

Singapore Urological Association Erectile Dysfunction Guidelines

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Overview

The introduction of oral therapies for erectile dysfunction has raised the awareness of this condition. Many men have realized that this condition can be effectively treated and have sought the help of physicians to treat this condition.

The incidence of erectile dysfunction increases with age. According to MMAS, the combined prevalence of mild, moderate and severe erectile dysfunction is 52% in non-institutionalized 40 to 70 year old men in the Boston area. In this study, the individual prevalences were 17.2%, 25.2% and 9.6% for minimal, moderate and complete ED.¹ Being a quality of life issue, many men have accepted erectile dysfunction as part and parcel of aging. However, with better medical care and increasing life expectancy, the quality of erectile and sexual function has become an important and integral part of issues relating to quality of life, as well as being an essential component to healthy aging.

At the level of the end organ – the penis, erection is mainly a vascular phenomenon, and this includes arterial dilatation, trabecular smooth muscle relaxation and activation of the corporeal veno-occlusive mechanism.^{2,3} During erection, there is increased blood flow through the cavernosal arteries. The sinusoidal spaces become filled with blood and the penis becomes skeletally rigid. During the period of maximal rigidity, there is absent venous return from the penis due to the compression of the subtunical venules. The nervous system is also important. At the higher level, it receives the psychic stimulus to initiate the chain of events leading to erection. The spinal cord contains centres that integrate the erectile responses. A proper functioning peripheral and autonomic nerves are necessary to coordinate the tumescence and detumescence phases of the erectile response. The endocrine system facilitates the erectile response. The presence of sex hormone, especially the male hormone, testosterone acts via a tropic effect on the erectile tissues. Imbalances of other hormones that can affect erection include prolactin and thyroid hormones.

From the mechanism of erection, it follows that healthy blood vessels; properly functioning nervous system, including the brain; and good endocrine balance are essential for tumescence. Traditionally, the aetiology of erectile dysfunction has been divided into psychogenic and organic causes. The organic causes are further subdivided into vasculogenic, neurogenic and endocrine causes. In the past, most of the erectile dysfunction was thought to be due to psychogenic causes. However, with better understanding of the erectile mechanism, more patients are found to have organic causes to their problem. The subdivision of the organic causes is also not mutually exclusive. For example, diabetes mellitus causes erectile dysfunction at several levels – it can cause atherosclerosis (vasculogenic), peripheral and autonomic neuropathy (neurogenic) and rarely hypogonadism (endocrine).

If erection is a mainly vascular phenomenon, then the erectile capability reflects cardiovascular health. Many men, who would otherwise not see a physician, would present to the doctor of this problem. This presents an opportunity to screen patients for cardiovascular diseases.

Grading of quality of available evidence

Category of evidence

Ia—meta-analysis of randomised controlled trials

Ib—at least one randomised controlled trial

IIa—at least one controlled study without randomisation

IIb—at least one other type of quasiexperimental study

III—non-experimental, descriptive studies, such as comparative studies, correlation studies, and case studies

IV—expert committee reports or the opinions or clinical experience of respected authorities, or both

Strength of recommendation

Grade A (levels Ia and Ib)—at least one randomised controlled trial as part of the body of literature of overall good quality and consistency addressing specific recommendations

Grade B (levels IIa, IIb, and III)—availability of well conducted clinical studies, but no randomised clinical trials on the topic of recommendation

Grade C (level IV)—evidence obtained from expert committee reports or the opinions or clinical experience of respected authorities, or both. Indicates absence of directly applicable clinical studies of good quality

Diagnosis

Erectile dysfunction is defined as persistent inability to sustain an erection of sufficient rigidity and duration to achieve satisfactory penetration during intercourse. Within the broad limits of this definition, erectile dysfunction is usually a subjective complaint.

History

The history should be taken in a relaxed environment. Some patients are shy about their problems and environment should be as conducive as possible, and privacy being the most important factor.⁴

The sexual history should include previous and current sexual relationships, current emotional status, onset and duration of the erectile problem. Generally, a sudden onset of erectile dysfunction in a young patient with acute precipitating factors (eg. Stressors like job loss, marital difficulties) point towards psychogenic cause of erectile dysfunction.

