Guidelines on Male Sexual Dysfunction:

Erectile dysfunction and premature ejaculation

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1. INTRODUCTION

1.1 Aim

The aim of these guidelines is to present the current evidence for the diagnosis and treatment of patients suffering from erectile dysfunction (ED) and premature ejaculation (PE). ED and PE are the two main complaints in male sexual medicine [1, 2]. Pharmacological 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.

1.2 Publication history

The first EAU Guidelines on Erectile Dysfunction were published in 2000 with subsequent updates in 2001, 2002, 2004, 2005, 2009, 2013 and 2014. In particular, the 2009 document presented a significant update of the previous publication with the inclusion of the topic “Premature Ejaculation” and the text was renamed to “EAU Guidelines on Male Sexual Dysfunction" [3]. In 2011 the Panel decided to develop separate guidelines addressing Penile Curvature, which resulted in a separate publication in 2012 [4]. In 2014 a guideline on Priapism was completed [5].

For this 2015 version a literature search was performed to identify the efficacy and safety of avanafil (a new phosphodiesterase type 5 inhibitors) in men with ED, and a section on the topic was included. Additionally, the text has been updated and significantly reduced so that only key information is included and re-formatted according to the EAU template for non-oncology Guidelines, so that all Guidelines follow a similar format.

Alongside several scientific summaries published in the EAU scientific journal, European Urology [6-10], a quick reference document (Pocket Guidelines) is available, both in print and in a number of versions for mobile devices, presenting the main findings of the Male Sexual Dysfunction guidelines. These are abridged versions which may require consultation together with the full text versions. All available material can be viewed and downloaded for personal use at the EAU website, which also includes a selection oftranslations produced by national urological associations: http://www.uroweb.org/guidelines/online-guidelines/.

This document was peer reviewed prior to publication.

1.3 Panel composition

The EAU Guidelines Panel on Male Sexual Dysfunction consists of urologists. Members of this Panel have been selected based on their expertise to represent the professionals treating patients suffering from ED.

2. METHODS

References used in this text are graded according to their Level of Evidence (LE) and Guidelines are given a Grade of Recommendation (GR). In this 2015 EAU Guidelines compilation, all standard information on LE and GR has been taken out of the individual Guidelines topics for the sake of brevity. The methodology section (see the introduction chapter of the complete book) outlines the LE and GR criteria which are used throughout the Guidelines, according to a classification system modified from the Oxford Centre for Evidence-based Medicine Levels of Evidence.

For both conditions (ED and PE) a systemic literature search was performed by the panel members.
The MedLine database was searched using the major Medical Subject Headings (MeSH) terms “erectile dysfunction”, “sexual dysfunction” “ejaculation”. All articles published between January 2009 (previous update) and October 2014 were considered for review. For Premature Ejaculation the MedLine search was supplemented by the term “premature ejaculation” in all search fields, for the 2015 print, covering a time frame up to October 2014. The Panel also identified critical problems and knowledge gaps, setting priorities for future clinical research.

3. THE GUIDELINE
3A ERECTILE DYSFUNCTION

3A.1 Epidemiology/aetiology/pathophysiology

Erection is a complex phenomenon which implies a delicate and coordinated equilibrium among the neurological, vascular and the tissue compartments. It includes arterial dilation, trabecular smooth muscle relaxation, and activation of the corporeal veno-occlusive mechanism [11]. ED is defined as the persistent inability to attain and maintain an erection sufficient to permit satisfactory sexual performance [12]. ED may affect physical and psychosocial health and may have a significant impact on the quality of life (QoL) of sufferers and their partners [13-15]. There is increasing evidence that ED can be an early manifestation of coronary artery and peripheral vascular disease. ED should not be regarded only as a QoL issue, but also as a potential warning sign of cardiovascular disease (CVD) [16-18].

3A.1.1 ***Epidemiology***

Epidemiological data have shown a high prevalence and incidence of ED worldwide. Among others, the Massachusetts Male Aging Study (MMAS) [13] reported an overall prevalence of 52% ED in non-institutionalised men aged 40-70 years in the Boston area; specific prevalence for minimal, moderate, and complete ED was 17.2%, 25.2%, and 9.6%, respectively. In the Cologne study of men aged 30-80 years, the prevalence of ED was 19.2%, with a steep age-related increase from 2.3% to 53.4% [19]. The incidence rate of ED (new cases per 1,000 men annually) was 26 in the long-term data from the MMAS study [20] and 19.2 (mean follow-up of 4.2 years) in a Dutch study [21]. In a cross-sectional real-life study among men seeking first medical help for new-onset ED, one in four patients was younger than 40 years, with almost 50% of the young men complaining of severe ED [22]. Differences between these studies can be explained by differences in methodology, in the ages, and socioeconomic and cultural status of the populations studied.

3A.1.2 ***Risk factors***

ED shares both unmodifiable and modifiable common risk factors with CVD (e.g., obesity, diabetes mellitus, dyslipidemia, metabolic syndrome, lack of exercise, and smoking) [15, 23, 24]. In this context, men with mild ED have similar risk factors to those of a general ED clinical trial population [25]. Thus, mild ED emerged as an important indicator of risk for associated underlying disease (CVDs) [25]. A number of studies have shown some evidence that lifestyle modification [18, 26] and pharmacotherapy [26, 27] for cardiovascular risk factors may be of help in improving sexual function in men with ED. However, it should be emphasised that more controlled prospective studies are necessary to determine the effects of exercise or other lifestyle changes in prevention or treatment of ED [17].

Epidemiological studies have demonstrated consistent evidences for an association between lower urinary tract symptoms (LUTS)/benign prostatic hyperplasia (BPH) and sexual dysfunction regardless of age, and other comorbidities, and various lifestyle factors [28]. The Multinational Survey on the Aging Male (MSAM-7) study – performed in the US, France, Germany, Italy, Netherlands, Spain, and UK - systematically investigated the relationship between LUTS and sexual dysfunction in > 12,000 men aged 50-80 years. Of 83% men self-reported to be sexually-active, the overall prevalence of LUTS was 90%, with an overall prevalence of ED of 49%, and a reported complete absence of erection in 10% of patients. Moreover, the overall prevalence of ejaculation disorders was 46% [29].

3A.1.3 ***Pathophysiology***

The pathophysiology of ED may be vasculogenic, neurogenic, anatomical, hormonal, drug-induced and/or psychogenic (Table 1) [11].

Table 1: Pathophysiology of ED

Vasculogenic	
-	Cardiovascular disease (hypertension, coronary artery disease, peripheral vasculopathy, etc.)
-	Diabetes mellitus
-	Hyperlipidaemia
-	Smoking
-	Major pelvic surgery (RP) or radiotherapy (pelvis or retroperitoneum)
Neurogenic	
Central causes	
-	Degenerative disorders (multiple sclerosis, Parkinson's disease, multiple atrophy, etc.)
-	Spinal cord trauma or diseases
-	Stroke
-	Central nervous system tumours
Peripheral causes	
-	Type 1 and 2 diabetes mellitus
-	Chronic renal failure
-	Polyneuropathy
-	Surgery (major surgery of pelvis/retroperitoneum, RP, colorectal surgery, etc.)
	Surgery of the urethra (urethral stricture urethroplasty, etc)
Anatomical or structural	
-	Hypospadias, epispedias
-	Micropenis
-	Peyronie's disease
Hormonal	
-	Hypogonadism
-	Hyperprolactinemia
-	Hyper- and hypothyroidism
-	Hyper- and hypocortisolism (Cushing's disease, etc.)
	Panhypopituitarism and multiple endocrine disorders
Drug-induced	
-	Antihypertensives (thiazide diuretics, etc.)
-	Antidepressants (selective serotonin reuptake inhibitors, tricyclics)
-	Antipsychotics (neuroleptics, etc.)
-	Antiandrogens (GnRH analogues and antagonists)
-	Recreational drugs (alcohol, heroin, cocaine, marijuana, methadone, synthetic drugs, anabolic steroids, etc.)
Psychogenic	
-	Generalised type (e.g., lack of arousability and disorders of sexual intimacy)
-	Situational type (e.g., partner-related, performance-related issues or due to distress)
Trauma	
-	Penile fracture
-	Pelvic fractures

3A.1.4 ***Post-radical prostatectomy ED, post-radiotherapy ED & post-brachytherapy ED***

Radical prostatectomy (RP) in any form (open, laparoscopic, or robotic) is a widely performed procedure for patients with clinically localised 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 [30, 31]. Research has shown that 25-75% of men experience post-operative ED [32]. Given the growing clinical importance of robot-assisted RP (RARP), this type of surgery is becoming the paradigm for post-operative functional results. A systematic review has shown a significant advantage in favour of RARP in comparison with retropubic RP in terms of 12-month potency rates [33], without significant difference between laparoscopic RP and RARP. However, more controlled prospective studies are necessary to determine the actual superiority of RARP in terms of post-operative ED rates [34]. Overall, patient age and surgical volume, with the consequent ability to preserve neurovascular bundles, seem to be the main factors in promoting the highest rates of post-operative potency [30, 31].

Pre-operative potency is a major factor associated with the recovery of erectile function (EF) after surgery. Patients being considered for nerve-sparing RP (NSRP) should ideally be potent pre-operatively [30, 31]. Overall, the temporal aspects are of major clinical importance in terms of post-operative recovery of EF. Available data confirm that post-operative EF recovery can also occur years following RP (and up to 48 months). Likewise, it is shared opinion that the timing of post-operative therapy (any type) should be as close as possible to the surgical procedure [31,32].

ED is also a common sequela after external beam radiotherapy and brachytherapy for PCa [35, 36]. The mechanisms contributing to ED after prostate irradiation involve injury to the neurovascular bundles, penile vasculature, and cavernosal structural tissue [35, 36]. Alternative treatments for PCa including cryotherapy and high-intensity focused ultrasound (US) are associated with equivalent or worsened rates of ED compared to surgery or radiation therapy [37, 38].

