

Guidelines on **Male Sexual Dysfunction:**

Erectile dysfunction and premature ejaculation

E. Wespes, E. Amar, I. Eardley, F. Giuliano, D. Hatzichristou,
K. Hatzimouratidis, F. Montorsi, Y. Vardi

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1. BACKGROUND

1.1 Introduction

Erectile dysfunction (ED, impotence) and premature ejaculation (PE) are the two main complaints in male sexual medicine. New oral therapies have completely changed the diagnostic and therapeutic approach to ED and the Guidelines Office of The European Association of Urology (EAU) has appointed an Expert Panel to update previously published EAU guidelines for ED or impotence (1).

The update is based on a review of available scientific information, current research and clinical practice in the field (1, 2). The Expert Panel has also identified critical problems and knowledge gaps, setting priorities for future clinical research.

Level of evidence and grade of recommendation have been included in these guidelines when possible. The aim of this practice is to provide transparency between the underlying evidence and the recommendation made (3).

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2. DIAGNOSIS

2.1 Epidemiology and risk factors

Erection is a neurovascular phenomenon under hormonal control. It includes arterial dilatation, trabecular smooth muscle relaxation and activation of the corporeal veno-occlusive mechanism (1).

Erectile dysfunction has been defined as 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 and families (2).

2.1.1 Epidemiology

Recent epidemiological data have shown a high prevalence and incidence of ED worldwide. The first large-scale, community-based study of ED was the Massachusetts Male Aging Study (MMAS). The study reported an overall prevalence of 52% ED in non-institutionalized 40- to 70-year-old men in the Boston area in the USA (3); specific prevalences for minimal, moderate and complete ED were 17.2%, 25.2% and 9.6%, respectively. In the Cologne study of men aged 30-80 years old, the prevalence of ED was 19.2%, with a steep age-related increase from 2.3% to 53.4% (4). In the National Health and Social Life Survey (NHSLs), the prevalence of sexual dysfunctions (not specific ED) was 31% (5). The incidence rate of ED (new cases per 1000 men annually) was 26 in the MMAS study (6), 65.6 (mean follow-up of 2 years) in a Brazilian study (7) and 19.2 (mean follow-up of 4.2 years) in a Dutch study (8). Differences between these studies can be explained by differences in methodology and in the ages and socio-economic status of the populations studied.

2.1.2 Risk factors

Erectile dysfunction shares common risk factors with cardiovascular disease (e.g. lack of exercise, obesity, smoking, hypercholesterolaemia, metabolic syndrome), some of which can be modified. In the MMAS, men who began exercising in midlife had a 70% reduced risk for ED compared to sedentary men and a significantly lower incidence of ED over an 8-year follow-up period of regular exercise (9). A multicentre, randomised, open-label study in obese men with moderate ED compared 2 years of intensive exercise and weight loss with a control group given general information about healthy food choices and exercise (10). Significant improvements in body mass index (BMI) and physical activity scores, as well as in erectile function, were observed in the

lifestyle intervention group. These changes were highly correlated with both weight loss and activity levels. However, it should be emphasized that controlled prospective studies are necessary to determine the effects of exercise or other lifestyle changes in prevention or treatment of ED.

2.1.3 Post-radical prostatectomy ED

Radical prostatectomy (RP) in any form (open, laparoscopic, or robotic) is a widely performed procedure for patients with clinically localized prostate cancer (PCa) and a life expectancy of at least 10 years. This procedure may lead to treatment-specific sequelae affecting health-related QoL. This outcome has become increasingly important with the more frequent diagnosis of PCa in younger patients (11-13). Research has shown that about 25-75% of men experience post-operative ED (14).

Post-RP ED is multifactorial. Cavernal nerve injury induces pro-apoptotic (loss of smooth muscle) and pro-fibrotic (increase in collagen) factors within the corpora cavernosa. These changes may also be caused by poor oxygenation due to changes in the blood supply to the cavernosa.

Because pre-operative potency is a major factor associated with the recovery of erectile function after surgery, patients being considered for a nerve-sparing radical prostatectomy (NSRP) should ideally be potent (15). It is also clear that cavernosal nerves must be preserved to ensure erectile function recovers after RP. In addition, the role of vascular insufficiency is of increasing interest in post-operative ED (16, 17).

2.2 Managing ED: implications for everyday clinical practice

Advances in basic and clinical research in ED during the past 15 years have led to the development of several new treatment options for ED, including new pharmacological agents for intracavernous, intraurethral, and, more recently, oral use (18-20). Treatment strategies have also changed following the poor outcomes seen in long-term follow-up of reconstructive vascular surgery (21, 22).

An increasing number of men are seeking help for ED due to the great media interest in ED and the availability of effective and safe oral drug therapy. However, there are many physicians evaluating and treating ED without appropriate background knowledge and clinical experience. Thus, some men with ED may receive little or no evaluation before treatment and will therefore not receive treatment for any underlying disease that may be causing their ED. Other men without ED may be requesting treatment simply to enhance their sexual performance. Given this situation, these EAU guidelines for the diagnosis and treatment of ED are a necessity.

2.3 Conclusions

Conclusion	LE	GR
• Erection is a neurovascular phenomenon under hormonal control in a physiogenic environment	2b	C
• ED is common worldwide	3	B
• ED shares several risk factors with cardiovascular disease	3	B
• Lifestyle modification (intensive exercise and a decrease in body mass index) can improve erectile function	1b	A
• ED is a symptom, not a disease. Some men may not be properly evaluated or receive treatment for an underlying disease or condition that may be causing ED.	4	C
• Radical prostatectomy is a common cause of ED	3	B

LE = level of evidence; GR = grade of recommendation; ED = erectile dysfunction.

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2.5 Diagnosis

2.5.1 Basic work-up

The first step in evaluating ED is always a detailed medical and psychological history of patients and partners (1, 2). Often it is not possible to include the partner on the patient's first visit, but an effort should be made to include the partner at the second visit. The pathophysiology of ED may be vasculogenic, neurogenic, hormonal, anatomical, drug-induced or psychogenic (Table 1) (3) and taking a medical history may reveal one of the many common disorders associated with ED

It is important to establish a relaxed atmosphere during history-taking. This will make it easier to ask questions about erectile function and other aspects of sexual history, particularly when patients do not find it easy to talk about their problem. It will also make it easier to explain the diagnosis and therapeutic approach to the patient and his partner.

Table 1: Pathophysiology of ED

Vasculogenic
• Cardiovascular disease
• Hypertension
• Diabetes mellitus
• Hyperlipidaemia
• Smoking
• Major surgery (radical prostatectomy) or radiotherapy (pelvis or retroperitoneum)
Neurogenic
<i>Central causes</i>
• Multiple sclerosis
• Multiple atrophy
• Parkinson's disease
• Tumours
• Stroke
• Disk disease
• Spinal cord disorders
<i>Peripheral causes</i>
• Diabetes mellitus
• Alcoholism
• Uraemia
• Polyneuropathy
• Surgery (pelvis or retroperitoneum, radical prostatectomy)
Anatomical or structural
• Peyronie's disease
• Penile fracture
• Congenital curvature of the penis
• Micropenis
• Hypospadias, epispadias
Hormonal
• Hypogonadism
• Hyperprolactinemia
• Hyper- and hypo-thyroidism
• Cushing's disease
Drug-induced
• Antihypertensives (diuretics and beta-blockers are the most common causes)
• Antidepressants
• Antipsychotics
• Antiandrogens
• Antihistamines
• Recreational drugs (heroin, cocaine, methadone)
Psychogenic
• Generalized type (e.g. lack of arousability and disorders of sexual intimacy)
• Situational type (e.g. partner-related, performance-related issues or due to distress)

2.5.1.1 Sexual history

The sexual history may include information about previous and current sexual relationships, current emotional status, onset and duration of the erectile problem, and previous consultations and treatments. A detailed description should be made of the rigidity and duration of both erotic and morning erections and of problems with arousal, ejaculation and orgasm. Validated questionnaires, such as the International Index for Erectile Function (IIEF), help to assess all sexual function domains (erectile function, orgasmic function, sexual desire, ejaculation, intercourse and overall satisfaction), as well as the impact of a specific treatment modality (4).

2.5.1.2 Physical examination

Every patient must be given a physical examination focused on the genitourinary, endocrine, vascular and neurological systems (1). A physical examination may reveal unsuspected diagnoses, such as Peyronie's disease, prostatic enlargement or cancer, or signs and symptoms suggesting hypogonadism (small testes, alterations in secondary sexual characteristics, diminished sexual desire and changes in mood) (2). A rectal examination should be performed in every patient older than 50 years. Blood pressure and heart rate should be measured if they have not been assessed in the previous 3-6 months. Particular attention must be given to patients with cardiovascular disease (see Section 2.5.2).

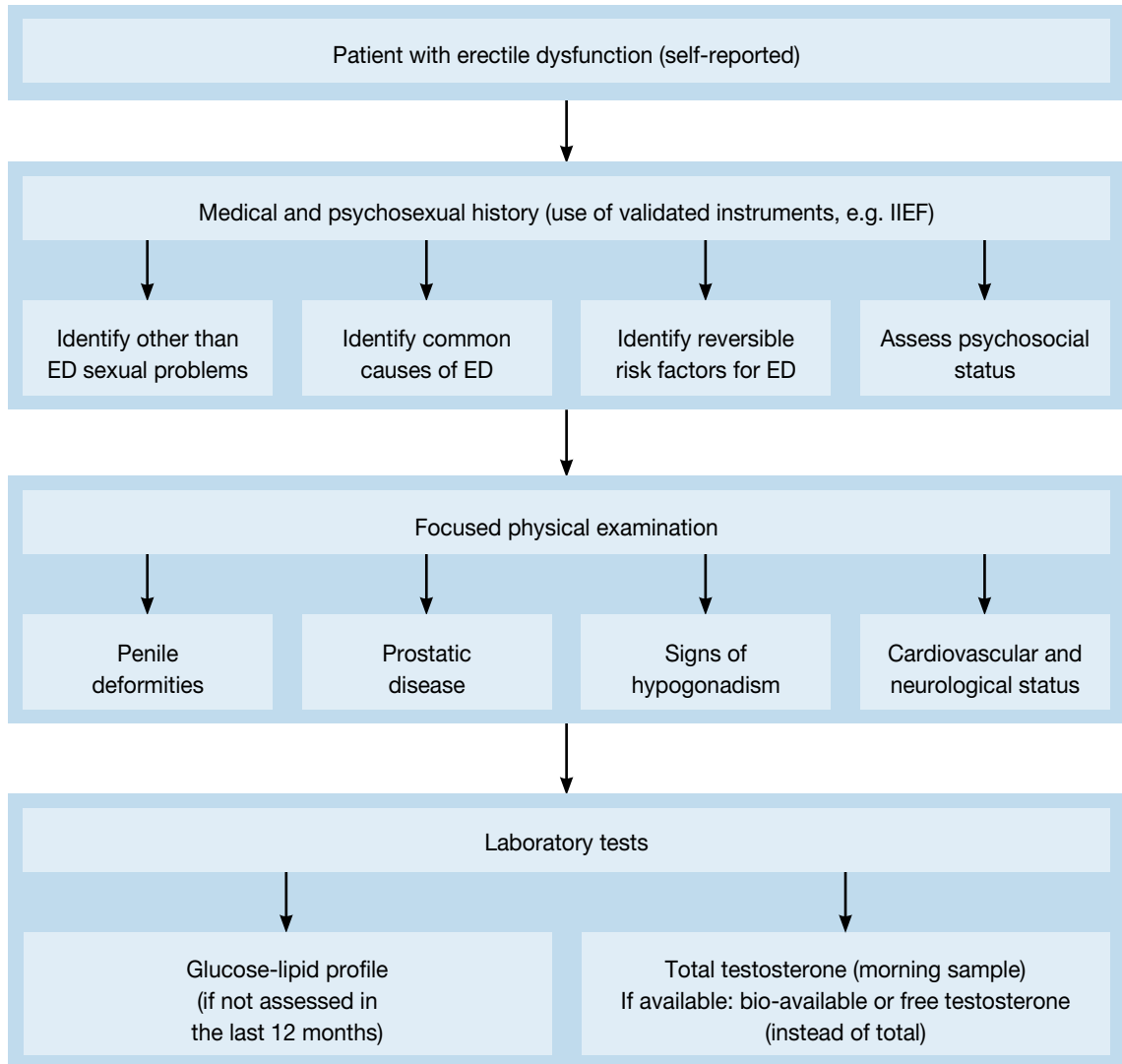
2.5.1.3 Laboratory testing

Laboratory testing must be tailored to the patient's complaints and risk factors. All patients must undergo a fasting glucose and lipid profile if not assessed in the previous 12 months. Hormonal tests must include a morning sample of total testosterone. Tests that measure bioavailable or calculated-free testosterone are preferred to total testosterone tests because they are better at establishing hypogonadism. Additional laboratory tests must be considered only in selected patients, e.g. prostate-specific antigen (PSA) for detection of prostate cancer.