General medical history is important as many diseases affect the erection process. As erection is a mainly vascular process, risk factors for cardiovascular diseases like hypertension (and its medications), diabetes mellitus, hyperlipidaemia and smoking play an important role in the pathogenesis of erectile dysfunction. Other important medical problems include systemic diseases like chronic renal failure, liver problems and cerebral vascular accidents.

Drug history should also be taken. Many drugs, particularly anti hypertensive and psychotropic drugs may cause ED.⁵ (Grade C, level IV)

Surgical history like penile surgery, anterior resection (which may affect the sacral plexus), and radical prostatectomy etc can affect erection.

The use of validated questionnaires, such as the International index for erectile function (IIEF) (Annex A) may be helpful in order to assess objectively not only the present status but also the impact of a specific treatment.⁶ (Grade B, level IIa)

Physical Examination

Physical examination includes a general examination to look for any gross endocrine problem eg. hypothyroidism. Also, it is useful to assess the degree of virilization of the men to look for hypogonadism. Blood pressure should be measured. The penis is examined for any structural abnormalities, or any plaques, the latter of which could suggest Peyronie's disease. The testicular size is assessed. Digital rectal examination is performed to assess the anal tone. Lower limb pulses and reflexes are also examined to assess for any vasculogenic or neurogenic problems. (Grade C, level IV)

Investigations

Recommended

The aetiologies of most patients can be obtained from the history and physical examination. Blood and urine investigations are not necessary before starting therapy. The physician may wish to perform certain tests to screen for possible risk factors of erectile dysfunction. A blood glucose specimen could be done to screen for diabetes mellitus. Endocrine blood tests of free thyroxine and thyroid stimulating hormone; prolactin; luteinizing hormone, follicle stimulating hormone and testosterone can be done. The yield from the endocrine blood tests is however low. (Grade C, level IV)

Optional

For erectile dysfunction which is refractory to first line oral therapy, further specialized investigations can be performed. Other circumstances which may dictate the need for specific diagnostic testing are:

- The patient with primary erectile disorder (not caused by organic disease or psychogenic disease).
- Young patients with a history of pelvic or perineal trauma who could benefit from potentially curative vascular surgery.
- For medico-legal reasons.

Colour Doppler ultrasound is useful to study the vascularity of the penis. A peak systolic blood flow higher than 30 cm/s and a resistance index higher than 0.8 are generally considered as normal.⁷ (Grade C, level IV)

Intracavernosal injection of the penis to induce an erection can be performed to look for any structural abnormalities in the penis, for example, penile curvature in Peyronie's disease. The injection test also offers limited information regarding vascular status. A positive test is defined as a rigid erectile response (unable to bend the penis) that appears within 10 minutes after the intracavernosal injection and lasts for 30 min. Such a response may be considered to be associated with normal arterial and veno-occlusive haemodynamics. (Grade C, level IV)

Cavernosography is a procedure whereby radiographic contrast is injected into the corporal bodies. This is a painful procedure. It allows the venous drainage of the penis to be studied and is useful to look for venous leak impotence. (Grade C, level IV)

Treatment

1st Line Treatment

Lifestyle Modifications

As erection is essentially a vascular event, lifestyle modifications which help to decrease atherosclerosis would also help penile health. It is recommended that patients should stop smoking, have regular exercises and take a healthy diet. Patients who have high risk of vascular diseases, eg. Those with hypertension, diabetes mellitus and hyperlipidaemia should have their conditions well controlled. (Grade C, level IV)

Phosphodiesterase type V inhibitors

The mainstay of oral therapy currently is phosphodiesterase type 5 (PDE₅) inhibitors. They act by inhibiting type V phosphodiesterase which would hydrolyze cyclic

guanosine monophosphate (cGMP) in the cavernosum tissue of the penis. cGMP is involved in the nitric oxide mediated smooth muscle relaxation, which in turn leads to increased arterial blood flow, vasodilatation and penile erection. Currently, 3 potent selective PDE₅ inhibitors are available - Sildenafil (Viagra)⁸, Vardenafil (Levitra)⁹ and Tadalafil (Cialis)¹⁰. They have similar side effect profiles.¹¹ Their pharmacokinetics parameters are reflected in table 1.

