

GUIDELINES ON MALE SEXUAL DYSFUNCTION: Erectile Dysfunction and Premature Ejaculation

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ERECTILE DYSFUNCTION

Definition, epidemiology and risk factors

Erectile dysfunction (ED) is the persistent inability to attain and maintain an erection sufficient to permit satisfactory sexual performance. Although ED is a benign disorder, it affects physical and psychosocial health and has a significant impact on the quality of life (QoL) of sufferers and their partners.

There is increasing evidence that ED can be an early manifestation of coronary artery and peripheral vascular disease; thus, ED should not be regarded only as a QoL issue but also as a potential warning sign of cardiovascular disease including lack of exercise, obesity, smoking, hypercholesterolaemia, and the metabolic syndrome. The risk of ED may be reduced by modifying these risk factors, particularly taking exercise or losing weight. Another risk factor for ED is radical prostatectomy (RP) in any form (open, laparoscopic, or robotic) because of the risk of cavernosal nerve injury, poor oxygenation of the corpora cavernosa, and vascular insufficiency.

Diagnosis and work-up

Basic work-up

The basic work-up (minimal diagnostic evaluation) outlined in Fig. 1 must be performed in every patient with ED.

Due to the potential cardiac risks associated with sexual activity, the three Princeton Consensus Conference stratified patients with ED wanting to initiate, or resume, sexual activity into three risk categories. The low-risk group includes asymptomatic patients with less than three risk factors for coronary artery disease (excluding male gender), mild or stable angina (evaluated and/or being treated), uncomplicated past myocardial infarction, left ventricular dysfunction or congestive heart failure (NYHA class I), post-successful coronary revascularisation, controlled hypertension, and mild valvular disease. All other patients are included in an intermediate- or high-risk category and require a cardiology consultation.

Specific examinations and tests

Although most patients with ED can be managed within the sexual care setting, some circumstances require specific diagnostic testing:

- Patients with primary erectile disorder (not caused by organic disease or psychogenic disorder).
- Young patients with a history of pelvic or perineal trauma who could benefit from potentially curative vascular surgery.
- Patients with penile deformities (e.g. Peyronie's disease, congenital curvature) that might require surgical correction.
- Patients with complex psychiatric or psychosexual disorders.
- Patients with complex endocrine disorders.
- Specific tests may also be indicated at the request of the patient or his partner.

- For medico-legal reasons (e.g. penile prosthesis implant, sexual abuse).

Specific diagnostic tests include:

- nocturnal penile tumescence and rigidity (NTPR) using Rigiscan®;
- vascular studies:
 - intracavernous vasoactive drug injection;
 - duplex ultrasound of the cavernous arteries;
 - dynamic infusion cavernosometry/cavernosography (DICC);
 - internal pudendal arteriography;
- neurological studies (e.g. bulbocavernosus reflex latency, nerve conduction studies);
- endocrinological studies;
- specialised psychodiagnostic evaluation.

The NTPR should take place for at least two nights. A functional erectile mechanism is indicated by an erectile event of at least 60% rigidity recorded on the tip of the penis, lasting for 10 min or longer.

The intracavernous injection test provides limited information about vascular status. However, Duplex ultrasound provides a simple way of assessing vascular status. Further vascular investigation is unnecessary if Duplex ultrasound is normal, as indicated by a peak systolic blood flow > 30 cm/s an end-diastolic velocity of < 3 cm/s and a resistance index > 0.8 . If ultrasound is abnormal, however, arteriography and DICC should be performed only in patients who are potential candidates for vascular reconstructive surgery.

| Recommendations for the diagnostic work-up | LE | GR |
|--|-----------|-----------|
| Clinical use of a validated questionnaire related to ED may help assess all sexual function domains and the effect of a specific treatment modality. | 3 | B |
| Physical examination is needed in the initial assessment of ED to identify underlying medical conditions associated with ED. | 4 | B |
| Routine laboratory tests, including glucose-lipid profile and total testosterone, are required to identify and treat any reversible risk factors and modifiable lifestyle factors. | 4 | B |
| Specific diagnostic tests are indicated by only a few conditions. | 4 | B |

