

EAU Guidelines on Erectile Dysfunction, Premature Ejaculation, Penile Curvature and Priapism

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1. INTRODUCTION

1.1 Aim

These guidelines include four 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). Erectile Dysfunction 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 [3]. 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 four hours and beyond, or is unrelated to sexual interest or stimulation [4]. Overall, erections lasting up to four hours are by consensus defined as 'prolonged'. 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 persons per year) [5, 6]. In men with sickle cell disease, the prevalence of priapism is up to 3.6% in men less than eighteen years of age [7] increasing up to 42% in men more than eighteen years of age [8-11].

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. Guidelines are not mandates and do not purport to be a legal standard of care.

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 "EAU Guidelines on Male Sexual Dysfunction" [12]. In 2011 the Panel decided to develop new guidelines addressing Penile Curvature, which resulted in a new publication in 2012 [13]. In 2014 a guideline on Priapism was completed [14].

The 2016 edition merged the previous EAU guidelines for ED, PE, penile curvature and priapism into one guideline [15]. In 2017 a scoping search was performed covering all areas of the guideline and it was updated accordingly.

1.3 Available Publications

Alongside several scientific summaries published in the EAU scientific journal, European Urology [16-20], 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 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, selected based on their expertise to represent the professionals treating patients suffering from ED, PE, penile curvature and priapism.

2. METHODS

2.1 Introduction

For the 2018 edition of the EAU Guidelines, the Guidelines Office have transitioned to a modified GRADE methodology across all 20 guidelines [21, 22]. For each recommendation within the guidelines there is an accompanying online strength rating form which addresses a number of key elements namely:

1. the overall quality of the evidence which exists for the recommendation, references used in this text are graded according to a classification system modified from the Oxford Centre for Evidence-Based Medicine Levels of Evidence [23];
2. the magnitude of the effect (individual or combined effects);
3. the certainty of the results (precision, consistency, heterogeneity and other statistical or study related factors);
4. the balance between desirable and undesirable outcomes;
5. the impact of patient values and preferences on the intervention;
6. the certainty of those patient values and preferences.

These key elements are the basis which panels use to define the strength rating of each recommendation. The strength of each recommendation is represented by the words 'strong' or 'weak' [24]. The strength of each recommendation is determined by the balance between desirable and undesirable consequences of alternative management strategies, the quality of the evidence (including certainty of estimates), and nature and variability of patient values and preferences. The strength rating forms will be made available online. Additional 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 viewed online at the above address.

For the 2018 print, a scoping search was performed covering all areas of the guideline covering the period May 2016 to May 2017. Embase, Medline and the Cochrane Central Register of Controlled Trials (RCTs) databases were searched, with a limitation to systematic reviews, meta-analyses or randomised controlled trials. A total of 2,220 unique records were identified, retrieved and screened for relevance, of which 58 were selected for inclusion. A detailed search strategy is available online: <http://www.uroweb.org/guideline/male-sexual-dysfunction/>.

2.2 Review

This document was subject to peer review prior to publication in 2015.

2.3 Future goals

The results of ongoing and new systematic reviews will be included in the 2019 update of the Male Sexual Dysfunction Guidelines. Ongoing systematic reviews include:

- What is the effectiveness (efficacy and safety) of non-operative treatment for Peyronie's disease?
- What is the effectiveness (efficacy and safety) of surgical treatment for Peyronie's disease?
- What are the benefits and harms of testosterone treatment for male sexual dysfunction? [25].

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 smooth muscle compartment. It includes arterial dilation, trabecular smooth muscle relaxation and activation of the corporeal veno-occlusive mechanism [26]. Erectile Dysfunction is defined as the persistent inability to attain and maintain an erection sufficient to permit satisfactory sexual performance [27]. Erectile Dysfunction may affect physical and psychosocial health and may have a significant impact on the quality of life (QoL) of sufferers and their partner's [28-30]. There is increasing evidence that ED can be an early manifestation of coronary artery and peripheral vascular disease. Erectile Dysfunction should not be regarded only as a QoL issue, but also as a potential warning sign of cardiovascular disease (CVD) [31-33].

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) [28] 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% [34]. The incidence rate of ED (new cases per 1,000 men annually) was 26 in the long-term data from the MMAS study [35] and 19.2 (mean follow-up of 4.2 years) in a Dutch study [36]. 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 [37]. 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

Erectile Dysfunction shares both unmodifiable and modifiable common risk factors with CVD (e.g., obesity, diabetes mellitus, dyslipidemia, metabolic syndrome, lack of exercise, and smoking) [30, 38-40]. The association between ED status and age, diabetes mellitus duration, poor glycaemic control, body mass index (BMI) [41, 42], obstructive sleep apnoea, hyperhomocysteinemia and chronic liver failure associated with hepatitis B has also been confirmed [43-45]. An association between ED status and vitamin D deficiency has also been reported [46, 47].

A number of studies have shown some evidence that lifestyle modification [32, 48] and pharmacotherapy [48, 49] for CVD 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 [33].

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 [50]. The Multinational Survey on the Aging Male (MSAM-7) study - performed in the USA, 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 the 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% [51]. An association between chronic prostatitis/chronic pelvic pain syndrome and ED has also been confirmed [52]. Effects on erectile function vary according to the type of surgery performed in men with LUTS/BPH [53].

Recent epidemiological data have also highlighted other unexpected risk factors potentially associated with ED including psoriasis [54-56], gouty arthritis [57, 58] and ankylosing spondylitis [59], non-alcoholic fatty liver [60], other chronic liver disorders [61], chronic periodontitis [62], open-angle glaucoma [63], inflammatory bowel disease [64] and following transrectal ultrasound (TRUS)-guided prostate biopsy [65].

3.1.1.3 Pathophysiology

The pathophysiology of ED may be vasculogenic, neurogenic, anatomical, hormonal, drug-induced and/or psychogenic (Table 1) [26]. In most cases, numerous pathophysiology pathways can be comorbid and concomitant negatively impacting on erectile function.

The proposed ED etiological and pathophysiological subdivision is to be considered mainly didactic. In most cases, erectile dysfunction recognises more than one organic pathophysiological element and very often, if not always, a psychological component. Likewise, organic components can negatively impact on erectile function with different and concomitant pathophysiological pathways. Therefore Table 1 must be considered for diagnosis orientation.

Table 1: Pathophysiology of ED

Vasculogenic
Recreational habits (e.g. cigarette smoking)
Lack of regular physical exercise
Obesity
Cardiovascular diseases (e.g. hypertension, coronary artery disease, peripheral vasculopathy, etc.)

Type 1 and 2 diabetes mellitus; hyperlipidaemia; metabolic syndrome; hyperhomocysteinemia, etc.
Major pelvic surgery (radical prostatectomy [RP]) or radiotherapy (pelvis or retroperitoneum)
Neurogenic
<i>Central causes</i>
Degenerative disorders (e.g., multiple sclerosis, Parkinson's disease, multiple atrophy, etc.)
Spinal cord trauma or diseases
Stroke
Central nervous system tumours
<i>Peripheral causes</i>
Type 1 and 2 diabetes mellitus
Chronic renal failure; chronic liver failure
Polyneuropathy
Surgery (major surgery of pelvis/retroperitoneum) or radiotherapy (pelvis or retroperitoneum)
Surgery of the urethra (urethral stricture, urethroplasty, etc.)
Anatomical or structural
Hypospadias; epispadias; micropenis
Phimosis
Peyronie's disease
Penile cancer (other tumors of the external genitalia)
Hormonal
Diabetes Mellitus; Metabolic Syndrome;
Hypogonadism (any type)
Hyperprolactinaemia
Hyper- and hypothyroidism
Hyper- and hypocortisolism (Cushing's disease, etc.)
Panhypopituitarism and multiple endocrine disorders
Mixed pathophysiology pathways
Chronic systemic diseases (e.g., diabetes mellitus, hypertension, metabolic syndrome, chronic renal failure, chronic liver disorders, hyperhomocysteinemia, obstructive sleep apnoea, etc.)
Psoriasis; gouty arthritis; ankylosing spondylitis; non-alcoholic fatty liver; chronic periodontitis; open-angle glaucoma; inflammatory bowel disease
Iatrogenic causes (e.g. TRUS-guided prostate biopsy, etc.)
Drug-induced
Antihypertensives (e.g., thiazide diuretics, beta-blockers, etc.)
Antidepressants (selective serotonin reuptake inhibitors, tricyclics)
Antipsychotics (e.g., neuroleptics, etc.)
Antiandrogens (GnRH analogues and antagonists; 5-ARIs)
Recreational drugs (e.g., 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

GnRH = gonadotropin-releasing hormone; 5-ARIs = 5 α -Reductase inhibitors.

3.1.1.3.1 Post-radical prostatectomy ED, post-radiotherapy ED & post-brachytherapy ED

Radical prostatectomy 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 ten years [66]. 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 [67, 68]. Research has shown that 25-75% of men experience post-RP ED [69]. Of clinical relevance, the rate of unassisted post-operative erectile function recovery is in the range between 20 and 25% in most studies; (these rates appear not to have been substantially improved or changed over the past seventeen years [70]. 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 twelve month potency rates [71], without significant differences

between laparoscopic RP and RARP. Some recent reports confirm that the possibility of achieving erectile function recovery is about twice as high for RARP compared with the open RP [72]. Recently a prospective, controlled, non-randomised trial of patients undergoing RP in fourteen Swedish centres comparing RARP versus retropubic RP, showed a small improvement regarding erectile function after RARP [73]. Conversely, a randomised controlled phase 3 study of men assigned to open RP or RARP showed that the two techniques yielded similar functional outcomes at twelve weeks [74]. As a whole, more controlled prospective studies, with longer term follow-up, are necessary to determine if RARP is superior to open RP in terms of post-operative ED rates [75]. 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 [69, 76, 77].

Pre-operative potency is a major factor associated with the recovery of erectile function after surgery [68]. Patients being considered for nerve-sparing RP (NSRP) should ideally be potent pre-operatively [67, 68]. Overall, the chronological 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) [78]. 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 [67, 69].

Erectile dysfunction is also a common sequela after external beam radiotherapy and brachytherapy for PCa [79-81]. The mechanisms contributing to ED after prostate irradiation involve injury to the neurovascular bundles, penile vasculature, and cavernosal structural tissue [79]. 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 [82, 83].

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 BMI) 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

Erectile dysfunction 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 terms 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 partner's [84]. In this context, taking a comprehensive medical history may reveal one of the many common disorders associated with ED [84]. 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 patient's 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 [85, 86]. Validated psychometric questionnaires, such as the International Index for Erectile Function (IIEF) [87] or its short version the Sexual Health Inventory for Men

(SHIM) [88], 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 [89]. In cases of clinical depression, the use of a two question scale for depression is recommended in everyday clinical practice, for example: “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?” [90]. 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. In this regard, although LUTS/BPH in itself does not represent a contraindication to treat a patient for late onset hypogonadism, screening for LUTS severity is clinically relevant [91].

3.1.3.1.2 Physical examination

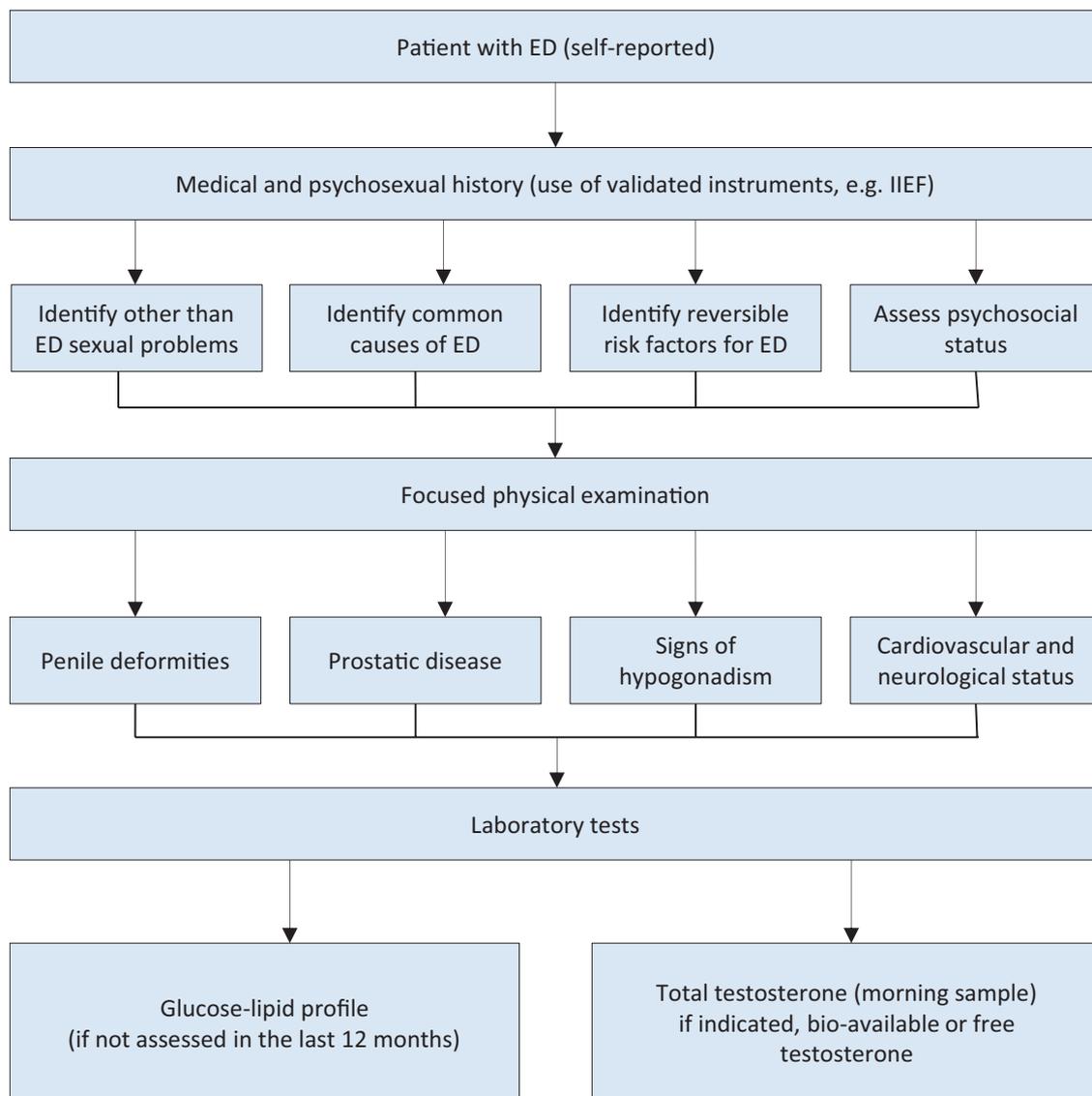
Every patient must be given a physical examination focused on the genitourinary, endocrine, vascular and neurological systems [92, 93]. A physical examination may reveal unsuspected diagnoses, such as Peyronie’s disease, pre-malignant or malignant genital lesions, prostatic enlargement or irregularity/nodularity, 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 three to six months. Likewise either BMI calculation or waist circumference measurement should be taken into consideration in every patient with comorbid conditions.

