# Erectile dysfunction

*Rany Shamloul, Hussein Ghanem*

**Erectile dysfunction is a common clinical entity that affects mainly men older than 40 years. In addition to the classical causes of erectile dysfunction, such as diabetes mellitus and hypertension, several common lifestyle factors, such as obesity, limited or an absence of physical exercise, and lower urinary tract symptoms, have been linked to the development of erectile dysfunction. Substantial steps have been taken in the study of the association between erectile dysfunction and cardiovascular disease. Erectile dysfunction is a strong predictor for coronary artery disease, and cardiovascular assessment of a non-cardiac patient presenting with erectile dysfunction is now recommended. Substantial advances have occurred in the understanding of the pathophysiology of erectile dysfunction that ultimately led to the development of successful oral therapies, namely the phosphodiesterase type 5 inhibitors. However, oral phosphodiesterase type 5 inhibitors have limitations, and present research is thus investigating cutting-edge therapeutic strategies including gene and cell-based technologies with the aim of discovering a cure for erectile dysfunction.**

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## Introduction

Inadequate penile erection, otherwise known as erectile dysfunction, is defined as the inability to attain or maintain a penile erection sufficient for successful vaginal intercourse.[1] This clinical disorder was described in early historical records, with descriptions of poor penile erection in men found in ancient Egyptian scriptures that are more than 5000 years old.[2,3] 1998 marked the milestone introduction of the first effective oral drug treatment, sildenafil citrate (Viagra, Pfizer, New York, NY, USA), for the treatment of erectile dysfunction.[4] Sildenafil belongs to a group of well-characterised drugs that are called selective phosphodiesterase type 5 inhibitors (PDE5-Is).[5–9] These drugs were all developed on the basis of a conceptual understanding of the fundamental role of nitric oxide (NO) smooth muscle relaxation in penile cavernous tissues.[10–12] Recognition of the important part NO plays in signalling smooth muscle relaxation in penile tissue led to a dramatic expansion of research focused on sexual dysfunction in men.

## Epidemiology

Erectile dysfunction is a common medical disorder that primarily affects men older than 40 years of age. A recent extensive analysis of published work on the prevalence of erectile dysfunction,[13] reported by the International Consultation Committee for Sexual Medicine on Definitions/Epidemiology/Risk Factors for Sexual Dysfunction, showed that the prevalence of erectile dysfunction was 1–10% in men younger than 40 years. Prevalence of erectile dysfunction range from 2% to 9% in men between the ages of 40 and 49 years. It then increases to 20–40% in men aged 60–69 years. In men older than 70 years, prevalence of erectile dysfunction ranges from 50% to 100%.[14–18] In a long-term follow-up investigation[19] of the landmark population-based study, the Massachusetts Male Aging Study, the crude incidence of erectile dysfunction was 26 per 1000 man-years. This number increased with age, reaching 46 per 1000 man-years for men aged 60–69 years. Moreover, the worldwide prevalence of erectile dysfunction has been predicted to reach 322 million cases by the year 2025.[20,21] Clearly, erectile dysfunction is now regarded as a major health problem for the increasingly healthy ageing population.

Findings from several cross-sectional and longitudinal studies have linked the development of erectile dysfunction to diabetes mellitus, hypertension, hyperlipidaemia, metabolic syndrome, depression, and lower urinary tract symptoms.[22–28] Several epidemiological studies reported that erectile dysfunction is a marker of cardiovascular disease (CVD).[23,26,28] A 2011 meta-analysis of 12 prospective cohort studies provided strong evidence that erectile dysfunction is indeed significantly and independently associated with an increased risk of not only CVD but also coronary heart disease, stroke, and all-cause mortality.[29] Findings from other studies have shown that certain environmental and lifestyle factors, such as smoking, obesity, and limited or an absence of physical exercise, might also be important predictors of erectile dysfunction.[29–31] In several studies, an extensive alteration of lifestyle habits, through modification of diet and encouragement to exercise, led to improvement of erectile dysfunction.[32–36]

### Search strategy and selection criteria

We searched PubMed for papers published in English between 1980 and March, 2012, with the terms "erectile dysfunction" and "impotence", "diagnosis", "treatment", "epidemiology", "physiology", and "pathophysiology". We also reviewed recent and past textbooks. We mainly focused on publications in the past 5 years; however, we did not ignore landmark relevant articles. Other relevant articles identified by review of the reference lists of selected articles were also included. We also reviewed abstracts from relevant scientific meetings. The diagnosis and treatment sections were written according to the guidelines and recommendations of the International Society for Sexual Medicine, the American Urological Association, and the European Association of Urology.

## Physiology of penile erection

NO, released from the endothelium and the parasympathetic nerve terminals, is the primary neurotransmitter involved in penile erection, although other transmitters can also be involved.[37] NO-dependent relaxation of the cavernosal smooth muscles leads to compression of the subtunical small veins, occluding local venous return and resulting in an erection (figure 1). Penile detumescence begins with activation of the adrenergic receptors on the cavernous arteries and trabecular smooth muscles, leading to a reduction in arterial inflow and a collapse of lacunar spaces. Decompression of the drainage venules from the cavernous bodies occurs, allowing venous drainage of the lacunar spaces and relief of the erection.[38]

## Pathophysiology and cause

Normal sexual function has been described as a biopsychosocial process that involves the coordination of psychological, endocrine, vascular, and neurological systems.[38] Erectile dysfunction is classified as psychogenic, organic (ie, neurogenic, hormonal, arterial, cavernosal, or drug induced), or mixed psychogenic and organic (panel 1). Erectile dysfunction is usually of a mixed psychogenic and organic nature.

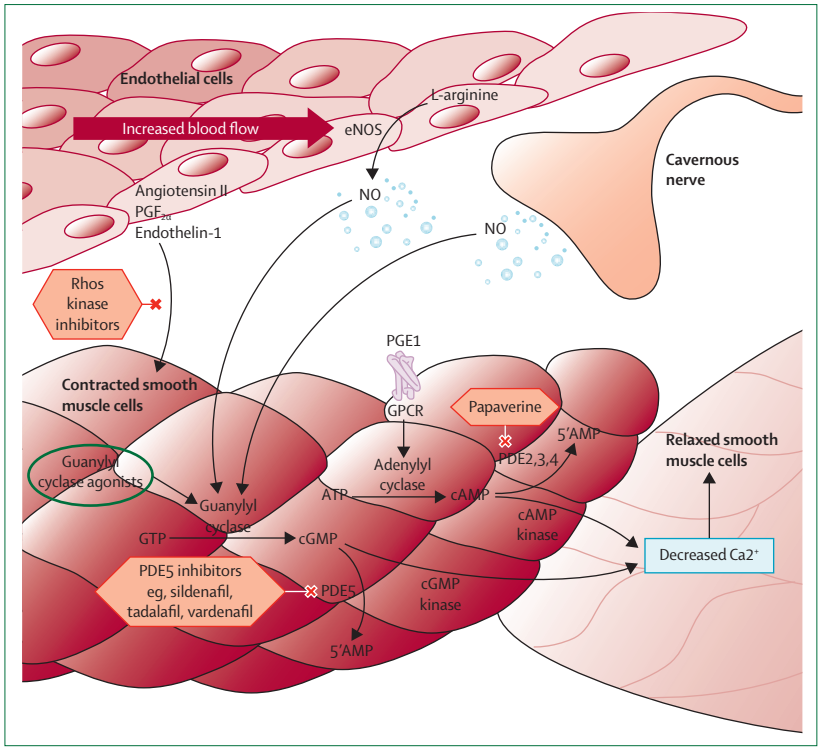


***Figure 1:*** **Microscopic mechanisms underlying penile smooth muscle relaxation**
NO is the primary mediator of penile smooth muscle relaxation. After sexual stimuli, NO concentration is significantly increased because of its release from the cholinergic and non-noradrenergic, non-cholinergic fibres and the endothelium. NO works via the GTP/cGMP pathway to decrease intracellular calcium leading to trabecular smooth muscle relaxation. 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. $PGF_{2\alpha}$=prostaglandin $F_{2\alpha}$. PGE1=prostaglandin E1. GTP=guanosine triphosphate. cGMP=cyclic guanosine monophosphate. NO=nitric oxide. eNOS=nitric oxide synthase. PDE5=phospodiesterase type 5. ATP=adenosine triphosphate. AMP=adenosine monophosphate. GPCR=G-protein-coupled receptor. Reproduced with permission from Haderer & Muller Biomedical Art, LLC (2009).

### Psychogenic erectile dysfunction

Psychological factors are involved in a significant number of cases of erectile dysfunction alone or in combination with organic causes. An important psychogenic factor related to erectile dysfunction is performance anxiety (fear of failure during intercourse).[39] Historical theories explaining psychological factors in erectile dysfunction have described multiple developmental, cognitive, affective, and interpersonal factors that predispose men to sexual dysfunction.[39] At present, psychogenic erectile dysfunction is thought to be primarily related to a group of predisposing, precipitating, and maintaining factors (panel 2).

### Neurogenic erectile dysfunction

Certain neurological disorders are frequently associated with erectile dysfunction, including multiple sclerosis, temporal lobe epilepsy, Parkinson's disease, stroke, Alzheimer's disease, and spinal cord injury.[40] Patients undergoing radical pelvic surgeries (eg, radical prostatectomy) have an especially high risk of cavernous nerve injury and subsequent neurogenic erectile dysfunction. However, recent advances in surgical techniques have significantly lowered the incidence of post-pelvic-surgery erectile dysfunction.[41]

### Endocrinological erectile dysfunction

Androgens play important parts in enhancing sexual desire and maintaining adequate sleep-related erections but have a limited effect on visually induced erections. Additionally, testosterone is important in the regulation of the expression of NO synthase (NOS) and PDE5 inside the penis.[42] Testosterone deficiency or hypogonadism has been recently associated with cardiovascular morbidity and mortality.[43] Hyperprolactinaemia leads to sexual dysfunction, due to low testosterone concentrations. Increased prolactin concentration leads to the inhibition of gonadotropin-releasing hormones, which, in turn, decreases the secretion of luteinising hormone, which is responsible for testosterone secretion.