Table 1 – Pharmacokinetics profile of PDE₅ inhibitors.

	Sildenafil (100 mg)	Vardenafil (20 mg)	Tadalafil (20 mg)
Tmax (hr)	1.16	0.75	2
Half life (hr)	3.82	4.7	17.5
Cmax (ng/ml)	327	31.8	278
AUC (ng/ml/hr)	1963	96.3	8066

Clinical trials performed in multiple countries had shown strong efficacy (improved erections in up to 84% of men) and good safety of PDE₅ inhibitors in the general population ([Grade A, level 1b](#)) as well as in a difficult to treat population such as diabetic patients, and patients who had undergone radical prostatectomy. There have been no published head to head clinical trials comparing Sildenafil, Vardenafil and Tadalafil. Patients should be encouraged to try all PDE₅ inhibitors and develop their own opinion. They will choose the compound that is perceived by them to have the best efficacy as well as other features such as time of onset, duration of action, window of opportunity and their own individual experience with side effects. ([Grade C, level IV](#))

Administration of PDE₅ inhibitors

For Sildenafil¹² and Vardenafil¹³, the patient is advised to take the medications about an hour before sexual intercourse. These 2 drugs are effective after about 30 – 60 minutes in the presence of sexual stimulation, and their effects can last up to 4 hours. If the drugs are taken with or just after heavy fatty meals, they may take a little longer to start working.

For Cialis¹⁴, the patient is advised to take the medication about 1 – 2 hours before the sexual intercourse. Because of its longer half-life, its effect can last up to 36 hours.

For all 3 drugs, patient should be limited to 1 dose within a 24-hour period. He should not mix any of the 3 drugs together within a single day. He should also be reminded that these drugs help them to achieve an erection when he is sexually stimulated, but will not get an erection just by taking the drugs.

Patients are advised to try 4 doses of the drug and counseled adequately before they are evaluated for efficacy of the drug. In many non-responders, they might be using the drug inappropriately. In a study of 100 Sildenafil non-responders, inappropriate use of Sildenafil was recognized in 56 patients. 45 patients had never used the highest recommended dose, 32 had taken the pill with a full stomach right after a meal, 22 had

taken the pill just before the initiation of sexual activity and 12 were not aware that sexual stimulation was mandatory to achieve an erection.¹⁵

For true non-responders, 2nd and 3rd line treatments can be considered.

Side Effects of PDE₅ inhibitors

The most common side effects of PDE₅ inhibitors include headaches (11-19%), flushing (5-19%), dyspepsia (6-17%), nasal congestion (5-7%), back pain (0-9%), visual disturbances (0-3%). (Grade A, level Ib)

It may be hazardous to prescribe PDE₅ inhibitors in patients with: (Grade C, level IV)

- Active coronary ischaemia
 - Congestive heart failure and borderline low blood pressure
 - Borderline low cardiac volume status
 - A complicated multi-drug anti-hypertensive program
 - Drug therapy that can prolong the half-life of PDE₅ inhibitors
- All 3 drugs are metabolized mainly via cytochrome P450 CYP3A4, a dose adjustment should be considered when given in combination with CYP3A4 inhibitors eg. Ketoconazole, erythromycin.¹⁶

Contraindications to PDE₅ inhibitors

Being on nitrates is an absolute contraindication to PDE₅ inhibitor treatment. This is because studies have shown that the combination of these 2 drugs resulted in severe hypotension. (Grade B, level IIa)

Patients with an inherited condition called retinitis pigmentosa should not use PDE₅ inhibitors. This is because PDE₅ inhibitors might also affect the retinal enzyme phosphodiesterase type 6 (PDE₆).