Additional hormonal tests, e.g. prolactin, follicle-stimulating hormone (FSH), luteinizing hormone (LH), must be carried out when low testosterone levels are detected. If any abnormality is observed, referral to another specialist may be necessary (5, 6).

Figure 1 gives the minimal diagnostic evaluation (basic work-up) in patients with ED.

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



2.5.2 Cardiovascular system and sexual activity: the patient at risk

Patients who seek treatment for sexual dysfunction have a high prevalence of cardiovascular disease. The cardiac risks associated with sexual activity are well established. Recent epidemiological studies have emphasized the association between cardiovascular and metabolic risk factors and sexual dysfunction in both men and women (7).

There has been an intensive investigation of the pharmacological properties of phosphodiesterase type 5 (PDE5) inhibitors, including their effects on cardiac smooth muscle activity and overall cardiovascular safety. The EAU Guidelines recommendations given here for using PDE5 inhibitors in PE have been adapted from previously published recommendations from consensus conferences on sexual dysfunction and cardiac risk (8, 9).

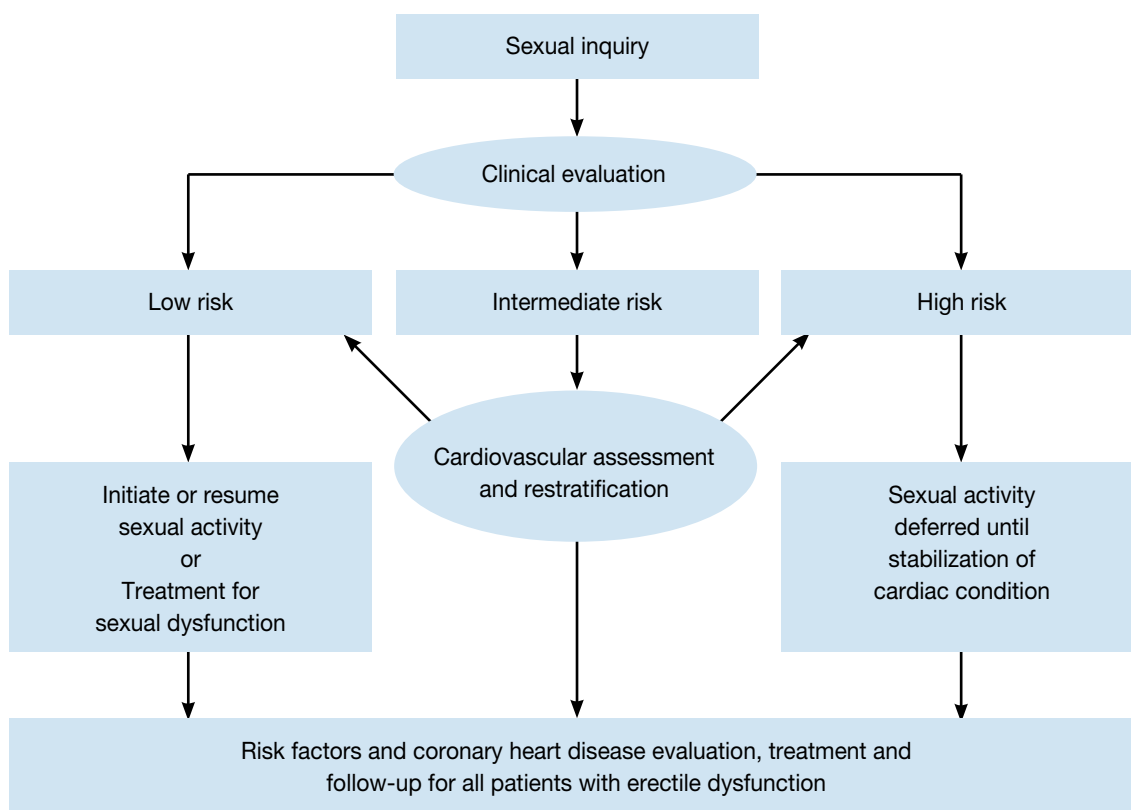
Patients with ED can be stratified into three cardiovascular risk categories (Table 2), which can be used as the basis for a treatment algorithm for initiating or resuming sexual activity (Figure 2). It is also possible for the clinician to estimate the risk of sexual activity in most patients from their level of exercise tolerance, determined when taking the patient's history.

Table 2: Cardiac risk stratification

Low-risk category	Intermediate-risk category	High-risk category
Asymptomatic, < 3 risk factors for CAD (excluding gender)	≥ 3 risk factors for CAD (excluding gender)	High-risk arrhythmias
Mild, stable angina (evaluated and/or being treated)	Moderate, stable angina	Unstable or refractory angina
Uncomplicated previous MI	Recent MI (> 2, < 6 weeks)	Recent MI (< 2 weeks)
LVD/CHF (NYHA class I)	LVD/CHF (NYHA class II)	LVD/CHF (NYHA class III/IV)
Post-successful coronary revascularization	Non-cardiac sequelae of atherosclerotic disease (e.g. stroke, peripheral vascular disease)	Hypertrophic obstructive and other cardiomyopathies
Controlled hypertension		Uncontrolled hypertension
Mild valvular disease		Moderate-to-severe valvular disease

CAD = coronary artery disease; CHF = congestive heart failure; LVD = left ventricular dysfunction; MI = myocardial infarction; NYHA = New York Heart Association.

Figure 2: Treatment algorithm for determining level of sexual activity according to cardiac risk in ED



2.5.2.1 Low-risk category

The low-risk category includes patients who do not have any significant cardiac risk associated with sexual activity. Low risk is typically implied by the ability to perform exercise of modest intensity, which is defined as six or more ‘metabolic equivalents of energy expenditure in the resting state’ (METs) without symptoms. According to current knowledge of the exercise demand or emotional stress associated with sexual activity, low-risk patients do not need cardiac testing or evaluation before the initiation or resumption of sexual activity or therapy for sexual dysfunction.

2.5.2.2 Intermediate-risk or indeterminate-risk category

The intermediate- or indeterminate-risk category consists of patients with an uncertain cardiac condition or patients whose risk profile requires testing or evaluation before the resumption of sexual activity. Based upon the results of testing, these patients may be moved to either the high- or low-risk group. A cardiology

consultation may be needed in some patients to help the primary physician determine the safety of sexual activity.

2.5.2.3 High-risk category

High-risk patients have a cardiac condition that is sufficiently severe and/or unstable for sexual activity to carry a significant risk. Most high-risk patients have moderately to severely symptomatic heart disease. High-risk individuals should be referred for cardiac assessment and treatment. Sexual activity should be stopped until the patient's cardiac condition has been stabilized by treatment or a decision made by the cardiologist and/or internist that it is safe to resume sexual activity.

2.5.3 Specialized diagnostic tests

Most patients with ED can be managed within the sexual care setting, but some patients may need specific diagnostic tests (Tables 3 and 4).

2.5.3.1 Nocturnal penile tumescence and rigidity (NPTR)

The nocturnal penile tumescence and rigidity (NPTR) assessment should be done on 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 that lasts for 10 min or more (10).

2.5.3.2 Intracavernous injection test

The intracavernous injection test gives limited information about vascular status. A positive test is a rigid erectile response (unable to bend the penis) that appears within 10 min after the intracavernous injection and lasts for 30 min (11). This response indicates a functional, but not necessarily normal, erection, as the erection may co-exist with arterial insufficiency or veno-occlusive dysfunction (12). A positive test shows that a patient will respond to the intracavernous injection programme. The test is inconclusive as a diagnostic procedure and Duplex ultrasound of the penile arteries should be requested.

2.5.3.3 Duplex ultrasound of penile arteries

A peak systolic blood flow higher than 30 cm/s and a resistance index higher than 0.8 are generally considered normal (10). Further vascular investigation is unnecessary when a Duplex examination is normal.

2.5.3.4 Arteriography and dynamic infusion cavernosometry or cavernosography

Arteriography and dynamic infusion cavernosometry or cavernosography (DICC) should be performed only in patients who are being considered for vascular reconstructive surgery (13).

2.5.3.5 Psychiatric assessment

Patients with psychiatric disorders must be referred to a psychiatrist who is particularly interested in ED. In younger patients (< 40 years) with long-term primary ED, psychiatric assessment may be helpful before any organic assessment is carried out.

2.5.3.6 Penile abnormalities

Surgical correction may be needed for patients with ED due to penile abnormalities, e.g. hypospadias, congenital curvature, or Peyronie's disease with preserved rigidity. Success rates are high.

2.5.4 Patient education – consultation and referrals

The consultation with the patient should include a discussion of the expectations and needs of both the patient and his partner. It should also review both the patient's and partner's understanding of ED and results of the diagnostic tests, and provide a rational selection of treatment options. Patient and partner education are an essential part of ED management (14, 15).

Table 3: Indications for specific diagnostic tests

Indications for specific diagnostic tests

- 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 that might require surgical correction, e.g. Peyronie's disease, congenital curvature
- Patients with complex psychiatric or psychosexual disorders
- Patients with complex endocrine disorders

- Specific tests may be indicated at the request of the patient or his partner
- Medicolegal reasons, e.g. implantation of penile prosthesis, sexual abuse

Table 4: Specific diagnostic tests

Diagnostic test	
•	Nocturnal penile tumescence and rigidity (NTPR) using Rigiscan®
•	Vascular studies
-	Intracavernous vasoactive drug injection
-	Duplex ultrasound of the cavernous arteries
-	Dynamic infusion cavernosometry or cavernosography (DICC)
-	Internal pudendal arteriography
•	Neurological studies, e.g. bulbocavernosus reflex latency, nerve conduction studies
•	Endocrinological studies
•	Specialized psychodiagnostic evaluation

2.5.5 Guidelines on the diagnosis of ED

Diagnostic guideline	LE	GR
• Clinical use of validated questionnaire related to ED may help to assess all sexual function domains and the effect of a specific treatment modality	3	B
• Physical examination is needed in the initial assessment of men with ED to identify underlying medical conditions that may be associated with ED	4	B
• Routine laboratory tests, including glucid-lipid profile and total testosterone, are required to identify and treat any reversible risk factors and lifestyle factors that can be modified	4	B
• Specific diagnostic tests are indicated by only a few conditions	4	B

LE = level of evidence; GR = grade of recommendation.