### Vasculogenic erectile dysfunction

Several frequent risk factors are associated with penile arterial insufficiency, including atherosclerosis, hypertension, hyperlipidaemia, cigarette smoking, diabetes mellitus, and pelvic irradiation.[44] Endothelial dysfunction is the common denominator to many vascular risk factors that can lead to arteriogenic erectile dysfunction.[45] Other studies have confirmed a significantly higher incidence and prevalence of erectile dysfunction in patients with hypertension, which can reach up to 68%.[45–47] Erectile dysfunction improved when the concentrations of

### *Panel 1:* Main organic causes of erectile dysfunction

**Neurogenic**
- Central (cerebral or spinal cord): for example, cerebral insult, multiple sclerosis, and spinal cord injury
- Peripheral: afferent (sensory neuropathy, eg, diabetes mellitus and polyneuropathy of various other causes)
- Efferent (autonomic neuropathy or after radical pelvic surgery)

**Endocrinological**
- Diabetes mellitus, hypogonadism, and hyperprolactinaemia

**Vasculogenic**
- Arterial: macro or micro angiopathy (eg, atherosclerosis and trauma)
- Venous: failure of the corporal veno-occlusive mechanism
- Sinusoidal: failure to relax (eg, fibrosis)

**Drug-induced depression**
- Drugs: for example, some antihypertensives, antidepressants, antiandrogens, and major tranquillisers
- Cigarette smoking, alcoholism, and recreational drug use (eg, marijuana and heroin)

**Systemic diseases and general ill health**
- For example, liver, renal, respiratory, and cardiovascular disease

**Local penile(cavernous) factors**
- For example, cavernous fibrosis after priapism or due to other reasons, Peyronie's disease, and penile fracture

### *Panel 2:* Factors related to the development of psychogenic erectile dysfunction[39]

**Predisposing factors**
- Traumatic past experiences
- Strict upbringing
- Inadequate sex education
- Physical and mental health problems

**Precipitating factors**
- Acute relationship problems
- Family or social pressures
- Major life events, such as pregnancy, childbirth, or loss of a job

**Maintaining factors**
- Relationship problems
- Physical or mental health problems
- Absence of knowledge of availability of various treatment options

Note: religious and cultural differences might influence the factors that affect the development of psychogenic erectile dysfunction.

elevated total and low-density lipoproteins, as well as cholesterol, were lowered, either by dietary measures or statin administration.[43] Also, diabetes mellitus, hypertension, dyslipidaemia, obesity, and smoking are all strong risk factors for coronary artery disease (CAD) and erectile dysfunction.

The present Princeton III consensus guidelines,[48] an expert opinion report, now recognise erectile dysfunction as a strong predictor of CVD and, in particular, CAD. This association between CVD and erectile dysfunction was confirmed in a study that reported that erectile dysfunction is a potent predictor of adverse cardiovascular events in high-risk cardiovascular patients.[49] In a landmark study, Inman and colleagues (2009)[23] biennially screened a random sample of more than 1400 community-dwelling men who had regular sexual partners and no known CAD for the presence of erectile dysfunction over a 10-year period. Overall, their data show that new incident CAD developed in 11% of men over the 10-year follow-up period, in which about 15% were due to myocardial infarction, 79% to angiographic anomalies, and 6% to sudden death. The cumulative incidence of CAD was strongly influenced by patient age. CAD incidence densities per 1000 person-years for men without erectile dysfunction were 0·94 (age 40–49 years), 5·09 (age 50–59 years), 10·72 (age 60–69 years), and 23·30 (age 70 years and older). For men with erectile dysfunction, the CAD incidence densities per 1000 person-years were 48·52 (age 40–49 years), 27·15 (age 50–59 years), 23·97 (age 60–69 years), and 29·63 (age 70 years and older). The most significant finding of this study is that when erectile dysfunction occurs in men younger than age 60 years, it is associated with a marked increase in the risk of future cardiac events compared with men with no erectile dysfunction; however, it has less predictive significance in older men.[23] There is no definite explanation of why this phenomenon happens in younger men. Inman and colleagues[23] suggested that erectile dysfunction shares the same risk factors as CAD, with endothelial dysfunction being an important underlying pathological change in both diseases. Other potential mechanisms involved in the development of endothelial dysfunction that can lead to erectile dysfunction and CAD include a dysfunctional L-arginine NO pathway, increased peripheral sympathetic activity, vascular structural alterations leading to decreased vascular dilatation capacity, and increased specific inflammatory mediators.[43–47] Montorsi and colleagues[50] suggested that this phenomenon might be related to the calibre of the blood vessels. Whereas the penile artery has a diameter of 1–2 mm, the proximal left anterior descending coronary artery is 3–4 mm in diameter. Thus, an equally sized atherosclerotic plaque developing in the smaller penile arteries would more likely compromise flow, presenting itself as an erectile dysfunction complaint much earlier than if the same amount of plaque developed in the larger coronary artery, causing angina. Inadequate venous occlusion is another important cause of vasculogenic erectile dysfunction.[51] Inadequate venous occlusion can

***Panel 3:*** **Drugs and recreational substances commonly associated with erectile dysfunction**

**Antiandrogens**
- Gonadotropin-releasing hormone agonists (leuprolide, goserelin, lupron, and zoladex)
- Chemotherapy (cyclophosphamide and busulfan)
- Flutamide
- Ketoconazole
- Spironolactone
- $H_2$ blockers
- Cimetidine

**Antihypertensives**
- Thiazide diuretics
- β blockers
- Calcium channel blockers

**Antiarrhythmics**
- Digoxin
- Amiodarone
- Disopyramide

**Statins**
- There is controversial evidence about the effects of atorvastatin on erectile function[56,57]

**Psychotropic drugs**
- Tricyclic antidepressants
- Selective serotonin reuptake inhibitors
- Phenothiazines
- Butyrophenones

**Recreational substances**
- Marijuana
- Opiates
- Cocaine
- Nicotine
- Alcohol

***Panel 4:*** **Risk factors and comorbidities associated with erectile dysfunction**

- Age
- Poor physical and psychological health
- Lifestyle factors
  - Sedentary lifestyle
  - Obesity
  - Cigarette smoking
  - Alcohol misuse
  - Recreational drug use (eg, marijuana and heroin)
- Metabolic risk factors and metabolic syndrome
  - Diabetes mellitus
  - Hypertension
  - Dyslipidaemia
  - Hypogonadism

occur as a result of the development of large venous channels draining the cavernous tissue. It might also be caused by severe degenerative, functional, or anatomical changes in the tunica albuginea, such as those that occur in Peyronie's disease.[52]

### Drug-induced erectile dysfunction

Psychotropic drugs and antihypertensives are among the most common drug classes involved in the development of erectile dysfunction.[53] Antidepressants are the most common psychotropic drugs associated with significant rates of erectile dysfunction, including the selective serotonin reuptake inhibitors and venlafaxine. Antipsychotics such as risperidone and olanzapine have the highest likelihood of all psychotropic drugs of causing erectile dysfunction.[54] Thiazides, followed by β blockers, are the most common groups of antihypertensive drugs that cause erectile dysfunction, whereas α blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers are the least likely of these drugs to cause erectile dysfunction.[55] Statins have also been implicated in the development of erectile dysfunction.[56] Panel 3 lists the most common groups of drugs that can cause erectile dysfunction. For more extensive lists of drugs that can affect erectile function, please consult other sources (eg, Baumhäkel and colleagues[57]).

### Erectile dysfunction due to ageing, lifestyle factors, and systemic diseases

Findings from epidemiological studies confirm that age is the primary risk factor for erectile dysfunction. The prevalence and severity of erectile dysfunction increases with age. In the Massachusetts Male Aging study,[13] 39% of men had some degree of erectile dysfunction by the age of 40 years. The prevalence of erectile dysfunction gradually increased, reaching 67% for men by the age of 70 years. The relation between increased age and increased prevalence and severity of erectile dysfunction was confirmed by two other independent, large-scale studies, which included 2476 Spanish men[58] and 1464 Middle Eastern men.[59]

Diabetes mellitus type 2 is the second most common risk factor for erectile dysfunction, which in turn develops in 50–75% of diabetics.[13] Erectile dysfunction also occurs three times more frequently in diabetics than non-diabetics (49·3% *vs* 15·6%, respectively).[60] Erectile dysfunction was the first sign of diabetes mellitus in 12% of patients.[61] A sedentary lifestyle, smoking, alcohol or drug misuse, sleep disorders, obesity, and metabolic syndromes have all been associated with erectile dysfunction (panel 4).[61–64] Also, persistent debilitating medical disorders, including chronic kidney,[65] liver,[66] and pulmonary diseases,[67] have all been associated with erectile dysfunction.

## Diagnosis

At present, the scientific consensus has been to adopt a goal-directed approach during the assessment of patients

complaining of erectile dysfunction.[68–71] The main goals of assessment of erectile dysfunction are to establish whether the disorder is truly erectile dysfunction, to identify the cause of the disorder, and to ascertain risk factors and potentially life-threatening comorbid disorders associated with erectile dysfunction.

