EAU Guidelines on

Erectile Dysfunction, Premature Ejaculation, Penile Curvature and Priapism

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1. INTRODUCTION

1.1 Aim

These guidelines include 4 sections. The aim of the first two sections 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.

The aim of the third section is to provide the practicing urologist with the most recent evidence on the diagnosis and management of penile curvature in order to assist in their decision-making. Penile curvature is a common urological disorder which can be congenital or acquired. Congenital curvature is briefly discussed in these guidelines as a distinct pathology in the adult population without any other concomitant abnormality present (such as urethral abnormalities). For paediatric congenital penile curvature, please refer to the EAU Guidelines on Paediatric Urology, Chapter on Congenital Penile Curvature. Acquired curvature is mainly due to Peyronie's disease but can also be due to the development of fibrosis following penile fracture.

The aim of the fourth section is to present the current evidence for the diagnosis and treatment of patients suffering from priapism. Priapism is a pathological condition representing a true disorder of penile erection that persists for more than 4 hours and is beyond, or is unrelated to, sexual interest or stimulation [3] (LE: 4). Overall, erections lasting up to 4 hours are by consensus defined as 'prolonged' (LE: 4). Priapism may occur at all ages. The incidence rate of priapism in the general population is low (0.5-0.9 cases per 100,000 person-years) [4, 5]. In men with sickle cell disease, the prevalence of priapism is up to 3.6% in men < 18 years of age [6] increasing up to 42% in men ≥ 18 years of age [7-10].

The Guidelines Office of the European Association of Urology (EAU) has appointed an Expert Panel to update previously published EAU guidelines for ED, PE, penile curvature and priapism.

It must be emphasised that clinical guidelines present the best evidence available to the experts. However, following guidelines recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when making treatment decisions for individual patients, but rather help to focus decisions – also taking personal values and preferences/individual circumstances of patients into account.

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" [11]. In 2011 the Panel decided to develop new guidelines addressing Penile Curvature, which resulted in a new publication in 2012 [12]. In 2014 a guideline on Priapism was completed [13].

In this 2016 edition, the phrasing of some recommendations has been updated including some minor corrections. This edition also merged the previous EAU guidelines for ED, PE, penile curvature and priapism into one guideline.

1.3 Available Publications

Alongside several scientific summaries published in the EAU scientific journal, European Urology [14-18], 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 version. All available material can be viewed and downloaded for personal use at the EAU website, which also includes a selection of translations produced by national urological associations: http://www.uroweb.org/guidelines/online-guidelines/.

1.4 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, PE, penile curvature and priapism.

2. METHODS

References used in this text are assessed according to their Level of Evidence (LE) and Guidelines are given a Grade of Recommendation (GR), according to a classification system modified from the Oxford Centre for Evidence-Based Medicine Levels of Evidence. Additional methodology information can be found in the general Methodology section of this print, and online at the EAU website: http://www.uroweb.org/guideline/. A list of Associations endorsing the EAU Guidelines can also be reviewed online at the above address.

For the topics of ED and PE, a systemic literature search was performed in 2015 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.

For PE, a systematic literature search of the Medline database was also performed in 2015. The controlled vocabulary of the Medical Subject Headings (MeSH) database uses the specific term 'penile induration' for Peyronie's disease. There is no specific MeSH term for congenital penile curvature. In order to identify relevant articles, the search included the MeSH terms 'congenital abnormalities', 'penis abnormalities' and 'male' as well as the free text term 'congenital penile curvature'. The search included all relevant articles published up to July 2014. A total of 199 articles were identified for congenital penile curvature while this number was 1,806 for Peyronie's disease. The panel reviewed and selected the articles with the highest evidence available. However, in several subtopics only articles with low LE were available and discussed accordingly.

Finally, the guidelines on Priapism are based on a systematic literature search performed by the Panel members in 2015. The MedLine database was searched using the major Medical Subject Headings term 'priapism' with search cut-off date of October 2014. This search yielded 1,688 articles (192 review articles, 485 original articles and 911 case reports). The Panel also identified critical problems and knowledge gaps, enabling priorities to be established for future clinical research.

2.1 Review

This document was subject to peer review prior to publication in 2015. The decision to re-review is made based on the extent of the revision. A major revision resulting in significant changes to the clinical recommendations presented in the text will warrant re-review.

3. MALE SEXUAL DYSFUNCTION

3.1 Erectile dysfunction

3.1.1 Epidemiology/aetiology/pathophysiology

Penile erection is a complex phenomenon which implies a delicate and co-ordinated 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 [19]. ED is defined as the persistent inability to attain and maintain an erection sufficient to permit satisfactory sexual performance [20]. ED may affect physical and psychosocial health and may have a significant impact on the quality of life (QoL) of sufferers and their partners [21-23]. 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) [24-26].

3.1.1.1 Epidemiology

Epidemiological data have shown a high prevalence and incidence of ED worldwide. Among others, the Massachusetts Male Aging Study (MMAS) [21] 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% [27]. The incidence rate of ED (new cases per 1,000 men annually) was 26 in the long-term data from the MMAS study [28] and 19.2 (mean follow-up of 4.2 years) in a Dutch study [29]. 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 [30]. Differences between these studies can be explained by differences in methodology, in the ages, and socio-economic and cultural status of the populations studied.

3.1.1.2 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) [23, 31, 32]. In this context, men with mild ED have similar risk factors to those of a general ED clinical trial population [33]. Thus, mild ED emerged as an important indicator of risk for associated underlying disease (CVDs) [33]. A number of studies have shown some evidence that lifestyle modification [25, 34] and pharmacotherapy [34, 35] 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 the prevention or treatment of ED [26].

Epidemiological studies have also demonstrated consistent evidence for an association between lower urinary tract symptoms (LUTS)/benign prostatic hyperplasia (BPH) and sexual dysfunction, regardless of age, other comorbidities and various lifestyle factors [36]. The Multinational Survey on the Aging Male (MSAM-7) study – performed in the US, France, Germany, Italy, Netherlands, Spain, and the UK - systematically investigated the relationship between LUTS and sexual dysfunction in > 12,000 men aged 50-80 years. From the 83% of men who self-reported to be sexually-active, the overall prevalence of LUTS was 90%, with an overall prevalence of ED being 49%, and a reported complete absence of erection in 10% of patients. Moreover, the overall prevalence of ejaculatory disorders was 46% [37].

3.1.1.3 Pathophysiology

The pathophysiology of ED may be vasculogenic, neurogenic, anatomical, hormonal, drug-induced and/or psychogenic (Table 1) [19].

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, radical prostatectomy (RP), colorectal surgery, etc.)
• Surgery of the urethra (urethral stricture, urethroplasty, etc.)
Anatomical or structural
• Hypospadias, epispadias
• Micropenis
• Peyronie's disease
• Penile cancer
• Phimosis
Hormonal
• Hypogonadism
• Hyperprolactinaemia
• 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

3.1.1.3.1 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 men [38, 39]. Research has shown that 25-75% of men experience post-operative ED [40]. 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 (SR) has shown a significant advantage in favour of RARP in comparison with open retropubic RP in terms of 12-month potency rates [41], without significant differences 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 [42]. Overall, patient age and surgical volume, with the consequent ability to preserve the neurovascular bundles, seem to be the main factors in promoting the highest rates of post-operative potency [38, 39].

Pre-operative potency is a major factor associated with the recovery of erectile function after surgery. Patients being considered for nerve-sparing RP (NSRP) should ideally be potent pre-operatively [38, 39]. Overall, the temporal aspects are of major clinical importance in terms of post-operative recovery of erectile function. Available data confirm that post-operative erectile function recovery can also occur years following RP (up to 48 months). Likewise, it is shared opinion that the timing of post-operative therapy (any type) should be commenced as close as possible to the surgical procedure [38, 40].

ED is also a common sequela after external beam radiotherapy and brachytherapy for PCa [43, 44]. The mechanisms contributing to ED after prostate irradiation involve injury to the neurovascular bundles, penile vasculature, and cavernosal structural tissue [43, 44]. Alternative treatments for PCa including cryotherapy and high-intensity focused ultrasound (HIFU) are also associated with equivalent or higher rates of ED compared to surgery or radiation therapy [45, 46].

3.1.1.3.2 Summary of evidence on the epidemiology/aetiology/pathophysiology of ED

Summary of evidence	**LE**
ED is common worldwide.	2b
ED shares common 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

*3.1.2 **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.

*3.1.3 **Diagnostic evaluation***

3.1.3.1 Basic work-up

The first step in evaluating ED is always a detailed medical and sexual history of patients and, when available, their partners [47, 48]. In this context, taking a comprehensive medical history may reveal one of the many common disorders associated with ED [47, 48]. It is important to establish a relaxed atmosphere during history-taking. This will make it easier to i) ask questions about erectile function and other aspects of the sexual history; and, ii) to explain the diagnosis and therapeutic approach to the patient and his partner. Figure 1 lists the minimal diagnostic evaluation (basic work-up) in patients with ED.

3.1.3.1.1 Sexual history

The sexual history must include 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 [47, 49]. Validated psychometric questionnaires, such as the International Index for Erectile Function (IIEF) [50] or its short version the Sexual Health Inventory for Men (SHIM), help to assess the different sexual function domains (i.e. sexual desire, erectile function, orgasmic function, intercourse, and overall satisfaction), as well as the potential impact of a specific treatment modality.

Psychometric analyses also support the use of the erectile hardness score for the assessment of penile rigidity in practice and in clinical trials research [51]. In cases of clinical depression, the use of a 2-question scale for depression is recommended in the every day 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?” [52]. 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 [53].

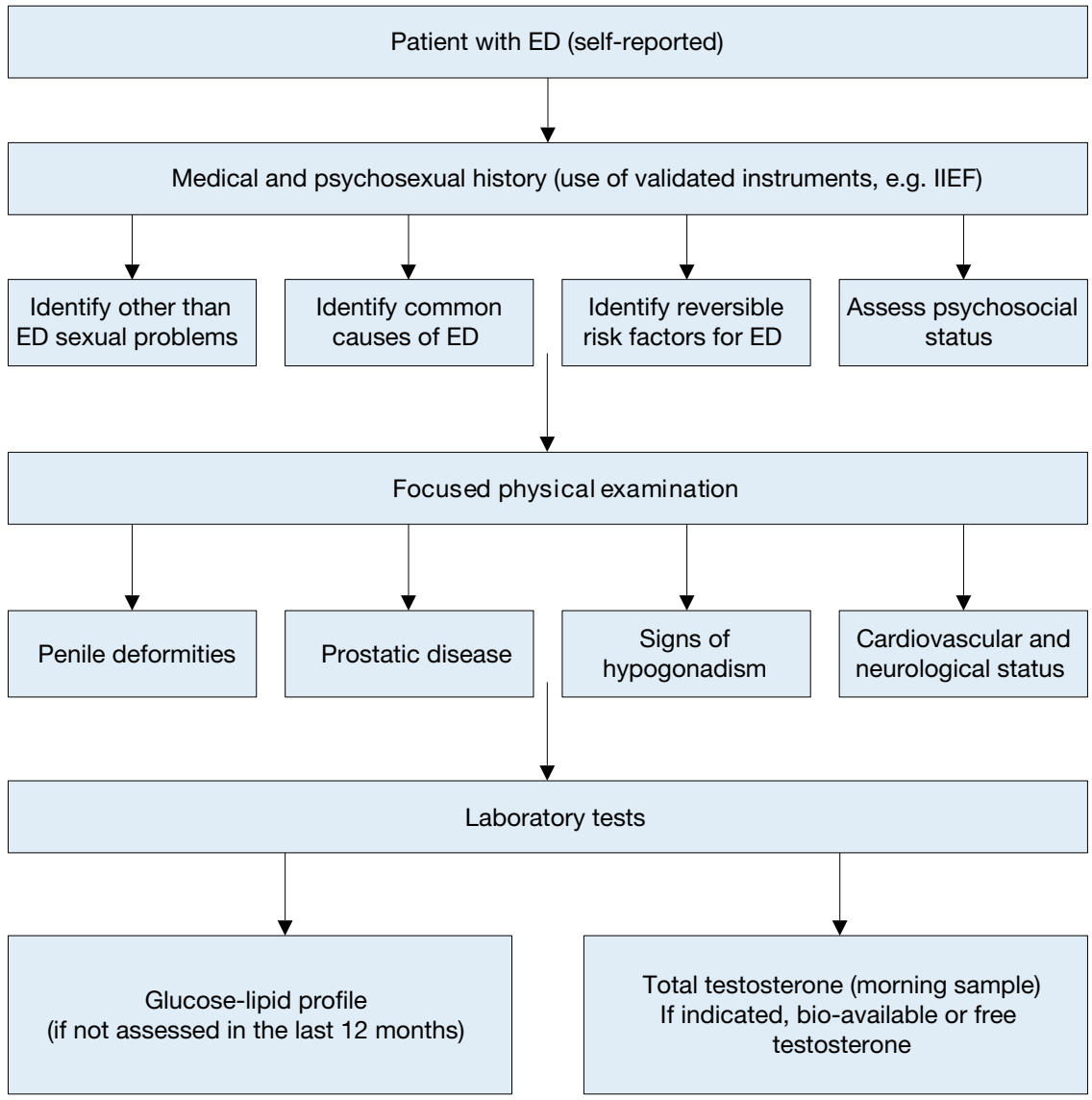
3.1.3.1.2 Physical examination

Every patient must be given a physical examination focused on the genitourinary, endocrine, vascular, and neurological systems [54, 55]. 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.

3.1.3.1.3 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 they have not recently been assessed. Hormonal tests include an early morning total testosterone. If indicated, the bioavailable or calculated-free testosterone may be needed to corroborate total testosterone measurements. However, the threshold of testosterone to maintain an erection is low and ED is usually a symptom of more severe cases of hypogonadism [31, 56-58]. For levels > 8 nmol/l the relationship between circulating testosterone and sexual functioning is very low [31, 56-58]. Additional laboratory tests may be considered in selected patients (e.g., prostate-specific antigen (PSA) [59]; prolactin, and luteinising hormone [60]. Although physical examination and laboratory evaluation of most men with ED may not reveal the exact diagnosis, these present opportunities to identify critical comorbid conditions that should not be missed [55].

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



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

3.1.3.1.4 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 [61] and women [62]. Overall, ED can improve the sensitivity of screening for asymptomatic CVD in men with diabetes [63, 64]. 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 [24, 25, 65].

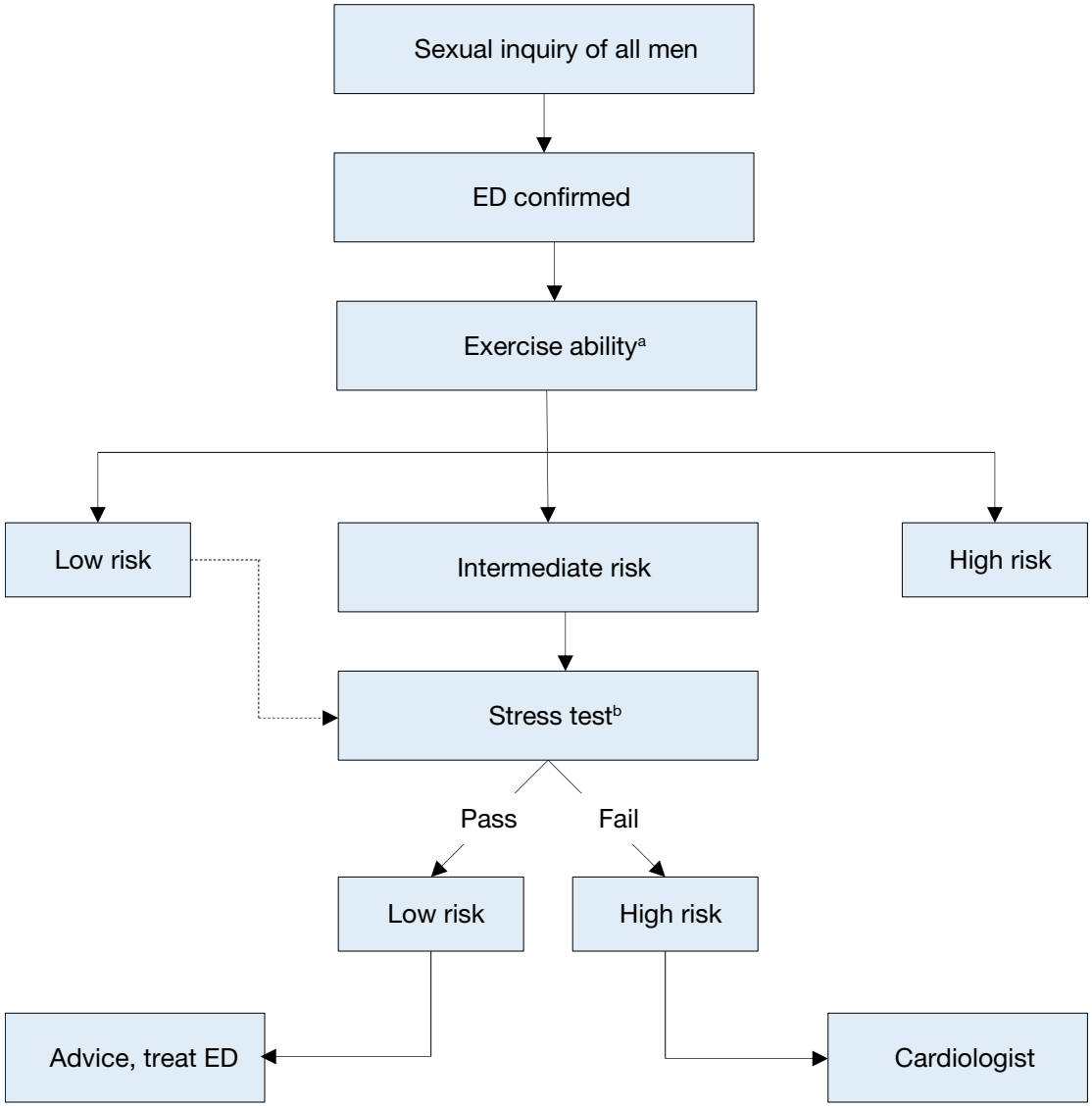
The EAU Guidelines for diagnosing and treating men with ED have been adapted from previously published recommendations from the Princeton Consensus conferences on sexual dysfunction and cardiac risk [24]. The Princeton Consensus (Expert Panel) Conference is dedicated to optimising sexual function and preserving cardiovascular health [66-68]. 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 [35].

