, possibly due to other common associated risk factors. The Sexual Human Inventory for Males or the 'SHIM' scores are used to assess Erectile dysfunction, which is actually an abridged version of the International Index of Erectile Function (IIEF) aimed to diagnose erectile dysfunction (Table I). The 'SHIM' questionnaire is a 5 point questionnaire with 5 points ascribed to each question; the final score is calculated by adding the scores of all the questions. A score of 21 or less is considered as ED, and can be further categorised into categories of mild, moderate and severe. The data from the European Male Ageing Study show that ED increases with age. The prevalence of severe ED, which is defined as an international index of erectile function score of between 1 to 7, increases at a higher rate than that of moderate ED (with score of 8 to 11) in men above 60 years of age. Another study showed that 22.1% of men less than 40 years of age had low (< 21) SHIM scores. ED is strongly related to age, general health status and emotional function.

Physiology of penile erection

Penile erection is a neurovascular event that is regulated by hormonal and psychological factors. Nitric oxide (NO) is the primary neurotransmitter responsible for penile erection

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Table I: SHIM Questionnaire Assessment.

OVER THE PAST 6 MONTHS:

1. How do you rate your confidence that you could get and keep an erection?		Very Low	Low	Moderate	High	Very High
		1	2	3	4	5
2. When you had erections with sexual stimulation, how often were your erections hard enough for penetration (entering your partner)?	No Sexual Activity	Almost Never or Never	A Few Times (much less than half the time)	Sometimes (about half the time)	Most Times (much more than, half the time)	Almost Always or Always
	0	1	2	3	4	5
3. During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?	Attempt Intercourse	Almost Never or Never	A Few Times (much less than half the time)	Sometimes (about half the time)	Most Times (much more than, half the time)	Almost Always or Always
	0	1	2	3	4	5
4. During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?	Did Not Attempt Intercourse	Extremely Difficult	Very Difficult	Difficult	Slightly Difficult	Not Difficult
	0	1	2	3	4	5
5. When you attempted sexual intercourse, how often was it satisfactory for you?	Did Not Attempt Intercourse	Almost Never or Never	A Few Times (much less than half the time)	Sometimes (about half the time)	Most Times (much more than, half the time)	Almost Always or Always
	0	1	2	3	4	5

Add the numbers corresponding to questions 1-5. **TOTAL:** _____

The Sexual Health Inventory for Men further classifies ED severity with the following breakpoints:

1-7 Severe ED **8-11 Moderate ED** **12-16 Mild to Moderate ED** **17-21 Mild ED**

and is mainly released from the endothelial cells and parasympathetic nerve terminals. Sexual stimulation generates nerve impulses, leading to the release of neurotransmitters from the cavernous nerve terminals and of relaxing factors from the endothelial cells, resulting in the relaxation of cavernosal arterial smooth muscles. This leads to manifold increase in the penile blood flow along with rapid expansion of the sinusoidal system as shown in Fig. 1. It causes compression of the subtunical small veins between tunica albuginea and the trabeculae, thus occluding the local venous return. This sequence of events traps the blood within the corpora cavernosa resulting in raising the penis from a dependent position to an erect position, with an estimated intracavernous pressure of almost 100 mmHg in the phase of full erection. Sexual activity triggers the bulbocavernous reflex forcing the ischiocavernous muscles to compress the base of the blood-filled corpora cavernosa leading to the penis becoming even harder, with an intracavernous pressure escalating to much higher than hundred millimeters of mercury in the phase of rigid erection. The inflow and outflow of blood temporarily stops during this phase.

Penile detumescence occurs with the sympathetic activation of the adrenergic receptors on the surface of cavernous arteries during ejaculation, cessation of the neurotransmitter release and hydrolysis of secondary messengers (cGMP) by phosphodiesterase type-5 in the trabecular smooth muscles. Thus, resulting in the reduction of arterial inflow and causing a collapse of the lacunar spaces

and decompression of the drainage venules of the cavernous bodies, thereby resulting in the relief of erection.