### History taking

The mainstay in the diagnosis of erectile dysfunction is adequate and comprehensive sexual and medical history taking (figure 2). During the initial visit, the primary-care physician should attempt to obtain a detailed psychosocial history from the patient, focusing on the patient's assessment of his own sexual performance and his general attitude and knowledge about sex. Interviewing the patient's partner during the erectile dysfunction assessment is also usually advisable. Occasionally, a medical history might reveal complex psychological problems, prompting psychiatric referral.

Patients who complain of weak erections might be actually suffering from premature ejaculation. In erectile dysfunction, erection loss occurs before orgasm, while with premature ejaculation, it happens afterwards. Assessment of whether the main cause of erectile dysfunction is organic or psychogenic is also important. The presence of rigid morning or night erections, or rigid erections at any sexual thought suggests a mainly psychogenic cause. Erectile dysfunction with a sudden onset, intermittent course, or short duration also suggests psychogenic factors. Conversely, erectile dysfunction with a gradual onset, progressive course, or long duration suggests a predominantly organic cause.[72] Relevant drug history, including alcohol, tobacco, or illicit drug use, and decreased or altered sex desire should also be reviewed. Past medical and surgical disorders should be thoroughly detailed.

Standardised questionnaires are frequently used to confirm that the disorder is truly erectile dysfunction and to measure its severity. They are also valuable research aids that help assess the response to different treatments. Several questionnaires are available. Two of the most practical and easily administered ones are the International Index of Erectile Function and the Sexual Health Inventory for Men.[73–75]

Recent findings that erectile dysfunction is a strong predictor of CAD and that the development of symptomatic erectile dysfunction 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.[76] A strong recommendation is that all men with erectile dysfunction 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 (table 1).[48] After cardiovascular risk stratification, further assessment for the presence of silent CAD is of major importance (figure 3). This assessment is particularly important in young men (<60 years old), who are at low risk of developing CVD, and in other patients with intermediate risk. In these men, a resting electrocardiogram (ECG) test should be done and, if abnormal, a further exercise ECG test is recommended.[76,77] If abnormal, more in-depth cardiovascular assessment (eg, angiography) with referral to a cardiologist is the logical next step. Other useful measurements of CAD in this specific population might include waist circumference,

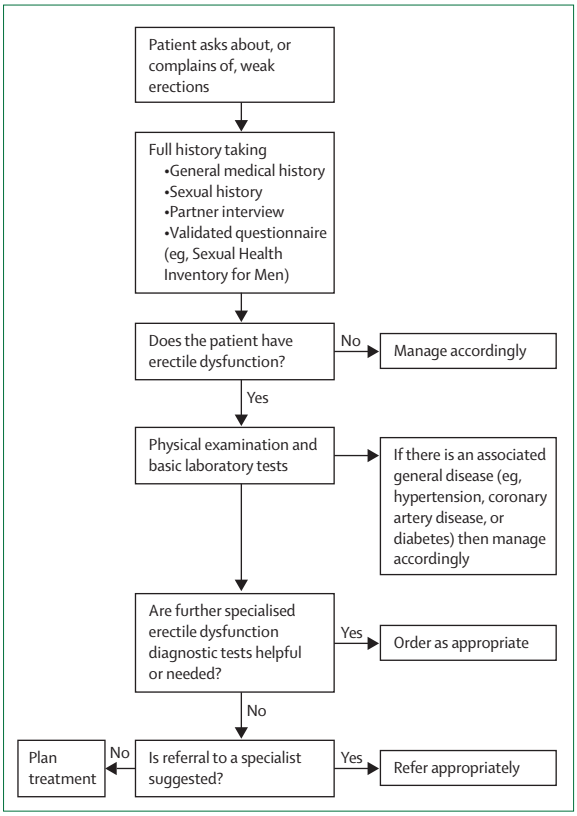


*Figure 2:* **Algorithm for the diagnosis of erectile dysfunction**

| | Recommended treatment |
|---|---|
| Low risk (asymptomatic after moderate-intensity exercise): asymptomatic and less than three major risk factors—controlled hypertension, mild valvular disease, LVD (NYHA class I), and NYHA class II | Sexual activity can be continued and oral PDE5-Is can be given |
| Intermediate or indeterminate risk: asymptomatic and at least three coronary artery disease risk factors—mild stable angina pectoris, asymptomatic after MI (>6–8 weeks), moderate stable angina pectoris, MI for over 2 weeks but less than 6 weeks, LVD or CHF (NYHA class III) peripheral arterial disease, history of stroke, or transient ischaemic attack | In-depth cardiovascular assessment to re-categorise the patient is needed before treatment of erectile dysfunction |
| High risk: unstable or refractory angina, uncontrolled hypertension, CHF (NYHA class IV), recent MI (<2 weeks), high-risk arrhythmias, obstructive hypertrophic cardiomyopathies, or moderate-to-severe valve disease | Sexual activity stopped. Stabilise cardiovascular condition first then proceed to treatment for erectile dysfunction |

MI=myocardial infarction. LVD=left ventricular disease. NYHA=New York heart classification. CHF=congestive heart failure. PDE5-Is= phosphodiesterase type 5 inhibitors. Adapted from Nehra and colleagues.[48]

*Table 1:* **Risk stratification and treatment of men with erectile dysfunction and cardiovascular disease**

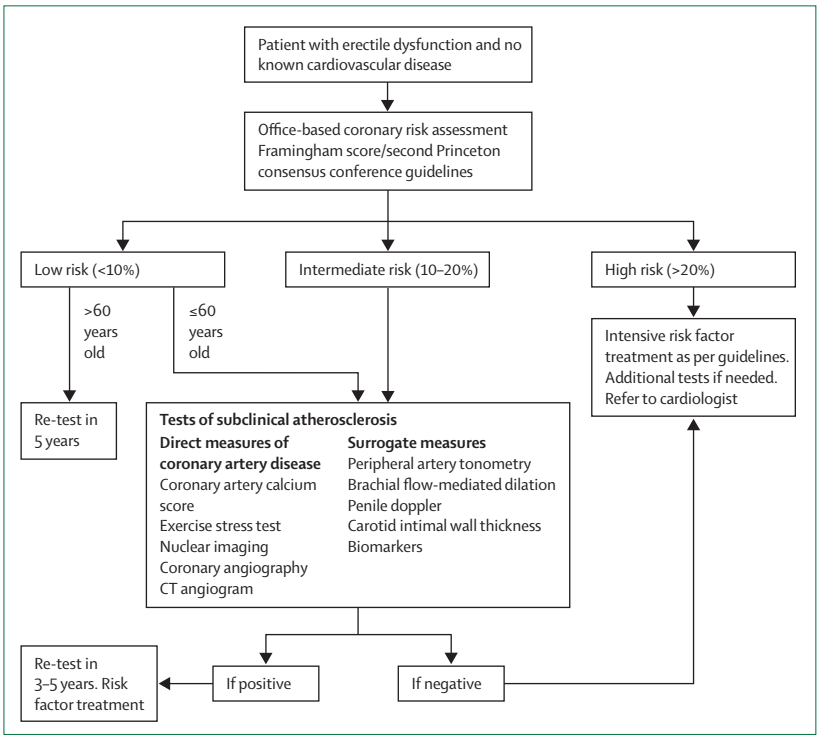


***Figure 3:*** **Algorithm for coronary risk assessment in erectile dysfunction**
Modified from Montorsi and colleagues[76] and Miner[77] with permission from the American Society of Andrology and Elsevier.

### *Panel 5:* Physical examinations in erectile dysfunction

**General**

- Secondary sex characteristics
- Pulses and sensations
- Scars from previous surgery or trauma

**Local**

- Penis: size, scars, fibrosis, urethral meatus, and elasticity
- Scrotum: testicular size and consistency
- Rectal exam: size and consistency of the prostate and seminal vesicles, and assessment of anal sphincter tone and bulbocavernous reflex

### *Panel 6:* Indications for referral to a specialist in erectile dysfunction

- Deep-rooted psychiatric problems
- CNS disorders
- Complex endocrine disorders
- Severe cardiovascular disease
- Lifelong erectile dysfunction
- Penile fibrosis (Peyronie's disease or post-priapism)
- Congenital penile anomalies (eg, hypospadias)
- Failure to respond to phosphodiesterase type 5 inhibitors

body mass index, and coronary artery calcification scoring, as measured by electron-beam CT, carotid intima-media thickness, peripheral arterial tonometry, and serum asymmetric vascular adhesion molecules.[76,77]

### Physical examination

General and more focused local examinations are recommended for all cases of erectile dysfunction. Panel 5 lists the main components of a physical examination. The local examination is a good opportunity for the physician to educate the patient, if necessary, on normal penile size and to explore any misconceptions the patient might have about the relation between penile length, masculinity, and erectile dysfunction.

### Laboratory assessment

Assessments of fasting blood sugar and total testosterone are the two basic laboratory investigations that should be done. However, because erectile dysfunction is a strong predictor of vascular disease, physicians could discuss with the patient the importance of also checking their lipid profile and other tests. Low concentrations of free or total testosterone necessitate further hormonal assessment, including that of luteinising hormone and prolactin. After the initial erectile dysfunction assessment, the primary-care physician might be faced with complex organic or psychological findings, or both, that warrant extensive assessment, which is preferably done by a specialist (panel 6).