3A.1.5 ***Conclusions on the epidemiology/aetiology/pathophysiology of ED***

	LE
ED is common worldwide.	2b
ED shares risk factors with cardiovascular disease.	2b
Lifestyle modification (regular exercise and decrease in body mass index) can improve erectile function.	1b
ED is a symptom, not a disease. Some patients may not be properly evaluated or receive treatment for an underlying disease or condition that may be causing ED.	4
ED is common after RP, irrespective of the surgical technique used.	2b
ED is common after external radiotherapy and brachytherapy.	2b
ED is common after cryotherapy and high-intensity focused US.	2b

3A.2 Classification

ED is commonly classified into three categories based on its aetiology. These include organic, psychogenic and mixed ED. However, this classification should be used with caution since most cases are actually of mixed aetiology. It is therefore suggested to use the term primary organic or primary psychogenic.

3A.3 Diagnostic evaluation

3A.3.1 ***Basic work-up***

The first step in evaluating ED is always a detailed medical and sexual history of patients, and partners when available [39, 40]. In this context, taking a comprehensive medical history may reveal one of the many common disorders associated with ED [39, 40]. It is important to establish a relaxed atmosphere during history-taking. This will make it easier to i) ask questions about EF and other aspects of the sexual history; and, ii) to explain the diagnosis and therapeutic approach to the patient and his partner. Figure 1 gives the minimal diagnostic evaluation (basic work-up) in patients with ED.

3A.3.2 ***Sexual history***

The sexual history must include (when available) information about sexual orientation, previous and current sexual relationships, current emotional status, onset and duration of the erectile problem, and previous consultations and treatments. The sexual health status of the partner(s) (when available) can also be useful. A detailed description should be made of the rigidity and duration of both sexually-stimulated and morning erections and of problems with sexual desire, arousal, ejaculation, and orgasm [39, 41]. Validated psychometric questionnaires, such as the International Index for Erectile Function (IIEF) [42] or its short version Sexual Health Inventory for Men (SHIM), help to assess the different sexual function domains (i.e. sexual desire, EF, orgasmic function, intercourse, and overall satisfaction), as well as the impact of a specific treatment modality. Psychometric analysis also supports the use of the erectile hardness score for the assessment of penile rigidity in practice and in clinical trials research [43]. In cases of clinical depression, the use of a 2-question scale for depression is recommended in the everyday clinical practice: “During the past month have you often been bothered by feeling down, depressed or hopeless? During the past month have you often been bothered by little interest or pleasure, doing things?”[44]. Patients should always be screened for symptoms of possible hypogonadism (= testosterone deficiency), including decreased energy, libido, fatigue, and cognitive impairment, as well as for LUTS. For this specific purpose, screening questionnaires, such as the International Prostate Symptom Score may be utilised [45].

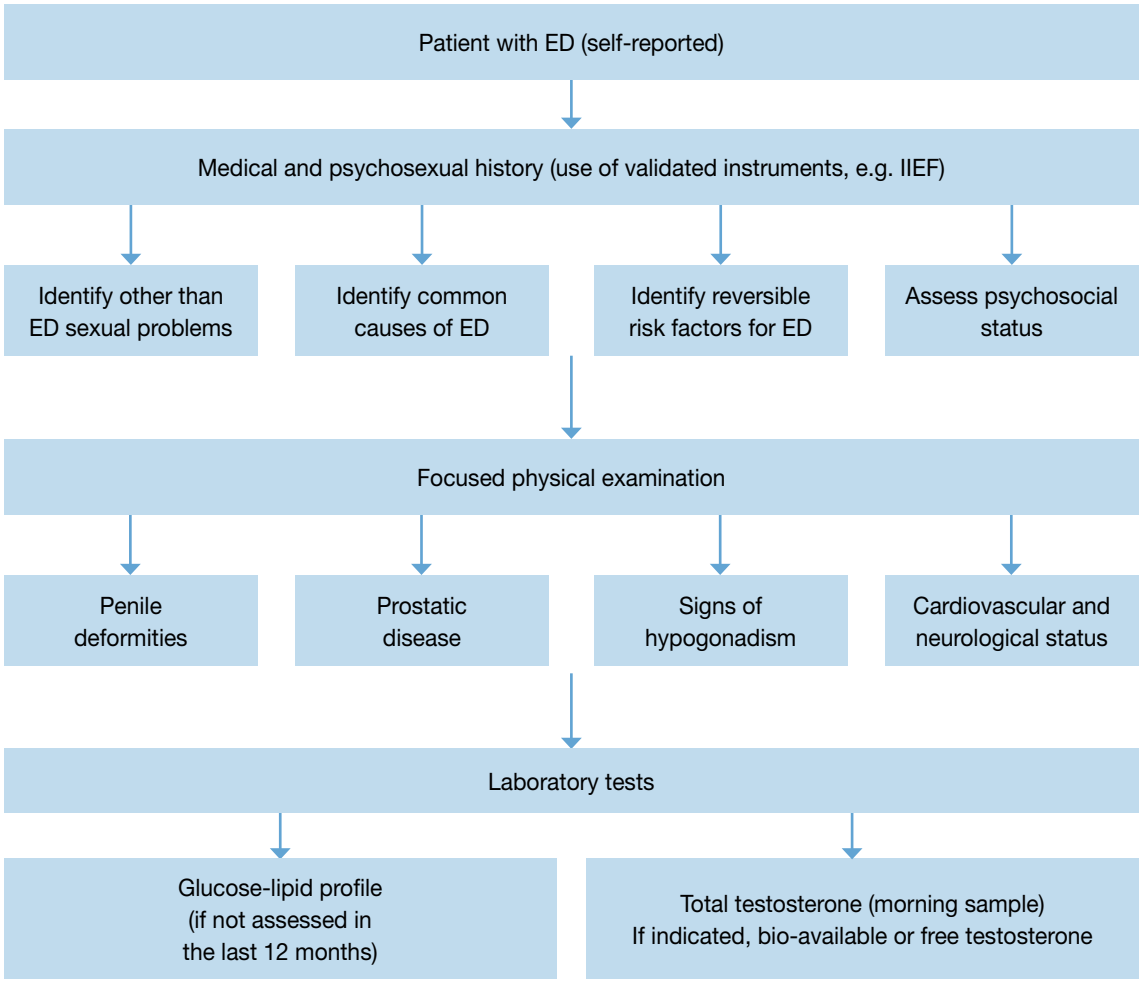
3A.3.3 ***Physical examination***

Every patient must be given a physical examination focused on the genitourinary, endocrine, vascular, and neurological systems [46, 47]. A physical examination may reveal unsuspected diagnoses, such as Peyronie's disease, pre-malignant or malignant genital lesions, prostatic enlargement or irregularity/nodularity, or signs and symptoms suggesting hypogonadism (small testes, alterations in secondary sexual characteristics etc). Blood pressure and heart rate should be measured if they have not been assessed in the previous 3-6 months.

3A.3.4 ***Laboratory testing***

Laboratory testing must be tailored to the patient's complaints and risk factors. Patients may need a fasting blood glucose or HbA1c and lipid profile if not recently assessed. Hormonal tests include an early morning total testosterone. If indicated, bioavailable or calculated-free testosterone may be needed to corroborate total testosterone measurements. However, the threshold of testosterone to maintain ED is low and ED is usually a symptom of more severe cases of hypogonadism [23, 48-50]. For levels > 8 nmol/l the relationship between circulating testosterone and sexual functioning is very low [23, 48-50]. Additional laboratory tests may be considered in selected patients (eg, prostate-specific antigen (PSA) [51]; prolactin, and luteinising hormone [52]). Although physical examination and laboratory evaluation of most men with ED may not reveal the exact diagnosis, these opportunities to identify critical comorbid conditions should not be missed [47].

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



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

3A.3.5 ***Cardiovascular system and sexual activity: the patient at risk***

Patients who seek treatment for sexual dysfunction have a high prevalence of CVDs. Epidemiological surveys have emphasised the association between cardiovascular and metabolic risk factors and sexual dysfunction in both men [53] and women [54]. Overall, ED can improve the sensitivity of screening for asymptomatic CVD in men with diabetes [55, 56]. ED significantly increases the risk of CVD, coronary heart disease, stroke, and all-cause mortality, and the increase is probably independent of conventional cardiovascular risk factors [16, 18, 57].

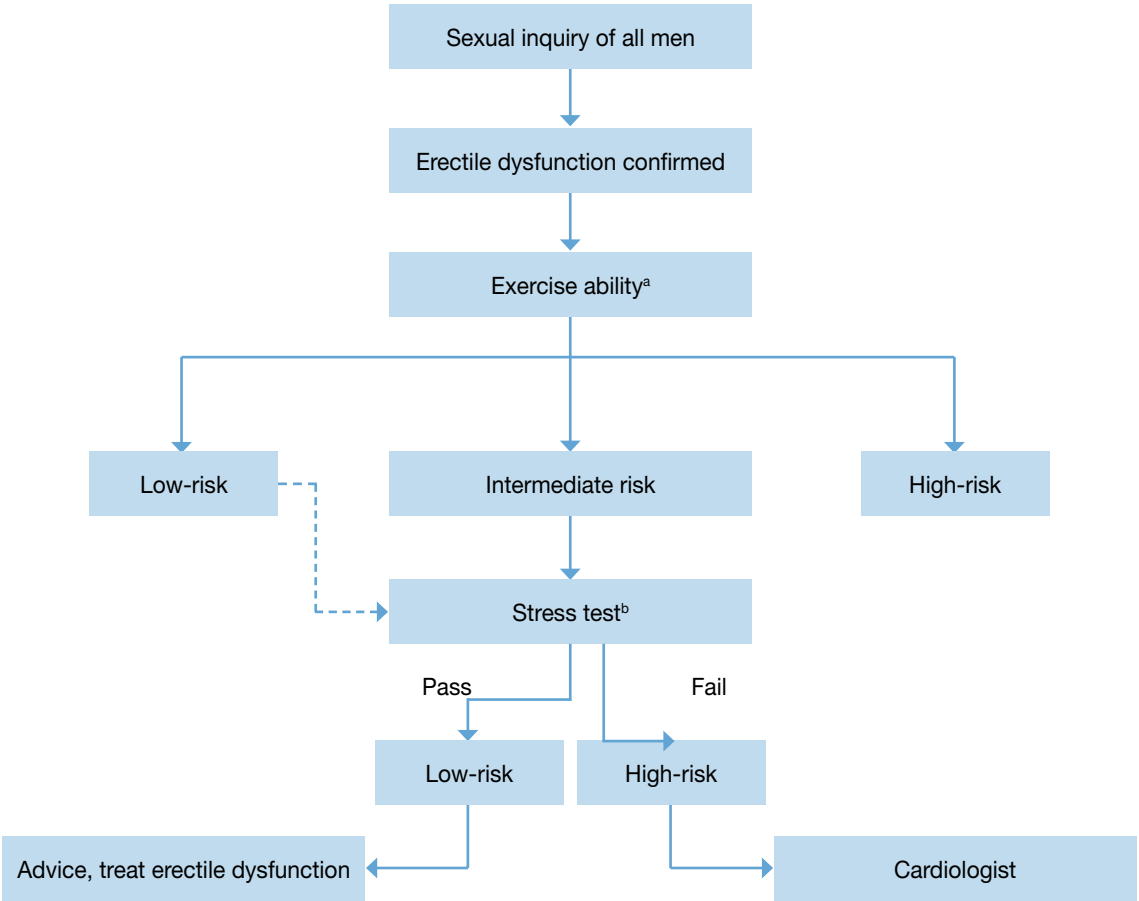
The EAU Guidelines for diagnosing and treating men with ED have been adapted from previously published recommendations from the Princeton Consensus conferences on sexual dysfunction and cardiac risk [16]. The Princeton Consensus (Expert Panel) Conference is dedicated to optimising sexual function and preserving cardiovascular health [58-60]. Accordingly, 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, which can be determined when taking the patient's history [27].