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 bio-available or calculated-free testosterone may be needed to corroborate total testosterone measurements. However, the threshold of testosterone required to maintain an erection is low and ED is usually a symptom of more severe cases of hypogonadism [39, 94-96]. For levels > 8 nmol/L the relationship between circulating testosterone and sexual functioning is very low [39, 94-96]. Additional laboratory tests may be considered in selected patients (e.g., prostate-specific antigen [PSA]) [97]; prolactin, and luteinising hormone [98]. 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 [93].

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 [99] and women [100]. Overall, ED can improve the sensitivity of screening for asymptomatic CVD in men with diabetes [101, 102]. Erectile dysfunction significantly increases the risk of CVD, coronary heart disease, stroke, and all these cause mortality, and the increase is probably independent of conventional cardiovascular risk factors [31, 32, 103, 104]. Longitudinal data from an observational population-based study of 965 men without CVD, showed that younger men (< 50 years) with persistent ED have an increased Framingham risk that is independent of traditional CVD risk factors [105].

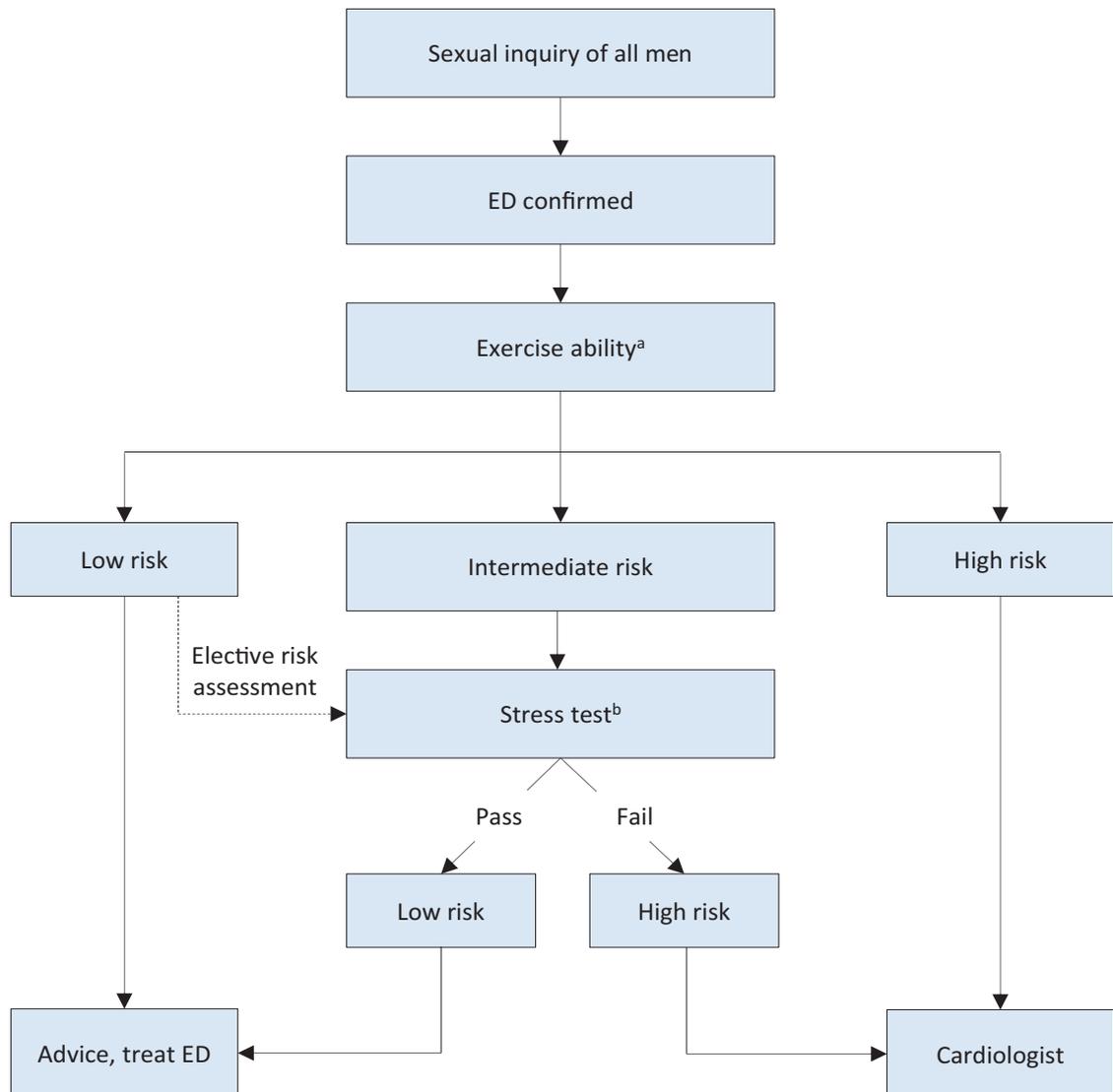
The EAU Guidelines for diagnosing and treating men with ED have been adapted from previously published recommendations from the Princeton Consensus conferences on sexual dysfunction and cardiac risk [106]. The Princeton Consensus (Expert Panel) Conference is dedicated to optimising sexual function and preserving cardiovascular health [106-108]. 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 [49].

Table 2: Cardiac risk stratification (based on 2nd and 3rd Princeton Consensus [106, 108])

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) [106]



^a Sexual activity is equivalent to walking 1 mile on the flat in 20 minutes or briskly climbing two flights of stairs in 10 seconds.

^b Sexual activity is equivalent to four minutes 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 based on medical and sexual history; 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 ten or more minutes [109].

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 ten minutes after the intracavernous injection and lasts for 30 minutes [110]. 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 [111, 112]. Further vascular investigation is unnecessary if a duplex ultrasound (US) 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 [113]. Recent data suggested the use of computed tomography angiography in cases of penile artery angioplasty for patients with ED and isolated penile artery stenoses [114].

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 [37], psychiatric assessment may be helpful before any clinical 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 [115]. Patient and partner education is an essential part of ED management [115, 116].

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 revascularisation surgery or angioplasty.
Patients with penile deformities which might require surgical correction (e.g., Peyronie's disease, congenital penile 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

Nocturnal Penile Tumescence and Rigidity (NTPR) using Rigiscan®
Vascular studies <ul style="list-style-type: none"> - 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	Strength rating
Take a comprehensive medical and sexual history in every patient.	Strong
Use a validated questionnaire related to erectile dysfunction to assess all sexual function domains and the effect of a specific treatment modality.	Strong
Include a physical examination in the initial assessment of men with erectile dysfunction (ED) to identify underlying medical conditions and comorbid genital disorders that may be associated with ED.	Strong
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.	Strong
Include specific diagnostic tests in the initial evaluation of ED in the presence of the conditions presented in Table 3.	Strong

3.1.4 Disease management

3.1.4.1 Treatment options

Erectile dysfunction may be associated with modifiable or reversible risk factors, including lifestyle or drug-related factors [33]. 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, 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 any ED treatment [117]. 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) [95, 98], 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 invasiveness, efficacy, safety, and cost, as well as patient preference [115]. In this context, physician-patient (partner, if available) 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 invasiveness 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 physical or/and pharmacological treatment. Major clinical potential benefits of lifestyle changes may be achieved in men with specific comorbid cardiovascular or metabolic disorders, such as diabetes or hypertension [33, 118].

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 recovery time for potency [67], although there is a lack of data to support any specific regimen for penile rehabilitation [119]. 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 still considered as the first-line therapy in patients who have undergone nerve-sparing (NS) surgery regardless of the surgical technique used [67, 68]. 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-RP erectile function [67, 68, 71, 120]. 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 [67, 121]. Early use of high-dose sildenafil after RP has been suggested to be associated with preservation of smooth muscle within the corpora cavernosa [122]. 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 [123]. Conversely, a recent prospective, randomised, placebo-controlled study, which assessed the effects of nightly sildenafil citrate therapy during penile rehabilitation using nocturnal penile rigidity score in addition to the IIEF-EF, showed no therapeutic benefit for nightly sildenafil when compared to on-demand dosing in determining recovery of erectile function post-prostatectomy [124].

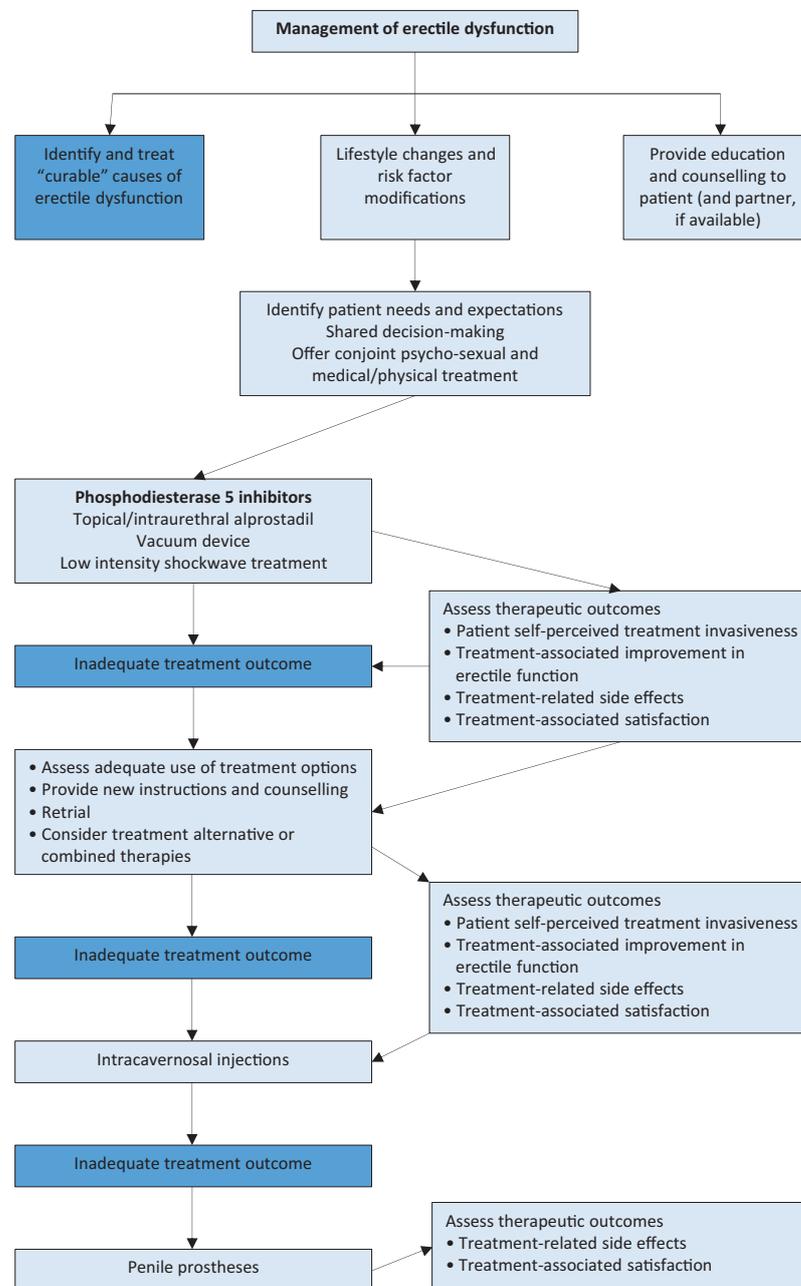
The effectiveness of tadalafil and vardenafil as on-demand treatment has been evaluated in post-RP ED. A large multicentre trial in Europe and the USA has investigated the effects of tadalafil in patients with ED following bilateral NS surgery. Erectile function was improved in 71% of patients treated 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 [125]. Similarly, vardenafil has been tested in patients with ED following NSRP in a randomised, multicentre, prospective, placebo-controlled study in North America [126]. 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 [127]. Moreover, a randomised, double-blind, double-placebo trial in men < 68 years of age and with normal pre-operative erectile function who underwent NSRP at 50 centres from nine European countries and Canada, compared tadalafil once daily with placebo [128]. Tadalafil was most effective for 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 maintaining penile length [128]. Unassisted erectile function was not improved after cessation of active therapy for nine months [128]. Moreover, taking tadalafil once daily significantly shortened time to erectile function recovery versus placebo over the nine month double/blind treatment period. Conversely tadalafil on demand did not [129]. Likewise, tadalafil once daily improved QoL post-operatively, both at double-blind treatment and open label treatment period [130].

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 [131]. In patients whose pre-operative erectile function domain score was > 26, vardenafil was efficacious when used on demand, supporting a paradigm shift towards on-demand dosing with PDE5Is in post-RP ED [131]. 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 twelve weeks showed significantly greater increases in sexual encounter profile (SEP) question 2 and SEP3 as well as in mean change of IIEF erectile function domain score with 100 and 200 mg avanafil vs. placebo ($p < 0.01$) [108].

For dosing with avanafil 36.4% (28 of 77) of sexual attempts (SEP3) at fifteen minutes or less were successful vs. 4.5% (2 of 44) for placebo ($p < 0.01$) [132]. A recently conducted meta-analysis confirmed that avanafil had comparable efficacy with sildenafil, vardenafil and tadalafil treatments [133]. Although some authors reported improved erectile function when long-term tadalafil 5 mg once daily is combined with sildenafil as needed [134], more safety analyses are required to recommend such a therapy.

Historically, the treatment options for post-RP ED have included intracavernous injections [135], urethral microsuppository [67, 136], vacuum device therapy [67, 119, 137, 138], and penile implants [67, 139, 140]. 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 [141] (Sections 3.1.4.3 and 3.1.4.4). There are currently several potential novel treatment modalities for ED, from innovative vasoactive agents and trophic factors to stem cell therapy and gene therapy. Most of these therapeutic approaches require further investigation in large-scale, blinded, placebo-controlled randomised studies in order to achieve an adequate evidence base and clinically-reliable grade of recommendation [142].