Penile flaccidity is maintained by the semi-contracted state of the intracorporeal smooth muscles that results from the intrinsic myogenic activity, adrenergic neurotransmission and endothelium derived contracting factors like endothelins and PGF-2 alpha. Calcium influx into cells is regulated by norepinephrine signalling and levels of inositol[1,4,5] trisphosphate, which is produced from phosphatidylinositol[4,5] bisphosphate by phospholipase-C in the cells. The increased intracellular calcium ions binds to calmodulin, facilitating the formation of the calmodulin – myosin light chain kinase (MLCK) complex leading to the phosphorylation of MLC, causing smooth muscle contraction and flaccid penis. Norepinephrine signalling also inhibits adenylyl cyclase and modulates the RHO-associated protein kinase (ROCK) pathway, which increases the sensitivity of MLC to ionic calcium, which is negatively regulated by testosterone. Endothelins and prostaglandins from the endothelium also trigger an increase in the intracellular calcium ions promoting smooth muscle contraction. There is minimal blood inflow through the cavernous artery when the smooth muscle is contracted and blood outflows freely through the subtunical venous plexus. Nitric oxide independent, pro-erectile mechanisms of androgens also regulate expression of smooth muscle myosin isoforms and sphingosine[1] phosphate (S1P). In endothelial cells, activation of S1P receptors trigger the phosphoinositide 3 kinase (PI3K) – AKT pathway, which enables the crosstalk between ROCK and the endothelial nitric oxide synthase (eNOS) pathways. These findings reinforce a beneficial role of androgens on many overlapping NO independent pathways (S1P, PI3K-AKT and ROCK) favouring erectile response[1].

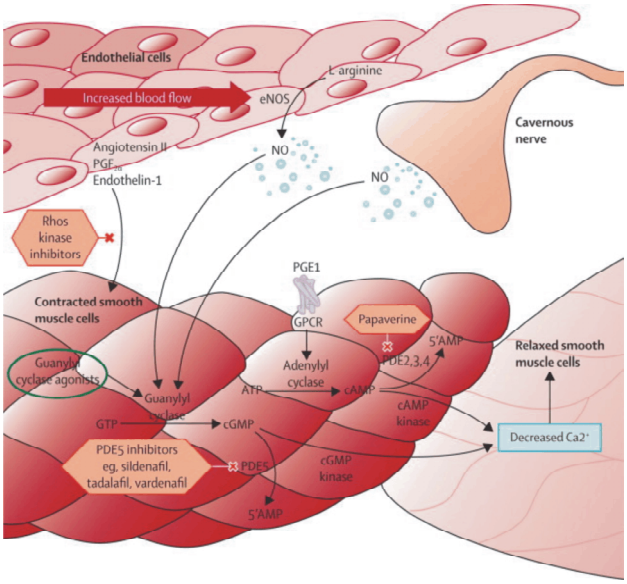

Fig. 1: *Microscopic mechanisms underlying penile smooth muscle relaxction.*

NO is the primary mediator of penile smooth muscle relaxction. After sexual stimuli, NO concentration is significantly increased because of its release from the cholinergic and non-noradrenergic, non-cholinergic fibres and the endothelium. NO works via the GPT/cGMP pathway to decrease intracellular calcium leading to trabecular smooth muscle relaxction. PDE5 enzyme regulates cGMP-dependent penile erection by stimulating hydrolysis of cGMP itself. Another mechanism that can decrease intracellular calcium concentrations is mediated by cAMP. Drugs that enhance erection include PDE5 inhibitors and prostaglandin E1. $PGF_{2\alpha}$ = prostagandin $F_{2\alpha}$. PGE1 = prostaglandin E1. GTP = phospodiesterase. cGMP = cyclic guanosine monophosphate. NO = nitric oxide. eNOS = nitric oxide synthase. PDE5 = phospodiesterase. ATP = adenosine triphosphate. AMP = adenosine monophosphate. GPCR = G-protein-coupled receptor. Reproduced with permission from Headerer and Muller biomedical Art, LLC (2009).

Pathophysiologic mechanisms of erectile dysfunction

ED can be classified into psychogenic, organic (neurogenic, vascular, hormonal, cavernosal or drug-induced) and mixed (both psychogenic and organic). Mixed variant is, usually, the most common cause.

Psychogenic erectile dysfunction

It is also known as adrenaline-mediated or noradrenaline-mediated or sympathetic-mediated ED, as noradrenaline is the primary erectolytic (anti-erectile) neurotransmitter.

Performance anxiety, lack of sexual arousability, strained relationship and overt psychiatric disorders such as depression and schizophrenia are some of the usual causes of psychogenic erectile dysfunction. Performance anxiety associated with sexual dysfunction itself leads to avoidance of sex, low self-esteem and depression.

