

ERECTILE DYSFUNCTION AND ITS MANAGEMENT: AN UPDATE

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Summary

Erectile dysfunction (ED) defined as “the inability to achieve or maintain an erection sufficient for sexual intercourse”—is one of the most common sexual dysfunctions in men. Some men assume that erectile failure is a natural part of the aging process and tolerate it, for others it is devastating. Withdrawal from sexual intimacy because of fear of failure can damage relationships and have a profound effect on overall wellbeing for the couple. Erectile dysfunction often accompanies chronic illnesses, such as diabetes mellitus, heart disease, hypertension, and a variety of neurological diseases. Therefore, physicians need to identify any underlying co-existing organic diseases in their patients presenting with ED. Whenever possible, patients are encouraged to attend their consultation sessions with their partners because ED is a condition affecting ‘the couple’ and not just the man. Psychogenic aspects of ED should also be explored during the consultation. The first-line treatment of ED is oral phosphodiesterase-5 inhibitors. For those who do not respond to oral therapy, there is no defined ‘step-ladder’ escalation in alternative therapy. It is up to the physician to discuss the options with the patient or couple and reach a decision based on their preference.

Key words

Erectile dysfunction; phosphodiesterase 5 inhibitors; alprostadil

1. Introduction

Erectile dysfunction (ED) is a significant but neglected health problem in Bangladesh. Erectile dysfunction not only destroy the sexual life of an individual, but it is detrimental to a man’s self-esteem, quality of life, and interpersonal relationships, and is increasingly considered an issue for the man and his female sexual partner [1].

ED is independently associated with cardiovascular (CV) events (angina, myocardial infarction, and stroke [2]. The economic burden of ED is not just limited to the cost of diagnosis and treatment. Other more subtle impacts on society that are difficult to quantify are lost time at work, decreased productivity and many more [3].

For more than last three decades effective oral drugs are available worldwide for treatment of ED, but unfortunately these drugs have been approved for use in Bangladesh very late. The aim of this review is to highlight the recent development in the management of ED.

2. Definition

According to the 1993 National Institute of Health Consensus Development panel on impotence in the United States of America, the term impotence was supplanted by erectile dysfunction (ED) [4]. The Second International Consultation on Sexual Dysfunction (ICSD2) defined ED as a ‘consistent or recurrent inability of a man to attain and/or maintain penile erection sufficient for sexual activity’ [5].

The condition must be present for a minimum of 3 months to establish the diagnosis. The exception to this is when ED is preceded by trauma or pelvic surgery. ED is part of a spectrum of male sexual dysfunction that encompasses sexual interest/desire dysfunction, early ejaculation, delayed ejaculation, anejaculation and orgasmic dysfunction.

3. Classification

Contemporary ED classification incorporates the aetiology into the classification system. An example of this was described by Lizza and Rosen (Table I) [6].

The initial hypothesis that ED had a purely psychogenic causality changed with our improved understanding of the physiology of penile erection. Views that organic disease accounted for most cases of ED (table II) became dominant in the 1980s. However, we currently recognise that the reality is probably somewhere in between, with both factors varying in importance in each individual patient.

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Table I : Classification of erectile dysfunction**Organic**

1. Vasculogenic
 - a) Arteriogenic
 - b) Cavernosal
 - c) Mixed
2. Endocrinological
3. Neurogenic
4. Anatomical

Psychogenic

1. Generalised type
 - a) Generalised unresponsiveness
 - i) Primary lack of sexual arousability
 - ii) Aging related decline in sexual arousability
 - b) Generalised inhibition
 - c) Chronic disorder of sexual intimacy
2. Situational type
 - a) Partner related
 - i) Lack of arousability in specific relationship
 - ii) Lack of arousability due to sexual object preference
 - iii) High central inhibition due partner conflict or treatment
 - b) Performance related
 - i) Associated with other sexual dysfunction/s
 - ii) Situation performance anxiety
 - c) Psychological distress or adjustment related
 - i) Associated with negative mood state or life stress

Table II : Diseases associated with erectile dysfunction

Cardiovascular disease
Atherosclerosis
Coronary artery disease
Hypertension
Neurological disease
Cerebrovascular disease
Epilepsy
Spinal injury
Dementias
Endocrine disease
Hyperprolactinaemia
Thyroid disease
Hypogonadism
Systemic disease
Diabetes mellitus
Chronic renal failure
Haemochromatosis
Liver cirrhosis
Arthritis
Malignancy
Other
Smoking
Alcohol
Surgery
Drugs
Depression
Penile abnormalities, eg. Peyronie's disease

4. Epidemiology

The worldwide prevalence of ED is very high and is expected to increase substantially in the aging populations of various regions over the next 25 years. In 1995, it was estimated that 152 million men worldwide had ED, and that by the year 2025, the number of men with ED would be about 322 million, an increase of nearly 170 million men. The greatest increases will be in the developing world, such as Africa, Asia and South America [7]. Establishing the prevalence of ED in these regions is important for understanding the need for services, which in turn depends on the functional expectations of men as they age.

