

Guidelines on Male Sexual Dysfunction:

Erectile dysfunction and premature ejaculation

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

TABLE OF CONTENTS

PAGE

1.	BACKGROUND	4
1.1	Introduction	4
1.2	References	4
2.	DIAGNOSIS	4
2.1	Epidemiology and risk factors	4
2.1.1	Epidemiology	4
2.1.2	Risk factors	4
2.1.3	Post-radical prostatectomy ED	5
2.2	Managing ED: implications for everyday clinical practice	5
2.3	Conclusions	5
2.4	References	5
2.5	Diagnosis	6
2.5.1	Basic work-up	6
2.5.1.1	Sexual history	7
2.5.1.2	Physical examination	8
2.5.1.3	Laboratory testing	8
2.5.2	Cardiovascular system and sexual activity: the patient at risk	9
2.5.2.1	Low-risk category	10
2.5.2.2	Intermediate-risk or indeterminate-risk category	10
2.5.2.3	High-risk category	10
2.5.3	Specialised diagnostic tests	10
2.5.3.1	Nocturnal penile tumescence and rigidity (NPTR)	10
2.5.3.2	Intracavernous injection test	10
2.5.3.3	Duplex ultrasound of penile arteries	10
2.5.3.4	Arteriography and dynamic infusion cavernosometry or cavernosography	10
2.5.3.5	Psychiatric assessment	10
2.5.3.6	Penile abnormalities	10
2.5.4	Patient education – consultation and referrals	10
2.5.5	Conclusions	11
2.6	References	11
3.	TREATMENT OF ED	12
3.1	Treatment options	12
3.2	Lifestyle management in ED with concomitant risk factors	14
3.3	Erectile dysfunction after radical prostatectomy (RP)	14
3.4	‘Curable’ causes of ED	15
3.4.1	Hormonal causes	15
3.4.2	Post-traumatic arteriogenic ED in young patients	15
3.4.3	Psychosexual counselling and therapy	15
3.5	First-line therapy	15
3.5.1	Oral pharmacotherapy	15
3.5.1.1	Sildenafil	15
3.5.1.2	Tadalafil	15
3.5.1.3	Vardenafil	16
3.5.1.4	Choice or preference between the different PDE5 inhibitors	16
3.5.1.5	On-demand or chronic use of PDE5 inhibitors	16
3.5.1.6	Safety issues for PDE5 inhibitors	17
3.5.1.6.1	Cardiovascular safety	17
3.5.1.6.2	Nitrates are totally contraindicated with PDE5 inhibitors	17
3.5.1.6.3	Antihypertensive drugs	17
3.5.1.6.4	Alpha-blocker interactions	18
3.5.1.6.5	Dosage adjustment	18
3.5.1.7	Management of non-responders to PDE5 inhibitors	18
3.5.1.7.1	Check that the patient has been using a licensed medication	18
3.5.1.7.2	Check that the medication has been properly prescribed and correctly used	18

	3.5.1.7.3 Possible manoeuvres in patients correctly using a PDE5 inhibitor	19
	3.5.1.8 Apomorphine sublingual	19
	3.5.1.9 Other oral agents	20
3.6	Topical pharmacotherapy	20
3.7	Vacuum constriction devices	20
3.8	Second-line therapy	20
	3.8.1 Intracavernous injections	21
	3.8.1.1 Alprostadil	21
	3.8.1.1.1 Action to be taken with a prolonged erection	21
	3.8.1.2 Combination therapy	21
	3.8.1.3 Intraurethral alprostadil	22
3.9	Third-line therapy (penile prostheses)	22
	3.9.1 Complications	22
	3.9.2 Conclusion	22
3.10	Recommendations	22
3.11	References	23
4.	PREMATURE EJACULATION (PE)	31
4.1	Introduction	31
4.2	Definition of PE	31
	4.2.1 Overview	31
	4.2.2 Classifications	32
4.3	Epidemiology of PE	32
	4.3.1 Prevalence	32
	4.3.2 Pathophysiology and risk factors	33
4.4	Impact of PE on QoL	33
4.5	Diagnosis of PE	33
	4.5.1 Intravaginal ejaculatory latency time (IELT)	33
	4.5.2 PE assessment questionnaires	34
	4.5.3 Physical examination and investigations	34
4.6	Redommendations	34
4.7	References	34
4.8	Treatment	37
	4.8.1 Psychological/behavioural strategies	38
	4.8.1.1 Guideline recommendation	38
	4.8.2 Topical anaesthetic agents	38
	4.8.2.1 Lidocaine-prilocaine cream	38
	4.8.2.2 SS-cream	39
	4.8.2.3 Guideline recommendation	39
	4.8.3 Selective serotonin reuptake inhibitors	39
	4.8.3.1 Dapoxetine	39
	4.8.3.2 Guideline recommendation	40
	4.8.4 Phosphodiesterase type 5 inhibitors	40
	4.8.4.1 Guideline recommendation	41
	4.8.5 Other drugs	41
	4.8.6 Guidelines on treatment of PE	41
4.9	References	43
5.	CONCLUSION	46
6.	ABBREVIATIONS USED IN THE TEXT	47

1. BACKGROUND

1.1 Introduction

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

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

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

1.2 References

1. Wespes E, Amar E, Hatzichristou DG, et al. European Association of Urology Guidelines on erectile dysfunction. *Eur Urol* 2002 Jan;41(1):1-5.
<http://www.ncbi.nlm.nih.gov/pubmed/11999460>
2. Rosenberg MT, Sadovsky R. Identification and diagnosis of premature ejaculation. *Int J Clin Pract* 2007 Jun;61(6):903-8.
<http://www.ncbi.nlm.nih.gov/pubmed/17504352>
3. Oxford Centre for Evidence-based Medicine Levels of Evidence (May 2001). Produced by Bob Phillips, Chris Ball, Dave Sackett, Doug Badenoch, Sharon Straus, Brian Haynes, Martin Dawes since November 1998.
<http://www.cebm.net/index.aspx?o=1025> [access date January 2011].

2. DIAGNOSIS

2.1 Epidemiology and risk factors

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

Erectile dysfunction has been defined as the persistent inability to attain and maintain an erection sufficient to permit satisfactory sexual performance. Although ED is a benign disorder, it affects physical and psychosocial health and has a significant impact on the quality of life (QoL) of sufferers and their partners and families (2).

2.1.1 Epidemiology

Recent epidemiological data have shown a high prevalence and incidence of ED worldwide. The first large-scale, community-based study of ED was the Massachusetts Male Aging Study (MMAS). The study reported an overall prevalence of 52% ED in non-institutionalised 40- to 70-year-old men in the Boston area in the USA (3); specific prevalences for minimal, moderate, and complete ED were 17.2%, 25.2%, and 9.6%, respectively. In the Cologne study of men aged 30-80 years old, the prevalence of ED was 19.2%, with a steep age-related increase from 2.3% to 53.4% (4). In the National Health and Social Life Survey (NHSLs), the prevalence of sexual dysfunctions (not specific ED) was 31% (5). The incidence rate of ED (new cases per 1,000 men annually) was 26 in the MMAS study (6), 65.6 (mean follow-up of 2 years) in a Brazilian study (7), and 19.2 (mean follow-up of 4.2 years) in a Dutch study (8). Differences between these studies can be explained by differences in methodology and in the ages and socio-economic status of the populations studied.

2.1.2 Risk factors

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

However, it should be emphasised that controlled prospective studies are necessary to determine the effects of exercise or other lifestyle changes in prevention or treatment of ED.

2.1.3 **Post-radical prostatectomy ED**

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

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

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

2.2 **Managing ED: implications for everyday clinical practice**

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

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

2.3 **Conclusions**

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

ED = erectile dysfunction.

2.4 **References**

1. Lue TF, Tanagho EA. Physiology of erection and pharmacological management of impotence. *J Urol* 1987 May;137(5):829-36.
<http://www.ncbi.nlm.nih.gov/pubmed/3553617>
2. Feldman HA, Goldstein I, Hatzichristou DG, et al. Impotence and its medical and psychosocial correlates: results of the Massachusetts Male Aging Study. *J Urol* 1994 Jan;151(1):54-61.
<http://www.ncbi.nlm.nih.gov/pubmed/8254833>
3. Wespes E. *Ejaculation et ses troubles*. Editions techniques EMC (Encyclopédie Médico-chirurgicale) (Paris) Néphrologie-Urologie, 18-710-A-10, 1992. [article in French] [Ejaculation and its disorders]
4. Braun M, Wassmer G, Klotz T, et al. Epidemiology of erectile dysfunction: results of the 'Cologne Male Survey'. *Int J Impot Res* 2000 Dec;12(6):305-11.
<http://www.ncbi.nlm.nih.gov/pubmed/11416833>
5. Laumann EO, Paik A, Rosen RC. Sexual dysfunction in the United States: prevalence and predictors. *JAMA* 1999 Feb;281(6):537-44.
<http://www.ncbi.nlm.nih.gov/pubmed/10022110>