PDE₅ inhibitors in patient with cardiovascular disease

Patient with history of ischaemic heart disease may need to be further evaluated before embarking on PDE₅ inhibitor therapy. This is not because PDE₅ inhibitors will harm patient with cardiovascular disease per se, but because sexual activity itself is a form of exertion that stresses the cardiovascular system, and patients need to be fit enough in this respect to perform sexual intercourse. Sexual activity increases physical exertion levels to 3 to 4 METS (1 MET is the amount of energy used at the resting state associated with oxygen consumption of approximately 3.5 ml/kg/min), and sympathetic activation during sexual activity may increase blood pressure and heart rate more than other types of exercise.¹⁷ Together, these factors result in a 2.5 fold greater relative risk of non fatal

myocardial infarction following sexual activity in healthy men than during noncoital activities and a 2.9 fold greater risk in men with a history of myocardial infarction. Even with this effect, the absolute risk of myocardial infarct during and for 2 hours following sexual activity is extremely low – only 20 chances per million per hour in post-myocardial infarct patients and even less in men without a history of MI.¹⁸ (Grade B, level III)

PDE₅ and diabetes mellitus

PDE₅ inhibitors are effective for patients with diabetes mellitus, but most require a higher dosage to be effective.¹⁹ (Grade B, level III)

PDE₅ inhibitors and NAION

A small number of men have lost eyesight in one eye some time after taking Sildenafil, Tadalafil, or Vardenafil. This type of vision loss is called non-arteritic anterior ischemic optic neuropathy (NAION). NAION causes a sudden loss of eyesight because blood flow is blocked to the optic nerve.

We do not know at this time if Sildenafil, Tadalafil, or Vardenafil causes NAION. NAION also happens in men who do not take these medicines. People who have a higher chance for NAION include those who:

- have heart disease
- are over 50 years old
- have diabetes
- have high blood pressure
- have high cholesterol
- smoke
- have certain eye problems

US Food and Drug Administration (FDA) has approved new labels for Sildenafil, Tadalafil, and Vardenafil to include information on possible eyesight loss (NAION).

Patients should be advised to stop using Sildenafil, Tadalafil, or Vardenafil if they have any loss of vision.²⁰ (Grade C, level IV)

PDE₅ inhibitors and alpha blockers

Many patients who suffer from erectile dysfunction also have lower urinary tract symptoms and they could be on alpha blockers like prazosin, terazosin or alfuzosin. As alpha blockers themselves can cause postural hypotension, patients are advised to time

their drug intake so that the interval separating alpha blockers and Sildenafil is at least 4 hrs apart.²¹ (Grade C, level IV)

Psychosexual therapy

The success of psychosexual therapy depends on the motivation of the patient, because it will require him to work with the therapist to find an understanding of what prevents him from experiencing normal sexual arousal. A review outcome studies in psychosexual therapy published since 1970 showed successful outcomes in 50-80% of patients.²² Psychosexual therapy may be used in conjunction with medications and therapies. (Grade C, level IV)

2nd Line Treatment

Intracavernosal injection

Intracavernosal injection involves the direct injection of vasoactive agent into the penis. One of the most commonly used agent is alprostadil (PGE₁). Other agents include phentolamine, vasointestinal polypeptide, phentolamine-papaverine.²³

Intracavernosal therapy is effective in 60-90% of ED. The erection appears after 5–15 minutes and lasts according to the dose injected.

Injection therapy is contraindicated in patients who are on anticoagulants. It is also contraindicated in men with history of hypersensitivity to the drug and in men at risk of priapism. It is not advised in men with limited manual dexterity but their partners may be taught the technique. Pain during the injection is the commonest side effect. Other side effects include prolonged erection or priapism. (Grade B, level IIa)

Priapism is prolonged erection lasting for more than 4 hours. This risk of priapism is higher with intracavernosal injection as compared to other erectile dysfunction therapies. Intracavernosal aspiration is the initial treatment for priapism. A 19-gauge needle is used to aspirate blood and therefore to decrease the intracavernous pressure. This simple method is usually sufficient to make the penis flaccid. However, if the penis becomes rigid again after this, phenylephrine intracavernous injection at a dose starting at 200 mcg every 5 minutes and increasing to 500 mcg, if necessary, is required. If phenylephrine is injected, the patient must be carefully observed for systemic, especially cardiovascular effect.

Vacuum constriction device

2 types of vacuum constriction device are currently available – manual and electric. Both involve placing a tube around the penis and creating a negative pressure within the tube,

causing influx of blood into the penis. Once the penis is erected, a rubber constriction band is placed at the base of the penis. An important reminder is to remove the rubber constriction band after 30 mins.