Table 2: Cardiac risk stratification (based on 2nd and 3rd Princeton Consensus [67, 68]**)**

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 or II)	LVD/CHF (NYHA class III)	LVD/CHF (NYHA class 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) [68]



[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.*

3.1.3.1.4.1 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.

3.1.3.1.4.2 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.

3.1.3.1.4.3 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.

3.1.3.2 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).

3.1.3.2.1 Nocturnal penile tumescence and rigidity test
The nocturnal penile tumescence and rigidity assessment should be performed on at least two separate 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 [69].

3.1.3.2.2 Intracavernous injection test
The intracavernous injection test gives limited information about the 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 [70]. Overall, the test is inconclusive as a diagnostic procedure and a duplex Doppler study of the penis should be requested, if clinically warranted.

3.1.3.2.3 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 [71]. Further vascular investigation is unnecessary when a Duplex examination is normal.

3.1.3.2.4 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 [72].

3.1.3.2.5 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 [30], psychiatric assessment may be helpful before any organic assessment is carried out.

3.1.3.2.6 Penile abnormalities
Surgical correction may be needed in patients with ED and penile abnormalities (e.g. hypospadias, congenital curvature, or Peyronie’s disease with preserved rigidity).

3.1.3.3 Patient education - consultation and referrals
Consultation with the patient should include a discussion of the expectations and needs of both the patient and their sexual partner. 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 [73]. Patient and partner education is an essential part of ED management [73, 74].

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 to document end stage ED, sexual abuse).

Table 4: Specific diagnostic tests

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

3.1.3.4 Recommendations for the diagnostic evaluation of ED

Recommendations	**LE**	**GR**
Take a comprehensive medical and sexual history in every patient.	3	B
Use a validated questionnaire related to ED to assess all sexual function domains and the effect of a specific treatment modality.	3	B
Include a physical examination in the initial assessment of men with ED to identify underlying medical conditions that may be associated with ED.	4	B
Assess routine laboratory tests, including glucose-lipid profile and total testosterone, to identify and treat any reversible risk factors and lifestyle factors that can be modified.	4	B
Include specific diagnostic tests in the initial evaluation only in the presence of the conditions presented in table 3.	4	B

ED = erectile dysfunction.

*3.1.4 **Disease management***

3.1.4.1 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 it cannot be cured. The only exceptions are psychogenic ED, post-traumatic arteriogenic ED in young patients, and hormonal causes (e.g. hypogonadism and hyperprolactinaemia [57, 60]), 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 [73]. 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.

3.1.4.1.1 Lifestyle management of 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 [26, 75].

3.1.4.1.2 Erectile dysfunction after radical prostatectomy

Use of pro-erectile drugs following RP is important in achieving post-operative erectile function. Several trials have shown higher rates of erectile function recovery after RP in patients receiving any drug (therapeutic or prophylactic) for ED. Early compared with delayed erectile function treatment seems to impact on the natural healing time of potency [38]. Currently available therapeutic armamentarium follows the treatment algorithm for ED which is shown in Figure 3.

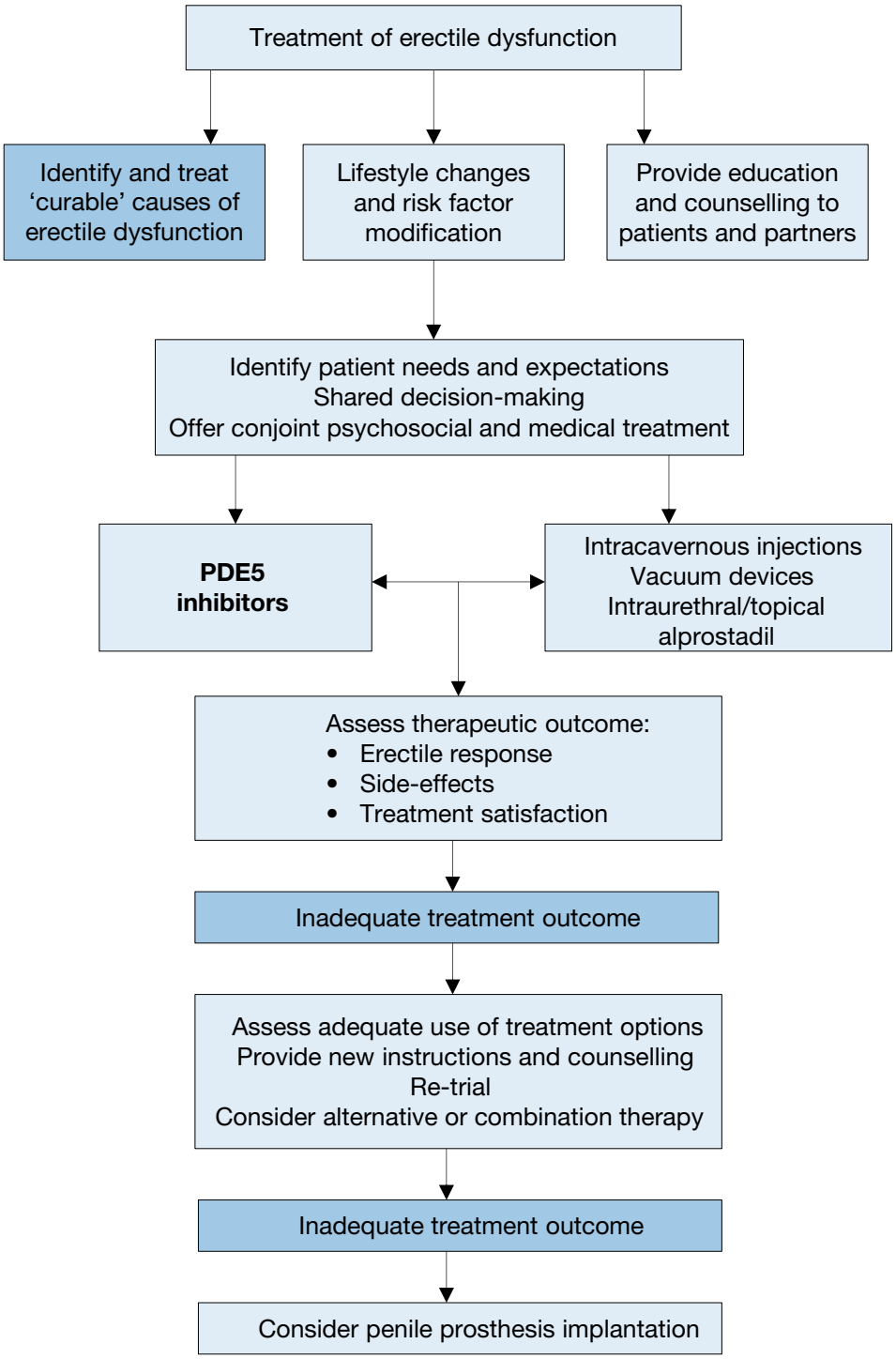
The management of post-RP ED has been revolutionised by the advent of phosphodiesterase 5 inhibitors (PDE5Is), with their demonstrated efficacy, ease of use, good tolerability, excellent safety, and positive impact on QoL. It must be emphasised that post-RP ED patients are poor responders to PDE5Is. However, PDE5Is are the first-line therapy in patients who have undergone nerve-sparing (NS) surgery regardless of the surgical technique used [38, 39]. 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 key factors in preserving post-operative erectile function [38, 39, 41]. 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 [38, 76]. Early use of high-dose sildenafil after RP has been suggested to be associated with preservation of smooth muscle within the corpora cavernosa [77]. Daily sildenafil also results in a greater return of spontaneous normal erectile function after RP compared to placebo following bilateral NSRP in patients who were fully potent before surgery [78].

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 [38, 79]. Similarly, vardenafil has been tested in patients with ED following NSRP in a randomised, multicentre, prospective, placebo-controlled study in North America [38, 80]. Following bilateral NSRP, erectile function 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 [38, 81]. Moreover, a randomised, double-blind, double-dummy trial in men $\leq$ 68 yr of age and normal pre-operative erectile function who underwent NSRP at 50 centres from nine European countries and Canada, compared tadalafil once daily with placebo [82]. Tadalafil was most effective on drug-assisted erectile function 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 erectile function and possibly protecting penile structural changes [82]. Unassisted erectile function was not improved after cessation of active therapy for 9 months [82]. Moreover, data suggested that the use of tadalafil once daily can significantly shorten the time to erectile function recovery post-NSRP compared to placebo [83].

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 erectile function domain score was $\geq$ 26, vardenafil was efficacious when used on demand, supporting a paradigm shift towards on-demand dosing with PDE5Is in post-RP ED [84]. 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 erectile function domain score with 100 and 200 mg avanafil vs. placebo ($p < 0.01$) [85]. 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 ($p < 0.01$) [85].

Historically, the treatment options for post-operative ED have included intracavernous injections [38, 86], urethral microsuppository [38, 87], vacuum device therapy [38, 88], and penile implants [38, 89, 90]. 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 3.1.4.3 and 3.1.4.4).

Figure 3: Treatment algorithm for erectile dysfunction



3.1.4.1.3 Causes of ED that can be potentially treated with a curative intent

3.1.4.1.3.1 Hormonal causes

The advice of an endocrinologist may be beneficial for managing patients with hormonal abnormalities [60]. 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) [60, 91]. When clinically indicated [33], testosterone supplementation (TS) (intramuscular, oral, or transdermal) is effective, but should only be used after other endocrinological causes for testicular failure have been excluded [31, 57, 92]. Before initiating TS, digital rectal examination, serum PSA test, haematocrit, liver function tests and lipid profile should be performed [31, 57]. Patients who are given TS should be monitored for clinical response, elevation of haematocrit and development of hepatic or prostatic disorders [31, 57]. TS is controversial in men with a history of PCa (LE: 4) [93]. 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 [94-99]. 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 [56]. However, a recent comprehensive SR 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 [100].

3.1.4.1.3.2 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 [101]. 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 [101].

3.1.4.1.3.3 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 [102].

3.1.4.2 First-line therapy
3.1.4.2.1 Oral pharmacotherapy
PDE5 hydrolyses cyclic guanosine monophosphate (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 followed by a penile erection [103]. Four potent selective PDE5Is have been approved by the European Medicines Agency (EMA) for the treatment of ED [104]. They are not initiators of erection and require sexual stimulation to facilitate an erection. Efficacy is defined as an erection with rigidity sufficient for penetration.

Sildenafil
Sildenafil was launched in 1998 and was the first PDE5I available on the market [105]. 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 delayed absorption. Efficacy may be maintained for up to 12 hours [106]. 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 [107, 108]. 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 [105]. 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. (GR: A, LE: 1). 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.

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 hours [109] and is not affected by food. It is administered in on-demand doses of 10 and 20 mg and also an alternative daily dose of 5 mg. 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 pre-marketing 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 [109]. 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 [110]. Daily tadalafil has also been licensed for the treatment of LUTS secondary to BPH. Therefore, it is useful in comorbid patients with ED and LUTS.

Vardenafil

Vardenafil became commercially available in March 2003 and is effective from 30 min after administration [110]. 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 [111]. Pharmacokinetic data of vardenafil are presented in Table 5. Adverse events (Table 6) are generally mild in nature and self-limited by continuous use [111]. 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 [111, 112]. Vardenafil significantly improved patient scores for IIEF, SEP2, SEP3, and GAQ and treatment satisfaction. Efficacy has been confirmed in post-marketing studies [111, 112]. 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 [112]. 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 [113]. The efficacy of vardenafil ODT has been demonstrated in several RCTs and did not seem to differ from the regular formulation [113, 114].

Avanafil

Avanafil is a highly-selective PDE5I that became commercially available in 2013 [115]. 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 [116]. 50, 100, and 200 mg doses have been approved for on-demand treatment of ED [115]. The recommended starting dose is 100 mg taken as needed approximately 15 to 30 minutes before sexual activity and the dosage may be adapted according to efficacy and tolerability [115, 117, 118]. 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 [115, 117]. Data from sexual attempts made within 15 minutes of dosing showed successful attempts in 64%, 67%, and 71% of 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 [117]. Pharmacokinetic data of avanafil are presented in Table 5 [115, 117]. Adverse events are generally mild in nature (Table 6) [115, 117]. 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 [114, 115]. Administration with food may delay the onset of effect compared with administration in the fasting state but avanafil can be taken with or without food. The efficacy of avanafil in many groups 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.

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.

Continuous use of PDE5 inhibitors

Animal studies have shown that chronic use of PDE5Is significantly improves or prevents the intracavernous structure alterations due to age, diabetes, or surgical damage [119-123]. No data exists for a human population. In humans, it has been clinically demonstrated that treatment with tadalafil 5 mg once daily in men complaining of ED of various severities was well tolerated and effective [124]. 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. 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 [124, 125]. 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 hours	2 hours	0.9 hours	0.5-0.75 hours
T1/2	2.6-3.7 hours	17.5 hours	3.9 hours	6-17 hours
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%

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

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.*

Safety issues for PDE5 inhibitors

Cardiovascular safety

Clinical trial results for 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 IV.

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) [126].

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 worsened by a background of antihypertensive medication, even when the patient is taking several antihypertensive agents.

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 hours following treatment with an α-blocker. A starting dose of 25 mg is recommended [107].
- 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 [110-112].
- Tadalafil is not recommended in patients taking doxazosin, but this is not the case for tamsulosin [109, 127].
- 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.

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.

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 [128]. The management of non-responders depends upon identifying the underlying cause.

Check that the patient has been using a licensed medication. There is a large counterfeit 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.

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 most common causes of incorrect drug use 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 medication is ineffective. Oral PDE5Is take different times to reach maximal plasma concentrations [106, 108, 113, 114, 129-131]. 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 minutes of oral ingestion [108, 113, 114, 129-131], most patients require a longer delay between taking the medication [111, 114, 132, 133]. Absorption of sildenafil can be delayed by a meal, and absorption of vardenafil can be delayed by a fatty meal [134]. Absorption of tadalafil is less affected provided there is enough delay between oral ingestion and an attempt at sexual intercourse [129]. 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 hours 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 [114-116].

It is possible to wait too long after taking the medication before attempting sexual intercourse. The half-life of sildenafil and vardenafil is about 4 hours, 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 hours. 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, erectile function can be effectively restored following re-administration of the relevant PDE5I [135-137].

Clinical strategies in patients correctly using a PDE5 inhibitor

There is controversial evidence suggesting that, in patients with testosterone deficiency, TS might improve response to a PDE5I [57, 138-140]. Modification of other risk factors may also be beneficial as discussed in section 3.1.4.1.1. Limited data suggest that some patients might respond better to one PDE5I than to another [141]. Although these differences might be explained by variations 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 [142]. If drug treatment fails, then patients should be offered an alternative therapy such as intracavernous injection therapy or use of a vacuum erection device (VED).

3.1.4.2.2 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% [143, 144]. Most men who discontinue use of VEDs do so within 3 months. Long-term use of VEDs decreases to 50-64% after 2 years [145]. The most common adverse events include pain, inability to ejaculate, petechiae, bruising, and numbness, which occur in < 30% of patients [144]. Serious adverse events (skin necrosis) can be avoided if patients remove the constriction ring within 30 minutes after intercourse.. 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 [143, 144].

3.1.4.2.3 Shockwave therapy

Recently, the use of low-intensity extracorporeal shock wave therapy (LI-SWT) was proposed as a novel treatment for ED [146]. 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 erectile function of men who respond to PDE5Is [147]. Moreover, there are preliminary data showing improvement in penile haemodynamics and endothelial function, as well as IIEF erectile function domain score in severe ED patients who are poor responders to PDE5Is [148, 149]. Current data are still limited and clear recommendations cannot be given.

3.1.4.3 Second-line therapy

Patients not responding to oral drugs may be offered intracavernous injections. The success rate is high (85%) [150, 151]. Intracavernous administration of vasoactive drugs was the first medical treatment for ED introduced more than 20 years ago [152, 153].

3.1.4.3.1 Intracavernous injections

3.1.4.3.1.1 Alprostadil

Alprostadil (CaverjectTM, Edex/ViridalTM) was the first and only drug approved for intracavernous treatment of ED [152, 153]. 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 minutes 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 the 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 [152, 153]. Complications of intracavernous alprostadil include penile pain (50% of patients reported pain only after 11% of total injections), prolonged erections (5%), priapism (1%), and fibrosis (2%) [152-154]. Pain is usually self-limited after prolonged use. It can be alleviated with the addition of sodium bicarbonate or local anaesthesia [152, 153, 155]. Cavernosal fibrosis (from a small haematoma) usually clears within a few months after temporary discontinuation of the injection programme. However, tunical fibrosis suggests early onset of Peyronie's disease and may indicate stopping intracavernous 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 [152, 153, 156, 157], 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 [158].

3.1.4.3.1.2 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. Papaverine is currently not licensed for the treatment of ED.
- 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 [159, 160]. 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 [161, 162]. 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 intracavernous therapies, is associated with a very low incidence of penile pain and virtually negligible risk of priapism [163].

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 [164]. However, combination therapy is associated with an increased 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 (LE: 4).

3.1.4.3.1.3 Intraurethral/topical alprostadil

A specific formulation of alprostadil (125-1000 µg) in a medicated pellet (MUSE™) has been approved as a treatment for ED [165]. 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 [165-167]. The application of a constriction ring at the root of the penis (ACTIS™) may improve efficacy [166, 167].