Table 2: Cardiac risk stratification (based on 2nd Princeton Consensus [59])

Low-risk category	Intermediate-risk category	High-risk category
Asymptomatic, < 3 risk factors for CAD (excluding sex)	≥ 3 risk factors for CAD (excluding sex)	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 Revascularisation	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 (based on 3rd Princeton Consensus) [60]



[a] *Sexual activity is equivalent to walking 1 mile on the flat in 20 min or briskly climbing two flights of stairs in 10 s.*

[b] *Sexual activity is equivalent to 4 min of the Bruce treadmill protocol.*

3A.3.5.1 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 ≥ 6 "metabolic equivalents of energy expenditure in the resting state" 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.

3A.3.5.2 Intermediate- 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.

3A.3.5.3 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 moderate-to-severe 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 stabilised by treatment, or a decision made by the cardiologist and/or internist that it is safe to resume sexual activity.

3A.3.6 ***Specialised diagnostic tests***

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

3A.3.6.1 Nocturnal penile tumescence and rigidity test

The nocturnal penile tumescence and rigidity 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 [61].

3A.3.6.2 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 [62]. Overall, the test is inconclusive as a diagnostic procedure and a duplex Doppler study of the penis should be requested, if clinically warranted.

3A.3.6.3 Duplex ultrasound of the penis

A peak systolic blood flow > 30 cm/s, an end-diastolic velocity of < 3 cm/s and a resistance index > 0.8 are generally considered normal [63]. Further vascular investigation is unnecessary when a Duplex examination is normal.

3A.3.6.4 Arteriography and dynamic infusion cavernosometry or cavernosography

Arteriography and dynamic infusion cavernosometry or cavernosography should be performed only in patients who are being considered for vascular reconstructive surgery [64].

3A.3.6.5 Psychiatric assessment

Whenever clinically indicated, patients with psychiatric disorders should be referred to a psychiatrist who is particularly interested in sexual health. In younger patients (< 40 years) with long-term primary ED [22], psychiatric assessment may be helpful before any organic assessment is carried out.

3A.3.6.6 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).

3A.3.7 ***Patient education - consultation and referrals***

Consultation with the patient should include a discussion of the expectations and needs of both the patient and his stable sexual partner, if available. It should also review both the patient's and partner's understanding of ED and the results of diagnostic tests, and provide a rational selection of treatment options [65]. Patient and partner education is an essential part of ED management [65, 66].

Table 3: Indications for specific diagnostic tests

Primary ED (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 which 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.
Medico-legal reasons (e.g., implantation of penile prosthesis, sexual abuse).

Table 4: Specific diagnostic tests

NTPR using Rigiscan
Vascular studies
- Intracavernous vasoactive drug injection
- Penile Dynamic Duplex Doppler study
- Penile Dynamic Infusion Cavernosometry and Cavernosography
- Internal pudendal arteriography
Neurological studies (e.g., bulbocavernosus reflex latency, nerve conduction studies)
Endocrinological studies
Specialised psychodiagnostic evaluation

3A.3.8 ***Recommendations for the diagnostic evaluation of ED***

	LE	GR
A comprehensive medical and sexual history is needed.	3	B
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 glucose-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

ED = erectile dysfunction.

3A.4. Disease management

3A.4.1 ***Treatment options***

ED may be associated with modifiable or reversible risk factors, including lifestyle or drug-related factors. These factors may be modified either before, or at the same time as, specific therapies are used. Likewise, ED may be associated with concomitant and underlying conditions (such as, for instance, endocrine disorders and metabolic disorders - e.g. diabetes - some cardiovascular problems - e.g. hypertension) which should always be well-controlled as the first step of ED treatment. 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 and hyperprolactinaemia [49, 52]), which potentially can be cured with specific treatment. Most men with ED will be treated with therapeutic 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 [65]. In this context, physician-patient (partner) dialogue is essential throughout the management of ED. The assessment of treatment options must be tailored according to patient and partner satisfaction, QoL factors as well as treatment-related safety and efficacy. A treatment algorithm for ED is shown in Figure 3.

3A.4.2 ***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 any pharmacological treatment. Major clinical potential benefits of lifestyle changes may be obtained in men with specific comorbid cardiovascular or metabolic disorders, such as diabetes or hypertension [17, 67].

3A.4.3 ***Erectile dysfunction after radical prostatectomy***

Use of pro-erectile drugs following RP is important in achieving post-operative EF. Several trials have shown higher rates of EF recovery after RP in patients receiving any drug (therapeutic or prophylactic) for ED. Early compared with delayed EF treatment seems to impact on the natural healing time of potency [31]. Currently available therapeutic armamentarium follows the treatment algorithm for ED which is shown in Figure 3.

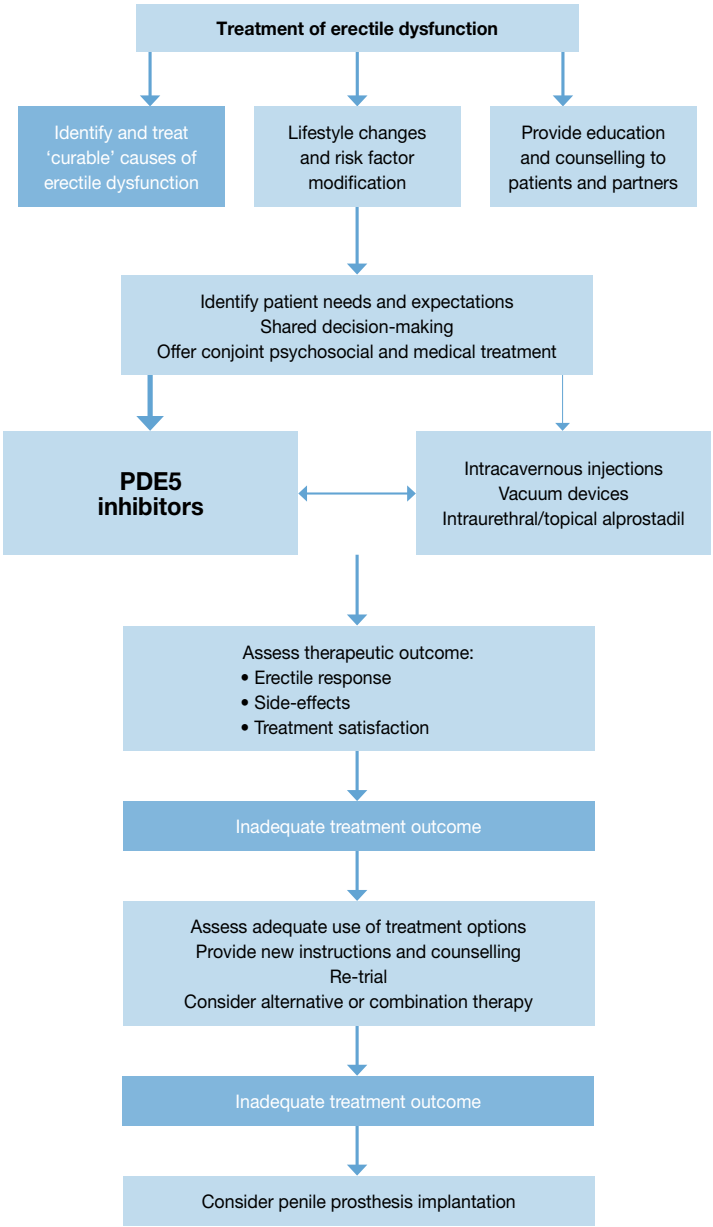
The management of post-RP ED has been revolutionised by the advent of phosphodiesterase 5 inhibitors (PDE5Is), with their demonstrated efficacy, ease of use, good tolerability, excellent safety, and positive impact on QoL. It must be emphasised that post-RP ED patients are poor responders to PDE5Is. However, PDE5Is are the first-line therapy in patients who have undergone nerve-sparing (NS) surgery regardless of the surgical technique used [30, 31]. A number of clinical parameters have been identified as potential predictors of PDE5Is in men undergoing RP. Patient age and quality of NS technique are a key factors in preserving post-operative EF [30, 31, 33]. The response rate to sildenafil treatment for ED after RP in different trials has ranged from 35% to 75% among those who underwent NSRP and from 0% to 15% among those who underwent non-NSRP [31, 68]. Early use of high-dose sildenafil after RP has been suggested to be associated with preservation of smooth muscle within the corpora cavernosa [69]. Daily sildenafil also results in a greater return of spontaneous normal EF after RP compared to placebo following bilateral NSRP in patients who were fully potent before surgery [70].

