Society for Men's Health
Singapore

SMHS

ERECTILE DYSFUNCTION (ED) GUIDELINES

SOCIETY FOR MEN'S HEALTH SINGAPORE ERECTILE DYSFUNCTION GUIDELINES 2020 WORKGROUP

Chairman

Dr Ng Kok Kit
Urologist
Changi General Hospital

Co-Chairman

Dr Ronny Tan
Urologist
Advanced Urology Associates Pte Ltd

Advisor

Prof Peter Lim
Urologist
Andrology, Urology and Continence Centre

Dr Colin Teo
Urologist
Colin Teo Urology

Member

Dr Joe Lee
Urologist
National University Hospital

Dr Elias Tam
Family and Aesthetic Physician
EHA Clinic

Dr Jonathan Teo
Urologist
Singapore General Hospital /
Sengkang General Hospital

Dr Yeo Khung Keong
Cardiologist
National Heart Centre Singapore

Published by:
Society for Men's Health Singapore
c/o Globewerks International Pte Ltd
(Secretariat)
22 Sin Ming Lane, #03-85 Midview City,
Singapore 573969
Tel : +65 6513 7310
Fax : +65 6659 8946
Email: smhs@globewerks.com
Website address: www.menshealth-sg.com

This publication is sponsored by: MENARINI

INTRODUCTION

Sexuality is the most important or at least a very important bonding factor of couples. Studies in Germany[1], Japan[2]and Perth[3], Australia provide convincing evidence that in the majority of even aged people from different cultures and ethnic groups, sexual activities (e.g. coitus, masturbation) play an important role and represent a bonding factor in the partnerships. Many studies reveal that sexual health is not maintained in many elderly men, a phenomenon which usually starts in the 5th decade and progressively increases in the age population.

Erectile dysfunction (ED) and premature ejaculation (PE) are the 2 main complaints in men presenting with male sexual dysfunction.

ED is defined as the persistent inability to attain and maintain an erection sufficient to permit satisfactory sexual performance. ED affects physical and psychosocial health and affects the quality of life (QoL) of the men and their partners[4]. In addition, ED has also been shown to be a harbinger of cardiovascular disease[5-9].

From a clinical standpoint, ED can be subdivided in:

- Primary ED: manifestation of ED with the first sexual activities, i.e. normally in early adolescence
- Secondary (acquired) ED: manifestation of ED after a period of normal sex life (normal erectile function)

It is not uncommon for a man to experience some episodes of ED in his lifespan. These short episodes are commonly situational and related to some stressor. More often than not, these episodes of temporary ED resolve once the underlying issues are settled but these men would still require a physician's consultation and aid. For men with longer lasting ED of more than 3-6 months, a thorough medical evaluation for the increasing risk of partnership problems and the likelihood of underlying and treatable medical causes for ED is recommended.

EPIDEMIOLOGY

In a population based cross sectional study of 729 men aged 30 and above in Singapore[10] using the IIEF-5 questionnaire, 51.3% of respondents reported some degree of erectile dysfunction. The prevalence of ED increased form 42.8% for men in the forties to 77.4% in the sixties. The prevalence of severe ED increased from 9.1% in men in the forties to 43.5% in the sixties and 77% in those aged 70 and above. In the multinational Men's Attitudes to Life Events and Sexuality (MALES) study[11] which involved 27839 men aged 20-75 years who were interviewed in 8 countries (United States, United Kingdom, Germany, France, Italy, Spain, Mexico and Brazil), the overall prevalence of ED was 16%. The prevalence of self-reported ED was also noted to be increasing with increasing age.

EVALUATION

Risk Factors

ED in patients 40 years and above is significantly associated with cardiovascular risk factors e.g. Diabetes Mellitus, hypertension, coronary artery disease, dyslipidaemia and atherosclerosis and metabolic syndrome[7,9,12,13]. ED and coronary artery disease (CAD) are frequently coexisting. In view of that, the third Princeton Consensus Panel[14] emphasized an approach to risk assessment that integrates multiple aspects of cardio metabolic health. The literature suggested that a comprehensive approach to cardiovascular risk reduction with improved overall vascular health and in so doing improve sexual function in terms of penile erections.

FACTORS	CAUSES
Psychogenic	Psychosexual development in childhood/adolescence (special sexual experiences etc) Sexual orientation problems Partnership problems
Lifestyle	Permanent stressing factors Sedentary lifestyle Nicotine Alcohol abuse Drug addictions
Cardiovascular Risk	Hypertension Dyslipidaemia Coronary Artery Disease (CAD) Peripheral Arterial Occlusive Disease Diabetes Mellitus (Type 1 and 2)
Endocrine	Hypogonadism Hyperprolactinaemia Thyroid disorders Adrenal disorders
Iatrogenic ED	Drug-induced Post-operative Post-radiation

Medical disorders	Benign prostate hyperplasia (BPH) Renal insufficiency Hepatic insufficiency Dyslipidaemia Respiratory disorders (eg. COPD, sleep apnoea) Neurologic disorders
Penile	Cavernous myopathy and fibrosis Peyronie's disease Penile fracture Post-traumatic ED

Table 1 – Risk factors for ED

With the increase in the number of men undergoing radical prostatectomy (RP) or radiotherapy for prostate cancer owing to the increased number of clinically localized prostate cancer being diagnosed in younger patients[15,16], this has led to treatment-specific sequelae of post-RP ED. 25-75% of men experience post-RP ED[17]. There is no significant literature to suggest that robot-assisted laparoscopic RP has any advantageous effect on preservation of erectile function. Only patients with good pre-operative erectile function will have a significant recovery of erectile function after surgery[18-23].

SEXUAL HISTORY

This history must include information about previous and current sexual relationships, onset and duration of erectile dysfunction, previous consultations and treatments. International Index of Erectile Function (IIEF – appendix I) is a validated psychometric questionnaire[24] which helps to assess the different sexual function domains as well as the impact of a specific treatment modality.

The 5 domains of sexual function in men include erection, orgasm, desire, satisfaction and overall satisfaction. A five-item brief form of the IIEF termed the Sexual Health Inventory for Men (SHIM) or IIEF-5 (appendix II) has been developed and validated, along with a diagnostic classification and an ED severity scale. The IIEF-5 is intended to complement, not supplant, clinical judgment and useful diagnostic assessments. It may be particularly useful as an initial screening instrument in a general practice setting.

PHYSICAL EXAMINATION

According to the Recommendations of the International Consultation in Sexual Medicine (ICSM), for the Clinical Evaluation of Men and Women with Sexual Dysfunction, physical examination and laboratory testing are highly recommended but not always necessary[25].

The aim of physical examination in men with ED is to review genital anatomy and identify any related abnormalities in the endocrine, vascular and neurological systems.

The presence of secondary sexual characteristics should be looked out for. The penis should be examined for any abnormalities e.g. tunical plaques suggestive of Peyronie's disease. The testes should be examined for size, consistency. A digital rectal examination should be performed in every patient older than 40 years. Blood pressure and heart rate should be measured if they have not been assessed in the previous 3-6 months.