Figure 3: Management algorithm for erectile dysfunction



3.1.4.1.3 Causes of ED that can be 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 [98]. 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) [98, 143]. When clinically indicated [144], testosterone supplementation (TS) (intramuscular, oral, or transdermal) is effective, but should only be used after other endocrinological causes for testicular failure have been excluded [39, 95, 145]. Before initiating TS, digital rectal examination (DRE), serum PSA, haematocrit, liver function tests and lipid profile should be performed [39, 95, 146]. Patients who are given TS should be monitored for a clinical response, elevation of haematocrit and development of hepatic or prostatic disorders [39, 95, 146]. Testosterone supplementation is controversial in men with a history of PCa (LE: 4) [147]. 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).

Testosterone supplementation is contraindicated in patients with unstable cardiac disease [91, 148]. 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 [149-154]. 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 testosterone in patients with heart disease to improve survival [94]. However, a comprehensive SR and meta-analysis of all placebo-controlled RCTs on the effect of TS on cardiovascular-related problems did not support a causal role between TS and adverse cardiovascular events [148].

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 [155, 156]. 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 [155].

3.1.4.1.3.3 Psychosexual counselling and therapy

For patients with a significant psychological problem [157], psychosexual therapy may be given either alone or with another therapeutic approach in order to improve couple sexual satisfaction and female sexual function [158]. Psychosexual therapy requires ongoing follow-up and has had variable results [159].

3.1.4.2 *Therapeutic Strategy*

Based on the currently available peer-reviewed literature and the consensus of the panel, the new therapeutic and decision-making algorithm (Figure 3) for treating ED considers both the level of invasiveness of each therapy and the efficacy of the therapy itself.

3.1.4.2.1 First-line therapy

3.1.4.2.1.1 Oral pharmacotherapy

Phosphodiesterase 5 hydrolyses (PDE5Is) 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 penile erection [160]. Four potent selective PDE5Is have been approved by the European Medicines Agency (EMA) for the treatment of ED [161]. 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 [117].

Sildenafil

Sildenafil was launched in 1998 and was the first PDE5I available on the market [162]. 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 [162]. Sildenafil is effective 30-60 minutes after administration [162]. Its efficacy is reduced after a heavy, fatty meal due to delayed absorption. Efficacy may be maintained for up to twelve hours [163]. The pharmacokinetic data for sildenafil is presented in Table 5. Adverse events (Table 6) are generally mild in nature and self-limited [164, 165]. 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 [166]. 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. (LE: 1), irrespective

of age [167]. Recently, an orally disintegrating tablet (ODT) of sildenafil citrate at a dosage of 50 mg has been developed mainly for the benefit of patients who have difficulty swallowing solid dosage forms.

Tadalafil

Tadalafil was licensed for treatment of ED in February 2003 and is effective from 30 minutes after administration, with peak efficacy after about two hours [168]. Efficacy is maintained for up to 36 hours [168] and is not affected by food. It is administered in on-demand doses of 10 and 20 mg or a 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 [168, 169]. Pharmacokinetic data for tadalafil is presented in Table 5. Adverse events (Table 6) are generally mild in nature and self-limited by continuous use. In pre-marketing studies, after twelve weeks of treatment 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 [168]. Tadalafil significantly improved patient scores for IIEF, SEP2, SEP3, and GAQ and treatment satisfaction [168].

Efficacy has been confirmed in post-marketing studies [161, 170]. The efficacy of tadalafil in almost every subgroup of patients with ED, including difficult-to-treat subgroups (e.g. diabetes mellitus), has been successfully established [171]. Daily tadalafil has also been licensed for the treatment of LUTS secondary to BPH. Therefore, it is useful in patients with concomitant ED and LUTS [172]. Recent data also states that 40% of men aged ≥ 45 years were combined responders for ED and LUTS/BPH to treatment with tadalafil 5 mg once daily, with symptoms improved after twelve weeks [173].

Vardenafil

Vardenafil became commercially available in March 2003 and is effective from 30 minutes after administration [171], with up to one out of three patients achieving satisfactory erections within 15 minutes of ingestion [174]. Its effect is reduced by a heavy, fatty meal ($> 57\%$ fat). Doses of 5, 10 and 20 mg 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 [175]. Pharmacokinetic data for vardenafil is presented in Table 5. Adverse events (Table 6) are generally mild in nature and self-limited by continuous use [175]. After twelve 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 [175, 176]. Vardenafil significantly improved patient scores for IIEF, SEP2, SEP3, and GAQ and treatment satisfaction. Efficacy has been confirmed in post-marketing studies [175, 176]. The efficacy of vardenafil in almost every subgroup of patients with ED, including difficult-to-treat subgroups (e.g. diabetes mellitus), has been successfully established. More recently, an ODT form of vardenafil has been released [176]. 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 bio-availability compared to film-coated tablets [177]. The efficacy of vardenafil ODT has been demonstrated in several RCTs and did not seem to differ from the regular formulation [177-179].

Avanafil

Avanafil is a highly-selective PDE5I that became commercially available in 2013 [180]. 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 [181]. Doses of 50 mg, 100 mg, and 200 mg have been approved for on-demand treatment of ED [180]. 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 [180, 182, 183]. 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 [180, 182]. Data from sexual attempts made within fifteen 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 [182]. Pharmacokinetic data for avanafil is presented in Table 5 [180, 182]. Adverse events are generally mild in nature (Table 6) [180, 182]. 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 [180, 184]. 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.

Choice or preference between the different PDE5Is

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, three to four 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. A recent meta-analysis demonstrated that ED patients who prioritise high efficacy must use sildenafil 50 mg whereas those who optimise tolerability should initially use tadalafil 10 mg and switch to udenafil 100 mg if the treatment is not sufficient [170]. Of clinical relevance, udenafil is not an EMEA or FDA approved drug. In addition, results of another clinical trial revealed that tadalafil 5 mg once daily may improve the erectile function outcomes among men who had a partial response to on-demand PDE5I therapy [185].

Continuous use of PDE5Is

Animal studies have shown that chronic use of PDE5Is significantly improves or prevents the intracavernous structure alterations due to age, diabetes, or surgical damage [186-190]. 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 [191]. In 2007, tadalafil 2.5 and 5 mg were approved by the EMA for daily treatment of ED. According to the 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 re-assessed periodically [191, 192]. A recently published integrated analysis showed that no clinical populations of patients with ED seemed to benefit overwhelmingly from tadalafil once daily over on-demand dosing regimen and *vice versa* [193]. 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 PDE5Is 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	1,685 µg.h/L	8,066 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 half-time; AUC: area under curve or serum concentration time curve.

Table 6: Common adverse events of the four PDE5Is 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 PDE5Is

(i) 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 six 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 [106, 194-196].

(ii) Nitrates are contraindicated with PDE5Is

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 such as “poppers” which are 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 hours if sildenafil (and probably also vardenafil) is used (half-life, four hours), or at least 48 hours if tadalafil is used (half-life, 17.5 hours), and for no less than twelve hours if avanafil is used (half-life, 6-17 hours) [197].

(iii) 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 [106]. 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 [198].

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 four hours following treatment with an α -blocker. A starting dose of 25 mg is recommended [164].
- 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 [171, 175, 176].
- Tadalafil is not recommended in patients taking doxazosin, but this is not the case for tamsulosin [168, 199].
- 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 CYP3A4 pathway will inhibit the metabolic breakdown of PDE5Is, thus increasing PDE5Is blood levels (e.g. 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 PDE5Is

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 [200]. 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.

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 [163, 165, 177, 184, 201-203]. 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 [165, 177, 184, 201-203], most patients require a longer delay between taking the medication [175, 184, 204, 205]. Absorption of sildenafil can be delayed by a meal, and absorption of vardenafil can be delayed by a fatty meal [206]. Absorption of tadalafil is less affected provided there is enough delay between oral ingestion and an attempt at sexual intercourse [201]. 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 [180, 181, 184].

It is possible to wait too long after taking the medication before attempting sexual intercourse. The half-life of sildenafil and vardenafil is about four hours, suggesting that the normal window of efficacy is six to eight hours following drug ingestion, although responses following this time period are well recognised. The half-life of avanafil is six to seventeen hours. Tadalafil has a longer half-life of ~17.5 hours, 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 [207-211]. 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 [207-209].

Recent data suggested that response to sildenafil treatment was also dependent on polymorphism in the PDE5A gene, which encodes the principal cGMP-catalysing enzyme in the penis, regulating cGMP clearance, and it is the primary target of sildenafil [212]. Overall, the findings of a meta-regression aimed at evaluating the effectiveness and prognostic factors of PDE5I to treat ED showed that PDE5Is are more effective in Caucasians than Asians, and in patients with more severe ED [213].

Clinical strategies in patients correctly using a PDE5Is

Data suggest that almost half of patients abandon first-generation PDE5Is within one year, with no single specific factor playing a major role in PDE5Is dropout rates [214].

There is controversial evidence suggesting that, in patients with testosterone deficiency, TS might improve a patient's response to a PDE5I [95, 215-218]. 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 [219]. 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 a short acting PDE5I (such as sildenafil), without any significant increase in terms of side-effects [220]. 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).

The combination of long-acting injectable testosterone undecanoate and tadalafil 5 mg once daily produced a significant improvement in terms of erectile function of combined treatment [221]. Moreover, the improvement in erectile function was well maintained, even after the cessation of treatment.

3.1.4.2.1.2 Vacuum erection devices

Vacuum erection devices (VED) 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% [222, 223]. Most men who discontinue use of VEDs do so within three months. Long-term use of VEDs decreases to 50-64% after two years [224]. The most common adverse events include pain, inability to ejaculate, petechiae, bruising, and numbness, which occur in < 30% of patients [223]. Serious adverse events (skin necrosis) can be avoided if patients remove the constriction ring within 30 minutes after intercourse. Vacuum erection devices are contraindicated in patients with bleeding disorders or on anticoagulant therapy. Vacuum erection devices 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 [222, 223, 225].

3.1.4.2.1.3 Topical/Intraurethral Alprostadil

The vasoactive agent alprostadil can be administered per urethra in two different ways. A first less invasive way is the topical route using a cream that includes a permeation enhancer in order to facilitate absorption of alprostadil (200 and 300µg) via the urethral meatus [226, 227]. Clinical data are still limited. Significant improvement compared to placebo was recorded for IIEF-EF domain score, SEP2 and SEP3 in a broad range of patients with mild-to-severe ED [228]. Side-effects include penile erythema, penile burning and pain that usually resolve within two hours of application. Systemic side effects are very rare. Topical alprostadil (VITAROSTM) at the dose of 300 µg is currently approved and it is available in some European countries.

The second route of administration is intraurethral insertion of a specific formulation of alprostadil (125-1000 µg) in a medicated pellet (MUSE™) [229]. Erections sufficient for intercourse are achieved in 30-65.9% of patients. In clinical practice, it is recommended that intra-urethral alprostadil be initiated at a dose of 500µg, as it has a higher efficacy than the 250 µg dose, with minimal differences with regard to adverse events. In case of unsatisfactory clinical response the dose can be increased to 1000 µg [229-231]. The application of a constriction ring at the root of the penis (ACTIS™) may improve efficacy [230, 231].

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 [232], with a very low rate (~30%) of adherence to long-term therapy. Intraurethral pharmacotherapy provides an alternative to intracavernous injections in patients who prefer a less-invasive, although less-efficacious treatment.

3.1.4.2.1.4 Shockwave therapy

The use of low-intensity extracorporeal shockwave therapy (LI-SWT) has been increasingly proposed as a treatment for ED over the last decade [233-239]. Overall, most of these studies reported encouraging results, regardless of variation in LI-SWT set-up parameters or treatment protocols [240]. As a whole these studies suggest that LI-SWT could significantly improve the IIEF and Erection Hardness Score of mild ED patients [241]. Likewise, data suggest that LI-SWT could ameliorate erection quality even in patients with severe ED who are PDE5Is non-responders [238, 242] or inadequate responders [241]. However, the publication of unequivocal evidence from additional RCTs and longer-term follow-up would provide more confidence regarding the use of LI-SWT (including detailed number of pulses per patient, treatment protocols) for ED patients [243]. Therefore clear and definitive recommendations cannot be given [240, 241].

3.1.4.2.2 Second-line therapy

Patients not responding to oral drugs may be offered intracavernous injections. The success rate is high (85%) [232, 244]. Intracavernous administration of vasoactive drugs was the first medical treatment for ED introduced more than twenty years ago [211, 245].

3.1.4.2.2.1 Intracavernous injections

3.1.4.2.2.1.1 Alprostadil

Alprostadil (Caverject™, Edex/Viridal™) was the first and only drug approved for intracavernous treatment of ED [211, 245]. 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 five to fifteen 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 population, as well as in patient subgroups (e.g. diabetes or CVD), with reported sexual activity of 94% after the injections and satisfaction rates of 87-93.5% in patients and 86-90.3% in partners [211, 245]. 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%) [211, 245, 246]. Pain is usually self-limited after prolonged use. It can be alleviated with the addition of sodium bicarbonate or local anaesthesia [211, 245, 247]. Cavernal 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 [211, 245, 248, 249], with most drop-outs occurring within the first two to three 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 [250].

3.1.4.2.1.2 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, moxislyte or calcitonin gene-related peptide, usually combined with the main drugs [251, 252]. 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 [253, 254]. 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).
- Vasoactive intestinal peptide (25 µg) plus phentolamine mesylate (1-2 mg Invicorp™), 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 [255].

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 [256]. 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).

3.1.4.2.3 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 [257]. The two currently available classes of penile implants include inflatable (2- and 3-piece) and semi-rigid devices (malleable, mechanical, soft flexible) [67, 139, 258-260]. 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. Semi-rigid prostheses result in a firm penis, which may be manually placed in an erect or flaccid state and offer the advantage of a feasible implant technique as well as a simpler use for the patient [67, 139, 258, 259]. On the contrary, they have the disadvantage of unnatural erection, reduce concealability, suboptimal penile length and girth [259, 261].

There are two main surgical approaches for penile prosthesis implantation: penoscrotal and infrapubic [258, 259, 261, 262]. 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 either placed blindly into the retropubic space, which can be a problem in patients with a history of major pelvic surgery (mainly radical cystectomy) or a separate incision in the abdomen is used to insert the reservoir under direct vision. 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 [67, 139, 258, 263-270]. 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 [67, 139, 271-273]. Structured psychosexual counselling may improve sexual activities and erotic functions in both patients and their partners after penile implants [274].

3.1.4.2.3.1 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/CXR™ and Coloplast Titan Zero degree™ resulted in mechanical failure rates of < 5% after five years of follow-up [139, 275, 276]. 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 [277-279]. The infection rate may be further reduced to 1-2% by implanting an antibiotic-impregnated prosthesis (AMS Inhibizone™) or hydrophilic-coated prosthesis (Coloplast Titan™) [139, 277, 280-283]. As a whole, growing evidence exists that the risk of penile prosthesis infection has reduced over the decades with device improvement and surgical expertise [284].