6. Johannes CB, Araujo AB, Feldman HA, et al. Incidence of erectile dysfunction in men 40 to 69 years old: longitudinal results from the Massachusetts Male Aging Study. *J Urol* 2000 Feb;163(2):460-3.
<http://www.ncbi.nlm.nih.gov/pubmed/10647654>
7. Moreira ED Jr, Lbo CF, Diament A, et al. Incidence of erectile dysfunction in men 40 to 69 years old: results from a population-based cohort study in Brazil. *Urology* 2003 Feb;61(2):431-6.
<http://www.ncbi.nlm.nih.gov/pubmed/12597962>
8. Schouten BW, Bosch JL, Bernsen RM, et al. Incidence rates of erectile dysfunction in the Dutch general population. Effects of definition, clinical relevance and duration of follow-up in the Krimpen Study. *Int J Impot Res* 2005 Jan-Feb;17(1):58-62.
<http://www.ncbi.nlm.nih.gov/pubmed/15510192>
9. Derby CA, Mohr BA, Goldstein I, et al. Modifiable risk factors and erectile dysfunction: can lifestyle changes modify risk? *Urology* 2000 Aug;56(2):302-6.
<http://www.ncbi.nlm.nih.gov/pubmed/10925098>
10. Esposito K, Giugliano F, Di Palo C, et al. Effect of lifestyle changes on erectile dysfunction in obese men: a randomized controlled trial. *JAMA* 2004 Jun;291(24):2978-84.
<http://www.ncbi.nlm.nih.gov/pubmed/15213209>
11. Cooperberg MR, Broering JM, Litwin MS, et al. The contemporary management of prostate cancer in the United States: lessons from the cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE), a national disease registry. *J Urol* 2004 Apr;171(4):1393-401.
<http://www.ncbi.nlm.nih.gov/pubmed/15017184>
12. Stanford JL, Feng Z, Hamilton AS, et al. Urinary and sexual function after radical prostatectomy for clinically localized prostate cancer; the Prostate Cancer Outcomes Study. *JAMA* 2000 Jan;283(3):354-60.
<http://www.ncbi.nlm.nih.gov/pubmed/10647798>
13. Heidenreich A. Radical prostatectomy in 2007: oncologic control and preservation of functional integrity. *Eur Urol* 2008 May;53(5):877-9.
<http://www.ncbi.nlm.nih.gov/pubmed/18243495>
14. Sanda MG, Dunn RL, Michalski J, et al. Quality of life and satisfaction with outcome among prostate-cancer survivors. *N Engl J Med* 2008 Mar;358(12):1250-61.
<http://www.ncbi.nlm.nih.gov/pubmed/18354103>
15. Montorsi F, Briganti A, Salonia A, et al. Current and future strategies for preventing and managing erectile dysfunction following radical prostatectomy. *Eur Urol* 2004 Feb;45:123-33.
<http://www.ncbi.nlm.nih.gov/pubmed/14733995>
16. Mulhall JP, Slovick R, Hotaling J, et al. Erectile dysfunction after radical prostatectomy: hemodynamic profiles and their correlation with the recovery of erectile function. *J Urol* 2002 Mar;167(3):1371-5.
<http://www.ncbi.nlm.nih.gov/pubmed/11832735>
17. Secin FP, Touijer K, Mulhall J, et al. Anatomy and preservation of accessory pudendal arteries in laparoscopic radical prostatectomy. *Eur Urol* 2007 May;51(5):1229-35.
<http://www.ncbi.nlm.nih.gov/pubmed/16989942>
18. Goldstein I, Lue TF, Padma-Nathan H, et al; Sildenafil Study Group. Oral sildenafil in the treatment of erectile dysfunction. 1998. *J Urol* 2002 Feb;167(2 Pt 2):1197-203.
<http://www.ncbi.nlm.nih.gov/pubmed/11905901>
19. Hellstrom WJ, Gittelman M, Karlin G, et al; Vardenafil Study Group. Sustained efficacy and tolerability of vardenafil, a highly potent selective phosphodiesterase type 5 inhibitor, in men with erectile dysfunction: results of a randomized, double-blind, 26-week placebo-controlled pivotal trial. *Urology* 2003 Apr;61(4 Suppl 1):8-14.
<http://www.ncbi.nlm.nih.gov/pubmed/12657355>
20. Brock GB, McMahon CG, Chen KK, et al. Efficacy and safety of tadalafil for the treatment of erectile dysfunction: results of integrated analyses. *J Urol* 2002 Oct;168(4 Pt 1):1332-6.
<http://www.ncbi.nlm.nih.gov/pubmed/12352386>
21. Wespes E, Schulman C. Venous impotence: pathophysiology, diagnosis and treatment. *J Urol* 1993 May;149(5 Pt 2):1238-45.
<http://www.ncbi.nlm.nih.gov/pubmed/8479008>
22. Rao DS, Donatucci CF. Vasculogenic impotence. Arterial and venous surgery. *Urol Clin North Am* 2001 May;28(2):309-19.
<http://www.ncbi.nlm.nih.gov/pubmed/11402583>

2.5 Diagnosis

2.5.1 Basic work-up

The first step in evaluating ED is always a detailed medical and psychological history of patients and partners

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

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

Table 1: Pathophysiology of ED

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

2.5.1.1 Sexual history

The sexual history may include information about previous and current sexual relationships, current emotional status, onset and duration of the erectile problem, and previous consultations and treatments. A detailed description should be made of the rigidity and duration of both erotic and morning erections and of problems with arousal, ejaculation, and orgasm. Validated questionnaires, such as the International Index for Erectile

Function (IIEF), help to assess all sexual function domains (erectile function, orgasmic function, sexual desire, ejaculation, intercourse, and overall satisfaction), as well as the impact of a specific treatment modality (4).

2.5.1.2 Physical examination

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

2.5.1.3 Laboratory testing

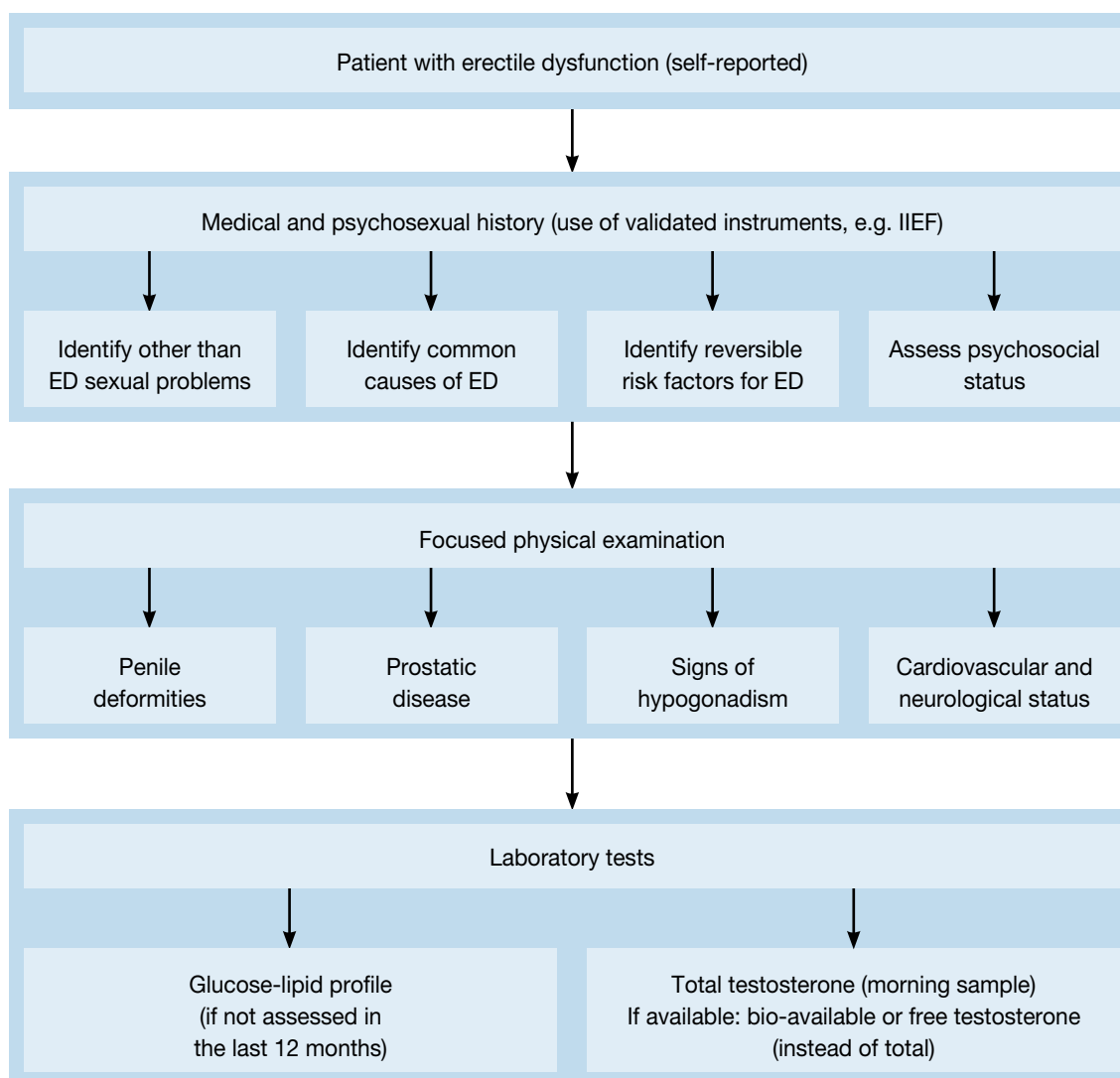
Laboratory testing must be tailored to the patient's complaints and risk factors. All patients must undergo a fasting glucose and lipid profile if not assessed in the previous 12 months. Hormonal tests must include a morning sample of total testosterone. Tests that measure bioavailable or calculated-free testosterone are preferred to total testosterone tests because they are better at establishing hypogonadism.