INVESTIGATIONS

Initial investigations

Treatment can be initiated without investigations, though it is good practice to evaluate risk factors for ED with the following initial investigations:

- Fasting glucose
- Lipid profile
- Serum total testosterone (morning sample should be taken - 8 am to 11 am, because serum testosterone level has a diurnal variation, and is usually highest in the morning)

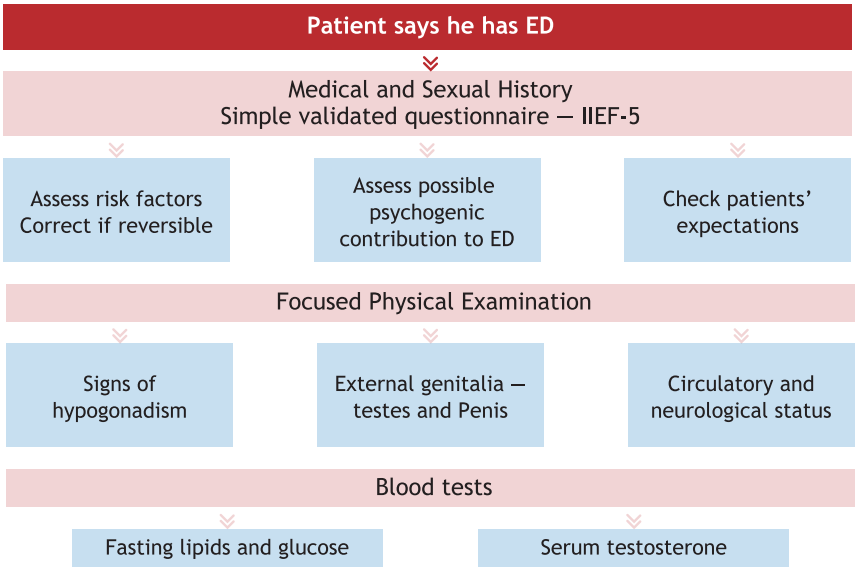


Figure 1: Initial Evaluation of Erectile Dysfunction

SPECIALIZED INVESTIGATIONS

Endocrine Evaluation

Luteinizing hormone, prolactin

These additional hormonal tests may be performed when low testosterone levels are detected[26,27]. Luteinizing hormone helps distinguish between primary and secondary hypogonadism. Hyperprolactinaemia is associated with erectile dysfunction. If hyperprolactinaemia is detected, the underlying cause (eg. pituitary adenoma) will need to be assessed.

Free testosterone

Total testosterone is 58% loosely bound to albumin, 40% tightly bound to sex-hormone-binding-globulin (SHBG) and the remaining 0.5-2% circulates freely (free testosterone), which is the fraction taken to be biologically active[28]. Free testosterone level should be done if the total testosterone is in the low-normal or normal range and yet there is clinical suspicion of hypogonadism.

PENILE COLOR DUPLEX DOPPLER ULTRASOUND[29]

The ultrasound should be performed in a relaxed state, scanning the entire penis (in B-mode image) using a 7.5 to 12 MHz linear array ultrasound probe. An intracorporeal injection of a single vasoactive agent (e.g. prostaglandin E1) is administered with the ultrasound being performed at various time points, preferably with audiovisual sexual stimulation. Peak systolic velocity (PSV) of 30 cm/s or greater indicates normal arterial flow after adequate pharmacological stimulation, whereas a PSV below 25 cm/s is diagnostic of arterial insufficiency as the cause of ED. End diastolic velocity (EDV) of 3 cm/s or less with a resistive index (RI) of greater than 0.8 is normal, whereas EDV greater than 6 cm/s with a RI of less than 0.6 is diagnostic of venous leak.

ARTERIOGRAPHY AND DYNAMIC CAVERNOSOMETRY OR CAVERNOSOGRAPHY

These tests should only be performed in patients who are being considered for vascular reconstructive surgery[30].

DETERMINATION OF FITNESS FOR SEXUAL ACTIVITY

As mentioned earlier, ED and cardiovascular disease share many common risk factors and ED could well be a harbinger of cardiovascular disease. Based on the Princeton III Consensus[14], the patients should have their cardiac risk stratified. This helps the physician determine which patients are fit to resume sexual activity and which patients would require reviews by the cardiologist. Importantly, according to the American Heat Assocation (AHA), sexual activity is reasonable for patients who can exercise >3 to 5 METS (approximately equal to climbing up 2 flights of stairs) without angina, excessive dyspnea, cyanosis, hypotension, or arrhythmia[31]. Unlike the Princeton III Consensus, the AHA

recommends that sexual activity is reasonable 1 or more weeks after uncomplicated MI if the patient is without cardiac symptoms during mild to moderate physical activity. Given that these recommendations are for non-cardiologists, we recommend adopting the Princeton III Consensus guidance.

LOW RISK	INTERMEDIATE RISK	HIGH RISK
Can perform exercise of modest intensity without symptoms		Moderately or severely symptomatic from their heart disease
		High-risk arrhythmias
Mild, stable angina (Able to walk up 2 flights of stairs)	Moderate, stable angina (Less than 2 flights of stairs)	Unstable or refractory angina
Uncomplicated previous MI	Recent MI (> 2, < 8 weeks) without revascularization	Recent MI (< 2 weeks) without intervention
Left ventricular dysfunction/ heart failure, NYHA class I and II	Left ventricular dysfunction/ heart failure, NYHA class III	Left ventricular dysfunction/ heart failure, NYHA class IV
Post-successful coronary revascularization	Non-cardiac sequelae of atherosclerotic disease eg. Peripheral arterial disease, stroke	Hypertrophic obstructive Cardiomyopathy with severe symptoms
Asymptomatic controlled hypertension		Uncontrolled hypertension
Mild valvular disease		Moderate-to-severe valvular disease (especially aortic stenosis)

Table 2: Cardiac risk stratification based on the Princeton III Consensus
CAD= coronary artery disease, MI=myocardial infarction, NYHA= New York Heart Association

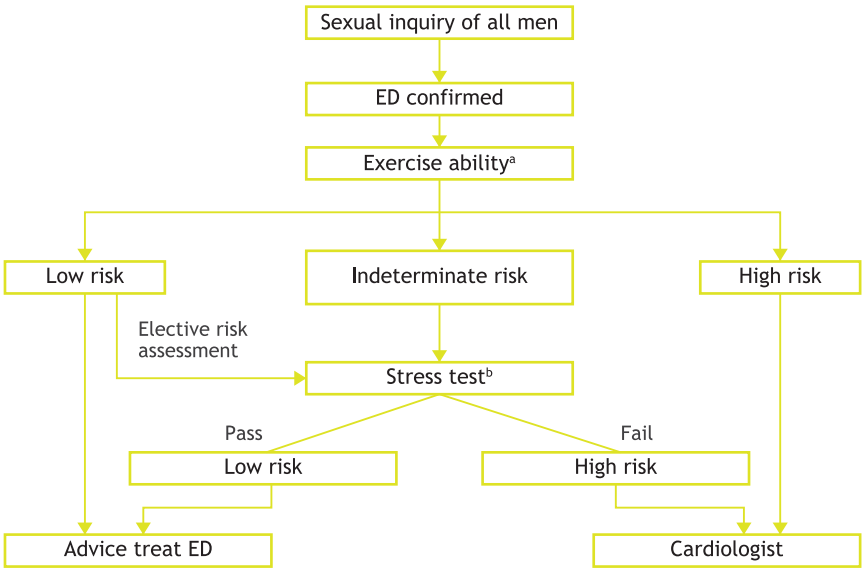


FIGURE. Management of erectile dysfunction (ED) in all men with ED, especially those with known cardiovascular disease. [a]Sexual activity is equivalent to walking 1 mile on the flat in 20 minutes or briskly climbing 2 flights of stairs in 10 seconds. [b]Sexual activity is equivalent to 4 minutes of the Bruce treadmill protocol.

Figure 2: Treatment algorithm for determining level of sexual activity according to cardiac risk in ED based on 3rd Princeton Consensus

FAQ

My patient come back complaining of poor erection after starting on atenolol, should I stop his beta-blocker and what are the alternatives?

If patients do complain of undue fatigue or erectile dysfunction from beta-blockers, they can change to third generation beta blockers like Nebivolol. Alternatively, if their cardiac functions are normal, nondihydropyridine calcium channel blockers like diltiazem or verapamil can be used in place of beta-blockers for patients with angina. Ivabradine (selective If channel inhibitor) can also be used if the patient is in sinus rhythm.