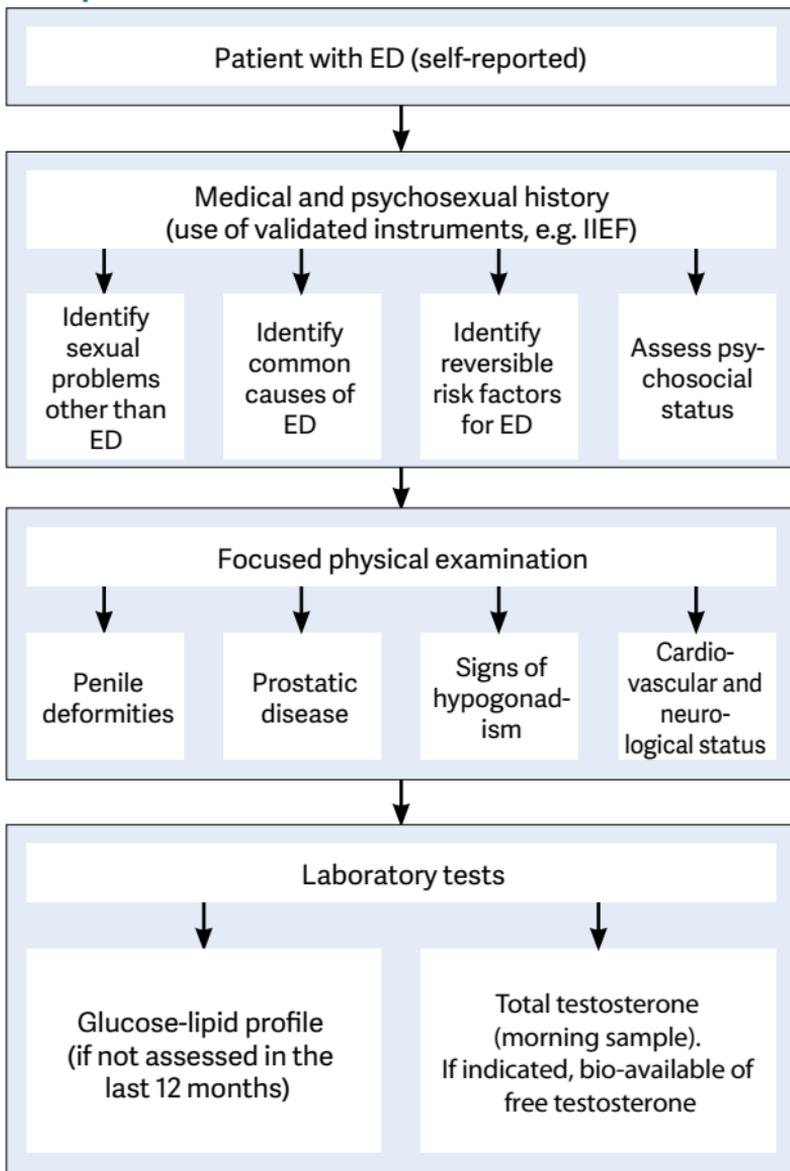
ED = *erectile dysfunction*.

Treatment of ED

As a rule, ED can be treated successfully with current treatment options, but cannot be cured, with the exception of:

- Psychogenic ED: psychosexual therapy may be given, either alone or with another therapeutic approach, but takes time and has had variable results.
- Post-traumatic arteriogenic ED in young patients: surgical penile revascularisation has a 60-70% long-term success rate.
- Hormonal causes of ED: testosterone replacement therapy is effective, but should only be used after other endocrinological causes for testicular failure have been excluded. Currently, it is contraindicated in men with untreated prostate cancer, unstable cardiac disease and severe LUT obstruction. Close follow-up is necessary, including digital rectal examination (DRE), serum prostate-specific antigen (PSA) and haematocrit assessment, as well as monitoring the development of hepatic or prostatic disease.

Fig. 1: Minimal diagnostic evaluation (basic work-up) in patients with ED



IIEF = International Index for Erectile Function; ED = erectile dysfunction.

The use of pro-erectile drugs following RP is very important in achieving erectile function after surgery. Rehabilitation should start as soon as possible following RP.

Most men with ED will be treated with treatment options that are not cause-specific. This approach requires a structured treatment strategy that depends on efficacy, safety, invasiveness, and cost, as well as patient and partner satisfaction. A treatment algorithm for ED is given in Fig. 2.