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3. TREATMENT OF ED

3.1 Treatment options

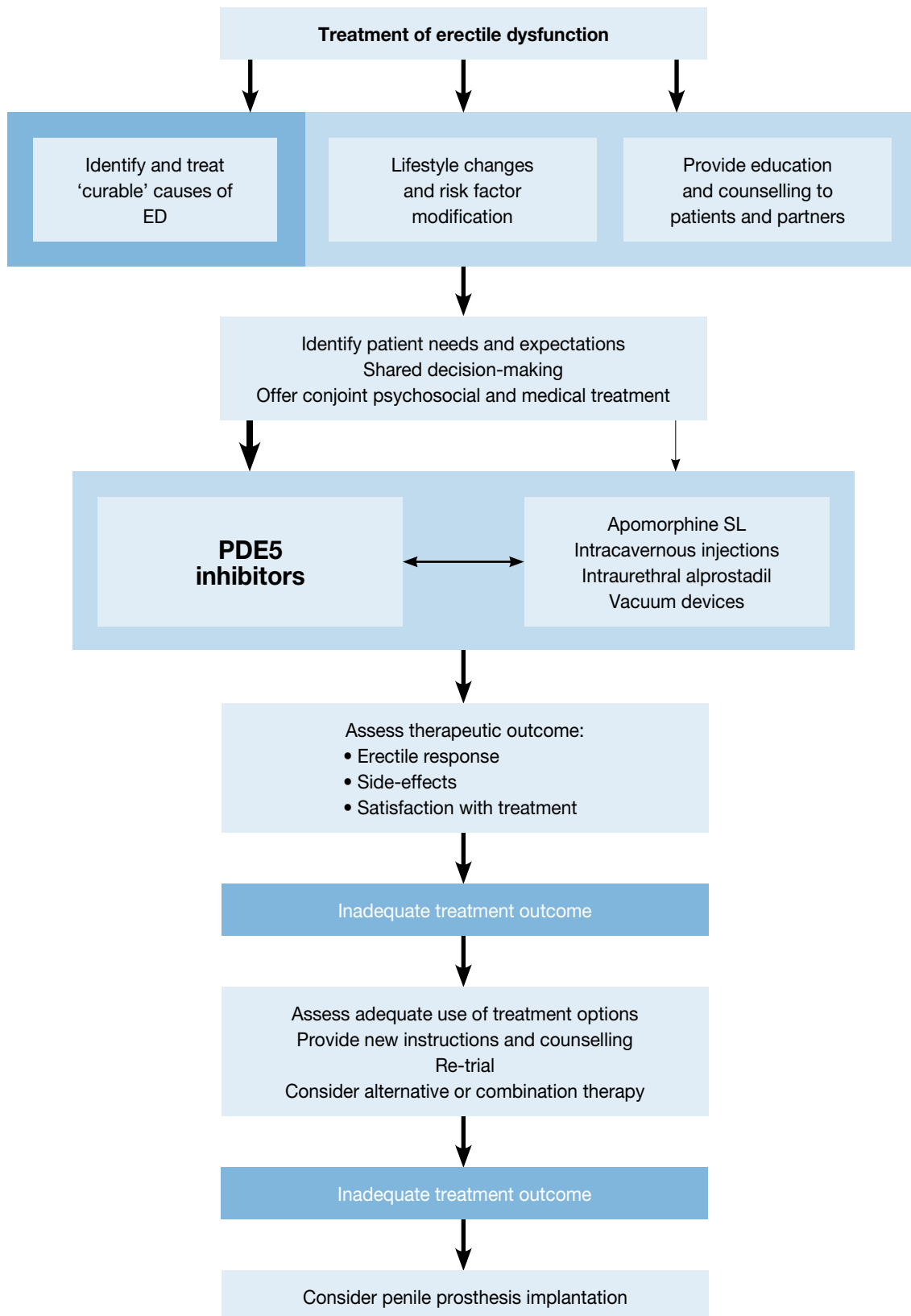
The primary goal in the management strategy of a patient with ED is to determine the aetiology of the disease and treat it when possible, and not to treat the symptom alone. Erectile dysfunction may be associated with modifiable or reversible factors, including lifestyle or drug-related factors. These factors may be modified either before, or at the same time as, specific therapies are used.

As a rule, ED can be treated successfully with current treatment options, but cannot be cured. The only exceptions are psychogenic ED, post-traumatic arteriogenic ED in young patients and hormonal causes (e.g. hypogonadism, hyperprolactinaemia), which can be potentially cured with specific treatment.

Most men with ED will be treated with treatment options that are not cause-specific. This results in a structured treatment strategy that depends on efficacy, safety, invasiveness and cost, as well as patient preference (1). To counsel patients properly with ED, physicians must be fully informed of all treatment options.

The assessment of treatment options must consider the effects on patient and partner satisfaction and other QoL factors as well as efficacy and safety. A treatment algorithm for ED is given in Figure 3.

Figure 3: Treatment algorithm for ED



PDE5 inhibitor = phosphodiesterase type 5 inhibitor

3.2 Lifestyle management in ED with concomitant risk factors

The basic work-up of the patient must identify reversible risk factors for ED. Lifestyle changes and risk factor modification must precede or accompany ED treatment.

The potential benefits of lifestyle changes may be particularly important in individuals with ED and specific comorbid cardiovascular or metabolic diseases, such as diabetes or hypertension (2-4). Besides improving erectile function, aggressive lifestyle changes may also benefit overall cardiovascular and metabolic health, with recent studies supporting the potential of lifestyle intervention to benefit both ED and overall health (5).

Although further studies are needed to make clear the role of lifestyle changes in the management of ED and related cardiovascular disease, lifestyle changes can be recommended alone or combined with PDE5 therapy. Some studies have suggested that the therapeutic effects of PDE5 inhibitors may be enhanced when other comorbidities or risk factors are aggressively managed (6). However, these results have yet to be confirmed in well-controlled, long-term studies. Because of the success of pharmacological therapy for ED, clinicians need to provide specific evidence for the benefits of lifestyle change and hopefully future research will show this.

3.3 Erectile dysfunction after radical prostatectomy (RP)

Use of pro-erectile drugs following RP is very important in achieving erectile function following surgery. Several trials have shown higher rates of erectile function recovery after RP in patients receiving any drug (therapeutic or prophylactic) for ED.

Historically, the treatment options for post-operative ED included intracavernous injections (7), urethral microsuppository (8), vacuum device therapy (9) and penile implants (10). Intracavernous injections and penile implants are still suggested as second- and third-line treatments, respectively, when oral compounds are not adequately effective or contraindicated for post-operative patients (see Sections 3.8 and 3.9).

The management of post-RP ED has been revolutionized by the advent of PDE5 inhibitors, with their demonstrated efficacy, ease of use, good tolerability, excellent safety, and positive impact on QoL. At present, PDE5 inhibitors are the first-line choice of oral pharmacotherapy for post-RP ED in patients who have undergone a nerve-sparing (NS) surgical approach. The choice of PDE5 inhibitors as first-line treatment is controversial because the experience (surgical volume) of the surgeon is a key factor in preserving post-operative erectile function in addition to patient age and NS technique (11-13). In fact, PDE5 inhibitors are most effective in patients who have undergone a rigorous NS procedure, which is more commonly performed by the largest-volume surgeons (12, 13).

The early use of a high dose of sildenafil after RP is associated with the preservation of smooth muscle within the human corpora cavernosa (14). Daily sildenafil also resulted in a greater return of spontaneous normal erectile function post RP compared to placebo following bilateral nerve-sparing RP (NSRP) in patients who were fully potent before surgery (15, 16). The response rate to sildenafil treatment for ED after RP in different trials ranged from 35% to 75% among those who underwent NSRP and from 0% to 15% among those who underwent non-NSRP (15-18).

The effectiveness of both tadalafil and vardenafil as on-demand treatment has also been evaluated in post-RP ED:

- A large multicentre trial in Europe and USA studied tadalafil in patients with ED following a bilateral NS procedure. Erectile function was improved in 71% of patients treated with tadalafil 20 mg versus 24% treated with placebo, while the rate of successful intercourse attempts was 52% with tadalafil 20 mg versus 26% with placebo (19).
- Similarly, vardenafil has been tested in patients treated with ED following either an unilateral or bilateral NS procedure in a multicentre, prospective, placebo-controlled, randomised North American study (20). Following bilateral NSRP, erectile function improved by 71% and 60% with vardenafil, 20 mg and 10 mg, respectively. An extended analysis of the same patients undergoing NSRP has underlined the benefit of vardenafil compared to placebo regarding intercourse satisfaction, hardness of erection, orgasmic function and overall satisfaction with sexual experience (21).

A randomized, double-blind, double-dummy, multicentre, parallel-group study in 87 centres across Europe, Canada, South Africa and the USA, compared on- demand and nightly dosing of vardenafil in men with ED following bilateral NSRP. In patients whose IIEF erectile function domain (IIEF-EF) score was ≥ 26 before surgery, vardenafil was efficacious when used on demand, supporting a paradigm shift towards on-demand dosing with PDE5 inhibitors in post-RP ED (22). Patients who do not respond to oral PDE5 inhibitors after NSRP should be treated with prophylactic intracorporeal alprostadil (23). A penile prosthesis remains a very satisfactory approach for patients who do not respond to either oral or intracavernous pharmacotherapy or to a vacuum device (24).

3.4 'Curable' causes of ED

3.4.1 Hormonal causes

An endocrinologist's advice is essential for managing patients with hormonal abnormalities. Testosterone deficiency is either a result of primary testicular failure or secondary to pituitary/hypothalamic causes, including a functional pituitary tumour resulting in hyperprolactinaemia.

Testosterone replacement therapy (intramuscular, oral or transdermal) is effective, but should only be used after other endocrinological causes for testicular failure have been excluded (25). Testosterone replacement is contraindicated in men with a history of prostate carcinoma or with symptoms of prostatism. Before initiating testosterone replacement, a digital rectal examination (DRE) and serum PSA test should be performed. Patients given androgen therapy should be monitored for clinical response and the development of hepatic or prostatic disease.

There is no contraindication for testosterone therapy in men with coronary artery disease who have been properly diagnosed with hypogonadism and/or ED. However, the haematocrit level should be monitored and a dose adjustment of testosterone may be necessary, especially in congestive heart failure.

Hormonal treatment is not always effective in the management of ED associated with hypogonadism (26).

3.4.2 Post-traumatic arteriogenic ED in young patients

In young patients with pelvic or perineal trauma, surgical penile revascularization has a 60-70% long-term success rate (27). The lesion must be demonstrated by Duplex ultrasound and confirmed by penile pharmacarteriography. Corporeal veno-occlusive dysfunction is a contraindication to revascularization and must be excluded by DICC (9, 10). Vascular surgery for veno-occlusive dysfunction is no longer recommended because of poor long-term results (28).

3.4.3 Psychosexual counselling and therapy

For patients with a significant psychological problem, psychosexual therapy may be given either alone or with another therapeutic approach. Psychosexual therapy takes time and has had variable results (29).

3.5 First-line therapy

3.5.1 Oral pharmacotherapy

The PDE5 enzyme hydrolyzes cyclic guanosine monophosphate (cGMP) in the cavernosum tissue of the penis. Inhibition of PDE5 results in increased arterial blood flow leading to smooth muscle relaxation, vasodilatation and penile erection (30).

Three potent selective PDE5 inhibitors have been approved by the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) for treatment of ED. They are not initiators of erection and require sexual stimulation to facilitate an erection.

3.5.1.1 Sildenafil

Sildenafil, launched in 1998, was the first PDE5 inhibitor available on the market. Efficacy is defined as an erection with rigidity sufficient for vaginal penetration. Sildenafil is effective from 30 to 60 min after administration. Its efficacy is reduced after a heavy fatty meal due to prolonged absorption. It is administered in 25, 50 and 100 mg doses. The recommended starting dose is 50 mg and should be adapted according to the patient's response and side-effects. Efficacy may be maintained for up to 12 h (31). The pharmacokinetic data of sildenafil are presented in Table 5. Adverse events (Table 6) are generally mild in nature and self-limited by continuous use. The drop-out rate due to adverse events is similar to placebo (32).

After 24 weeks in a dose-response study, improved erections were reported by 56%, 77% and 84% of men taking 25, 50 and 100 mg of sildenafil, respectively, compared to 25% of men taking placebo (33). Sildenafil statistically improved patient scores in IIEF, sexual encounter profile 2 (SEP2), SEP3 and general assessment question (GAQ) and treatment satisfaction.

The efficacy of sildenafil in almost every subgroup of patients with ED has been successfully established. In diabetic patients, 66.6% reported improved erections (GAQ) and 63% successful intercourse attempts compared to 28.6% and 33% of men taking placebo, respectively (34).

3.5.1.2 Tadalafil

Tadalafil, licenced for the treatment of ED as of February 2003, is effective from 30 min after administration, with peak efficacy after about 2 h. Efficacy is maintained for up to 36 h (35) and is not affected by food. It is administered in 10 and 20 mg doses. The recommended starting dose is 10 mg and should be adapted according to the patient's response and side-effects. Pharmacokinetic data of tadalafil are presented in Table 5. Adverse events (Table 6) are generally mild in nature, self-limited by continuous use. The drop-out rate due to adverse events is similar to placebo (36).

In pre-marketing studies, after 12 weeks of treatment and in a dose-response study, improved erections were reported by 67% and 81% of men taking 10 mg and 20 mg of tadalafil compared to 35% of men in the control placebo group (36). Tadalafil statistically improved patient scores in IIEF, SEP2, SEP3 and GAQ and treatment satisfaction. These results were confirmed in post-marketing studies (37).

Tadalafil also improved erections in difficult-to-treat subgroups. In diabetic patients, 64% reported improved erections (i.e. improved GAQ) versus 25% of patients in the control group and the change in the final score for IIEF-EF was 7.3 compared to 0.1 for placebo (38).