TREATMENT OPTIONS

First Line Therapy

Lifestyle modifications

Regular physical activity and or weight loss by controlled diet significantly improves erectile function and reduces the risk of cardiovascular diseases or events[32]. These effects can be seen as early as 8 weeks after initiation of lifestyle modification and can improve the efficacy of PDE 5 inhibitors.

ED is a known indicator for cardiovascular risk. The presence of ED may help lead clinicians to explore the cardiovascular risk factors in these patients. Interventions to control specific cardiovascular risk factors (eg, hypertension, diabetes, hyperlipidemia, obstructive sleep apnea) may help to improve not only the patients' erectile function[8], which is a quality of life issue, but also his quantity of life (prevention of acute myocardial infarct, cerebrovascular accidents and early death).

Phosphodiesterase 5 (PDE 5) inhibitors

PDE5 inhibitors are currently the mainstay of first-line treatment of ED. PDE 5 is an enzyme found in the cavernosal tissue, degrades cGMP, thus reversing smooth muscle relaxation causing penile detumescence. PDE 5 inhibitors elevate after adequate sexual stimulation the concentrations of cGMP above the threshold level that is needed to trigger erection. This mechanism generally works in the overwhelming majority of ED etiologies except where severe damage of the parasympathetic cavernous nerves prevents any cGMP formation e.g. after major pelvic cancer surgery with resection of bilateral cavernous nerves or in diabetes or neurological diseases where there is severe autonomic neuropathy.

The first PDE5 inhibitor used to treat ED was sildenafil and it was launched in 1998. Sildenafil is effective from 30-60 minutes after administration. However, its efficacy is reduced after a heavy, fatty meal. It is administered in doses of 50 and 100 mg. The recommended starting dose is 50 mg and should be adapted according to the patient's response and side effects.

Vardenafil was commercially available in 2003 and is effective from 30 minutes after administration. Like sildenafil, its effect is also reduced by a heavy, fatty meal. It is administered in doses of 10 and 20 mg with a recommended started dose of 10 mg and should be adapted according to the patient's response and side effects.

Tadalafil was also commercially available in 2003 and is effective from 30 minutes after administration, with peak efficacy after 2 hours. The efficacy is maintained up to 36 hours and is not affected by food. There are 2 ways to use Tadalafil – on demand or daily dosing. On demand dosing for Tadalafil is 20mg prn. It should be taken 1 to 2 hours before sexual intercourse as opposed to the shorter acting PDE5 inhibitors (which are taken 30 minutes to 1 hour before sexual intercourse) for optimum effect. Tadalafil 5mg daily[33] has been approved for the treatment of ED alone or ED with concurrent lower urinary tract symptoms (LUTS) due to benign prostate hypertrophy (BPH).

There have not been many head-to-head studies comparing the above PDE5 inhibitors, making it difficult to report the most effective agent with absolute confidence. A critical review in 2010[34] examined literature since 2000, including preference studies that included either 2 (Tadalafil and Sildenafil) or 3 PDE 5 inhibitors (Tadalafil, Sildenafil and Vardenafil). It was documented that 52-65% of patients prefer tadalafil, 12-20% Vardenafil and 8-30% Sildenafil. All founded studies have serious limitations, particularly in terms of dosing differences. The preference for tadalafil was mainly due to its longer duration of action that increased the patient's opportunity to have penetrative intercourse.

The newest PDE 5 inhibitor would be the second generation PDE 5 inhibitor Avanafil, which will be available in Singapore in 2020. Avanafil has a rapid onset and shorter duration of action than current PDE5 inhibitors. It reaches maximal plasma levels in less than 30 minutes and improves erectile function in less than 15 minutes after dosing. Avanafil remains effective for 6 hours and may maintain benefits longer in some patients. Its brief plasma half-life (3–5 hours) reduces the risk of drug-drug interactions – an important property in a patient population that is often taking medications for other health related conditions. Notably, avanafil has fewer hemodynamic side effects and appears safe to use in patients on blood-pressure lowering medications. As a significant group of patients with ED have concomitant cardiovascular conditions, this quality may make second-generation PDE5 inhibitors with minimal effects on blood pressure a tolerable treatment for many patients. Avanfil comes in 100 mg and 200 mg tablets to be taken as a on demand basis on an empty stomach[35].

Nitrates are absolute contraindications for the use of all PDE 5 inhibitors[36]. They result in cGMP accumulation and unpredictable falls in blood pressure and symptoms of hypotension. If a PDE 5 inhibitor is taken and the patient develops chest pain, nitroglycerine (GTN) must be withheld for at least 24 hours if sildenafil or Vardenafil is used and for at least 48 hours if tadalafil is used. Should the patient develop angina while taking a PDE 5 inhibitor, other agents may have to be used in place of GTN till the appropriate time has passed.

Avanafil has been shown to have weaker and shorter duration of its potentiating effects on nitroglycerin-induced hypotension as compared to sildenadil. In general, avanafil has a weaker and briefer interaction with organic nitrates. Despite this, the same precautions with nitrates still applies, as in the other PDE 5 inhibitors[37].

Amyl nitrite
Isosorbide dinitrate (ISDN eg. Isordil)
Isosorbide mononitrate (ISMN eg. Imdur)
Nitroglycerine (eg. GTN)
Sodium nitroprusside

Table 3: Commonly Used Nitrates / Nitrites
Note that trade names given as examples are not exhaustive

While prescribing PDE5i, physicians should take note of supplements and herbal therapies as well. Currently, we do not recommend the use of herbal therapy for treatment of erectile dysfunction, as their efficacies are not conclusively proven in well conducted trials, uncertainty of their active ingredients and variance in the manufacturing practices. Despite this, many patients are taking herbal therapies as they are easily available over the counter, from unregulated sources and over the internet. Some of these products may be adulterated with unregulated doses of PDE5i and other pharmaceutically active agents which may endanger the health of the patients.

FAQ

What are the contraindications to PDE5i therapy?

The absolute contraindication to PDE5i is when patients are on nitrates or nitrites. Table 3 shows a list of nitrates that patients may be on. If a PDE 5 inhibitor is taken and the patient develops chest pain, nitroglycerine (GTN) must be withheld for at least 24 hours if Sildenafil or Avanafil or Vardenafil is used and for at least 48 hours if Tadalafil is used.

What type of PDE5i should I choose for my patient?

It depends on patient's preference and sexual activity.
If he prefers short-acting and on-demand drugs, short acting PDE5i like Sildenafil or Avanafil or Vardenafil can be prescribed.

When he is not sure of the timing of his sexual intercourse, a long acting PDE5i like Tadalafil 20 mg can be prescribed, which has efficacy of up to 36 hours.
When he has frequent sexual intercourse, eg. Twice or more per week, he can consider taking daily Tadalafil 5 mg.

If he has bothersome side effects from the use of the long acting PDE5i, he can consider Avanafil as it is more rapidly washed out of the system.
If the patient also has lower urinary tract symptoms (LUTS), he can consider taking daily Tadalafil 5 mg to treat both his ED and LUTS.

What should I tell my patient on how to take PDE5i?

For all PDE5i, the patient would need sexual stimulation like foreplay to initiate the erection. PDE5i does not in itself initiate erection. It increases the rigidity and duration of erection once initiated.

For short acting PDE5i like Sildenafil, Avanfil and Vardenafil, it should be taken about 30 minutes to 1 hour before the sexual intercourse, preferably on an empty stomach, to help improve its efficacy. As Avanafil reaches peak plasma levels much more quickly, it has a rapid onset of action and can even be taken 15 minutes before the sexual intercourse.