First-line therapy

Oral pharmacotherapy

Three potent, selective PDE5 inhibitors (PDE5Is) have been approved by the European Medicines Agency (EMA) for the treatment of ED. They are not initiators of erection and require sexual stimulation for an erection to occur. Efficacy is defined as rigidity sufficient for vaginal penetration.

Sildenafil (Viagra™)

Sildenafil is effective after 30-60 min from administration. A heavy, fatty meal may reduce or prolong absorption. It is administered in 25, 50 and 100 mg doses. The recommended starting dose is 50 mg and adapted according to patient response and side-effects. Efficacy may be maintained for up to 12 h. Efficacy rates (erections sufficient for successful intercourse) are 56%, 77% and 84% of men taking 25, 50 and 100 mg of sildenafil, respectively. The efficacy of sildenafil in almost every subgroup of patients with ED has been well established.

Tadalafil (Cialis™)

Tadalafil is effective from 30 min after administration but its peak efficacy occurs after about 2 h. Efficacy is maintained for up to 36 h and is not affected by food. It is administered in 10 and 20 mg doses. The recommended starting dose is 10

mg and is adapted according to patient response and side-effects. Efficacy rates are 67% and 81% of men taking 10 mg and 20 mg of tadalafil, respectively. Tadalafil also improves erections in difficult-to-treat subgroups.

Vardenafil (Levitra™)

Vardenafil is effective after 30 min from administration. A fatty meal, > 57% in fat, reduces its effect. It is administered in 5, 10 and 20 mg doses. The recommended starting dose is 10 mg and adapted according to the response and side-effects. In vitro, it is 10-fold more potent than sildenafil. However, this does not necessarily mean greater clinical efficacy. Efficacy rates are 66%, 76% and 80% of men taking 5 mg, 10 mg and 20 mg of vardenafil, respectively. Vardenafil also improves erections in difficult-to-treat subgroups.

Choice of, or preference for, different PDE5Is

The choice of a PDE5I depends on the frequency of intercourse (occasional use or regular therapy, 3-4 times weekly) and the patient's personal experience of the agent. Patients need to know whether a drug is short- or long-acting, possible disadvantages, and how to use it.

On-demand or chronic use of PDE5Is

Although PDE5Is were introduced as on-demand treatment, in 2008, tadalafil was also approved for continuous, everyday use in 2.5 and 5 mg doses. Daily dosing was well tolerated and significantly improved erectile function. Similar results have been found in diabetic patients. Daily tadalafil provides an alternative to on-demand dosing for couples that prefer spontaneous rather than scheduled sexual activity or who have frequent sexual activity.

Adverse events

Common adverse events include headache, flushing, dizzi-

ness, dyspepsia, and nasal congestion. Sildenafil and vardenafil have been associated with visual abnormalities in less than 2% of patients, while tadalafil has been associated with back pain/myalgia in 6% of patients. However, adverse events are generally mild in nature, self-limited by continuous use, and the dropout rate due to adverse events is similar to placebo.

Cardiovascular safety

Clinical trials and post-marketing data of all PDE5Is have demonstrated no increase in myocardial infarction rates. No PDE5I has adversely affected total exercise time or time to ischaemia during exercise testing in men with stable angina. In fact, they may improve exercise tests.

Nitrates are totally contraindicated with all PDE5Is due to unpredictable hypotension. The duration of interaction between organic nitrates and PDE5Is varies according to the PDE5I and nitrate. If a patient develops angina while using a PDE5I, other antiangina agents may be used instead of nitroglycerine or until after the appropriate time has passed (24 h for sildenafil or vardenafil and 48 h for tadalafil).

In general, the adverse event profile of the PDE5I is not worsened, even when the patient is on multiple antihypertensive agents.

Alpha-blocker interactions

All PDE5Is appear to interact with alpha-blockers, which under some conditions may result in orthostatic hypotension. Patients should be stable on alpha-blocker therapy prior to initiating combined treatment, and that the lowest dose should be started initially of PDE5Is.

Dosage adjustments

Lower doses of PDE5Is may be required in patients taking

ketoconazole, itraconazole, erythromycin, clarithromycin, and HIV protease inhibitors (ritonavir, saquinavir). Higher doses of PDE5Is may be necessary in patients taking rifampicin, phenobarbital, phenytoin, or carbamazepine. Kidney or hepatic dysfunction may require dose adjustments. In patients with hypogonadism, androgen supplementation improves erectile response.