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 [151]. 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 administering alprostadil. It is a cream that includes a permeation enhancer in order to facilitate absorption of alprostadil (200 and 300µg) through the urethral meatus [168]. 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 [169]. Side-effects include penile erythema, penile burning and pain. Systemic side-effects are very rare. Topical alprostadil is approved and it is only available in some European countries.

3.1.4.4 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 [38, 89, 170, 171]. 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 at 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 [38, 89, 170, 171].

There are two main surgical approaches for penile prosthesis implantation: penoscrotal and infrapubic [170-173]. 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 penile 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 [38, 89, 170, 174-180]. 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 [38, 89, 181-183].

3.1.4.4.1 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 [89, 184, 185]. 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 and in high volume centres. The infection rate may be further reduced to 1-2% by implanting an antibiotic-impregnated prosthesis (AMS Inhibizone™) or hydrophilic-coated prosthesis (Coloplast Titan™) [89, 186-189]. 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 [15, 89, 170, 190-192]. 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 [190, 192, 193]. 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.

3.1.4.4.2 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.

3.1.4.5 Recommendations for the treatment of ED

Recommendations	**LE**	**GR**
Enact lifestyle changes and risk factor modification prior to or accompanying ED treatment.	1a	A
Start pro-erectile treatments at the earliest opportunity after RP.	1b	A
Treat a curable cause of ED first, when found.	1b	B
Use PDE5Is as first-line therapy.	1a	A
Assess all patients for inadequate/incorrect prescriptions and poor patient education, since they are the main causes of a lack of response to PDE5Is.	3	B
Use VED as a first-line therapy in well-informed older patients with infrequent sexual intercourse and comorbidity requiring non-invasive, drug-free management of ED.	4	C
Use intracavernous injections as second-line therapy.	1b	B
Use implantation of a penile prosthesis as third-line therapy.	4	C

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

3.1.4.6 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 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.

3.2 Premature ejaculation

*3.2.1 **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].

3.2.1.1 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 [194]. The highest prevalence rate of 31% (men aged 18-59 years) was found by the USA National Health and Social Life Survey (NHSLS) study [195]. 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 [196]. According to the four PE subtypes proposed by Waldinger *et al.* [197], the prevalence rates were 2.3% (lifelong PE), 3.9% (acquired PE), 8.5% (natural variable PE) and 5.1% (premature-like ejaculatory dysfunction) [198]. 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 of less than 2 minutes [199].

3.2.1.2 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 [200]. 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 [201]. 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 NHSLS, the prevalence of PE is not affected by age [195, 196], unlike ED, which increases with age. PE is not affected by marital or income status [195]. However, PE is more common in black men, Hispanic men and men from Islamic backgrounds [202, 203] and may be higher in men with a lower educational level [195, 201]. Other risk factors may include a genetic predisposition [204], poor overall health status and obesity [195], prostate inflammation [205, 206], thyroid hormone disorders [207], emotional problems and stress [195, 208], and traumatic sexual experiences [195, 201]. In the only published study on risk modification/prevention strategies [209], successful eradication of causative organisms in patients with chronic prostatitis and PE produced marked improvements in intravaginal ejaculatory latency time (IELT) and ejaculatory control compared to untreated patients [210].

3.2.1.3 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 [211, 212]. 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 [211, 213]. Sex drive and overall interest in sex does not appear to be affected by PE [214]. However, the partner's satisfaction with the sexual relationship decreases with increasing severity of the man's condition [215]. Despite the possible serious psychological and QoL consequences of PE, few men seek treatment. In the Global Study of Sexual Attitudes and Behaviors survey, 78% of men who self-reported a sexual dysfunction sought no professional help or advice for their sexual problems [201], with men more likely to seek treatment for ED than for PE [201]. In the Premature Ejaculation Prevalence and Attitudes survey, only 9% of men with self-reported PE consulted a doctor [196]. The main reasons for not discussing PE with their physician are 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 [216, 217]. Physicians need to encourage their patients to talk about PE.

3.2.2 ***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*' [218]. This DSM definition has been recently updated in the DSM V edition [219].
- 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*' [220].

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*' [200].

The International Society for Sexual Medicine (ISSM) has adopted a completely new definition of PE which is the first evidence-based definition [221]:
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 IELT [219].

Recently, two more PE syndromes have been proposed [222]:

- '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 [223].

3.2.3 ***Diagnostic evaluation***

Diagnosis of PE is based on the patient's medical and sexual history [224, 225]. 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 [226]. 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 [227]. There are several overlapping definitions of PE, with four shared factors (Table 7), resulting in a multidimensional diagnosis [228].

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

3.2.3.1 *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 [229, 230]. 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 [231]. 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 [232]. Self-estimated and stopwatch-measured IELT are interchangeable and correctly assign PE status with 80% sensitivity and 80% specificity [233]. 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 [234].

3.2.3.2 *PE assessment questionnaires*

The need to assess PE objectively has led to the development of several questionnaires based on the use of PROs [228]. 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 [235, 236]. 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 [237]. 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 [238]. Questionnaires are a significant step in simplifying the methodology of PE drug studies, although further cross-cultural validation is needed [239]. Other questionnaires used to characterise PE and determine treatment effects include the PEP [230], Index of Premature Ejaculation (IPE) (61) and Male Sexual Health Questionnaire Ejaculatory Dysfunction (MSHQ-EjD) [240]. Currently, their role is optional in everyday clinical practice.

3.2.3.3 *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 [224].

3.2.3.4 *Recommendations for the diagnostic evaluation of PE*

Recommendations	LE	GR
Perform the diagnosis and classification of PE based on medical and sexual history, which should include assessment of IELT (self-estimated), perceived control, distress and interpersonal difficulty due to the ejaculatory dysfunction.	1a	A
Do not use stopwatch-measured IELT in clinical practice.	2a	B
Do not use patient-reported outcomes (PROs) in clinical practice.	3	C
Include physical examination in the initial assessment of PE to identify anatomical abnormalities that may be associated with PE or other sexual dysfunctions, particularly ED.	3	C
Do not perform routine laboratory or neurophysiological tests. 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.

3.2.4 ***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).

3.2.4.1 Psychological/behavioural strategies

Behavioural strategies mainly include the 'stop-start' programme developed by Semans [241] 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 [242].

Psychological factors may be associated with PE and should be addressed in treatment. These factors 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 [243, 244]. 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 [245]. Furthermore, clinical experience suggests that improvements achieved with these techniques are generally not maintained long-term [246, 247]. Behavioural therapy may be most effective when used to 'add value' to medical interventions. Combination of dapoxetine and behavioural treatment was more effective than dapoxetine alone in patients with lifelong PE in a prospective, randomised trial [248]. Validated assessment instruments need to be used as end-points. Longer follow-up periods are necessary to confirm these findings.

3.2.4.2 Pharmacotherapy

3.2.4.2.1 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) [249]. Dapoxetine has been investigated in 6,081 subjects to date [250]. 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 [251, 252]. 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 [252]. 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 [232]. There was no indication of an increased risk of suicidal ideation or suicide attempts and little indication of withdrawal symptoms with abrupt dapoxetine cessation [253].

Regarding a combination of PDE5Is with dapoxetine, the addition of dapoxetine to a given regimen of PDE5Is may increase the risk of possible prodromal symptoms that may progress to syncope compared to both PDE5Is inhibitors and selective serotonin re-uptake inhibitors (SSRIs) administered alone. Generally, when dapoxetine is co-administered with a PDE5Is, it is well tolerated, with a safety profile consistent with previous phase 3 studies of dapoxetine alone [254]. 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 [255].

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 5-HT 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 [256].

3.2.4.2.2 Off-label use of antidepressants: SSRIs and clomipramine

Ejaculation is commanded by a spinal ejaculation generator [257, 258] under excitatory or inhibitory influences from the brain and the periphery [259]. 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 [256].

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 one to two weeks to be effective in PE [256]. Administration of chronic SSRIs causes prolonged increases in synaptic cleft serotonin, which desensitises the 5-HT1A and 5-HT1B receptors [260]. Clomipramine, the most serotoninergic tricyclic antidepressant, was first reported in 1973 as an effective PE treatment [261]. SSRIs have revolutionised treatment of PE, but they have also changed our understanding of PE since the first publication on paroxetine in 1970 [262]. 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 [263]. 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 [264, 265].

Ejaculation delay may start a few days after drug intake, but it is more evident after one to two 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 six to twelve months [261]. Common side-effects of SSRIs include fatigue, drowsiness, yawning, nausea, vomiting, dry mouth, diarrhoea and perspiration; which are usually mild and gradually improve after two to three weeks [223, 251]. Decreased libido, anorgasmia, anejaculation and ED have also been reported.

Because of a theoretical risk of suicidal thoughts 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 thoughts. 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 [232].

In one controlled trial, on-demand use of clomipramine (but not paroxetine), three to five hours before intercourse, was reported to be efficacious, though IELT improvement was inferior compared to daily treatment with the same drug [266]. However, on-demand treatment may be combined with an initial trial of daily treatment or concomitant low-dose daily treatment reducing adverse effects [267, 268]. 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.

3.2.4.2.3 Topical anaesthetic agents

The use of local anaesthetics to delay ejaculation is the oldest form of pharmacological therapy for PE [269]. Several trials [270, 271] support the hypothesis that topical desensitising agents reduce the sensitivity of the glans penis thereby delaying ejaculatory latency, but without adversely affecting the sensation of ejaculation.

3.2.4.2.3.1 Lidocaine-prilocaine cream

In a randomised, double-blind, placebo-controlled trial, lidocaine-prilocaine cream increased the IELT from one minute in the placebo group to 6.7 minutes in the treatment group [272]. 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) [273]. 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 [272]. 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 contra-indicated in patients or partners with an allergy to any ingredient in 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 ($p < 0.001$) [274].

3.2.4.2.3.2 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 five to seven hours. For analgesic purposes, tramadol can be administered between three and four 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 [275]. 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 [276].

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 [277]. 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.

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.

3.2.4.2.4 Other drugs

3.2.4.2.4.1 Phosphodiesterase type 5 inhibitors

There is only one well-designed, randomised, double-blind, placebo-controlled study comparing sildenafil to placebo [278]. 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 [279].
- Sildenafil combined with sertraline improved IELT and satisfaction significantly vs. sertraline alone [280].
- Sildenafil combined with paroxetine and psychological and behavioural counselling significantly improved IELT and satisfaction in patients in whom other treatments failed [281].
- Finally, sildenafil combined with behavioural therapy significantly improved IELT and satisfaction vs. behavioural therapy alone [282].

There are very limited data on the efficacy of other PDE5Is (tadalafil and vardenafil) [283, 284]. The role of PDE5Is in PE patients without ED is not established, with only minimal double-blind placebo controlled data available.

3.2.4.3 Summary of evidence on the epidemiology/aetiology/pathophysiology of ED

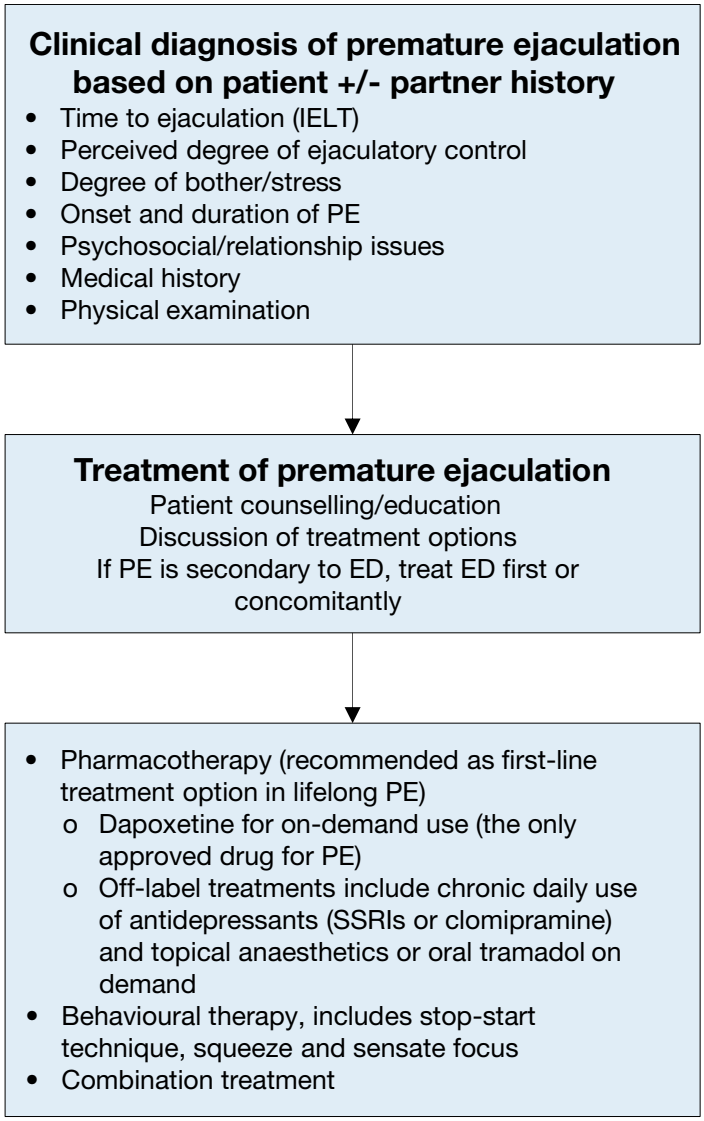
Summary of evidence	**LE**
Pharmacotherapy includes either dapoxetine on demand (a short-acting SSRI that is the only approved pharmacological treatment for premature ejaculation) or other off-label antidepressants, i.e. daily SSRIs and clomipramine, that are not amenable to on-demand dosing. With all antidepressant treatment for premature ejaculation, recurrence is likely after treatment cessation.	1a

3.2.4.4 Recommendations for the treatment of PE

Recommendations	**LE**	**GR**
Treat erectile dysfunction, other sexual dysfunction or genitourinary infection (e.g. prostatitis first.	2a	B
Use pharmacotherapy as first-line treatment of lifelong premature ejaculation.	1a	A
Use off-label topical anaesthetic agents as a viable alternative to oral treatment with SSRIs.	1b	A
Use tramadol on demand as a weak alternative to SSRI's.	2a	B
Do not use PDE5Is in patients with PE without ED.	3	C
Use psychological/behavioural therapies in combination with pharmacological treatment in the management of acquired premature ejaculation.	3	C

SSRI = selective serotonin reuptake inhibitor.

Figure 4: Management of Premature Ejaculation*



* Adapted from Lue *et al.* 2004 [285].
ED = erectile dysfunction; PE = premature ejaculation; IELT = intravaginal ejaculatory latency time; SSRI = selective serotonin receptor inhibitor.

3.3 Penile curvature

*3.3.1 **Congenital penile curvature***

3.3.1.1 Epidemiology/aetiology/pathophysiology

Congenital curvature is rare: one well-performed study reports an incidence of less than 1% [286] while there are reports from studies with poor quality which claim that it is more common with prevalence rates of 4-10% in the absence of hypospadias [287].

Congenital penile curvature results from disproportionate development of the tunica albuginea of the corporal bodies and is not associated with urethral malformation. In the majority of cases the curvature is ventral but it can also be lateral and rarely dorsal.

3.3.1.2 Diagnostic evaluation

Taking a medical and sexual history is usually sufficient to establish the diagnosis of congenital penile curvature. Patients usually present after reaching puberty as the curvature becomes more apparent with erections, and severe curvature can make intercourse difficult or impossible. Physical examination during erection (autophotograph or after intracavernous injection of vasoactive drugs) is useful to document curvature and exclude other pathologies [288].

3.3.1.3 Disease management

The treatment of this disorder is surgical correction deferred until after puberty. Surgical treatments for congenital penile curvature generally share the same principles as in Peyronie's disease (presented in detail in the next section). Nesbit procedure with excision of an ellipse of the tunica albuginea is the gold standard of treatment but many other techniques have been described and employed. Plication techniques are widely used including techniques producing a de-rotation of the corporal bodies [289]. Most of the time, dissection of the dorsal neurovascular bundle is required in order to avoid loss of sensation and ischaemic lesions in the glans penis [290-292].

3.3.1.4 Summary of evidence and recommendation for congenital penile curvature

Summary of evidence	LE
Medical and sexual history are usually sufficient to establish the diagnosis of congenital penile curvature. Physical examination during erection is useful for documentation of the curvature and exclusion of other pathologies.	3
Surgery is the only treatment option which is deferred until after puberty and can be performed at any time in adult life.	3

Recommendation	LE	GR
Use Nesbit and other plication techniques for the treatment of congenital penile curvature in patients who undergo surgery.	3	B

3.3.2 ***Peyronie's Disease***

3.3.2.1 Epidemiology/aetiology/pathophysiology

3.3.2.1.1 Epidemiology

Epidemiological data on Peyronie's (PD) disease are limited. Prevalence rates of 0.4-9% have been published, with a higher prevalence in patients with erectile dysfunction (ED) and diabetes [293-300]. The typical age of a patient with PD is 55-60 years.

3.3.2.1.2 Aetiology

The aetiology of Peyronie's disease is unknown. However, an insult (repetitive microvascular injury or trauma) to the tunica albuginea is the most widely accepted hypothesis on the aetiology of the disease [301]. A prolonged inflammatory response will result in the remodelling of connective tissue into a fibrotic plaque [301-303]. Penile plaque formation can result in curvature which, if severe, may prevent penetrative sexual intercourse.

3.3.2.1.3 Risk factors

The most commonly associated comorbidities and risk factors are diabetes, hypertension, lipid abnormalities, ischaemic cardiopathy, ED, smoking, and excessive consumption of alcohol [296, 300, 304, 305]. Dupuytren's contracture is more common in patients with Peyronie's disease affecting 9-39% of patients [297, 306-308] while 4% of patients with Dupuytren's contracture reported Peyronie's disease [307].