Additional laboratory tests must be considered only in selected patients, e.g. prostate-specific antigen (PSA) for detection of prostate cancer.

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

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

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



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

2.5.2 Cardiovascular system and sexual activity: the patient at risk

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

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

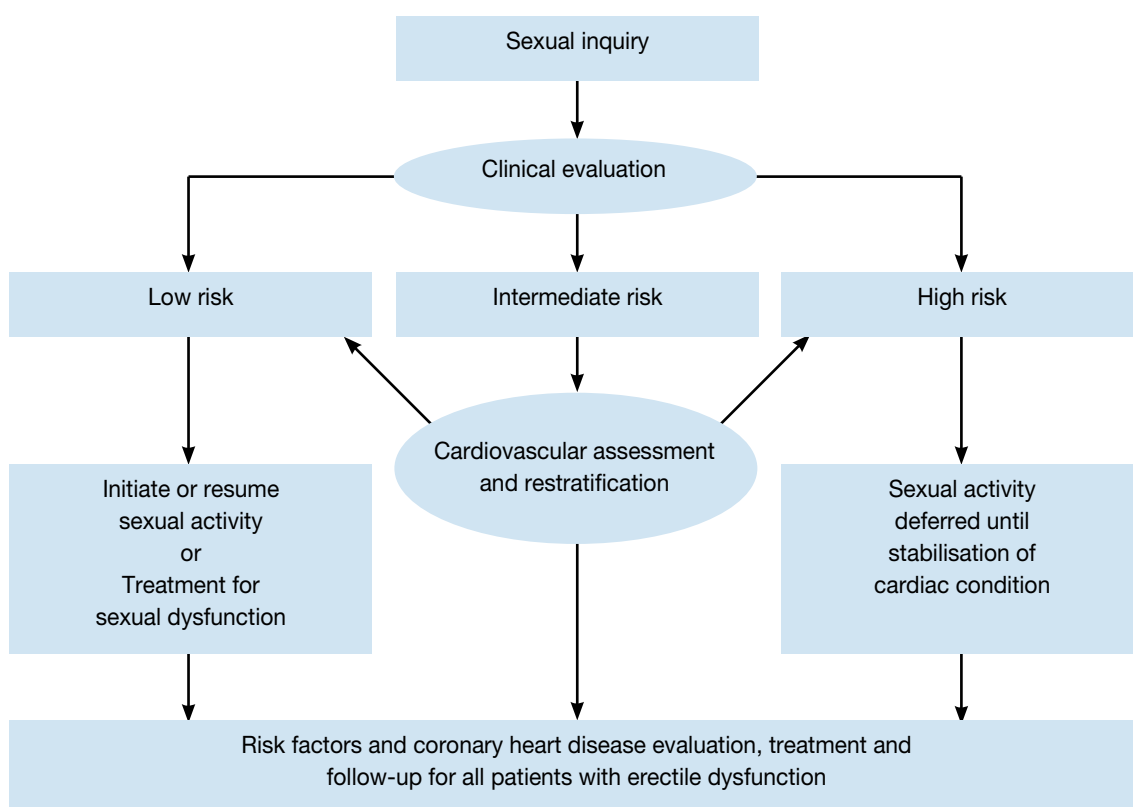
Patients with ED can be stratified into three cardiovascular risk categories (Table 2), which can be used as the basis for a treatment algorithm for initiating or resuming sexual activity (Figure 2). It is also possible for the clinician to estimate the risk of sexual activity in most patients from their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

Table 2: Cardiac risk stratification

Low-risk category	Intermediate-risk category	High-risk category
Asymptomatic, < 3 risk factors for CAD (excluding gender)	≥ 3 risk factors for CAD (excluding gender)	High-risk arrhythmias
Mild, stable angina (evaluated and/or being treated)	Moderate, stable angina	Unstable or refractory angina
Uncomplicated previous MI	Recent MI (> 2, < 6 weeks)	Recent MI (< 2 weeks)
LVD/CHF (NYHA class I)	LVD/CHF (NYHA class II)	LVD/CHF (NYHA class III/IV)
Post-successful coronary 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



2.5.2.1 *Low-risk category*

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

2.5.2.2 *Intermediate-risk or indeterminate-risk category*

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

2.5.2.3 *High-risk category*

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

2.5.3 **Specialised diagnostic tests**

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

2.5.3.1 *Nocturnal penile tumescence and rigidity (NPT)*

The nocturnal penile tumescence and rigidity assessment should be done on at least two nights. A functional erectile mechanism is indicated by an erectile event of at least 60% rigidity recorded on the tip of the penis that lasts for 10 min or more (10).

2.5.3.2 *Intracavernous injection test*

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

2.5.3.3 *Duplex ultrasound of penile arteries*

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

2.5.3.4 *Arteriography and dynamic infusion cavernosometry or cavernosography*

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

2.5.3.5 *Psychiatric assessment*

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

2.5.3.6 *Penile abnormalities*

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

2.5.4 **Patient education – consultation and referrals**

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

Table 3: Indications for specific diagnostic tests

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

Table 4: Specific diagnostic tests

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

2.5.5 Conclusions

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

2.5.6 References

- Davis-Joseph B, Tiefer L, Melman A. Accuracy of the initial history and physical examination to establish the etiology of erectile dysfunction. *Urology* 1995 Mar;45(3):498-502.
<http://www.ncbi.nlm.nih.gov/pubmed/7879338>
- Hatzichristou D, Hatzimouratidis K, Bekas M, et al. Diagnostic steps in the evaluation of patients with erectile dysfunction. *J Urol* 2002 Aug;168(2):615-20.
<http://www.ncbi.nlm.nih.gov/pubmed/12131320>
- Lewis RW. Epidemiology of erectile dysfunction. *Urol Clin North Am* 2001 May;28(2):209-16, vii.
<http://www.ncbi.nlm.nih.gov/pubmed/11402575>
- Rosen RC, Riley A, Wagner G, et al. The international index of erectile function (IIEF): a multidimensional scale for assessment of erectile dysfunction. *Urology* 1997 Jun;49(6):822-30.
<http://www.ncbi.nlm.nih.gov/pubmed/9187685>
- Morales A, Heaton JP. Hormonal erectile dysfunction. Evaluation and management. *Urol Clin North Am* 2001 May;28(2):279-88.
<http://www.ncbi.nlm.nih.gov/pubmed/11402581>
- Lue TF, Giuliano F, Montorsi F, et al. Summary of the recommendations on sexual dysfunctions in men. *J Sex Med* 2004 Jul;1(1):6-23.
<http://www.ncbi.nlm.nih.gov/pubmed/16422979>
- Laumann EO, Paik A, Rosen RC. The epidemiology of erectile dysfunction: results from the National Health and Social Life Survey. *Int J Impot Res* 1999 Sep;11(Suppl 1):S60-4.
<http://www.ncbi.nlm.nih.gov/pubmed/10554933>
- DeBusk R, Drory Y, Goldstein I, et al. Management of sexual dysfunction in patients with cardiovascular disease: recommendations of the Princeton Consensus Panel. *Am J Cardiol* 2000 Jul;86(2):175-81.
<http://www.ncbi.nlm.nih.gov/pubmed/10913479>

9. Kostis J, Jackson G, Rosen R, et al. Sexual dysfunction and cardiac risk (the Second Princeton Consensus Conference). *Am J Cardiol* 2005 Jul;96(2):313-21.
<http://www.ncbi.nlm.nih.gov/pubmed/16018863>
10. Hatzichristou DG, Hatzimouratidis K, Ioannides E, et al. Nocturnal penile tumescence and rigidity monitoring in young potent volunteers: reproducibility, evaluation criteria and the effect of sexual intercourse. *J Urol* 1998 Jun;159(6):1921-6.
<http://www.ncbi.nlm.nih.gov/pubmed/9598488>
11. Meuleman EJ, Diemont WL. Investigation of erectile dysfunction. Diagnostic testing for vascular factors in erectile dysfunction. *Urol Clin North Am* 1995 Nov;22(4):803-19.
<http://www.ncbi.nlm.nih.gov/pubmed/7483130>
12. Hatzichristou DG, Hatzimouratidis K, Apostolidis A, et al. Hemodynamic characterization of a functional erection. Arterial and corporeal veno-occlusive function in patients with a positive intracavernosal injection test. *Eur Urol* 1999;36(1):60-7.
<http://www.ncbi.nlm.nih.gov/pubmed/10364657>
13. Wespes E, Schulman C. Venous impotence: pathophysiology, diagnosis and treatment. *J Urol* 1993 May;149(5 Pt 2):1238-45.
<http://www.ncbi.nlm.nih.gov/pubmed/8479008>
14. Rosen RC, Leiblum SR, Spector IP. Psychologically based treatment for male erectile disorder: a cognitive-interpersonal model. *J Sex Marital Ther* 1994 Summer;20(2):67-85.
<http://www.ncbi.nlm.nih.gov/pubmed/8035472>
15. Hatzichristou D, Rosen RC, Broderick G, et al. Clinical evaluation and management strategy for sexual dysfunction in men and women. *J Sex Med* 2004 Jul;1(1):49-57.
<http://www.ncbi.nlm.nih.gov/pubmed/16422983>