3.5.1.3 Vardenafil

Vardenafil, commercially available as of March 2003, is effective from 30 min after administration. Its effect is reduced by a heavy fatty meal (> 57% fat). It is administered in 5, 10 and 20 mg doses. The recommended starting dose is 10 mg and should be adapted according to the patient's response and side-effects. In vitro, it is 10-fold more potent than sildenafil, though this does not necessarily mean greater clinical efficacy (39). Pharmacokinetic data of vardenafil are presented in Table 5. Adverse events (Table 6) are generally mild in nature and self-limited by continuous use, with a drop-out rate similar to placebo (40).

After 12 weeks in a dose-response study, improved erections were reported by 66%, 76% and 80% of men taking 5 mg, 10 mg and 20 mg of vardenafil, respectively, compared with 30% of men taking placebo (41). Vardenafil statistically improved patient scores for IIEF, SEP2, SEP3 and GAQ and treatment satisfaction. Efficacy was confirmed in post-marketing studies (42).

Vardenafil improved erections in difficult-to-treat subgroups. In diabetic patients, 72% reported improved erections (i.e. improved GAQ) compared to 13% of patients taking placebo and the final IIEF-EF score was 19 compared to 12.6 for placebo (43).

3.5.1.4 Choice or preference between the different PDE5 inhibitors

To date, no data are available from double- or triple-blind multicentre studies comparing the efficacy and/or patient preference for sildenafil, tadalafil and vardenafil. Choice of drug will depend on the frequency of intercourse (occasional use or regular therapy, 3-4 times weekly) and the patient's personal experience. Patients need to know whether a drug is short- or long-acting, possible disadvantages and how to use it.

3.5.1.5 On-demand or chronic use of PDE5 inhibitors

Animal studies have shown that chronic use of PDE5 inhibitors improves or prevents significantly the intracavernous structure alterations due to age, diabetes or surgical damage (44-50).

In humans, a randomised study (n = 145) showed that daily tadalafil led to a significantly higher IIEF-EF score and higher completion of successful intercourse attempts compared to on-demand tadalafil (51). Two major double-blind randomised studies, using daily 5 and 10 mg tadalafil for 12 weeks (n = 268) (52) and daily 2.5 and 5 mg tadalafil for 24 weeks (n = 286) (53), showed that daily dosing was well tolerated and significantly improved erectile function. However, these studies lacked an on-demand treatment arm. An open-label extension was carried out of both studies in 234 patients for 1 year and 238 patients for 2 years. Tadalafil, 5 mg once daily, was shown to be well tolerated and effective (54). Tadalafil, 5 mg once daily, therefore provides an alternative to on-demand dosing of tadalafil for couples who prefer spontaneous rather than scheduled sexual activities or who anticipate frequent sexual activity, with the advantage that dosing and sexual activity no longer need to be temporally linked. Nevertheless, in the 1-year open-label 5 mg tadalafil extension study followed by 4 weeks of wash-out, erectile function was not maintained after discontinuation of therapy in most patients (about 75%).

A double-blind, placebo-controlled, multicentre, parallel-group study was conducted in 236 men with mild-to-moderate ED randomised to receive once-daily vardenafil 10 mg plus on-demand placebo for 12 or 24 weeks, or once-daily placebo plus on-demand vardenafil 10 mg for 24 weeks, followed by 4 weeks of wash-out (55). Despite preclinical evidence, the results suggested that once-daily dosing of vardenafil 10 mg does not offer any sustainable effect after cessation of treatment compared to on-demand administration in patients with mild-to-moderate ED.

Other studies (open-label, randomised, cross-over studies with limited patient numbers) showed that chronic, but not on-demand, tadalafil treatment improved endothelial function with sustained effect after its discontinuation (56, 57). This was confirmed in another study of chronic sildenafil in men with type 2 diabetes (58).

Recently, in the first double-blind placebo-controlled study, enrolling 298 men with diabetes and ED for 12 weeks, once-daily tadalafil 2.5 mg and 5 mg was efficacious and well tolerated. This regimen provides an alternative to on-demand treatment for some diabetic men (59).

However, when patients have the choice, it seems that they prefer on-demand rather than continuous therapy (60).

Table 5: Summary of the key pharmacokinetic data for the three PDE5 inhibitors used to treat ED*

Parameter	Sildenafil, 100 mg	Tadalafil, 20mg	Vardenafil, 20 mg
C _{max}	560 µg/L	378 µg/L	18.7 µg/L
T _{max}	0.8-1 h	2 h	0.9 h
T _{1/2}	2.6-3.7 h	17.5	3.9 h
AUC	1685 µg/h/L	8066 µg.h/L	56.8 µg.h/L
Protein binding	96%	94%	94%
Bioavailability	41%	NA	15%

C_{max}: maximal concentration, T_{max}: time-to-maximum plasma concentration; T_{1/2}: plasma elimination half-time; AUC: area under curve or serum concentration time curve.

* Fasted state, higher recommended dose. Data adapted from EMEA statements on product characteristics.

Sildenafil: <http://www.emea.europa.eu/humandocs/Humans/EPAR/viagra/viagra.htm>

Tadalafil: <http://www.emea.europa.eu/humandocs/Humans/EPAR/ cialis/cialis.htm>

Vardenafil: <http://www.emea.europa.eu/humandocs/Humans/EPAR/levitra/levitra.htm>

Table 6: Common adverse events of the three PDE5 inhibitors used to treat ED*

Adverse event	Sildenafil	Tadalafil	Vardenafil
Headache	12.8%	14.5%	16%
Flushing	10.4%	4.1%	12%
Dyspepsia	4.6%	12.3%	4%
Nasal congestion	1.1%	4.3%	10%
Dizziness	1.2%	2.3%	2%
Abnormal vision	1.9%		<2%
Back pain		6.5%	
Myalgia		5.7%	

* Adapted from EMEA statements on product characteristics.

Sildenafil: <http://www.emea.europa.eu/humandocs/Humans/EPAR/viagra/viagra.htm>

Tadalafil: <http://www.emea.europa.eu/humandocs/Humans/EPAR/ cialis/cialis.htm>

Vardenafil: <http://www.emea.europa.eu/humandocs/Humans/EPAR/levitra/levitra.htm>

3.5.1.6 Safety issues for PDE5 inhibitors

Cardiovascular safety

Clinical trial results and post-marketing data of sildenafil, tadalafil and vardenafil have demonstrated no increase in myocardial infarction rates in patients receiving PDE5 inhibitors, as part of either double-blind, placebo-controlled trials or open-label studies, or compared to expected rates in age-matched male populations.

None of the PDE5 inhibitors had an adverse effect on total exercise time or time-to-ischaemia during exercise testing in men with stable angina (61, 62). In fact, they may improve exercise tests. Sildenafil does not alter cardiac contractility, cardiac output or myocardial oxygen consumption according to available evidence. Chronic or on-demand use is well tolerated with a similar safety profile.

Nitrates are totally contraindicated with PDE5 inhibitors

Organic nitrates (e.g. nitroglycerine, isosorbide mononitrate, isosorbide dinitrate) and other nitrate preparations used to treat angina, as well as amyl nitrite or amyl nitrate ('poppers' used for recreation), are absolute contraindications with the use of PDE5 inhibitors. They result in cGMP accumulation and unpredictable falls in blood pressure and symptoms of hypotension. The duration of interaction between organic nitrates and PDE5 inhibitors depends upon the PDE5 inhibitor and nitrate used.

If a PDE5 inhibitor is taken and the patient develops chest pain, nitroglycerine must be withheld for at least 24 h if sildenafil (and probably also vardenafil) was used (half-life, 4 h), and for at least 48 h if tadalafil was used (half-life, 17.5 h).

If a patient develops angina while taking a PDE5 inhibitor, other agents may be given instead of nitroglycerine until the appropriate time has passed. If nitroglycerine must be re-introduced following administration of a PDE5 inhibitor, the patient should receive it only after an appropriate interval has elapsed, as described above, and under close medical observation.

Antihypertensive drugs

Co-administration of PDE5 inhibitors with antihypertensive agents (angiotensin-converting enzyme inhibitors,

angiotensin-receptor blockers, calcium blockers, beta-blockers, diuretics) may result in small additive drops in blood pressure, which are usually minor. In general, the adverse event profile of a PDE5 inhibitor is not made worse by a background of antihypertensive medication, even when the patient is taking several antihypertensive agents.

Alpha-blocker interactions

All PDE5 inhibitors show some interaction with alpha-blockers, which under some conditions may result in orthostatic hypotension.

- Sildenafil labelling currently advises that 50 or 100 mg of sildenafil should not be taken within 4 h following treatment with an alpha-blocker. This restriction does not apply to 25 mg dose of sildenafil.
- In the USA, vardenafil is absolutely contraindicated with alpha-blockers.
- Co-administration of vardenafil with tamsulosin is not associated with clinically significant hypotension (63).
- Tadalafil is contraindicated in patients taking alpha-blockers, except for tamsulosin, 0.4 mg (64).

These interactions are more pronounced when PDE5 inhibitors are given to healthy volunteers not previously taking alpha-blockers. Further research is needed into the interaction between other PDE5 inhibitors and other alpha-blockers (e.g. alfuzosin, once-daily), or mixed alpha-/beta-blockers (e.g. carvedilol, labetalol).

Dosage adjustment

Drugs that inhibit the CYP3A4 pathway will inhibit the metabolic breakdown of PDE5 inhibitors. They include ketoconazole, itraconazole, erythromycin, clarithromycin and HIV protease inhibitors (ritonavir, saquinavir). Such agents may increase blood levels of PDE5 inhibitors, so that lower doses of PDE5 inhibitors are necessary.

However, other agents, such as rifampin, phenobarbital, phenytoin and carbamazepine, may induce CYP3A4 and enhance the breakdown of PDE5 inhibitors, so that higher doses of PDE5 inhibitors are required. Severe kidney or hepatic dysfunction may require dose adjustments or warnings.

3.5.1.7 Management of non-responders to PDE5 inhibitors

The two main reasons why patients fail to respond to a PDE5 inhibitor are either incorrect drug use or inefficacy of the drug. The management of a non-responder depends upon identifying the underlying cause.

Check that the patient has been using a licensed medication

There is a very large 'black market' in PDE5 inhibitors. The amount of active drug in these medications varies enormously and it is important to check how and from which source the patient has obtained his medication.

Check that the medication has been properly prescribed and correctly used

The main reason why a patient fails to use his medication correctly is inadequate counselling from his physician. The main ways in which a drug may be incorrectly used are:

- failure to use adequate sexual stimulation
- failure to use an adequate dose
- failure to wait an adequate amount of time between taking the medication and attempting sexual intercourse.

Lack of adequate sexual stimulation: PDE5 inhibitors depend for their action upon the release of nitric oxide (NO) by the parasympathetic nerves of the penis. The usual stimulus for NO release is sexual stimulation, and without adequate sexual stimulation (and NO release), the drugs cannot work.

Not enough time between taking the medication and intercourse attempt: Oral PDE5 inhibitors take different times to reach maximal plasma concentrations (65-67). Although pharmacological activity is achieved at plasma levels well below the maximal plasma concentration, there will be a period of time following oral ingestion of the medication during which the drug is ineffective. Even though all three drugs have an onset of action in some patients within 30 min of oral ingestion (68-70), most patients require a longer delay between taking the medication, with at least 60 min being required for men using sildenafil and vardenafil and up to 2 h being required for men using tadalafil.

Food may affect drug absorption: sildenafil's absorption can be delayed by a meal (65), while vardenafil's absorption can be delayed by a fatty meal (71). Tadalafil's absorption is less affected provided there is enough delay between oral ingestion and an attempt at sexual intercourse (67).

Too much time between taking medication and intercourse attempt: It is also possible to wait too long after

taking medication before attempting sexual intercourse. The half-life of sildenafil and vardenafil is about 4 h, suggesting that the normal window of efficacy is about 6-8 h following ingestion of the medication, though responses following this time period are well recognized. Tadalafil had a longer half-life of about 17.5 h, so the window of efficacy is much longer at about 36 h.

Insufficient dose: For financial reasons, some physicians may prescribe only the lower doses of a medication. It is important to check that the patient has had an adequate trial of the maximal dose of the drug. Data suggests an adequate trial involves at least six attempts with a particular drug (72).

Benefit of education for a non-responding patient: Data from uncontrolled studies suggests patient education can help salvage an apparent non-responder to a PDE5 inhibitor. After emphasizing the importance of dose, timing and sexual stimulation to the patient, erectile function was effectively restored following re-administration of the relevant PDE5 inhibitor (73-76).