Factors related to the development of psychogenic erectile dysfunction:-

Predisposing factors

- Traumatic past/childhood experiences.
- Strict upbringing.
- Physical and mental health problems.
- Inadequate sex education.

Precipitating factors

- Acute relationship problems.
- Family or social pressures.
- Major life events; such as pregnancy, childbirth, recent bereavement or loss of a job.

Maintaining factors

- Physical or mental health problems.

- Relationship problems.
- Absence of knowledge of availability of various treatment options.

Religious and cultural differences also influence factors that affect the development of psychogenic erectile dysfunction.

Neurogenic erectile dysfunction

It is caused by a defect in the nerve signalling or conduction to the corpora cavernosa. Such deficits can occur in neurological conditions like – lumbar disc disease, traumatic brain injury, spinal cord injury, multiple sclerosis, Parkinson's disease, radical pelvic surgery (radical prostatectomy, radical cystectomy or abdominoperineal resection) and diabetes mellitus, etc.

Functional and structural alterations owing to the decreased innervation is usually caused by sacral cord lesions (S2 - S4, *nervi erigentes*, being responsible for reflexogenic erections). Reduction of nitric oxide load, that is available to the effectual smooth muscles, results in the functional changes.

Vasculogenic erectile dysfunction

The risk factors associated with penile arterial insufficiency include atherosclerosis, hypertension, diabetes mellitus, dyslipidaemia, cigarette smoking and pelvic irradiation. It's the secondary arterial wall changes in the form of reduced elasticity, and not hypertension per se, that results in ED. Broadly speaking, endothelial dysfunction is the root cause of vasculogenic ED. When ED occurs in men younger than age 60 years, it is strongly associated with an increase in the risk of future cardiac events when compared with men without ED. Blunt pelvic or perineal trauma, (e.g., sustained from bicycling accidents) may result in focal stenosis of the common penile artery causing ED.

Veno-occlusive dysfunction may be caused by the formation of large venous channels draining the corpora cavernosa, degenerative changes to the tunica albuginea (due to Peyronie's disease, old age or diabetes mellitus) or traumatic injury (penile fracture), resulting in ED. Shunts acquired as a result of operative correction of priapism may also cause failure of erection.

Endocrinological erectile dysfunction

Androgen deficiency results in diminished nocturnal erections and libido, although erection in response to visual sexual stimulation is preserved in men with hypogonadism, thus indicating that androgen is not fundamentally necessary for penile erection.

The physiological effects of testosterone are well defined in the regions of the brain that control sexual arousal like – amygdala, medial pre-optic area and hypothalamic nuclei, at the spinal cord level (affecting neuronal firing from the pelvic ganglia) and within the penis (regulating endothelial and smooth muscle cell function). Testosterone is known to regulate the release of nitric oxide from non-cholinergic & non-adrenergic fibres, and the functioning of NO synthase in the endothelial cells. In the smooth muscle, testosterone modulates the activity of phosphodiesterase type 5, the kinase that regulates Ca2+ and K+ levels, and adrenergic receptor sensitivity.

Hyperprolactinaemia from any cause results in both reproductive and sexual dysfunction as prolactin inhibits central dopaminergic activity causing diminished secretion of gonadotropin-releasing hormone, thereby resulting in hypogonadotropic hypogonadism.

Thus, prolactin should be considered for screening, together with testosterone and luteinizing hormone in ED.

Drug-induced erectile dysfunction

Cigarette smoking is known to cause vasoconstriction and penile venous leakage, due to the contractility of the cavernous smooth muscle. Ethanol in small quantities may improve penile erection and also increases libido because of its vasodilatory effect and allaying anxiety, but larger amounts can lead to central sedation, diminished libido and transient ED. Chronic alcohol consumption in significant amount may also result in hypogonadism and polyneuropathy, affecting penile nerve function.

Central neurotransmitters like noradrenergic, serotonergic and dopaminergic pathways are important in the normal sexual functioning and are altered by centrally acting antihypertensive drugs, antipsychotics and antidepressants.

Beta-adrenergic blockers cause ED by potentiating alpha-1 adrenergic activity in the penis. Thiazide diuretics and Digoxin have been implicated in ED, with unknown mechanism. Spironolactone also cause ED as well as gynaecomastia with decreased libido.

H-2 receptor antagonist cimetidine, has been reported to reduce libido and cause ED by acting as an antiandrogen and causing hyperprolactinaemia. Estrogens and some other drugs with anti-androgenic action, such as ketoconazole and cyproterone acetate, are known to cause ED.