The Massachusetts male ageing study was one of the first population-based studies of ED and demonstrated a 52% prevalence across all severities (1290 men aged 40–70 years) [8]. A more recent European study found a 30% prevalence of ED across eight European centres (3369 men aged 40–79 years) [9]. Studies on ED prevalence from countries across various regions of Asia, the Middle East and Africa where socio-cultural and religious characteristics are similar, have been documented [10-13]. For example, in three studies in Nigeria, prevalence rates of 57.4%, 50.7% and 46.9%, respectively, have been reported [13-15]. Different definitions of ED, age distributions and risk factor profiles, as well as methodological differences, may explain much of the variance in reported prevalence rates [16]. Due to its sensitive nature ED may be under-reported. This is an absolute truth in Bangladesh where no data is available on the prevalence of ED.

5. Risk factors

Comorbidities such as heart disease, diabetes, dyslipidemia, hypertension, and depression have been described as primary risk factors for the development of ED [17-21]. Additionally, a number of modifiable lifestyle factors, including physical activity, smoking, alcohol consumption, diabetes control, and obesity, have been associated with ED [18-20, 22-27]. Certain medications may cause or contribute to erectile dysfunction in as many as 25% of men who present for evaluation table III [28].

Table III : Drugs associated with erectile dysfunction

Drug class	Examples
Diuretics	Thiazides, spironolactone
Antihypertensive drugs	Calcium-channel blockers, beta-blockers, methyldopa, clonidine, reserpine, guanethidine
Cardiac or cholesterol drugs	Digoxin, gemfibrozil, clofibrate
Antidepressants	Selective serotonin-reuptake inhibitors, tricyclic antidepressants, lithium, monoamine oxidase inhibitors
Tranquilizers	Butyrophenones, phenothiazines
H ₂ antagonists	Ranitidine, cimetidine
Hormones	Progesterone, estrogens, corticosteroids, luteinizing hormone-releasing hormone agonists, 5 α -reductase inhibitors, cyproterone acetate
Cytotoxic agents	Methotrexate
Immunomodulators	Interferon- α
Anticholinergic agents	Disopyramide, anticonvulsants
Recreational drugs	Alcohol, Cocaine

6. Relevant anatomy and physiology penile erection

6.1 Corpora

The penis contains three corpora the ventrally placed corpus spongiosum and two dorsal corpora cavernosa (CC) each surrounded by tunica albuginea. Collectively, the corpora are enclosed in Buck's fascia which contains the deep dorsal vein and a number of sensory nerves. Arterial inflow is provided by the internal pudendal arteries via the cavernosal arteries. The cavernosal arteries branch to form helicine arteries which open directly into the cavernosal spaces which contain a network of communicating venous sinuses. Blood drains from these cavernosal spaces into venules which coalesce to form larger veins which ultimately drain to the deep dorsal, cavernosal or crural veins [29].

6.2 Neural pathways

The neural pathways involved in penile erection are complex and effective co-ordination between them is necessary for adequate tumescence. The blood vessels and trabecular smooth muscle receive motor sympathetic and parasympathetic innervations via the thoracolumbar and lumbosacral regions of the peripheral nervous system, respectively [30].

The perineal striated muscles receive a somatic innervation via the lumbosacral somatics. The sympathetic supply reaches the penis via the cavernous nerves, having synapsed with preganglionic sympathetics from either the pelvic, cavernous, pudendal or hypogastric nerves. The parasympathetic supply arises predominately from the sacral spinal cord segments, emerging in the anterior roots as the nervi erigentes through which they reach the pelvic plexus. This plexus is vital in the regulation of penile erection. These complex neural pathways are mediated via a combination of adrenergic, cholinergic and non-adrenergic, non-cholinergic nerves.

6.3 Physiology of the penile erection

Penile erection is determined by a delicate balance between contracting and relaxing factors at the level of the CC. In its flaccid state, the smooth muscle within both the penile arteries and the CC are contracted arterial inflow is limited and venous outflow is unobstructed. In response to the central processing of tactile, visual and olfactory stimuli, smooth muscle relaxation occurs resulting in a rapid arterial inflow to the lacunar spaces of the CC [31]. With progressive inflow, the trabecular walls and tunica albuginea expand and elongate, causing compression of the venules which pierce the tunica. This process of increasing inflow combined with a simultaneous venous outflow obstruction results in tumescence. Detumescence results from a reversal of this process with smooth muscle contraction in the CC resulting in a decrease in arterial inflow together with restoration of venous outflow.