Effectiveness of tadalafil and vardenafil as on-demand treatment has been evaluated in post-RP ED. A large multicentre trial in Europe and the USA has studied tadalafil in patients with ED following bilateral NS surgery. Erectile function was improved in 71% of patients treated with 20 mg tadalafil vs. 24% of those treated with placebo, while the rate of successful intercourse attempts was 52% with 20 mg tadalafil vs. 26% with placebo [31, 71]. Similarly, vardenafil has been tested in patients with ED following NSRP in a randomised, multicentre, prospective, placebo-controlled study in North America [31, 72]. Following bilateral NSRP, EF improved by 71% and 60% with 10 and 20 mg vardenafil, respectively. An extended analysis of the same cohort of patients showed the benefit of vardenafil compared to placebo in terms of intercourse satisfaction, hardness of erection, orgasmic function, and overall satisfaction with sexual experience [31, 73]. Moreover, a randomised, double-blind, double-dummy trial in men ≤ 68 yr of age and normal pre-operative EF who underwent NSRP at 50 centres from nine European countries and Canada, compared tadalafil once daily with placebo [74]. Tadalafil was most effective on drug-assisted EF in men with ED following NSRP, and data suggested a potential role for tadalafil once daily - provided early after surgery - in contributing to the recovery of post-operative EF and possibly protecting from penile structural changes [74]. Unassisted EF was not improved after cessation of active therapy for 9 months [74]. Moreover, data suggested that the use of tadalafil once daily can significantly shorten the time to EF-recovery post-NSRP compared to placebo [75].

A randomised, 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 pre-operative IIEF EF domain score was ≥ 26, vardenafil was efficacious when used on demand, supporting a paradigm shift towards on-demand dosing with PDE5Is in post-RP ED [76]. A double-blind, placebo-controlled, parallel-group, study in 298 patients with ED after bilateral NSRP randomised to 100 or 200 mg avanafil or placebo (taken 30 minutes before sexual activity) for 12 weeks showed significantly greater increases in SEP2 (sexual encounter profile) and SEP3 and change in mean IIEF-EF domain score with 100 and 200 mg avanafil vs. placebo ($p < 0.01$) [77]. Following dosing with avanafil 36.4% (28 of 77) of sexual attempts (SEP3) at 15 minutes or less were successful vs. 4.5% (2 of 44) for placebo
($p < 0.01$) [77].

Historically, the treatment options for post-operative ED have included intracavernous injections [31, 78], urethral microsuppository [31, 79], vacuum device therapy [31, 80], and penile implants [31, 81, 82]. Intracavernous injections and penile implants are still suggested as second- and third-line treatments, respectively, when oral PDE5Is are not adequately effective or contraindicated for post-operative patients (Sections 3A.4.6 and 3A.4.7).

Figure 3: Treatment algorithm for erectile dysfunction



*3A.4.4 **Causes of ED that can be potentially treated with a curative intent***

3A.4.4.1 Hormonal causes

The advice of an endocrinologist may be beneficial for managing patients with hormonal abnormalities [52]. Testosterone deficiency is either a result of primary testicular failure or secondary to pituitary/hypothalamic causes (e.g. a functional pituitary tumour resulting in hyperprolactinaemia) [52, 83]. When clinically indicated [25], testosterone supplementation (TS) (intramuscular, oral, or transdermal) is effective, but should only be used after other endocrinological causes for testicular failure have been excluded [23, 49, 84]. Before initiating TS, digital rectal examination, serum PSA test, haematocrit, liver function tests and lipid profile should be performed [23, 49]. Patients who are given TS should be monitored for clinical response, elevation of the haematocrit and development of hepatic or prostatic disorders [23, 49]. TS is controversial in men with a history of PCa (LE: 4) [85]. Since there is limited evidence suggesting that TS may not pose an undue risk of PCa recurrence or progression, TS is contraindicated in patients with untreated PCa (LE: 4).

TS is contraindicated in patients with unstable cardiac disease. Conversely, the role of testosterone in the cardiovascular health of men is controversial. Clinical trials examining TS have been insufficiently powered to provide definitive and unequivocal evidence of adverse events in terms of cardiovascular outcomes [86-91]. As a matter of fact, current guidelines from the Endocrine Society make no recommendations on whether patients with heart disease should be screened for hypogonadism and do not recommend supplementing patients

with heart disease to improve survival [48]. However, a recent comprehensive systematic review and meta-analysis of all placebo-controlled randomised clinical trials (RCTs) on the effect of TS on cardiovascular-related problems did not support a causal role between TS and adverse cardiovascular events [92].

3A.4.4.2 Post-traumatic arteriogenic ED in young patients

In young patients with pelvic or perineal trauma, surgical penile revascularisation has a 60-70% long-term success rate [93]. The lesion must be confirmed by penile pharmaco-arteriography. Corporeal veno-occlusive dysfunction is a contraindication to revascularisation and must be excluded by dynamic infusion cavernosometry or cavernosography. Vascular surgery for veno-occlusive dysfunction is no longer recommended because of poor long-term results [93].

3A.4.4.3 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 requires ongoing follow-up and has had variable results [94].

3A.4.5 ***First-line therapy***

3A.4.5.1 Oral pharmacotherapy

PDE5 hydrolyses cGMP in the cavernosal tissue. Inhibition of PDE5 results in smooth muscle relaxation with increased arterial blood flow, leading to compression of the subtunical venous plexus and penile erection [95]. Four potent selective PDE5Is have been approved by the European Medicines Agency (EMA) for the treatment of ED [96]. They are not initiators of erection and require sexual stimulation to facilitate an erection. Efficacy is defined as an erection with rigidity sufficient for vaginal penetration.

3A.4.5.1.1 Sildenafil

Sildenafil was launched in 1998 and was the first PDE5I available on the market [97]. It is administered in doses of 25, 50 and 100 mg. The recommended starting dose is 50 mg and should be adapted according to the patient's response and side-effects. Sildenafil is effective from 30-60 min after administration. Its efficacy is reduced after a heavy, fatty meal due to prolonged absorption. Efficacy may be maintained for up to 12 h [98]. 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 [99, 100]. After 24 weeks in a dose-response study, improved erections were reported by 56%, 77% and 84% of a general ED population taking 25, 50 and 100 mg sildenafil, respectively, compared to 25% of men taking placebo [97]. Sildenafil significantly improved patient scores for IIEF, SEP2, SEP3, and General Assessment Questionnaire (GAQ) and treatment satisfaction. The efficacy of sildenafil in almost every subgroup of patients with ED has been successfully established. The overall level of evidence and grade of recommendation is Level 1 Grade A. Recently, an orally disintegrating tablet (ODT) of sildenafil citrate at the dosage of 50 mg has been developed mainly for the benefit of patients who have difficulty swallowing solid dosage forms.

3A.4.5.1.2 Tadalafil

Tadalafil was licenced for treatment of ED in February 2003 and is effective from 30 min after administration, with peak efficacy after about 2 h. Efficacy is maintained for up to 36 h [101] and is not affected by food. It is administered in on-demand doses of 10 and 20mg and also an alternative daily dose of 5mg. The recommended on-demand 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 and self-limited by continuous use. In premarketing studies, after 12 weeks of treatment and in a dose-response study, improved erections were reported by 67% and 81% of a general ED population taking 10 and 20 mg tadalafil, respectively, compared to 35% of men in the control placebo group [101]. Tadalafil significantly improved patient scores for IIEF, SEP2, SEP3, and GAQ and treatment satisfaction. Efficacy has been confirmed in post-marketing studies. The efficacy of tadalafil in almost every subgroup of patients with ED, thus including difficult-to-treat subgroups (e.g. diabetes mellitus), has been successfully established. The overall level of evidence and grade of recommendation is Level 1 Grade A [102].

3A.4.5.1.3 Vardenafil

Vardenafil became commercially available in March 2003 and is effective from 30 min after administration [102]. Its effect is reduced by a heavy, fatty meal (> 57% fat). Five, 10 and 20 mg doses have been approved for on-demand treatment of ED. The recommended starting dose is 10 mg and should be adapted according to the patient's response and side-effects [103]. Pharmacokinetic data of vardenafil are presented in Table 5. Adverse events (Table 6) are generally mild in nature and self-limited by continuous use [103].
After 12 weeks in a dose-response study, improved erections were reported by 66%, 76% and 80% of a

general ED population taking 5, 10 and 20 mg vardenafil, respectively, compared with 30% of men taking placebo [103, 104]. Vardenafil significantly improved patient scores for IIEF, SEP2, SEP3, and GAQ and treatment satisfaction. Efficacy has been confirmed in post-marketing studies [103, 104]. The efficacy of vardenafil in almost every subgroup of patients with ED, thus including difficult-to-treat subgroups (e.g. diabetes mellitus), has been successfully established. The overall level of evidence and grade of recommendation is Level 1 Grade A. More recently, an ODT of vardenafil has been released [104]. Orodispersable tablet formulations offer improved convenience over film-coated formulations and may be preferred by patients. Absorption is unrelated to food intake and they exhibit better bioavailability compared to film-coated tablets [105]. The efficacy of vardenafil ODT has been demonstrated in several randomised controlled trials and did not seem to differ from the regular formulation [105, 106].

3A.4.5.1.4 Avanafil

Avanafil is a highly-selective PDE5I that recently became commercially available (EMA authorisation June 2013) [107]. Avanafil has a high ratio of inhibiting PDE5 as compared with other PDE subtypes allowing for the drug to be used for ED while minimising adverse effects [108]. Fifty, 100, and 200 mg doses have been approved for on-demand treatment of ED [107]. The recommended dose is 100 mg taken as needed approximately 15 to 30 minutes before sexual activity and should be adapted according to efficacy and tolerability [107, 109, 109a]. In the general population with ED, the mean percentage of attempts resulting in successful intercourse was approximately 47%, 58%, and 59% for the 50 mg, 100 mg, and 200 mg avanafil groups, respectively, as compared with approximately 28% for placebo [107, 109]. Data from sexual attempts made within 15 minutes of dosing showed successful attempts in 64%, 67%, and 71% cases, with avanafil 50, 100, and 200 mg, respectively. The maximum recommended dosing frequency is once per day. Dosage adjustments are not warranted based on renal function, hepatic function, age or gender [109]. Pharmacokinetic data of avanafil are presented in Table 5 [107, 109]. Adverse events (Table 6) are generally mild in nature [107, 109]. Pairwise meta-analytic data from available studies suggested that avanafil significantly improved patient scores for IIEF, SEP2, SEP3, and GAQ, with an evident dose-response relationship [106, 107]. Administration with food may delay the onset of effect compared with administration in the fasted state but avanafil can be taken with or without food. The efficacy of avanafil in many subgroup of patients with ED, including difficult-to-treat subgroups (e.g diabetes mellitus), has been successfully established. The overall level of evidence and grade of recommendation is Level 1 Grade A.