5α-reductase inhibitors used in treatment of benign prostatic hyperplasia, anti-androgens and luteinizing hormone-releasing agonists/antagonists used to treat prostate cancer also cause ED[2].

Erectile dysfunction due to aging and systemic/ metabolic diseases

Sexual function declines progressively in healthy aging

men. With increasing age, there is a decline in penile sensitivity to tactile stimulation, decrease in concentration of serum testosterone and an increase in the tone of cavernous muscle. Also, the latent period between sexual stimulation and erection increases, erections are less turgid, ejaculation is less forceful, the ejaculatory volume decreases, and the refractory period between erections lengthens with aging.

More than 50 per cent of men with long standing diabetes mellitus have ED. In addition to affecting the smaller blood vessels, diabetes mellitus adversely affects the cavernous nerve terminals and endothelial function, thereby resulting in the deficiency of neurotransmitters.

Chronic kidney disease is frequently associated with diminished erectile function, impaired libido and infertility. The mechanism is multifactorial, involving low serum testosterone levels, vascular insufficiency, polypharmacy, somatic and autonomic neuropathy, and psychological stress. Individuals with coronary artery disease or cardiac failure usually have ED due to depression, anxiety, polypharmacy and associated penile arterial insufficiency[3].

Diagnosis and screening[4]

The identification of causative factors involved in ED is the mainstay of an accurate diagnosis and successful treatment. ED could be the presenting symptom of a variety of diseases, such as diabetes mellitus, coronary artery disease, dyslipidaemia, hypertension, pituitary tumour and spinal cord pathology.

The main goals of assessment are to establish whether the disorder is actually ED, to identify the cause of the disorder, and to ascertain the risk factors and potentially life-threatening co-morbid conditions associated with ED.

The initial workup includes an assessment of all the aforesaid factors, establishing an accurate medical and sexual history; a detailed general and focused genitourinary examination; and the requisite hormonal and biochemical tests.

A detailed psychosocial history is essential to know any deep-seated psychological problems or relationship conflicts that can be effectively managed only by mental health specialists.

The general physical examination must include the evaluation of the hair distribution and other secondary sexual characters; palpation of peripheral pulses; presence of arterial bruit; blood pressure measurement; examination of local penile deformities like – Peyronie's disease, phimosis, frenulum breve and testing of genital and perineal sensations including bulbocavernous reflex.

Recommended laboratory tests should include urinalysis, complete haemogram, and assessment of serum glucose, thyroid profile, kidney and liver functions, lipid profile and testosterone levels. If the serum testosterone levels are low then serum free testosterone, prolactin, and luteinizing hormone levels should be determined.

Some specific investigations for ED include penile duplex doppler ultrasonography to assess for vascular function and evaluate for Peyronie's disease; nocturnal penile tumescence and rigidity testing using the Rigi Scan device to differentiate between psychogenic and organic causes. Arteriography and dynamic infusion cavernosometry (measuring cavernosal blood pressure) and cavernosography (to assess for venous leak) are done in young individuals only who may be potential candidates for vascular reconstructive surgery after traumatic arterial insufficiency or venous leakage.

Management

In the absence of any specific reversible aetiology, the treatment for ED is mostly empirical and is provided in a step-wise manner. Initial therapy is based on lifestyle modification and psychosexual counselling, followed by first-line therapies, primarily PDE5 inhibitors and vacuum erection devices (VEDs). Intra-urethral suppository (IUS) of prostaglandin E1 (alprostadil) and intracavernosal injection (ICI) of vasoactive substances constitute the second-line therapy. Surgical intervention is only reserved as the last option after conservative options have been exhausted.

Lifestyle modifications

They have a significant role in younger individuals with identifiable reversible risk factors which may contribute to the patient's ED, such as precipitating medications, poor dietary habits, lack of physical exercise, endocrinopathies, stress and anxiety. The major drawback remains the lack of interventional studies assessing the effect of lifestyle changes on ED.

Cessation of cigarette smoking plays a major role in improving ED as there is a direct dose-response relationship between greater number of packs of cigarettes smoked or more years of smoking, with increased erectile difficulties. Mild alcohol consumption might improve erectile function by allaying anxiety; however, chronic alcohol use can have deleterious effects on the liver functions, resulting in low testosterone levels and increased levels of estrogen, both of which contribute to erectile dysfunction. Patients with performance anxiety, interpersonal relationship issues and current life stressors may benefit from confidence restoration with erectogenic medications and/or counselling with a psychologist or a mental health expert specializing in sexual dysfunction.