One study (74) went further, and in those patients who still did not respond to the PDE5 inhibitor, a second-line adjustment was instituted. Patients taking tadalafil were advised to wait at least 2 h between oral ingestion and attempting intercourse. Patients taking vardenafil were advised to use the drug only after a fast. In both patient groups, further apparent non-responders were 'salvaged'. No patients using sildenafil were included in this study.

Possible manoeuvres in patients correctly using a PDE5 inhibitor

When the patient is using an adequate dose of the drug properly and the response is still inadequate, there are a number of changes that may improve the efficacy of the medication, though the evidence supporting these interventions is limited.

Modification of associated risk factors: ED is typically a symptom of an underlying condition, such as diabetes, hypertension, dyslipidaemia, etc. Limited evidence suggests that, in a hypogonadal patient, normalization of the serum testosterone might improve the patient's response to a PDE5 inhibitor (77). So far, modification of other risk factors, such as diabetic control, hypertension and dyslipidaemia, has not been shown to be effective in improving response to a PDE5 inhibitor.

Change the PDE5 inhibitor: A randomised trial suggested vardenafil might benefit non-responders to sildenafil (78), but the results are considered to overstate the benefits of switching PDE5 inhibitors because of poor study design. However, a randomized, open-label, crossover trial comparing sildenafil and tadalafil indicated that some patients might respond better to one PDE5 inhibitor than to another (79). According to the IIEF-EF score, 17% of patients had a better response (≥ 5 points) to tadalafil than to sildenafil, while 14% had a better response to sildenafil than tadalafil.

Although these differences might be explained by variation in drug pharmacokinetics, they do raise the possibility that, despite an identical mode of action, switching to a different PDE5 inhibitor might be helpful.

Regular dosing of PDE5 inhibitor: Two non-randomised trials have suggested that daily dosing with a PDE5 inhibitor might salvage some non-responders to intermittent dosing. In one trial (80), some men benefited from regular dosing with either vardenafil or tadalafil, while in the other trial (75) daily dosing with tadalafil salvaged some men who had failed to respond to intermittent dosing with a PDE5 inhibitor.

Currently, there are no randomized trials to support this intervention. Although tadalafil is licensed for daily dosing at a dose of 2.5 mg and 5 mg, neither sildenafil nor vardenafil are licensed for use in this way.

Introduction of an alternative therapeutic modality: If drug treatment fails, then the patient should be offered an alternative therapy, with intracavernosal injection therapy or with a vacuum erection device. Intraurethral therapy is usually ineffective in these patients.

3.5.1.8 Apomorphine sublingual

Apomorphine is a centrally acting dopamine agonist that improves erectile function by enhancing the natural central erectile signals that normally occur during sexual stimulation (81, 82). It is administered sublingually on demand in 2 or 3 mg doses. Apomorphine has been approved for ED treatment in several countries but not in the USA.

Efficacy rates (erections sufficient for intercourse) range from 28.5% to 55% (83-85). Due to rapid absorption, 71% of erections are achieved within 20 min. The most common adverse events are nausea (7%), headache (6.8%) and dizziness (4.4%). These events are generally mild in nature and self-limited (85). Severe events, such as syncope, are extremely rare (<0.2%) (86).

Apomorphine is not contraindicated in patients taking nitrates or antihypertensive drugs (of all classes)

and it does not affect vital signs (87, 88). There was no marked improvement in sexual desire, but a slight improvement in orgasmic function was noticed.

Comparative studies clearly show that apomorphine is associated with significantly lower efficacy and satisfaction rates than sildenafil (89-91). The most significant strength of apomorphine is its safety profile (92). Even in pre-marketing studies, apomorphine significantly improves erectile function, intercourse and overall satisfaction domains of the IIEF compared to placebo.

Its use is limited to patients with mild-to-moderate ED or psychogenic causes of sexual dysfunction due to reduced efficacy rates. It may also be a first-line treatment in patients with certain contraindications for the use of PDE5 inhibitors, e.g. nitrates.

3.5.1.9 Other oral agents

Several other drugs have been used in the treatment of ED with various mechanisms of action (93), but today there is no place for these drugs in the treatment of ED.

- Yohimbine is a centrally and peripherally active alpha-2 adrenergic antagonist used as an aphrodisiac for almost a century.
- Delequamine is a more specific and selective alpha-2 adrenergic antagonist than yohimbine.
- Trazodone is a serotonin reuptake inhibitor (antidepressant) associated with prolonged erections and priapism. It is also a non-selective alpha-adrenergic antagonist in the corporal smooth muscle cells.
- L-arginine is a nitric oxide donor and nalmefene/naltrexone is an opioid-receptor antagonist.
- Red Korea ginseng is a formulation with an unknown mechanism of action (though it may possibly act as a nitric oxide donor).
- Limaprost is an alprostadil derivative for oral use.
- An oral formulation of phentolamine (non-selective alpha-adrenergic antagonist) has undergone phase III clinical trials (94).

Randomised trials have shown that yohimbine and trazodone have a similar efficacy to placebo in patients with organic causes of ED (95, 96). Oral phentolamine had efficacy rates (erections sufficient for intercourse) of about 50% (94), but possible carcinogenesis in animal models stopped further development. Efficacy data on Red Korea ginseng suggested it might have a role in treatment of ED (97). There are no efficacy data on the other drugs listed above.

3.6 Topical pharmacotherapy

Several vasoactive drugs (2% nitroglycerine, 15-20% papaverine gel and 2% minoxidil solution or gel) have been used for topical application to the penis. To overcome the poor drug absorption through the thick and dense tunica albuginea, several drug absorption enhancers have been developed for combination with vasoactive drugs (98). The combination (Topiglan™) of alprostadil gel 1% with 5% SEPA® (absorption enhancer) resulted in an erection sufficient for vaginal penetration in 38.9% of patients compared to 6.9% of placebo-treated patients (99). Adverse events include skin and glans erythema, burning sensation, allergic reactions and side-effects in the partner (hypotension, headache) due to vaginal absorption.

No topical therapy has been approved and currently these agents have no role in treatment of ED.

3.7 Vacuum constriction devices

Vacuum constriction devices (VCD) provide passive engorgement of the corpora cavernosa together with a constrictor ring placed at the base of the penis to retain blood within the corpora. Thus, erections with these devices are not normal since they do not use physiological erection pathways. Efficacy, in terms of erections satisfactory for intercourse, is as high as 90%, regardless of the cause of ED and satisfaction rates range between 27% and 94% (100). Men with a motivated, interested and understanding partner report the highest satisfaction rates. Long-term use of VCDs decreases to 50-64% after 2 years (101). Most men who discontinue use of VCDs do so within 3 months.

The commonest adverse events include pain, inability to ejaculate, petechiae, bruising and numbness, which occur in less than 30% of patients (102). Serious adverse events (skin necrosis) can be avoided if patients remove the constriction ring within 30 min. Vacuum constriction devices are contraindicated in patients with bleeding disorders or on anticoagulant therapy.

Vacuum constriction devices are generally unacceptable to younger patients. They may be the treatment of choice in well-informed older patients with infrequent sexual intercourses and comorbidities requiring a non-invasive, drug-free management of ED.

3.8 Second-line therapy

Patients not responding to oral drugs may be offered intracavernous injections. Success rate is high (85%) (100). Intracavernous administration of vasoactive drugs was the first medical treatment for ED more than 20 years ago (103).

3.8.1 Intracavernous injections

3.8.1.1 Alprostadil

Alprostadil (Caverject™, Edex/Viridal™) is the first and only drug approved for intracavernous ED treatment (104). It is the more efficacious monotherapy for intracavernous treatment in 5-40 µg doses. The erection appears after 5-15 min and lasts according to the dose injected. An office-training programme (one or two visits) is required for the patient to learn the correct injection process. In cases of limited manual dexterity, the technique may be taught to their partners. The use of an automatic special pen that avoids a view of the needle can resolve fear of penile puncture and simplifies the technique.

Efficacy rates for intracavernous alprostadil of more than 70% have been found in general ED populations, as well as in patient subgroups (e.g. diabetes or cardiovascular disease), with reported sexual activity after 94% of the injections and satisfaction rates of 87-93.5% in patients and 86-90.3% in partners (105-107).

Complications of intracavernous alprostadil include penile pain (50% of patients, after 11% of injections), prolonged erections (5%), priapism (1%) and fibrosis (2%) (108). Pain is usually self-limited after prolonged use. It can be alleviated with the addition of sodium bicarbonate or local anaesthesia (109, 110). Fibrosis requires temporary discontinuation of the injection programme for several months. Systemic side-effects are uncommon. The most common is mild hypotension especially when using higher doses.

Contraindications include men with a history of hypersensitivity to alprostadil, men at risk of priapism and men with bleeding disorders.

Despite these favourable data, intracavernous pharmacotherapy is associated with high drop-out rates and limited compliance. Drop-out rates of 41-68% have been described (111-113), with most drop outs occurring within the first 2-3 months. In a comparative study, alprostadil monotherapy had the lowest discontinuation rates (27.5%) compared to overall drug combinations (37.6%), with an attrition rate after the first few months of therapy of 10% per year. Reasons for discontinuation included desire for a permanent modality of therapy (29%), lack of a suitable partner (26%), poor response (23%) (especially among early drop out patients) fear of needles (23%), fear of complications (22%) and lack of spontaneity (21%). Careful counselling of patients during the office-training phase as well as close follow-up is important in addressing patient withdrawal from an intracavernous injection programme (114).

Today, intracavernous pharmacotherapy is considered a second-line treatment. Patients not responding to oral drugs may be offered intracavernous injections with a high success rate of 85%. Most long-term injection users can switch to sildenafil despite underlying pathophysiology (115-117). However, almost one-third of long-term intracavernous injections users who subsequently responded also to sildenafil preferred to continue with an intracavernous injection programme (117, 118).

Action to be taken with a prolonged erection

After 4 h of erection, patients are advised to consult their physician to avoid any damage to the intracavernous muscle, which would provoke permanent impotence. A 19-gauge needle is used to aspirate blood and thereby decrease intracavernous pressure. This simple method is usually sufficient to make the penis flaccid. However, if the penis becomes rigid again after this, an intracavernous injection of phenylephrine is required, starting at a dose of 200 µg every 5 min and increasing to 500 µg if necessary. The risk of having a prolonged erection during following subsequent injections cannot be predicted. When this problem occurs, the dose is usually reduced for the next injection.

3.8.1.2 Combination therapy

Combination treatment enables a patient to take advantage of the different modes of action of the drugs being used, as well as alleviating side-effects by using lower doses of each drug.

- Papaverine (20-80 mg) was the first oral drug used for intracavernous injections. It is only used in combination therapy today due to its high incidence of side-effects as monotherapy.
- Phentolamine has been used in combination therapy to increase efficacy. As monotherapy, it produces a poor erectile response.
- Sparse data in the literature support the use of other drugs, such as vasoactive intestinal peptide (VIP), NO donors (linsidomine), forskolin, potassium channel openers, moxisylyte or calcitonin gene-related peptide (CGRP), usually combined with the main drugs (119, 120). Most combinations are not standardized and some drugs have limited availability worldwide.
- Papaverine (7.5-45 mg) plus phentolamine (0.25-1.5 mg), and papaverine (8-16 mg) plus phentolamine (0.2-0.4 mg) plus alprostadil (10-20 µg), have been widely used with improved efficacy rates, although they have never been licensed for ED (121-123). The triple combination regimen of papaverine, phentolamine and alprostadil had the highest efficacy rates, reaching 92%; this combination had similar side-effects as alprostadil monotherapy, but a lower incidence of penile pain due to lower doses of alprostadil. However, fibrosis was more common (5-10%) when papaverine was used

(depending on total dose). In addition, mild hepatotoxicity has been reported with papaverine (124).

Despite high efficacy rates, 5-10% of patients will not respond to combination intracavernous injections. The combination of sildenafil with intracavernous injection of the triple combination regimen may salvage as many as 31% of patients who do not respond to the triple combination alone (125). However, combination therapy was associated with an incidence of adverse effects in 33% of patients, including dizziness in 20% of patients.

This strategy can be considered in carefully selected patients before proceeding to a penile implant.