3A.4.5.1.5 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, vardenafil, and avanafil. 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, its possible disadvantages, and how to use it.

3A.4.5.1.6 Continuous use of PDE5 inhibitors

Animal studies have shown that chronic use of PDE5Is improves or prevents significantly the intracavernous structure alterations due to age, diabetes, or surgical damage [110-114]. No data exist for a human population. In humans, it has been clinically demonstrated that tadalafil 5 mg once daily in men complaining of ED of various severities was well tolerated and effective [115]. In 2007, tadalafil 2.5 and 5 mg have been approved by the EMA for daily treatment of ED. According to EMA, a once daily regimen with tadalafil 2.5 mg or 5 mg might be considered suitable, based on patient choice and the physician's judgement. In these patients, the recommended dose is 5 mg taken once a day at approximately the same time of day. Overall, tadalafil, 5 mg once daily, 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. The appropriateness of the continuous use of a daily regimen should be reassessed periodically [115, 116]. Continuous dosing may also be used in the comorbid patient with LUTS and ED.

Table 5: Summary of the key pharmacokinetic data for the four PDE5 inhibitors currently EMA-approved to treat ED*

Parameter	Sildenafil, 100 mg	Tadalafil, 20 mg	Vardenafil, 20 mg	Avanafil 200mg
C_{max}	560 µg/L	378 µg/L	18.7 µg/L	5.2 µg/L
T_{max} (median)	0.8-1 h	2 h	0.9 h	0.5-0.75 h
T1/2	2.6-3.7 h	17.5 h	3.9 h	6 – 17 h
AUC	1685 µg.h/L	8066 µg.h/L	56.8 µg.h/L	11.6 µg.h/L
Protein binding	96%	94%	94%	99%
Bioavailability	41%	NA	15%	8-10%

C_{max}: maximal concentration, T_{max}: time-to-maximum plasma concentration; T1/2: plasma elimination halftime; AUC: area under curve or serum concentration time curve.

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

Table 6: Common adverse events of the four PDE5 inhibitors currently EMA-approved to treat ED*

Adverse event	Sildenafil	Tadalafil	Vardenafil	Avanafil 200mg
Headache	12.8%	14.5%	16%	9.3%
Flushing	10.4%	4.1%	12%	3.7%
Dyspepsia	4.6%	12.3%	4%	uncommon
Nasal congestion	1.1%	4.3%	10%	1.9%
Dizziness	1.2%	2.3%	2%	0.6%
Abnormal vision	1.9%		< 2%	none
Back pain		6.5%		< 2%
Myalgia		5.7%		< 2%

** Adapted from EMA statements on product characteristics.*

3A.4.5.1.7 Safety issues for PDE5 inhibitors

3A.4.5.1.7.1 Cardiovascular safety

Clinical trial results of the four PDE5Is and post-marketing data of sildenafil, tadalafil, and vardenafil have demonstrated no increase in myocardial infarction rates in patients receiving PDE5Is, as part of either RCTs or open-label studies, or compared to expected rates in age-matched male populations. None of the PDE5Is had an adverse effect on total exercise time or time-to-ischaemia during exercise testing in men with stable angina. Chronic or on-demand use is well tolerated with a similar safety profile. All PDE5Is are contraindicated in: i) patients who have suffered from a myocardial infarction, stroke, or life-threatening arrhythmia within the last 6 months; ii) patients with resting hypotension (blood pressure < 90/50 mmHg) or hypertension (blood pressure > 170/100 mmHg); iii) patients with unstable angina, angina with sexual intercourse, or congestive heart failure categorised as New York Heart Association Class 2 or greater.

3A.4.5.1.7.2 Nitrates are contraindicated with PDE5 inhibitors

Absolute contraindication to PDE5Is is represented by patients who are using any form of organic nitrate (e.g. nitroglycerine, isosorbide mononitrate, and isosorbide dinitrate) or nitric oxide (NO) donors (e.g. other nitrate preparations used to treat angina, as well as amyl nitrite or amyl nitrate ("poppers" used for recreation). They result in cGMP accumulation and unpredictable falls in blood pressure and symptoms of hypotension. The duration of interaction between organic nitrates and PDE5Is depends upon the PDE5I and nitrate used. If a PDE5I is taken and the patient develops chest pain, nitroglycerine must be withheld for at least 24 h if sildenafil (and probably also vardenafil) is used (half-life, 4 h), or at least 48 h if tadalafil is used (half-life, 17.5 h), and for no less than 12 h if avanafil is used (half-life, 6-17 h) [117].

3A.4.5.1.7.3 Antihypertensive drugs

Co-administration of PDE5Is with antihypertensive agents (angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, calcium blockers, β-blockers, and diuretics) may result in small additive decreases in blood pressure, which are usually minor. In general, the adverse event profile of a PDE5I is not made worse by a background of antihypertensive medication, even when the patient is taking several antihypertensive agents.

3A.4.5.1.7.4 α-Blocker interactions

All PDE5Is show some interaction with α-blockers, which under some conditions may result in orthostatic hypotension.

- Sildenafil labelling advises that 50 or 100 mg sildenafil should be used with caution in patients taking an α-blocker (especially doxazosin). Hypotension is more likely to occur within 4 h following treatment with an α-blocker. A starting dose of 25 mg is recommended [99].
- Concomitant treatment with vardenafil should only be initiated if the patient has been stabilised on his α-blocker therapy. Co-administration of vardenafil with tamsulosin is not associated with clinically significant hypotension [102-104].
- Tadalafil is not recommended in patients taking doxazosin, but this is not the case for tamsulosin [101, 118].
- Avanafil labelling currently reports that patients should be stable on α-blocker therapy prior to initiating avanafil. In these patients, avanafil should be initiated at the lowest dose of 50 mg. Conversely, in those patients already taking an optimised dose of avanafil, α-blocker therapy should be initiated at the lowest dose.

3A.4.5.1.7.5 Dosage adjustment
Drugs that inhibit the CYP34A pathway will inhibit the metabolic breakdown of PDE5Is, thus increasing PDE5Is blood levels (among them, ketoconazole, ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir and telithromycin). Therefore, lower doses of PDE5Is are necessary. However, other agents, such as rifampin, phenobarbital, phenytoin and carbamazepine, may induce CYP3A4 and enhance the breakdown of PDE5Is, so that higher doses of PDE5Is are required. Severe kidney or hepatic dysfunction may require dose adjustments or warnings.

3A.4.5.1.8 Management of non-responders to PDE5 inhibitors
The two main reasons why patients fail to respond to a PDE5I are either incorrect drug use or lack of efficacy of the drug. Data suggest that an adequate trial involves at least six attempts with a particular drug [119]. The management of non-responders depends upon identifying the underlying cause.

3A.4.5.1.8.1 Check that the patient has been using a licensed medication
There is a large black market in PDE5Is. 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.

3A.4.5.1.8.2 Check that the medication has been properly prescribed and correctly used
The main reason why patients fail to use their medication correctly is inadequate counselling from their physician. The main ways in which a drug may be incorrectly used are: i) failure to use adequate sexual stimulation; ii) failure to use an adequate dose; and, iii) failure to wait an adequate amount of time between taking the medication and attempting sexual intercourse.

Lack of adequate sexual stimulation: PDE5I action is dependent on the release of NO by the parasympathetic nerve endings in the erectile tissue of the penis. The usual stimulus for NO release is sexual stimulation, and without adequate sexual stimulation (and NO release), the drugs cannot work. Oral PDE5Is take different times to reach maximal plasma concentrations [98, 100, 105, 106, 120-122]. 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 four drugs have an onset of action in some patients within 15-30 min of oral ingestion [100, 105, 106, 120-122], most patients require a longer delay between taking the medication [103, 106, 123, 124]. Absorption of sildenafil can be delayed by a meal, and absorption of vardenafil can be delayed by a fatty meal [125]. Absorption of tadalafil is less affected provided there is enough delay between oral ingestion and an attempt at sexual intercourse [120]. When avanafil is taken with a high fat meal, the rate of absorption is reduced with a mean delay in T_{max} of 1.25 h and a mean reduction in C_{max} of 39% (200 mg). There is no effect on the extent of exposure (AUC). The small changes in avanafil C_{max} are considered to be of minimal clinical significance [106-108].

It is 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 6-8 h following drug ingestion, although responses following this time period are well recognised. The half-life of avanafil is 6-17 h. Tadalafil has a longer half-life of ~17.5 h, so the window of efficacy is much longer at ~36 h. Data from uncontrolled studies suggest patient education can help salvage an apparent non-responder to a PDE5I. After emphasising the importance of dose, timing, and sexual stimulation to the patient, EF can be effectively restored following re-administration of the relevant PDE5I [126-128].

3A.4.5.1.8.3 Possible manoeuvres in patients correctly using a PDE5 inhibitor
There is controversial and not-univocal evidence suggesting that, in patients with testosterone deficiency, TS

might improve response to a PDE5I [49, 129-131]. Modification of other risk factors may also be beneficial as discussed in section 3A.4.2. Few data suggest that some patients might respond better to one PDE5I than to another [132]. 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 PDE5I might be helpful. Moreover, mainly in patients with severe ED, it has been suggested to combine tadalafil daily dosing with short acting PDEI (such as sildenafil), without any significant increase in terms of side-effects [133].
If drug treatment fails, then patients should be offered an alternative therapy such as intracavernosal injection therapy or use of a vacuum erection device (VED).

3A.4.5.2 Vacuum erection devices
VEDs 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. Published data report that 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% [134, 135]. Most men who discontinue use of VEDs do so within 3 months. Long-term use of VEDs decreases to 50-64% after 2 years [136]. The commonest adverse events include pain, inability to ejaculate, petechiae, bruising, and numbness, which occur in < 30% of patients [135]. Serious adverse events (skin necrosis) can be avoided if patients remove the constriction ring within 30 min. VEDs are contraindicated in patients with bleeding disorders or on anticoagulant therapy. VEDs may be the treatment of choice in well-informed older patients with infrequent sexual intercourse and comorbidity requiring non-invasive, drug-free management of ED [134, 135].