Adults should do atleast 30 minutes of moderate-intensity aerobic exercises or sporting activities on most days of the week. Weight loss in obese or overweight men, and switching over to a Mediterranean diet, plus exercise, has been shown to improve sexual health.

The European Association of Urology recommends that "lifestyle changes and modification of risk factors must precede or accompany any ED therapy", and classifies the level of evidence for lifestyle modifications as 1b with a grade A recommendation.

Nonsurgical interventions

PDE5-inhibitors[5]

Oral PDE5-inhibitors are the mainstay of the treatment of ED. These drugs facilitate penile erection by inhibiting the phosphodiesterase-5 (PDE5) enzyme, which is responsible for the degradation of cyclic guanosine monophosphate (cGMP) in the cavernous smooth muscles. This inhibition results in the prolonged activity of cGMP resulting in decreased intracellular calcium concentrations and thus maintaining the smooth muscle relaxation, leading to rigid penile erections. Individuals need to be reminded that PDE5-inhibitors still require both physical and mental sexual stimulation, to create arousal and initiate rise in the available nitric oxide levels in order to generate cGMP. They must be administered with adequate time interval before sexual intercourse, to allow for peak drug levels at the appropriate time. Patients should be instructed on optimal conditions for medications to work effectively.

Daily use of PDE5-inhibitors in erectile dysfunction can significantly improve endothelial dysfunction with the potential for a cure. Potential advantages of their daily use include salvage of on-demand PDE5-inhibitor non-responders, apparent disease modification, and development of a more natural sexual function. PDE5-inhibitors lead to improvement of sexual performance and not increase in libido. PDE5-inhibitors lead to shortening of the refractory period and better ejaculatory control in young and potent individuals. Hypogonadal patients who do not respond to treatment with PDE5-inhibitors alone, might show clinical response to a combination of testosterone and PDE5-inhibitors. Physicians should consider trying all available PDE5-inhibitors (Table II) until it is known which one has the best effects on the patient's erections with the least overall side-effects. These drugs should be tried at least four times before deeming them successful or not.

PDE5-inhibitors are contraindicated in nitrate users as they increase the risk of severe hypotension and should be used with caution in patients with serious cardiovascular diseases, uncontrolled hypertension, unstable angina, and in those taking alpha-blockers for blood pressure control. Side-effects related to these drugs are generally mild and well tolerated; like headache, heartburn, facial flushing, nasal congestion and myalgias (especially with tadalafil).

Occurrence of priapism is also a concern but only rarely seen. There have also been concerns regarding PDE5-inhibitors use and auditory changes like hearing loss and tinnitus. Some vision-related conditions are also cause for increased concerns, including retinitis pigmentosa, macular degeneration and non-arteritic anterior ischaemic optic neuropathy. They are contraindicated in patients with vision

Table II: Characteristic properties of PDE5-inhibitors.

	Sildenafil	Vardenafil	Tadalafil	Udenafil	Mirodenafil
Dosage	25, 50, and 100 mg. Usually start with 50 mg. Maximum dose 100 mg daily	2·5, 5, 10, and 20 mg. Usually start with 10 mg. Maximum dose 20 mg daily	2·5, 5, 10, and 20 mg. Usually start with 10 mg. Maximum dose 20 mg daily	100 mg. Maximum dose 200 mg daily	50 or 100 mg. Maximum dose 100 mg daily
Onset	30–60 min	30 min	45 min	30–60 min	30–60 min
Duration	4–8 h	4–8 h	Up to 36 h	12 h	6–12 h
Efficacy	>65%	>65%	>65%	>65%	>65%
Side-effects	Headache, flushing, and dyspepsia	As for sildenafil	Flushing, back pain, and general myalgia	Facial flushing, nasal congestion, ocular hyperemia, and headache	Facial flushing, headache, nausea, and eye redness
Contraindications	Nitrate-containing compounds, recent serious cardiovascular events, non-arteritic ischaemic optic neuropathy, and α blockers	As for sildenafil, but also type 1 or 3 antiarrythmics and congenital prolonged QT syndrome	As for sildenafil	As for sildenafil	As for sildenafil
Food and alcohol interaction	Interacts with food, administer while fasting. No alcohol interaction	Interacts with food, administer while fasting. No alcohol interaction	No food or alcohol interaction	No food or alcohol interaction	No alcohol interaction. Data on food interaction not available

loss due to non-arteritic anterior ischaemic optic neuropathy.