Penile erection is under both central and local neuromediation [30]. A large number of substances have been demonstrated experimentally to act at the supraspinal level, these include dopamine, oxytocin, adrenocorticotrophic hormone, nitric oxide, serotonin, gamma-aminobutyric acid and cannabinoids. Locally, a number of vasoactive mediators are released by the endothelial and smooth muscle cells of the CC. The final common pathway of these substances is to modulate intracellular calcium (Ca²⁺) levels and/or alter the calcium sensitivity of proteins involved in smooth muscle contraction [30].

7. Pathophysiology of erectile dysfunction

Organic ED underlined by multifaceted, complex mechanisms, involving nerve, vascular, and hormonal signaling at its core [30]. Normal erectile function requires the coordination of psychological, hormonal, neurological, vascular, and cavernosal factors. Alteration in any one of these factors is sufficient to cause erectile dysfunction. Not uncommonly, a combination of factors is involved [32,33].

Molecular mechanism of penile smooth muscle relaxation [34]

Outflow from the parasympathetic nervous system leads to relaxation of the cavernous sinusoids in two ways, both of which increase the concentration of nitric oxide (NO) in smooth-muscle cells. First, nitric oxide is the neurotransmitter in nonadrenergic, noncholinergic (NANC) fibers, second, stimulation of endothelial nitric oxide synthase (eNOS) through cholinergic output causes increased production of nitric oxide. The nitric oxide produced in the endothelium then diffuses into the smooth-muscle cells. With the increase in nitric oxide content, the smooth-muscle cell decreases its intracellular calcium concentration through a pathway mediated by cyclic guanosine monophosphate (cGMP), which leads to relaxation. A separate mechanism that decreases the intracellular calcium level is mediated by cyclic adenosine monophosphate (cAMP). With increased cavernosal blood flow, as well as increased levels of vascular endothelial growth factor (VEGF), the endothelial release of nitric oxide is further sustained through the phosphatidylinositol 3 (PI3) kinase pathway. Active treatments include drugs that affect the cGMP pathway (phosphodiesterase [PDE] type 5 inhibitors and guanylyl cyclase agonists), the cAMP pathway (alprostadil), or both pathways (papaverine), along with neural-tone mediators (phentolamine and Rho kinase inhibitors). Parasympathetic outflow is impaired in patients with diabetes, depression, and central and peripheral neuropathic diseases that inhibit neural output; outflow is also impaired by destruction of the nonadrenergic, noncholinergic nerves themselves. Exposure to tobacco smoke and lower urinary tract symptoms of benign prostatic hyperplasia are associated with an increase in outflow from the sympathetic nervous system that inhibits relaxation forces. Lower urinary tract symptoms may also impair the nitric oxide content in the penis, prostate, and bladder and account for the association between such symptoms and erectile dysfunction. Diabetes, the metabolic syndrome, hyperlipidemias, atherosclerosis, and smoking also directly reduce the activity of nitric oxide synthase and induce apoptosis of endothelial and smoothmuscle cells.

8. Evaluation

A goal directed approach has been successfully used for the management of patients with erectile dysfunction [35]. The patient's medical and sexual history should be taken, and details of any concomitant medication, tobacco and alcohol consumption, and the presence of risk factors for erectile dysfunction (for example, vascular or surgical)

should be noted. Preservation of nocturnal and early morning erections generally means that there is no organic basis for erectile dysfunction [36]. The differences between organic and psychogenic ED are shown in table IV [3].

The quality of erections during sleep can be assessed with portable home devices (such as Rigiscan) that measure changes in penile girth and rigidity, or in a sleep laboratory. Measurement of blood pressure, palpation of peripheral pulses, and a neurological examination should be undertaken, including the bulbocavernous reflex and anal sphincter tone. The secondary sexual characteristics should be examined for signs of hypogonadism and any local abnormality in the external genitalia should be noted. The penis should be palpated for Peyronie's plaques and the testes examined for size and consistency. Further investigations are likely to be guided by the clinical findings, but should include measurement of free testosterone, prolactin, TSH, LH and FSH concentrations. The basic work-up (minimal diagnostic evaluation) outlined in Fig: 1 must be performed in every patient with ED [37-38].

Vascular evaluation of the penis

A complete diagnostic investigation, and therefore a full vascular assessment, may not be important for most patients, since only a few will be treated surgically [39]. The best minimally invasive method currently available for studying arterial blood supply to the penis is colour duplex Doppler ultrasound, which assesses the integrity of the arterial supply to the penis and provides some useful information on the veno-occlusive mechanism [40]. More precise assessment of this mechanism requires specialised invasive tests eg. cavernosometry and cavernosography which are performed if surgery is contemplated [39].

9. Treatment

Within the past the two decades, major advances have been made in the treatment of ED. Successful treatment naturally requires a patient who is willing to admit to himself and his partner that a problem exists. The patient also needs to be willing to be counseled, have the treatment options explained and then make an informed decision about therapy [37].