3.3.2.1.4 Pathophysiology

Two phases of the disease can be distinguished [309]. The first is the acute inflammatory phase, which may be associated with pain in the flaccid state or painful erections and a palpable nodule or plaque in the tunica of the penis; typically a penile curvature begins to develop. The second is the fibrotic phase (chronic phase) with the formation of hard palpable plaques that can be calcified, which also results in disease stabilisation and no further progressive curvature. With time, penile curvature is expected to worsen in 30-50% of patients or stabilise in 47-67% of patients, while spontaneous improvement has been reported by only 3-13% of patients [304, 310, 311]. Pain is present in 35-45% of patients during the early stages of the disease [312]. Pain tends to resolve with time in 90% of men, usually during the first 12 months after the onset of the disease [310, 311].

In addition to the physiological and functional alteration of the penis, affected men also suffer significant distress. Validated mental health questionnaires have shown that 48% of men with Peyronie's disease have mild or moderate depression, sufficient to warrant medical evaluation [313].

3.3.2.1.5 Summary of evidence on Peyronie's disease

Summary of evidence	LE
Peyronie's disease is a connective tissue disorder, characterised by the formation of a fibrotic lesion or plaque in the tunica albuginea, which leads to penile deformity.	2b
The contribution of associated comorbidities or risk factors (e.g. diabetes, hypertension, lipid abnormalities and Dupuytren's contracture) to the pathophysiology of Peyronie's disease is still unclear.	3
Two phases of the disease can be distinguished. The first phase is the acute inflammatory phase (painful erections, 'soft' nodule/plaque), and the second phase is the fibrotic/calcifying phase with formation of hard palpable plaques (disease stabilisation).	2b
Spontaneous resolution is uncommon (3-13%) and most patients experience disease progression (30-50%) or stabilisation (47-67%). Pain is usually present during the early stages of the disease but tends to resolve with time in 90% of men.	2a

3.3.2.2 Diagnostic evaluation

The aim of the initial evaluation is to provide information on the presenting symptoms and their duration (erectile pain, palpable nodules, curvature, length, rigidity, and girth) and erectile function status. It is mandatory to obtain information on the distress provoked by the symptoms and the potential risk factors for ED and Peyronie's disease. A disease-specific questionnaire (PDQ) has been designed to collect data, and it has been validated for use in clinical practice [314].

Major attention should be given to whether the disease is still active, as this will influence medical treatment or the timing of surgery. Patients who are still likely to have an active disease are those with a short symptom duration, pain during erection, or a recent change in penile curvature. Resolution of pain and stability of the curvature for at least three months are well-accepted criteria of disease stabilisation and patients' referral for surgical intervention when indicated [310].

The examination should start with a routine genitourinary assessment, which is then extended to the hands and feet for detecting possible Dupuytren's contracture or Ledderhose scarring of the plantar fascia [311]. Penile examination is performed to assess the presence of a palpable node or plaque. There is no correlation between plaque size and the degree of curvature [315]. Measurement of penile length during erection is important because it may have impact on the subsequent treatment decisions [316].

An objective assessment of penile curvature with an erection is mandatory. This can be obtained by a home (self) photograph of a natural erection (preferably) or using a vacuum-assisted erection test or an intracavernous injection using vasoactive agents [317]. Erectile function can be assessed using validated instruments such as the IIEF although this has not been validated in Peyronie's disease patients [33]. ED is common in patients with Peyronie's disease (> 50%) but it is important to define whether it pre- or post-dates the onset of Peyronie's disease. It is mainly due to penile vascular disease [19, 30]. The presence of ED and psychological factors may impact on the treatment strategy [318].

Ultrasound (US) measurement of the plaque's size is inaccurate and it is not recommended in everyday clinical practice [319]. Doppler US may be required for the assessment of vascular parameters [318].

3.3.2.2.1 Summary of evidence and recommendations for the diagnosis of Peyronie's disease

Summary of evidence	LE
US measurement of the plaque's size is inaccurate and operator dependent.	3
Doppler US is required to ascertain vascular parameters associated with erectile dysfunction.	2a

Recommendations	LE	GR
In the medical and sexual history in patients with Peyronie's disease, include duration of the disease, penile pain, change of penile deformity, difficulty in vaginal intromission due to deformity, and erectile dysfunction.	2b	B
In the physical examination, include assessment of palpable plaques, penile length, extent of curvature (self-photograph, vacuum-assisted erection test or pharmacological-induced erection) and any other possibly related diseases (Dupuytren's contracture, Ledderhose disease).	2a	B
Do not use PDQ in everyday clinical practice.	2a	B
Do not use US measurement of plaque size in everyday clinical practice.	3	C
Use Doppler US only in the case of diagnostic evaluation of ED, to ascertain vascular parameters associated with erectile dysfunction.	2a	B

PDQ = Peyronie's disease-specific questionnaire; US = ultrasound.

3.3.2.3 Disease management

3.3.2.3.1 Non-operative treatment

Conservative treatment of Peyronie's disease is primarily focused on patients in the early stage of the disease [311, 320]. Several options have been suggested, including oral pharmacotherapy, intralesional injection therapy and other topical treatments (Table 8). Shockwave treatment of calcified plaques and clostridial collagenase injection in patients with densely fibrotic or calcified plaques have been also suggested [309, 321]. Clostridium collagenase is the only drug approved for the treatment of Peyronie's disease by the FDA. No single drug has been approved by the EMA for the treatment of Peyronie's disease at this time. The results of the studies on conservative treatment for Peyronie's disease are often contradictory making it difficult to provide recommendations in the everyday, real-life setting. This is due to several methodological problems including uncontrolled studies, limited number of patients treated, short-term follow-up and different outcome measures [321]. Moreover, the efficacy of conservative treatment in distinct patient populations in terms of early (inflammatory) or late (fibrotic) phases of the disease is not yet available.

Table 8: Non-operative treatments for Peyronie's disease

Oral treatments
Vitamin E
Potassium para-aminobenzoate (Potaba)
Tamoxifen
Colchicine
Acetyl esters of carnitine
Pentoxifylline
Phosphodiesterase type 5 inhibitors (PDE5i)
Intralesional treatments
Steroids
Verapamil
Clostridium collagenase
Interferon
Topical treatments
Verapamil
Iontophoresis
Extracorporeal shock wave treatment (ESWT)
Traction devices
Vacuum devices

3.3.2.3.1.1 Oral treatment

Vitamin E

Vitamin E (tocopherol, a fat-soluble compound that acts as a natural antioxidant to reduce the number of oxygen-free radicals produced in energy metabolism) is commonly prescribed by the majority of urologists at once or twice daily doses of 400 IU because of its wide availability, low cost and safety [322]. A double-blind, placebo-controlled crossover study failed to show a significant effect on penile deformity or plaque size [323]. Moreover, there is conflicting evidence as to long-term cardiovascular effects of vitamin E usage at large doses, which urologists use for penile deformity treatment [324].

Potassium para-aminobenzoate (Potaba)
Potassium para-aminobenzoate is thought to exert an antifibrotic effect through an increase in oxygen uptake by the tissues, a rise in the secretion of glycosaminoglycans, and an enhancement of the activity of monoamine oxidases [325]. Preliminary studies reported an improvement in penile curvature, penile plaque size, and penile pain during erection [326]. In a prospective double-blinded controlled study in 41 patients with Peyronie's disease, Potaba (12 g/day for 12 months) improved penile pain significantly, but not penile curvature or penile plaque size [327]. In another similar study in 103 patients with Peyronie's disease, Potaba decreased penile plaque size significantly, but had no effect on penile curvature or penile pain [328]. However, the pre-existing curvature under Potaba remained stable, suggesting a protective effect on the deterioration of penile curvature. Treatment-related adverse events are nausea, anorexia, pruritus, anxiety, chills, cold sweats, confusion and difficulty concentrating, but no serious adverse events were reported [329].

Tamoxifen
Tamoxifen is a non-steroidal oestrogen receptor antagonist modulating transforming growth factorβ1 (TGFβ1) secretion by fibroblasts. Preliminary studies reported that tamoxifen (20 mg twice daily for three months) improved penile pain, penile curvature, and reduced the size of penile plaque [330]. However, a placebo-controlled, randomised study (in only 25 patients, at a late stage of the disease with a mean duration of 20 months) using the same treatment protocol, failed to show any significant improvement in pain, curvature, or plaque size in patients with Peyronie's disease [331].

Colchicine
Colchicine has been introduced into the treatment of Peyronie's disease on the basis of its anti-inflammatory effect [332]. Clinical data should be interpreted with caution since they come from only uncontrolled studies. Preliminary results showed that half of the men given colchicine (0.6-1.2 mg daily for three to five months) found that painful erections and penile curvature improved, while penile plaque decreased or disappeared in 50% out of 24 men [333]. In another study in 60 men (colchicine 0.5-1 mg daily for 3-5 months with escalation to 2 mg twice daily), penile pain resolved in 95% and penile curvature improved in 30% [332]. Similar results have been reported in another uncontrolled retrospective study in 118 patients [334]. Reported treatment-related adverse events with colchicine are gastrointestinal effects (nausea, vomiting, diarrhoea) that can be improved with dose escalation [332].

The combination of vitamin E and colchicine (600 mg/day and 1 mg every twelve hours, respectively) for six months in patients with early-stage Peyronie's disease resulted in significant improvement in plaque size and curvature, but not in pain compared to ibuprofen 400 mg/day for 6 months [335].

Acetyl esters of carnitine
Acetyl-L-carnitine and propionyl-L-carnitine are proposed to inhibit acetyl coenzyme-A and produce an antiproliferative effect on human endothelial cells. This may eventually suppress fibroblast proliferation and collagen production, thus reducing penile fibrosis. In a randomised, double-blind study in 48 patients with early-stage Peyronie's disease, patients were randomised to acetyl-L-carnitine (1 g twice daily) compared to tamoxifen (20 mg twice daily). After 3 months, acetyl-L-carnitine was significantly more effective than tamoxifen in pain and curvature reduction and inhibition of disease progression, but not in penile plaque size reduction (both drugs significantly reduced plaque size) [336]. Tamoxifen induced significantly more side-effects.

Finally, the combination of intralesional verapamil (10 mg weekly for ten weeks) with propionyl-l-carnitine (2 g/day for 3 months) significantly reduced penile curvature, plaque size, and disease progression compared to intralesional verapamil combined with tamoxifen (40 mg/day) for three months [337].

Pentoxifylline
Pentoxifylline is a non-specific phosphodiesterase inhibitor which down-regulates TGFβ1 and increases fibrinolytic activity [338]. Moreover, an increase of NO levels may be effective in preventing progression of Peyronie's disease or reversing fibrosis [339]. Preliminary data from a case report showed that pentoxifylline (400 mg three times daily for six months) improved penile curvature and the findings on US of the plaque [339]. In another study in 62 patients with Peyronie's disease, pentoxifylline treatment for six months appeared to stabilise or reduce calcium content in penile plaques [340].

Phosphodiesterase type 5 inhibitors
The rationale for the use of PDE5Is in Peyronie's disease comes from animal studies showing that they can reduce the collagen/smooth muscle and collagen III/I ratios and increase the apoptotic index in the Peyronie's disease-like plaque [341]. In a retrospective controlled study, daily tadalafil (2.5 mg for six months) resulted in

statistically significant ($p < 0.05$) resolution of septal scar in 69% of patients compared to 10% in the control group (no treatment). However, this study included patients with isolated septal scars without evidence of penile deformity [342]. Therefore, no recommendation can be given for PDE5Is in patients with Peyronie's disease.

3.3.2.3.1.2 Intralesional treatment

Injection of pharmacologically active agents directly into penile plaques represents another treatment option. It allows a localised delivery of a particular agent that provides higher concentrations of the drug inside the plaque. However, delivery of the compound to the target area is difficult to ensure particularly when a dense or calcified plaque is present.

Steroids

Intralesional steroids are thought to act by opposing the inflammatory milieu responsible for Peyronie's plaque progression via inhibition of phospholipase A2, suppression of the immune response and by decreasing collagen synthesis [343]. In small, non-randomised, studies, a decrease in penile plaque size and pain resolution was reported [344, 345]. In the only single-blind, placebo-controlled study with intralesional administration of betamethasone, no statistically significant changes in penile deformity, penile plaque size, and penile pain during erection were reported [346]. Adverse effects include tissue atrophy, thinning of the skin and immunosuppression [344].

Verapamil

The rationale for intralesional use of verapamil (a calcium channel antagonist) in patients with Peyronie's disease is based on in-vitro research [347, 348]. A number of studies have reported that intralesional verapamil injection may induce a significant reduction in penile curvature and plaque volume [349-353]. These findings suggested that intralesional verapamil injections could be advocated for the treatment of non-calcified acute phase or chronic plaques to stabilise disease progression or possibly reduce penile deformity, although large scale, placebo-controlled trials have not yet been conducted [352]. Side-effects are uncommon (4%). Minor side-effects include nausea, light-headedness, penile pain, and ecchymosis [352]. However, in the only randomised, placebo-controlled study, no statistically significant differences on plaque size, penile curvature, penile pain during erection or plaque 'softening' were reported [354]. Younger age and larger baseline penile curvature were found to be predictive of favourable curvature outcomes in a case-series study [355].

Clostridium collagenase

Clostridium collagenase (CCH) is a chromatographically purified bacterial enzyme that selectively attacks collagen, which is known to be the primary component of the Peyronie's disease plaque [356-358]. Clostridium collagenase is now approved by the the FDA for PD in adult men with a palpable plaque and a curvature deformity of at least 30° at the start of therapy. Findings from two independent, double-blind, placebo controlled studies, reveal the efficacy and tolerability of CCH for improving the co-primary outcomes of physical penile curvature and the psychological subject reported PD symptom bother domain of the PDQ in adults with PD. Participants were given up to four treatment cycles of CCH or placebo and were then followed for 52 weeks. Overall, of 551 treated men with CCH 60.8% were global responders compared with 29.5% of 281 who received placebo. The most commonly reported side-effects were penile pain, penile swelling, and ecchymosis at the site of injection [359]. Of note, CCH is available in the US only through a restricted programme under a Risk Evaluation and Mitigation Strategy (REMS) because of the risks of serious adverse reactions, including penile fracture and other serious penile injury. CCH should be administered by a healthcare professional who is experienced in the treatment of male urological diseases. The REMS requires participating healthcare professionals to be certified within the programme by enrolling and completing training in the administration of CCH treatment for Peyronie's disease. The REMS also requires healthcare facilities to be certified within the program and ensure that CCH is dispensed only for use by certified healthcare professionals [360].

Interferon

Interferon α-2b has been shown to decrease fibroblast proliferation, extracellular matrix production and collagen production from fibroblasts and improved the wound healing process from Peyronie's disease plaques in-vitro [361]. Intralesional injections (5×10^6 units of interferon α-2b in 10 mL saline, two times per week for twelve weeks) significantly improved penile curvature, plaque size and density, and pain compared to placebo [362, 363]. Side-effects include myalgias, arthralgia, sinusitis, fever and flu-like symptoms. They can be effectively treated with non-steroidal anti-inflammatory drugs before interferon injection.

3.3.2.3.1.3 Topical treatments

Topical verapamil

There is no evidence that topical treatments applied to the penile shaft result in adequate levels of the active compound within the tunica albuginea. Verapamil gel has been used in this context [364]. Iontophoresis – now known as transdermal electromotive drug administration (EMDA) - has been introduced to try and overcome limitations on the local uptake of the drugs themselves. Small studies using Iontophoresis with verapamil 5 mg and dexamethasone 8 mg resulted in inconsistent results [365, 366].

Extracorporeal shock wave treatment

The mechanism of action involved in shock wave treatment (ESWT) for Peyronie's disease is still unclear, but there are two hypotheses. In the first hypothesis, shock wave therapy works by directly damaging and remodelling the penile plaque. In the second hypothesis, shock wave lithotripsy increases the vascularity of the area by generating heat resulting in an inflammatory reaction, with increased macrophage activity causing plaque lysis and eventually leading to plaque resorption [367]. Most uncontrolled studies failed to show significant improvements in patients with Peyronie's disease [368-370]. In a prospective, randomised, double-blind, placebo-controlled study, four weekly treatment sessions of ESWT, with each session consisting of 2,000 focused shock waves, resulted in significant improvement only for penile pain [371].

Traction devices

The application of continuous traction in Dupuytren's contracture increases the activity of degradative enzymes [372]. This initially leads to a loss of tensile strength and ultimately to solubilisation. It is followed by an increase in newly synthesised collagen [372]. This concept has been applied in an uncontrolled study, including ten patients with Peyronie's disease. The FastSize Penile Extender was applied as the only treatment for two to eight hours/day for six months [89]. Reduced penile curvature of 10-40° was found in all men with an average reduction of 33% (range: 51-34º). The stretched penile length increased 0.5-2.0 cm and the erect girth increased 0.5-1.0 cm, with a correction of hinge effect in four out of four men. Treatment can be uncomfortable and inconvenient due to use of the device two to eight hours daily for an extended period, but has been shown to be tolerated by highly motivated patients [307]. There were no serious adverse events, including skin changes, ulcerations, hypoesthesia or diminished rigidity.

In another prospective study, there was a significant reduction in penile curvature (mean 20° reduction). Erectile function and erection hardness also improved significantly. The percentage of patients who were not able to achieve penetration decreased from 62% to 20% ($p < 0.03$). Importantly, the need for surgery was reduced in 40% of patients who would otherwise have been candidates for surgery and simplified the complexity of the surgical procedure (from grafting to plication) in one in three patients [373].

Vacuum devices

The application of vacuum devices follows the same principles as traction devices with the drawback of being non-continuous precluding remodelling of the plaque. Their efficacy has been assessed in an uncontrolled study (31 patients completed the study) [374]. Half of the patients were satisfied with the outcome and the remaining had their curvature corrected surgically.