3. TREATMENT OF ED

3.1 Treatment options

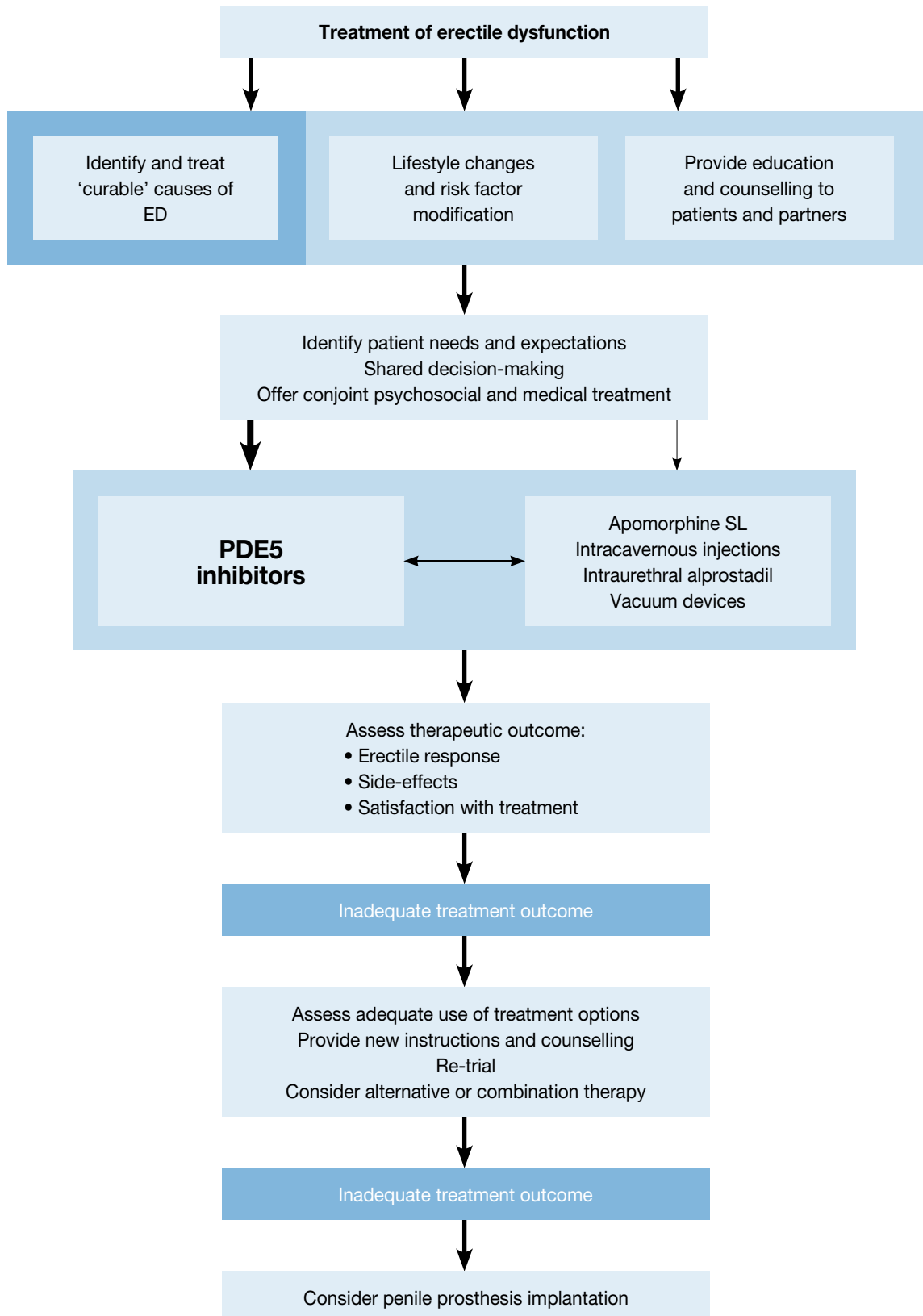
The primary goal in the management strategy of a patient with ED is to determine the aetiology of the disease and treat it when possible, and not to treat the symptom alone. Erectile dysfunction may be associated with modifiable or reversible factors, including lifestyle or drug-related factors. These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

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

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

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

Figure 3: Treatment algorithm for ED



PDE5 inhibitor = phosphodiesterase type 5 inhibitor.

3.2 Lifestyle management in ED with concomitant risk factors

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

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

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

3.3 Erectile dysfunction after radical prostatectomy (RP)

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

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

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

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

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

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

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

3.4 'Curable' causes of ED

3.4.1 Hormonal causes

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

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

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

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

3.4.2 Post-traumatic arteriogenic ED in young patients

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

3.4.3 Psychosexual counselling and therapy

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

3.5 First-line therapy

3.5.1 Oral pharmacotherapy

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

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

3.5.1.1 Sildenafil

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

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

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

3.5.1.2 Tadalafil

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

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

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

3.5.1.3 *Vardenafil*

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

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

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

3.5.1.4 *Choice or preference between the different PDE5 inhibitors*

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

3.5.1.5 *On-demand or chronic use of PDE5 inhibitors*

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

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

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

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

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

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

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

Parameter	Sildenafil, 100 mg	Tadalafil, 20mg	Vardenafil, 20 mg
Cmax	560 µg/L	378 µg/L	18.7 µg/L
Tmax	0.8-1 h	2 h	0.9 h
T1/2	2.6-3.7 h	17.5 h	3.9 h
AUC	1685 µg.h/L	8066 µg.h/L	56.8 µg.h/L
Protein binding	96%	94%	94%
Bioavailability	41%	NA	15%

Cmax: maximal concentration, Tmax: time-to-maximum plasma concentration; T1/2: plasma elimination half-time; AUC: area under curve or serum concentration time curve.

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

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

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

* Adapted from EMEA statements on product characteristics.

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

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

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

3.5.1.6 Safety issues for PDE5 inhibitors

3.5.1.6.1 Cardiovascular safety

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

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

3.5.1.6.2 Nitrates are totally contraindicated with PDE5 inhibitors

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

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

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

3.5.1.6.3 Antihypertensive drugs

Co-administration of PDE5 inhibitors with antihypertensive agents (angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, calcium blockers, beta-blockers, diuretics) may result in small additive drops in blood pressure, which are usually minor. In general, the adverse event profile of a PDE5 inhibitor is

not made worse by a background of antihypertensive medication, even when the patient is taking several antihypertensive agents.

3.5.1.6.4 Alpha-blocker interactions

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

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

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

3.5.1.6.5 Dosage adjustment

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

However, other agents, such as rifampin, phenobarbital, phenytoin, and carbamazepine, may induce CYP3A4 and enhance the breakdown of PDE5 inhibitors, so that higher doses of PDE5 inhibitors are required.

Severe kidney or hepatic dysfunction may require dose adjustments or warnings.

3.5.1.7 Management of non-responders to PDE5 inhibitors

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

3.5.1.7.1 Check that the patient has been using a licensed medication

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

3.6.1.7.2 Check that the medication has been properly prescribed and correctly used

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

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

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

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

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

Too much time between taking medication and intercourse attempt: It is also possible to wait too long after taking medication before attempting sexual intercourse. The half-life of sildenafil and vardenafil is about 4 h,

suggesting that the normal window of efficacy is about 6-8 h following ingestion of the medication, though responses following this time period are well recognised. Tadalafil had a longer half-life of about 17.5 h, so the window of efficacy is much longer at about 36 h.

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

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

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

3.5.1.7.3 Possible manoeuvres in patients correctly using a PDE5 inhibitor

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

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

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

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

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

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

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

3.5.1.8 Apomorphine sublingual

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

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

Apomorphine is not contraindicated in patients taking nitrates or antihypertensive drugs (of all classes) and it does not affect vital signs (87,88). There was no marked improvement in sexual desire, but a slight improvement in orgasmic function was noticed.

Comparative studies clearly show that apomorphine is associated with significantly lower efficacy and

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

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

3.5.1.9 Other oral agents

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

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

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

3.6 Topical pharmacotherapy

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

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

3.7 Vacuum constriction devices

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

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

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

3.8 Second-line therapy

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

3.8.1 **Intracavernous injections**

3.8.1.1 *Alprostadil*

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

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

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

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

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

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

Action to be taken with a prolonged erection

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

3.8.1.2 *Combination therapy*

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

- Papaverine (20-80 mg) was the first oral drug used for intracavernous injections. It is only used in combination therapy today due to its high incidence of side-effects as monotherapy.
- Phentolamine has been used in combination therapy to increase efficacy. As monotherapy, it produces a poor erectile response.
- Sparse data in the literature support the use of other drugs, such as vasoactive intestinal peptide (VIP), NO donors (linsidomine), forskolin, potassium channel openers, moxislyte or calcitonin gene-related peptide (CGRP), usually combined with the main drugs (119,120). 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 (121-123). The triple combination regimen of papaverine, phentolamine and alprostadil had the highest efficacy rates, reaching 92%; this combination had similar side-effects as alprostadil monotherapy, but a lower incidence of penile pain due to lower doses of alprostadil. However, fibrosis was more common (5-10%) when papaverine was used

(depending on total dose). In addition, mild hepatotoxicity has been reported with papaverine (124). Despite high efficacy rates, 5-10% of patients will not respond to combination intracavernous injections. The combination of sildenafil with intracavernous injection of the triple combination regimen may salvage as many as 31% of patients who do not respond to the triple combination alone (125). However, combination therapy was associated with an incidence of adverse effects in 33% of patients, including dizziness in 20% of patients.