Treatment strategy can be categorized as

1. Changing habit and lifestyle
2. Psychosexual therapy
3. Pharmacological
4. Vacuum constriction device
5. Surgical treatment

9.1 Changing habit and lifestyle

Encouraging regular exercise, healthy diet, cessation of smoking and moderating alcohol consumption can all be helpful. With regard to exercise, long distance cycling is a risk factor and an alternative form of exercise should be considered if vascular compromise is suspected, although changing the bicycle seat may also help [41].

9.2 Psychosexual therapy

Psychosexual therapy includes psychotherapy and sex therapy as described by Masters and Johnson [42]. However, modern sexologists argue that psychoanalytic therapy is rarely indicated and a symptom-orientated treatment is preferred by many psychologists. The main elements of symptom orientated treatment are explanation of the cause, reassurance, encouragement, and advice. Symptom orientated counseling has replaced the individual psychoanalytic therapy as the more effective treatment choice [43].

Table IV : Characteristics of organic and psychogenic erectile dysfunction

Characteristic	Organic	Psychogenic
Age	Older	Younger
Onset	Gradual (except in trauma or surgery)	Acute
Circumstances	Global	Situational
Symptom	Consistent or progressive	Intermittent
Morning erection	Poor	Rigid
Desire	Normal	Decreased
Organic risks	Present	Absent, variable
Partner problem	Secondary	At onset
Anxiety and fear	Secondary	Primary

9.3 Pharmacological therapy

i) Phosphodiesterase 5 inhibitors (PDE5-Is)

The PDE5-Is is currently used as a first line therapy for the treatment of ED. It is a selective inhibitor of PDE-5, which enhances the effect of nitric oxide to increase smooth muscle relaxation and inflow of blood to the corpus cavernosum. They are not initiators of erection and require sexual stimulation for an erection to occur. Efficacy is defined as rigidity sufficient for vaginal penetration.

Three potent selective PDE5-Is have been approved by the Federal Drug Administration (FDA) and European Medicines Agency (EMA) for the treatment of ED [43].

Sildenafil launched in 1998, was the first PDE5-I available. It is effective 30–60 min from administration. A heavy fatty meal may reduce or prolong absorption. It is administered in 25mg, 50mg and 100mg doses. The recommended starting dose is 50 mg, which is adapted according to patient response and side-effects. Efficacy may last for up to 12 hours. In premarketing studies, after 24 wk of treatment in a dose-response study, improved erections were reported by 56%, 77%, and 84% of men taking 25mg, 50mg and 100mg of sildenafil, respectively, compared with 25% of men taking placebo. The efficacy of sildenafil in almost every subgroup of patients with ED has been well established in pre and postmarketing studies.

Tadalafil was licensed for ED in 2003. It is effective from 30 min after administration, but its peak efficacy occurs after about 2 hours. Efficacy is maintained for up to 36 hours. Its efficacy is not affected by food. It is administered in 10mg and 20mg doses. The recommended starting dose is 10mg, which is adapted according to patient response and side effects. In premarketing dose response studies, improved erections were reported after 12 wk of treatment by 67% and 81% of men taking 10 mg and 20 mg of tadalafil, respectively, compared with 35% of men taking placebo. The results were confirmed in postmarketing studies. Tadalafil also improved erections in difficult to treat subgroups.

Vardenafil was licensed for ED in 2003. It is effective 30 min from administration. A fatty meal (>57% in fat) reduces its effect. It is administered in 5mg, 10mg and 20mg doses. The recommended starting dose is 10 mg, which is adapted according to the response and side effects. In vitro, it is 10 fold more potent than sildenafil; however, this does not necessarily mean greater clinical efficacy. In premarketing dose response studies, improved erections after 12 wk of treatment were reported by 66%, 76%, and 80% of men taking 5 mg, 10 mg and 20 mg of vardenafil, respectively, compared with 30% of men taking placebo. Efficacy was confirmed in postmarketing studies. Vardenafil also improved erections in difficult to treat subgroups.