PDE5-Inhibitors are a good first-line therapy, but upto 35% of the patients with ED fail to respond adequately. The common causes of treatment failure include diabetes mellitus and severe neurological and vascular diseases. Although there is no consensus on how to define the failure to PDE5-inhibitors therapy; the inability to attain or maintain adequate penile erection during sexual intercourse on at least four consecutive occasions, despite optimum drug dosing, is an acceptable definition. Management of PDE5-inhibitor treatment failure is dependent on the underlying cause and includes patient counselling, switching over to another PDE5-inhibitor, intracavernosal injection therapy, intraurethral drug administration, combination therapy, or referral to the expert for further evaluation. Patients not responding to any of the medical treatment options may be candidates for penile implant surgery.

Recent findings that ED is a strong predictor of CAD and that the development of symptomatic ED might precede the occurrence of a cardiovascular event by 2 - 3 years have led to stricter measures during the assessment of patients who present with poor erections. A strong recommendation is that all men with ED who are free from any cardiac symptoms should be considered to be cardiac (or vascular) patients, until proven otherwise. After a full medical assessment, the patient's cardiovascular risk should be assessed with stratification to high, medium, or low risk levels as per the Princeton III consensus recommendations (Table III)[6].

Vacuum erection devices

Vacuum erection devices (VED) operate by applying continuous negative pressure to the shaft of the penis drawing blood inside lacunar spaces inside the corpora cavernosa causing tumescence. In order to prevent the backflow of blood, a constriction band is placed at the base of the penis in these devices. About 70% of diabetic men who do not respond to PDE5-inhibitors, are able to have sexual intercourse when using a VED to achieve tumescence. On the other hand, discontinuation rates of nearly 35% are reported owing to bruising on the penis, pivoting at the base of the penis, coldness or numbness of the penis, pain related to the constriction band and/or decreased ability to achieve orgasm. Successful usage of VED requires obtaining a tight seal of the cylinder against the body of the penis using a lubricant and trimming the pubic hair.

Intraurethral Suppository

Table III: Princeton III consensus recommendations[6].

Profile	Description	Sexual activity and PDE5 inhibitor use
Low	• Fewer than three risk factors for coronary artery disease* (excluding sex) • Controlled hypertension • Class I or II stable angina‡ • Successful coronary revascularization • History of uncomplicated myocardial infarction • Mild valvular disease, congestive heart failure without left ventricular dysfunction and/or New York Heart Association class I heart failure	• Cleared to resume sexual activity • Cleared to take PDE5 inhibitors
Intermediate	• At least three risk factors for coronary artery disease* (excluding sex) • Class I or II stable angina‡ • Recent myocardial infarction (within 2–6 weeks) • Left ventricular dysfunction and/or New York Heart Association class II congestive heart failure • Noncardiac sequela from atherosclerotic disease (stroke and/or peripheral vascular disease)	• Cardiac evaluation necessary prior to resuming sexual activity • No contraindication to PDE5 inhibitor use
High	• Unstable or refractory angina • Uncontrolled hypertension • New York Heart Association class III–IV congestive heart failure • Recent myocardial infarction (within 2 weeks) • High-risk arrhythmias • Severe cardiomyopathy • Moderate to severe vascular disease	Sexual activity delayed until cardiac condition stabilized

**Major cardiovascular risk factors include age, male gender, hypertension, type 1 and type 2 diabetes mellitus, smoking, dyslipidemia, sedentary lifestyle and family history of premature cardiovascular disease.*

‡Defined by the Canadian Cardiovascular Society.

The use of intraurethral suppository (IUS) involves the placement of a prostaglandin E1-loaded pellet within the urethra before sexual intercourse. The patient should then massage that area of the penis to help disperse the medication. The absorption of the drug through the urethra into the corpora cavernosa increases the intracellular levels of cyclic AMP (cAMP), leading to decreased intracellular Ca2+ levels, increased smooth muscle relaxation and tumescence. It is a second-line therapy to PDE5-inhibitors, showing efficacy in approximately 55% patients with primarily organic ED. The medication may cause localized pain and burning. Some adverse effects include penile pain, urethral pain, dizziness and priapism. Repeated use with wrong technique may lead to urethral stricture.