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

3.8.1.3 Intraurethral alprostadil

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

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

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

3.9 Third-line therapy (penile prostheses)

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

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

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

3.9.1 Complications

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

3.9.2 Conclusion

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

3.10 Recommendations

Recommendations	LE	GR
Lifestyle changes and risk factor modification must precede or accompany ED treatment.	1b	A
Pro-erectile treatments have to be given at the earliest opportunity after radical prostatectomy.	1b	A
When a curable cause of ED is found, the cause must be treated first.	1b	B
PDE5 inhibitors are first-line therapy.	1a	A
Daily administration of PDE5 inhibitors may improve results and restore erectile function.	1b	A

Inadequate/incorrect prescription and poor patient education are the main causes of a lack of response to PDE5 inhibitors.	3	B
Testosterone replacement restores efficacy in hypogonadic non-responders to PDE5 inhibitors.	1b	B
Apomorphine can be used in mild-to-moderate ED or psychogenic causes or in patients with contraindications for the use of PDE5 inhibitors.	1b	B
A vacuum constriction device can be used in patients with stable relationship.	4	C
Intracavernous injection is second-line therapy.	1b	B
Penile implant is third-line therapy.	4	C

PDE5 inhibitor = phosphodiesterase type 5 inhibitor; ED = erectile dysfunction.

3.11 References

- Hatzichristou D, Rosen RC, Broderick G, et al. Clinical evaluation and management strategy for sexual dysfunction in men and women. *J Sex Med* 2004 Jun;1(1):49-57.
<http://www.ncbi.nlm.nih.gov/pubmed/16422983>
- Derby CA, Mohr BA, Goldstein I, et al. Modifiable risk factors and erectile dysfunction: can lifestyle changes modify risk? *Urology* 2000 Aug;56(2):302-6.
<http://www.ncbi.nlm.nih.gov/pubmed/10925098>
- Moyad MA, Barada JH, Lue TF, et al; Sexual Medicine Society Nutraceutical Committee. Prevention and treatment of erectile dysfunction using lifestyle changes and dietary supplements: what works and what is worthless, part I. *Urol Clin North Am* 2004 May;31(2):249-57.
<http://www.ncbi.nlm.nih.gov/pubmed/15123405>
- Moyad MA, Barada JH, Lue TF, et al; Sexual Medicine Society Nutraceutical Committee. Prevention and treatment of erectile dysfunction using lifestyle changes and dietary supplements: what works and what is worthless, part II. *Urol Clin North Am* 2004 May;31(2):259-73.
<http://www.ncbi.nlm.nih.gov/pubmed/15123406>
- Esposito K, Giugliano F, Di Palo C, et al. Effect of lifestyle changes on erectile dysfunction in obese men: a randomized controlled trial. *JAMA* 2004 Jun;291(24):2978-84.
<http://www.ncbi.nlm.nih.gov/pubmed/15213209>
- Guay AT. Optimizing response to phosphodiesterase therapy: impact of risk-factor management. *J Androl* 2003 Nov-Dec;24(6 Suppl):S59-S62.
<http://www.ncbi.nlm.nih.gov/pubmed/14581497>
- Montorsi F, Guazzoni G, Strambi LF, et al. Recovery of spontaneous erectile function after nerve-sparing radical retropubic prostatectomy with and without early intracavernous injections of alprostadil: results of a prospective, randomized trial. *J Urol* 1997 Oct;158(4):1408-10.
<http://www.ncbi.nlm.nih.gov/pubmed/9302132>
- Raina R, Pahlajani G, Agarwal A, et al. The early use of transurethral alprostadil after radical prostatectomy potentially facilitates an earlier return of erectile function and successful sexual activity. *BJU Int* 2007 Dec;100(6):1317-21.
<http://www.ncbi.nlm.nih.gov/pubmed/17850385>
- Raina R, Agarwal A, Ausmundson S, et al. Early use of vacuum constriction device following radical prostatectomy facilitates early sexual activity and potentially earlier return of erectile function. *Int J Impot Res* 2006 Jan-Feb;18(1):77-81.
<http://www.ncbi.nlm.nih.gov/pubmed/16107868>
- Lane BR, Abouassaly R, Angermeier KW, et al. Three-piece inflatable penile prostheses can be safely implanted after radical prostatectomy through a transverse scrotal incision. *Urology* 2007 Sep;70(30):539-42.
<http://www.ncbi.nlm.nih.gov/pubmed/17686509>
- Bianco F, Kattan M, Eastham J, et al. Surgeon and surgical volume as predictors of erectile function outcomes following radical prostatectomy. *J Sex Med* 2004;1(Suppl 1):34. abstr O17.
- Ayyathurai R, Manoharan M, Nieder AM, et al. Factors affecting erectile function after radical retropubic prostatectomy: results from 1620 consecutive patients. *BJU Int* 2008 Apr;101(7):833-6.
<http://www.ncbi.nlm.nih.gov/pubmed/18190627>
- Hollenbeck BK, Dunn RL, Wei JT, et al. Determinants of long-term sexual health outcome after radical prostatectomy measured by a validated instrument. *J Urol* 2003 Apr;169(4):1453-7.
<http://www.ncbi.nlm.nih.gov/pubmed/12629382>
- Schwartz EJ, Wong P, Graydon RJ. Sildenafil preserves intracorporeal smooth muscle after radical retropubic prostatectomy. *J Urol* 2004 Feb;171(2 Pt 4):771-4.
<http://www.ncbi.nlm.nih.gov/pubmed/14713808>

15. Padma-Nathan H, McCullough AR, Levine LA, et al, Study Group. Collaborators (12) Andrienne R, Bell D, Broderick G, Carrier S, Cuzin B, Deeths HJ, Hellstrom W, Herschorn S, Lewis RW, Rosen RC, Shabsigh R, Stricker P. Randomized, double-blind, placebo-controlled study of postoperative nightly sildenafil citrate for the prevention of erectile dysfunction after bilateral nerve-sparing radical prostatectomy. *Int J Impot Res* 2008 Sep-Oct;20(5):479-86.
<http://www.ncbi.nlm.nih.gov/pubmed/18650827>
16. Bannowsky A, Schulze H, van der Horst C, et al. Recovery of erectile function after nerve-sparing radical prostatectomy: improvement with nightly low-dose sildenafil. *BJU Int* 2008 May;101(10):1279-83.
<http://www.ncbi.nlm.nih.gov/pubmed/18284406>
17. Raina R, Lakin MM, Agarwal A, et al. Efficacy and factors associated with successful outcome of sildenafil citrate use for erectile dysfunction after radical prostatectomy. *Urology* 2004 May;63(5):960-6.
<http://www.ncbi.nlm.nih.gov/pubmed/15134989>
18. McCullough AR, Levine LA, Padma-Nathan H. Return of nocturnal erections and erectile function after bilateral nerve-sparing radical prostatectomy in men treated nightly with sildenafil citrate: subanalysis of a longitudinal randomized double-blind placebo-controlled trial. *J Sex Med* 2008 Feb;5(2):476-84.
<http://www.ncbi.nlm.nih.gov/pubmed/18086170>
19. Montorsi F, Nathan HP, McCullough A, et al. Tadalafil in the treatment of erectile dysfunction following bilateral nerve sparing radical retropubic prostatectomy: a randomized, double-blind, placebo controlled trial. *J Urol* 2004 Sep;172(3):1036-41.
<http://www.ncbi.nlm.nih.gov/pubmed/15311032>
20. Brock G, Nehra A, Lipshultz LI, et al. Safety and efficacy of vardenafil for the treatment of men with erectile dysfunction after radical retropubic prostatectomy. *J Urol* 2003 Oct;170(4 Pt 1):1278-83.
<http://www.ncbi.nlm.nih.gov/pubmed/14501741>
21. Nehra A, Grantmyre J, Nadel A, Thibonnier M, et al. Vardenafil improved patient satisfaction with erectile hardness, orgasmic function and sexual experience in men with erectile dysfunction following nerve sparing radical prostatectomy. *J Urol* 2005 Jun;173(6):2067-71.
<http://www.ncbi.nlm.nih.gov/pubmed/15879836>
22. Montorsi F, Brock G, Lee J, et al. Effect of nightly versus on-demand vardenafil on recovery of erectile function in men following bilateral nerve-sparing radical prostatectomy. *Eur Urol* 2008 Oct;54(4):924-31.
<http://www.ncbi.nlm.nih.gov/pubmed/18640769>
23. Mulhall J, Land S, Parker M, et al. The use of an erectogenic pharmacotherapy regimen following radical prostatectomy improves recovery of spontaneous erectile function. *J Sex Med* 2005 Jul;2(4):532-40.
<http://www.ncbi.nlm.nih.gov/pubmed/16422848>
24. Montague DK. Penile prosthesis implantation for end-stage erectile dysfunction after radical prostatectomy. *Rev Urol* 2005;7(Suppl 2):S51-7.
<http://www.ncbi.nlm.nih.gov/pubmed/16985898>
25. Greenstein A, Mabeesh NJ, Sofer M, et al. Does sildenafil combined with testosterone gel improve erectile dysfunction in hypogonadal men in whom testosterone supplement therapy alone failed? *J Urol* 2005 Feb;173(2):530-2.
<http://www.ncbi.nlm.nih.gov/pubmed/15643239>
26. Morales A, Heaton JP. Hormonal erectile dysfunction. Evaluation and management. *Urol Clin North Am* 2001 May;28(2):279-88.
<http://www.ncbi.nlm.nih.gov/pubmed/11402581>
27. Rao DS, Donatucci CF. Vasculogenic impotence. Arterial and venous surgery. *Urol Clin North Am* 2001 May;28(2):309-19.
<http://www.ncbi.nlm.nih.gov/pubmed/11402583>
28. Wespes E, Wildschutz T, Roumeguere T, et al. The place of surgery for vascular impotence in the third millennium. *J Urol* 2003 Oct;170(4 Pt 1):1284-6.
<http://www.ncbi.nlm.nih.gov/pubmed/14501742>
29. Rosen RC. Psychogenic erectile dysfunction. Classification and management. *Urol Clin North Am* 2001 May;28(2):269-78.
<http://www.ncbi.nlm.nih.gov/pubmed/11402580>
30. Lue TF. Erectile dysfunction. *N Engl J Med* 2000 Jun;342(24):1802-13.
<http://www.ncbi.nlm.nih.gov/pubmed/10853004>