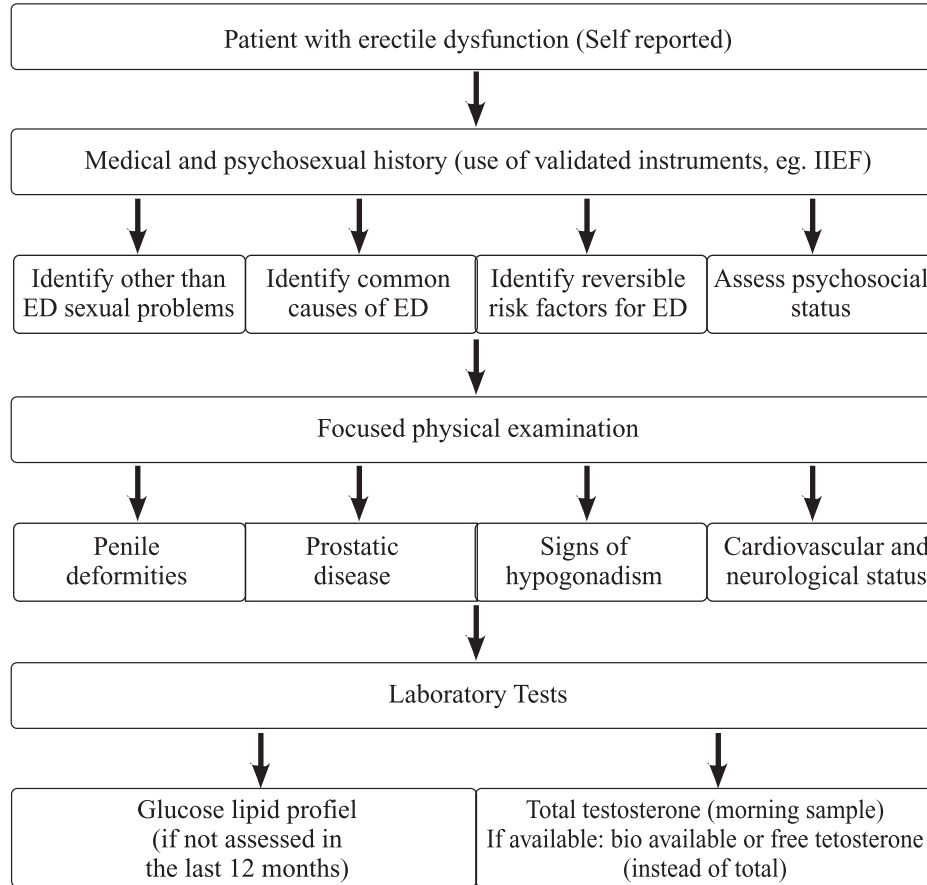


Fig 1: Basic diagnostic work-up in patients with erectile dysfunction
 ED = Erectile dysfunction; IIEF = International Index of Erectile Function

Choice of or preference for different phosphodiesterase type 5 inhibitors

The choice of a PDE5-I depends on the frequency of intercourse (occasional use or regular therapy, three to four times weekly) and the patient’s personal experience with the agent. Consideration should be given to which drug better fits the patient’s sexual habit with his partner to optimise response. Patients need to know whether a drug is short or long acting, its possible disadvantages, and how to use it. In a study on patients’ PDE5 inhibitor preference by Eardley and colleagues’ [44] it was reported that despite both sildenafil and tadalafil being effective more patients preferred tadalafil.

On demand or chronic use of phosphodiesterase type 5 inhibitors

Although PDE5-Is were initially introduced as on demand treatment, in 2008, tadalafil was also approved for continuous, everyday use in 2.5mg and 5mg doses. Two studies assessing daily use of 5mg and 10mg tadalafil for 12 wk and daily use of 2.5mg and 5mg tadalafil for 24 wk showed that daily dosing was well tolerated and significantly improved erectile function [45-46]. Similar results have been found in diabetic patients [47]. These studies, however, lacked an on demand treatment arm. Daily tadalafil provides an alternative to on demand dosing for couples who prefer spontaneous rather than scheduled sexual activity or who have frequent sexual activity.

Daily dosing overcomes the requirement for dosing and sexual activity to be temporally linked. Other studies have shown that chronic but not on demand tadalafil treatment improved endothelial function, with sustained effects after its discontinuation. This finding was confirmed in another study of chronic sildenafil use in men with type 2 diabetes [48]. In contrast, a randomised clinical study found that once daily dosing of vardenafil at 10 mg/d did not offer any sustainable effect after cessation of treatment compared with on demand vardenafil in patients with mild to moderate ED [49].

Adverse events

Common adverse events include headache (10–16%), flushing (5–12%), dyspepsia (4–12%), nasal congestion (1–10%), and dizziness (2–3%) [50]. Sildenafil and vardenafil have been associated with visual abnormalities in <2% of patients, while tadalafil has been associated with back pain/myalgia in 6% of patients. Adverse events are generally mild in nature and self-limited by continuous use, and the dropout rate due to adverse events is similar to that seen with placebo.

Cardiovascular safety

Clinical trials and postmarketing data of all PDE5-Is have demonstrated no increase in myocardial infarction rates [48]. No PDE5-I has adversely affected total exercise time or time to ischemia during exercise testing in men with stable angina. In fact, they may improve exercise tests.