Higher-risk populations include patients undergoing revision surgery, those with impaired host defences (immunosuppression, diabetes mellitus, spinal cord injury) or those with penile corporal fibrosis [17, 139, 258, 279, 285, 286]. 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 [278, 279, 285, 287]. The majority of revisions are secondary to mechanical failure and combined erosion or infection [282, 288]. 93% of cases are successfully revised, providing functioning penile prosthesis [277-279, 289, 290].

3.1.4.2.3.2 Conclusions third-line therapy

Penile implants are an effective 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 [291].

Table 7: Penile prostheses models available on the market

Semi-rigid prostheses	Inflatable prostheses	
	Two-piece	Three-piece
Spectra™ [AMS]	Ambicor™ [AMS]	Titan OTR™ (One Touch Release) [Coloplast]
Genesis™ [Mentor]		Titan OTR NB™ (Narrow base) [Coloplast]
		Titan Zero Degree™
Tube™ [Promedon]		AMS 700 CX™ [Boston Scientific]
ZSI 100™ [Zephyr]		AMS 700 LGX™ [Boston Scientific]
Virilis II™ [Subrini]		AMS 700 CXR™ [Boston Scientific]
		ZSI 475™ [Zephyr]

3.1.4.3 Recommendations for the treatment of ED

Recommendations	Strength rating
Enact lifestyle changes and risk factor modification prior to or accompanying erectile dysfunction (ED) treatment.	Strong
Support the resumption of sexual activity through pro-erectile treatments at the earliest opportunity after radical prostatectomy.	Strong
Treat a curable cause of ED first, when found.	Weak
Use phosphodiesterase type 5 inhibitors (PDE5Is) as first-line therapy.	Strong

Assess all patients for inadequate/incorrect information about the mechanism of action and the ways in which drugs should be taken, since they are the main causes of a lack of response to PDE5Is.	Weak
Use vacuum erection devices as a first-line therapy in well-informed older patients with infrequent sexual intercourse and comorbidity requiring non-invasive, drug-free management of ED.	Weak
Use low intensity shockwave treatment in mild organic ED patients or poor responders to PDE5Is.	Weak
Use topical/intraurethral Alprostadil as an alternative to intracavernous injections in patients who prefer a less-invasive therapy.	Weak
Use intracavernous injections as second-line therapy.	Strong
Use implantation of a penile prosthesis as third-line therapy.	Strong

3.1.4.4 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 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 [292]. The highest prevalence rate of 31% (men aged 18-59 years) was found by the USA National Health and Social Life Survey (NHSLs) study [293]. 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 [294]. According to the four PE subtypes proposed by Waldinger *et al.* [295], the prevalence rates were 2.3% (lifelong PE), 3.9% (acquired PE), 8.5% (natural variable PE) and 5.1% (premature-like ejaculatory dysfunction) [296]. 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 [297].

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 [298]. 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 [299, 300]. 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 [293, 294], unlike ED, which increases with age. Premature ejaculation is not affected by marital or income status [293]. However, PE is more common in Black men, Hispanic men and men from Islamic backgrounds [301, 302] and may be higher in men with a lower educational level [293, 300]. Other risk factors may include a genetic pre-disposition [303], poor overall health status and obesity [293], prostate inflammation [304-306], thyroid hormone disorders [307], diabetes [308, 309], lack of physical activity [310], emotional problems and stress [293, 311, 312], and traumatic sexual experiences [293, 300]. In the only published study on risk modification/prevention strategies [313], 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 [314].

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 [315, 316]. However, the negative impact of PE extends beyond sexual dysfunction. Premature ejaculation can have a detrimental

effect on self-confidence and the relationship with the partner, and may sometimes cause mental distress, anxiety, embarrassment and depression [315, 317]. Sex drive and overall interest in sex does not appear to be affected by PE [318]. However, the partner's satisfaction with the sexual relationship decreases with increasing severity of the man's condition [319]. 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 [300], with men more likely to seek treatment for ED than for PE [300]. In the Premature Ejaculation Prevalence and Attitudes survey, only 9% of men with self-reported PE consulted a doctor [294]. 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 [320, 321]. 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'* [322]. This DSM definition has been recently updated in the DSM V edition [323].

The International Society for Sexual Medicine (ISSM) has adopted a completely new definition of PE which is the first evidence-based definition [324]. Premature ejaculation (lifelong and acquired) is a male sexual dysfunction characterised by the following:

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

Two more PE syndromes have been proposed [325]:

- '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 [326].

3.2.3 **Diagnostic evaluation**

Diagnosis of PE is based on the patient's medical and sexual history [327, 328]. 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 [299, 329]. 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 [330]. There are several overlapping definitions of PE, with four shared factors (Table 7), resulting in a multidimensional diagnosis [331].

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 [332, 333]. Intravaginal ejaculatory latency time 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 [334]. 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 [335]. Self-estimated and stopwatch-measured IELT are interchangeable and correctly assign PE status with 80% sensitivity and 80% specificity [336]. 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, self-estimated IELT may be over-estimated by approximately one minute and therefore it must be carefully substituted with stopwatch-measured IELT while identifying men with the complaint of lifelong PE in a clinical setting [337]. 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 [338].

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 [331]. 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 [339, 340]. 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 [341]. 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 [342]. Questionnaires are a significant step in simplifying the methodology of PE drug studies, although further cross-cultural validation is needed [343]. Other questionnaires used to characterise PE and determine treatment effects include the PEP [333], Index of Premature Ejaculation (IPE) [344] and Male Sexual Health Questionnaire Ejaculatory Dysfunction (MSHQ-EjD) [345]. 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 [327].

3.2.3.4 Recommendations for the diagnostic evaluation of PE

Recommendations	Strength rating
Perform the diagnosis and classification of premature ejaculation (PE) based on medical and sexual history, which should include assessment of intravaginal ejaculatory latency time (IELT) (self-estimated), perceived control, distress and interpersonal difficulty due to the ejaculatory dysfunction.	Strong
Do not use stopwatch-measured IELT in clinical practice.	Weak
Use patient-reported outcomes in daily clinical practice.	Weak
Include physical examination in the initial assessment of PE to identify anatomical abnormalities that may be associated with PE or other sexual dysfunctions, particularly erectile dysfunction.	Strong
Do not perform routine laboratory or neuro-physiological tests. They should only be directed by specific findings from history or physical examination.	Strong

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 firstly to treat, if present, ED 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 re-uptake 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 [346] and its modification, the 'squeeze' technique, proposed by Masters and Johnson [347]:

- 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 [348].

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 [316]. 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 [349, 350].

Overall, short-term success rates of 50-60% have been reported [349, 350] with limited evidence on the efficacy of these behavioural therapies on IELT improvement [351]. A double-blind, randomised, crossover study showed that pharmacological treatment (clomipramine, sertraline, paroxetine and sildenafil) resulted in greater IELT prolongation than behavioural therapy [352]. Furthermore, clinical experience suggests that improvements achieved with these techniques are generally not maintained long-term [353, 354]. Behavioural therapy may be most effective when used to 'add value' to medical interventions. A combination of dapoxetine and behavioural treatment was more effective than dapoxetine alone in patients with lifelong PE in a prospective, randomised trial [355]. 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) [356]. Dapoxetine has been investigated in 6,081 subjects to date [357]. 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 a baseline average ELT of < 0.5 minutes [358, 359].

In RCTs, dapoxetine, 30 mg or 60 mg one to two 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 [359-361]. 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 [335]. There was no indication of an increased risk of suicidal ideation or suicide attempts and little indication of withdrawal symptoms with abrupt dapoxetine cessation [362]. Moreover, dapoxetine is found to be safer compared with other anti-depressants which are used for the treatment of PE [363].

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 SSRIs administered alone. Generally, when dapoxetine is co-administered with PDE5Is, it is well tolerated, with a safety profile consistent with previous phase 3 studies of dapoxetine alone [364]. 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 [365].

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 re-uptake 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 auto-receptor activation and compensation reported using chronic SSRIs, or these effects occur, but they simply cannot prevent the action of short-acting SSRIs [366].

3.2.4.2.2 Off-label use of antidepressants: SSRIs and clomipramine

Ejaculation is commanded by a spinal ejaculation generator [367, 368] under excitatory or inhibitory influences from the brain and the periphery [308]. 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 [366].

Selective serotonin re-uptake inhibitors 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 [366]. Administration of chronic SSRIs causes prolonged increases in synaptic cleft serotonin, which desensitises the 5-HT1A and 5-HT1B receptors [369]. Clomipramine, the most serotonergic tricyclic antidepressant, was first reported in 1973 as an effective PE treatment [370]. Selective serotonin re-uptake inhibitors have revolutionised treatment of PE, but they have also changed our understanding of PE since the first publication on paroxetine in 1970 [371]. 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.

Several SRs and meta-analyses 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 [372, 373]. 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 [374, 375].

Ejaculation delay may start a few days after drug intake, but it is more evident after one to two weeks since receptor de-sensitisation 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 [370]. 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 [326, 358]. Decreased libido, anorgasmia, anejaculation and ED have also been reported.

Because of a theoretical risk of suicidal ideation or suicide attempts, caution is suggested in prescribing SSRIs to young adolescents with PE aged eighteen years or less, and to men with PE and a comorbid depressive disorder, particularly when associated with suicidal ideation. Patients should be advised to avoid sudden cessation or rapid dose reduction of daily dosed SSRIs which may be associated with a SSRI withdrawal syndrome [335].

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 [376]. However, on-demand treatment may be combined with an initial trial of daily treatment or concomitant low-dose daily treatment reducing adverse effects [377, 378]. 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 [379]. Several trials [380, 381] 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. A recent meta-analysis confirmed the efficacy and safety of these agents for the treatment of PE [382].

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 [383]. In another randomised, double-blind, placebo-controlled trial, lidocaine-prilocaine cream significantly increased the stop-watch-measured IELT from 1.49 to 8.45 minutes while no difference was recorded in the placebo group (1.67 to 1.95 minutes). A recent internet-based prospective study revealed that lidocaine-based spray may be beneficial for men with subjective PE as well [384].

Alternatively, the condom may be removed prior to sexual intercourse and the penis washed clean of any residual active compound. Although no significant side-effects have been reported, topical anaesthetics are contraindicated in patients or partners with an allergy to any 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 five 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 three months of double-blind treatment; a 3.3-fold delay in ejaculation compared with placebo ($p < 0.001$) [385].

3.2.4.2.4 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 [386]. 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 [387].

A large, randomised, double-blind, placebo-controlled, multicentre twelve week study was carried out to evaluate the efficacy and safety of two doses of tramadol (62 and 89 mg) by ODT in the treatment of PE [388]. 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 twelve-week study period was acceptable. Several other studies also reported that tramadol exhibits a significant dose-related efficacy and side-effects over placebo for treatment of PE [389]. Moreover, the efficacy and safety of tramadol have been confirmed in SRs and meta-analyses [390, 391].

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 central nervous system 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.

3.2.4.2.5 Phosphodiesterase type 5 inhibitors

There is only one well-designed, randomised, double-blind, placebo-controlled study comparing sildenafil to placebo [392]. 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 PDE5Is combined with an SSRI is superior to SSRI monotherapy:

- Sildenafil combined with paroxetine improved IELT significantly and satisfaction vs. paroxetine alone [393];
- Sildenafil combined with sertraline improved IELT and satisfaction significantly vs. sertraline alone [394];
- Sildenafil combined with paroxetine and psychological and behavioural counselling significantly improved IELT and satisfaction in patients in whom other treatments failed [395];
- Sildenafil combined with dapoxetine (30 mg.) improved IELT, satisfaction scores and PEDT vs. in comparison with dapoxetine, paroxetine or sildenafil monotherapy [396];
- Tadalafil combined with paroxetine significantly improved IELT and satisfaction vs. paroxetine and tadalafil alone [397];
- Finally, sildenafil combined with behavioural therapy significantly improved IELT and satisfaction vs. behavioural therapy alone [398].

There are very limited data on the efficacy of other PDE5Is (tadalafil and vardenafil) [399, 400]. However, recent meta-analyses demonstrated that the combined use of SSRIs and PDE5Is may be more effective compared with SSRIs or PDE5Is monotherapy [401-404].

3.2.4.2.6 Other drugs

In addition to the aforementioned drugs, there is continuous research for other treatment options. Considering the abundant alpha 1a adrenergic receptors in seminal vesicles and prostate, and the role of sympathetic system in the ejaculation physiology, the efficacy of selective alpha-blockers in the treatment of PE has been assessed [405]. A recent study demonstrated that wake-promoting agent modafinil may be effective in delaying ejaculation and improving the patient reported outcome measures [406]. Some authors compared the efficacy of acupuncture and dapoxetine for the treatment of PE [407]. Although the authors demonstrated that acupuncture had a significant ejaculation-delaying effect, this was less effective compared with that of dapoxetine.

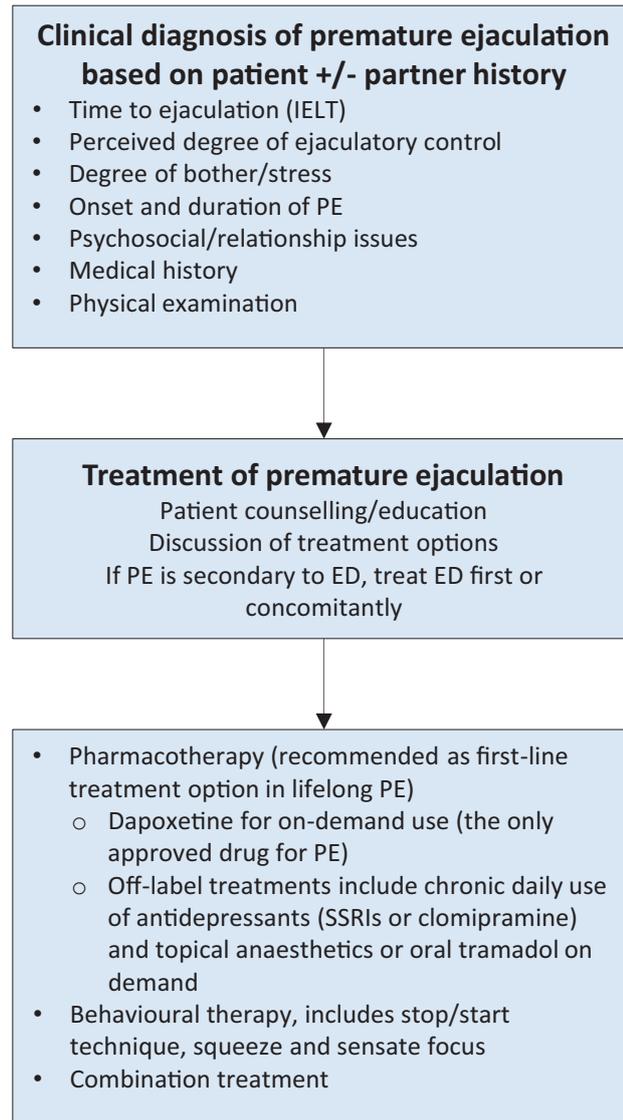
3.2.5 Summary of evidence on the epidemiology/aetiology/pathophysiology of PE

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

3.2.6 Recommendations for the treatment of PE

Recommendations	Strength rating
Treat erectile dysfunction (ED), other sexual dysfunction or genitourinary infection (e.g. prostatitis) first.	Strong
Use pharmacotherapy as first-line treatment for lifelong premature ejaculation (PE).	Strong
Use off-label topical anaesthetic agents as a viable alternative to oral treatment with selective serotonin re-uptake inhibitor (SSRIs).	Strong
Use tramadol on demand as a weak alternative to SSRIs.	Strong
Use PDE5Is alone or in combination with other therapies in patients with PE (without ED).	Strong
Use psychological/behavioural therapies in combination with pharmacological treatment in the management of acquired PE.	Weak

Figure 4: Management of Premature Ejaculation*



* Adapted from Lue *et al.* 2004 [408].