3.3.2.3.1.4 Summary of evidence and recommendations for non-operative treatment of Peyronie's disease

Summary of evidence	LE
Conservative treatment for Peyronie's disease is primarily aimed at treating patients in the early stage of the disease.	3
Oral treatment with potassium para-aminobenzoate may result in a significant reduction in penile plaque size and penile pain as well as penile curvature stabilisation.	1b
Intralesional treatment with verapamil may induce a significant reduction in penile curvature and plaque volume.	1b
Intralesional treatment with clostridium collagenase showed significant decreases in the deviation angle, plaque width and plaque length.	1b
Intralesional treatment with interferon may improve penile curvature, plaque size and density, and pain.	1b
Topical verapamil gel 15% may improve penile curvature and plaque size.	1b
Iontophoresis with verapamil 5 mg and dexamethasone 8 mg may improve penile curvature and plaque size.	1b
Extracorporeal shock-wave treatment does not improve penile curvature and plaque size, but it may be offered for penile pain.	1b
Intralesional treatment with steroids is not associated with significant reduction in penile curvature, plaque size or penile pain.	2b

Recommendations	LE	GR
Use conservative treatment in patients not fit for surgery or when surgery is not acceptable to the patient.	3	C
Do not use extracorporeal shock-wave treatment to improve penile curvature and plaque size.	1b	C
Use penile traction devices and vacuum devices to reduce penile deformity and increase penile length.	2b	C
Do not use intralesional treatment with steroids to reduce penile curvature, plaque size or pain.	1b	B
Do not use oral treatment with vitamin E and tamoxifen for significant reduction in penile curvature or plaque size.	2b	B
Do not offer other oral treatments (acetyl esters of carnitine, pentoxifylline, colchicine).	3	C

3.3.2.3.2 Surgical treatment

Although conservative treatment for Peyronie's disease should resolve painful erections in most men, only a small percentage will experience any significant straightening of the penis. The aim of surgery is to correct curvature and allow satisfactory intercourse. Surgery is indicated in patients with penile curvature that does not allow satisfactory intercourse and which is associated with sexual bother [73]. Patients must have a stable disease for at least three months, although a six to twelve month period has also been suggested [375].

The potential aims and risks of surgery should be discussed with the patient so that he can make an informed decision. Specific issues that should be mentioned during this discussion are the risks of penile shortening, ED, penile numbness, the risk of recurrent curvature, the potential for palpation of knots and stitches underneath the skin, and the potential need for circumcision at the time of surgery [309]. Two major types of repair may be considered for both congenital penile curvature and Peyronie's disease: penile shortening and penile lengthening procedures [376].

Penile shortening procedures include the Nesbit wedge resection and the plication techniques performed on the convex side of the penis. Penile lengthening procedures are performed on the concave side of the penis and require the use of a graft. They aim to minimise penile shortening caused by Nesbit or plication of the tunica albuginea or correct complex deformities. Penile degloving with associated circumcision (as a means of preventing post-operative phimosis) is considered the standard approach for all types of procedures [376]. However, recent data suggest that circumcision is not always necessary e.g. in cases where the foreskin is normal pre-operatively [377]. Finally, in patients with Peyronie's disease and ED not responding to medical treatments, surgical correction of the curvature with concomitant penile prosthesis implantation should be considered [378].

Selection of the most appropriate surgical intervention is based on penile length assessment, curvature severity and erectile function status, including response to pharmacotherapy in cases of ED [309]. Patient expectations from surgery must also be included in the pre-operative assessment. There are no standardised questionnaires

for the evaluation of surgical outcomes [73]. Data from well-designed prospective studies are scarce, with a low level of evidence. Most data are mainly based on retrospective studies, typically non-comparative and non-randomised, or on expert opinion [309, 379].

3.3.2.3.2.1 Penile shortening procedures

In 1965, Nesbit was the first to describe the removal of tunical ellipses opposite a non-elastic corporal segment to treat congenital penile curvature [380]. Fourteen years later, this technique became a successful treatment option, also for Peyronie's disease [381]. This operation is based on a 5-10 mm transverse elliptical excision of the tunica albuginea or approximately 1 mm for each 10° of curvature [376]. The overall short- and long-term results of the Nesbit operation are excellent. Complete penile straightening is achieved in more than 80% of patients [382]. Recurrence of the curvature and penile hypoesthesia are uncommon (about 10%) and the risk of post-operative ED is minimal [376, 383]. Penile shortening is the most commonly reported outcome of the Nesbit procedure [383]. However, shortening of only 1-1.5 cm has been reported for about 85% of patients, which is rarely the cause of post-operative sexual dysfunction [381, 384]. Patients often perceive the loss of length as greater than it actually is [382, 383]. It is therefore advisable to measure and document the penile length peri-operatively, both before and after the straightening procedure, whatever the technique used. Only one modification of the Nesbit procedure has been described (partial thickness shaving instead of conventional excision of a wedge of tunica albuginea) [385].

Plication procedures are based on the same principle as the Nesbit operation but are simpler to perform. Many of them have been described as Nesbit modifications in the older literature. They are based on single or multiple longitudinal incisions on the convex side of the penis closed in a horizontal way, applying the Heineke-Miculicz principle, or plication is performed without making an incision [386-391]. Another modification has been described as the '16 dot' technique with minimal tension under local anaesthesia [392]. The use of non-absorbable sutures reduced recurrence of the curvature. Results and satisfaction rates are similar to the Nesbit procedure [376]. However, numerous different modifications have been described and the level of evidence is not sufficient to recommend one method over the other.

3.3.2.3.2.2 Penile lengthening procedures

Tunical lengthening procedures entail an incision in the short (concave) side of the tunica to increase the length of this side, creating a tunical defect, which is covered by a graft. However, plaque removal may be associated with high rates of post-operative ED due to venous leak [393].

Devine and Horton introduced dermal grafting in 1974 [394]. Since then, a variety of grafting materials and techniques have been reported (Table 10) [395-409]. Unfortunately, the ideal material for grafting has yet to be identified. In addition, grafting procedures are associated with ED rates as high as 25%. Despite excellent initial surgical results, graft contracture and long-term failures resulted in a 17% re-operation rate [410].

Vein grafts have the theoretical advantage of endothelial-to-endothelial contact when grafted to underlying cavernosal tissue. Saphenous vein is the most common vein draft used, followed by dorsal penile vein [376]. In the first case, a secondary incision for graft harvesting is avoided. Postoperative curvature (20%), penile shortening (17%) and graft herniation (5%) have been reported after vein graft surgery [400, 405, 408]. Tunica vaginalis is relatively avascular, easy to harvest and has little tendency to contract due to its low metabolic requirements [398].

Dermal grafts are commonly associated with contracture resulting in recurrent penile curvature (35%), progressive shortening (40%), and a 17% re-operation rate at 10 years [411]. Cadaveric pericardium (Tutoplast®) offers good results by coupling excellent tensile strength and multi-directional elasticity/expansion by 30% [409]. In a retrospective telephone interview, 44% of patients with pericardium grafting reported recurrent curvature, although most of them continued to have successful intercourse and were pleased with their outcomes [409, 411].

Small intestinal submucosa (SIS, a collagen-based xenogenic graft derived from the submucosal layer of the porcine small intestine) has been shown to promote tissue-specific regeneration, and supports the growth of endothelial cells. Small intestinal submucosa acts as a scaffold to promote angiogenesis, host cell migration and differentiation, resulting in tissue structurally and functionally similar to the original. It has been used successfully to repair severe chordee and Peyronie's disease, without significant contraction or histological alterations, but data are limited [406].

More recently the use of buccal mucosa grafts (BMG) has been advocated. BMG provided excellent short-term

results, suggested by the fast return of spontaneous erections and prevented shrinkage, which is the main cause of graft failure. It also proved to be safe and reproducible, thus representing a valuable treatment option for PD [397].

Tunical incision, preferably with grafting, offers an excellent surgical option for men with curvatures over 60º as well as patients with an hour-glass deformity and good erectile function that are willing to risk a higher rate of post-operative ED [412]. The presence of pre-operative ED, the use of larger grafts, age more than 60 years, and ventral curvature are considered poor prognostic factors for functional outcome after grafting surgery [378]. Although the risk for penile shortening is significantly less compared to the Nesbit or plication procedures, it is still an issue and patients must be informed accordingly [376]. The use of geometric principles introduced by Egydio helps to determine the exact site of the incision, and the shape and size of the defect to be grafted [399].

The use of a penile extender device on an 8- to 12-hour daily regimen has been advocated as an effective and safe treatment for loss of penile length in patients operated on for Peyronie's disease [413].

Table 9: Types of grafts used in Peyronie's disease surgery

Autologous grafts
Dermis
Vein grafts
Tunica albuginea
Tunica vaginalis
Temporalis fascia
Buccal mucosa
Allografts
Cadaveric pericardium
Cadaveric fascia lata
Cadaveric dura matter
Cadaveric dermis
Xenografts
Porcine small intestinal submucosa
Bovine pericardium
Porcine dermis
Synthetic grafts
Gore-Tex
Dacron

3.3.2.3.2.3 Penile prosthesis

Penile prosthesis implantation is typically reserved for the treatment of Peyronie's disease in patients with ED, especially when they are non-responders to PED5Is [376]. Although all types of penile prosthesis can be used, the implantation of inflatable penile prosthesis seems to be most effective in these patients [408].

Most patients with mild-to-moderate curvature can expect an excellent outcome simply by cylinder insertion. In cases of severe deformity, intra-operative 'modelling' of the penis over the inflated cylinders (manually bent on the opposite side of the curvature for 90 seconds, often accompanied by an audible crack) has been introduced as an effective treatment [415, 416]. If there is a residual curvature of less than 30º, no further treatment is recommended, as the prosthesis will act as a tissue expander and will result in complete correction of curvature after a few months of cycling the prosthesis [415]. While this technique is effective in most patients, a Nesbit/plication procedure or plaque excision/incision and grafting may be required in order to achieve adequate straightening [414, 417, 418].

The risk of complications (infection, malformation, etc.) is not increased compared to the general population. However, a small risk of urethral perforation (3%) has been reported in patients with 'modelling' over the inflated prosthesis [416].

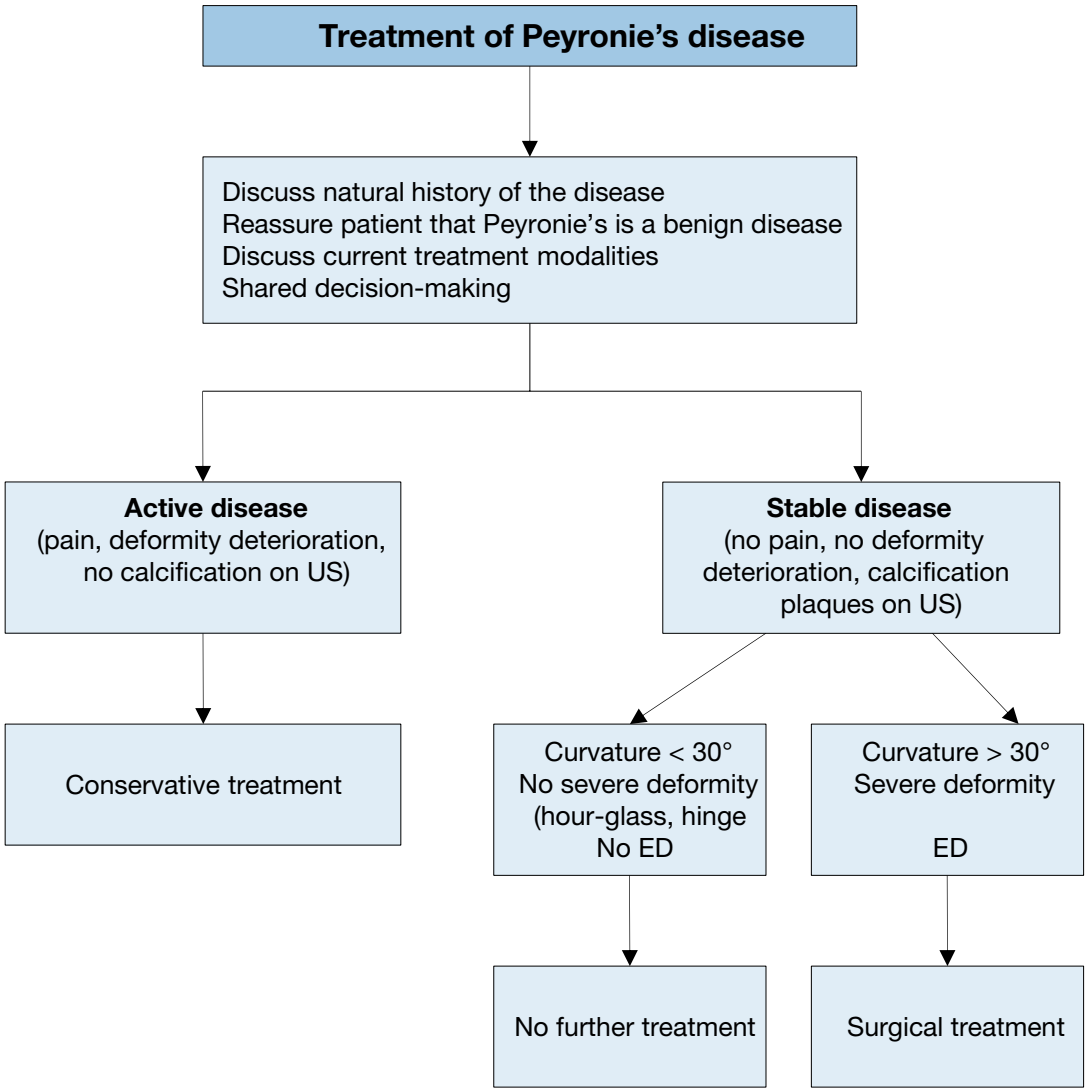
Table 10: Results of surgical treatments for Peyronie's disease (data from different, non-comparable studies) [381, 383-409, 411, 412]

	Tunical lengthening procedures		**Tunical shortening procedures**
	Nesbit	**Plication**	**Grafts**
Penile shortening	4.7-30.8%	41-90%	0-40%
Penile straightening	79-100%	58-100%	74-100%
Persistent or recurrent curvature	4-26.9%	7.7-10.6%	0-16.7%
Post-operative erectile dysfunction	0-13%	0-22.9%	0-15%
Penile hypoesthesia	2-21%	0-21.4%	0-16.7%
Technical modifications	1	At least 3	Many types of grafts and techniques used

Treatment algorithm

The decision on the most appropriate surgical procedure to correct penile curvature is based on pre-operative assessment of penile length, the degree of the curvature and erectile function status. If the degree of curvature is less than 60°, penile shortening is acceptable and the Nesbit or plication procedures are usually the method of choice. This is typically the case for congenital penile curvature. If the degree of curvature is over 60° or is a complex curvature, or if the penis is significantly shortened in patients with a good erectile function (with or without pharmacological treatment), then a grafting procedure is feasible. If there is ED, which is not responding to pharmacological treatment, the best option is the implantation of an inflatable penile prosthesis, with or without an associated procedure over the penis (modelling, plication or even grafting plus the prosthesis). The treatment algorithm is presented in Figure 5.

Figure 5: Treatment algorithm for Peyronie's disease



ED = erectile dysfunction; US = Ultrasound.

The results of the different surgical approaches are presented in Table 10. It must be emphasised that there are no RCTs available addressing surgery in Peyronie's disease. The risk of erectile dysfunction seems to be greater for penile lengthening procedures [309, 376]. Recurrent curvature implies either failure to wait until the disease has stabilised, a reactivation of the condition following the development of stable disease, or the use of re-absorbable sutures that lose their strength before fibrosis has resulted in acceptable strength of the repair [94]. Accordingly, it is recommended that only non-absorbable sutures or slowly reabsorbed absorbable sutures be used. Although with non-absorbable sutures, the knot should be buried to avoid troublesome irritation of the penile skin but this issue may be alleviated by the use of slowly re-absorbed absorbable sutures [383]. Penile numbness is a potential risk of any surgical procedure involving mobilisation of the dorsal neurovascular bundle. This will usually be a neuropraxia, due to bruising of the dorsal sensory nerves. Given that the usual deformity is a dorsal deformity, the procedure most likely to induce this complication is a lengthening (grafting) procedure for a dorsal deformity [376].

3.3.2.3.2.4 Recommendations for the surgical treatment of penile curvature

Recommendations	LE	GR
Perform surgery only when Peyronie's disease has been stable for at least 3 months (without pain or deformity deterioration), which is usually the case after 12 months from the onset of symptoms, and intercourse is compromised due to deformity.	3	C
Prior to surgery, assess penile length, curvature severity, erectile function (including response to pharmacotherapy in case of erectile dysfunction) and patient expectations.	3	C
Use tunical shortening procedures, especially plication techniques as the first treatment option for congenital penile curvature and for Peyronie's disease with adequate penile length, curvature < 60° and absence of special deformities (hour-glass, hinge).	2b	B
Use grafting techniques for patients with Peyronie's disease and normal erectile function, with no adequate penile length, curvature > 60º and presence of special deformities (hour-glass, hinge).	2b	B
Use penile prosthesis implantation, with or without any additional procedure (modelling, plication or grafting), in Peyronie's disease patients with erectile dysfunction not responding to pharmacotherapy.	2b	B

3.4 Priapism

*3.4.1 **Ischaemic (Low-Flow or Veno-Occlusive) Priapism***

3.4.1.1 Epidemiology/aetiology/pathophysiology

Ischaemic priapism is the most common form of priapism, accounting for more than 95% of all priapism episodes [419, 420]. It is usually painful, with a rigid erection characterised clinically by absent or reduced intracavernous arterial inflow (often proximally there is a compensated high velocity picture with little flow distally). In ischaemic priapism, there are time-dependent modifications in the corporal metabolic environment, progressively leading to hypoxia, hypercapnia, glucopenia and acidosis.

Ischaemic priapism beyond four hours is considered the same as a compartment syndrome, characterised by supraphysiological pressure within the closed space of the corpora cavernosa, which severely compromises cavernous circulation. Emergency medical intervention is required to minimise potential irreversible consequences, such as smooth muscle necrosis, corporal fibrosis and permanent ED [421, 422]. The duration of priapism represents the most significant predictor for the development of ED. In this context, interventions beyond 48-72 hours since the onset may help to relieve the erection and pain, but have little benefit in preventing long-term ED.