### Specific investigations

For many patients, especially young men and their partners, knowing whether or not the disorder is reversible is part of the treatment. Additionally, certain types of erectile dysfunction might be associated with potentially life-threatening cardiovascular disorders.[76] The routine use of investigative procedures in erectile dysfunction is generally not advisable, because patients might be subjected to expensive invasive procedures that will not alter the management plan.[68–70] Table 2 lists the most common specific diagnostic tests for erectile dysfunction and their benefits and limitations. Recent research-based techniques that attempt to assess penile endothelial dysfunction include the penile NO release test[78] and Endo-PAT2000[79] and the measurement of specific serum (eg, endothelin-1 and C-reactive protein)[80,81] and cellular (circulating endothelial progenitor cells)[82–84] markers.

## Treatment

Overall, oral PDE5-Is are the mainstay of treatment of erectile dysfunction. Other treatment modalities include lifestyle modification, injection therapies, testosterone therapy, penile devices, and psychotherapy (figure 4).[68–70]

### Psychosexual, couple, and partner therapy

Psychosexual therapy is indicated particularly where significant psychological problems are recognised. It is

| | Main benefits | Limitations |
|---|---|---|
| Questionnaires | Easy to administer, well tested, and validated. Assess presence and severity of erectile dysfunction | Do not define the cause of erectile dysfunction |
| Intracavernosal injection | Rapid and easy. Can assess severity of erectile dysfunction | Risk of prolonged erection, priapism, and faulty injection |
| Colour doppler ultrasound | Tested against a historical gold standard (pharmaco-arteriography) to diagnose arteriogenic erectile dysfunction. Might suggest other vascular disease (eg, coronary artery disease) | Less reliable in diagnosing venogenic erectile dysfunction. Incomplete smooth muscle relaxation due to anxiety or sympathetic overtone might lead to false-positive results. Redosing and retesting are frequently needed |
| Pharmaco-arteriography | Outlines arterial anatomy before arterial surgery in post-traumatic and congenital cases | Invasive. Affected by methodology and timing |
| Pharmaco-cavernosometry or cavernosography | Suggests venogenic erectile dysfunction. Delineates site of leak and cavernosal abnormalities | Moderately invasive. Incomplete smooth muscle relaxation due to anxiety or sympathetic overtone might lead to false-positive results |
| Neurological testing | Assess somatic pathways | Does not directly assess autonomic nerve function. No universally accepted and reproducible criteria. Complex and time consuming |
| Nocturnal penile tumescence testing | Closest to a gold standard in differentiating between psychogenic and organic erectile dysfunction | Nocturnal erections might be regulated by different pathways. Does not detect sensory deficit impotence. False-positive results can occur if patients do not sleep well. Physical disorders might alter nocturnal penile tumescence testing. Assesses only radial not axial rigidity. Does not correlate well with International Index of Erectile Function domain scores |

***Table 2:*** **Uses and limitations of commonly used specific erectile dysfunction investigations**

best used in men with predominantly psychogenic erectile dysfunction. Techniques of psychosexual therapy include sensate focus, sex education, and interpersonal therapy. Data regarding the efficacy of such techniques are largely inconclusive.

## Lifestyle modification

Findings from recent basic and clinical studies have shown that targeting several lifestyle factors commonly associated with erectile dysfunction, such as smoking, alcohol consumption, obesity, and limited physical activity, can have significant effects on improvement of erectile function.[85–93] Mannino and colleagues[88] reported that men who quit smoking had a lower erectile dysfunction rate compared with present smokers (2·0% *vs* 3·7%). Guay and colleagues[89] reported a significant and rapid improvement in erectile function upon smoking cessation in patients who had smoked over 30 pack-years (calculated by multiplying the number of cigarette packs a person smokes per day by the total number of years this person smoked; ie, 30 pack-years means the person smoked a pack of cigarettes every day for 30 years).

The present published work is not absolutely clear on whether or not alcohol consumption adversely affects erectile function.[13,90–92]

In a landmark study, 110 obese men with erectile dysfunction were randomly assigned to either an extensive weight loss programme with dietary counselling and exercise advice or to educational guidance on weight loss only.[32] 2 years later, the former group weighed significantly less, practised more physical activities and had a significant improvement in their erectile dysfunction scores compared with the latter group. These data were further confirmed by later studies.[33–36] Furthermore, in 2011 Gupta and colleagues[94] reported data on their meta-analysis of six randomised controlled trials (740 participants) assessing the effects of lifestyle modification and reduction of cardiovascular risk factors on the severity of erectile dysfunction. Their findings suggest that adoption of lifestyle modifications and cardiovascular risk factor reduction can provide incremental benefits on erectile function regardless of PDE5-I use. Suggested mechanisms by which weight reduction and increased physical exercise can improve erectile function include interference with endothelial dysfunction, insulin resistance, and the low-grade inflammatory state already associated with diabetes

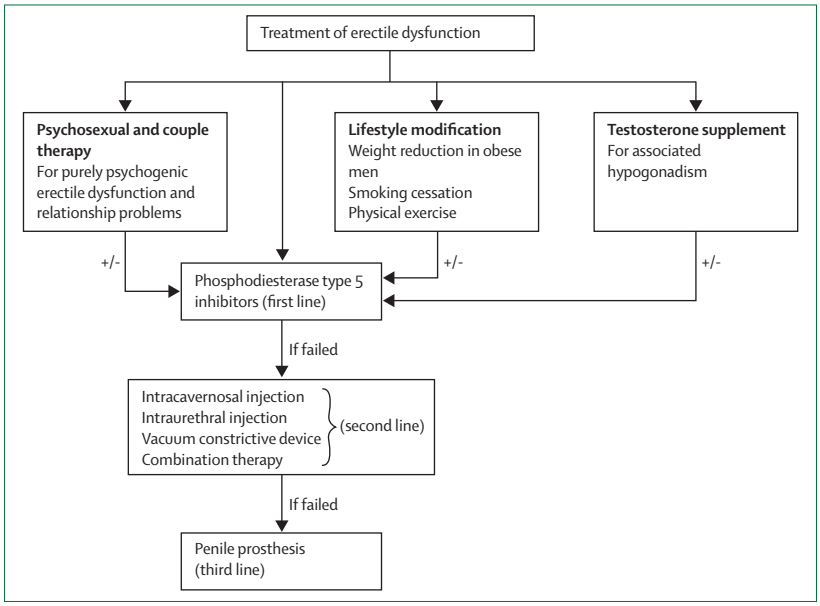


***Figure 4:*** **Algorithm for the treatment of erectile dysfunction**
Lifestyle modification, testosterone supplementation, and psychosexual therapy can all be associated with medical treatment for erectile dysfunction.

mellitus and metabolic disease, which are all well-known risk factors for erectile dysfunction.[94]

Even though the present evidence suggests that modifying certain lifestyle factors can lead to significant improvements in men with erectile dysfunction, solid conclusions cannot be reached without several properly designed, prospective, and large-scale controlled studies. Also, present research suggests that lifestyle modification can positively affect erectile function but after at least 2 years, a considerably long time.[32] Conversely, a combined approach of oral PDE5-Is and lifestyle modification can improve the results after 3 months.[93] Finally, successful available treatments for erectile dysfunction should not be suspended awaiting lifestyle modification.

## Oral PDE5-Is

Oral PDE5-Is are now regarded as the first-line treatment for erectile dysfunction.[95,96] These drugs facilitate erection by inhibiting the PDE5 enzyme, which is specifically responsible for the degradation of cyclic guanosine monophosphate (cGMP) in the cavernous smooth muscles. This inhibition results in the prolonged activity of cGMP, which further decreases intracellular calcium concentrations, maintains smooth muscle relaxation and, hence, results in rigid penile erections. There are now five commercially available oral PDE5-Is, which are sildenafil (Viagra; Pfizer, New York, NY, USA), tadalafil (Cialis; Lilly, Indianapolis, IN, USA), vardenafil (Levitra, Staxyn; Bayer, West Haven, CT, USA), udenafil (Zydena; Dong-A PharmTech, South Korea), and mirodenafil (Mvix; SK Chemical, South Korea). The first three drugs are available worldwide. Other PDE5-Is under investigation for the treatment of erectile dysfunction include avanafil, lodenafil, and SLx-2101.[97] All five commercially available PDE5-Is have an appropriate onset of action and duration and a success rate of at least 65% (table 3).[96–102] Physicians should consider trying all available PDE5-Is 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.[103]

Findings from several studies have shown that chronic or daily use of PDE5-Is in erectile dysfunction can significantly improve endothelial dysfunction with the potential for a cure.[104–110] Tadalafil 5 mg is the only PDE5-I clinically approved for daily use in the treatment of erectile dysfunction. Potential benefits of daily use of PDE5-Is include salvage of on-demand PDE5-I non-responders, apparent disease modification, and development of a more natural sexual function. Disadvantages are limited to the high cost compared with on-demand use, absence of long-term safety profile data, and incomplete understanding of the mechanisms of action.[110]

The main advantage of PDE5-Is lies in improvement of sexual performance and not libido. In young and potent men, PDE5-Is can lead to shortening of the refractory period (a temporary period of physiological erectile flaccidity immediately after ejaculation during which a man cannot be sexually aroused) and better ejaculatory control.[111,112] Concomitant PDE5-I use is contraindicated in nitrate users because it increases the risk of severe hypotension.[70] There was no increase in the rates of myocardial infarction or death, nor did PDE5-I use worsen ischaemia or cardiac haemodynamics upon exercise testing in patients with CAD or heart failure.[113] However, PDE5-Is should be used with caution in patients with serious CVDs, such as uncontrolled hypertension and unstable angina, and in patients taking α blockers for blood pressure control. The concurrent use of other antihypertensive drugs, such as calcium-channel blockers, is well tolerated by men taking any of the available PDE5-Is.[70] Vardenafil is not recommended in patients who

| | 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 |

*Table 3:* **Characteristics of commercially available phosphodiesterase type 5 inhibitors**[96-102]

take type-1A (eg, quinidine or procainamide) or type-3 (eg, sotalol or amiodarone) antiarrhythmics or in patients who have congenital prolonged QT syndrome.[113]

Side-effects related to PDE5-Is are generally mild and well tolerated. The most common is headache, followed by flushing. Tadalafil can cause myalgia and pain at different body sites (table 3). PDE5-I-related priapism has been reported in a few case reports.[114,115] A direct link between PDE5-Is and non-arteritic ischaemic optic neuropathy could not be established.[116,117] Patients using PDE5-Is should be also warned about a possible link between PDE5-I use, especially sildenafil, and occurrence of hearing impairment.[118]

Although PDE5-Is are a good first-line treatment, up to 35% of patients with erectile dysfunction may fail to respond to this treatment. Common causes of this response failure are diabetes mellitus and severe neurological or vascular diseases. Although there is no consensus on how to define the failure of PDE5-Is, the inability to attain or maintain adequate penile erection during sexual intercourse on at least four consecutive occasions, in spite of optimum drug dosing, is an acceptable definition.[103] Management of PDE5-I failure is mostly dependent on the cause and can include proper patient counselling, switching to another PDE5-I, intracavernosal injection, intraurethral drug administration (MUSE [Vivus, CA, USA]), combination therapy, and referral to a specialist for further assessment. Patients not responding to any of the medical treatment options for erectile dysfunction might be candidates for penile implant surgery.