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% [409] while there are reports from studies which claim that it is more common with prevalence rates of 4-10% in the absence of hypospadias [410].

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 though rarely dorsal.

3.3.1.2 Diagnostic evaluation

Taking a medical and sexual history is usually sufficient to establish a 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 [411].

3.3.1.3 Disease management

The treatment of this disorder is surgical correction deferred until after puberty. Results from a recent survey suggest that men with possible untreated ventral penile curvature reported more dissatisfaction with penile appearance, increased difficulty with intercourse, and more unhealthy mental days therefore supporting correction of congenital penile curvature in childhood [412]. 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 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 [413]. A new modification of the latter technique has been suggested; Shaeer’s corporal rotation enables correction of ventral congenital penile curvature, with minimal narrowing and shortening [414]. 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 [415-417].

3.3.1.4 Summary of evidence for congenital penile curvature

Summary of evidence	LE
Medical and sexual history are usually sufficient to establish a 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

3.3.1.5 Recommendation for the treatment congenital penile curvature

Recommendation	Strength rating
Use Nesbit and other plication techniques for the treatment of congenital penile curvature in patients who undergo surgery.	Strong

3.3.2 Peyronie’s Disease

3.3.2.1 Epidemiology/aetiology/pathophysiology

3.3.2.1.1 Epidemiology

Epidemiological data on Peyronie’s disease (PD) are limited. Prevalence rates of 0.4-9% have been published, with a higher prevalence in patients with ED and diabetes [418-425]. A recent, well conducted survey indicates that the prevalence of definitive and probable cases of PD in the US is 0.7% and 11%, respectively, suggesting that PD is an under-diagnosed problem [426]. The typical age of a patient with PD is 55-60 years.

3.3.2.1.2 Aetiology

The aetiology of PD 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 [427]. A prolonged inflammatory response will result in the remodelling of connective tissue into a fibrotic plaque [427-429]. 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 [421, 425, 430, 431]. Dupuytren’s contracture is more common in patients with PD affecting 9-39% of patients [422, 432-434] while 4% of patients with Dupuytren’s contracture reported Peyronie’s disease [433].

3.3.2.1.4 Pathophysiology

Two phases of the disease can be distinguished [435]. 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 [430, 436, 437]. Pain is present in 35-45% of patients during the early stages of the disease [438]. Pain tends to resolve with time in 90% of men, usually during the first twelve months after the onset of the disease [436, 437].

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 PD have mild or moderate depression, sufficient to warrant medical evaluation [439].

3.3.2.1.5 Summary of evidence on epidemiology/aetiology/pathophysiology of 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 PD 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/calculifying 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 PD. A disease-specific questionnaire (Peyronie's disease questionnaire (PDQ)) has been designed to collect data, and it has been validated for use in clinical practice [440]. Also, the utility of the PDQ for monitoring PD-specific psychosexual symptom severity, progression, and treatment response, both clinically and in trials of men with PD has been reported [441].

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 [436].

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 [437]. 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 [442]. Measurement of penile length during erection is important because it may have an impact on the subsequent treatment decisions [443].

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 [444]. Erectile function can be assessed using validated instruments such as the IIEF although this has not been validated in PD patients [87]. Erectile dysfunction is common in patients with PD (> 50%) but it is important to define whether it pre- or post-dates the onset of PD. It is mainly due to penile vascular disease [430, 442]. The presence of ED and psychological factors may impact on the treatment strategy [445].

Ultrasound measurement of the plaque's size is inaccurate and it is not recommended in everyday clinical practice [446]. Doppler US may be required for the assessment of vascular parameters [445].

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

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

3.3.2.2.2 Recommendations for the diagnosis of Peyronie's disease

Recommendations	Strength rating
In the medical and sexual history of 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 (ED).	Strong
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).	Strong
Do not use Peyronie's disease specific questionnaire in everyday clinical practice.	Weak
Do not use ultrasound (US) measurement of plaque size in everyday clinical practice.	Weak
Use Doppler US only in the case of diagnostic evaluation of ED, to ascertain vascular parameters associated with ED.	Weak

3.3.2.3 Disease management

3.3.2.3.1 Non-operative treatment

Conservative treatment of PD is primarily focused on patients in the early stage of the disease [437, 447]. Several options have been suggested, including oral pharmacotherapy, intralesional injection therapy and other topical treatments (Table 8). Shockwave treatment of calcified plaques and clostridium collagenase (CCH) injection in patients with densely fibrotic or calcified plaques have also been suggested [435, 448]. Clostridium collagenase is the only drug approved for the treatment of PD by the FDA and the EMA. The results of the studies on conservative treatment for PD 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 [448]. 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
Intralesional treatments
Steroids
Verapamil
Clostridium collagenase
Interferon
Topical treatments
Verapamil
Iontophoresis
H-100 gel
Extracorporeal shockwave treatment
Traction 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 at once or twice daily doses of 400 IU because of its wide availability, low cost and safety [449]. A double-blind, placebo-controlled crossover study failed to show a significant effect on penile deformity or plaque size [450]. Moreover, there is conflicting evidence as to the long-term cardiovascular effects of vitamin E usage at the large doses, which urologists use for penile deformity treatment [451].

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 [452]. Preliminary studies reported an improvement in penile curvature, penile plaque size, and penile pain during erection [453]. In a prospective double-blinded controlled study in 41 patients with PD, Potaba (12 g/day for twelve months) improved penile pain significantly, but not penile curvature or penile plaque size [454]. In another similar study in 103 patients with PD, Potaba decreased penile plaque size significantly, but had no effect on penile curvature or penile pain [455]. 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 [456].

Tamoxifen

Tamoxifen is a non-steroidal oestrogen receptor antagonist modulating transforming growth factor β 1 (TGF β 1) 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 [457]. However, a placebo-controlled, randomised study (in only 25 patients, at a late stage of the disease with a mean duration of twenty months) using the same treatment protocol, failed to show any significant improvement in pain, curvature, or plaque size in patients with PD [458].

Colchicine

Colchicine has been introduced into the treatment of PD on the basis of its anti-inflammatory effect [459]. 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% of 24 men [460]. In another study in 60 men (colchicine 0.5-1 mg daily for three to five months with escalation to 2 mg twice daily), penile pain resolved in 95% and penile curvature improved in 30% [459]. Similar results have been reported in another uncontrolled retrospective study in 118 patients [461]. Reported treatment-related adverse events with colchicine are gastrointestinal effects (nausea, vomiting, diarrhoea) that can be improved with dose escalation [459].

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 PD resulted in significant improvement in plaque size and curvature, but not in pain compared to ibuprofen 400 mg/day for six months [462].

Acetyl esters of carnitine

Acetyl-L-carnitine and propionyl-L-carnitine are proposed to inhibit acetyl coenzyme-A and produce an anti-proliferative 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 PD, patients were randomised to acetyl-L-carnitine (1 g twice daily) compared to tamoxifen (20 mg twice daily). After three 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) [463]. 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 three months) significantly reduced penile curvature, plaque size, and disease progression compared to intralesional verapamil combined with tamoxifen (40 mg/day) for three months [464].

Pentoxifylline

Pentoxifylline is a non-specific phosphodiesterase inhibitor which down-regulates TGF β 1 and increases fibrinolytic activity [465]. Moreover, an increase of NO levels may be effective in preventing progression of PD or reversing fibrosis [466]. 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 [466]. In another study in 62 patients with PD, pentoxifylline treatment for six months appeared to stabilise or reduce calcium content in penile plaques [467].

Phosphodiesterase type 5 inhibitors

The rationale for the use of PDE5Is in PD comes from animal studies showing that they can reduce the collagen/smooth muscle and collagen III/I ratios and increase the apoptotic index in a PD-like plaque [468]. 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 [469]. Therefore, no recommendation can be given for PDE5Is in patients with PD.

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 [470]. In small, non-randomised studies, a decrease in penile plaque size and pain resolution was reported [471, 472]. 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 [473]. Adverse effects include tissue atrophy, thinning of the skin and immunosuppression [471].

Verapamil

The rationale for intralesional use of verapamil (a calcium channel antagonist) in patients with PD is based on *in-vitro* research [474, 475]. A number of studies have reported that intralesional verapamil injection may induce a significant reduction in penile curvature and plaque volume [476-480]. 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 [479]. Side-effects are uncommon (4%). Minor side-effects include nausea, light-headedness, penile pain, and ecchymosis [479]. 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 [481]. Younger age and larger baseline penile curvature were found to be predictive of favourable curvature outcomes in a case-series study [482].

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 PD plaque [483-485]. Clostridium collagenase is now approved by 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 patient 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 the 551 treated men with CCH 60.8% were global responders compared with 29.5% of the 281 patients who received the placebo. The most commonly reported side-effects were penile pain, penile swelling, and ecchymosis at the site of injection [484]. The data from these two large RCTs were analysed by subgroups including: baseline penile curvature deformity, PD duration, degree of penile calcification, and baseline erectile function severity with better results in patients with less than 60° of curvature, more than two years of evolution, no calcification in the plaque and good erectile function [486].

Clostridium collagenase was approved by the EMA in 2014 who specified that CCH should be administered by a healthcare professional who is experienced in the treatment of male urological diseases. The Risk Management Plan (RMP) requires participating healthcare professionals to be certified within the programme by enrolling and completing training in the administration of CCH treatment for PD [487].

A recent paper which studied a pooled safety analysis of 1,044 CCH-treated patients from six clinical studies showed that the majority of Peyronie's patients experienced at least one adverse reaction (Global Safety database, 92.5%). Most adverse reactions were localised to the penis or groin and the majority of these events were of a mild or moderate severity. Most of these resolved within fourteen days of the injection. The adverse reaction profile was similar after each injection, regardless of the number of injections administered. The most frequently reported treatment-related adverse events in the clinical trials in subjects with PD (Global Safety database) were penile haematoma (50.2%), penile pain (33.5%), penile swelling (28.9%) and injection site pain (24.1%) [488].

Interferon

Interferon α -2b has been shown to decrease fibroblast proliferation, extracellular matrix production and collagen production from fibroblasts and improve the wound healing process from PD plaques *in-vitro* [489]. 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 [490, 491]. 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.

Hyaluronic Acid

In a prospective, single-arm, multicentre pilot study, 65 patients underwent a ten week cycle of weekly intraplaque injections with hyaluronic acid. Plaque size significantly decreased, penile curvature decreased in 37%, as well as overall sexual satisfaction and seems preferably indicated in the early (active) phase of the disease [492].

In a case controlled, single site study, 81 patients underwent a ten week cycle of weekly plaque injections. Patients included had curvatures $< 45^\circ$ and were in the active phase of the disease. Hyaluronic acid demonstrated statistically significant improvement over controls (non-treatment, $n=81$) in plaque size, penile curvature (-9.01° , $p<0.0001$), and improvement in penile rigidity (mean IIEF score $+3.8$) at twelve months [493].

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 [494]. 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 [495, 496].

H-100 Gel

H-100 Gel is composed of nicardipine, superoxide dismutase and emu oil. Twenty-two patients (PD twelve months duration) were studied in a prospective randomised, double-blind, placebo-controlled study. H-100 showed significant improvement in all PD parameters at six months: mean stretched penile length increase (22.6%, $p=0.0002$), mean curvature reduction (40.8%, $p=0.0014$), and mean pain level reduction (85.7%, $p=0.004$). Placebo group showed no significant improvement except for mean stretched penile length increase (6.8%, $p=0.009$). Crossover patients from placebo to H-100 showed significant improvement in all parameters: mean stretched penile length increase (17.5%, $p=0.000007$), mean curvature reduction (37.1%, $p=0.006$), and mean pain level reduction (40%, $p=0.17$). Treatment was well tolerated. A self-limited rash was the only side-effect in three patients. Statistically significant improvements in flaccid-stretched penile length, curvature and pain suggest that H-100 is a safe and possibly effective non-invasive, topically applied treatment for acute phase PD [497].

Extracorporeal shockwave treatment

The mechanism of action involved in shockwave treatment (ESWT) for PD is still unclear, but there are two hypotheses. In the first hypothesis, shockwave therapy works by directly damaging and remodelling the penile plaque. In the second hypothesis, shockwave 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 [498]. Most uncontrolled studies failed to show significant improvements in patients with PD [499-501]. In a prospective, randomised, double-blind, placebo-controlled study, four weekly treatment sessions of ESWT, with each session consisting of 2,000 focused shockwaves, resulted in significant improvement only for penile pain [502].

Traction devices

The application of continuous traction in Dupuytren's contracture increases the activity of degradative enzymes [503]. This initially leads to a loss of tensile strength and ultimately to solubilisation. It is followed by an increase in newly synthesised collagen [503]. This concept has been applied in an uncontrolled study, including ten patients with PD. The FastSize Penile Extender was applied as the only treatment for two to eight hours per day for six months [139]. Reduced penile curvature of $10-40^\circ$ was found in all men with an average reduction of 33% (range: $51-34^\circ$). The stretched penile length increased 0.5-2.0 cm and the erect girth [139] 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 for two to eight hours daily for an extended period, but has been shown to be tolerated by highly motivated patients [433]. 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 [504].