Intracavernosal injection

It involves injecting vasoactive substances directly into the corpora cavernosa via a 28G needle. The vasoactive agents include prostaglandin E1, papaverine and phentolamine (and also, atropine), which work alone or in conjunction to elicit penile erection. Phentolamine is an alpha1 adrenergic receptor inhibitor that prevents vasoconstriction to maintain tumescence. Papaverine is a nonspecific phosphodiesterase-inhibitor causing increased levels of cAMP and cGMP. Prostaglandin E1 is approved as a single-agent intracavernosal injection (ICI) for erectile dysfunction, increasing cAMP levels.

Priapism is the major concern with ICI. If it occurs, then the patient needs urgent medical attention, requiring local blood aspiration or surgical shunt formation or ICI of phenylephrine to induce cavernosal vasoconstriction. Dropout rates are high because of fear of penile injections, local pain and occasional bruising[7].

Surgical Interventions

Penile prostheses/implants

Surgical interventions are suitable options in patients who are refractory to medical therapy, have contraindications or adverse effects to first-line drug therapy; in patients having troublesome priapism or local infections; have penile fibrosis due to Peyronie's disease; and in patients with vascular or anatomical penile defects or in cases of genital or pelvic trauma. The current surgical options include insertion of a penile prosthesis and vascular reconstructive surgery. The corporal tissue is irreversibly altered once the penile prosthesis surgery is done and smooth muscle relaxation is impossible thereafter.

Penile implants consist of malleable or inflatable devices as shown in Fig. 2. The malleable penile prosthesis involves two semi-rigid rods that are placed in the corpora cavernosa. The implant does change in size when it is bent upwards before intercourse (Fig.2a). Two-piece inflatable penile prostheses (IPPs) consist of two cylinders with a scrotal pump, enabling transfer of fluid to the cylinder chambers whenever an erection is desired (Fig. 2b). Three-piece inflatable penile prostheses are considered the gold standard. They involve the placement of two inflatable cylinders (in the corpora cavernosa), a pump in the scrotum and a fluid reservoir in the lower abdomen alongside the bladder (Fig. 2c). The pressure applied to the pump causes a transfer of fluid from the reservoir to the cylinders, leading to penile rigidity. The pump has a release valve or button to transfer the fluid back from the cylinders to the reservoir at the end of intercourse. Maximum girth expansion and penile rigidity occurs with these devices, as and when an erection is desired, alongside maximum flaccidity on deflating.

Penile revascularisation surgery

Penile revascularisation surgery was developed to anastomose the inferior epigastric artery to either the dorsal artery or deep dorsal vein (arterialisation), with or without venous ligation to improve penile vascular inflow while reducing venous outflow, on similar principles of coronary artery bypass grafting in coronary artery disease. It is recommended for younger men (< 55 years) who are non-diabetic, non-smokers and have a documented isolated