### Testosterone

Although testosterone has important actions in maintaining adequate erectile function, its role in the treatment of erectile dysfunction is limited. Testosterone-replacement therapy is recommended in men with erectile dysfunction who have confirmed low concentrations of bioavailable testosterone. In a meta-analysis of 16 studies, improvement in erectile dysfunction was significantly more common in men with hypogonadism who were treated with testosterone than in those who received placebo (57·0% *vs* 16·7%).[119] Testosterone has also been used as part of a successful combination therapy with PDE5-Is in elderly men (age ≥65 years) with low testosterone concentrations who were initially unresponsive to PDE5-Is.[120,121]

### Intracavernosal injection and transurethral therapy

Regarded as a second-line treatment for erectile dysfunction, the main advantage of this type of treatment is that the erection achieved is predictable and occurs rapidly. Men or their partners, or both, learn to inject the penis, after adequate training, with small 28–30-gauge needles. Erection usually occurs in less than 10 min, independent of sexual desire. Intracavernosal injection is usually prescribed to men who disliked or failed oral treatment and those with spinal cord injuries or post-radical prostatectomy. Commonly used drugs include alprostadil (prostaglandin E1), papaverine, phentolamine, and vasoactive intestinal polypeptide. Intracavernosal mixture treatment with two or more vasoactive drugs can also be used. Although alprostadil has a high efficacy rate, reaching up to 70%, the trimix solution has a 90% success rate.[122,123] Side-effects associated with intracavernosal injections are priapism and penile fibrosis, but these can be avoided with proper patient education and monitoring. Penile pain is commonly associated with alprostadil injection. High rates (>50%) of injection dropouts occur primarily because of inconvenience.[123] Alprostadil is also available as an intraurethral pellet (MUSE). Success rates are between 43% and 69%.[122,124] Side-effects include penile pain, urethral pain or burning, hypotension, syncope, and priapism.

### Vacuum constrictive devices

Vacuum constrictive devices operate by applying continuous negative pressure to the shaft of the penis, which helps to draw blood inside the corpora cavernosa, which is further retained by an elastic band at the base of the penis. These devices are inexpensive and have very limited drawbacks. However, the erections created using this method are unnatural, being mechanical with a cold penis sensation, and nearly half of patients are not satisfied with this method.[125] Vacuum constrictive devices are usually reserved for patients with stable relationships, who failed oral PDE5-Is, and who have refused other more invasive options such as intracavernosal injection or penile prosthesis implantation. Side-effects include petechiae, penile numbness, and delayed ejaculation.[126]

### Penile prostheses

Penile prosthesis implantation, the third-line treatment for erectile dysfunction, is one of the few successful surgical treatments for erectile dysfunction. Implantation of a penile prosthesis is usually the last resort for treatment of erectile dysfunction, when other modalities have failed or are not preferred by the patient. Once the penile prosthesis surgery is done, the corporal tissue is irreversibly changed and no further smooth muscle relaxation is possible. There are two main types of penile prostheses. The semi-rigid prosthesis is usually easy to implant and lasts longer than the inflatable one. However, a semi-rigid prosthesis cannot produce a fully erect penis, and the device is difficult to conceal. Inflatable prostheses are usually made of two or three parts, including two penile cylinders with a scrotal pump for inflation. The scrotal pump is used to transfer fluid from a retropubic reservoir into the cylinders, thus creating a rigid erection. The device can be deflated by bending the penis mid-shaft.

The hydraulic three-piece implant is the most popular penile prosthesis in the USA. Satisfaction rates of patients with penile implants and their partners are high, reaching up to 70% and 90%, respectively.[127] The most common

complication of penile prostheses is infection, which occurs in 2–4% of cases.[128] Other surgical treatments for erectile dysfunction include arterial bypass procedures, which are specifically indicated for traumatic injuries of penile arteries (and can potentially lead to cure of the erectile dysfunction), and venous ligation surgery for young men with congenital abnormal venous leakage; however, vascular surgery is rarely done nowadays.

## Future perspectives

Although PDE5-Is are undoubtedly a huge step forward in the management of erectile dysfunction, they are far from flawless. Well-known shortcomings of PDE5-Is are their non-universal success rate, absence of spontaneity, and life-long drug commitment. At present, specific treatments that target more than just the inhibition of the PDE5 enzyme are being developed. For example, several guanylate cyclase activators have already undergone preclinical trials and promising results have been reported.[129] Other potential drugs undergoing experimental research include potassium channel inhibitors,[130] Rho kinase inhibitors,[131] and melanocortin system activators.[132]

The invention of the coronary artery stent has revolutionised the treatment of men with ischaemic heart disease. In the Pelvic Angiography in Non-responders to Phosphodiesterase-5 Inhibitors (PANPI) pilot study,[133] the stenosis in the coronary arteries typically mirrored that of the pudendal arteries, which ranged from a mean of 52% in the right internal pudendal artery to 60% in the left internal pudendal artery. The zotarolimus-eluting peripheral stent system for the treatment of erectile dysfunction in males with suboptimal response to PDE5 inhibitors (ZEN) trial,[134] which was initiated in 2009, is the first feasibility safety trial in human beings. A concurrent study, the Incidence of Male Pudendal Artery Stenosis in Suboptimal Erections Study (IMPASSE; NCT01341483), was designed to assess the angiographic patterns of atherosclerosis in erectile-related arteries in men with suspected or known CAD or peripheral artery disease undergoing diagnostic angiography. In a preliminary study, percutaneous treatment of pudendal artery stenosis with endovascular stents provided significant benefit to three patients with erectile dysfunction and peripheral arterial disease.[135] Several issues with patient selection, long-term efficacy and safety, and potential complications in this study should be addressed before peripheral vascular stents are recognised as a valid treatment option for erectile dysfunction. Also, low intensity extracorporeal shockwave therapy has been used successfully to treat vasculogenic erectile dysfunction in a highly selected group of patients.[136,137] However, although this technology is available for clinical use (eg, in Israel and Canada), confirmatory data from well-designed, double-blind, multicentre, long-term comparative studies are essential before it can be incorporated as a standard therapeutic option for erectile dysfunction.

An interesting new method for the treatment of erectile dysfunction is the application of gene therapy principles. The penis is one of the few organs that provides an ideal location for gene therapy because of its ease of access and homogeneous parenchymatous content, which enable the convenient delivery and spread of transfected genetic material.[138] After many studies successfully used preclinical genetic approaches—with molecules such as vasoactive intestinal peptide, brain-derived neurotrophic factor, and the maxi-K (calcium-sensitive potassium) channel—a breakthrough clinical study using the latter molecule was published in 2006.[139] Unfortunately, the small number of patients involved in this study (n=14), the absence of a control arm, and the low statistical power prevent a definitive conclusion on the efficacy of gene therapy for erectile dysfunction treatment from being reached. However, this landmark study does open new horizons in the specialty, giving researchers new hope for a potentially successful long-term treatment plan or cure for erectile dysfunction. Other hot areas of research include application of specific factors to stimulate endogenous neuropathic factors[140] and cell-based therapy.[141]

## Conclusions

Substantial advances in our understanding of the physiology of erection and the pathophysiology of erectile dysfunction led to the development of the first successful group of oral treatments for erectile dysfunction—PDE5-Is. Erectile dysfunction is now recognised as an early predictor of CAD. Despite these advances, there is still a great need for more effective therapeutic drugs that can provide long-lasting improvement for erectile dysfunction. Future promising therapeutic strategies, including gene and cell-based therapy, might lead to a cure for erectile dysfunction.

**Contributors**

RS developed the idea for the manuscript, designed the outline, searched the relevant published work, and wrote the manuscript. HG wrote the cause and diagnosis section of the manuscript and contributed to the writing of the manuscript.

**Conflicts of interest**

RS is on a clinical research fellowship at the Ottawa Hospital Research Institute supported by Lilly Pharmaceuticals. HS declares that he has no conflicts of interest.

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**References**

1 National Institutes of Health. Consensus development conference statement. Impotence. December 7–9, 1992. *Int J Impot Res* 1993; **5:** 181–284.