For long acting PDE5i like Tadalafil 20 mg, it should be given much earlier, at 1 to 2 hours before sexual intercourse for optimum effect.

What are the common side effects of PDE5i and how do I deal with it?

Common side effects would include facial flushing (due to peripheral vasodilatation), nasal congestion, headache and dyspepsia. These symptoms are usually tolerable and do not lead to the discontinuation of PDE5i. If headache is severe, he can take a mild analgesia like paracetamol.

If patient has visual changes from Sildenafil or Vardenafil, he should discontinue the medication.

Patients may have increased back pain and myalgia from Tadalafil.

Can PDE5i be used to treat psychogenic ED?

Yes, PDE5i is a safe, simple and effective in patients with ED, including those patients who have psychogenic ED. Prior to the advent of effective medical treatment for ED, psychotherapy and sexual counseling has been advocated as the mainstay of treatment for psychogenic ED. However, such treatment requires much time, effort and expense on the part of the patient. A randomized controlled study comparing the effectiveness between group psychotherapy plus Sildenafil vs Sildenafil only has shown that patients who have undergone group psychotherapy have increased satisfaction, confidence and 'naturalness' of their erections[38].

Despite PDE5i being such an effective treatment for psychogenic ED, it is still worthwhile to for the practitioner to look for and treat any underlying psychological causes, which may cure the patients of their problems without the long-term use of medications. The initial use of PDE5i gives these patients confidence in their sexual performance, and can be withdrawn when they less worried about their erections.

Can the patient have ED and Premature Ejaculation (PE) at the same time?

Yes. PE occurs when the patient has a short duration of erection before ejaculation, finds difficulty in controlling his ejaculation and suffers distress from this lack of control. Dapoxetine is an on-label pharmacotherapy for premature ejaculation.

Can PDE5i and Dapoxetine (used for PE treatment) be given together?

Yes, they can be taken together. The timing for taking Dapoxetine and short acting PDE5i is about the same – 30 minutes to 1 hour before sexual intercourse. Do note that the patient should be well hydrated prior to taking these two medications, otherwise there may be a risk of postural hypotension.

Many of my patients have ED as well as Lower Urinary Tract Symptoms (LUTS) due to Benign Prostatic Hyperplasia (BPH), can PDE5i be taken together with alpha blockers?

For all the PDE5i, there are cautions in the drug insets regarding about mixing with alpha-blockers, which might lead to postural hypotension. Some physicians tell the patient to space the alpha-blockers for at least 4 hours from the short acting PDE5i.

Alternatively, the patient can take Tadalafil 5 mg once a day alone to help with both his ED and LUTS.

What would constitute a reasonable trial with PDE5i drugs before determining their efficacy?

At least 6 to 8 attempts with the top dose of respective PDE5i should be done as studies[39] have clearly shown that several attempts are required to maximize the response rate to PDE5i.

What if PDE5i fails?

Check the patient's administration – he may be taking short acting PDE5i with food, or he may be taking Tadalafil only very shortly before his sexual intercourse.

Increasing the dosage may help – the maximum dosage for Sildenafil is 100 mg, Avanafil is 200 mg, Vardenafil is 20 mg and Tadalafil is 20 mg per day. Changing to a different PDE5i may also help.

Check the serum testosterone for Testosterone Deficiency Syndrome, and consider initiating Testosterone Replacement Therapy if patient has hypogonadism.

Can PDE5i be used together with Testosterone Replacement Therapy (TRT)?

Yes, PDE5i can be used together with testosterone supplementation. In fact, this form of combination therapy is usually synergistic. When patient has ED and Testosterone Deficiency Syndrome, options of therapy include:

- Giving TRT first to see whether ED improves.
- Treating with PDE5i first if symptoms are mainly ED.
- Giving TRT and PDE5i simultaneously.

For details regarding TRT, please refer to the SMHS Testosterone Deficiency Syndrome (TDS) Guidelines.

What if PDE5i still fails?

Second line therapy like intracavernosal injection therapy or vacuum erection device can be prescribed for the patient.

If these fail, the patient can be referred to the specialist for specialized procedures or surgery. As certain of these procedures are still investigational, the patient will need specialist assessment and follow up to be treated within or outside the context of a clinical trial.

If all else fails, penile prosthesis surgery offer a permanent and effective solution for the patient.

My patient does not like western medicine and has been taking over the counter treatment. He said that one of these treatments - "Tongkat Ali", that he bought from a provision shop from the neighbouring country helps. How do I advise him?

There are many different traditional remedies that have been used to improve the treatment of erectile dysfunction. However. their mechanisms of action are vague. There are some small-scale studies that show that they work but there are no large scale double blind randomized placebo controlled trials to prove their efficacy. It is important to have a placebo in these trials as erectile function can be subjected to the placebo effect. Some of the tablets might even contain active pharmaceutical ingredients like PDE5i and other drugs, which could be dangerous as their dosages are not regulated and patient might not be aware of them, resulting in possible undesirable drug interactions.

Testosterone replacement therapy (TRT)

Testosterone plays an important role in the maintenance of a man's sexual functions and health. TRT in hypogonadal men with sexual disorders should be started first, followed by PDE 5 inhibitors. Recovery of sexual function usually takes 4-12 weeks, depending on the sexual symptoms in question and the baseline testosterone levels. Responsiveness to PDE 5 inhibitors is substantially impaired in untreated hypogonadal men if testosterone levels are less than 3 ng/ml (10.4 nmol/l). TRT is not recommended in men with ED who are not hypogonadal. General practitioners who are comfortable with TRT may proceed with this line of treatment with the proper follow-up as stated in TRT guidelines. Otherwise, these patients should be referred to the urologists or endocrinologists with an interest in sexual medicine.

Second Line Therapy

Intracavernosal Injection (ICI) Therapy

Prostaglandin E1 (PGE1) or Alprostadil is used as ICI for both diagnostic and therapeutic purposes. As mentioned earlier, artificial erections are induced with PGE1 during penile colour duplex Doppler ultrasound for the evaluation of vasculogenic ED. Commonly used doses are 10 mcg and 20 mcg. The erection appears within 5-15 minutes and lasts according to the dose injected. The main complications of ICI include penile pain, cavernosal fibrosis and priapism.

ICI can be performed safely for men on antiplatelets or anticoagulation with no reported increase in risks of bleeding or ecchymosis[37]

The procedure includes proper injection technique on the lateral side of the penile shaft using 27G- 30G needles and application of pressure to the site of injection after that.

Combination ICI e.g. Trimix and Bimix is popular in America and Europe but these are only available from compounding pharmacy.

Vacuum Erection Device (VED)

The concept of the VED was first described by American physician John King in 1874, where a small vacuum pump was used to improve erections. After granting various patents for vacuum device therapy both in Germany and the United States of America, the American entrepreneur Gedding Osbon finally produced a vacuum device in 1982 and the first report on the efficacy and safety of the VED was published in 1986[41].

VED provides passive engorgement of the corpora cavernosal and with the use of a constrictor ring placed at the base of the penis retains the blood within the corpora. Common adverse events include pain, difficulty with ejaculation, petechiae, bruising and numbness. The patients must be educated on the importance of removing the constriction ring within 30 minutes lest they develop skin necrosis.

Low-intensity Extracorporeal Shockwave Treatment (LiESWT)

The application of low-intensity shockwave therapy in the treatment of erectile dysfunction was first reported in 2010[42]. Subsequent randomized controlled trials[43][44][45] and meta-analyses has shown this treatment to be efficacious with improvement of IIEF score and erection hardness. Different protocols have been reported and no single protocol that has been found to be superior. Based on studies, LiESWT induces neovascularization and the release of NO, VEGF and PCNA, which improves cavernosal arterial flow and erectile function. The procedure is generally safe and complications which include skin abrasion, hematoma or urethral injury are very rare.