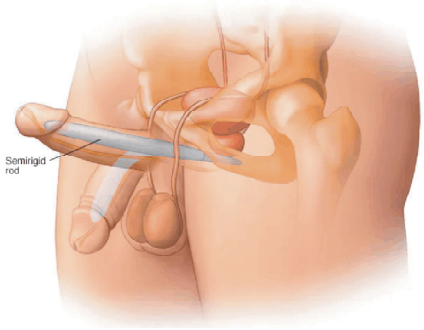

Fig. 2a

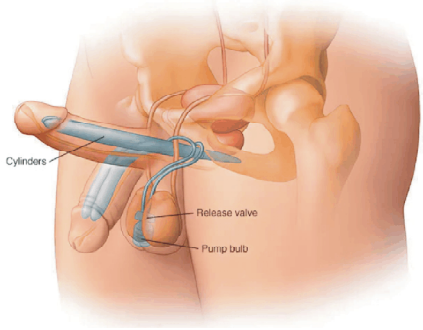

Fig. 2b

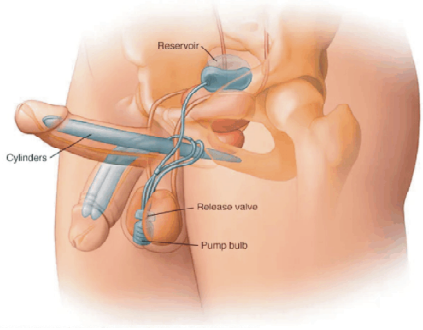

Fig. 2c

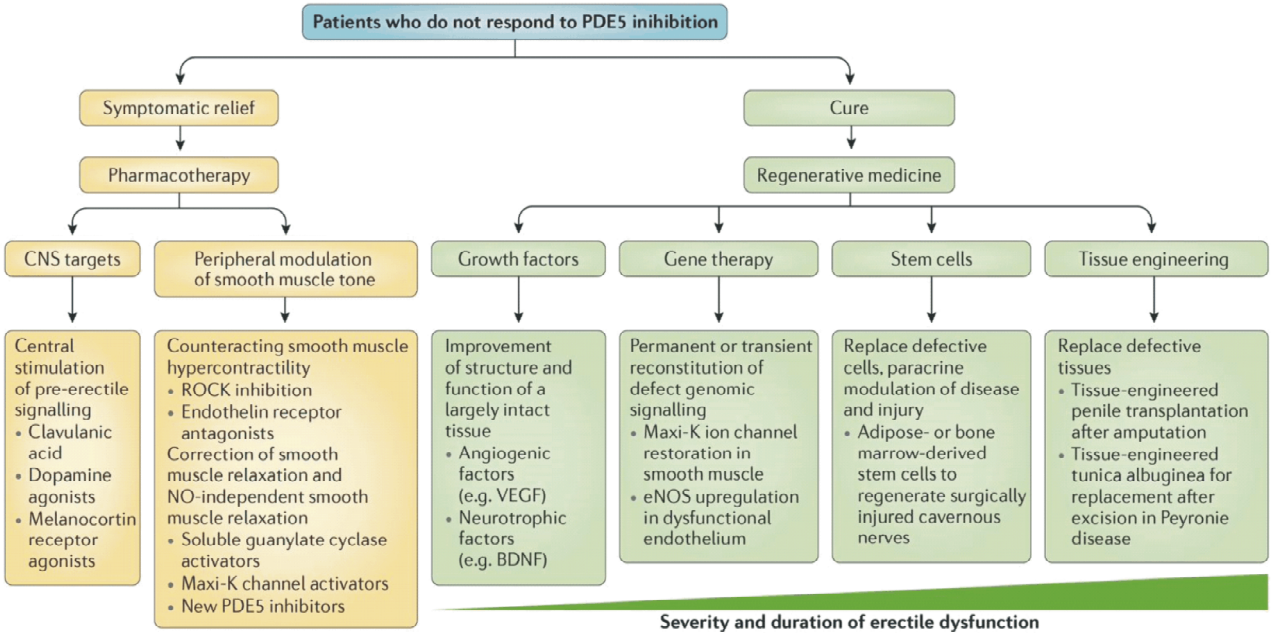

Fig. 3: *Summary of potential future treatment options.*

stenotic segment of the internal pudendal artery without concomitant venous leak. Potential complications of penile revascularisation procedures include glans hyperaemia, shunt thrombosis and inguinal hernias[8].

Potential future treatment options for erectile dysfunction

Only temporary symptomatic relief is provided by the current therapeutic options as they do not halt or slow down the primary disease process. Bioavailability of nitric oxide (NO) is essential for phosphodiesterase type 5 (PDE5) inhibitors, which are the most preferred therapy, to exhibit any effect. Hence, prospective pharmacological interventions will need efficacy in individuals not responding to PDE5 inhibition, particularly in men with neurogenic ED. The site of action may be either the central or the peripheral nervous system controlling the balance between the vasorelaxation & vasoconstriction. The ROCK (RHO-associated protein kinase) pathway plays an important part in maintaining the flaccid state of the penis. ROCK phosphorylates and inactivates myosin light chain phosphatase. This allows the myosin light chain to stay phosphorylated and bind to the smooth muscle actin. ROCK inhibition, Maxi-K channel activators and soluble guanylate cyclise activators provide alternative mechanisms that are independent to nitric oxide mediated smooth muscle relaxation. Central stimulation signalling with clavulanic acid, dopamine agonists and melanocortin receptor agonists are under investigation for utility in therapy for ED.

Stem cell therapy or regenerative medicine might provide definitive symptomatic relief by reversing or halting the disease progression in ED. Regenerative medicine can probably alter the disease course and in many instances possibly regenerate damaged cells, tissues or whole organ systems. Various tools such as gene transfer, stem cells, angiogenic and neurotrophic growth factors and tissue engineering can be used to achieve this goal. Fig. 3 provides a summary of all future options.

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