The device is suitable for a wide range of patients with chronic or occasional erectile dysfunction, whatever the cause. One study quoted an overall clinical success rate of around 90%, with more than 80% of patients continuing with the device, but in another study only 23% of patients asked for a prescription after a two week trial and only 53% of these reported complete or reasonable satisfaction.^{24,25} (Grade B, level IIa)

Vacuum constriction device should not be used in patients who are on anticoagulants. The most common side effects are bruising and pain at the rubber constriction band site.

3rd Line Treatment

3rd line treatment would involve surgical treatment.

Penile Implant Surgery

Penile implant surgery is reserved for erectile dysfunction that is refractory to all other forms of intervention. It involves the replacement of the corporal bodies with prostheses. If the penile implant fails, patients would have no other means of erection, except for a revision/replacement penile implant.

The infection rate after penile implant surgery is 1.06% (prosthesis with hydrophilic coating).²⁶ Prostatic infection is the most problematic complication following surgery as the combination of infection and a foreign body requires the removal of the prosthesis. The patients most commonly affected by infection problems are diabetics. The mechanical failure rate of penile implant in 5 yrs time ranges from 6 to 16%. (Grade B, level III)

Penile Vascular Surgery

Penile vascular surgeries do not work for all patients, even those with vascular problems. However, in a certain subset of patients, it may prove useful. These operations do not involve the removal of corporal cavernosal body tissues, and do not preclude penile implant surgery if they fail. (Grade C, level IV)

Venous Ligation

This involves the ligation of the dorsal vein of the penis and its main tributaries. This is usually performed together with crural plication – the plication of superficial veins on the

crural bodies. This operation may be indicated for patients with venous leak impotence, as demonstrated on colour Doppler ultrasound or cavernosography.²⁷

Penile Revascularization

Various methods of penile revascularization have been reported – anastomosis of inferior epigastric artery to dorsal penile artery (dorsal artery arterialization), anastomosis of the inferior epigastric artery to the dorsal penile vein (dorsal vein arterialization). Satisfactory outcome, measured by objective criteria, occurred in 36% to 91% of patients.^{28, 29}

Arterial reconstructive surgery is a treatment option only in healthy individuals with recently acquired erectile dysfunction secondary to focal arterial occlusion and in the absence of any evidence of generalized vascular disease.³⁰

Annex A – International Index of Erectile Dysfunction

The original International Index of Erectile Dysfunction (IIEF) has 15 questions.³¹ Of the 15 questions, six had moderate or good discrimination between men with and without erectile dysfunction. Five questions were chosen (IIEF-5) in which the maximum score was 25 and the minimum 5.³² Men without erectile dysfunction had a mean score of 23 and men with erectile dysfunction had a mean score of 11. These were evaluated in a number of ways, but principally to define a cut point above which erectile dysfunction would be unlikely, and below which it would be likely. That cut point was determined to be a score of 21. This score had a sensitivity of 98% and specificity of 88%, giving a likelihood ratio for a positive test of 8 and for a negative result of 0.02.

IIEF-5 is useful to screen for erectile dysfunction, and to follow up on the efficacies of the various forms of erectile dysfunction therapies.

IIEF-5 scoring system

	Score				
Over the past six months:	1	2	3	4	5
How do you rate your confidence that you could get and keep an erection?	Very low	Low	Moderate	High	Very high
When you had erections with sexual stimulation, how often were your erections hard enough for penetration?	Almost never or never	Much less than half the time	About half the time	Much more than half the time	Almost always or always
During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?	Almost never or never	Much less than half the time	About half the time	Much more than half the time	Almost always or always
During sexual intercourse how difficult was it to maintain your erection to the completion of intercourse?	Extremely difficult	Very difficult	Difficult	Slightly difficult	Not difficult
When you attempted sexual intercourse, how often was it satisfactory for you?	Almost never or never	Much less than half the time	About half the time	Much more than half the time	Almost always or always
The IIEF-5 score is the sum of questions 1 to 5. The lowest score is 5 and the highest score 25.					
Scores					
22 – 25 - no erectile dysfunction					
17 – 21 - mild erectile dysfunction					
12- 16 - mild to moderate ED					
8 – 11 - moderate erectile dysfunction					
5 – 7 - severe erectile dysfunction					

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