LiESWT can benefit patients who are unable or unwilling to use PDE5i or patients who are partial or non-responders to PDE5i.

Penile revascularization

The principles of penile revascularization are derived from cardiac surgery with the re-establishment of coronary blood flow after bypass procedures for patients who suffer from angina and myocardial infarcts.

Penile arteriography is the gold standard in assessing a man's suitability for arterial reconstructive surgery, but concomitant corporal veno-occlusive dysfunction (CVOD) must be excluded with preoperative dynamic infusion cavernosography and cavernosometry. Arterial revascularization surgery has beneficial outcomes in young men who have sustained perineal or pelvic trauma whereas surgical intervention for CVOD is currently still considered investigational.

Endovascular treatment

Currently, the experience with transluminal angioplasty for the treatment of ED is limited. The majority of studies are case reports or case series focused on large vessel inflow disease of the iliac or internal pudendal arteries. The Zotarolimus-Eluting Peripheral Stent System for the Treatment of Erectile Dysfunction in Males with Sub-Optimal Response to Phosphodiesterase type 5 Inhibitors (ZEN) trial[46] prospectively enrolled 30 men with ED and internal pudendal artery stenosis. These patients underwent stenting of the internal pudendal artery with drug-eluting stents and technical success was achieved in all patients with no post-procedural death or episodes of perineal gangrene at 30 days. At 3 months' follow-up, 68% of the patients had improvement in IIEF-EF, demonstrating short-term safety of angioplasty and stenting and improvement of erectile function. The Incidence of Male Pudendal Artery Stenosis in Suboptimal Erections Study (IMPASS) registry was designed to document penile arterial insufficiency and establish an angiographic protocol since the challenge with endovascular treatment was the angioplasty of the correct vessel. However, this study was terminated. Clinical research is on-going and until randomized data or larger clinical studies become available, endovascular treatment for ED remains at the investigational stage[47].

Penile Prosthesis

The placement of a penile prosthesis is the gold standard treatment for severe or refractory ED. It can be offered early in the course of ED treatment if clinically indicated. With proper counseling, the penile prosthesis can be offered to patients who prefer a permanent solution to their problem. This is especially with the increase in the number of patients who undergo treatment for localized prostate cancer at a younger age.

Penile implants can be broadly classified as malleable devices versus the inflatable devices. The inflatable devices come in the form of 2-piece and 3-piece implants. The inflatable devices are more popular due to the physiological flaccid state when deflated and a more "natural" erect state when inflated. 3-piece implants provide the best rigidity and best flaccidity and 2-piece implants are usually placed in patients who have an anatomy that makes placement of the abdominal reservoir unsafe or technically difficult. Men who have poor manual dexterity could have a malleable implant inserted instead of the inflatables for ease of use, although this can be alleviated by the willingness of the partner to be involved in pumping up the inflatables during sexual activity. In patients with spinal cord injuries, malleables may carry a higher risk of erosion especially in patients with insensate penises.

The satisfaction rates in patients who have undergone placement of the penile prosthesis are generally high and many would recommend to a friend to have it performed. A recent study[48] looked at partner satisfaction and reported not only a significant improvement of IIEF-EF scores from 8.88 to 20.97 with a mean patients' EDIT (Erectile Dysfunction Inventory for Treatment and Satisfaction) score of 75.48 and a mean female partners' score of 70, highlighting post-treatment satisfaction for both.

The main complications of penile prosthesis placement are mechanical failure and infection. Revision surgeries are technically difficult and associated with a higher risk of infection. Management of the infected prosthesis is also a challenge. Hence, it is recommended that penile prosthesis should be implanted by urologists who have undergone formal training in urological prosthetic surgery.

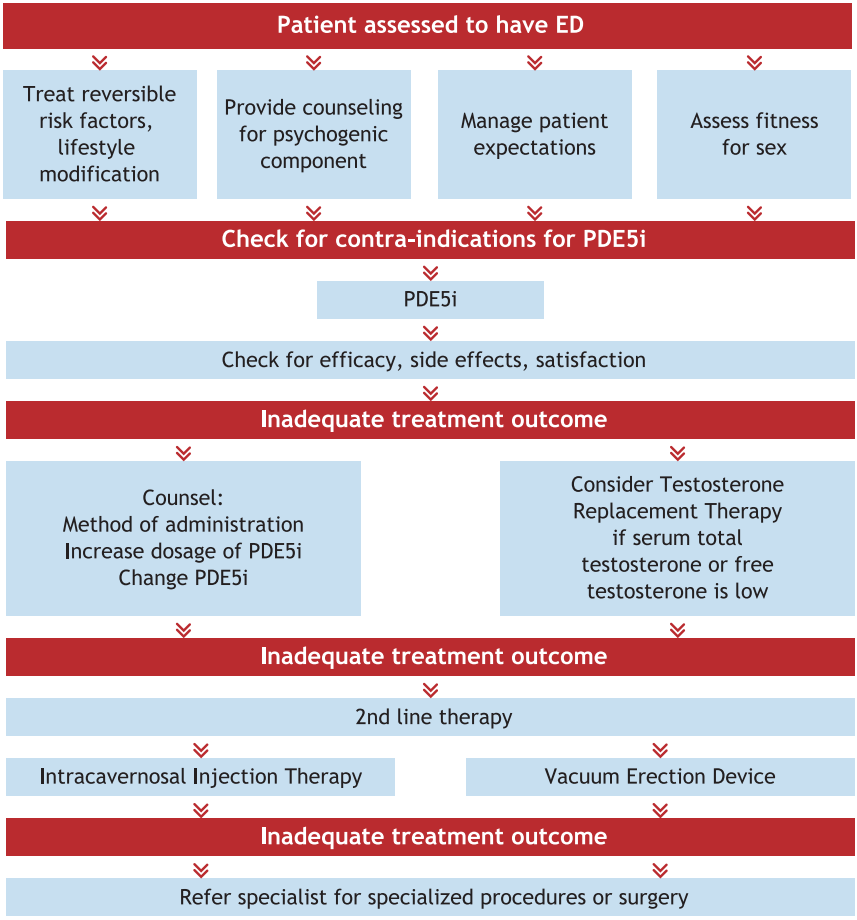


Figure 2: Treatment of ED

PENILE REHABILITATION

Management of post-pelvic surgery or post-radiation ED should be referred to the urologist as there are post-RP penile rehabilitation protocols that have been shown to be effective. Penile rehabilitation is not simply the treatment of ED. The goal of penile rehabilitation is to restore the pre-RP erectile function using single or multiple modalities to achieve the desired outcome. Penile rehabilitation is beyond the scope of this clinical practice guideline on ED.

APPENDIX I - INTERNATIONAL INDEX OF ERECTILE FUNCTION (IIEF)

Instructions: These questions ask about the effects your erection problems have had on your sex life, over the past 4 weeks. Please answer the following questions as honestly and clearly as possible. In answering these questions, the following definitions apply:

Definitions:

- Sexual activity includes intercourse, caressing, foreplay and masturbation
- Sexual intercourse is defined as vaginal penetration of the partner (you entered the partner)
- Sexual stimulation includes situations like foreplay with a partner, looking at erotic pictures, etc.
- Ejaculate is defined as the ejection of semen from the penis (or the feeling of this)

Mark ONLY one circle per question (Score 0 if not done):

1. **Over the past 4 weeks, how often were you able to get an erection during sexual activity?**

   (0) No sexual activity
   (1) Almost always or always
   (2) Most times (much more than half the time)
   (3) Sometimes (about half the time)
   (4) A few times (much less than half the time)
   (5) Almost never or never

2. **Over the past 4 weeks, when you had erections with sexual stimulation, how often were your erections hard enough for penetration?**

   (0) No sexual activity
   (1) Almost always or always
   (2) Most times (much more than half the time)
   (3) Sometimes (about half the time)
   (4) A few times (much less than half the time)
   (5) Almost never or never

Questions 3, 4 and 5 will ask about erections you may have had during sexual intercourse.