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

Summary of evidence	LE
Conservative treatment for PD 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 CCH 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 shockwave 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

3.3.2.3.1.5 Recommendations for non-operative treatment of Peyronie's disease

Recommendations	Strength rating
Use conservative treatment in patients not fit for surgery or when surgery is not acceptable to the patient.	Weak
Do not use extracorporeal shockwave treatment to improve penile curvature and reduce plaque size.	Weak
Use penile traction devices and vacuum devices to reduce penile deformity and increase penile length.	Weak
Do not use intralesional treatment with steroids to reduce penile curvature, plaque size or pain.	Weak
Do not use oral treatment with vitamin E and tamoxifen for significant reduction in penile curvature or plaque size.	Strong
Do not offer other oral treatments (acetyl esters of carnitine, pentoxifylline, colchicine) for the treatment of PD.	Weak

3.3.2.3.2 Surgical treatment

Although conservative treatment for PD 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 [115]. Patients must have a stable disease for at least three months, although a six to twelve month period has also been suggested [505].

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 [435]. Two major types of repair may be considered for both congenital penile curvature and PD: penile shortening and penile lengthening procedures [506].

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 de-gloving with associated circumcision (as a means of preventing post-operative phimosis) is considered the standard approach for all types of procedures [506]. However, recent data suggest that circumcision is not always necessary e.g. in cases where the foreskin is normal pre-operatively [507]. Finally, in patients with PD and ED not responding to medical treatments, surgical correction of the curvature with concomitant penile prosthesis implantation should be considered [508].

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 [435]. Patient expectations from surgery must also be included in the pre-operative assessment. There are no standardised questionnaires for the evaluation of surgical outcomes [115]. 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 [435, 509].

3.3.2.3.2.1 Penile shortening procedures

In 1965, Nesbit was the first to describe the removal of the tunical ellipses opposite a non-elastic corporal segment to treat congenital penile curvature [510]. Fourteen years later, this technique became a successful treatment option, also for PD [511]. 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 [506]. The overall short- and long-term results of the Nesbit operation are excellent. Complete penile straightening is achieved in more than 80% of patients [512]. Recurrence of the curvature and penile hypoesthesia are uncommon (about 10%) and the risk of post-operative ED is minimal [506, 513]. Penile shortening is the most commonly reported outcome of the Nesbit procedure [513]. Shortening of 1-1.5 cm has been reported for about 85% of patients, which is rarely the cause of post-operative sexual dysfunction [511, 514]. Patients often perceive the loss of length as greater than it actually is [512, 513]. 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) [515].

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 [516-521]. Another modification has been described as the '16 dot' technique with minimal tension under local anaesthesia [522]. The use of non-absorbable sutures reduced recurrence of the curvature. Results and satisfaction rates are similar to the Nesbit procedure [506]. 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 [523].

Devine and Horton introduced dermal grafting in 1974 [524]. Since then, a variety of grafting materials and techniques have been reported (Table 10) [525-539]. Unfortunately, the ideal material for grafting has yet to be identified [540]. 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 [541].

Vein grafts have the theoretical advantage of endothelial-to-endothelial contact when grafted to underlying cavernosal tissue. The Saphenous vein is the most common vein graft used, followed by the dorsal penile vein [506]. Post-operative curvature (20%), penile shortening (17%) and graft herniation (5%) have been reported after vein graft surgery [530, 535, 538]. Tunica vaginalis is relatively avascular, easy to harvest and has little tendency to contract due to its low metabolic requirements [528].

Dermal grafts are commonly associated with contracture resulting in recurrent penile curvature (35%), progressive shortening (40%), and a 17% re-operation rate at ten years [542]. Cadaveric pericardium (Tutoplast®) offers good results by coupling excellent tensile strength and multidirectional elasticity/expansion by 30% [539]. 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 [539, 542].

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 PD, without significant contraction or histological alterations, but data are limited [536].

More recently the use of buccal mucosa grafts (BMG) has been advocated. Buccal mucosa grafts 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 [527].

Grafting by collagen fleece (TachoSil®) in PD is feasible and promising. Major advantages are decreased operative times and easy application. Moreover, an additional haemostatic effect is provided [543].

Tunical incision, preferably with grafting, offers an excellent surgical option for men with curvatures over 60° 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 [469]. 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 [508]. 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 [506]. 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 [529].

The use of a penile extender device on an eight to twelve hour daily regimen has been advocated as an effective and safe treatment for loss of penile length in patients operated on for PD [544].

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®
Collagen fleece (TachoSil®)

3.3.2.3.2.3 Penile prosthesis

Penile prosthesis (PP) implantation is typically reserved for the treatment of PD in patients with ED, especially when they are non-responders to PED5Is [433]. Although all types of penile prosthesis can be used, the implantation of inflatable penile prosthesis seems to be most effective in these patients [538].

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 [545, 546]. If there is a residual curvature of less than 30°, 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 [545]. 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 [547-549].

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 [546].

In selected cases of end-stage PD with ED and significant penile shortening, a lengthening procedure, which involves simultaneous PP implantation and penile length restoration, such as the ‘sliding’ technique, can be considered but only in the hands of experienced high-volume surgeons [550].

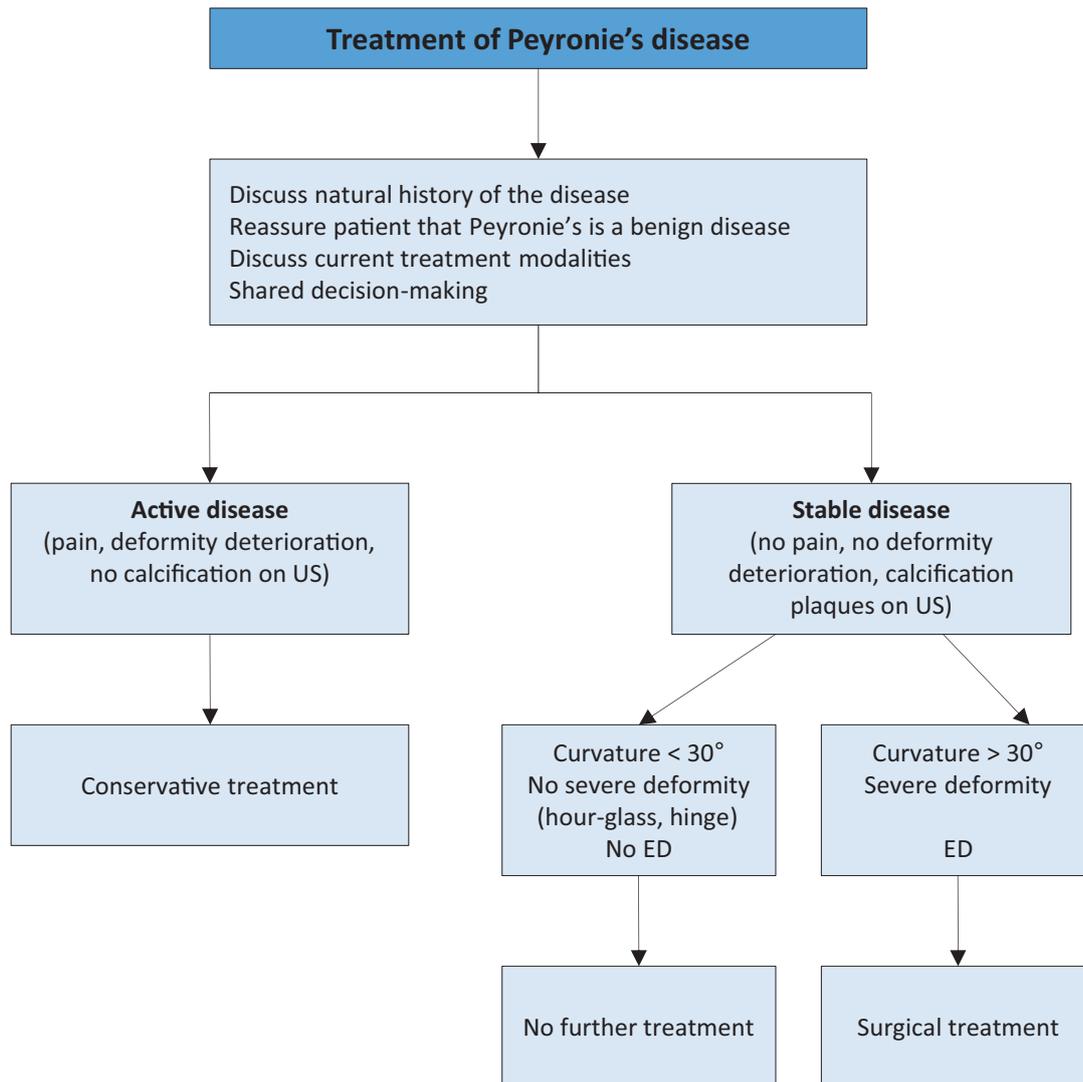
Table 10: Results of surgical treatments for Peyronie’s disease (data from different, non-comparable studies) [469, 523-539, 542]

	Tunica1 shortening procedures		Tunica1 lengthening 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 PP, 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 PD. The risk of ED seems to be greater for penile lengthening procedures [435, 506]. Recurrent curvature implies either failure to wait until the disease has stabilised, a re-activation 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 [149]. Accordingly, it is recommended that only non-absorbable sutures or slowly re-absorbed 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 [513]. 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 [506].

3.3.2.3.2.4 Recommendations for the surgical treatment of penile curvature

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

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 of the priapism subtypes, accounting for more than 95% of all priapism episodes [551, 552]. It presents as a painful rigid erection characterised clinically by an absent or reduced intracavernous arterial inflow (although proximally there is a compensated high velocity picture with little flow distally [553]. In ischaemic priapism, there are time-dependent metabolic alterations within the corpus cavernosum progressively leading to hypoxia, hypercapnia, glucopenia and acidosis [554].

Ischaemic priapism which lasts beyond four hours is similar to a compartment syndrome, characterised by the development of ischaemia within the closed space of the corpora cavernosa, which severely compromises cavernous circulation. Emergency medical intervention is required to minimise irreversible consequences, such as smooth muscle necrosis, corporal fibrosis and the development of permanent ED [555, 556]. The duration of ischaemic priapism represents the most significant predictor for the development of ED. In this context, interventions beyond 48-72 hours of onset may help to relieve the erection and pain, but have little benefit in preventing long-term ED [557].

Histological analysis of corporal smooth muscle biopsies show that at twelve hours, there are features of interstitial oedema, progressing to destruction of the sinusoidal endothelium, exposure of the basement membrane and thrombocyte adherence by 24 hours. At 48 hours, thrombi can be found in the sinusoidal spaces and smooth muscle necrosis with fibroblast-like cell transformation is evident [479].

In terms of the pathophysiology (Table 11), no specific cause can be identified in the majority of cases [552, 558] although the common aetiological factors for ischaemic priapism include sickle cell disease, haematological dyscrasias, neoplastic syndromes, and with the use of a number of pharmacological agents. Ischaemic priapism may occur (0.4-35%) after intracavernous injections of erectogenic agents [244, 552, 555, 559, 560]. The risk is higher with papaverine-based combinations, while the risk of priapism is < 1% following prostaglandin E1 injection [561].

Since their introduction onto the market, a few cases of priapism have been described in men who have taken PDE5Is [552]. However, most of these men also had other risk factors for priapism, and it is unclear whether PDE5Is per se can cause ischaemic priapism [552]. Since most men who experienced priapism following PDE5I use had additional risk factors for ischaemic priapism, PDE5I use is usually not regarded as 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 [561], with a lifetime probability of developing ischaemic priapism of 29-42% in men with sickle cell disease [561-563] (LE: 4). Mechanisms of sickle cell disease associated priapism may involve dysfunctional NO synthase and Rho-associated protein kinase (ROCK) signalling, and increased oxidative stress associated with nicotinamide adenine dinucleotide phosphate (NADPH) oxidase mediated signalling [564].

Priapism resulting from metastatic or regional infiltration by tumour is rare and usually reflects an infiltrative process [565]. 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 of the penis and be offered supportive

care and medical intervention for their primary cancer. In selected cases where palliative treatment options fail to control penile pain, a palliative penectomy can be considered.

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 segmental thrombosis of the corpus cavernosum, is a very rare condition. It is often classified as a subtype of priapism limited to a single crura but ischaemia does not develop, rather it is a thrombus within the corpus. Its aetiology is unknown, but bicycle riding, trauma, drug usage, sexual intercourse, haematological diseases and α -blockers have been associated with partial segmental thrombosis [566]. The presence of a congenital web within the corpora is also a risk factor [567].

Table 11: Aetiological factors for the development of priapism

Idiopathic
Haematological dyscrasias (sickle cell disease, thalassaemia, 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
Vasoactive erectile agents (i.e. papaverine, phentolamine, prostaglandin E1/alprostadil, combination of intracavernous therapies)
α -adrenergic receptor antagonists (i.e. prazosin, terazosin, doxazosin, tamsulosin)
Anti-anxiety agents (hydroxyzine)
Anticoagulants (heparin, warfarin)
Antidepressants and antipsychotics (i.e. trazodone, bupropion, fluoxetine, sertraline, lithium, clozapine, risperidone, olanzapine, chlorpromazine, thiorizadine, phenothiazines)
Antihypertensives (i.e. hydralazine, guanethidine, propranolol)
Hormones (i.e. gonadotropin-releasing hormone, testosterone)
Recreational drugs (i.e. alcohol, marijuana, cocaine [intranasal and topical], crack, cocaine)

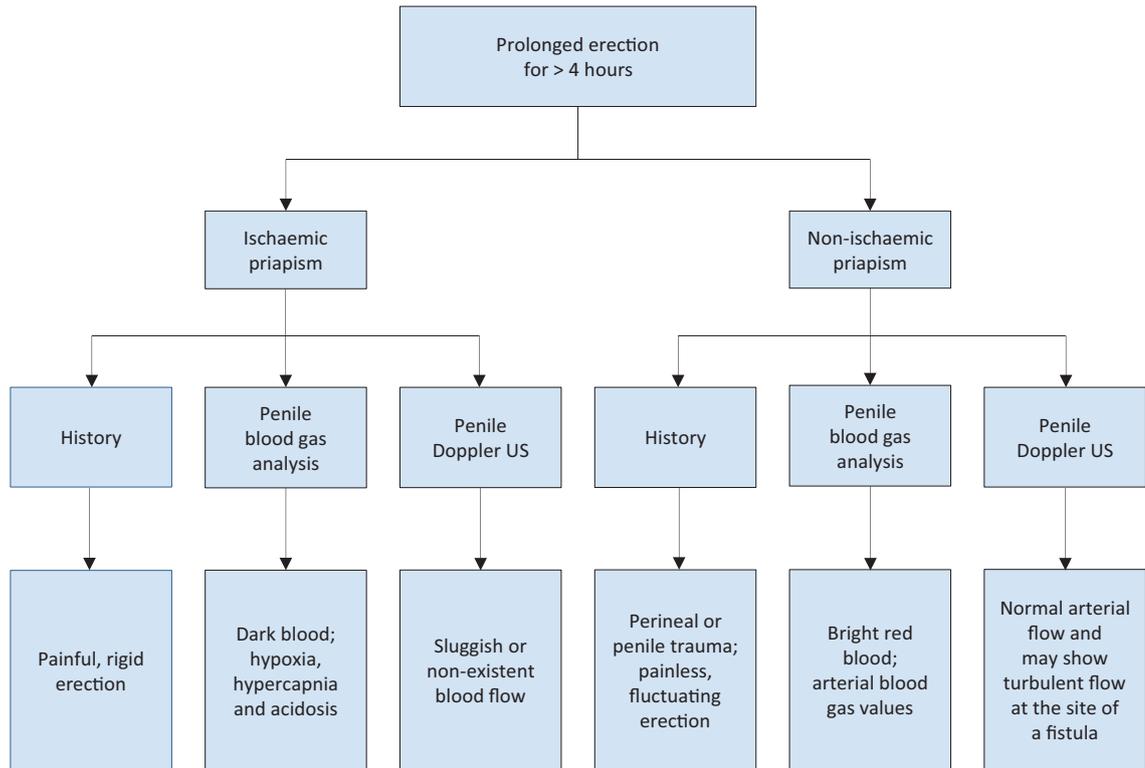
3.4.1.1.1 Summary of evidence on the epidemiology, aetiology and pathophysiology of ischaemic priapism

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 (about 5%) 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

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 [552]. The patient typically complains of penile pain and examination reveals a rigid erection. Resolution of ischaemic priapism is characterised by a return to a flaccid non-painful state. 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 ischaemic priapism is left untreated, resolution may take days and ED invariably results.