31. Moncada I, Jara J, Subirá D, et al. Efficacy of sildenafil citrate at 12 hours after dosing: re-exploring the therapeutic window. *Eur Urol* 2004 Sep;46(3):357-60; discussion 360-1.
<http://www.ncbi.nlm.nih.gov/pubmed/15306108>
32. Langtry HD, Markham A. Sildenafil: a review of its use in erectile dysfunction. *Drugs* 1999 Jun;57(6): 967-89.
<http://www.ncbi.nlm.nih.gov/pubmed/10400408>
33. Goldstein I, Lue TF, Padma-Nathan H, et al; Sildenafil Study Group. Oral sildenafil in the treatment of erectile dysfunction. 1998. *J Urol* 2002 Feb;167(2 Pt 2):1197-203.
<http://www.ncbi.nlm.nih.gov/pubmed/11905901>
34. Stuckey BG, Jadzinsky MN, Murphy LJ, et al. Sildenafil citrate for treatment of erectile dysfunction in men with type 1 diabetes: results of a randomized controlled trial. *Diabetes Care* 2003 Feb;26(2): 279-84.
<http://www.ncbi.nlm.nih.gov/pubmed/12547849>
35. Porst H, Padma-Nathan H, Giuliano F, et al. Efficacy of tadalafil for the treatment of erectile dysfunction at 24 and 36 hours after dosing: a randomized controlled trial. *Urology* 2003 Jul;62(1): 121-5; discussion 125-6.
<http://www.ncbi.nlm.nih.gov/pubmed/12837435>
36. Brock GB, McMahon CG, Chen KK, et al. Efficacy and safety of tadalafil for the treatment of erectile dysfunction: results of integrated analyses. *J Urol* 2002 Oct;168(4 Pt 1):1332-6.
<http://www.ncbi.nlm.nih.gov/pubmed/12352386>
37. Montorsi F, Verheyden B, Meuleman E, et al. Long-term safety and tolerability of tadalafil in the treatment of erectile dysfunction. *Eur Urol* 2004 Mar;45(3):339-44; discussion 344-5.
<http://www.ncbi.nlm.nih.gov/pubmed/15036680>
38. Sáenz de Tejada I, Anglin G, Knight JR, et al. Effects of tadalafil on erectile dysfunction in men with diabetes. *Diabetes Care* 2002 Dec;25(12):2159-64.
<http://www.ncbi.nlm.nih.gov/pubmed/12453954>
39. Bischoff E, Schneider K. A conscious-rabbit model to study vardenafil hydrochloride and other agents that influence penile erection. *Int J Impot Res* 2001 Aug;13(4):230-5.
<http://www.ncbi.nlm.nih.gov/pubmed/11494080>
40. Keating GM, Scott LJ. Vardenafil: a review of its use in erectile dysfunction. *Drugs* 2003;63(23):2673-703.
<http://www.ncbi.nlm.nih.gov/pubmed/14636086>
41. Porst H, Rosen R, Padma-Nathan H, et al. The efficacy and tolerability of vardenafil, a new, oral, selective phosphodiesterase type 5 inhibitor, in patients with erectile dysfunction: the first at-home clinical trial. *Int J Impot Res* 2001 Aug;13(4):192-9.
<http://www.ncbi.nlm.nih.gov/pubmed/11494074>
42. Potempa AJ, Ulbrich E, Bernard I, et al. Efficacy of vardenafil in men with erectile dysfunction: a flexible-dose community practice study. *Eur Urol* 2004 Jul;46(1):73-9.
<http://www.ncbi.nlm.nih.gov/pubmed/15183550>
43. Goldstein I, Young JM, Fischer J, et al; Vardenafil Diabetes Study Group. Vardenafil, a new phosphodiesterase type 5 inhibitor, in the treatment of erectile dysfunction in men with diabetes: a multicentre double-blind placebo-controlled fixed-dose study. *Diabetes Care* 2003 Mar;26(3):777-83.
<http://www.ncbi.nlm.nih.gov/pubmed/12610037>
44. Ahn GJ, Yu JY, Choi SM, et al. Chronic administration of phosphodiesterase 5 inhibitor improves erectile and endothelial function in a rat model of diabetes. *Int J Androl* 2005 Oct;28(5):260-6.
<http://www.ncbi.nlm.nih.gov/pubmed/16128985>
45. Kovanecz I, Rambhatia A, Ferrini MG, et al. Chronic daily tadalafil prevents the corporal fibrosis and veno-occlusive dysfunction that occurs after cavernosal nerve resection. *BJU Int* 2008 Jan;101(2): 203-10.
<http://www.ncbi.nlm.nih.gov/pubmed/17888043>
46. Ferrini MG, Davila HH, Kovanecz I, et al. Vardenafil prevents fibrosis and loss of corporal smooth muscle that occurs after bilateral cavernosal nerve resection in the rat. *Urology* 2006 Aug;68(2): 429-35.
<http://www.ncbi.nlm.nih.gov/pubmed/16904479>
47. Vignozzi L, Filippi S, Morelli A, et al. Effect of chronic tadalafil administration on penile hypoxia induced by cavernous neurotomy in the rat. *J Sex Med* 2006 May;3(3):419-31.
<http://www.ncbi.nlm.nih.gov/pubmed/16681467>

48. Ferrini MG, Kovanecz I, Sanchez S, et al. Long-term continuous treatment with sildenafil ameliorates aging-related erectile dysfunction and the underlying corporal fibrosis in the rat. *Biol Reprod* 2007 May;76(5):915-23.
<http://www.ncbi.nlm.nih.gov/pubmed/17287493>
49. Behr-Roussel D, Gorny D, Mevel K, et al. Chronic sildenafil improves erectile function and endothelium-dependent cavernosal relaxation in rats: lack of tachyphylaxis. *Eur Urol* 2005 Jan;47(1):87-91.
<http://www.ncbi.nlm.nih.gov/pubmed/15582254>
50. McMahon C. Efficacy and safety of daily tadalafil in men with erectile dysfunction previously unresponsive to on-demand tadalafil. *J Sex Med* 2004 Nov;1(3):292-300.
<http://www.ncbi.nlm.nih.gov/pubmed/16422959>
51. McMahon C. Comparison of efficacy, safety and tolerability of on-demand tadalafil and daily dosed tadalafil for the treatment of erectile dysfunction. *J Sex Med* 2005 May;2(3):415-25.
<http://www.ncbi.nlm.nih.gov/pubmed/16422874>
52. Porst H, Giuliano F, Glina S, et al. Evaluation of the efficacy and safety of once-a-day dosing of tadalafil 5mg and 10mg in the treatment of erectile dysfunction: results of a multicenter, randomized, double-blind, placebo-controlled trial. *Eur Urol* 2006 Aug;50(2):351-9.
<http://www.ncbi.nlm.nih.gov/pubmed/16766116>
53. Rajfer J, Aliotta PJ, Steidle CP, et al. Tadalafil dosed once a day in men with erectile dysfunction: a randomized, double-blind, placebo-controlled study in the US. *Int J Impot Res* 2006;19(1):95-103.
<http://www.ncbi.nlm.nih.gov/pubmed/16871272>
54. Porst H, Rajfer J, Casabé A, et al. Long-term safety and efficacy of tadalafil 5 mg dosed once daily in men with erectile dysfunction. *J Sex Med* 2008 Sep;5(9):2160-9.
<http://www.ncbi.nlm.nih.gov/pubmed/18557812>
55. Zumbé J, Porst H, Sommer F, et al. Comparable efficacy of once-daily versus on-demand vardenafil in men with mild-to-moderate erectile dysfunction: findings of the RESTORE study. *Eur Urol* 2008 Jul;54(1):204-10.
<http://www.ncbi.nlm.nih.gov/pubmed/18395326>
56. Rosano GM, Aversa A, Vitale C, et al. Chronic treatment with tadalafil improves endothelial function in men with increased cardiovascular risk. *Eur Urol* 2005 Feb;47(2):214-20.
<http://www.ncbi.nlm.nih.gov/pubmed/15661417>
57. Aversa A, Greco E, Bruzziches R, et al. Relationship between chronic tadalafil administration and improvement of endothelial function in men with erectile dysfunction: a pilot study. *Int J Impot Res* 2007 Mar-Apr;19(2):200-7.
<http://www.ncbi.nlm.nih.gov/pubmed/16943794>
58. Aversa A, Vitale C, Volterrani M, et al. Chronic administration of Sildenafil improves markers of endothelial function in men with Type 2 diabetes. *Diabet Med* 2008 Jan;25(1):37-44.
<http://www.ncbi.nlm.nih.gov/pubmed/18199130>
59. Hatzichristou D, Gambla M, Rubio-Aurioles E, et al. Efficacy of tadalafil once daily in men with diabetes mellitus and erectile dysfunction. *Diabet Med* 2008 Feb;25(2):138-46.
<http://www.ncbi.nlm.nih.gov/pubmed/18290855>
60. Mirone V, Costa P, Damber JE, et al. An evaluation of an alternative dosing regimen with tadalafil, 3 times/week, for men with erectile dysfunction: SURE study in 14 European countries. *Eur Urol* 2005 Jun;47(6):846-54.
<http://www.ncbi.nlm.nih.gov/pubmed/15925082>
61. Kloner RA. Novel phosphodiesterase type 5 inhibitors: assessing hemodynamic effects and safety parameters. *Clin Cardiol* 2004 Apr;27(4 Suppl 1):I20-5.
<http://www.ncbi.nlm.nih.gov/pubmed/15115192>
62. Thadani U, Smith W, Nash S, et al. The effect of vardenafil, a potent and highly selective phosphodiesterase-5 inhibitor for the treatment of erectile dysfunction, on the cardiovascular response to exercise in patients with coronary artery disease. *J Am Coll Cardiol* 2002 Dec;40(11):2006-12.
<http://www.ncbi.nlm.nih.gov/pubmed/12475462>
63. Vardi Y, Bulus M, Reisner S, et al. Effects of sildenafil citrate (Viagra) on hemodynamic parameters during exercise testing and occurrence of ventricular arrhythmias in patients with erectile dysfunction and cardiovascular disease. *Eur Urol* 2003 May;43(5):544-51.
<http://www.ncbi.nlm.nih.gov/pubmed/12706001>
64. Auerbach SM, Gittelman M, Mazzu A, et al. Simultaneous administration of vardenafil and tamsulosin does not induce clinically significant hypotension in patients with benign prostatic hyperplasia. *Urology* 2004 Nov;64(5):998-1003; discussion 1003-4.
<http://www.ncbi.nlm.nih.gov/pubmed/15533493>