3A.4.5.3 Shockwave therapy
Recently, the use of low-intensity extracorporeal shock wave therapy (LI-SWT) was proposed as a novel treatment for ED [137]. In the first randomised, double-blind, sham-controlled study, it was demonstrated that LI-SWT had a positive short-term clinical and physiological effect on the EF of men who respond to PDE5Is [138]. Moreover, there are preliminary data showing improvement in penile haemodynamics and endothelial function, as well as IIEF-EF domain score in severe ED patients who are poor responders to PDE5Is [139, 140]. Current data are still limited and clear recommendations cannot be given.

3A.4.6 ***Second-line therapy***
Patients not responding to oral drugs may be offered intracavernous injections. Success rate is high (85%) [141, 142]. Intracavernous administration of vasoactive drugs was the first medical treatment for ED more than 20 years ago [143, 144].

3A.4.6.1 Intracavernous injections
3A.4.6.1.1 Alprostadil
Alprostadil (CaverjectTM, Edex/ViridalTM) was the first and only drug approved for intracavernous treatment of ED [143, 144]. Intracavernous alprostadil is most efficacious as monotherapy at a dose of 5-40 µg (of note, 40 µg dose is not registered in every European country). The erection appears after 5-15 min and lasts according to the dose injected. An office-training programme 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 >70% have been found in general ED populations, as well as in patient subgroups (e.g. diabetes or CVD), with reported sexual activity after 94% of the injections and satisfaction rates of 87-93.5% in patients and 86-90.3% in partners [143, 144]. Complications of intracavernous alprostadil include penile pain (50% of patients reported pain but pain reported only after 11% of total injections), prolonged erections (5%), priapism (1%), and fibrosis (2%) [143-145]. Pain is usually self-limited after prolonged use. It can be alleviated with the addition of sodium bicarbonate or local anaesthesia [143, 144, 146]. Cavernosal fibrosis (from a small hematoma) usually clears within a few months after temporary discontinuation of the injection program. However, tunical fibrosis suggests early onset of Peyronie's disease and may indicate stopping intracavernosal injections indefinitely. 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, drop-out rates of 41-68% have been described for intracavernous pharmacotherapy [143, 144, 147, 148], with most drop-outs occurring within the first 2-3 months. In a comparative study, alprostadil monotherapy had the lowest discontinuation rate (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 [149].

3A.4.6.1.2 Combination therapy

Combination therapy 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 most commonly used in combination therapy due to its high incidence of side-effects as monotherapy. Currently unlicensed.
- 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, usually combined with the main drugs [150, 151]. Most combinations are not standardised 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 [152, 153]. The triple combination regimen of papaverine, phentolamine and alprostadil has the highest efficacy rates, reaching 92%; this combination has similar side-effects as alprostadil monotherapy, but a lower incidence of penile pain due to lower doses of alprostadil. However, fibrosis is more common (5-10%) when papaverine is used (depending on total dose).
- VIP (25 µg) + phentolamine mesylate (1-2 mg) (InvicorpTM, currently licensed in Scandinavia), is a combination of two active components with complementary modes of action. Clinical studies showed that the combination is an effective treatment for intracavernous injections in ≥ 80% of men with ED, including those who have failed to respond to other therapies and, unlike existing intracavernosal therapies, is associated with a very low incidence of penile pain and virtually negligible risk of priapism [154].

Despite high efficacy rates, 5-10% of patients do 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 [155]. However, combination therapy is 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 [Level 4].

3A.4.6.1.3 Intraurethral/topical alprostadil

A specific formulation of alprostadil (125-1000 µg) in a medicated pellet (MUSE™) has been approved as a treatment for ED [156]. Erections sufficient for intercourse are achieved in 30-65.9% of patients. In clinical practice, only the higher doses (500 and 1000 µg) have been used with low consistency response rates [156-158]. The application of a constriction ring at the root of the penis (ACTIS™) may improve efficacy [157, 158]. The most common adverse events are local pain (29-41%) and dizziness with possible hypotension (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 [142]. Intraurethral pharmacotherapy is a second-line therapy and provides an alternative to intracavernous injections in patients who prefer a less-invasive, although less-efficacious treatment.
Topical alprostadil is another way of giving alprostadil. It is actually a cream that includes a permeation enhancer in order to facilitate absorption of alprostadil (200 and 300µg) through the urethral meatus [159]. Clinical data are limited. Significant improvement compared to placebo was recorded for IIEF, SEP2 and SEP3 in a broad range of patients with mild to severe ED [160]. Side-effects include penile erythema, penile burning and pain. Systemic side-effects are very rare. Topical alprostadil is approved and it is available in some European countries.

3A.4.7 ***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. The two currently available classes of penile implants include inflatable (2- and 3-piece) and malleable devices [31, 81, 161, 162]. Most patients prefer the 3-piece inflatable devices due to the more “natural” erections obtained. Likewise, 3-piece inflatable devices provide the best rigidity and the best flaccidity because they will fill every part of the corporal bodies. However, the 2-piece inflatable prosthesis can be a viable option among patients who are deemed high-risk of complications with reservoir placements. Malleable prostheses result in a firm penis, which may be manually placed in an erect or flaccid state [31, 81, 161, 162].

There are two main surgical approaches for penile prosthesis implantation: penoscrotal and infrapubic [161-164]. The penoscrotal approach provides an excellent exposure, it affords proximal crural exposure if necessary, avoids dorsal nerve injury and permits direct visualisation of pump placement. However, with this approach the reservoir is blindly placed into the retropubic space, which can be a problem in patients with a history of major pelvic surgery (mainly radical cystectomy). The infrapubic approach has the advantage of reservoir placement under direct vision, but the implantation of the pump may be more challenging, and patients are at a slightly increased risk of dorsal nerve injury. Revision surgery is associated with decreased outcomes and may be more challenging. Regardless of the indication, prosthesis implantation has one of the highest satisfaction rates (92-100% in patients and 91-95% in partners) among the treatment options for ED based on appropriate consultation [31, 81, 161, 165-171]. In patients with favourable oncologic prognosis after RP for PCa, combination surgery for treatment of ED, with the implant of a penile prosthesis, and stress urinary incontinence (male sling or artificial urinary sphincter) is effective and durable and has an established, definitive role to address this problem [31, 81, 172-174].

3A.4.7.1 Complications

The two main complications of penile prosthesis implantation are mechanical failure and infection. Several technical modifications of the most commonly used 3-piece prosthesis (AMS 700CX/CXRTM and Coloplast Alpha ITM) resulted in mechanical failure rates of < 5% after 5 years of follow-up [81, 175, 176]. Careful surgical techniques with proper antibiotic prophylaxis against Gram-positive and Gram-negative bacteria reduces infection rates to 2-3% with primary implantation in low-risk patients. The infection rate may be further reduced to 1-2% by implanting an antibiotic-impregnated prosthesis (AMS Inhibizone™) or hydrophilic-coated prosthesis (Coloplast Titan™) [81, 177-180]. Higher risk populations include patients undergoing revision surgery, those with impaired host defenses (immunosuppression, diabetes mellitus, spinal cord injury) or those with penile corporal fibrosis [9, 81, 161, 181-183]. Infection requires removal of the prosthesis and antibiotic administration. Alternatively, removal of the infected device with immediate replacement with a new prosthesis has been described using a washout protocol with successful salvages achieved in > 80% of cases [181, 183, 184]. The majority of revisions are secondary to mechanical failure and combined erosion or infection. Ninety three percent of cases are successfully revised, providing functioning penile prosthesis.

3A.4.7.2 Conclusions third-line therapy

Penile implants are an attractive solution for patients who do not respond to more conservative therapies. There is sufficient evidence to recommend this approach in patients not responding to less-invasive treatments due to its high efficacy, safety and satisfaction rates.

3A.4.8 ***Recommendations for the treatment of ED***

	LE	GR
Lifestyle changes and risk factor modification must precede or accompany ED treatment.	1a	A
Pro-erectile treatments have to be given at the earliest opportunity after RP.	1b	A
When a curable cause of ED is found, it must be treated first.	1b	B
PDE5Is are first-line therapy.	1a	A
Inadequate/incorrect prescription and poor patient education are the main causes of a lack of response to PDE5Is.	3	B
A VED can be used in patients with a stable relationship.	4	C
Intracavernous injection is second-line therapy.	1b	B
Penile implant is third-line therapy.	4	C

ED = erectile dysfunction; RP = radical prostatectomy; VED = vacuum erection devices; PDE5I = phosphodiesterase type 5 [inhibitors].

3A.5 Follow-up

Follow-up is important in order to assess efficacy and safety of the treatment provided. It is also essential to assess patient satisfaction since a successful treatment for ED goes beyond efficacy and safety. Physicians must be aware that there is no single treatment that fits all patients or all situations as described in detail in the previous section.

3B PREMATURE EJACULATION

3B.1 Epidemiology/aetiology/pathophysiology

Although premature ejaculation (PE) is a 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 [2].

*3B.1.1 **Epidemiology***

The major problem in assessing the prevalence of PE is the lack of an accurate (validated) definition at the time the surveys were conducted [185]. The highest prevalence rate of 31% (men aged 18-59 years) was found by the National Health and Social Life Survey (NHSLS) study in USA [186]. Prevalence rates were 30% (18-29 years), 32% (30-39 years), 28% (40-49 years) and 55% (50-59 years). It is, however, unlikely that the PE prevalence is as high as 20–30% based on the relatively low number of men who present for treatment of PE. 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 [187]. According to the four PE subtypes proposed by Waldinger et al [188] , the prevalence rates were 2.3% (lifelong PE), 3.9% (acquired PE), 8.5% (natural variable PE) and 5.1% (premature-like ejaculatory dysfunction) [189]. An approximately 5% prevalence of acquired PE and lifelong PE in general populations is consistent with epidemiological data indicating that around 5% of the population have an ejaculation latency less than 2 minutes [190].