Figure 6: Differential diagnosis of priapism



3.4.1.3.1 History

Taking a comprehensive history is critical in priapism diagnosis [552, 568]. The medical history must specifically ask about sickle cell disease or any other haematological abnormality [9, 569] and a history of pelvic, genital or perineal trauma. The sexual history must include details relating to the duration of the 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 priapism subtype (Table 13). Ischaemic priapism is classically associated with progressive penile pain and the erection is rigid. Non-ischaemic priapism however is often painless and the erections fluctuating.

Table 12: Key points in the history for a priapism patient (adapted from Broderick *et al.* [552])

Duration of erection
Presence and severity 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 drug use
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 severe pain. Pelvic examination may reveal an underlying pelvic or genitourinary 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 [552, 568].

Aspiration of blood from the corpora cavernosa shows dark ischaemic blood (Table 13) (LE: 2b). Blood gas analysis is essential to differentiate between ischaemic and non-ischaemic priapism (Table 14). Further laboratory testing should be directed by the history, clinical examination 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 US of the penis and perineum is recommended and can differentiate ischaemic from non-ischaemic priapism as an alternative or adjunct to blood gas analysis [553, 570-572] (LE: 2b). If possible, scanning of the penis should be performed before corporal blood aspiration in ischaemic priapism to prevent aberrant blood flow which can mimic a non-ischaemic picture.

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 [552, 572, 573]. After aspiration, a reactive hyperaemia may develop with a high arterial flow proximally that may mislead the diagnosis as non-ischaemic priapism.

Penile MRI can be used in the diagnostic evaluation of priapism and is helpful in selected cases of ischaemic priapism to assess the viability of the corpora cavernosa and the presence of penile fibrosis. In a prospective study of 38 patients with ischaemic priapism, the sensitivity of MRI in predicting non-viable smooth muscle was 100%, when correlated with corpus cavernosum biopsies [574]. In this study, all patients with viable smooth muscle on MRI maintained erectile function on clinical follow-up with the non-viable group being offered an early prosthesis (LE: 3).

Table 13: Key findings in priapism (adapted from Broderick *et al.* [552])

	Ischaemic priapism	Non-ischaemic priapism
Corpora cavernosa fully rigid	Usually	Seldom
Penile pain	Usually	Seldom
Abnormal penile blood gas	Usually	Seldom
Haematological abnormalities	Sometimes	Seldom
Recent intracavernosal injection	Sometimes	Sometimes
Perineal trauma	Seldom	Usually

Table 14: Typical blood gas values (adapted from Broderick *et al.* [552])

Source	pO ₂ (mmHg)	pCO ₂ (mmHg)	pH
Normal arterial blood (room air) [similar values are found in non-ischaemic 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

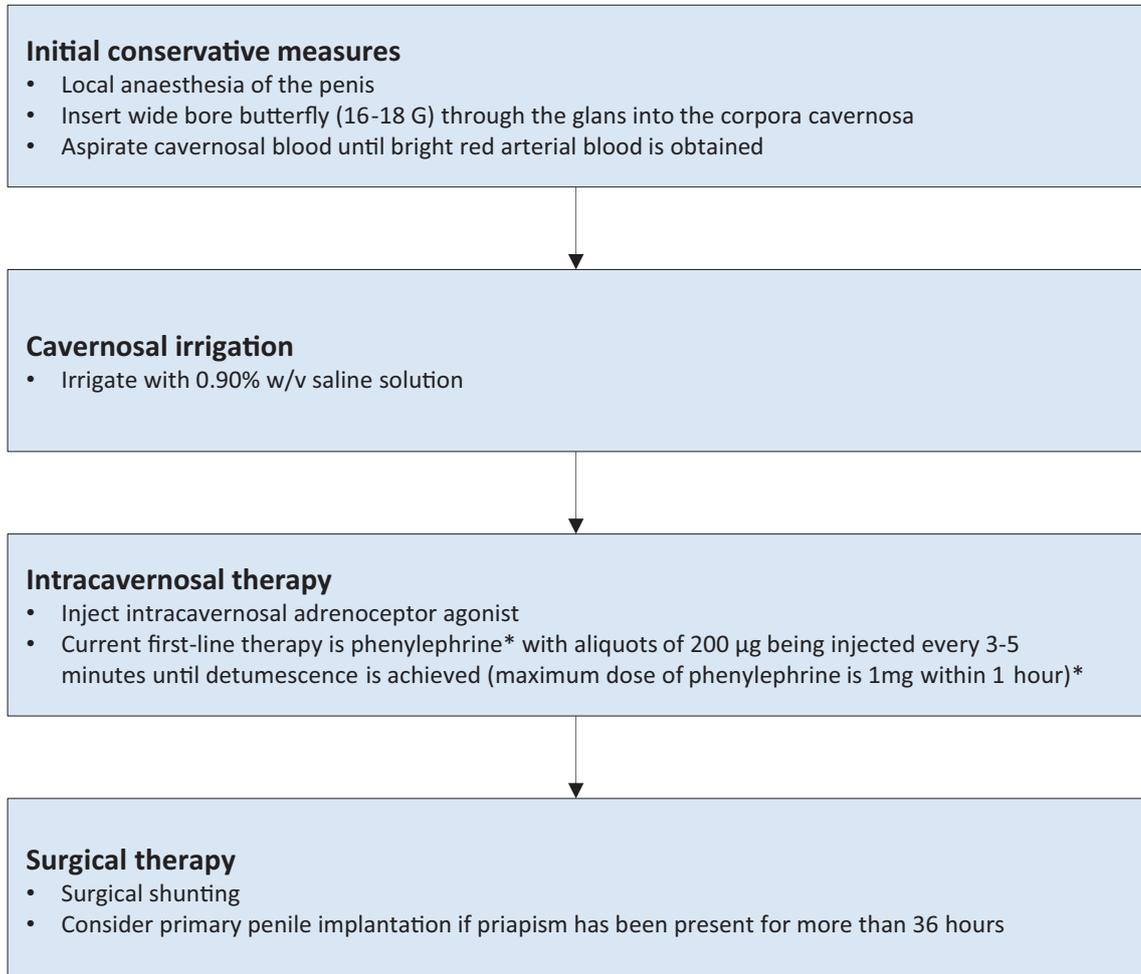
Recommendations	Strength rating
Take a comprehensive history to establish the diagnosis which can help to determine the priapism subtype.	Strong
Include a physical examination of the genitalia, the perineum and the abdomen in the diagnostic evaluation.	Strong
For laboratory testing, include complete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

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 detumescence, without pain, in order to prevent long-term 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. 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 more than four 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 [552]. 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 [575].

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 0.9% w/v saline solution

The first intervention for an episode of priapism lasting more than four hours consists of corporal blood aspiration (LE: 4) to drain stagnant blood from the corporal bodies, making it possible to relieve the compartment syndrome-like condition within the corpus cavernosum. 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 16 G or 18 G angiocatheter or butterfly needle. The needle must penetrate the skin, the subcutaneous tissue and the tunica albuginea to drain blood from 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 [562] (LE: 4). Aspiration should be continued until bright 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 0.9% 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 [4, 552, 576] (LE: 4). Pharmacological agents include sympathomimetic drugs or α -adrenergic agonists. Options for intracavernous sympathomimetic agents include phenylephrine, etilephrine, ephedrine, epinephrine, norepinephrine and metaraminol with a resolution rate of up to 80%. [552, 576-584] (LE: 2b). The use of intracavernous adrenaline injection alone has also been sporadically reported [585].

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 [577, 581, 582] (LE: 4).

Phenylephrine is diluted in normal saline to a concentration of 100-500 μ g/mL. Usually 200 μ g are given every three to five minutes directly into the corpus cavernosum. The 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 [552, 576-578, 581, 582] and it is recommended that blood pressure and pulse are monitored every fifteen minutes for an hour after the injection. This is particularly important in older men with pre-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, cardiac arrhythmias and sporadic subarachnoid haemorrhage [48]. Monitoring of blood pressure, pulse and cardiac rhythm 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

Etilephrine 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 [578] (LE: 3).

Methylene blue

Methylene blue is a guanylate cyclase inhibitor, which may be a potential inhibitor of endothelial-mediated cavernous relaxation. It has been used for treating short-term pharmacologically induced priapism [586, 587] (LE: 3). Methylene blue, 50-100 mg [586], should be injected intracavernously and left for five minutes. It is then aspirated and the penis compressed for an additional five minutes [587]. 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 [585]), has been used in patients with ischaemic priapism due to an intracavernous injection of vasoactive agents. A 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 β -2-agonist with minor β -1 effects and some α -agonist activity. A dose of 5 mg has been suggested to treat prolonged erections lasting more than two and a half hours, after intracavernous injection of vasoactive agents, although the mechanism of action is not yet fully understood [588-590] (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 [590].

Table 15: Medical treatment of ischaemic priapism

Drug	Dosage/Instructions for use
Phenylephrine	<ul style="list-style-type: none">Intracavernous injection of 200 μg every three to five minutes.Maximum dosage is 1 mg within one hour.Lower doses are recommended in children and patients with severe cardiovascular disease.
Etilephrine	<ul style="list-style-type: none">Intracavernosal injection at a concentration of 2.5 mg in 1-2 mL normal saline.
Methylene blue	<ul style="list-style-type: none">Intracavernous injection of 50-100 mg, left for five minutes. It is then aspirated and the penis compressed for an additional five minutes.
Adrenaline	<ul style="list-style-type: none">Intracavernous injection of 2 mL of 1/100,000 adrenaline solution up to five times over a twenty-minute period.
Terbutaline	<ul style="list-style-type: none">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

Urgent intervention is essential (LE: 4) and the general approach is similar to that described for other cases of ischaemic priapism and should be co-ordinated with a haematologist [591-593] (LE: 4).

However, as with other haematological disorders, other therapeutic practices may also need to be implemented [591, 593, 594]. 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 [563, 592].

Exchange blood transfusion has also been proposed, with the aim of increasing the tissue delivery of oxygen [595]. The transfused blood should be HbS negative, Rh and Kell antigen matched [596]. 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 [597]. although a series of ten patients with sickle cell related priapism, reported that it was safe to perform exchange transfusion [595]. Due to 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 other 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

anoxia, severe glucopenia, absence of cavernosal artery inflow by penile colour duplex US, and elevated intracorporal pressures by pressure monitoring (LE: 4).

3.4.1.4.2.1 Penile shunt surgery

Penile shunt surgery aims to produce an outflow 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 [552, 576, 598].

In general, the type of shunt procedure chosen is according to the surgeon's preference and familiarity with the procedure. It is conventional for distal shunt procedures to be tried before considering proximal shunting (LE: 4). Cavernosal smooth muscle biopsy has been used to diagnose smooth muscle necrosis (which, if present, would suggest that shunting is likely to fail) which helps decision making and patient counselling, particularly if they are being considered for an acute prosthesis.

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) [552, 576, 599, 600].

The recovery rates of erectile function in men undergoing shunt surgery following prolonged episodes of priapism are low and directly relate to the duration of the priapism [599, 600]. Priapism for more than 36 hours appears to irreversibly impair erectile tissue both structurally and functionally [599]. In general, shunt procedures undertaken after this time period may only serve to limit pain without any benefit for erectile function (LE: 4) [557, 601].

Four categories of shunt procedures have been reported [4, 552, 598, 601]. The limited available data preclude any recommendation for one procedure over another based on outcomes (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 [4, 552, 561, 602, 603] (LE: 3). Post-operative sequelae are uncommon [604]. Winter's shunt is easy to perform, but has been reported as the least successful operation to create a distal shunt [600].

Ebbehoj's technique: this technique involves making 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 [4, 552, 602, 605, 606] (LE: 3).

T-Shunt: this technique involves performing a bilateral procedure using a scalpel with a size 10 blade inserted through the glans just lateral to the meatus until it enters the tip of the corpus cavernosum. The blade is then rotated 90° away from the urethral meatus and withdrawn [4, 552, 602, 607] (LE: 3). If unsuccessful the procedure is repeated on the opposite side. This is followed by a tunneling procedure using a size 20 dilator inserted through the glans and into the corpora which can also be performed using US for guidance, mainly in order to avoid urethral injury [607]. The entry sites in the glans are sutured following detumescence.

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 [4, 552, 602, 608, 609] (LE: 3).

Burnett's technique (Snake manoeuvre): a modification of the Al-Ghorab corpora-glanular shunt 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 is closed as in the Al-Ghorab procedure [4, 552, 602, 610, 611] (LE: 3). Reported complications include wound infection, penile skin necrosis and an urethrocutaneous fistula [611].

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 cavernosum and the corpus spongiosum. The most frequent complications include an unwanted urethro-cavernous fistula and urethral stricture or the development of cavernositis [4, 552, 598, 612]. 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 [4, 552, 613-615] (LE: 3).

Immediate penile prosthesis implantation

Refractory, therapy-resistant, acute ischaemic priapism or episodes lasting more than 48-72 hours usually result in complete ED, possibly along with significant penile deformity in the long term. In these cases, immediate penile prosthesis surgery has been advocated [616-619] (LE: 3).