Histologically, by twelve hours, corporal specimens show interstitial oedema, progressing to destruction of sinusoidal endothelium, exposure of the basement membrane and thrombocyte adherence at 24 hours. At 48 hours, thrombi can be found in the sinusoidal spaces and smooth muscle necrosis with fibroblast-like cell transformation is evident [422]. In terms of pathophysiology (Table 11), no specific cause can be identified in the majority of cases [420, 423]. However, ischaemic priapism can be associated with sickle cell disease, haematological dyscrasias, neoplastic syndromes, and with the use of several different medications. Ischaemic priapism may occur (0.4-35%) after intracavernous injections of erectogenic agents [150, 420, 421, 424, 425]. The risk is highest with papaverine-based combinations, while the risk of priapism is < 1% following prostaglandin E1 injection [425].

Since their introduction on the market, a few cases of priapism have been described in men who have taken PDE5Is [420]. Most of these men however, had other risk factors for priapism, and it is unclear whether PDE5Is alone can cause ischaemic priapism [420]. Since most men who experienced priapism following PDE5I use had additional risk factors for ischaemic priapism, PDE5I use is usually not regarded a risk factor in itself.

Sickle cell disease is the most common cause in childhood, accounting for 63% of the cases. It is the primary aetiology in 23% of adult cases [426], with a lifetime probability of developing ischaemic priapism of 29-42% in men with sickle cell disease [420, 426-428] (LE: 4). Mechanisms of sickle cell disease associated priapism may involve dysfunctional nitric oxide synthase and Rho-associated protein kinase (ROCK) signaling, and increased oxidative stress associated with nicotinamide adenine dinucleotide phosphate (NADPH) oxidase mediated signaling [429].

Priapism resulting from metastatic or regional infiltration is rare and usually reflects an infiltrative process [430]. As such, the recommendations for pharmacological treatment are unlikely to work and certainly all of these

men should have a magnetic resonance imaging (MRI) scan and be offered supportive care for their primary cancer.

Priapism in children is extremely rare and is most commonly related to malignancy, haematological or otherwise. The investigative focus should be on identifying any underlying causes.

Partial priapism, or idiopathic partial thrombosis of the penis, is a very rare condition. It is a subtype of priapism limited to a single crura. Its aetiology is unknown, but bicycle riding, trauma, drug usage, sexual intercourse, haematological diseases and α-blockers have been associated with partial priapism [431]. There may be a congenital web in the corpora which poses a risk factor [432].

Table 11: Potential causative factors for ischaemic priapism

•	Idiopathic
•	Haematological dyscrasias (sickle cell disease, thalassemia, leukaemia; multiple myeloma, Hb Olmsted variant, fat emboli during hyperalimentation, haemodialysis, glucose-6-phosphate dehydrogenase deficiency, Factor V Leiden mutation)
•	Infections (toxin-mediated) (i.e. scorpion sting, spider bite, rabies, malaria)
•	Metabolic disorders (i.e. amyloidosis, Fabry's disease, gout)
•	Neurogenic disorders (i.e. syphilis, spinal cord injury, cauda equina syndrome, autonomic neuropathy, lumbar disc herniation, spinal stenosis, cerebrovascular accident, brain tumour, spinal anaesthesia)
•	Neoplasms (metastatic or regional infiltration) (i.e. prostate, urethra, testis, bladder, rectal, lung, kidney)
•	Medications
o	Vasoactive erectile agents (i.e. papaverine, phentolamine, prostaglandin E1/alprostadil, combination of intracavernous therapies)
o	Alpha-adrenergic receptor antagonists (i.e. prazosin, terazosin, doxazosin, tamsulosin)
o	Antianxiety agents (hydroxyzine)
o	Anticoagulants (heparin, warfarin)
o	Antidepressants and antipsychotics (i.e. trazodone, bupropion, fluoxetine, sertraline, lithium, clozapine, risperidone, olanzapine, chlorpromazine, thiorizadine, phenothiazines)
o	Antihypertensives (i.e. hydralazine, guanethidine, propranolol)
o	Hormones (i.e. gonadotropin-releasing hormone, testosterone)
o	Recreational drugs (i.e. alcohol, marijuana, cocaine [intranasal and topical], crack, cocaine)

3.4.1.1.1 Summary of evidence on the epidemiology, aetiology and pathophysiology of ischaemic priapism

Summary of evidence	**LE**
Ischaemic priapism is most common, accounting for more than 95% of all cases.	1b
Ischaemic priapism is identified as idiopathic in the vast majority of patients, while sickle cell anaemia is the most common cause in childhood.	1b
Ischaemic priapism occurs relatively often (up to 35%) after intracavernous injections of papaverine based combinations, while it is rare (< 1%) after prostaglandin E1 monotherapy.	2a
Priapism is rare in men who have taken PDE5Is with only sporadic cases reported.	1a

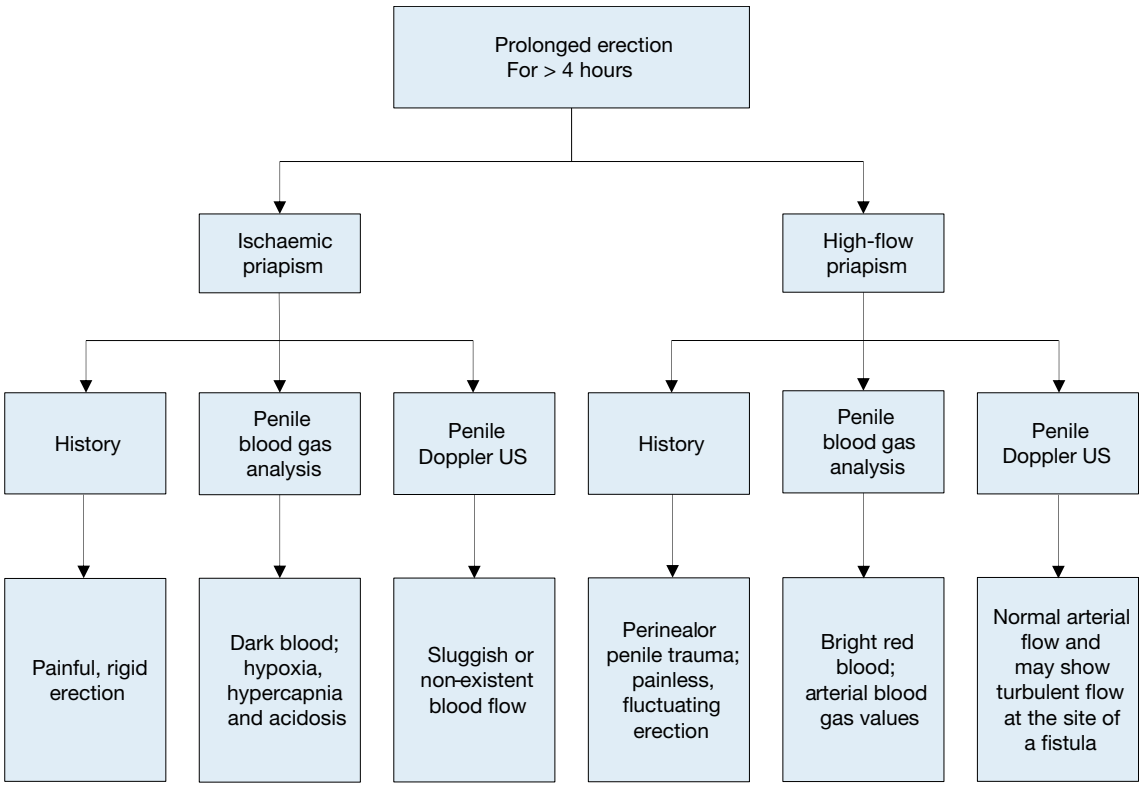
PDE5Is = phosphodiesterase type 5 inhibitors.

3.4.1.2 Classification

Ischaemic priapism is a persistent erection marked by rigidity of the corpora cavernosa and by little or no cavernous arterial inflow [420]. The patient typically complains of penile pain and examination reveals a rigid erection. Resolution of ischaemic priapism is characterised by return to a flaccid non-painful state. However, in many cases, persistent penile oedema, ecchymosis and partial erections can occur and may mimic unresolved priapism. The partial erections may reflect reactive hyperaemia and are sometimes misdiagnosed as persistent priapism. When left untreated, resolution may take days and ED invariably results.

3.4.1.3 Diagnostic evaluation

Figure 6: Differential diagnosis of priapism



3.4.1.3.1 History

A comprehensive history taking is the mainstay in priapism diagnosis [420, 433]. The medical history must include a history of sickle cell disease or any other haematological abnormality [8, 434] and a history of pelvic, genital or perineal trauma. The sexual history must include complete details of the duration of erection, the presence and degree of pain, prior medical drug use, any previous history of priapism and erectile function prior to the last priapism episode (Table 12). The history can help to determine the underlying type of priapism (Table 13). Ischaemic priapism is associated with progressive penile pain and the erection is rigid.

Table 12: Key points in taking the history of priapism (adapted from Broderick *et al.* [420])

Duration of erection
Presence and degree of pain
Previous episodes of priapism and method of treatment
Current erectile function, especially the use of any erectogenic therapies prescription or nutritional supplements
Medications and recreational drugs
Sickle cell disease, haemoglobinopathies, hypercoagulable states
Trauma to the pelvis, perineum, or penis

3.4.1.3.2 Physical examination

In ischaemic priapism, the corpora are fully rigid and tender, but the glans penis is soft. The patient complains of pain. Pelvic examination may reveal cases of underlying malignancy.

3.4.1.3.3 Laboratory testing

Laboratory testing should include a complete blood count, white blood count with blood cell differential, platelet count and coagulation profile to assess anaemia and detect haematological abnormalities [420, 433].

Blood aspiration from the corpora cavernosa shows dark ischaemic blood (Table 13) (LE: 2b). Blood gas analysis is essential to differentiate between ischaemic and arterial priapism (Table 14).

Further laboratory testing should be directed by history, clinical and laboratory findings. These may include specific tests for the diagnosis of sickle cell anaemia or other haemoglobinopathies (e.g. haemoglobin electrophoresis) or urine and plasma toxicological studies when there is suspected use of recreational psychoactive drugs.

3.4.1.3.4 Penile imaging

Colour Doppler ultrasound (US) of the penis and perineum is recommended and can differentiate ischaemic from arterial priapism as an alternative or adjunct to blood gas analysis [435-437] (LE: 2b). Scanning of the penis should be performed before corporal blood aspiration in ischaemic priapism.

Examination of the penile shaft and perineum is recommended. In ischaemic priapism there will be an absence of blood flow in the cavernous arteries. The return of the cavernous artery waveform will result in successful detumescence [420, 437, 438]. After aspiration, a reactive hyperaemia may develop with a high arterial flow proximally that may mislead the diagnosis as arterial priapism.

The role of MRI in the diagnostic evaluation of priapism is controversial. It may be helpful in cases of ischaemic priapism to assess the viability of the corpora cavernosa and the presence of penile fibrosis. In a prospective study in 38 patients with ischaemic priapism, the sensitivity of MRI in predicting non-viable smooth muscle was 100%, as confirmed by corporal biopsy [439]. In this study, all patients with viable smooth muscle on MRI maintained erectile function on clinical follow-up (LE: 3).

Table 13: Key findings in priapism (adapted from Broderick *et al.* [420])

	Ischaemic priapism	**Arterial priapism**
Corpora cavernosa fully rigid	Usually	Seldom
Penile pain	Usually	Seldom
Abnormal penile blood gas	Usually	Seldom
Haematological abnormalities	Usually	Seldom
Recent intracorporeal injection	Sometimes	Sometimes
Perineal trauma	Seldom	Usually

Table 14: Typical blood gas values (adapted from Broderick *et al.* [420]

Source	**pO_2 (mmHg)**	**pCO_2 (mmHg)**	**pH**
Normal arterial blood (room air) [similar values are found in arterial priapism]	> 90	< 40	7.40
Normal mixed venous blood (room air)	40	50	7.35
Ischaemic priapism (first corporal aspirate)	< 30	> 60	< 7.25

3.4.1.3.5 Recommendations for the diagnosis of ischaemic priapism

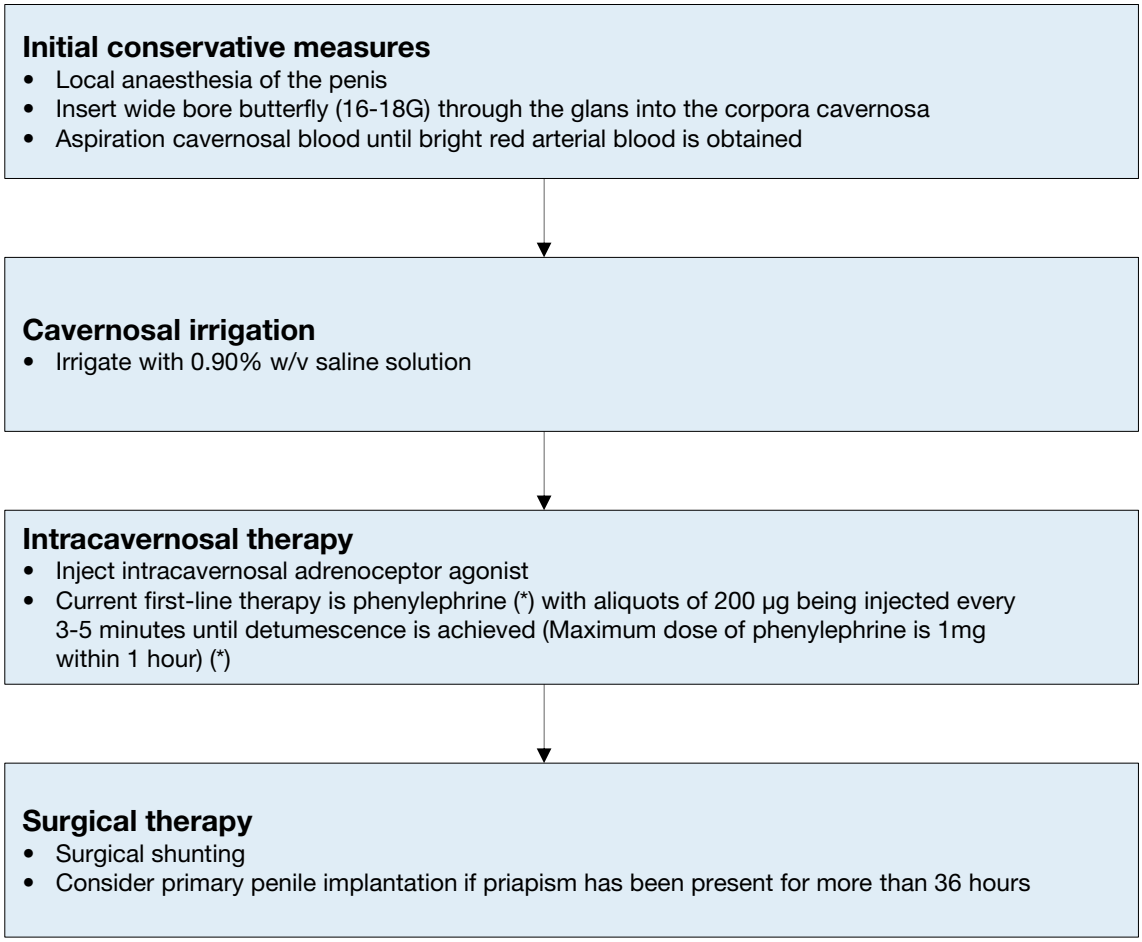
Recommendations	**GR**
Take a comprehensive history for diagnosis which can help to determine the underlying type of priapism.	B
Include physical examination of the genitalia, the perineum and the abdomen in the diagnostic evaluation which may help to determine the underlying type of priapism.	B
For laboratory testing, include complete blood count, white blood count with blood cell differential, platelet count and coagulation profile. Direct further laboratory testing by the history and clinical and laboratory findings. In children with priapism, perform a complete evaluation of all possible causes.	B
Analyse blood gas of blood aspirated from the penis for the differentiation between ischaemic and arterial priapism.	B
Perform colour duplex ultrasound of the penis and perineum for the differentiation between ischaemic and arterial priapism as an alternative or adjunct to blood gas analysis.	B
In cases of prolonged ischaemic priapism, use magnetic resonance imaging of the penis to predict smooth muscle viability and confirm erectile function restoration.	B
Perform selected pudendal arteriogram when embolisation is planned for the management of arterial priapism.	B

3.4.1.4 Disease management

Acute ischaemic priapism is a medical emergency. Urgent intervention is compulsory (LE: 4), and should follow a stepwise approach. The aim of any treatment is to restore penile flaccidity, without pain, in order to prevent damage to the corpora cavernosa.

Figure 7: Treatment of ischaemic priapism

The treatment is sequential and the physician should move on to the next stage if the treatment fails.



(*) The dose of phenylephrine should be reduced in children. It can result in significant hypertension and should be used with caution in men with cardiovascular disease and monitoring of pulse, blood pressure and electrocardiogram (ECG) is advisable in all patients during administration and for 60 minutes afterwards. Its use is contraindicated in men with a history of cerebro-vascular disease and significant hypertension.

3.4.1.4.1 First-line treatments

First-line treatments in ischaemic priapism of > 4 hours duration are strongly recommended before any surgical treatment (LE: 4). Conversely, first-line treatments initiated beyond 72 hours while relieving the priapism have little documented benefit in terms of long-term potency preservation (LE: 4).

Historically, several first-line treatments have been described including exercise, ejaculation, ice packs, cold baths, and cold water enemas [420]. However, there is lack of evidence of benefit for such measures.

Partial priapism usually resolves spontaneously with analgesic treatment while surgical intervention is rarely needed [440].