Management of non-responders to PDE5Is

Physicians should check that the patient is using a licensed medication and that the medication has been properly prescribed and correctly used (adequate sexual stimulation, dosage, and enough time between taking the medication and attempt at intercourse).

Provided a patient is using a PDE5I appropriately, there are several ways of improving efficacy. They include modification of associated risk factors, treatment of associated hypogonadism, changing to another PDE5I, or continuous use of a PDE5I.

Vacuum erection devices

A vacuum erection device (VED) applies a negative pressure to the penis to draw venous blood into the penis, which is then retained by application of a visible constricting band at the base of the penis. Efficacy, defined by an erection satisfactory for intercourse, is as high as 90%. Satisfaction rates range between 27% and 94%. Adverse events include penile pain, numbness, and delayed ejaculation and occur in less than 30% of patients. VED is acceptable for couples in a stable relationship.

Second-line therapy

Patients not responding to oral drugs may be offered intracavernous injections. Alprostadil (Caverject®, Edex/Viridal®) is the only drug approved for intracavernous treatment of ED. It is the most efficacious monotherapy for intracavernous treatment using 5-40 µg doses. The patient should be rolled in an office-based training programme (one or two visits) to learn the correct injection process.

Complications of intracavernosal prostatic prostadil include penile pain (50% of patients), prolonged erections (5%), priapism (1%), and fibrosis (2%). Drug combinations (mainly the three-drug combination of alprostadil + papaverine + phentolamine) may increase efficacy by up to 90%. Fibrosis was found to be more common (5-10%) if papaverine was used (depending on total dose).

After 4 h of erection, patients are advised to consult their doctor to avoid any damage to the intracavernous muscle, as this will result in permanent impotence. Blood aspiration and injection of phenylephrine are used to treat prolonged erections. If this problem occurs, the dosage of the next intracavernosal injection is usually reduced.

Prostaglandin E1 may be administered intra-urethraly as a semi-solid pellet (125-1000 µg). A band placed at the base of the penis improves the resulting rigidity. The clinical success rate is lower than with intracavernosal injections, but about 70% of patients are satisfied with treatment. Side-effects include local pain (29-41%), dizziness (1.9-14%), and urethral bleeding (5%).

Third-line therapy (penile prostheses)

Surgical implantation of a penile prosthesis may be considered in patients who fail pharmacotherapy or who want a

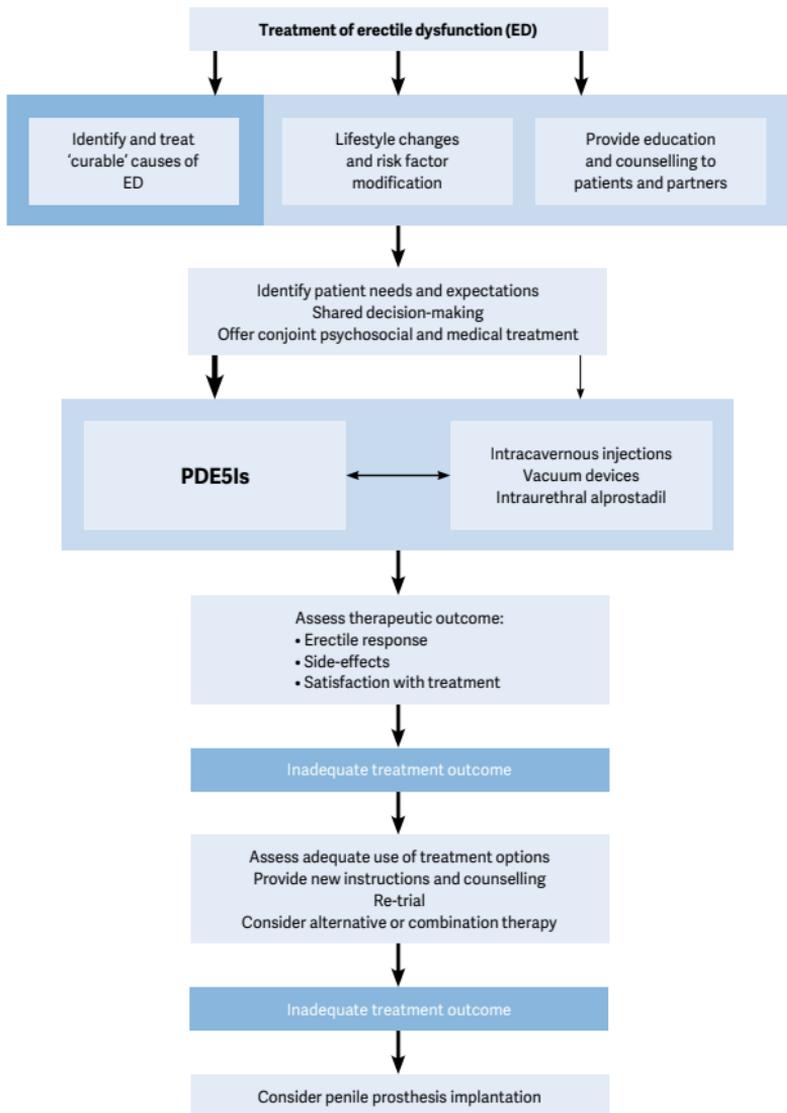
permanent solution. Prostheses are either malleable (semi rigid) or inflatable (two- or three-piece). Most patients prefer the three-piece inflatable devices because erections are more 'natural', but these implants are much more expensive. Satisfaction rates of 70-87% are reported from patients after appropriate consultation.