65. Kloner RA, Jackson G, Emmick JT, et al. Interaction between the phosphodiesterase 5 inhibitor, tadalafil and 2 alpha-blockers, doxazosin and tamsulosin in healthy normotensive men. *J Urol* 2004 Nov;172(5 Pt 1):1935-40.
<http://www.ncbi.nlm.nih.gov/pubmed/15540759>
66. Nichols DJ, Muirhead GJ, Harness JA. Pharmacokinetics of sildenafil citrate after single oral doses in healthy male subjects: absolute bioavailability, food effects and dose proportionality. *Br J Clin Pharmacol* 2002;53(Suppl 1):5S-12S.
<http://www.ncbi.nlm.nih.gov/pubmed/11879254>
67. Forgue ST, Patterson BE, Bedding AW, et al. Tadalafil pharmacokinetics in healthy subjects. *Br J Clin Pharmacol* 2006 Mar;61(3):280-8.
<http://www.ncbi.nlm.nih.gov/pubmed/16487221>
68. Klotz T, Sachse R, Heidrich A, et al. Vardenafil increases penile rigidity and tumescence in erectile dysfunction patients: a RigiScan and pharmacokinetic study. *World J Urol* 2001 Feb;19(1):32-9.
<http://www.ncbi.nlm.nih.gov/pubmed/11289568>
69. Padma-Nathan H, Stecher VJ, Sweeney M, et al. Minimal time to successful intercourse after sildenafil citrate: results of a randomized, double-blind, placebo-controlled trial. *Urology* 2003 Sep;62(3):400-3.
<http://www.ncbi.nlm.nih.gov/pubmed/12946731>
70. Rosen RC, Padma-Nathan H, Shabsigh R, et al. Determining the earliest time within 30 minutes to erectogenic effect after tadalafil 10 and 20 mg: a multicenter, randomized, double-blind, placebo-controlled, at-home study. *J Sex Med* 2004 Sep;1(2):193-200.
<http://www.ncbi.nlm.nih.gov/pubmed/16422974>
71. Montorsi F, Padma-Nathan H, Buvat J, et al; Vardenafil Study Group. Earliest time to onset of action leading to successful intercourse with vardenafil determined in an at-home setting: a randomized, double-blind, placebo-controlled trial. *J Sex Med* 2004 Sep; 1(2):168-78.
<http://www.ncbi.nlm.nih.gov/pubmed/16422971>
72. Rajagopalan P, Mazzu A, Xia C, et al. Effect of high-fat breakfast and moderate-fat evening meal on the pharmacokinetics of vardenafil, an oral phosphodiesterase-5 inhibitor for the treatment of erectile dysfunction. *J Clin Pharmacol* 2003 Mar;43(3):260-7.
<http://www.ncbi.nlm.nih.gov/pubmed/12638394>
73. McCullough AR, Barada JH, Fawzy A, et al. Achieving treatment optimization with sildenafil citrate (Viagra) in patients with erectile dysfunction. *Urology* 2002 Sep;60(2 Suppl 2):28-38.
<http://www.ncbi.nlm.nih.gov/pubmed/12414331>
74. Hatzichristou D, Moysidis K, Apostolidis A, et al. Sildenafil failures may be due to inadequate patient instructions and follow-up: a study on 100 non-responders. *Eur Urol* 2005 Apr;47(4):518-22.
<http://www.ncbi.nlm.nih.gov/pubmed/15774252>
75. Hatzimouratidis K, Moysidis K, Bekos A, et al. Treatment strategy for 'non-responders' to tadalafil and vardenafil: a real-life study. *Eur Urol* 2006 Jul;50(1):126-32.
<http://www.ncbi.nlm.nih.gov/pubmed/16564127>
76. Gruenwald I, Shenfeld O, Chen J, et al. Positive effect of counseling and dose adjustment in patients with erectile dysfunction who failed treatment with sildenafil. *Eur Urol* 2006 Jul;50(1):134-40.
<http://www.ncbi.nlm.nih.gov/pubmed/16527391>
77. Shabsigh R, Kaufman JM, Steidle C, et al. Randomized study of testosterone gel as adjunctive therapy to sildenafil in hypogonadal men with erectile dysfunction who do not respond to sildenafil alone. *J Urol* 2004 Aug;172(2):658-63.
<http://www.ncbi.nlm.nih.gov/pubmed/15247755>
78. Carson CC, Hatzichristou DG, Carrier S, et al; Patient Response with Vardenafil in Sildenafil Non-Responders (PROVEN) Study Group. Erectile response with vardenafil in sildenafil nonresponders: a multicentre, double-blind, 12-week, flexible-dose, placebo-controlled erectile dysfunction clinical trial. *BJU Int* 2004 Dec;94(9):1301-9.
<http://www.ncbi.nlm.nih.gov/pubmed/15610110>
79. Eardley I, Montorsi F, Jackson G, et al. Factors associated with preference for sildenafil citrate and tadalafil for treating erectile dysfunction in men naive to phosphodiesterase 5 inhibitor therapy: post hoc analysis of data from a multicentre, randomized, open-label, crossover study. *BJU Int* 2007 Jul;100(1):122-9.
<http://www.ncbi.nlm.nih.gov/pubmed/17552960>
80. McMahon C. Efficacy and safety of daily tadalafil in men with erectile dysfunction previously unresponsive to on-demand tadalafil. *J Sex Med* 2004 Nov;1(3):292-300.
<http://www.ncbi.nlm.nih.gov/pubmed/16422959>