3. **Over the past 4 weeks, when you attempted sexual intercourse, how often were you able to penetrate (enter) your partner?**

   (0) Did not attempt intercourse
   (1) Almost always or always
   (2) Most times (much more than half the time)
   (3) Sometimes (about half the time)
   (4) A few times (much less than half the time)
   (5) Almost never or never

4. **Over the past 4 weeks, during sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?**

   (0) Did not attempt intercourse
   (1) Almost always or always
   (2) Most times (much more than half the time)
   (3) Sometimes (about half the time)
   (4) A few times (much less than half the time)
   (5) Almost never or never

5. **Over the past 4 weeks, during sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?**

   (0) Did not attempt intercourse
   (1) Almost always or always
   (2) Most times (much more than half the time)
   (3) Sometimes (about half the time)
   (4) A few times (much less than half the time)
   (5) Almost never or never

6. **Over the past 4 weeks, how many times have you attempted sexual intercourse?**

   (0) No attempts
   (1) 1-2 attempts
   (2) 3-4 attempts
   (3) 5-6 attempts
   (4) 7-10 attempts
   (5) 11 or more attempts

7. **Over the past 4 weeks, when you attempted sexual intercourse how often was it satisfactory for you?**

   (0) Did not attempt intercourse
   (1) Almost always or always
   (2) Most times (much more than half the time)
   (3) Sometimes (about half the time)
   (4) A few times (much less than half the time)
   (5) Almost never or never

8. **Over the past 4 weeks, how much have you enjoyed sexual intercourse?**

   (0) No intercourse
   (1) Very highly enjoyable
   (2) Highly enjoyable
   (3) Fairly enjoyable
   (4) Not very enjoyable
   (5) Not enjoyable

9. **Over the past 4 weeks, when you had sexual stimulation or intercourse how often did you ejaculate?**

   (0) Did not attempt intercourse
   (1) Almost always or always
   (2) Most times (much more than half the time)
   (3) Sometimes (about half the time)
   (4) A few times (much less than half the time)
   (5) Almost never or never

10. Over the past 4 weeks, when you had sexual stimulation or intercourse how often did you have the feeling of orgasm or climax (with or without ejaculation)?

(0) No sexual stimulation or intercourse
(1) Almost always or always
(2) Most times (much more than half the time)
(3) Sometimes (about half the time)
(4) A few times (much less than half the time)
(5) Almost never or never

Questions 11 and 12 ask about sexual desire. Let's define sexual desire as a feeling that may include wanting to have a sexual experience (for example, masturbation or intercourse), thinking about having sex or feeling frustrated due to a lack of sex.

11. Over the past 4 weeks, how often have you felt sexual desire?

(0) Almost always or always
(1) Most times (much more than half the time)
(2) Sometimes (about half the time)
(3) A few times (much less than half the time)
(4) Almost never or never

12. Over the past 4 weeks, how would you rate your level of sexual desire?

(0) Very high
(1) High
(2) Moderate
(3) Low
(4) Very low or none at all

13. Over the past 4 weeks, how satisfied have you been with you overall sex life?

(0) Very satisfied
(1) Moderately satisfied
(2) About equally satisfied and dissatisfied
(3) Moderately dissatisfied
(4) Very dissatisfied

14. **Over the past 4 weeks, how satisfied have you been with your sexual relationship with your partner?**

(0) Very satisfied
(1) Moderately satisfied
(2) About equally satisfied and dissatisfied
(3) Moderately dissatisfied
(4) Very dissatisfied

15. **Over the past 4 weeks, how do you rate your confidence that you can get and keep your erection?**

(0) Very high
(1) High
(2) Moderate
(3) Low
(4) Very low

Scoring Algorithm for IIEF

All items are scored in 5 domains as follows:

Domain	Items	Range	Score Max Score
Erectile Function	1, 2, 3, 4, 5, 15	0-5	30
Orgasmic Function	9, 10	0-5	10
Sexual Desire	11,12	0-5	10
Intercourse Satisfaction	6, 7, 8	0-5	15
Overall Satisfaction	13,14	0-5	10

Clinical Interpretation

I. Erectile function total scores can be interpreted as follows:

Score	Interpretation
0-6	Severe dysfunction
7-12	Moderate dysfunction
13-18	Mild to moderate dysfunction
19-24	Mild dysfunction
25-30	No dysfunction

II. Orgasmic function total scores can be interpreted as follows:

Score	Interpretation
0-2	Severe dysfunction
3-4	Moderate dysfunction
5-6	Mild to moderate dysfunction
7-8	Mild dysfunction
9-10	No dysfunction

III. Sexual desire total scores can be interpreted as follows:

Score	Interpretation
0-2	Severe dysfunction
3-4	Moderate dysfunction
5-6	Mild to moderate dysfunction
7-8	Mild dysfunction
9-10	No dysfunction

IV. Intercourse satisfaction total scores can be interpreted as follows:

Score	Interpretation
0-3	Severe dysfunction
4-6	Moderate dysfunction
7-9	Mild to moderate dysfunction
10-12	Mild dysfunction
13-15	No dysfunction

V. Overall satisfaction total scores can be interpreted as follows:

Score	Interpretation
0-2	Severe dysfunction
3-4	Moderate dysfunction
5-6	Mild to moderate dysfunction
7-8	Mild dysfunction
9-10	No dysfunction

Source: 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 Jun; 49(6):822-30.

APPENDIX II - SEXUAL HEALTH INVENTORY FOR MEN (SHIM) OR IIEF-5

Please encircle the response that best describes you for the following five questions:

Over the past 6 months:

1. How do you rate your confidence that you could get and keep an erection?	Very Low	Low	Moderate	High	Very high
	1	2	3	4	5
2. When you had erections with sexual stimulation, how often were your erections hard enough for penetration?	Almost never or never	A few times (much less than half the time)	Sometimes (about half the time)	Most times (much more than half the time)	Almost always or always
	1	2	3	4	5
3. During sexual intercourse, how often were you able to maintain your erection after you had penetrated your partner?	Almost never or never	A few times (much less than half the time)	Sometimes (about half the time)	Most times (much more than half the time)	Almost always or always
	1	2	3	4	5
4. During sexual intercouse, how difficult was it to maintain your erection to completion of intercourse?	Extremely difficult	Very difficult	Difficult	Slightly difficult	Not difficult
	1	2	3	4	5
5. When you attempted sexual intercourse, how often was it satisfactory for you?	Almost never or never	A few times (much less than half the time)	Sometimes (about half the time)	Most times (much more than half the time)	Almost always or always
	1	2	3	4	5

Total Score: _____

1-7: Severe ED 8-11: Moderate ED 12-16: Mild-moderate ED 17-21: Mild ED 22-25: No ED

Source: Rosen RC, Cappelleri JC, Smith MD, et al. 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 Dec;11(6):319-26.