*3B.1.2 **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 [191]. In addition, the pathophysiology of PE is largely unknown. All the physiological events leading up to the forceful expulsion of sperm at the urethral meatus are not impaired in PE patients. A significant proportion of men with ED also experience PE [192]. 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 [186, 187], unlike ED, which increases with age. PE is not affected by marital or income status [186]. However, PE is more common in black men, Hispanic men and men from Islamic backgrounds [193, 194] and may be higher in men with a lower educational level [186, 192]. Other risk factors may include a genetic predisposition [195], poor overall health status and obesity [186], prostate inflammation [196, 197], thyroid hormone disorders (37), emotional problems and stress [186, 198], and traumatic sexual experiences [186, 192]. In the only published study on risk modification/prevention strategies [199], successful eradication of causative organisms in patients with chronic prostatitis and PE produced marked improvements in IELT and ejaculatory control compared to untreated patients [200].

*3B.1.3 **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 [201, 202]. However, the negative impact of PE extends beyond sexual dysfunction. PE can have a detrimental effect on self-confidence and the relationship with the partner, and may sometimes cause mental distress, anxiety, embarrassment and depression [201, 203]. Sex drive and overall interest in sex does not appear to be affected by PE [204]. However, the partner's satisfaction with the sexual relationship decreases with increasing severity of the man's condition [205]. Despite the possible 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 [192], with men more likely to seek treatment for ED than for PE [192]. In the PEPA survey, only 9% of men with self-reported PE consulted a doctor [187]. 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 [206, 207]. Physicians need to encourage their patients to talk about PE.

3B.2 Classification

There have previously been two official definitions of PE, neither of which have been 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*' [208]. This DSM definition has been recently updated in the DSM V edition [209].

- 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*' [210].

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*' [191].

The International Society for Sexual Medicine (ISSM) has adopted a completely new definition of PE which is the first evidence-based definition [211]:
PE (lifelong and acquired) is a male sexual dysfunction characterised by the following:

1. Ejaculation that always or nearly always occurs prior to or within about 1 minute of vaginal penetration (lifelong PE) or a clinically significant and bothersome reduction in latency time, often to about 3 minutes or less (acquired PE).
2. The inability to delay ejaculation on all or nearly all vaginal penetrations.
3. Negative personal consequences, such as distress, bother, frustration, and/or the avoidance of sexual intimacy.

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) [209].

Recently, two more PE syndromes have been proposed [212]:

- 'Variable PE' is characterised by inconsistent and irregular early ejaculations, representing a normal variation in sexual performance.
- 'Subjective PE' is characterised 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 [213].

3B.3 Diagnostic evaluation

Diagnosis of PE is based on the patient's medical and sexual history [214, 215]. 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 [216]. 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 [217]. There are several overlapping definitions of PE, with four shared factors (Table 7), resulting in a multidimensional diagnosis [218].

Table 7: Common factors in different definitions of PE

• Time to ejaculation assessed by IELT
• Perceived control
• Distress
• Interpersonal difficulty related to the ejaculatory dysfunction

3B.3.1 Intravaginal ejaculatory latency time

The use of IELT alone is not sufficient to define PE, as there is significant overlap between men with and without PE [219, 220]. 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 [221]. 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 [222]. Self-estimated and

stopwatch-measured IELT are interchangeable and correctly assign PE status with 80% sensitivity and 80% specificity [223]. 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. While IELT is an objective tool for PE assessment, a recent study reported that sexual satisfaction and distress correlated more strongly with the feeling of control than with the self-reported latency time [224].

3B.3.2 ***PE assessment questionnaires***

The need to assess PE objectively has led to the development of several questionnaires based on the use of PROs [218]. 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 [225, 226]. A total score ≥ 11 suggests a diagnosis of PE, a score of 9 or 10 suggests a probable diagnosis of PE while a score of ≤ 8 indicates a low likelihood of PE.
- 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 [227]. A cut-off score of 30 (range of scores 7-35) discriminated best PE diagnosis. Severity of PE was classified as severe (score: 7-13), moderate (score: 14-19), mild to moderate (score: 20-25) and mild (score: 26-30).

The most widely used tool is the PEDT. However, there is a low correlation between a diagnosis provided by PEDT and a self-reported diagnosis. A recent study reported that only 40% of men with PEDT-diagnosed PE and 19% of men with probable PE self-reported the condition [228]. Questionnaires are a significant step in simplifying the methodology of PE drug studies, although further cross-cultural validation is needed [229]. Other questionnaires used to characterise PE and determine treatment effects include the PEP [220], Index of Premature Ejaculation (IPE) (61) and Male Sexual Health Questionnaire Ejaculatory Dysfunction (MSHQ-EjD) [230]. Currently, their role is optional in everyday clinical practice.

3B.3.3 ***Physical examination and investigations***

Physical examination may be part of the initial assessment of men with PE. It may include a brief examination of the endocrine and neurological systems to identify underlying medical conditions associated with PE or other sexual dysfunctions, such as endocrinopathy, 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 [214].

3B.3.4 ***Recommendations for the diagnostic evaluation of PE***

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

PE = premature ejaculation; IELT = intravaginal ejaculatory latency time; ED = erectile dysfunction.

3B.4 Disease management

In men for whom PE causes few, if any problems, treatment is limited to psychosexual counselling and education. Before beginning treatment, it is essential to discuss the patient's expectations thoroughly. Furthermore, it is important to treat first, if present, ED especially and possibly prostatitis.

Various behavioural techniques have been beneficial 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 perform. In addition, long-term outcomes of behavioural techniques for PE are unknown.

Pharmacotherapy is the basis of treatment in lifelong PE. Dapoxetine is the only on-demand pharmacological treatment approved for PE in many countries except for the USA. All other medications used in PE are off-label indications. Chronic antidepressants including selective serotonin reuptake inhibitors (SSRIs) and clomipramine, a tricyclic antidepressant and on-demand topical anaesthetic agents have consistently shown efficacy in PE. Long-term outcomes for pharmacological treatments are unknown.

An evidence-based analysis of all current treatment modalities was performed. Levels of evidence and grades of recommendation are provided and a treatment algorithm is presented (Figure 4).

3B.4.1 ***Psychological/behavioural strategies***

Behavioural strategies mainly include the 'stop-start' programme developed by Semans [231] 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 to recognise 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 younger men. Following masturbation, the penis is desensitised resulting in greater ejaculatory delay after the refractory period is over. In a different approach, the man learns to recognise 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 'Stop-start' programme [232].

Psychological factors may be associated with PE and should be addressed in treatment. These factors, if any, mainly relate to anxiety, but could also include relationship factors. The limited studies available suggest that behavioural therapy, as well as functional sexological treatment, lead to improvement in the duration of intercourse and sexual satisfaction.

Overall, short-term success rates of 50-60% have been reported [233, 234]. 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 [235]. Furthermore, clinical experience suggests that improvements achieved with these techniques are generally not maintained long-term [236, 237]. Behavioural therapy may be most effective when used to 'add value' to medical interventions, although this suggestion requires proof from further randomised clinical trials. Validated assessment instruments need to be used as end-points. Longer follow-up periods are necessary to confirm these findings.

3B.4.2 ***Dapoxetine***

Dapoxetine hydrochloride is a short-acting SSRI, with a pharmacokinetic profile suitable for on-demand treatment for PE. It has a rapid T_{max} (1.3 hours) and a short half-life (95% clearance rate after 24 hours) [238]. Dapoxetine has been investigated in 6081 subjects to date [239]. It is approved for on-demand treatment of PE in European countries and elsewhere, but not in the USA.

Both available doses of dapoxetine (30 mg and 60 mg) have shown 2.5- and 3.0-fold increases, respectively, in IELT overall, rising to 3.4- and 4.3-fold in patients with baseline average IELT < 0.5 minutes [240, 241]. In RCTs, dapoxetine, 30 mg or 60 mg 1-2 hours before intercourse, was effective from the first dose on IELT and increased ejaculatory control, decreased distress, and increased satisfaction. Dapoxetine has shown a similar efficacy profile in men with lifelong and acquired PE [241]. Treatment-related side-effects were dose-

dependent and included nausea, diarrhoea, headache and dizziness. Side-effects were responsible for study discontinuation in 4% (30 mg) and 10% (60 mg) of subjects [222]. There was no indication of an increased risk of suicidal ideation or suicide attempts and little indication of withdrawal symptoms with abrupt dapoxetine cessation [242].

Regarding a combination of PDE5 inhibitors with dapoxetine, the addition of dapoxetine to a given regimen of PDE5 inhibitor may increase the risk of possible prodromal symptoms that may progress to syncope compared to both PDE5I inhibitors and SSRIs administered alone. Generally, when dapoxetine is co-administered with a PDE5I inhibitor, it is well tolerated, with a safety profile consistent with previous phase 3 studies of dapoxetine alone [243]. A low rate of vasovagal syncope was reported in phase 3 studies. According to the summary of product characteristics, orthostatic vital signs (blood pressure and heart rate) must be measured prior to starting dapoxetine. No cases of syncope were observed in a post-marketing observational study, which had identified patients at risk for orthostatic reaction using the patient's medical history and orthostatic testing [244].

The mechanism of action of short-acting SSRIs in PE is still speculative. Dapoxetine resembles the antidepressant SSRIs in the following ways: the drug binds specifically to the 5-HT reuptake transporter at subnanomolar levels, has only a limited affinity for 5-HT receptors and is a weak antagonist of the 1A-adrenoceptors, dopamine D1 and 5-HT2B receptors. The rapid absorption of dapoxetine might lead to an abrupt increase in extracellular 5HT following administration that might be sufficient to overwhelm the compensating autoregulation processes. Does the mechanism of action of short-acting SSRIs differ from that of the conventional chronic SSRI mechanism of action? Either such agents do not cause the autoreceptor activation and compensation reported using chronic SSRIs, or these effects occur, but they simply cannot prevent the action of short-acting SSRIs [245].

3B.4.3 ***Off-label use of antidepressants: SSRIs and clomipramine***

Ejaculation is commanded by a spinal ejaculation generator [246, 247] under excitatory or inhibitory influences from the brain and the periphery [248]. 5-hydroxytryptamine (5-HT or serotonin) is involved in ejaculatory control, with its ejaculation-retarding effects likely to be attributable to activation of 5-HT1B and 5-HT2C receptors, both spinally and supraspinally. By contrast, stimulation of 5-HT1A receptors precipitates ejaculation [245].