Nitrates are totally contraindicated with all PDE5-Is due to unpredictable hypotension. The duration of interaction between organic nitrates and PDE5-Is varies according to the PDE5-I and nitrate. If a patient develops angina while using a PDE5-I, other antiangina agents may be used instead of nitroglycerine or until the appropriate time has passed (24 hours for sildenafil or vardenafil and 48 h for tadalafil) [48]. Other contraindications are severe hepatic impairment, hypotension, recent history of stroke or MI, hereditary degenerative retinal disorders, hypersensitivity to the active substance or excipients, and other conditions where sexual activity is inadvisable [50]. Special precautions should be taken to use PDE5-Is in the following conditions: anatomical deformation of the penis (angulation, cavernosal fibrosis or Peyronie's disease) predisposition to priapism (sickle-cell anaemia, multiple myeloma, leukaemia) bleeding disorders or active peptic ulceration [50].

Alpha blockers interactions

The concomitant use of PDE5-Is with α -blockers may result in orthostatic hypotension under some conditions. The labelling for sildenafil currently includes a precaution advising that 50mg or 100 mg (not 25 mg) of sildenafil should not be taken within 4 hours of taking an α blocker. The use of vardenafil with an α blocker is not recommended, however, coadministration of vardenafil with tamsulosin is not associated with clinically significant hypotension. Tadalafil is contraindicated in patients taking α blockers, except for tamsulosin [50]. Generally, the patient should be stable in his α blocker therapy before using a PDE5-I. The long-acting α blockers (doxazosin, terazosin) should be avoided in this concomitant use. Alfuzosin and tamsulosin are the preferred α blockers.

Dosage adjustments

Lower doses of PDE5-Is may be required in patients taking ketoconazole, itraconazole, erythromycin, clarithromycin, and HIV protease inhibitors (ritonavir, saquinavir) [43]. Higher doses of PDE5-Is may be necessary in patients taking rifampicin, phenobarbital, phenytoin, or carbamazepine. Kidney or hepatic dysfunction may require dose adjustments. In patients with hypogonadism, androgen supplementation improves erectile response.

Management of nonresponders to phosphodiesterase type 5 inhibitors

The two main reasons that patients fail to respond to a PDE5-I are either incorrect drug use or inefficacy of the drug [43]. Physicians should check that the patient is using a licensed medication and that the medication has been properly prescribed and correctly used (ie, that there is adequate sexual stimulation and dosage and enough time between taking the medication and an attempt at intercourse). Provided that a patient is using a PDE5-I appropriately, efficacy can be improved in several ways, including modification of associated risk factors, treatment of associated hypogonadism, changing to another PDE5-I, or continuous use of a PDE5-I. Limited evidence supports using these interventions [51]. Additionally, an accumulating body of evidence supports the use of psychosexual educational counselling in combination with pharmaceutical treatments to further optimise response.

ii) Sublingual apomorphine

Apomorphine is a dopamine D2-receptor agonist which acts in the CNS. The sublingual (SL) formulation is rapidly absorbed. Clinical trials have shown improvement in percentage of attempts resulting in successful sexual intercourse and an improvement [52]. A recent preference study suggests that patients prefer PDE5 inhibitors to apomorphine SL [53]. Therefore, its present use in the treatment of ED is diminishing and its future is uncertain.

iii) Intracavernosal injection therapy

Alprostadil (prostaglandin E1) acts primarily on specific receptors found on cavernosal smooth muscle cells [3]. It stimulates the activity of adenylate cyclase enzyme causing an elevation in the levels of intracellular cyclic adenosine monophosphate (cAMP). This leads to a fall in intracellular calcium and smooth muscle relaxation. It also reduces the release of noradrenaline (norepinephrine) from presynaptic noradrenergic nerve terminals with a resultant synergistic effect. Alprostadil can be combined for injection therapy with papaverine and phentolamine.

Papaverine was the first widely used drug as an intracavernosal agent. It inhibits breakdown of cGMP and cAMP by inhibiting PDE 2, 3 and 5. The resulting effect is a fall in intracellular calcium and cavernosal smooth muscle relaxation.

Phentolamine is a competitive inhibitor of α_1 and α_2 adrenoceptors. It also has an effect on serotonin receptors. When injected, phentolamine inhibits sympathetic neuronal activity. Its primary site of action is believed to be the arteriolar smooth muscle in the penis, leading to increased arteriolar blood flow. It can produce a useful synergistic effect when combined with alprostadil and papaverine.

iv) Intraurethral and topical agents

Intraurethral alprostadil is available through an applicator device in 125 μ g, 250 μ g, 500 μ g and 1000 μ g doses [3]. It is applied after micturition directly into the urethra. The applicator releases a dissolvable pellet containing alprostadil. Patients are advised to massage their penis after instillation and avoid lying down for 10–15 minutes. Erection develops within 15 minutes of instillation and lasts 30–60 minutes. In some patients, a penile constriction ring may be applied to the base of the penis prior to instillation to enhance the erection. Common adverse effects are penile pain, urethral bleeding and pain in the upper thighs.