3.4.1.4.1.1 Penile anaesthesia/systemic analgesia

It is possible to perform blood aspiration and intracavernous injection of a sympathomimetic agent without any anaesthesia. However, anaesthesia may be necessary when there is severe penile pain. While it is recognised that the anaesthesia may not alleviate the ischaemic pain, cutaneous anaesthesia will facilitate subsequent therapies. The treatment options for penile anaesthesia/systemic analgesia include:

- dorsal nerve block;
- circumferential penile block;
- subcutaneous local penile shaft block;
- oral conscious sedation (for paediatric patients).

3.4.1.4.1.2 Aspiration ± irrigation with 0.90% w/v saline solution

The first intervention for an episode of priapism lasting > 4 hours consists of corporal aspiration (LE: 4) to drain stagnant blood from the corporal bodies, making it possible to relieve the compartment syndrome-like condition of the penis. Blood aspiration may be performed with intracorporeal access either through the glans or via percutaneous needle access on the lateral aspect of the proximal penile shaft, using a 16G or 18G angiocatheter or butterfly needle. The needle must penetrate the skin, the subcutaneous tissue and the tunica albuginea to drain the corpus cavernosum (LE: 4).

Some clinicians use two angiocatheters or butterfly needles at the same time to accelerate drainage, as well as aspirating and irrigating simultaneously with a saline solution [427] (LE: 4). Aspiration should be continued until fresh red, oxygenated, blood is aspirated (LE: 4).

This approach has up to a 30% chance of resolving the priapism. There are insufficient data to determine whether aspiration followed by saline intracorporeal irrigation is more effective than aspiration alone (LE: 4).

3.4.1.4.1.3 Aspiration ± irrigation with 0.90% w/v saline solution in combination with intracavernous injection of pharmacological agents

This combination is currently considered the standard of care in the treatment of ischaemic priapism [3, 420, 441] (LE: 4). Pharmacological agents include sympathomimetic drugs or alpha-adrenergic agonists. Options for intracavernous sympathomimetic agents include phenylephrine, etilephrine, ephedrine, epinephrine, norepinephrine and metaraminol with a resolution rate of up to 80%. [420, 441-449] (LE: 2b). The use of intracavernous adrenalin injection alone has also been sporadically reported [450].

Phenylephrine

Phenylephrine is currently the drug of choice due to its high selectivity for the α-1-adrenergic receptor, without concomitant β-mediated inotropic and chronotropic cardiac effects [442, 446, 447] (LE: 4).

Phenylephrine is diluted in normal saline to a concentration of 100-500 µg/mL. Usually 200 µg are given every three to five minutes directly into the corpus cavernosum. Maximum dosage is 1 mg within one hour (LE: 4). A lower concentration or volume is applicable for children and patients with severe cardiovascular disease (LE: 4).

Phenylephrine use has potential cardiovascular side-effects [420, 441-443, 446, 447] and it is recommended that blood pressure and pulse are monitored every 15 minutes for an hour after the injection. This is particularly important in older men with existing cardiovascular diseases. After injection, the puncture site should be compressed and the corpora cavernosa massaged to facilitate drug distribution.

The potential treatment-related side-effects of intracavernous phenylephrine (and other sympathomimetic agents) include headache, dizziness, hypertension, reflex bradycardia, tachycardia and palpitations, irregular cardiac rhythms and sporadic subarachnoid haemorrhage [34]. Monitoring of blood pressure and pulse with ECG should be performed during intracavernous administration of sympathomimetic agents.

Overall, the administration of intracavernous sympathomimetic agents is contraindicated in patients suffering from malignant or poorly controlled hypertension and in those who are concurrently taking monoamine oxidase inhibitors (LE: 4).

Etilephrine

Etilefrine is the second most widely used sympathomimetic agent, administered by intracavernous injection at a concentration of 2.5 mg in 1-2 mL normal saline [443] (LE: 3).

Methylene blue

Methylene blue is a guanylate cyclase inhibitor, which may be a potential inhibitor of endothelial-mediated cavernous relaxation. It has therefore been suggested for treating short-term pharmacologically induced priapism [451, 452] (LE: 3). Methylene blue, 50-100 mg [451], should be injected intracavernously and left for 5 minutes. It is then aspirated and the penis compressed for an additional 5 minutes [452]. Treatment-related side-effects include a transient burning sensation and blue discolouration of the penis.

Adrenaline
Intracavernosal adrenaline (dosage of 2 mL of 1/100,000 adrenaline solution up to five times over a 20-minute period [450]), has been used in patients with ischaemic priapism due to an intracavernous injection of vasoactive agents. Success rate of over 50% after a single injection, with an overall success rate of 95% with repeated injections is achieved (LE: 3).

Oral terbutaline
Oral terbutaline is a beta-2-agonist with minor β-1 effects and some alpha-agonist activity. A dose of 5 mg has been suggested to treat prolonged erections lasting more than 2.5 hours, after intracavernous injection of vasoactive agents, although the mechanism of action is not yet fully understood [453-455] (LE: 1b). Its main use is in the prevention of recurrent episodes of prolonged erection. Terbutaline should be given cautiously in patients with coronary artery disease, increased intravascular fluid volume, oedema and hypokalaemia [455].

Table 15: Medical treatment of ischaemic priapism

Drug	Dosage/Instructions for use
Phenylephrine	• Intracavernous injection of 200 µg every 3-5 minutes. • Maximum dosage is 1 mg within 1 hour. • The lower doses are recommended in children and patients with severe cardiovascular disease.
Etilephrine	• Intracavernosal injection at a concentration of 2.5 mg in 1-2 mL normal saline.
Methylene blue	• Intracavernous injection of 50-100 mg, left for 5 minutes. It is then aspirated and the penis compressed for an additional 5 minutes.
Adrenaline	• Intracavernous injection of 2 mL of 1/100,000 adrenaline solution up to five times over a 20-minute period.
Terbutaline	• Oral administration of 5 mg for prolonged erections lasting more than 2.5 hours, after intracavernous injection of vasoactive agents.

Management of sickle cell disease related priapism
Rapid intervention is essential (LE: 4) and the general approach is similar to that described in other cases of ischaemic priapism and should be coordinated with a haematologist [456-458] (LE: 4).

However, as with other haematological disorders, other therapeutic practices may also need to be implemented [456, 458, 459]. Specific measures for sickle cell disease related priapism include intravenous hydration and parental narcotic analgesia while preparing the patient for aspiration and irrigation. In addition, supplemental oxygen administration and alkalinisation with bicarbonate can be helpful [428, 457].

Exchange blood transfusion has also been proposed, with the aim of increasing the tissue delivery of oxygen. The transfused blood should be HbS negative, Rh and Kell antigen matched [460]. However, the evidence is inconclusive as to whether exchange transfusion itself helps to resolve the priapism in these men. It should also be noted that several reports suggest that this treatment may result in serious neurological sequelae [461]. Because of these considerations, the routine use of this therapy is not recommended (LE: 4).

3.4.1.4.2 Second-line treatments
Second-line intervention typically refers to surgical intervention in the form of penile shunt surgery and should only be considered when conservative management options fail (LE: 4). There is no evidence detailing the amount of time allowed for first-line treatment before moving on to surgery. Consensus recommendations suggest a period of at least one hour of first-line therapy prior to moving to surgery (LE: 4). A number of clinical indicators suggest failure of first-line treatment including continuing corporal rigidity, cavernosal acidosis and anoxia, absence of cavernosal artery inflow by penile colour duplex US, and elevated intracorporal pressures by pressure monitoring (LE: 4).

3.4.1.4.3 Penile shunt surgery
Penile shunt surgery aims to produce an exit for ischaemic blood from the corpora cavernosa thereby allowing the restoration of normal circulation within these structures. Accordingly, any shunt creates an opening in the tunica albuginea, which may communicate with either the glans, the corpus spongiosum or a vein for blood drainage [420, 441, 462].

In general, the type of shunt procedure chosen is according to the surgeon's preference and procedure familiarity (LE: 4). It is conventional for distal shunt procedures to be tried before proximal shunting is considered (LE: 4). Cavernous biopsy has been used to identify muscle necrosis (which, if present, would suggest that shunting is likely to fail) although this has mainly a medico-legal role.

It is important to assess the success of surgery by either direct observation or by investigation (e.g. cavernous blood gas testing, penile colour duplex US) (LE: 4) [420, 441].

The recovery rates of erectile function in men undergoing shunt surgery for prolonged erections are low and directly relate to the duration of the priapism [463, 464]. Priapism for more than 36 hours appears to irreversibly impair erectile tissue both structurally and functionally [463]. In general, shunt procedures undertaken after this time period may only serve to limit pain without any benefit for erectile function (LE: 4) [465, 466].

Four categories of shunt procedures have been reported [3, 420, 462]. The limited available data preclude any recommendation for one procedure over another based on outcome (LE: 4).

Percutaneous distal (corpora-glanular) shunts
Winter's procedure: this procedure uses a Trucut biopsy needle to create a fistula between the glans penis and each corpora cavernosa body [3, 420, 426, 467, 468] (LE: 3). Postoperative sequelae are uncommon [469]. Winter's shunt is easy to perform, but has been reported as the least successful operation to create a distal shunt [464].

Ebbehoj's technique: this technique involves the execution of multiple tunical incision windows between the glans and each tip of the corpus cavernosum by means of a size 11 blade scalpel passed several times percutaneously [3, 420, 467, 470, 471] (LE: 3).

T-Shunt: this technique involves performing a bilateral procedure using a size 10 blade scalpel placed vertically through the glans until fully within the corpus cavernosum. The blade is then rotated 90° away from the urethra and pulled out [3, 420, 467, 472] (LE: 3). This is followed by a tunneling procedure using a size 8 dilator inserted through the glans and into the corpora which can be performed using US for guidance, mainly in order to avoid urethral injury [472].

Open distal (corpora-glanular) shunts
Al-Ghorab's procedure: this procedure consists of an open bilateral excision of circular cone segments of the distal tunica albuginea via the glans penis, along with a subsequent glans closure by means of a running suture with absorbable material [3, 420, 467, 473, 474] (LE: 3).

Burnett's technique (Snake manoeuvre): a modification of the Al-Ghorab corpora-glanular shunt surgery involves the retrograde insertion of a 7/8 Hegar dilator into the distal end of each corpus cavernosum through the original Al-Ghorab glanular excision. After removal of the dilator from the corpus cavernosum, blood evacuation is facilitated by manual compression of the penis sequentially from a proximal to distal direction. After detumescence, the glans penis skin is closed as in the Al-Ghorab procedure [3, 420, 467, 475, 476] (LE: 3). Reported complications included wound infection, penile skin necrosis and a urethrocutaneous fistula [476].

Open proximal (corporospongiosal) shunts
Quackles's technique: through a trans-scrotal or perineal approach, a proximal open shunt technique creates a communication between the corpus cavenosum and the corpus spongiosum. The most frequent complications include an unwanted urethra-cavernous fistula and urethral stricture or the development of cavernositis [3, 420, 462, 477]. The risk of urethral injury is less with a perineal approach to the bulb of the corpus spongiosum (LE: 3).

Vein anastomoses/shunts
Grayhack's procedure: this mobilises the saphenous vein below the junction of the femoral vein and anastomoses the vein end-to-side onto the corpus cavernosum. Venous shunts may be complicated by saphenofemoral thrombus formation and by pulmonary embolism [3, 420, 478-480] (LE: 3).

Immediate surgical prosthesis implantation
Intractable, therapy-resistant, acute ischaemic priapism or episodes lasting more than 48-72 hours usually result in complete ED, possibly along with major penile deformity. In these cases, immediate penile prosthesis surgery has been suggested [481-484] (LE: 3).

The immediate insertion of a penile prosthesis has been recommended to avoid the difficulty and complications of delayed surgery in the presence of corporal fibrosis. Potential complications that could compromise immediate penile prosthesis implantation include distal erosion and cavernositis [481, 483], along with a mild rate of revision surgery [481]. Early surgery also offers the opportunity to maintain penile size, and prevent penile curvature due to cavernosal fibrosis .

Currently, there are no clear indications for immediately implanting a penile prosthesis in a man with acute ischaemic priapism [441]. Relative indications include [420] (LE: 4):

- ischaemia that has been presented for more than 36 hours [484];
- failure of aspiration and sympathomimetic intracavernous injections;
- failure of distal and proximal shunting (although in delayed cases, implantation might be considered ahead of shunt surgery);
- MRI or corporal biopsy evidence of corporal smooth muscle necrosis [420, 481] (LE: 4).

Surgery for non-acute sequelae after ischaemic priapism
Structural changes may occur after ischaemic priapism including cavernosal tissue necrosis and fibrosis with consequent penile scarring, megalophallic deformities, penile shortening, and occasional penile loss, [462, 481, 485, 486]. Erectile dysfunction is also often observed [420, 487]. Unfortunately, these outcomes can still occur despite apparently successful first-line or second-line treatment.

Prosthesis implantation is occasionally indicated in sickle cell patients with severe ED since other therapeutic options such as PDE5Is and intracavernous injections are avoided as they may provoke a further priapism event [420, 441]. In severe corporal fibrosis, semi-rigid prosthetic devices are preferable to inflatable implants [481, 488] (LE: 3). Following severe priapism that has resulted in penile destruction with complicated deformities or even loss of penile tissue, penile reconstruction and concomitant prosthesis implant may be considered [489] (LE: 3).

3.4.1.5 Summary of evidence and recommendations for the treatment of ischaemic priapism

Summary of evidence	**LE**
Intervene rapidly for ischaemic priapism, which is an emergency condition.	B
Treatment aims to restore painless penile flaccidity, in order to prevent chronic damage to the corpora cavernosa.	C
Erectile function preservation is directly related to the duration of ischaemic priapism.	B
Phenylephrine is the recommended drug due to its favourable safety profile on the cardiovascular system compared to other drugs. Phenylephrine is usually diluted in normal saline with a concentration of 100-500 µg/mL and given in 200 µg doses every 3-5 minutes directly into the corpus cavernosum. Maximum dosage is 1 mg within 1 hour. Patients at high cardiovascular risk should be given lower doses. Patient monitoring is highly recommended.	B
The efficacy of shunt procedures for ischaemic priapism is questionable. Diagnose muscle necrosis when needed with cavernous biopsy. No clear recommendation on one type of shunt over another can be given.	C
Erectile dysfunction is inevitable in prolonged cases or priapism. Implantation of penile prosthesis at a later stage can be difficult due to severe corporal fibrosis.	B

Recommendations	GR
Start management of ischaemic priapism as early as possible (within four to six hours) and follow a stepwise approach.	B
First, decompress the corpora cavernosa by penile aspiration until fresh red blood is obtained.	C
In priapism secondary to intracavernous injections of vasoactive agents, replace blood aspiration with intracavernous injection of a sympathomimetic drug as the first step.	C
In priapism that persists despite aspiration, proceed to the next step, which is intracavernous injection of a sympathomimetic drug.	B
In cases that persist despite aspiration and intracavernous injection of a sympathomimetic drug, repeat these steps several times before considering surgical intervention.	C
Treat ischaemic priapism due to sickle cell anaemia in the same fashion as idiopathic ischaemic priapism. Provide other supportive measures (intravenous hydration, oxygen administration with alkalisation with bicarbonates, blood exchange transfusions), but do not delay initial treatment to the penis.	B
Proceed to surgical treatment only when blood aspiration and intracavernous injection of sympathomimetic drugs have failed or for priapism events lasting < 72 hours.	C
Perform distal shunt surgical procedures first followed by proximal procedures in case of failure.	C
Discuss the immediate implantation of a penile prosthesis with the patient in cases of priapism presenting > 36 hours after onset, or in cases for which all other interventions have failed.	B

3.4.1.6 Follow-up

Follow-up of ischaemic priapism after successful treatment should include modification of risk factors (if any) in order to avoid a new event and assessment of erectile function since it may be severely compromised especially after surgical treatment with a shunt. Penile fibrosis is usually easily identified with clinical examination of the penis.

*3.4.2 **Arterial (high-flow or non-ischaemic) priapism***

3.4.2.1 Epidemiology/aetiology/pathophysiology

Epidemiological data on arterial priapism are almost exclusively derived from small case series [420, 437, 438, 490, 491]. The most frequent cause of high-flow priapism is blunt perineal or penile trauma [81]. The injury results in a laceration in the cavernosal artery leading to a high-flow fistula between the artery and the lacunar spaces of the sinusoidal tissue [491]. This unregulated flow results in a persistent erection, and has been proposed to occur via a mechanism that involves stimulation of endothelial nitric oxide synthase by the turbulent blood flow [492]. Partial erections are enhanced after sexual stimulation, as the trabecular smooth muscle fully relaxes, activating the corporal veno-occlusive mechanism [491, 493].

There is often a delay between the injury and the development of the priapism that may be up to two to three weeks [493]. This has been suggested to reflect either spasm or ischaemic necrosis of the injured artery, with the fistula only developing as the spasm resolves or when the ischaemic segment blows out.

Occasional cases are associated with metastatic malignancy to the penis [494, 495], with acute spinal cord injury [496] and occasionally following intracavernous injections or aspiration due to a lacerated cavernous artery or branch [497, 498]. Under these circumstances, it may complicate low-flow priapism. It has also been reported to occur following internal urethrotomy [499] and a Nesbit procedure [500]. Although sickle cell disease is usually associated with low-flow priapism, occasional cases of high-flow priapism have been reported [501].

3.4.2.1.1 Summary of Evidence on the epidemiology, aetiology and pathophysiology of arterial priapism

Summary of evidence	LE
Arterial priapism usually occurs after blunt perineal or penile trauma.	2

3.4.2.2 Classification

Arterial priapism is a persistent erection caused by unregulated cavernous arterial inflow [420]. The patient typically reports an erection that is not fully rigid and is not associated with pain although fully rigid erections may occur with sexual stimulation.