3.8.1.3 Intraurethral alprostadil

A specific formulation of alprostadil (125-1000 µg) in a medicated pellet (MUSE™) has been approved for use in ED (126). A vascular interaction between the urethra and the corpora cavernosa enables drug transfer between these structures (127). Erections sufficient for intercourse were achieved in 30-65.9% of patients. In clinical practice, only the higher doses (500 and 1000 µg) have been used with low consistency rates (127-129). The application of a constriction ring at the root of the penis (ACTIS™) may improve efficacy (130).

The most common adverse events are local pain (29-41%) and dizziness (1.9-14%). Penile fibrosis and priapism are very rare (< 1%). Urethral bleeding (5%) and urinary tract infections (0.2%) are adverse events related to the mode of administration.

Efficacy rates are significantly lower than intracavernous pharmacotherapy (131). Intraurethral pharmacotherapy is a second-line therapy and provides an alternative to intracavernous injections in patients who prefer a less invasive, though less efficacious, treatment.

3.9 Third-line therapy (penile prostheses)

The surgical implantation of a penile prosthesis may be considered in patients who do not respond to pharmacotherapy or who prefer a permanent solution to their problem. Two types of prosthesis exist: malleable (semi-rigid) and inflatable (two- or three-piece).

Most patients prefer the three-piece inflatable devices due to the more 'natural' erections obtained. However, the two-piece inflatable prosthesis can be a reliable option with fewer mechanical complications and is easier to implant. A semi-rigid prosthesis provides a constantly rigid penis and may be suitable in older patients with infrequent sexual intercourse (132). The inflatable prosthesis is much more expensive. In several countries, patients are reimbursed for the cost of the prosthesis provided the ED has an organic cause and the patient has undergone a complete impotence assessment.

Prosthesis implantation has one of the highest satisfaction rates (70-87%) among treatment options for ED based on appropriate consultation (133-137).

3.9.1 Complications

The two main complications of penile prosthesis implantation are mechanical failures and infection. Several technical modifications of the most commonly used three-piece prosthesis (AMS 700CX/CXM™ and Mentor Alpha I™) resulted in mechanical failure rates of less than 5% at 5-year follow-up (136, 137). Careful surgical technique with proper antibiotic prophylaxis against Gram-positive and Gram-negative bacteria reduced infections rates to 2-3%. The infection rate may be further reduced to 1% by implanting an antibiotic-impregnated prosthesis (AMS Inhibizone™) or hydrophilic-coated prosthesis (Mentor Titan™) (138, 139). Although diabetes is considered to be one of the main risk factors for infection, this is not supported by current data (132). Infections, as well as erosions, are significantly higher (9%) in patients with spinal cord injuries (9%) (132). Infection requires removal of the prosthesis, antibiotic administration and re-implantation after 6-12 months. However, salvage therapy with removal and re-implantation at the same time, after copious irrigation of the corpora with multi-drug solutions, had an 82% success rate (140).

3.9.2 Conclusion

Penile implants are an attractive solution for patients who do not respond to oral therapy (141).

3.10 Guideline recommendations for the treatment of ED

Recommendation	LE	GR
• Lifestyle changes and risk factor modification must precede or accompany ED treatment	1b	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, the cause must be treated first	1b	B
• PDE5 inhibitors are first-line therapy	1a	A

• Daily administration of PDE5 inhibitors may improve results and restore erectile function	1b	A
• Inadequate/incorrect prescription and poor patient education are the main causes of a lack of response to PDE5 inhibitors	3	B
• Testosterone replacement restores efficacy in hypogonadic non-responders to PDE5 inhibitors	1b	B
• Apomorphine can be used in mild-to-moderate ED or psychogenic causes or in patients with contraindications for the use of PDE5 inhibitors	1b	B
• A vacuum constriction 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

LE = level of evidence; GR = grade of recommendation; ED = erectile dysfunction; PDE5 inhibitor = phosphodiesterase type 5 inhibitor.

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4. PREMATURE EJACULATION (PE)

4.1 Introduction

Although PE is a very common male sexual dysfunction, it is poorly understood. Patients are often unwilling to discuss their symptoms and many physicians do not know about effective treatments. As a result, patients may be misdiagnosed or mistreated (1). In addition, there is currently no registered pharmacological treatment for PE.

These guidelines provide an evidence-based analysis (2) of published data on definition, clinical evaluation and treatment. It provides recommendations to clinicians on the diagnosis and treatment of PE, without pre-empting physician judgement on individual cases.

4.2 Definition of PE

4.2.1 Overview

There have previously been two official definitions of PE, neither of which were universally accepted:

- In the Diagnostic and Statistical Manual of Mental Disorders IV-Text Revision (DSM-IV-TR), PE is defined as a *'persistent or recurrent ejaculation with minimal sexual stimulation before, on, or shortly after penetration and before the person wishes it. The clinician must take into account factors that affect duration of the excitement phase, such as age, novelty of the sexual partner or situation, and recent frequency of sexual activity'* (3).
- In the World Health Organization's International Classification of Diseases-10 (ICD-10), PE is defined as *'the inability to delay ejaculation sufficiently to enjoy lovemaking, which is manifested by either an occurrence of ejaculation before or very soon after the beginning of intercourse (if a time limit is required: before or within 15 seconds of the beginning of intercourse) or ejaculation occurs in the absence of sufficient erection to make intercourse possible. The problem is not the result of prolonged absence from sexual activity'* (4).

Recently, two more definitions have been proposed:

- The Second International Consultation on Sexual and Erectile Dysfunction defined PE as *'ejaculation with minimal stimulation and earlier than desired, before or soon after penetration, which causes bother or distress, and over which the sufferer has little or no voluntary control'* (5).
- The International Society for Sexual Medicine (ISSM) has adopted a completely new definition of 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'*. It must be noted that this definition is limited to men with lifelong PE who engage in vaginal intercourse since there are insufficient objective data to propose an evidence-based definition for acquired PE (6).

All four definitions have taken into account the time to ejaculation, the inability to control or delay ejaculation and negative consequences (bother/distress) from PE. However, the major point of debate is quantifying the time to ejaculation, which is usually described by intravaginal ejaculatory latency time (IELT). Several proposals for updating the definition of PE in the forthcoming DSM-V and ICD-11 have been presented (7-11).

4.2.2 Classifications

Premature ejaculation is classified as 'lifelong' (primary) or 'acquired' (secondary) (12). Lifelong PE is characterized by onset from the first sexual experience, remains so during life and ejaculation occurs too fast (before vaginal penetration or <1-2 min after). Acquired PE is characterized by a gradual or sudden onset following normal ejaculation experiences before onset and time to ejaculation is short (usually not as short as in lifelong PE).

Recently, two more PE syndromes have been proposed (11):

- 'Natural variable PE' is characterized by inconsistent and irregular early ejaculations, representing a normal variation in sexual performance.
- 'Premature-like ejaculatory dysfunction' is characterized by subjective perception of consistent or inconsistent rapid ejaculation during intercourse, while ejaculation latency time is in the normal range or can even last longer. It should not be regarded as a symptom or manifestation of true medical pathology.

The addition of these new types may aid patient stratification, diagnosis and treatment, but their exact role remains to be defined (13).

4.3 Epidemiology of PE

4.3.1 Prevalence

The major problem in assessing the prevalence of PE is the lack of an accurate (validated) definition at the time the surveys were conducted (14). However, epidemiological research has consistently shown that PE, at least according to the DSM-IV definition, is the most common male sexual dysfunction, with prevalence rates of 20-30% (15-17).

The highest prevalence rate of 31% (men aged 18-59 years) was found by the NHLS study in USA (16). Prevalence rates from 18 to 29 years, 30 to 39 years, 40 to 49 years and 50 to 59 years were 30%, 32%, 28% and 55%, respectively. These high prevalence rates may be a result of the dichotomous scale (yes/no) in a single question asking if ejaculation occurred too early, as the prevalence rates in European studies have been significantly lower. A British mailed questionnaire survey estimated that the prevalence rate of PE was between 14% (3 months) and 31% (life-time) (18). A French telephone survey of men aged 18 to 69 years estimated the life-time prevalence of early ejaculation at 15%, including 5% who often had experienced ejaculation prior to penetration and 10% who often had ejaculated too rapidly after vaginal intromission (19). A Swedish interview reported an overall prevalence rate of 9% in men aged 18 to 74 years (20), with prevalence by age being 4% for 18-24 years, 7% for 25-34 years, 8% for 35-49 years, 8% for 50-65 years and 14% for 66-74 years. A Danish study about sexual problems using a questionnaire (12 questions) and an interview (23 questions) reported the prevalence rate for PE to be 14% in men aged 51 years (21). An Italian questionnaire survey recorded a prevalence rate of 21% (22). Finally, in a self-administered questionnaire survey in the Netherlands, the prevalence rate was 13% in men aged 50-78 years (23).

The prevalence of PE in the Premature Ejaculation Prevalence and Attitudes (PEPA) survey (a multinational, internet-based survey) was 22.7% (24.0% in the USA, 20.3% in Germany, and 20.0% in Italy) (17). The Global Study of Sexual Attitudes and Behaviors (GSSAB) survey was conducted in men between 40 and 80 years old in 29 different countries using personal and telephone interviews and self-completed mailed questionnaires; it confirmed that the worldwide prevalence of PE was almost 30%. Except for a low reported rate of PE in Middle Eastern countries (10-15%), prevalence was relatively similar throughout the rest of the world (15). Finally, the prevalence rate of PE was 18% in a five-country European Observational study using the IELT and the Premature Ejaculation Profile (PEP) (24), comparable to those obtained in a similarly designed US observational study (25).

Further research is needed on the prevalence of lifelong and acquired PE. Limited data suggests that the prevalence of lifelong PE, defined as IELT <1-2 min, is about 2-5% (20, 25). These results are supported by the moderate genetic influence on PE (26) and low prevalence rates of IELT <1 min (27).

4.3.2 Pathophysiology and risk factors

The aetiology of PE is unknown, with little data to support suggested biological and psychological hypotheses, including anxiety, penile hypersensitivity and 5-HT receptor dysfunction (5). In addition, the pathophysiology of PE is largely unknown. In contrast to ED, there is no impairment of the physiological events leading up to the forceful expulsion of sperm at the urethral meatus.

A significant proportion of men with ED also experience PE (15). High levels of performance anxiety related to ED may worsen PE, with a risk of misdiagnosing PE instead of the underlying ED.

According to the NHLS, the prevalence of PE is not affected by age (16, 17), unlike ED, which increases with age. Premature ejaculation is not affected by marital or income status (16). However, PE is more common in blacks, Hispanic men and men from Islamic backgrounds (28, 29) and may be higher in men with a lower educational level (15, 16). Other risk factors may include a genetic predisposition (30), poor overall health status and obesity (16), prostate inflammation (31, 32), thyroid hormone disorders (33), emotional problems and stress (16, 34), and traumatic sexual experiences (15, 16).

In the only published study on risk modification/prevention strategies (35), successful eradication of causative organisms in patients with chronic prostatitis and PE produced marked improvements in IELT and ejaculatory control compared to untreated patients.

4.4 Impact of PE on QoL

Men with PE are more likely to report low satisfaction with their sexual relationship, low satisfaction with sexual intercourse, difficulty relaxing during intercourse and less frequent intercourse (36, 37). However, the negative impact of PE extends beyond sexual dysfunction. PE has a detrimental effect on self-confidence and the relationship with the partner, and may cause mental distress, anxiety, embarrassment and depression (36, 38). Sex drive and overall interest in sex does not appear to be affected by PE (39). However, the partner's satisfaction with the sexual relationship decreased with increasing severity of the man's condition (40).

Despite the serious psychological and QoL consequences of PE, few men seek treatment. In the GSSAB survey, 78% of men who self-reported a sexual dysfunction sought no professional help or advice for their sexual problems (15), with men more likely to seek treatment for ED than for PE (15). In the PEPA survey,

only 9% of men with self-reported PE consulted a doctor (17).

The main reasons for not discussing PE with their physician are patient embarrassment and a belief that there is no treatment. Physicians are often uncomfortable discussing sexuality with their patients usually because of embarrassment and a lack of training or expertise in treating PE (41, 42). Physicians need to encourage patients to talk about PE.

4.5 Diagnosis of PE

Diagnosis of PE is based on the patient's medical and sexual history (43, 44). 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 duration 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.

Many patients with ED develop secondary PE caused by the anxiety associated with difficulty in attaining and maintaining an erection (45). Furthermore, some patients are not aware that loss of erection after ejaculation is normal and may erroneously complain of ED, while the actual problem is PE (46).

There are several overlapping definitions of PE, with four shared factors (Table 7), resulting in a multidimensional diagnosis (47).