Single agent topical therapy such as nitroglycerin (glyceryl trinitrate) and alprostadil are available, but their efficacy has been low (approximately 40%) in clinical trials [54]. Topical agents using a combination of agents such as aminophylline, dinitrate and co-dergocrine (ergoloid mesylates) have produced better efficacy in clinical trials (approximately 58%) [55]. The role of intraurethral and topical agents in ED is diminishing, but they may be an alternative in patients who have not responded to PDE5 therapy but find injection therapy unacceptable.

v) Androgen replacement therapy

The routine use of androgen replacement therapy (ART) in the treatment of ED has been a controversial issue, because hypogonadism can be demonstrated in only a small proportion of men with ED [56]. The efficacy of ART in enhancing erectile function is uncertain, although libido is improved [57]. ED patients with concurrent hypogonadism demonstrated by history, clinical examination and laboratory test may be commenced on ART after appropriate counselling. Potential detrimental effects on the cardiovascular system, prostate cancer and breast cancer risks must be disclosed to the patient.

ART can be administered through a variety of routes, including intramuscular injection, scrotal patches, transdermal patches and gel, as well as buccal and subcutaneous implants. Adverse effects of ART include peripheral oedema, raised haematocrit, gynaecomastia, headache, anxiety, acne, hirsutism, local reactions, cholestatic jaundice, hepatitis, hepatocellular carcinoma and peliosis hepatis.

ART is contraindicated in patients with suspected or confirmed prostate cancer, breast cancer and those who desire fertility [58]. The American Association of Clinical Endocrinologists (AACE) recommends 3–4 month follow ups in the first year and a 6–12 month follow up for the following 18 months [58]. At follow up, the assessments should include testosterone levels, digital rectal examination, an enquiry into lower urinary tract symptoms, PSA testing, breast examination, haematocrit testing and assessment of sleep apnoea.

9.4 Vacuum constriction devices

A vacuum constriction device (VCD) applies negative pressure to the penis to draw venous blood into the penis, which is then retained by application of a visible constricting band at the base of the penis. This method seems more acceptable to older patients [59].

Efficacy, defined by an erection satisfactory for intercourse, is as high as 90%. Satisfaction rates range between 27 to 94 percent. After 2 years, only 50–64% of men continue to use VCDs. Most men who discontinue use of VCDs do so within 3 mo. The adverse effects associated with vacuum therapy are penile pain, numbness, and delayed ejaculation, these effects occur in <30% of patients.

9.5 Surgical therapy

i) Penile prostheses

Surgical implantation of a penile prosthesis may be considered in patients who fail pharmacotherapy or who want a permanent solution. Prostheses are either malleable (semirigid) or inflatable (two or three piece). Most patients prefer the three piece inflatable devices because erections are more “natural,” but these implants are much more expensive. Satisfaction rates of 70–87% are reported from patients after appropriate consultation [60]. The two main complications of penile prosthesis implantation are mechanical failure (<5% after 5-yr followup with currently available three-piece prostheses) and infection [61].

ii) Penile vascular surgery

When arterial disease is the cause of ED, a bypass involving the inferior epigastric artery is the common technique utilised. Outcomes from surgical procedures have been difficult to compare in the literature because of the variation in diagnostic criteria, patient selection criteria, surgical technique, follow up duration and outcome assessments. Only a few studies used objective parameters, such as penile Doppler ultrasonography measurements before and after surgery and correlated these to clinical outcomes. The published results suggest that, although the initial patient satisfaction was high, the long term results have been rather disappointing [62]. Complications arising from this procedure include penile hyperaemia, altered sensation of the glans penis, infection and haematoma.

In veno occlusive disease, venous ligation and embolisation techniques have been utilised. Outcomes are again difficult to compare for the same reasons as for bypass procedures. Venous embolisation both percutaneous and open – has also been attempted in veno-occlusive ED, with long-term success rates of 26–69 percent [63-64].

Techniques used in arterial disease have been shown to be effective only in men aged <40 years. This is regarded as a specialised surgery, which should be attempted only in large centres with specialist interest and experience.

Most men with ED will be treated with options that are not cause specific [65]. This approach requires a structured treatment strategy that depends on efficacy, safety, invasiveness, and cost as well as patient and partner satisfaction. The choice of treatment options must consider the effects on patient and partner satisfaction and other QoL factors as well as efficacy and safety. A treatment algorithm for ED is given in Fig : 2.

10. Conclusion and recommendation

10.1 Diagnostic work up of erectile dysfunction (ED)

- Clinical history related to ED may help assess all sexual function domains and the effect of a specific treatment modality.
- Physical examination is needed in the initial assessment of ED to identify underlying medical conditions associated with ED.
- Routine laboratory tests, including glucose, lipid profile, testosterone, prolactin and TSH are required to identify and treat any reversible risk factors and modifiable lifestyle factors.
- Specific diagnostic tests are indicated by only a few conditions.