Complications include mechanical failures and infections. With antibiotic prophylaxis, the infection rate is 2-3% and may be further reduced by using an antibiotic-impregnated or hydrophilic-coated implant. Infection requires removing the prosthesis, antibiotic administration and re-implantation after 6-12 months.

| Recommendations for ED treatment | LE | GR |
|---|-----------|-----------|
| Lifestyle changes and risk factor modification must precede or accompany ED treatment. | 1a | A |
| Pro-erectile treatments have to be given at the earliest opportunity after radical prostatectomy. | 1b | A |
| When a curable cause of ED is found, it must be treated first. | 1b | B |
| PDE5Is are first-line therapy. | 1a | A |
| Daily administration of PDE5Is may improve results and restore erectile function. | 1b | A |
| A vacuum erection device can be used in patients with stable relationship. | 4 | C |
| Intracavernous injection is second-line therapy. | 1b | B |
| Penile implant is third-line therapy. | 4 | C |

PDE5I = phosphodiesterase type 5 inhibitor.

Fig. 2: Treatment algorithm for ED



PDE5 inhibitor = phosphodiesterase type 5 inhibitor.

PREMATURE EJACULATION

Definition, epidemiology and risk factors

The International Society for Sexual Medicine (ISSM) has adopted a completely new definition of lifelong PE, which is the first evidence-based definition: *'Premature ejaculation is a male sexual dysfunction characterized by ejaculation which always or nearly always occurs prior to or within about one minute of vaginal penetration; and inability to delay ejaculation on all or nearly all vaginal penetrations; and negative personal consequences, such as distress, bother, frustration and/or the avoidance of sexual intimacy'*.

Thus, PE may be classified as 'lifelong' (primary) or 'acquired' (secondary). Lifelong PE is characterised by onset from the first sexual experience and remains a problem during life. Acquired PE is characterised by a gradual or sudden onset with ejaculation being normal before onset of the problem. Time to ejaculation is short, but not usually as fast as in lifelong PE.

Premature ejaculation has a detrimental effect on self-confidence and relationship with the partner. It may cause mental distress, anxiety, embarrassment, and depression. However, most men with PE do not seek help.

Diagnostic work-up

Diagnosis of PE is based on the patient's medical and sexual history. The history should classify PE as lifelong or acquired and determine whether PE is situational (under specific circumstances or with a specific partner) or consistent. Special attention should be given to the length of time of ejaculation, degree of sexual stimulus, impact on sexual activity and QoL, and drug use or abuse. It is also important to distinguish PE from ED.

| Recommendations for diagnosis of PE | LE | GR |
|--|-----------|-----------|
| Diagnosis and classification of PE is based on medical and sexual history. | | |
| It should be multidimensional and assess IELT, perceived control, distress, and interpersonal difficulty due to the ejaculatory dysfunction. | 1a | A |
| Clinical use of self-estimated IELT is adequate. Stopwatch-measured IELT is necessary in clinical trials. | 2a | B |
| Patient-reported outcomes have the potential to identify men with PE. Further research is needed before they can be recommended for clinical use. | 3 | C |
| Physical examination may be necessary in initial assessment of PE to identify underlying medical conditions associated with PE or other sexual dysfunctions particularly ED. | 3 | C |
| Routine laboratory or neurophysiological tests are not recommended. Additional tests should be directed by specific findings from history or physical examination. | 3 | C |

IELT = intravaginal ejaculatory latency time.