3.4.2.3 Diagnostic evaluation

3.4.2.3.1 History

A comprehensive history is also mandatory in arterial priapism diagnosis and follows the same principles as described in Table 12. Arterial priapism is suspected when there is no pain and erections are not fully rigid (Table 13). It can be associated with full erections under sexual stimulation and when there is a history of coital trauma or blunt trauma to the penis. The onset of post-traumatic high-flow priapism in adults and children may be delayed by hours to days following the initial injury. Sexual intercourse is usually not compromised.

3.4.2.3.2 Physical examination

In arterial priapism, the corpora are tumescent but not fully rigid (Table 13). Abdominal, penile and perineal examination may reveal evidence of trauma.

3.4.2.3.3 Laboratory testing

Blood aspiration from the corpora cavernosa shows bright red arterial blood in arterial priapism, while blood is dark in ischaemic priapism (Table 13) (LE: 2b). Blood gas analysis is essential to differentiate between arterial and ischaemic priapism (Table 14).

3.4.2.3.4 Penile imaging

Colour duplex US of the penis and perineum is recommended and can differentiate arterial from ischaemic priapism as an alternative or adjunct to blood gas analysis [435-437] (LE: 2b). Examination of the penile shaft and perineum is recommended. In arterial priapism US will show turbulent flow at the fistula, which helps to localise the site of trauma since patients with arterial priapism have normal to high blood velocities in the cavernous arteries.

A selective pudendal arteriogram can reveal a characteristic blush at the site of the injury to the cavernosal artery in arterial priapism [502, 503]. However, due to its invasiveness it should be reserved for the management of arterial priapism, when embolisation is being considered [420, 433] (LE: 3).

The role of MRI in the diagnostic evaluation of priapism is controversial. In arterial priapism, its role is limited since the small penile vessels and arteriovenous fistulae cannot be easily demonstrated [504].

3.4.2.3.5 Recommendations for the diagnosis of arterial priapism

The same recommendations as in section 3.4.1.3.5 apply.

3.4.2.4 Disease management

The management of high-flow priapism is not an emergency because the penis is not ischaemic. Definitive management can therefore be considered and should be discussed with the patient so that they understand the risks and complications of treatment [420, 433] (LE: 3).

3.4.2.4.1 Conservative management

This may include applying ice to the perineum or site-specific perineal compression [437, 490, 505, 506]. It is an option in all cases, particularly children [507a] (LE: 3). The fistula occasionally closes spontaneously. Even in those cases when it does not, the response to a sexual stimulus does allow for intercourse. Androgen deprivation therapy (leuprolide injections, bicalutamide and ketoconazole) has been reported in case series to enable closure of the fistula reducing spontaneous and sleep-related erections [507b]. However, sexual dysfunction due to these treatments must be considered.

Blood aspiration is not helpful for the treatment of arterial priapism and the use of alpha-adrenergic antagonists is not recommended due to potential severe adverse effects, e.g. transfer of the drug into the systemic circulation.

3.4.2.4.1.1 Selective arterial embolisation

Selective arterial embolisation can be performed using either an autologous clot [508-510], gel foam or sponge [509, 511], or more permanent substances, such as coils [509, 511-513] or acrylic glue [514] (LE: 3). Success rates of up to 89% have been reported [515] in relatively small, non-randomised studies. There are no robust data to demonstrate the relative merits of the different substances. At least theoretically, the use of an autologous clot has some attractions. It temporarily seals the fistula, but when the clot is lysed, the arterial damage has usually resolved and the blood flow of the penis can return to normal. The use of a permanent device, such as a coil, would permanently block an artery and may lead to adverse effects upon spontaneous sexual function. Other potential complications include penile gangrene, gluteal ischaemia, cavernositis and perineal abscess [420, 516].

Following percutaneous embolisation, a follow-up is appropriate within one to two weeks. Assessment by clinical examination and by colour duplex US can determine whether the embolisation has been successful [436]. If there is doubt, a repeat arteriogram is required. Recurrence rates of 7-27% after a single treatment of embolisation have been reported [509, 510, 517] (LE: 3). In a few cases, repeat embolisation is necessary. Sexual function following embolisation can be adversely affected although there is full restoration of potency in around 80% of men [517, 518] (LE: 3).

Embolisation in children, although reportedly successful, is technically challenging and requires treatment within a specialist paediatric vascular radiology department [445, 519].

3.4.2.4.2 Surgical management

Selective ligation of the fistula through a transcorporeal approach under the guidance of colour duplex US is possible [3, 434, 520]. Surgery is technically challenging and may pose significant risks, mainly ED due to accidental ligation of the cavernous artery instead of the fistula. It is rarely performed and should only be considered when there are contraindications for selective embolisation, no availability of the technique or embolisation failure (LE: 4).

3.4.2.4.3 Summary of evidence and recommendations for the treatment of arterial priapism

Summary of evidence	**GR**
Because high-flow priapism is not an emergency, perform definitive management at the discretion of the treating physician.	B
Conservative management with the use of ice applied to the perineum or site-specific perineal compression may be successful particularly in children. The use androgen deprivation therapy may enable closure of the fistula reducing spontaneous and sleep-related erections.	C
Artery embolisation, using temporary or permanent substances, has high success rates. No definitive statement can be made on the best substance for embolisation in terms of sexual function preservation.	B
Repeat the procedure for the recurrence of arterial priapism following selective artery embolisation.	B
Reserve selective surgical ligation of the fistula as a last treatment option when embolisation has failed.	C

Recommendations	**GR**
Because high-flow priapism is not an emergency, perform definitive management at the discretion of the treating physician.	B
Manage conservatively with the use of ice applied to the perineum or site-specific perineal compression as the first step, especially in children. Use androgen deprivation therapy only in adults.	C
Perform selective artery embolisation, using temporary or permanent substances.	B
Repeat the procedure for the recurrence of arterial priapism following selective artery embolisation.	B
Reserve selective surgical ligation of the fistula as a final treatment option when embolisation has failed.	C

3.4.2.4.4 Follow-up

Follow-up after successful treatment of arterial priapism should include assessment of erectile function and clinical examination to identify signs of recurrence especially after embolisation.

*3.4.3 **Stuttering (recurrent or intermittent) priapism***

3.4.3.1 Epidemiology/aetiology/pathophysiology

Robust epidemiological studies of stuttering priapism are lacking [7, 521]. However, recurrent priapism episodes are common in men with sickle cell disease (42-64%) [522, 523] while in adolescents and young men the incidence of priapism is 35%, of whom 72% have a history of stuttering priapism [7].

The aetiology of stuttering priapism is similar to that of ischaemic priapism. While sickle cell disease is the most common cause, idiopathic cases and cases due to a neurological disorder have been reported. Moreover, men who have suffered from an acute ischaemic priapic event, especially one which has been prolonged (more than four hours) are at risk for developing stuttering priapism [487].

Recently, several studies have proposed alternative mechanisms including inflammation, cellular adhesion, nitric oxide metabolism, vascular reactivity and coagulation [420, 429, 457, 524, 525].

3.4.3.1.1 Summary of evidence on the epidemiology, aetiology and pathophysiology of stuttering priapism

Summary of evidence	LE
Stuttering priapism is similar to ischaemic priapism in that it is low flow, ischaemic and if left untreated would result in significant penile damage, with sickle cell disease being the most common cause. But the cause can also be idiopathic and in rare cases may be due to a neurological disorder.	3

3.4.3.2 Classification

Stuttering priapism, also termed intermittent or recurrent priapism, is a distinct condition that is characterised by repetitive and painful episodes of prolonged erections. Erections are self-limited with intervening periods of detumescence [457, 524]. These are analogous to repeated episodes of low flow (or ischaemic) priapism. The duration of the erectile episodes is generally shorter than in ischaemic priapism [3]. The frequency and/or duration of these episodes is variable and a single episode can sometimes progress into a major ischaemic priapic episode.

3.4.3.3 Diagnostic evaluation

3.4.3.3.1 History

A comprehensive history is mandatory and follows the same principles as described in Table 12. There is a history of recurrent episodes of prolonged erections. The onset of the priapic episodes usually occurs during sleep and detumescence does not occur upon waking. Many of these priapic episodes are painful and may be the reason that the patient seeks medical help.

3.4.3.3.2 Physical examination

Erections are painful and the penis is rigid as in ischaemic priapism, but the duration of events is usually shorter. Between erections the penis is usually normal, but in some cases signs of fibrosis can be found. Rarely, the penis may become enlarged, a condition known as megalophallus.

3.4.3.3.3 Laboratory testing

Laboratory testing follows the same principles as in the two other types of priapism. It is recommended to identify possible causes and should be directed by history, clinical and laboratory findings.

3.4.3.3.4 Penile imaging

There are no specific findings for stuttering priapism. Colour duplex US of the penis and perineum and MRI are recommended and can differentiate arterial from ischaemic type of priapism.

3.4.3.3.5 Recommendations for the diagnosis of stuttering priapism

The same recommendations as described in section 3.4.1.3.5 apply. Stuttering priapism is a recurrent or intermittent type of ischaemic priapism.

3.4.3.4 Disease management

The primary goal in the management of patients with stuttering priapism is the prevention of future episodes, which can usually be achieved pharmacologically. The management of each acute episode is similar to that for ischaemic priapism; aspiration/irrigation in combination with intracavernous injections of α-adrenergic agonists. Unfortunately, the efficacy and safety of the various treatment modalities reported in the medical literature are poorly characterised. Specifically, most reports are from small case series and the Panel is not aware of any published, well-designed, controlled studies on the efficacy and safety of these treatments [428, 457, 524].

3.4.3.4.1 Alpha-adrenergic agonists

Studies of oral α-adrenergic agonists have suggested some benefit for daily dosing of these agents as effective prevention [526]. Side-effects include tachycardia and palpitations. Pseudoephedrine, widely used as an oral decongestant, can also be used as a first-line treatment [454]. However, its effect on corporal smooth muscle is not fully understood. Etilefrine has been used successfully to prevent stuttering priapism due to sickle cell anaemia. It is taken orally at doses of 50-100 mg daily, with response rates of up to 72% [10, 527, 528]. In one randomised, placebo-controlled, clinical study looking at medical prophylaxis with etilefrine and ephedrine,there was no difference in efficacy between the two drugs.

3.4.3.4.2 Hormonal manipulations of circulating testosterone

The aim of hormonal manipulation is to down-regulate circulating testosterone levels to suppress the action of androgens on penile erection [428, 457, 529]. This can be done through the use of gonadotropin-releasing hormone (GnRH) agonists or antagonists, antiandrogens or oestrogens [530] (LE: 4). Potential side-effects may include hot flushes, gynaecomastia, impaired erectile function, loss of libido and asthenia. All approaches have a similar efficacy profile (LE: 4) while the potential cardiovascular toxicity of oestrogens limits their clinical use. Alternative endocrine approaches that have been used with some success include 5-alpha-reductase inhibitors [531] (LE: 3) and ketoconazole, an antifungal agent that reduces adrenal and testicular androgen production [529, 532] (LE: 4).

Of the hormonal agents suggested for preventing priapism, GnRH agonists and anti-androgens appear to be the most efficacious and safe. They are recommended as primary treatments for the management of stuttering priapism in adult men (LE: 4).

The duration of hormonal treatment for effective suppression of recurrent priapic events is problematic. It is not possible to make any conclusions on the efficacy, dose and the duration of treatment. Moreover, hormonal agents have a contraceptive effect and interfere with normal sexual maturation. Caution is therefore strongly advised when prescribing hormonal treatments to prepubertal boys, adolescents or men who are trying for their female partner to conceive. Castrate levels of testosterone, which have a contraceptive effect, interfere with growth, and significantly affect sexual function.

3.4.3.4.3 Digoxin

Digoxin (a cardiac glycoside and a positive inotrope) is used to treat patients with congestive heart failure. Digoxin regulates smooth muscle tone through a number of different pathways leading to penile detumescence [428, 457, 533]. The use of maintenance digoxin doses (0.25-0.5 mg daily) in idiopathic stuttering priapism has been proven to reduce the number of hospital visits and to improve QoL [457]. A small, clinical, double-blind, placebo-controlled study, using digoxin, produced a decrease in sexual desire and excitement with a concomitant reduction in penile rigidity, regardless of any significant change in plasma levels of testosterone, oestrogens and luteinising hormone [533] (LE: 2b). Side-effects may include a decreased libido, anorexia, nausea, vomiting, confusion, blurred vision, headache, gynaecomastia, rash and arrhythmia.

3.4.3.4.4 Terbutaline

Terbutaline is a beta-agonist that causes vasodilation, resulting in smooth muscle relaxation of the vasculature [428, 457] and has been used to prevent stuttering priapism with detumescence rates of 36% in patients with alprostadil-induced priapism [45] (LE: 3). The only randomised, placebo-controlled study (n = 68) in patients with pharmacologically-induced priapism, showed detumescence in 42% of the terbutaline-treated group compared to only 15% in the placebo-treated group [455] (LE: 1b). Side-effects include nervousness, shakiness, drowsiness, heart palpitations, headache, dizziness, hot flashes, nausea and weakness.

3.4.3.4.5 Gabapentin

Gabapentin has anticonvulsant, antinociceptive and anxiolytic properties and is widely used as an analgesic and antiepileptic agent. Its proposed mechanism of action is to inhibit voltage-gated calcium channels, which attenuates synaptic transmission [529], and reduces testosterone- and follicle-stimulating hormone levels [534]. It is given at a dose of 400 mg, four times a day, up to 2400 mg daily, until complete penile detumescence occurs, with subsequent maintenance administration of gabapentin, 300 mg daily [535] (LE: 4). Side-effects include anorgasmia and impaired erectile function.

3.4.3.4.6 Baclofen

Baclofen is a gamma-aminobutyric acid (GABA) derivative that acts as a muscle relaxant and anti-muscle spasm agent. It can inhibit penile erection and ejaculation through GABA activity and prevents recurrent reflexogenic erections or prolonged erections from neurological diseases [428]. Oral baclofen has little efficacy and it is not usually used in stuttering priapism but intrathecal baclofen dosing is more effective [457, 536-538] (LE: 4). Side-effects include drowsiness, confusion, dizziness, weakness, fatigue, headache, hypotension and nausea.

3.4.3.4.7 Hydroxyurea

Hydroxyurea blocks the synthesis of deoxyribonucleic acid (DNA) by inhibiting ribonucleotide reductase, which has the effect of
arresting cells in the S-phase [529, 539]. It is an established treatment for ameliorating sickle cell disease and improving their life expectancy [456, 540]. For such patients with recurrent priapism there is limited evidence to suggest a medical prophylactic role (LE: 3) [529, 539, 541]. Side-effects include oligozoospermia and leg ulcers.

3.4.3.4.8 Phosphodiesterase type 5 inhibitors (PDE5Is)

Low doses of PDE5Is have a paradoxical effect in alleviating and preventing stuttering priapism, mainly in patients with idiopathic and sickle cell disease-associated priapism [428, 457, 542-546] (LE: 3). It is important to remember that therapy should be started when the penis is in its flaccid state and not during an acute episode. There is a delay of one week before treatment is effective. There are no reported impairments in male sexual function (LE: 3). PDE5Is probably act in priapism by increasing the concentration of cGMP in the smooth muscle in a NO dysfunctional state. This can occur in priapism and may result in a change in the nitric oxide pathway, with down-regulation of cavernosal PDE5 thereby preventing the complete degradation of cGMP in the corpora cavernosa [428, 457, 542, 545].

3.4.3.4.9 Intracavernosal injections

Some patients with stuttering priapism, who have been started on systemic treatments to prevent recurrence of unwanted erections, may not see therapeutic benefits immediately and may temporarily require intracavernous self-injections at home with sympathomimetic agents [428, 457]. The most commonly used drugs are phenylephrine and etilephrine (as described in the treatment of ischaemic priapism) [3, 420, 521, 528] (LE: 3). Side-effects include hypertension, coronary ischaemia and cardiac arrhythmias.

Tissue plasminogen activator (TPA) is a secreted serine protease that converts the proenzyme plasminogen to plasmin, which acts as a fibrinolytic enzyme. Limited clinical data have suggested that a single intracavernous injection of TPA can successfully treat patients with recalcitrant priapism [529, 547] (LE: 3). Mild bleeding is the most commonly observed side-effect.

3.4.3.4.10 Summary of evidence and recommendations for the treatment of stuttering priapism

Summary of evidence	**GR**
The primary goal in the management of patients with stuttering priapism is the prevention of future episodes, which can generally be achieved pharmacologically.	B
PDE5Is have a paradoxical effect in alleviating and preventing stuttering priapism, mainly in patients with idiopathic and sickle cell disease associated priapism.	C
The evidence with other systemic drugs (digoxin, alpha-adrenergic agonists, baclofen, gabapentin, terbutaline) is very limited.	C

Recommendations	**GR**
Manage each acute episode similar to that for ischaemic priapism.	B
Use hormonal therapies (mainly gonadotropin-receptor hormone agonists or antagonists) and/or antiandrogens for the prevention of future episodes in patients with frequent relapses. Do not use them before sexual maturation is reached.	C
Initiate treatment with phosphodiesterase type 5 inhibitors (PDE5Is) only when the penis is in its flaccid state.	C
Use digoxin, α-adrenergic agonists, baclofen, gabapentin or terbutaline) only in patients with very frequent and uncontrolled relapses.	C
Use intracavernous self-injections at home of sympathomimetic drugs for the treatment of acute episodes on an interim basis until ischaemic priapism has been alleviated.	C

3.4.3.5 Follow-up

Follow-up for stuttering priapism include history and clinical examination to assess the efficacy of treatments in preventing or alleviating erectile events as well as assessing erectile function and penile fibrosis.

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5. CONFLICT OF INTEREST

All members of the EAU Male Sexual Dysfunction Guidelines Panel have provided disclosure statements of all relationships which they have and which may be perceived as a potential source of conflict of interest. This information is kept on file in the European Association of Urology Central Office database. This document was developed with the financial support of the European Association of Urology. No external sources of funding and support have been involved. The EAU is a non-profit organisation and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.