2 Smith GE. Papyrus ebers. English translation. Chicago: Ares Publishers, 1974.

3 Shah J. Erectile dysfunction through the ages. *BJU Int* 2002; **90:** 433–41.

4 Goldstein I, Lue TF, Padma-Nathan H, Rosen RC, Steers WD, Wicker PA, for the Sildenafil Study Group. Oral sildenafil in the treatment of erectile dysfunction. *N Engl J Med* 1998; **338:** 1397–404.

5 Guay AT, Perez JB, Jacobson J, Newton RA. Efficacy and safety of sildenafil citrate for treatment of erectile dysfunction in a population with associated organic risk factors. *J Androl* 2001; **22:** 793–97.

6 Kouvelas D, Goulas A, Papazisis G, Sardeli C, Pourzitaki C. PDE5 inhibitors: in vitro and in vivo pharmacological profile. *Curr Pharm Des* 2009; **15:** 3464–75.

7 Fisher WA, Rosen RC, Eardley I, et al. The multinational Men's Attitudes to Life Events and Sexuality (MALES) study phase II: understanding PDE5 inhibitor treatment seeking patterns, among men with erectile dysfunction. *J Sex Med* 2004; **1:** 150–60.

8 Sairam K, Kulinskaya E, Hanbury D, Boustead G, McNicholas T. Oral sildenafil (Viagra) in male erectile dysfunction: use, efficacy and safety profile in an unselected cohort presenting to a British district general hospital. *BMC Urol* 2002; **2:** 4.

9 Tomlinson J, Wright D. Impact of erectile dysfunction and its subsequent treatment with sildenafil: qualitative study. *BMJ* 2004; **328:** 1037.

10 Mehrotra N, Gupta M, Kovar A, Meibohm B. The role of pharmacokinetics and pharmacodynamics in phosphodiesterase-5 inhibitor therapy. *Int J Impot Res* 2007; **19:** 253–64.

11 Supuran CT, Mastrolorenzo A, Barbaro G, Scozzafava A. Phosphodiesterase 5 inhibitors—drug design and differentiation based on selectivity, pharmacokinetic and efficacy profiles. *Curr Pharm Des* 2006; **12:** 3459–65.

12 Carson CC, Lue TF. Phosphodiesterase type 5 inhibitors for erectile dysfunction. *BJU Int* 2005; **96:** 257–80.

13 Lewis RW, Fugl-Meyer KS, Corona G, et al. Definitions/epidemiology/risk factors for sexual dysfunction. *J Sex Med* 2010; **7:** 1598–607.

14 Bejin A. The epidemiology of premature ejaculation and of its association with erectile dysfunction. *Adrologie* 1999; **9:** 211–25.

15 Braun M, Wassmer G, Klotz T, Reifenrath B, Mathers M, Engelmann U. Epidemiology of erectile dysfunction: results of the 'Cologne Male Survey'. *Int J Impot Res* 2000; **12:** 305–11.

16 Pinnock CB, Stapleton AM, Marshall VR. Erectile dysfunction in the community: a prevalence study. *Med J Aust* 1999; **171:** 353–57.

17 Nicolosi A, Glasser DB, Kim SC, Marumo K, Laumann EO, for the GSSAB Investigators' Group. Sexual behaviour and dysfunction and help-seeking patterns in adults aged 40–80 years in the urban population of Asian countries. *BJU Int* 2005; **95:** 609–14.

18 Nicolosi A, Moreira ED Jr, Shirai M, Bin Mohd Tambi MI, Glasser DB. Epidemiology of erectile dysfunction in four countries: cross-national study of the prevalence and correlates of erectile dysfunction. *Urology* 2003; **61:** 201–06.

19 Johannes CB, Araujo AB, Feldman HA, Derby CA, Kleinman KP, McKinlay JB. Incidence of erectile dysfunction in men 40 to 69 years old: longitudinal results from the Massachusetts Male Aging Study. *J Urol* 2000; **163:** 460–63.

20 Bacon CG, Mittleman MA, Kawachi I, Giovannucci E, Glasser DB, Rimm EB. Sexual function in men older than 50 years of age: results from the health professionals follow-up study. *Ann Intern Med* 2003; **139:** 161–68.

21 Ayta IA, McKinlay JB, Krane RJ. The likely worldwide increase in erectile dysfunction between 1995 and 2025 and some possible policy consequences. *BJU Int* 1999; **84:** 50–56.

22 Rosen RC, Link CL, O'Leary MP, Giuliano F, Aiyer LP, Mollon P. Lower urinary tract symptoms and sexual health: the role of gender, lifestyle and medical comorbidities. *BJU Int* 2009; **103** (suppl 3)**:** 42–47.

23 Inman BA, Sauver JL, Jacobson DJ, et al. A population-based, longitudinal study of erectile dysfunction and future coronary artery disease. *Mayo Clin Proc* 2009; **84:** 108–13.

24 Thompson IM, Tangen CM, Goodman PJ, Probstfield JL, Moinpour CM, Coltman CA. Erectile dysfunction and subsequent cardiovascular disease. *JAMA* 2005; **294:** 2996–3002.

25 Quek KF, Sallam AA, Ng CH, Chua CB. Prevalence of sexual problems and its association with social, psychological and physical factors among men in a Malaysian population: a cross-sectional study. *J Sex Med* 2008; **5:** 70–76.

26 Clark NG, Fox KM, Grandy S, for the SHIELD Study Group. Symptoms of diabetes and their association with the risk and presence of diabetes: findings from the Study to Help Improve Early evaluation and management of risk factors Leading to Diabetes (SHIELD). *Diabetes Care* 2007; **30:** 2868–73.

27 Ponholzer A, Gutjahr G, Temml C, Madersbacher S. Is erectile dysfunction a predictor of cardiovascular events or stroke? A prospective study using a validated questionnaire. *Int J Impot Res* 2010; **22:** 25–29.

28 Chung SD, Chen YK, Lin HC, Lin HC. Increased risk of stroke among men with erectile dysfunction: a nationwide population-based study. *J Sex Med* 2011; **8:** 240–46.

29 Dong JY, Zhang YH, Qin LQ. Erectile dysfunction and risk of cardiovascular disease: meta-analysis of prospective cohort studies. *J Am Coll Cardiol* 2011; **58:** 1378–85.

30 Cheng JY, Ng EM. Body mass index, physical activity and erectile dysfunction: an U-shaped relationship from population-based study. *Int J Obes (Lond)* 2007; **31:** 1571–78.

31 Rosen RC, Wing R, Schneider S, Gendrano N 3rd. Epidemiology of erectile dysfunction: the role of medical comorbidities and lifestyle factors. *Urol Clin North Am* 2005; **32:** 403–17, v.

32 Esposito K, Giugliano F, Di Palo C, et al. Effect of lifestyle changes on erectile dysfunction in obese men: a randomized controlled trial. *JAMA* 2004; **291:** 2978–84.

33 Esposito K, Ciotola M, Giugliano F, et al. Effects of intensive lifestyle changes on erectile dysfunction in men. *J Sex Med* 2009; **6:** 243–50.

34 Esposito K, Giugliano D. Lifestyle/dietary recommendations for erectile dysfunction and female sexual dysfunction. *Urol Clin North Am* 2011; **38:** 293–301.

35 Esposito K, Giugliano F, De Sio M, et al. Dietary factors in erectile dysfunction. *Int J Impot Res* 2006; **18:** 370–74.

36 Esposito K, Ciotola M, Giugliano F, et al. Mediterranean diet improves erectile function in subjects with the metabolic syndrome. *Int J Impot Res* 2006; **18:** 405–10.

37 Lue TF. Erectile dysfunction. *N Engl J Med* 2000; **342:** 1802–13.

38 Prieto D. Physiological regulation of penile arteries and veins. *Int J Impot Res* 2008; **20:** 17–29.

39 Carson C, Dean J, Wylie M. Management of erectile dysfunction in clinical practice. New York: Springer Medical Publishing, 2006.

40 Siddiqui MA, Peng B, Shanmugam N, et al. Erectile dysfunction in young surgically treated patients with lumbar spine disease: a prospective follow-up study. *Spine (Phila Pa 1976)* 2012; **37:** 797–801.

41 Mulhall JP. Penile rehabilitation following radical prostatectomy. *Curr Opin Urol* 2008; **18:** 613–20.

42 Traish AM, Munarriz R, O'Connell L, et al. Effects of medical or surgical castration on erectile function in an animal model. *J Androl* 2003; **24:** 381–87.

43 Corona G, Rastrelli G, Monami M, et al. Hypogonadism as a risk factor for cardiovascular mortality in men: a meta-analytic study. *Eur J Endocrinol* 2011; **165:** 687–701.

44 Jackson G. The importance of risk factor reduction in erectile dysfunction. *Curr Urol Rep* 2007; **8:** 463–66.

45 Virag R, Bouilly P, Frydman D. Is impotence an arterial disorder? A study of arterial risk factors in 440 impotent men. *Lancet* 1985; **1:** 181–84.

46 Mittawae B, El-Nashaar AR, Fouda A, Magdy M, Shamloul R. Incidence of erectile dysfunction in 800 hypertensive patients: a multicenter Egyptian national study. *Urology* 2006; **67:** 575–78.

47 Burchardt M, Burchardt T, Baer L, et al. Hypertension is associated with severe erectile dysfunction. *J Urol* 2000; **164:** 1188–91.

48 Nehra A, Jackson G, Miner M, et al. The Princeton III consensus recommendations for the management of erectile dysfunction and cardiovascular disease. *Mayo Clin Proc* 2012; **87:** 766–78.