10.2 Treatment of erectile dysfunction (ED)

- Lifestyle changes and risk factor modification must precede or accompany ED treatment.
- If a curable cause of ED is found, treat the cause first.
- PDE5-Is are first line therapy.

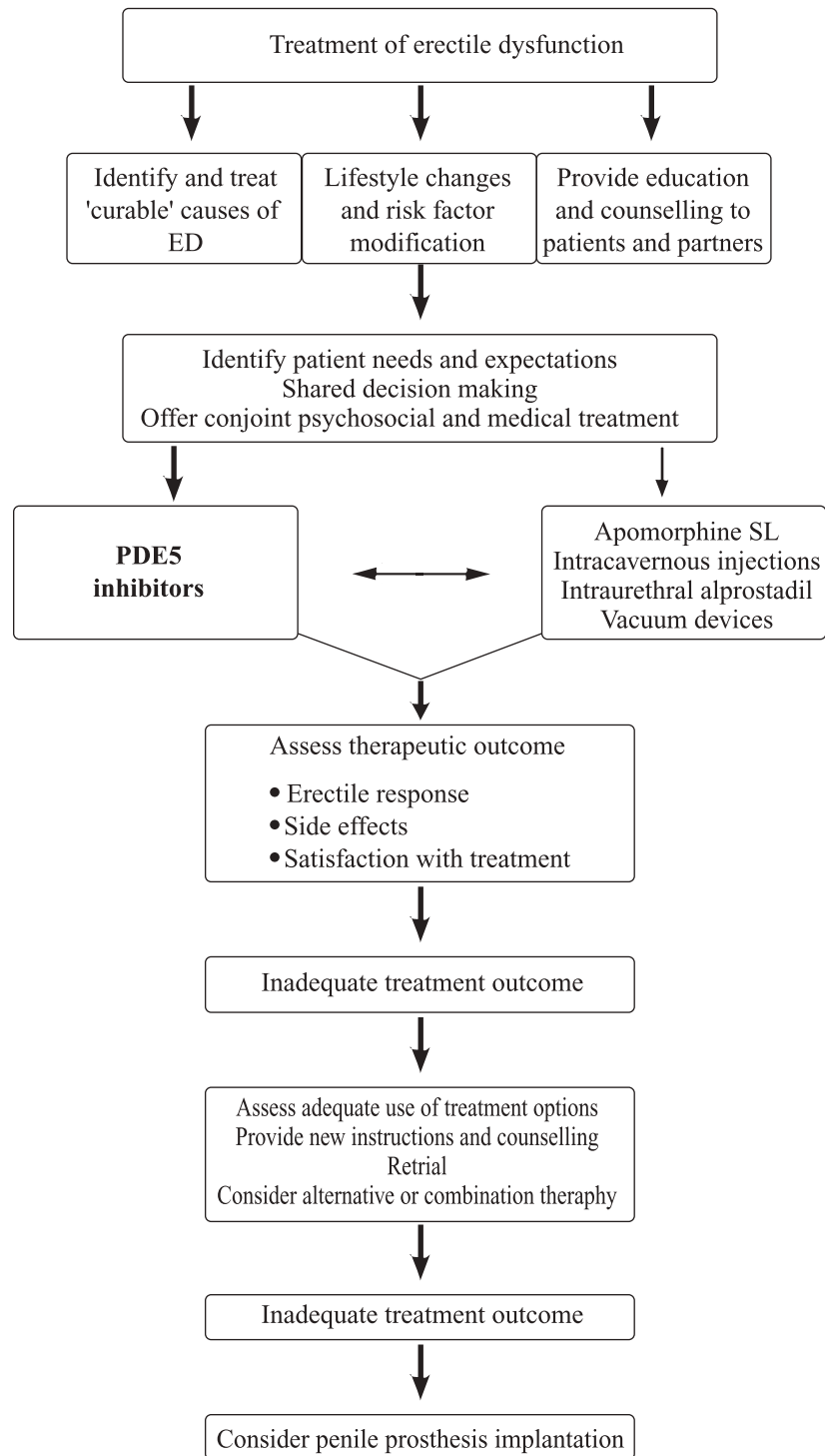


Fig 2 : Treatment algorithm for erectile dysfunction (ED)
PDE5 = Phosphodiesterase type 5

- Daily administration of PDE5-Is may improve results and restore erectile function.
- Inadequate/incorrect prescription and poor patient education are the main causes of a lack of response to PDE5-Is.
- Testosterone replacement restores efficacy in hypogonadic nonresponders to PDE5-Is.
- Apomorphine can be used in mild to moderate ED, psychogenic ED, or in patients with contraindications to PDE5-Is.
- A vacuum constriction device can be used in patients with stable relationship.
- Intracavernous injection is second line therapy.
- Penile implant is third line therapy.
- Surgery is rarely used except in specific indication.

Disclosure

The authors declared no competing interests.

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