Table 7: Common factors in different definitions of ED

4.5.1 Intravaginal ejaculatory latency time (IELT)

The use of IELT alone is not sufficient to define PE, as there is significant overlap between men with and without PE (24, 25). Moreover, IELT has a significant direct effect on perceived control over ejaculation, but not a significant direct effect on ejaculation-related personal distress or satisfaction with sexual intercourse (48). In addition, perceived control over ejaculation has a significant direct effect on both ejaculation-related personal distress and satisfaction with sexual intercourse (each showing direct effects on interpersonal difficulty related to ejaculation).

In everyday clinical practice, self-estimated IELT is sufficient. Self-estimated and stopwatch-measured IELT are interchangeable and correctly assign PE status with 80% sensitivity and 80% specificity (49). Specificity can be improved further to 96% by combining IELT with a single-item patient-reported outcome (PRO) on control over ejaculation and satisfaction with sexual intercourse (scale ranging from 0 = very poor to 4 = very good) and on personal distress and interpersonal difficulty (0 = not at all to 4 = extremely). However, stopwatch-measured IELT is necessary in clinical trials.

4.5.2 PE assessment questionnaires

The need to assess PE objectively has led to the development of several questionnaires based on the use of PROs (47). Only two questionnaires can discriminate between patients who have PE and those who do not:

- Premature Ejaculation Diagnostic Tool (PEDT): five-item questionnaire based on focus groups and interviews from the USA, Germany and Spain. Assesses control, frequency, minimal stimulation, distress and interpersonal difficulty (50, 51).
- Arabic Index of Premature Ejaculation (AIPE): seven-item questionnaire developed in Saudi Arabia assesses sexual desire, hard erections for sufficient intercourse, time to ejaculation, control, satisfaction for the patient and partner, anxiety or depression (52).

These tools are a significant step in simplifying the methodology of PE drug studies, though further cross-cultural validation is needed (53).

Other questionnaires used to characterize PE and determine treatment effects include the Premature Ejaculation Profile (PEP) (25), Index of Premature Ejaculation (IPE) (54) and Male Sexual Health Questionnaire Ejaculatory Dysfunction (MSHQ-EJD) (55). Currently, their role is optional in everyday clinical practice.

4.5.3 Physical examination and investigations

Physical examination is part of the initial assessment of men with PE. It includes a brief examination of the vascular, endocrine and neurological systems to identify underlying medical conditions associated with PE or other sexual dysfunctions, such as chronic illness, endocrinopathy, autonomic neuropathy, Peyronie's disease, urethritis or prostatitis. Laboratory or physiological testing should be directed by specific findings from history or physical examination and is not routinely recommended (44).

4.6 Guidelines on diagnosis of PE

Recommendation	LE	GR
<ul style="list-style-type: none"> 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
<ul style="list-style-type: none"> Clinical use of self-estimated IELT is adequate. Stopwatch-measured IELT is necessary in clinical trials 	2a	B
<ul style="list-style-type: none"> Patient-reported outcomes (PROs) have the potential to identify men with PE. Further research is needed before PROs can be recommended for clinical use 	3	C
<ul style="list-style-type: none"> Physical examination may be necessary in initial assessment of PE to identify underlying medical conditions that may be associated with PE or other sexual dysfunctions, particularly ED 	3	C
<ul style="list-style-type: none"> Routine laboratory or neurophysiological tests are not recommended. They should only be directed by specific findings from history or physical examination 	3	C

LE = level of evidence; GR = grade of recommendation.

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4.8 Treatment

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, in particular, 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 and are indicated for patients uncomfortable with pharmacological therapy. 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. In addition, long-term outcomes of behavioural techniques for PE are unknown.

Pharmacotherapy is the basis of treatment in lifelong PE. Since no drug for PE has been approved by the EMEA or FDA, 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. Again, long-term outcomes for pharmacological treatments are unknown.

An evidence-based analysis of all current treatment modalities was performed. Levels of evidence and grade of recommendation are provided and a treatment algorithm is presented (Figure 3).

4.8.1 Psychological/behavioural strategies

Behavioural strategies mainly include the 'stop-start' programme developed by Semans (1) and its modification, the 'squeeze' technique, proposed by Masters and Johnson.

- In the 'stop-start' programme, the partner stimulates the penis until the patient feels the urge to ejaculate. At this point, he instructs his partner to stop, waits for the sensation to pass and then stimulation is resumed.
- The 'squeeze' technique is similar but the partner applies manual pressure to the glans just before ejaculation until the patient loses his urge.

Both these procedures are typically applied in a cycle of three pauses before proceeding to orgasm.

Behavioural strategies are based on the hypothesis that PE occurs because the man fails to appreciate the sensations of heightened arousal and recognize the feelings of ejaculatory inevitability. Re-training may attenuate stimulus-response connections by gradually exposing the patient to progressively more intense and more prolonged stimulation, while maintaining the intensity and duration of the stimulus just below the threshold for triggering the response.

There are several modifications of these techniques making comparison difficult.

Masturbation before anticipation of sexual intercourse is a technique used by many younger men. Following masturbation, the penis is desensitized resulting in greater ejaculatory delay after the refractory period is over. In a different approach, the man learns to recognize the signs of increased sexual arousal and

how to keep his level of sexual excitement below the intensity that elicits the ejaculatory reflex. Efficacy is similar to the 'start-stop' programme (2).

Overall, success rates of 50-60% have been reported short term (3, 4). However, there is no controlled research to support the efficacy of behavioural techniques, while a double-blind, randomised, crossover study showed that pharmacological treatment (chlomipramine, sertraline, paroxetine and sildenafil) resulted in greater IELT prolongation than behavioural therapy (5). Furthermore, clinical experience suggests that improvements achieved with these techniques are generally not maintained long term (6, 7).

4.8.1.1 Guideline recommendation

Treatment of PE	Level of evidence	Grade of recommendation
Psychological/behavioural therapies	3	C

4.8.2 Topical anaesthetic agents

The use of local anaesthetics to delay ejaculation is the oldest form of pharmacological therapy for PE (8). Several trials (9, 10) support the hypothesis that topical desensitizing agents reduce the sensitivity of the glans penis so delaying ejaculatory latency, but without adversely affecting the sensation of ejaculation.

4.8.2.1 Lidocaine-prilocaine cream

In a randomised, double-blind, placebo-controlled trial, lidocaine-prilocaine cream increased the IELT from 1 min in the placebo group to 6.7 min in the treatment group (11). In another randomised, double-blind, placebo-controlled trial, lidocaine-prilocaine cream significantly increased the stopwatch-measured IELT from 1.49 to 8.45 min while no difference was recorded in the placebo group (1.67 to 1.95 min) (12). Lidocaine-prilocaine cream (5%) is applied for 20 to 30 min prior to intercourse. Prolonged application of topical anaesthetic (30 to 45 min) may result in loss of erection due to numbness of the penis in a significant percentage of men (11). A condom is required to avoid diffusion of the topical anaesthetic agent into the vaginal wall causing numbness in the partner. Alternatively, the condom may be removed prior to sexual intercourse and the penis washed clean of any residual active compound. Although no significant side-effects have been reported, topical anaesthetics are contraindicated in patients or partners with an allergy to any component of the product.

An aerosol formulation of lidocaine 7.5 mg plus prilocaine 2.5 mg (Topical Eutectic Mixture for Premature Ejaculation, TEMPE (13) has been evaluated in a phase II study (14). Intravaginal ejaculatory latency time increased from a baseline of 1 min to 4.9 min in the TEMPE-treated group compared to an increase from baseline of 0.9 min to 1.6 min ($p < 0.01$) in the placebo-treated group. It has been suggested that lidocaine-prilocaine can penetrate the glans within 5-10 min, but penetrates intact keratinized skin less easily, reducing penile numbness and ED (14, 15).

Finally, in a randomised, double-blind, placebo-controlled, parallel-group study, lidocaine-prilocaine cream showed similar efficacy to combination with sildenafil (50 mg before coitus) and significantly better efficacy than sildenafil alone (16). However, no specific data on estimated IELT were provided.

4.8.2.2 SS-cream

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. SS-cream increased the vibratory threshold in a dose-dependent fashion, as well as the latency and amplitude of somatosensory-evoked potentials measured at the glans penis (17, 18). In a double-blind, randomised, placebo-controlled study (19), application of 0.2 g SS-cream improved IELT from 1.37 min to 10.92 min in the treatment group versus 2.45 min in the placebo group. Sexual satisfaction improved by 82% in the treatment group versus 20% in 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.

4.8.2.3 Guideline recommendation

Topical therapy for PE	Level of evidence	Grade of recommendation
Lidocaine-prilocaine cream	1B	A
SS-cream	1B	A

4.8.3 Selective serotonin reuptake inhibitors

Ejaculation is mediated by a spinal ejaculation generator (20, 21) and by descending supraspinal modulation from several brain regions. The neurotransmitter 5-hydroxytryptamine (5-HT, serotonin) is also involved in ejaculatory control. The retarding effect of 5-HT on ejaculation is probably due to central activation (i.e. spinally

and supraspinally) of 5-HT1B and 5-HT2C receptors, while stimulation of 5-HT1A receptors precipitates ejaculation.

Selective serotonin reuptake inhibitors (SSRIs) are used to treat mood disorders, but can delay ejaculation and are therefore widely used 'off-label' for PE. As in depression, SSRIs must be given for 1 to 2 weeks to be effective in PE (22). Chronic SSRI administration causes prolonged increases in synaptic cleft serotonin, which desensitize the 5-HT1A and 5-HT1B receptors (23). Clomipramine, the most serotonergic tricyclic antidepressant, was first reported in 1973 as an effective PE treatment (24). Selective serotonin reuptake inhibitors have revolutionized treatment of PE, but they have also changed our understanding of PE since the first publication on paroxetine in 1970 (25). Today, daily treatment with SSRIs has become the first choice of treatment in PE. Commonly used SSRIs include citalopram, fluoxetine, fluvoxamine, paroxetine and sertraline, all of which have a similar pharmacological mechanism of action.

A systematic review and meta-analysis of all drug treatment studies reported that, despite methodological problems in most studies, there still remained several, well-designed, double-blind, placebo-controlled trials supporting the therapeutic effect of daily SSRIs on PE (26). Open-design studies and studies using subjective reporting or questionnaires showed greater variation in ejaculation delay than double-blind studies in which the ejaculation delay was prospectively assessed with a stopwatch.

Based on this meta-analysis, SSRIs 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. Sertraline was superior to fluoxetine, whereas the efficacy of clomipramine was not significantly different from fluoxetine and sertraline. Paroxetine was evaluated in doses of 20-40 mg, sertraline 25-200 mg, fluoxetine 10-60 mg and clomipramine 25-50 mg; there was no significant relationship between dose and response among the various drugs. There is limited evidence that citalopram may be less efficacious compared to other SSRIs, while fluvoxamine may not be effective (27, 28).

Ejaculation delay may start a few days after drug intake, but it is more evident after 1 to 2 weeks since receptor desensitization requires time to occur. While efficacy may be maintained for several years, tachyphylaxis (decreasing response to a drug following chronic administration) may occur after 6 to 12 months (24).

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 to 3 weeks (24). Decreased libido, anorgasmia, anejaculation and ED have been also reported.

In one controlled trial, on-demand use of clomipramine (but not paroxetine), 3 to 5 h before intercourse, was reported to be efficacious, though IELT improvement was inferior compared to daily treatment with the same drug (29). However, on-demand treatment may be combined with an initial trial of daily treatment or concomitant low-dose daily treatment reducing adverse effects (30, 31).

4.8.3.1 *Dapoxetine*

Dapoxetine is a potent SSRI, which has been designed as an on-demand oral treatment for PE. It is quickly absorbed with a T_{max} of 1.5 h and is rapidly cleared, avoiding accumulation.

An integrated analysis of two, double-blind, randomised, controlled trials (1958 patients) with dapoxetine was published (32). Dapoxetine, 30 and 60 mg, was administered 1 to 3 h before intercourse. Intravaginal ejaculatory latency time improved from a baseline of 0.9 min to 1.75 min, 2.78 min and 3.32 min in the patient groups treated with placebo, 30 mg dapoxetine, and 60 mg dapoxetine, respectively. Improved ejaculation control was reported by 51% and 58% of patients in the 30 mg and 60 mg groups, respectively. Both dapoxetine doses were effective on the first dose. Common adverse events for 30 mg and 60 mg doses of dapoxetine, respectively, were nausea (8.7%, 20.1%), diarrhoea (3.9%, 6.8%), headache (5.9%, 6.8%), and dizziness (3.0%, 6.2%).