References

1. Braun M, Wassmer G, Klotz T, Reifenrath B, Mathers M, Engelmann U. Epidemiology of erectile dysfunction: results of the 'Cologne Male Survey'. International journal of impotence research. 2000;12(6):305-11.
2. Y K, T T, T S. Epidemiological study on aging changes of sexual activity in Japanese men and women. The Aging Male. 2000;3(9):Abstract O 18.
3. Hyde Z, Flicker L, Hankey GJ, Almeida OP, McCaul KA, Chubb SA, et al. Prevalence of sexual activity and associated factors in men aged 75 to 95 years: a cohort study. Annals of internal medicine. 2010;153(11):693-702.
4. Feldman HA, Goldstein I, Hatzichristou DG, Krane RJ, McKinlay JB. Impotence and its medical and psychosocial correlates: results of the Massachusetts Male Aging Study. The Journal of urology. 1994;151(1):54-61.
5. Batty GD, Li Q, Czernichow S, Neal B, Zoungas S, Huxley R, et al. Erectile dysfunction and later cardiovascular disease in men with type 2 diabetes: prospective cohort study based on the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified-Release Controlled Evaluation) trial. Journal of the American College of Cardiology. 2010;56(23):1908-13.
6. Dong JY, Zhang YH, Qin LQ. Erectile dysfunction and risk of cardiovascular disease: meta-analysis of prospective cohort studies. Journal of the American College of Cardiology. 2011;58(13):1378-85.
7. Guo W, Liao C, Zou Y, Li F, Li T, Zhou Q, et al. Erectile dysfunction and risk of clinical cardiovascular events: a meta-analysis of seven cohort studies. The journal of sexual medicine. 2010;7(8):2805-16.
8. 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. Archives of internal medicine. 2011;171(20):1797-803.
9. Jackson G, Boon N, Eardley I, Kirby M, Dean J, Hackett G, et al. Erectile dysfunction and coronary artery disease prediction: evidence-based guidance and consensus. International journal of clinical practice. 2010;64(7):848-57.
10. Tan JK, Hong CY, Png DJ, Liew LC, Wong ML. Erectile dysfunction in Singapore: prevalence and its associated factors-a population-based study. Singapore medical journal. 2003;44(1):20-6.
11. Rosen RC, Fisher WA, Eardley I, Niederberger C, Nadel A, Sand M, et al. The multinational Men's Attitudes to Life Events and Sexuality (MALES) study: I. Prevalence of erectile dysfunction and related health concerns in the general population. Current medical research and opinion. 2004;20(5):607-17.
12. Baumhakel M, Schlimmer N, Kratz M, Hackett G, Jackson G, Bohm M. Cardiovascular risk, drugs and erectile function-a systematic analysis. International journal of clinical practice. 2011;65(3):289-98.

13. Vlachopoulos C, Ioakeimidis N, Terentes-Printzios D, Stefanadis C. The triad: erectile dysfunction--endothelial dysfunction-cardiovascular disease. Current pharmaceutical design. 2008;14(35):3700-14.

14. Nehra A, Jackson G, Miner M, Billups KL, Burnett AL, Buvat J, et al. The Princeton III Consensus recommendations for the management of erectile dysfunction and cardiovascular disease. Mayo Clinic proceedings. 2012;87(8):766-78.

15. Salonia A, Burnett AL, Graefen M, Hatzimouratidis K, Montorsi F, Mulhall JP, et al. Prevention and management of postprostatectomy sexual dysfunctions. Part 1: choosing the right patient at the right time for the right surgery. European urology. 2012;62(2):261-72.

16. Salonia A, Burnett AL, Graefen M, Hatzimouratidis K, Montorsi F, Mulhall JP, et al. Prevention and management of postprostatectomy sexual dysfunctions part 2: recovery and preservation of erectile function, sexual desire, and orgasmic function. European urology. 2012;62(2):273-86.

17. Sanda MG, Dunn RL, Michalski J, Sandler HM, Northouse L, Hembroff L, et al. Quality of life and satisfaction with outcome among prostate-cancer survivors. The New England journal of medicine. 2008;358(12):1250-61.

18. Barry MJ, Gallagher PM, Skinner JS, Fowler FJ, Jr. Adverse effects of robotic-assisted laparoscopic versus open retropubic radical prostatectomy among a nationwide random sample of medicare-age men. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2012;30(5):513-8.

19. Ferronha F, Barros F, Santos VV, Ravery V, Delmas V. Is there any evidence of superiority between retropubic, laparoscopic or robot-assisted radical prostatectomy? International braz j urol : official journal of the Brazilian Society of Urology. 2011;37(2):146-58; discussion 59-60.

20. Ficarra V, Novara G, Ahlering TE, Costello A, Eastham JA, Graefen M, et al. Systematic review and meta-analysis of studies reporting potency rates after robot-assisted radical prostatectomy. European urology. 2012;62(3):418-30.

21. Hatzimouratidis K, Burnett AL, Hatzichristou D, McCullough AR, Montorsi F, Mulhall JP. Phosphodiesterase type 5 inhibitors in postprostatectomy erectile dysfunction: a critical analysis of the basic science rationale and clinical application. European urology. 2009;55(2):334-47.

22. Magheli A, Burnett AL. Erectile dysfunction following prostatectomy: prevention and treatment. Nature reviews Urology. 2009;6(8):415-27.

23. Vickers A, Savage C, Bianco F, Mulhall J, Sandhu J, Guillonneau B, et al. Cancer control and functional outcomes after radical prostatectomy as markers of surgical quality: analysis of heterogeneity between surgeons at a single cancer center. European urology. 2011;59(3):317-22.

24. 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(6):822-30.

25. Hatzichristou D, Rosen RC, Derogatis LR, Low WY, Meuleman EJ, Sadovsky R, et al. Recommendations for the clinical evaluation of men and women with sexual dysfunction. The journal of sexual medicine. 2010;7(1 Pt 2):337-48.

26. Morales A, Heaton JP. Hormonal erectile dysfunction. Evaluation and management. The Urologic clinics of North America. 2001;28(2):279-88. journal of sexual medicine. 2004;1(1):6-23.

27. Lue TF, Giuliano F, Montorsi F, Rosen RC, Andersson KE, Althof S, et al. Summary of the recommendations on sexual dysfunctions in men. The journal of sexual medicine. 2004;1(1):6-23.

28. Vermeulen A, Verdonck L, Kaufman JM. A critical evaluation of simple methods for the estimation of free testosterone in serum. The Journal of clinical endocrinology and metabolism. 1999;84(10):3666-72.

29. Sikka SC, Hellstrom WJ, Brock G, Morales AM. Standardization of vascular assessment of erectile dysfunction: standard operating procedures for duplex ultrasound. The journal of sexual medicine. 2013;10(1):120-9.

30. Wespes E, Schulman C. Venous impotence: pathophysiology, diagnosis and treatment. The Journal of urology. 1993;149(5 Pt 2):1238-45.

31. Kostis JB, Jackson G, Rosen R, Barrett-Connor E, Billups K, Burnett AL, et al. Sexual dysfunction and cardiac risk (the Second Princeton Consensus Conference). The American journal of cardiology. 2005;96(2):313-21.

32. La Vignera S, Condorelli R, Vicari E, D'Agata R, Calogero AE. Physical activity and erectile dysfunction in middle-aged men. Journal of andrology. 2012;33(2):154-61.

33. Porst H, Roehrborn CG, Secrest RJ, Esler A, Viktrup L. Effects of tadalafil on lower urinary tract symptoms secondary to benign prostatic hyperplasia and on erectile dysfunction in sexually active men with both conditions: analyses of pooled data from four randomized, placebo-controlled tadalafil clinical studies. The journal of sexual medicine. 2013;10(8):2044-52.

34. Morales AM, Casillas M, Turbi C. Patients' preference in the treatment of erectile dysfunction: a critical review of the literature. International journal of impotence research. 2011;23(1):1-8.

35. Katz EG, Tan RBW, Rittenberg D, Hellstrom WJ. Avanafil for erectile dysfunction in elderly and younger adults: differential pharmacology and clinical utility. Ther Clin Risk Manag. 2014; 10:701-711.