Treatment of PE

In many relationships, PE causes few, if any, problems. In such cases, treatment should be limited to psychosexual counselling. Before beginning treatment, it is essential to discuss patient expectations thoroughly. Erectile dysfunction or other sexual dysfunction or genitourinary infection (e.g. prostatitis) should be treated first or at the same time as PE. Various behavioural techniques have demonstrated benefit in treating PE. In lifelong PE, behavioural techniques are not recommended for first-line treatment. They are time-intensive, require the support of a partner, and can be difficult to do.

Pharmacotherapy is the basis of treatment in lifelong PE but all medical treatments are off-label indications. Only chronic selective serotonin reuptake inhibitors (SSRIs) and on-demand topical anaesthetic agents have consistently shown efficacy in PE. A treatment algorithm for PE is presented in Fig. 3.

Psychological/behavioural strategies

Behavioural strategies mainly include the 'stop-start' programme developed by Semans and its modification, the 'squeeze' technique, proposed by Masters and Johnson (several modifications exist). Masturbation before anticipation of sexual intercourse is another technique used by many younger men.

Overall, success rates of 50-60% have been reported short term. Improvements achieved with these techniques are generally not maintained long term.

Topical anaesthetic agents

Lidocaine-prilocaine cream (5%) is applied for 20-30 min prior to intercourse. A condom is required to avoid diffusion of the topical anaesthetic agent into the vaginal wall causing numbness in the partner. In two RCTs, lidocaine-prilocaine cream significantly increased the stopwatch-measured IELT compared to placebo. No significant side-effects have been reported. An aerosol formulation of lidocaine 7.5 mg plus prilocaine 2.5 mg (Topical Eutectic Mixture for Premature Ejaculation, TEMPE) is under evaluation and has shown similar results.

SS-cream is a topical anaesthetic agent made from the extracts of nine herbs. It is applied to the glans penis 1 h before and washed off immediately prior to coitus. In a RCT, application of 0.2 g SS-cream significantly improved IELT

and satisfaction compared to the placebo group. Mild local burning and mild pain were reported by 18.5% of patients. No adverse effects on sexual function or partner or systemic side-effects were observed.

Selective serotonin reuptake inhibitors

Commonly used selective serotonin reuptake inhibitors (SSRIs) include paroxetine (20-40 mg/day), sertraline (25-200 mg/day), and fluoxetine (10-60 mg). Selective serotonin reuptake inhibitors were expected to increase the geometric mean IELT by 2.6-fold to 13.2-fold. Paroxetine was found to be superior to fluoxetine, clomipramine, and sertraline.

Ejaculation delay may start a few days after drug intake, but it is more evident after 1-2 weeks and may be maintained for several years. Common side-effects of SSRIs include fatigue, drowsiness, yawning, nausea, vomiting, dry mouth, diarrhoea, and perspiration; they are usually mild and gradually improve after 2-3 weeks. Decreased libido, anorgasmia, anejaculation, and ED have been also reported. On-demand treatment is inferior to daily dosing, but may be combined with an initial trial of daily treatment or concomitant low-dose daily treatment to reduce adverse effects.

Dapoxetine is a potent SSRI, which has been specially designed as an on-demand oral treatment for PE. An integrated analysis of two RCTs reported that dapoxetine, 30 and 60 mg, improved IELT significantly compared to placebo. Improved ejaculation control was reported by 51% and 58% of patients in the 30 mg and 60 mg dosage groups, respectively. Both dapoxetine doses were effective on the first dose. Common adverse events were nausea, diarrhoea, headache, and dizziness. Dapoxetine has been approved (December 2008) for the on-demand treatment of PE in seven European countries (Sweden, Austria, Finland, Germany, Spain, Italy, and Portugal). This is currently the first and only drug approved for

such an indication.