49 Böhm M, Baumhäkel M, Teo K, et al, for the ONTARGET/TRANSCEND Erectile Dysfunction Substudy Investigators. Erectile dysfunction predicts cardiovascular events in high-risk patients receiving telmisartan, ramipril, or both: The ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial/Telmisartan Randomized AssessmeNt Study in ACE iNtolerant subjects with cardiovascular Disease (ONTARGET/TRANSCEND) Trials. *Circulation* 2010; **121:** 1439–46.

50 Montorsi P, Montorsi F, Schulman CC. Is erectile dysfunction the "tip of the iceberg" of a systemic vascular disorder? *Eur Urol* 2003; **44:** 352–54.

51 Wespes E, Schulman C. Venous impotence: pathophysiology, diagnosis and treatment. *J Urol* 1993; **149:** 1238–45.

52 Dean RC, Lue TF. Physiology of penile erection and pathophysiology of erectile dysfunction. *Urol Clin North Am* 2005; **32:** 379–95, v.

53 Aversa A, Rossi F, Francomano D, et al. Early endothelial dysfunction as a marker of vasculogenic erectile dysfunction in young habitual cannabis users. *Int J Impot Res* 2008; **20:** 566–73.

54 Serretti A, Chiesa A. A meta-analysis of sexual dysfunction in psychiatric patients taking antipsychotics. *Int Clin Psychopharmacol* 2011; **26:** 130–40.

55 Thomas A, Woodard C, Rovner ES, Wein AJ. Urologic complications of nonurologic medications. *Urol Clin North Am* 2003; **30:** 123–31.

56 Do C, Huyghe E, Lapeyre-Mestre M, Montastruc JL, Bagheri H. Statins and erectile dysfunction: results of a case/non-case study using the French Pharmacovigilance System Database. *Drug Saf* 2009; **32:** 591–97.

57 Baumhäkel M, Schlimmer N, Kratz M, Hackett G, Jackson G, Böhm M. Cardiovascular risk, drugs and erectile function—a systematic analysis. *Int J Clin Pract* 2011; **65:** 289–98.

58 Martin-Morales A, Sanchez-Cruz JJ, Saenz de Tejada I, Rodriguez-Vela L, Jimenez-Cruz JF, Burgos-Rodriguez R. Prevalence and independent risk factors for erectile dysfunction in Spain: results of the Epidemiologia de la Disfuncion Erectil Masculina Study. *J Urol* 2001; **166:** 569–74, discussion 574–75.

59 El-Sakka AI. Association of risk factors and medical comorbidities with male sexual dysfunctions. *J Sex Med* 2007; **4:** 1691–700.

60 Ponholzer A, Temml C, Mock K, Marszalek M, Obermayr R, Madersbacher S. Prevalence and risk factors for erectile dysfunction in 2869 men using a validated questionnaire. *Eur Urol* 2005; **47:** 80–85, discussion 85–86.

61 Gatti A, Mandosi E, Fallarino M, et al. Metabolic syndrome and erectile dysfunction among obese non-diabetic subjects. *J Endocrinol Invest* 2009; **32:** 542–45.

62 Demir O, Akgul K, Akar Z, et al. Association between severity of lower urinary tract symptoms, erectile dysfunction and metabolic syndrome. *Aging Male* 2009; **12:** 29–34.

63 Hirshkowitz M, Karacan I, Arcasoy MO, Acik G, Narter EM, Williams RL. Prevalence of sleep apnea in men with erectile dysfunction. *Urology* 1990; **36:** 232–34.

64 Holden CA, McLachlan RI, Pitts M, et al. Determinants of male reproductive health disorders: the Men in Australia Telephone Survey (MATeS). *BMC Public Health* 2010; **10:** 96.

65 Bellinghieri G, Santoro D, Mallamace A, Savica V. Sexual dysfunction in chronic renal failure. *J Nephrol* 2008; **21** (suppl 13)**:** S113–17.

66 Huyghe E, Kamar N, Wagner F, et al. Erectile dysfunction in end-stage liver disease men. *J Sex Med* 2009; **6:** 1395–401.

67 Köseoğlu N, Köseoğlu H, Ceylan E, Cimrin HA, Ozalevli S, Esen A. Erectile dysfunction prevalence and sexual function status in patients with chronic obstructive pulmonary disease. *J Urol* 2005; **174:** 249–52, discussion 252.

68 The Process of Care Consensus Panel. The process of care model for evaluation and treatment of erectile dysfunction. *Int J Impot Res* 1999; **11:** 59–70, discussion 70–74.

69 Hatzichristou D, Rosen RC, Derogatis LR, et al. Recommendations for the clinical evaluation of men and women with sexual dysfunction. *J Sex Med* 2010; **7:** 337–48.

70 Eardley I, Donatucci C, Corbin J, et al. Pharmacotherapy for erectile dysfunction. *J Sex Med* 2010; **7:** 524–40.

71 Hatzimouratidis K, Amar E, Eardley I, et al, for the European Association of Urology. Guidelines on male sexual dysfunction: erectile dysfunction and premature ejaculation. *Eur Urol* 2010; **57:** 804–14.

72 Montorsi F, Adaikan G, Becher E, et al. Summary of the recommendations on sexual dysfunctions in men. *J Sex Med* 2010; **7:** 3572–88.

73 Rosen RC, Cappelleri JC, Smith MD, Lipsky J, Peña BM. Development and evaluation of an abridged, 5-item version of the International Index of Erectile Function (IIEF-5) as a diagnostic tool for erectile dysfunction. *Int J Impot Res* 1999; **11:** 319–26.

74 Rosen RC, Riley A, Wagner G, Osterloh IH, Kirkpatrick J, Mishra A. The international index of erectile function (IIEF): a multidimensional scale for assessment of erectile dysfunction. *Urology* 1997; **49:** 822–30.

75 Ghanem H, Shamloul R. An evidence-based perspective to commonly performed erectile dysfunction investigations. *J Sex Med* 2008; **5:** 1582–89.

76 Montorsi P, Ravagnani PM, Galli S, et al. Association between erectile dysfunction and coronary artery disease: matching the right target with the right test in the right patient. *Eur Urol* 2006; **50:** 721–31.

77 Miner MM. Erectile dysfunction: a harbinger or consequence: does its detection lead to a window of curability? *J Androl* 2011; **32:** 125–34.

78 Vardi Y, Dayan L, Apple B, Gruenwald I, Ofer Y, Jacob G. Penile and systemic endothelial function in men with and without erectile dysfunction. *Eur Urol* 2009; **55:** 979–85.

79 Peled N, Shitrit D, Fox BD, et al. Peripheral arterial stiffness and endothelial dysfunction in idiopathic and scleroderma associated pulmonary arterial hypertension. *J Rheumatol* 2009; **36:** 970–75.

80 El Melegy NT, Ali ME, Awad EM. Plasma levels of endothelin-1, angiotensin II, nitric oxide and prostaglandin E in the venous and cavernosal blood of patients with erectile dysfunction. *BJU Int* 2005; **96:** 1079–86.

81 Bocchio M, Desideri G, Scarpelli P, et al. Endothelial cell activation in men with erectile dysfunction without cardiovascular risk factors and overt vascular damage. *J Urol* 2004; **171:** 1601–04.

82 Baumhäkel M, Werner N, Böhm M, Nickenig G. Circulating endothelial progenitor cells correlate with erectile function in patients with coronary heart disease. *Eur Heart J* 2006; **27:** 2184–88.

83 Foresta C, Caretta N, Lana A, Cabrelle A, Palù G, Ferlin A. Circulating endothelial progenitor cells in subjects with erectile dysfunction. *Int J Impot Res* 2005; **17:** 288–90.

84 Esposito K, Ciotola M, Maiorino MI, et al. Circulating CD34+ KDR+ endothelial progenitor cells correlate with erectile function and endothelial function in overweight men. *J Sex Med* 2009; **6:** 107–14.

85 Derby CA, Mohr BA, Goldstein I, Feldman HA, Johannes CB, McKinlay JB. Modifiable risk factors and erectile dysfunction: can lifestyle changes modify risk? *Urology* 2000; **56:** 302–06.

86 Hannan JL, Maio MT, Komolova M, Adams MA. Beneficial impact of exercise and obesity interventions on erectile function and its risk factors. *J Sex Med* 2009; **6** (suppl 3)**:** 254–61.

87 Hannan JL, Heaton JP, Adams MA. Recovery of erectile function in aging hypertensive and normotensive rats using exercise and caloric restriction. *J Sex Med* 2007; **4:** 886–97.

88 Mannino DM, Klevens RM, Flanders WD. Cigarette smoking: an independent risk factor for impotence? *Am J Epidemiol* 1994; **140:** 1003–08.

89 Guay AT, Perez JB, Heatley GJ. Cessation of smoking rapidly decreases erectile dysfunction. *Endocr Pract* 1998; **4:** 23–26.

90 Horasanli K, Boylu U, Kendirci M, Miroglu C. Do lifestyle changes work for improving erectile dysfunction? *Asian J Androl* 2008; **10:** 28–35.

91 Chew KK, Bremner A, Stuckey B, Earle C, Jamrozik K. Alcohol consumption and male erectile dysfunction: an unfounded reputation for risk? *J Sex Med* 2009; **6:** 1386–94.

92 Miller NS, Gold MS. The human sexual response and alcohol and drugs. *J Subst Abuse Treat* 1988; **5:** 171–77.

93 Maio G, Saraeb S, Marchiori A. Physical activity and PDE5 inhibitors in the treatment of erectile dysfunction: results of a randomized controlled study. *J Sex Med* 2010; **7:** 2201–08.

94 Gupta BP, Murad MH, Clifton MM, Prokop L, Nehra A, Kopecky SL. The effect of lifestyle modification and cardiovascular risk factor reduction on erectile dysfunction: a systematic review and meta-analysis. *Arch Intern Med* 2011; **171:** 1797–803.