36. Limin M, Johnsen N, Hellstrom WJ. Avanafil, a new rapid-onset phosphodiesterase 5 inhibitor for the treatment of erectile dysfunction. Expert Opin Investig Drugs. 2010;19(11):1427–1437.

37. Burke RM, Evans JD. Avanafil for treatment of erectile dysfunction: review of its potential. Vasc Health Risk Manag. 2012;8:517–523)

38. Melnik T, Abdo CH, de Moraes JF, Riera R. Satisfaction with the treatment, confidence and 'naturalness' in engaging in sexual activity in men with psychogenic erectile dysfunction: preliminary results of a randomized controlled trial of three therapeutic approaches. BJU international. 2012;109(8):1213-9.

39. McCullough AR, Barada JH, Fawzy A, Guay AT, Hatzichristou D. Achieving treatment optimization with sildenafil citrate (Viagra) in patients with erectile dysfunction. Urology. 2002;60(2 Suppl 2):28-38.

40. Limoge JP, Olins E, Henderson D, Donatucci CF. Minimally invasive therapies in the treatment of erectile dysfunction in anticoagulated cases: a study of satisfaction and safety. The Journal of urology. 1996;155(4):1276-9.

41. Nadig PW, Ware JC, Blumoff R. Noninvasive device to produce and maintain an erection-like state. Urology. 1986;27(2):126-31.

42. Vardi Y, Appel B, Jacob G, Massarwi O, Gruenwald I. Can low-intensity extracorporeal shockwave therapy improve erectile function? A 6-month follow-up pilot study in patients with organic erectile dysfunction. European urology. 2010;58(2):243-8.

43. 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. The Journal of urology. 2012;187(5):1769-75.

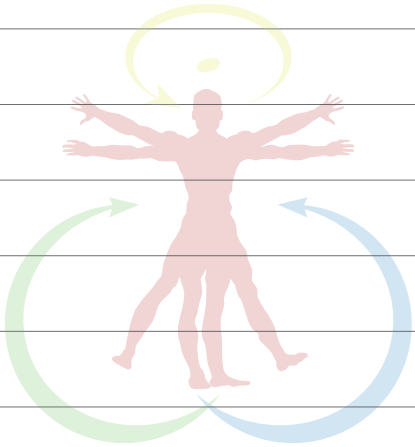
44. Srini VS, Reddy RK, Shultz T et al: Low intensity extracorporeal shockwave therapy for erectile dysfunction: a study in an Indian population. Can J Urol 2015; 22: 7614.

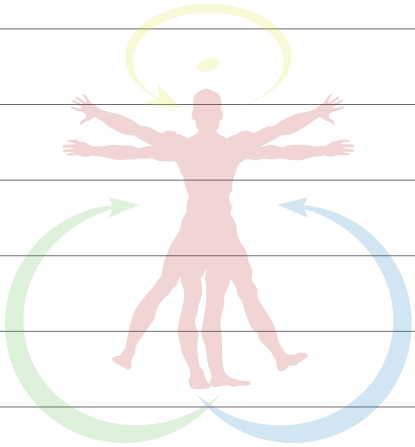
45. Olsen AB, Persiani M, Boie S et al: Can low-intensity extracorporeal shockwave therapy improve erectile dysfunction? A prospective, randomized, double-blind, placebo-controlled study. Scand J Urol 2015; 49: 329.

46. Rogers JH, Goldstein I, Kandzari DE, Kohler TS, Stinis CT, Wagner PJ, et al. Zotarolimus-eluting peripheral stents for the treatment of erectile dysfunction in subjects with suboptimal response to phosphodiesterase-5 inhibitors. Journal of the American College of Cardiology. 2012;60(25):2618-27.

47. Philip F, Shishehbor MH. Current state of endovascular treatment for vasculogenic erectile dysfunction. Current cardiology reports. 2013;15(5):360

48. Vakalopoulos I, Kampantais S, Ioannidis S, Laskaridis L, Dimopoulos P, Toutziaris C, et al. High patient satisfaction after inflatable penile prostheses implantation correlates with female partner satisfaction. The journal of sexual medicine. 2013;10(11):2774-81.





SPEDRA® MEANS SEX SOONER[1,2*]

*Within 15 minutes of dosing vs. placebo (n=646)[2]

A multicenter, randomised, double-blinded, placebo-controlled evaluation of the safety and efficacy of avanafil (50mg, 100mg, 200mg) in 646 subjects with mild to severe erectile dysfunction, throughout a 12-week treatment period. Improvement in erectile function (EF) was measured by Sexual Encounter Profile questions 2 and 3 (SEP2 and SEP3) and by the EF domain of the International Index of Erectile Function (IIEF) questionnaire. Mean change in percentage of successful sexual attempts (SEP2 and SEP3) and IIEF-EF domain score significantly favoured all doses of avanafil over placebo ($P \leq 0.001$). Secondary analyses demonstrated achievement of successful intercourse by subjects within 15 minutes of dosing. Following 12 weeks of avanafil treatment without food or alcohol restrictions, significant improvements in sexual function were observed with all 3 doses of avanafil compared with placebo. Successful intercourse was observed as early as 15 minutes and →6 hours after dosing in some subjects. Avanafil was generally well tolerated for the treatment of ED.

In this study, treatment with Spedra® was generally well tolerated[2]

References: 1) SPEDRA® SG Product Information, Aug 2018. 2) Goldstein I, *et al.* A Randomized, Double-Blind, Placebo-Controlled Evaulation of the Safety and Efficacy of Avanafil in Subjects with Erectile Dysfunction. *J Sex Med.* 2012.

Abbreviated Prescribing Information: Spedra Tablets. **Indications**: Treatment of erectile dysfunction in adult men. In order for Spedra to be effective, sexual stimulation is required. **Dosing**: Use in adult men. Take 100mg as needed approximately 15 to 30 minutes before sexual activity. Based on individual efficacy and tolerability, the dose may be increased to a maximum dose of 200mg or decreased to 50mg. The maximum recommended dosing frequency is once per day. Sexual stimulation is required for a response to treatment. **Contraindications**: Hypersensitivity to the active substance or to any of the excipients. Patients who are using any form of organic nitrate or nitric oxide donors. The co-administration of PDE5 inhibitors with guanylate cyclase stimulators. Patients who have suffered from a myocardial infarction, stroke, or life-threatening arrhythmia within the last 6 months. Patients with: resting hypotension or hypertension; unstable angina, angina with sexual intercourse, or congestive heart failure categorised as New York Heart Association Class 2 or greater; severe hepatic impairment; severe renal impairment; known hereditary degenerative retinal disorders. Patients who have loss of vision in one eye because of non-arteritic anterior ischemic optic neuropathy (NAION). Concomitant treatment of potent CYP3A4 inhibitors. **Precautions**: The cardiovascular status of the patient should be considered. Patients who experience erections lasting 4 hours or more (priapism) should be instructed to seek immediate medical assistance. The patient should be advised that in case of sudden visual effects, or in the event of sudden decrease or loss of hearing, he should stop taking Spedra and consult a physician immediately. Concomitant use of avanafil with alpha-blockers, CYP3A4 inhibitors, alcohol. **Adverse events**: The most common adverse reactions reported in clinical studies were headache, flushing, nasal and sinus congestion and back pain.

Full prescribing information is available upon request. For Healthcare Professionals Only

MENARINI

A. Menarini Singapore Pte. Ltd.
30 Pasir Panjang Road, #08-32 Mapletree Business City. Singapore 117440.
Tel: +65 6494 3400 Fax: +65 6777 1786. www.menariniapac.com
SG-SPE-202008-003 (Aug/2020)

Spedra® avanafil