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 for depression, SSRIs must be given for 1 to 2 weeks to be effective in PE [245]. Administration of chronic SSRIs causes prolonged increases in synaptic cleft serotonin, which desensitises the 5-HT1A and 5-HT1B receptors [249]. Clomipramine, the most serotoninergic tricyclic antidepressant, was first reported in 1973 as an effective PE treatment [250]. SSRIs have revolutionised treatment of PE, but they have also changed our understanding of PE since the first publication on paroxetine in 1970 [251]. Before dapoxetine, daily treatment with SSRIs was 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 [252]. Nevertheless, despite significant increase in IELT, there are no data available concerning the PROs in PE patients treated with daily SSRIs.

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 [253, 254].

Ejaculation delay may start a few days after drug intake, but it is more evident after 1 to 2 weeks since receptor desensitisation requires time to occur. Although efficacy may be maintained for several years, tachyphylaxis (decreasing response to a drug following chronic administration) may occur after 6 to 12 months [250]. 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 [213, 240]. Decreased libido,

anorgasmia, anejaculation and ED have also been reported.

Because of a theoretical risk of suicidal ideation or suicide attempts, caution is suggested in prescribing SSRIs to young adolescents with PE aged 18 years or less, and to men with PE and a comorbid depressive disorder, particularly when associated with suicidal ideation. Patients should be advised to avoid sudden cessation or rapid dose reduction of daily dosed SSRIs which may be associated with a SSRI withdrawal syndrome [222].

In one controlled trial, on-demand use of clomipramine (but not paroxetine), 3 to 5 hours before intercourse, was reported to be efficacious, though IELT improvement was inferior compared to daily treatment with the same drug [255]. However, on-demand treatment may be combined with an initial trial of daily treatment or concomitant low-dose daily treatment reducing adverse effects [256, 257].

Individual countries' regulatory authorities strongly advise against prescribing medication for indications if the medication in question is not licensed/approved and prescription of off-label medication may present difficulties for physicians.

*3B.4.4 **Topical anaesthetic agents***

The use of local anaesthetics to delay ejaculation is the oldest form of pharmacological therapy for PE [258]. Several trials [259, 260] support the hypothesis that topical desensitising agents reduce the sensitivity of the glans penis so delaying ejaculatory latency, but without adversely affecting the sensation of ejaculation.

3B.4.4.1 Lidocaine-prilocaine cream

In a randomised, double-blind, placebo-controlled trial, lidocaine-prilocaine cream increased the IELT from 1 minute in the placebo group to 6.7 minutes in the treatment group [261]. In another randomised, double-blind, placebo-controlled trial, lidocaine-prilocaine cream significantly increased the stopwatch-measured IELT from 1.49 to 8.45 minutes while no difference was recorded in the placebo group (1.67 to 1.95 minutes) [262].

Lidocaine-prilocaine cream (5%) is applied for 20-30 minutes prior to intercourse. Prolonged application of topical anaesthetic (30-45 minutes) may result in loss of erection due to numbness of the penis in a significant percentage of men [261]. A condom will prevent 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 part of the product.

An experimental aerosol formulation of lidocaine, 7.5 mg, plus prilocaine, 2.5 mg (Topical Eutectic Mixture for Premature Ejaculation [TEMPE]), was applied 5 minutes before sexual intercourse in 539 males. There was an increase in the geometric mean IELT from a baseline of 0.58 minutes to 3.17 minutes during 3 months of double-blind treatment; a 3.3-fold delay in ejaculation compared with placebo ($p < 0.001$) [263].

3B.4.5 Tramadol

Tramadol is a centrally acting analgesic agent that combines opioid receptor activation and re-uptake inhibition of serotonin and noradrenaline. Tramadol is readily absorbed after oral administration and has an elimination half-life of 5-7 hours. For analgesic purposes, tramadol can be administered between 3 and 4 times daily in tablets of 50-100 mg. Side-effects were reported at doses used for analgesic purposes (up to 400 mg daily) and include constipation, sedation and dry mouth. Tramadol is a mild-opioid receptor agonist, but it also displays antagonistic properties on transporters of noradrenaline and 5-HT [264]. This mechanism of action distinguishes tramadol from other opioids, including morphine. However, in May 2009, the US Food and Drug Administration released a warning letter about tramadol's potential to cause addiction and difficulty in breathing [265].

A large, randomised, double-blind, placebo-controlled, multicentre 12-week study was carried out to evaluate the efficacy and safety of two doses of tramadol (62 and 89 mg) by orally disintegrating tablet (ODT) in the treatment of PE [266]. Previously, a bioequivalence study had previously been performed that demonstrated equivalence between tramadol ODT and tramadol HCl. In patients with a history of lifelong PE and an IELT < 2 minutes, increases in the median IELT of 0.6 minutes (1.6-fold), 1.2 minutes (2.4-fold) and 1.5 minutes (2.5-fold) were reported for placebo, 62 mg of tramadol ODT, and 89 mg of tramadol ODT, respectively. It should be noted that there was no dose-response effect with tramadol. The tolerability during the 12-week study period was acceptable.

Overall, tramadol has shown a moderate beneficial effect with a similar efficacy as dapoxetine. From what is known about the neuropharmacology of ejaculation and the mechanism of action of tramadol, the delaying effect on ejaculation could be explained by combined CNS μ-opioid receptor stimulation and increased brain 5-HT availability. However, efficacy and tolerability of tramadol would have to be confirmed in more patients and longer-term.

3B.4.6 ***Other drugs***

3B.4.6.1 Phosphodiesterase type 5 inhibitors

There is only one well-designed, randomised, double-blind, placebo-controlled study comparing sildenafil to placebo [267]. 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.

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 vs. paroxetine alone [268].
- Sildenafil combined with sertraline improved IELT and satisfaction significantly vs. sertraline alone [269].
- Sildenafil combined with paroxetine and psychological and behavioural counselling significantly improved IELT and satisfaction in patients in whom other treatments failed [270].
- Finally, sildenafil combined with behavioural therapy significantly improved IELT and satisfaction vs. behavioural therapy alone [271].

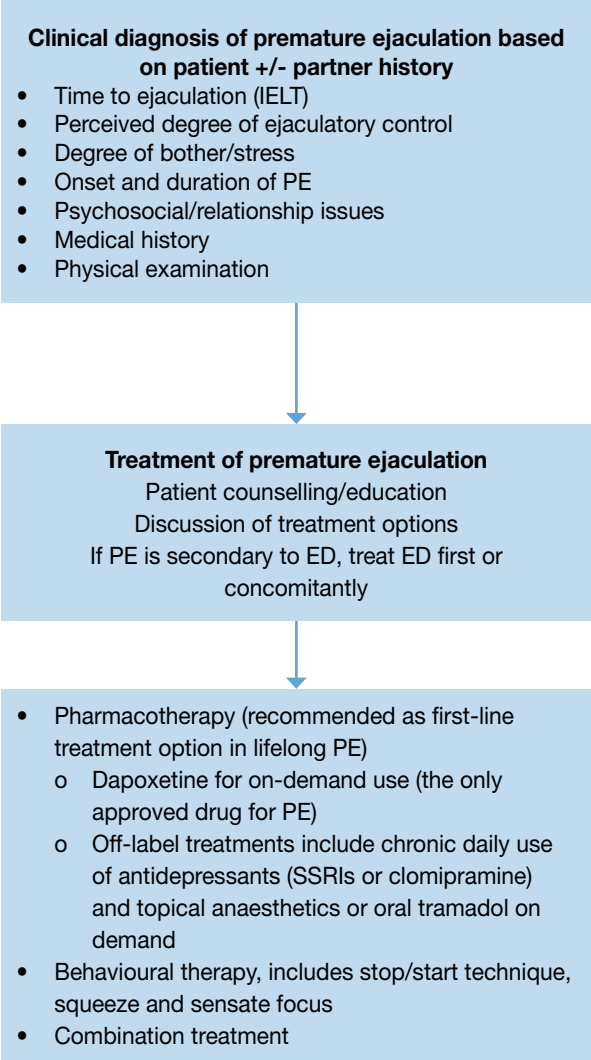
There are very limited data on the efficacy of other PDE5Is (tadalafil and vardenafil) [272, 273]. The role of PDE5Is in PE patients without ED is not established, with only minimal double-blind placebo controlled data available.

3B 4.7 ***Recommendations for the treatment of PE***

Recommendations	**LE**	**GR**
Erectile dysfunction, other sexual dysfunction or genitourinary infection (e.g. prostatitis) should be treated first.	2a	B
Pharmacotherapy should be given as first-line treatment of lifelong premature ejaculation.	1a	A
Pharmacotherapy includes either dapoxetine on demand (a short-acting SSRI that is the only approved pharmacological treatment for premature ejaculation) or other off-label antidepressants, i.e. daily SSRIs and clomipramine, that are not amenable to on-demand dosing. With all antidepressant treatment for premature ejaculation, recurrence is likely after treatment cessation.	1a	A
Off-label topical anaesthetic agents can be offered as a viable alternative to oral treatment with SSRIs.	1b	A
Behavioural and sexological therapies have a role in the management of acquired premature ejaculation. They are most likely to be best used in combination with pharmacological treatment.	3	C
Psychological/behavioural therapies.	3	C
On-demand treatment of premature ejaculation		
PDE5 inhibitor.	3	C
Dapoxetine on demand.	1a	A
Tramadol on demand.	2a	B
Chronic treatment of premature ejaculation		
Off-label chronic treatment i.e. daily with selective serotonin receptor inhibitors (SSRIs) and clomipramine antidepressants.	1a	A
On-demand topical therapy for premature ejaculation		
Lidocaine-prilocaine cream.	1b	A

SSRI = selective serotonin reuptake inhibitor.

Figure 4: Management of PE*



* Adapted from Lue et al. 2004 [274].
ED = erectile dysfunction; PE = premature ejaculation; IELT = intravaginal ejaculatory latency time; SSRI = selective serotonin receptor inhibitor.

4. FOLLOW-UP

Follow-up is important in order to assess efficacy and safety of the provided treatment as well as the satisfaction of the patient and his partner as discussed in detail in the previous section.

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6. CONFLICT OF INTEREST

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