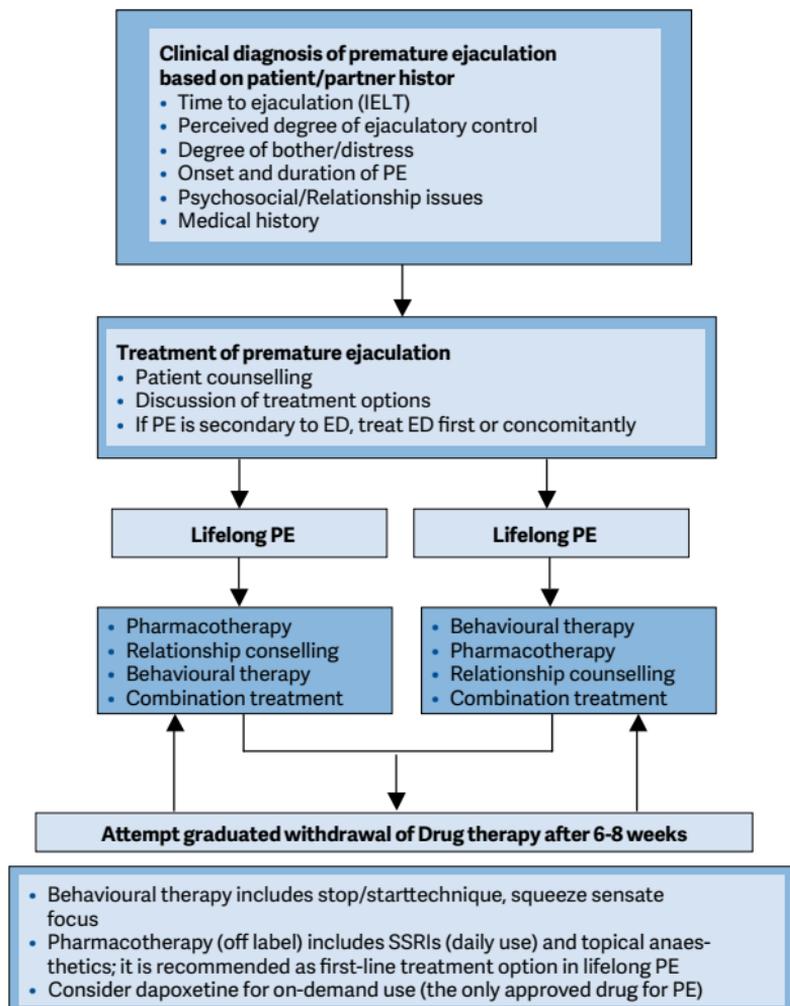
Phosphodiesterase type 5 inhibitors

Several recent studies have supported the therapeutic role of PDE5Is in PE. However, there is only one RCT comparing sildenafil to placebo. Although IELT was not significantly improved, sildenafil increased confidence, the perception of ejaculatory control and overall sexual satisfaction, reduced anxiety, and decreased the refractory time to achieve a second erection after ejaculation.

| Recommendations for PE treatment | LE | GR |
|--|----|----|
| Erectile dysfunction, other sexual dysfunction, or genitourinary infection (e.g. prostatitis) should be treated first. | 2a | B |
| Behavioural techniques can benefit PE. However, they are time intensive, require the support of a partner, and can be difficult to do. | 3 | C |
| Pharmacotherapy is the basis of treatment in lifelong PE. | 1a | A |
| Daily SSRIs are first-line, off-label, pharmacological treatment for PE. The pharmacokinetic profile of currently available SSRIs is not amenable to on-demand dosing. | 1a | A |
| Dapoxetine, a short-acting SSRI, has already been approved for the on-demand treatment of PE in seven European countries. | 1a | A |
| Topical anaesthetic agents provide viable alternatives to SSRIs (off-label). | 1b | A |
| A trial of PDE5Is may be attempted. | 2b | C |
| Recurrence is likely after treatment cessation. | 1b | A |
| Behavioural therapy may augment pharmacotherapy to enhance prevention of relapse. | 3 | C |

SSRI = selective serotonin reuptake inhibitor.

Fig. 3: Management of PE



PE = premature ejaculation; IELT = intravaginal ejaculatory latency time; ED = erectile dysfunction; SSRI = selective serotonin receptor inhibitor.

Adapted from Lue et al. Summary of the recommendations on sexual dysfunctions in men. *J Sex Med* 2004;1:6-23.



This short booklet text is based on the more comprehensive EAU guidelines (ISBN 978-90-79754-71-7), available to all members of the European Association of Urology at their website, <http://www.uroweb.org>.