The immediate insertion of a malleable penile prosthesis has been recommended to avoid the difficulty and complications of delayed prosthesis surgery in the presence of corporal fibrosis. Potential complications that could compromise immediate penile prosthesis implantation include distal erosion and cavernositis [616, 618], along with a small rate of revision surgery [616]. Early surgery also offers the opportunity to maintain penile size, and prevent penile curvature due to cavernosal fibrosis. The prosthesis can be exchanged for an inflatable prosthesis at a later date which also allows upsizing of the implant cylinders [620].

Currently, there are no clear indications for immediately implanting a penile prosthesis in a man with acute ischaemic priapism [576]. Relative indications include [552] (LE: 4):

- ischaemia that has been presented for more than 36 hours [619];
- 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 [552, 616] (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, [598, 616, 621, 622]. Erectile dysfunction is also often observed [552, 623]. Unfortunately, these outcomes can still occur despite apparently successful first- or second-line treatment.

Penile 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 [552, 576]. In severe corporal fibrosis, narrow-based prosthetic devices are preferable since they are easy to insert and need less dilatation [616] (LE: 3). Following severe priapism that has resulted in penile destruction with complicated deformities or even loss of penile tissue, penile reconstruction using grafts and concomitant prosthesis implant may be considered [624] (LE: 3).

3.4.1.5 Summary of evidence for the treatment of ischaemic priapism

Summary of evidence	LE
Urgent intervention for ischaemic priapism is required as it is an emergency condition.	2b
Treatment aims to restore painless penile detumescence, in order to prevent chronic damage to the corpora cavernosa.	3
Erectile function preservation is directly related to the duration of ischaemic priapism.	2b
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 three to five minutes directly into the corpus cavernosum. Maximum dosage is 1 mg within one hour. Patients at high cardiovascular risk should be given lower doses. Patient monitoring is highly recommended.	2b
The efficacy of shunt procedures for ischaemic priapism is questionable. Diagnose smooth muscle necrosis when needed with a biopsy of the cavernosal smooth muscle. No clear recommendation on one type of shunt over another can be given.	3
Erectile dysfunction is inevitable in prolonged cases or ischaemic priapism. Implantation of penile prosthesis at a later stage can be difficult due to severe corporal fibrosis.	2b

3.4.1.6 Recommendations for the treatment of ischaemic priapism

Recommendations	Strength rating
Start management of ischaemic priapism as early as possible (within four to six hours) and follow a stepwise approach.	Strong
First, decompress the corpora cavernosa by penile aspiration until fresh red blood is obtained.	Weak
In priapism secondary to intracavernous injections of vasoactive agents, replace blood aspiration with intracavernous injection of a sympathomimetic drug as the first step.	Strong
In priapism that persists despite aspiration, proceed to the next step, which is intracavernous injection of a sympathomimetic drug.	Strong
In cases that persist despite aspiration and intracavernous injection of a sympathomimetic drug, repeat these steps several times before considering surgical intervention.	Strong
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 alkalinisation with bicarbonates, blood exchange transfusions), but do not delay initial treatment to the penis.	Strong
Proceed to surgical treatment only when blood aspiration and intracavernous injection of sympathomimetic drugs have failed or for priapism events lasting < 72 hours.	Strong
Perform distal shunt surgical procedures first followed by proximal procedures in case of failure.	Strong
Consider insertion of a penile prosthesis if priapism episode is > 36 hours after onset, or in cases for which all other interventions have failed.	Strong

3.4.1.7 Follow-up

Follow-up of ischaemic priapism after successful treatment should include modification of risk factors (if any) in order to avoid a further episode 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 Non-ischaemic (high-flow or arterial) priapism

3.4.2.1 Epidemiology/aetiology/pathophysiology

Epidemiological data on non-ischaemic priapism are almost exclusively derived from small case series [552, 572, 573, 625, 626]. The most frequent cause of non-ischaemic priapism is blunt perineal or penile trauma [627]. The injury results in a laceration in the cavernosal artery leading to a fistula between the artery and the lacunar spaces of the sinusoidal tissue [626]. This unregulated blood flow results in a persistent erection, and has been proposed to occur via a mechanism that involves stimulation of endothelial NO synthase by the turbulent blood flow [628]. Partial erections are enhanced after sexual stimulation, as the trabecular smooth muscle fully relaxes, activating the corporal veno-occlusive mechanism [626, 629].

There is often a delay between the injury and the development of the priapism that may be up to two to three weeks [629]. 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 [630, 631], acute spinal cord injury [632] and occasionally following intracavernous injections or aspiration due to a lacerated cavernosal artery or branch [633, 634]. Under these circumstances, it may complicate ischaemic priapism. It has also been reported to occur following internal urethrotomy [635] and a Nesbit procedure [636]. Although sickle cell disease is usually associated with ischaemic priapism, occasional cases of non-ischaemic priapism have been reported [637].

3.4.2.1.1 Summary of evidence on the epidemiology, aetiology and pathophysiology of non-ischaemic priapism

Summary of evidence	LE
Non-ischaemic priapism usually occurs after blunt perineal or penile trauma.	2

3.4.2.2 Classification

Non-ischaemic priapism is a persistent erection caused by unregulated cavernous arterial inflow [552]. 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 mandatory in non-ischaemic priapism diagnosis and follows the same principles as described in Table 12. Non-ischaemic 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 non-ischaemic priapism in adults and children may be delayed by hours to weeks following the initial injury. Sexual intercourse is usually not compromised.

3.4.2.3.2 Physical examination

In non-ischaemic 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 non-ischaemic priapism, while blood is dark in ischaemic priapism (Table 13) (LE: 2b). Blood gas analysis is essential to differentiate between non-ischaemic 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 non-ischaemic from ischaemic priapism as an alternative or adjunct to blood gas analysis [570-572] (LE: 2b). Examination of the penile shaft and perineum is recommended. In non-ischaemic priapism US will show turbulent flow at the fistula, which helps to localise the site of trauma since patients with non-ischaemic 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 non-ischaemic priapism [638, 639]. However, due to its invasiveness it should be reserved for the management of non-ischaemic priapism, when embolisation is being considered [552, 568] (LE: 3).

The role of MRI in the diagnostic evaluation of priapism is controversial. In non-ischaemic priapism, its role is limited since the small penile vessels and arteriovenous fistulae cannot be easily demonstrated [640].

3.4.2.3.5 Recommendations for the diagnosis of non-ischaemic priapism

The same recommendations as in section 3.4.1.3.5 apply.

3.4.2.4 *Disease management*

The management of non-ischaemic priapism is not an emergency because the corpus cavernosum does not contain ischaemic blood. Definitive management can therefore be considered and should be discussed with the patient so that they understand the risks and complications of treatment [552, 568] (LE: 3).

3.4.2.4.1 Conservative management

This may include applying ice to the perineum or site-specific perineal compression [572, 625, 641, 642]. It is an option in all cases, particularly children [643] (LE: 3). The fistula occasionally closes spontaneously. Even in those cases where the fistula remains patent, the response to sexual stimulation still allows intercourse to be possible. 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 [644]. However, sexual dysfunction due to these treatments must be considered. Very infrequently, patients may develop ED or distal flaccidity whilst undergoing conservative treatment, earlier selective embolisation should be considered [645].

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

3.4.2.4.2 Selective arterial embolisation

Selective arterial embolisation can be performed using either an autologous clot [646-648], gel foam or sponge [647, 649], or more permanent substances, such as coils [647, 649-651] or acrylic glue [652] (LE: 3). Success rates of up to 89% have been reported [653] 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 [552, 654].

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 [571]. If there is doubt, a repeat arteriogram is required. Recurrence rates of 7-27% after a single treatment with embolisation have been reported [647, 648, 655] (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 [655, 656] (LE: 3).

Embolisation in children, although reportedly successful, is technically challenging and requires treatment within a specialist paediatric vascular radiology department [580, 657].

3.4.2.4.3 Surgical management

Selective ligation of the fistula through a transcorporeal approach under the guidance of colour duplex US is possible [4, 569, 658]. 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).

3.4.2.5 Summary of evidence for the treatment of non-ischaemic priapism

Summary of evidence	LE
Because non-ischaemic priapism is not an emergency, perform definitive management at the discretion of the treating physician and plan the treatment after a short period of conservative treatment.	2b
Conservative management with the use of ice applied to the perineum or site-specific perineal compression may be successful particularly in children. The use of androgen deprivation therapy may enable closure of the fistula reducing spontaneous and sleep-related erections.	3
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.	3
Repeat the procedure for the recurrence of non-ischaemic priapism following selective artery embolisation.	2b
Reserve selective surgical ligation of the fistula as a last treatment option when embolisation has failed.	3

3.4.2.6 Recommendations for the treatment of non-ischaemic priapism

Recommendations	Strength rating
Because non-ischaemic priapism is not an emergency, perform definitive management at the discretion of the treating physician.	Weak
Manage conservatively with the use of site specific perineal compression as the first step, especially in children. Consider androgen deprivation therapy only in adults.	Weak
Perform superselective arterial embolisation, using temporary material.	Strong
Repeat the procedure with temporary or permanent material for recurrent non-ischaemic priapism following selective arterial embolisation.	Weak
Reserve selective surgical ligation of a fistula as a final treatment option when embolisation has failed.	Weak

3.4.2.7 Follow-up

Follow-up after successful treatment of non-ischaemic 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 [8, 659]. However, recurrent priapism

episodes are common in men with sickle cell disease (42-64%) [660, 661] while in adolescents and young men the incidence of priapism is 35%, of whom 72% have a history of stuttering priapism [8].

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 priapism event, especially one which has been prolonged (more than four hours) are at risk for developing stuttering priapism [623].

Recently, several studies have proposed alternative mechanisms including inflammation, cellular adhesion, NO metabolism, vascular reactivity and coagulation [552, 564, 592, 662, 663].

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-limiting with intervening periods of detumescence [592, 662]. These are analogous to repeated episodes of ischaemic priapism. In stuttering priapism the duration of the erections is generally shorter than in ischaemic priapism [4]. The frequency and/or duration of these episodes is variable and a single episode can sometimes progress into a prolonged ischaemic priapism 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 priapism episodes usually occurs during sleep and detumescence does not occur upon waking. These episodes can be painful and may be the reason that the patient first seeks medical attention.

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 the history, clinical and laboratory findings.

3.4.3.3.4 Penile imaging

There are no specific findings on imaging for stuttering priapism. Colour duplex US of the penis and perineum and MRI are recommended and can differentiate non-ischaemic from ischaemic 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 further episodes and limiting the chances of developing a prolonged ischaemic priapism which is refractory to conventional treatment options. In the majority of cases, stuttering priapism can be managed with pharmacological treatment. 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 [563, 592, 662].

3.4.3.4.1 α -adrenergic agonists

Studies of oral α -adrenergic agonists have suggested some benefit for daily dosing of these agents as effective prevention [664]. Side-effects include tachycardia and palpitations. Pseudoephedrine, widely used as an oral decongestant, can also be used as a first-line treatment option [589]. However, its effect on corporal smooth muscle is not fully understood. Etilephrine 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% [11, 665, 666]. In one randomised placebo-controlled clinical study looking at medical prophylaxis with etilephrine 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 [563, 592, 667]. This can be achieved through the use of GnRH agonists or antagonists, antiandrogens or oestrogens [668] (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- α -reductase inhibitors [669] (LE: 3) and ketoconazole, an antifungal agent that reduces adrenal and testicular androgen production [667, 670] (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 priapism 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 and spermatogenesis. Caution is therefore strongly advised when prescribing hormonal treatments to pre-pubertal boys, adolescents or men who are trying with 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 [563, 592, 671]. 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 [592]. 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 [671] (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 β -agonist that causes vasodilation, resulting in smooth muscle relaxation of the vasculature [563, 592] and has been used to prevent stuttering priapism with detumescence rates of 36% in patients with alprostadil-induced priapism [589] (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 [590] (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 [667], and reduces testosterone- and FSH levels [672]. It is given at a dose of 400 mg, four times a day, up to 2,400 mg daily, until complete penile detumescence occurs, with subsequent maintenance administration of gabapentin, 300 mg daily [673] (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 [563]. Oral baclofen has little efficacy

and it is not usually used in stuttering priapism but intrathecal baclofen dosing is more effective [592, 674-676], (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 [667, 677]. It is an established treatment for ameliorating sickle cell disease and improving patient life expectancy [591, 678]. For such patients with recurrent priapism there is limited evidence to suggest a medical prophylactic role (LE: 3), [667, 677, 679]. Side-effects include oligozoospermia and leg ulcers.

3.4.3.4.8 Phosphodiesterase type 5 inhibitors

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 [563, 592, 680-684] (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). Phosphodiesterase type 5 inhibitors use in stuttering priapism is possibly mediated by and an increase in 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 NO pathway, with down-regulation of cavernosal PDE5 thereby preventing the complete degradation of cGMP in the corpora cavernosa [563, 592, 680, 683].

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 [563, 592]. The most commonly used drugs are phenylephrine and etilephrine (as described in the treatment of ischaemic priapism) [4, 552, 659, 666] (LE: 3). Side-effects include hypertension, coronary ischaemia and cardiac arrhythmias.

Tissue plasminogen activator (TPA) is a secreted serine protease that converts the pro-enzyme 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 [667, 685] (LE: 3). Mild bleeding is the most commonly observed side-effect.

3.4.3.5 Summary of evidence for the treatment of stuttering priapism

Summary of evidence	LE
The primary goal in the management of patients with stuttering priapism is the prevention of future episodes, which can generally be achieved pharmacologically.	2b
PDE5Is have a paradoxical effect in alleviating and preventing stuttering priapism, mainly in patients with idiopathic and sickle cell disease associated priapism.	3
The evidence with other systemic drugs (digoxin, α -adrenergic agonists, baclofen, gabapentin, terbutaline) is very limited.	3

3.4.3.6 Recommendations for the treatment of stuttering priapism

Recommendations	Strength rating
Manage each acute episode similar to that for ischaemic priapism.	Strong
Use hormonal therapies (mainly gonadotropin-receptor hormone agonists or antagonists) and/or anti-androgens for the prevention of future episodes in patients with frequent relapses. Do not use them before sexual maturation is reached.	Weak
Initiate treatment with phosphodiesterase type 5 inhibitors only when the penis is in its flaccid state.	Weak
Use digoxin, α -adrenergic agonists, baclofen, gabapentin or terbutaline only in patients with very frequent and uncontrolled relapses.	Weak
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.	Weak

3.4.3.7 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 publically accessible through the EAU website <https://uroweb.org/guideline/>. 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.

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