In a subanalysis of these two studies (33), 32% of men reported a two-category (from a 5-point scale, 'very poor' to 'very good') or greater increase in control and satisfaction with sexual intercourse after treatment. More than 95% of those men rated their PE as 'slightly better', 'better', or 'much better' on the global impression of change (7-point scale, 'much worse' to 'much better') while 67.1% gave ratings of 'better' or 'much better.' They also had greater improvements in IELT than men with less than a two-category increase in control, with a mean (SD) change from baseline of 3.7 (4.3) vs 0.77 (1.8) min, respectively. The proportions of men with a two-category or greater increase in control with dapoxetine 30 and 60 mg were 36.3% and 44.5%, respectively (vs 15% with placebo).

In another randomized, double-blind, parallel-group, placebo-controlled, phase II trial including 1162 men in 22 countries (34), mean average IELT increased from 0.9 min at baseline (all groups) to 1.9 min, 3.2 min, and 3.5 min with placebo and dapoxetine 30 mg and dapoxetine 60 mg, respectively, at study end point. The geometric mean IELT increased from 0.7 min at baseline to 1.1 min, 1.8 min, and 2.3 min, respectively, at study end point. All PEP measures and IELTs improved significantly with dapoxetine versus placebo at week 12 and week 24 ($p < 0.001$ for all). The most common adverse effects were nausea, dizziness, diarrhea, and headache.

Adverse effects led to discontinuation in 1.3%, 3.9%, and 8.2% of subjects with placebo and dapoxetine 30 mg. Finally, in a randomized, double-blind, placebo controlled, phase III trial (1238 men in USA and Canada), dapoxetine reduced the personal distress and interpersonal difficulty associated with PE (35).

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.

4.8.3.2 Guideline recommendation

Treatment for PE	Level of evidence	Grade of recommendation
Selective serotonin receptor inhibitors (SSRIs)	1A	A

4.8.4 Phosphodiesterase type 5 inhibitors

Several recent studies have supported the therapeutic role of PDE5 inhibitors in PE. They may reduce performance anxiety due to better erections and may down-regulate the erectile threshold to a lower level of arousal so that greater arousal is required to achieve the ejaculation threshold. However, many of the mechanisms involved remain speculative (33, 36-38).

There is only one well-designed, randomised, double-blind, placebo-controlled study comparing sildenafil to placebo (39). 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.

In another randomised, double-blind, placebo-controlled study, lidocaine-prilocaine had similar efficacy to combination with sildenafil (50 mg before intercourse), while the efficacy of sildenafil was similar to placebo (no IELT data provided) (16). In contrast, in a randomised, double-blind, parallel group study, sildenafil significantly improved IELT and satisfaction and reduced overall anxiety compared to several SSRIs and the 'pause-squeeze' technique. From a baseline of IELT at 1 min, IELT improved to 15 min with sildenafil, 4 min with clomipramine, 3 min with sertraline, 4 min with paroxetine and 3 min with the 'pause-squeeze' technique (5).

Finally, several open-label studies showed that sildenafil combined with an SSRI is superior to SSRI monotherapy. Sildenafil combined with paroxetine improved IELT significantly and satisfaction versus paroxetine alone (40). Sildenafil combined with sertraline improved IELT and satisfaction significantly versus sertraline alone (41). Sildenafil combined with paroxetine and psychological and behavioural counselling significantly improved IELT and satisfaction in patients in whom other treatments failed (42). Finally, sildenafil combined with behavioural therapy significantly improved IELT and satisfaction versus behavioural therapy alone (43).

There is limited data on the efficacy in PE of other PDE5 inhibitors (tadalafil and vardenafil) (37, 38). Overall, the role of PDE5 inhibitors in PE patients without ED is not established, with only minimal double-blind placebo controlled data are available.

4.8.4.1 Guideline recommendation

Treatment for PE	Level of evidence	Grade of recommendation
PDE5 inhibitors	2B	C

4.8.5 Other drugs

Adrenergic blockade for PE aims to decrease the sympathetic tone of the seminal tract and therefore delay ejaculation (44). Tramadol is a centrally acting analgesic agent that combines opioid receptor activation and re-uptake inhibition of serotonin and noradrenaline.

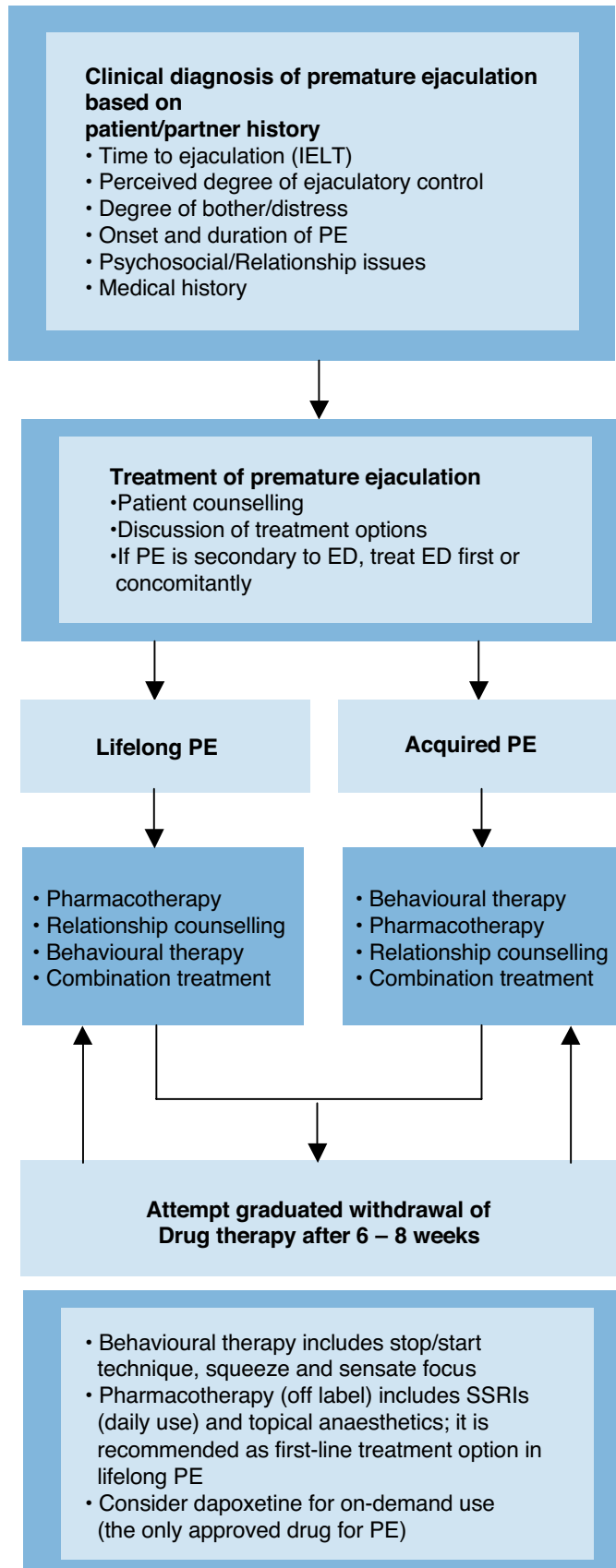
Research suggests that the alpha-1 adrenergic antagonists, terazosin and alfuzosin (45, 46), and tramadol (47, 48) may have some efficacy in PE. However, further research is needed to investigate their role fully. Currently they are not recommended in clinical practice (49).

4.8.6 Guidelines on treatment of PE

Recommendation	LE	GR
• ED, other sexual dysfunction or genitourinary infection (e.g. prostatitis) should be treated first	2a	B
• Behavioural techniques have demonstrated benefit in treating 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 SSRIs is not amenable to pm 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-line)	1b	A
• Recurrence is likely after treatment cessation	1b	A
• Behavioural therapy may augment pharmacotherapy to enhance relapse prevention	3	C

LE = level of evidence; GR = grade of recommendation; ED = erectile dysfunction; PE = premature ejaculation; SSRI = selective serotonin reuptake inhibitor ; pm = on-demand administration

Figure 4. Management of PE*



* Adapted from Lue et al. 2004 (49).

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

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5. CONCLUSION

Modern treatment of ED has been revolutionized by the worldwide availability of three PDE5 inhibitors for oral use – sildenafil, tadalafil and vardenafil. These drugs have high efficacy and safety rates, even in difficult-to-treat populations, such as patients with diabetes mellitus or who have undergone RP. Patients should be encouraged to try all three PDE5 inhibitors. Patients should make up their own minds about which compound has the best efficacy, while also considering other factors, such as time of onset, duration of action, window of opportunity and how side-effects affect them individually.

Treatment options for patients who do not respond to oral drugs, or for whom drugs are contraindicated, include intracavernous injections, intraurethral alprostadil, vacuum constriction devices or implantation of a penile prosthesis.

It is very important that the physician warns the patient that sexual intercourse is a vigorous physical activity, which increases heart rate as well as cardiac work. Physicians should assess the cardiac fitness of patients prior to treating ED.

Any successful pharmacological treatment for erectile failure demands a degree of integrity of the penile mechanisms of erection. Further studies of individual agents and synergistic activity of available substances are underway. The search for the ideal pharmacological therapy for erectile failure aims to fulfil the following characteristics: good efficacy, easy administration, freedom from toxicity and side-effects, with a rapid onset and a possible long-acting effect.

Premature ejaculation (PE) is another very common male sexual dysfunction, with prevalence rates of 20% to 30%. Four major definitions of PE are currently used and the most widely accepted classification of PE includes “lifelong” (primary) and “acquired” (secondary) forms (syndromes).

Diagnosis of PE in everyday clinical practice is based on medical and sexual history assessing IELT, perceived control, distress, and interpersonal difficulty related to the ejaculatory dysfunction. Physical examination and laboratory testing may be needed in selected patients only.

Pharmacotherapy is the basis of treatment in lifelong PE including daily dosing of SSRI's and topical anesthetics. Behavioral techniques may be efficacious as a monotherapy or in combination with pharmacotherapy, but they can be difficult to perform. In every case, recurrence is likely to occur after treatment withdrawal

6. ABBREVIATIONS USED IN THE TEXT

This list is not comprehensive for the most common abbreviations

AIPE	Arabic Index of Premature Ejaculation
AUC	area under curve - serum concentration time curve
BMI	body mass index
CAD	coronary artery disease
cGMP	cyclic guanosine monophosphate
CGRP	calcitonin gene-related peptide
CHF	congestive heart failure
C _{max}	maximal concentration
DICC	dynamic infusion cavernosometry or cavernosography
DRE	digital rectal examination
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders IV-Text Revision
EAU	European Association of Urology
ED	erectile dysfunction
EMA	European Medicines Agency
FDA	(US) Food and Drug Administration
FSH	follicle-stimulating hormone
GAQ	General Assessment Question
GSSAB	Global Study of Sexual Attitudes and Behaviors
ICD-10	International Classification of Diseases-10
IELT	intra vaginal ejaculatory latency time
IIEF	International Index for Erectile Function
IPE	Index of Premature Ejaculation
ISSM	International Society for Sexual Medicine
LH	luteinizing hormone
MET	metabolic equivalent of energy expenditure in the resting state
MI	myocardial infarction
MMAS	Massachusetts Male Aging Study
NHLS	National Health and Social Life Survey
MSHQ-EJD	Male Sexual Health Questionnaire Ejaculatory Dysfunction
NS	nerve sparing
NO	nitric oxide
NPTR	nocturnal penile tumescence and rigidity
NSRP	nerve-sparing radical prostatectomy
NYHA	New York Heart Association
PDE5	phosphodiesterase type 5 [inhibitors]
PE	premature ejaculation
PEDT	Premature Ejaculation Diagnostic Tool
PEP	Premature Ejaculation Profile
PEPA	Premature Ejaculation Prevalence and Attitudes
PRO	Patient reported outcome
PSA	prostate-specific antigen
PCa	prostate cancer
QoL	quality of life
RP	radical prostatectomy
SEP	sexual encounter profile
SSRI	selective serotonin reuptake inhibitor
TEMPE	topical eutectic mixture for premature ejaculation
T _{max}	time to maximum plasma concentration
VCD	vacuum constriction devices
VIP	vasointestinal peptide

Conflict of interest

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