95 Konstantinos G, Petros P. Phosphodiesterase-5 inhibitors: future perspectives. *Curr Pharm Des* 2009; **15:** 3540–51.

96 Brant WO, Bella AJ, Lue TF. Treatment options for erectile dysfunction. *Endocrinol Metab Clin North Am* 2007; **36:** 465–79.

97 Andersson KE. Mechanisms of penile erection and basis for pharmacological treatment of erectile dysfunction. *Pharmacol Rev* 2011; **63:** 811–59.

98 Viagra (sildenafil citrate) prescribing information. http://www.pfizer.com/files/products/uspi_viagra.pdf (accessed March 1, 2012).

99 Levitra (vardenafil hydrochloride) prescribing information. http://www.levitra.com/assets/pdf/PI.pdf (accessed March 1, 2012).

100 Cialis (tadalafil) prescribing information. http://pi.lilly.com/us/cialis-pi.pdf (accessed March 1, 2012).

101 Setter SM, Iltz JL, Fincham JE, Campbell RK, Baker DE. Phosphodiesterase 5 inhibitors for erectile dysfunction. *Ann Pharmacother* 2005; **39:** 1286–95.

102 Carson CC 3rd. Phosphodiesterase type 5 inhibitors: state of the therapeutic class. *Urol Clin North Am* 2007; **34:** 507–15, vi.

103 Kendirci M, Tanriverdi O, Trost L, Hellstrom WJ. Management of sildenafil treatment failures. *Curr Opin Urol* 2006; **16:** 449–59.

104 Behr-Roussel D, Gorny D, Mevel K, et al. Chronic sildenafil improves erectile function and endothelium-dependent cavernosal relaxations in rats: lack of tachyphylaxis. *Eur Urol* 2005; **47:** 87–91.

105 Ferrini MG, Kovanecz I, Sanchez S, et al. Long-term continuous treatment with sildenafil ameliorates aging-related erectile dysfunction and the underlying corporal fibrosis in the rat. *Biol Reprod* 2007; **76:** 915–23.

106 McMahon CG. Treatment of erectile dysfunction with chronic dosing of tadalafil. *Eur Urol* 2006; **50:** 215–17.

107 Porst H, Giuliano F, Glina S, et al. Evaluation of the efficacy and safety of once-a-day dosing of tadalafil 5 mg and 10 mg in the treatment of erectile dysfunction: results of a multicenter, randomized, double-blind, placebo-controlled trial. *Eur Urol* 2006; **50:** 351–59.

108 Wrishko R, Sorsaburu S, Wong D, Strawbridge A, McGill J. Safety, efficacy, and pharmacokinetic overview of low-dose daily administration of tadalafil. *J Sex Med* 2009; **6:** 2039–48.

109 Porst H, Rajfer J, Casabé A, et al. Long-term safety and efficacy of tadalafil 5 mg dosed once daily in men with erectile dysfunction. *J Sex Med* 2008; **5:** 2160–69.

110 Bella AJ, Deyoung LX, Al-Numi M, Brock GB. Daily administration of phosphodiesterase type 5 inhibitors for urological and nonurological indications. *Eur Urol* 2007; **52:** 990–1005.

111 Gruenwald I, Leiba R, Vardi Y. Effect of sildenafil on middle-aged sexually active males with no erectile complaints: a randomized placebo-controlled double-blind study. *Eur Urol* 2009; **55:** 969–76.

112 Ekmekçioğlu O, Inci M, Demirci D, Tatlişen A. Effects of sildenafil citrate on ejaculation latency, detumescence time, and refractory period: placebo-controlled, double-blind, crossover laboratory setting study. *Urology* 2005; **65:** 347–52.

113 Morganroth J, Ilson BE, Shaddinger BC, et al. Evaluation of vardenafil and sildenafil on cardiac repolarization. *Am J Cardiol* 2004; **93:** 1378–83, A6.

114 Aoyagi T, Hayakawa K, Miyaji K, Ishikawa H, Hata M. Sildenafil induced priapism. *Bull Tokyo Dent Coll* 1999; **40:** 215–17.

115 King SH, Hallock M, Strote J, Wessells H. Tadalafil-associated priapism. *Urology* 2005; **66:** 432.

116 Tomsak R. PDE5 inhibitors and permanent visual loss. *Int J Impot Res* 2005; **17:** 547–49.

117 Carson CC, Burnett AL, Levine LA, Nehra A. The efficacy of sildenafil citrate (Viagra) in clinical populations: an update. *Urology* 2002; **60** (suppl 2)**:** 12–27.

118 McGwin G Jr. Phosphodiesterase type 5 inhibitor use and hearing impairment. *Arch Otolaryngol Head Neck Surg* 2010; **136:** 488–92.

119 Jain P, Rademaker AW, McVary KT. Testosterone supplementation for erectile dysfunction: results of a meta-analysis. *J Urol* 2000; **164:** 371–75.

120 Shabsigh R, Kaufman JM, Steidle C, Padma-Nathan H. Randomized study of testosterone gel as adjunctive therapy to sildenafil in hypogonadal men with erectile dysfunction who do not respond to sildenafil alone. *J Urol* 2008; **179** (suppl)**:** S97–102.

121 Shamloul R, Ghanem H, Fahmy I, et al. Testosterone therapy can enhance erectile function response to sildenafil in patients with PADAM: a pilot study. *J Sex Med* 2005; **2:** 559–64.

122 Hatzimouratidis K, Hatzichristou DG. A comparative review of the options for treatment of erectile dysfunction: which treatment for which patient? *Drugs* 2005; **65:** 1621–50.

123 Perimenis P, Konstantinopoulos A, Perimeni PP, et al. Long-term treatment with intracavernosal injections in diabetic men with erectile dysfunction. *Asian J Androl* 2006; **8:** 21924.

124 Williams G, Abbou CC, Amar ET, et al, for the MUSE Study Group. Efficacy and safety of transurethral alprostadil therapy in men with erectile dysfunction. *Br J Urol* 1998; **81:** 889–94.

125 Glina S, Porst H. Vacuum erection devices. In: Porst H, Buvat J, eds. Standard practice in sexual medicine. Malden, MA: Blackwell/ISSM, 2006: 121–25.

126 Wessels H. Vacuum erection devices. In: Mulcahy J, ed. Male sexual function, a guide to clinical management. Totowa, NJ: Humana Press, 2006: 323–29.

127 Bettocchi C, Palumbo F, Spilotros M, et al. Patient and partner satisfaction after AMS inflatable penile prosthesis implant. *J Sex Med* 2010; **7:** 304–09.

128 Selph JP, Carson CC 3rd. Penile prosthesis infection: approaches to prevention and treatment. *Urol Clin North Am* 2011; **38:** 227–35.

129 Brioni JD, Nakane M, Hsieh GC, Moreland RB, Kolasa T, Sullivan JP. Activators of soluble guanylate cyclase for the treatment of male erectile dysfunction. *Int J Impot Res* 2002; **14:** 8–14.

130 Venkateswarlu K, Giraldi A, Zhao W, et al. Potassium channels and human corporeal smooth muscle cell tone: diabetes and relaxation of human corpus cavernosum smooth muscle by adenosine triphosphate sensitive potassium channel openers. *J Urol* 2002; **168:** 355–61.

131 Chitaley K, Wingard CJ, Clinton Webb R, et al. Antagonism of Rho-kinase stimulates rat penile erection via a nitric oxide-independent pathway. *Nat Med* 2001; **7:** 119–22.

132 Martin WJ, McGowan E, Cashen DE, et al. Activation of melanocortin MC(4) receptors increases erectile activity in rats ex copula. *Eur J Pharmacol* 2002; **454:** 71–79.

133 Rogers JH, Karimi H, Kao J, et al. Internal pudendal artery stenoses and erectile dysfunction: correlation with angiographic coronary artery disease. *Catheter Cardiovasc Interv* 2010; **76:** 882–87.

134 Chung E, Brock GB. Emerging and novel therapeutic approaches in the treatment of male erectile dysfunction. *Curr Urol Rep* 2011; **12:** 432–43.

135 Babaev A, Jhaveri RR. Angiography and endovascular revascularization of pudendal artery atherosclerotic disease in patients with medically refractory erectile dysfunction. *J Invasive Cardiol* 2012; **24:** 236–40.

136 Vardi Y, Appel B, Kilchevsky A, Gruenwald I. Does low intensity extracorporeal shock wave therapy have a physiological effect on erectile function? Short-term results of a randomized, double-blind, sham controlled study. *J Urol* 2012; **187:** 1769–75.

137 Burnett AL. Erectile dysfunction management for the future. *J Androl* 2009; **30:** 391–96.

138 Burchardt M, Burchardt T, Anastasiadis AG, et al. Application of angiogenic factors for therapy of erectile dysfunction: protein and DNA transfer of VEGF 165 into the rat penis. *Urology* 2005; **66:** 665–70.

139 Melman A, Bar-Chama N, McCullough A, Davies K, Christ G. hMaxi-K gene transfer in males with erectile dysfunction: results of the first human trial. *Hum Gene Ther* 2006; **17:** 1165–76.

140 Xie D, Annex BH, Donatucci CF. Growth factors for therapeutic angiogenesis in hypercholesterolemic erectile dysfunction. *Asian J Androl* 2008; **10:** 23–27.

141 Bivalacqua TJ, Deng W, Kendirci M, et al. Mesenchymal stem cells alone or ex vivo gene modified with endothelial nitric oxide synthase reverse age-associated erectile dysfunction. *Am J Physiol Heart Circ Physiol* 2007; **292:** H1278–90.