81. Hagemann JH, Berding G, Bergh S, et al. Effects of visual sexual stimuli and apomorphine SL on cerebral activity in men with erectile dysfunction. *Eur Urol* 2003 Apr;43(4):412-20.
<http://www.ncbi.nlm.nih.gov/pubmed/12667723>
82. Montorsi F, Perani D, Anchisi D, et al. Brain activation patterns during video sexual stimulation following the administration of apomorphine: results of a placebo-controlled study. *Eur Urol* 2003 Apr;43(4):405-11.
<http://www.ncbi.nlm.nih.gov/pubmed/12667722>
83. Heaton JP. Apomorphine: an update of clinical trial results. *Int J Impot Res* 2000 Oct;12(Suppl 4):S67-73.
<http://www.ncbi.nlm.nih.gov/pubmed/11035390>
84. Dula E, Bukofzer S, Perdok R, et al. Double-blind, crossover comparison of 3 mg apomorphine SL with placebo and with 4 mg apomorphine SL in male erectile dysfunction. *Eur Urol* 2001 May;39(5):558-3; discussion 564.
<http://www.ncbi.nlm.nih.gov/pubmed/11464037>
85. Martínez R, Puigvert A, Pomerol JM, et al. Clinical experience with apomorphine hydrochloride: the first 107 patients. *J Urol* 2003 Dec;170(6 Pt 1):2352-5.
<http://www.ncbi.nlm.nih.gov/pubmed/14634414>
86. Buvat J, Montorsi F. Safety and tolerability of apomorphine SL in patients with erectile dysfunction. *BJU Int* 2001 Oct;88 (Suppl 3):30-5.
<http://www.ncbi.nlm.nih.gov/pubmed/11578277>
87. Bukofzer S, Livesey N. Safety and tolerability of apomorphine SL (Uprima). *Int J Impot Res* 2001 Aug;13(Suppl 3):S40-4.
<http://www.ncbi.nlm.nih.gov/pubmed/11477491>
88. Fagan TC, Buttler S, Marbury T, et al; SLAPO Study Group. Cardiovascular safety of sublingual apomorphine in patients on stable doses of oral antihypertensive agents and nitrates. *Am J Cardiol* 2001 Oct;88(7):760-6.
<http://www.ncbi.nlm.nih.gov/pubmed/11589843>
89. Eardley I, Wright P, MacDonagh R, et al. An open-label, randomized, flexible-dose, crossover study to assess the comparative efficacy and safety of sildenafil citrate and apomorphine hydrochloride in men with erectile dysfunction. *BJU Int* 2004 Jun;93(9):1271-5.
<http://www.ncbi.nlm.nih.gov/pubmed/15180621>
90. Perimenis P, Gyftopoulos K, Giannitsas K, et al. A comparative, crossover study of the efficacy and safety of sildenafil and apomorphine in men with evidence of arteriogenic erectile dysfunction. *Int J Impot Res* 2004 Feb;16(1):2-7.
<http://www.ncbi.nlm.nih.gov/pubmed/14963464>
91. Afif-Abdo J, Teloken C, Damião R, et al. Comparative cross-over study of sildenafil and apomorphine for treating erectile dysfunction. *BJU Int* 2008 Sep;102(7):829-34.
<http://www.ncbi.nlm.nih.gov/pubmed/18537952>
92. Montorsi F. Tolerability and safety of apomorphine SL (Ixense™). *Int J Impot Res* 2003 Apr;15 (Suppl 2):S7-9.
<http://www.ncbi.nlm.nih.gov/pubmed/12825097>
93. Padma-Nathan H, Christ G, Adaikan G, et al. Pharmacotherapy for erectile dysfunction. *J Sex Med* 2004 Sep;1(2):128-40.
<http://www.ncbi.nlm.nih.gov/pubmed/16422967>
94. Goldstein I. Oral phentolamine: an alpha-1, alpha-2 adrenergic antagonist for the treatment of erectile dysfunction. *Int J Impot Res* 2000 Mar;12(Suppl 1):S75-80.
<http://www.ncbi.nlm.nih.gov/pubmed/10845768>
95. Telöken C, Rhoden EL, Sogari P, et al. Therapeutic effects of high dose yohimbine hydrochloride on organic erectile dysfunction. *J Urol* 1998 Jan;159(1):122-4.
<http://www.ncbi.nlm.nih.gov/pubmed/9400452>
96. Costabile RA, Spevak M. Oral trazodone is not effective therapy for erectile dysfunction: a double-blind, placebo controlled trial. *J Urol* 1999 Jun;161(6):1819-22.
<http://www.ncbi.nlm.nih.gov/pubmed/10332444>
97. Hong B, Ji YH, Hong JH, et al. A double-blind crossover study evaluating the efficacy of korean red ginseng in patients with erectile dysfunction: a preliminary report. *J Urol* 2002 Nov;168(5):2070-3.
<http://www.ncbi.nlm.nih.gov/pubmed/12394711>
98. Montorsi F, Salonia A, Zanoni M, et al. Current status of local penile therapy. *Int J Impot Res* 2002 Feb;14(Suppl 1):S70-81.
<http://www.ncbi.nlm.nih.gov/pubmed/11850739>

99. Goldstein I, Payton TR, Schechter PJ. A double-blind, placebo-controlled, efficacy and safety study of topical gel formulation of 1% alprostadil (Topiglan) for the in-office treatment of erectile dysfunction. *Urology* 2001 Feb;57(2):301-5.
<http://www.ncbi.nlm.nih.gov/pubmed/11182341>
100. Levine LA, Dimitriou RJ. Vacuum constriction and external erection devices in erectile dysfunction. *Urol Clin North Am* 2001 May;28(2):335-41, ix-x.
<http://www.ncbi.nlm.nih.gov/pubmed/11402585>
101. Cookson MS, Nadig PW. Long-term results with vacuum constriction device. *J Urol* 1993 Feb;149(2):290-4.
<http://www.ncbi.nlm.nih.gov/pubmed/8426404>
102. Lewis RW, Witherington R. External vacuum therapy for erectile dysfunction: use and results. *World J Urol* 1997;15(1):78-82.
<http://www.ncbi.nlm.nih.gov/pubmed/9066099>
103. Shabsigh R, Padma-Nathan H, Gittleman M, et al. Intracavernous alprostadil alfadex (EDEX/VIRIDAL) is effective and safe in patients with erectile dysfunction after failing sildenafil (Viagra). *Urology* 2000 Apr;55(4):477-80.
<http://www.ncbi.nlm.nih.gov/pubmed/10736486>
104. Leungwattanakij S, Flynn V Jr, Hellstrom WJ. Intracavernosal injection and intraurethral therapy for erectile dysfunction. *Urol Clin North Am* 2001 May;28(2):343-54.
<http://www.ncbi.nlm.nih.gov/pubmed/11402586>
105. Linet OI, Ogrinc FG. Efficacy and safety of intracavernosal alprostadil in men with erectile dysfunction. The Alprostadil Study Group. *N Engl J Med* 1996 Apr;334(14):873-7.
<http://www.ncbi.nlm.nih.gov/pubmed/8596569>
106. Porst H. The rationale for prostaglandin E1 in erectile failure: a survey of worldwide experience. *J Urol* 1996 Mar;155(3):802-15.
<http://www.ncbi.nlm.nih.gov/pubmed/8583582>
107. Heaton JP, Lording D, Liu SN, et al. Intracavernosal alprostadil is effective for the treatment of erectile dysfunction in diabetic men. *Int J Impot Res* 2001 Dec;13(6):317-21.
<http://www.ncbi.nlm.nih.gov/pubmed/11918246>
108. Lakin MM, Montague DK, VanderBrug Medendorp S, et al. Intracavernous injection therapy: analysis of results and complications. *J Urol* 1990 Jun;143(6):1138-41.
<http://www.ncbi.nlm.nih.gov/pubmed/2342174>
109. Kattan S. Double-blind randomized crossover study comparing intracorporeal prostaglandin E1 with combination of prostaglandin E1 and lidocaine in the treatment of organic impotence. *Urology* 1995 Jun;45(6):1032-6.
<http://www.ncbi.nlm.nih.gov/pubmed/7771004>
110. Moriel EZ, Rajfer J. Sodium bicarbonate alleviates penile pain induced by intracavernous injections for erectile dysfunction. *J Urol* 1993 May;149(5 Pt 2):1299-300.
<http://www.ncbi.nlm.nih.gov/pubmed/8386779>
111. Flynn RJ, Williams G. Long-term follow-up of patients with erectile dysfunction commenced on self injection with intracavernosal papaverine with or without phentolamine. *Br J Urol* 1996 Oct;78(4):628-31.
<http://www.ncbi.nlm.nih.gov/pubmed/8944522>
112. Sundaram CP, Thomas W, Pryor LE, et al. Long-term follow-up of patients receiving injection therapy for erectile dysfunction. *Urology* 1997 Jun;49(6):932-5.
<http://www.ncbi.nlm.nih.gov/pubmed/9187703>
113. Gupta R, Kirschen J, Barrow RC 2nd, et al. Predictors of success and risk factors for attrition in the use of intracavernous injection. *J Urol* 1997 May;157(5):1681-6.
<http://www.ncbi.nlm.nih.gov/pubmed/9112505>
114. Vardi Y, Sprecher E, Gruenwald I. Logistic regression and survival analysis of 450 impotent patients treated with injection therapy: long-term dropout parameters. *J Urol* 2000 Feb;163(2):467-70.
<http://www.ncbi.nlm.nih.gov/pubmed/10647656>
115. Montorsi F, Althof SE, Sweeney M, et al. Treatment satisfaction in patients with erectile dysfunction switching from prostaglandin E(1) intracavernosal injection therapy to oral sildenafil citrate. *Int J Impot Res* 2003 Dec;15(6):444-9.
<http://www.ncbi.nlm.nih.gov/pubmed/14671665>
116. Raina R, Lakin MM, Agarwal A, et al. Long-term intracavernous therapy responders can potentially switch to sildenafil citrate after radical prostatectomy. *Urology* 2004 Mar;63(3):532-7; discussion 538.
<http://www.ncbi.nlm.nih.gov/pubmed/15028452>

117. Hatzichristou DG, Apostolidis A, Tzortzis V, et al. Sildenafil versus intracavernous injection therapy: efficacy and preference in patients on intracavernous injection for more than 1 year. *J Urol* 2000 Oct;164(4):1197-200.
<http://www.ncbi.nlm.nih.gov/pubmed/10992365>
118. Buvat J, Lemaire A, Ratajczyk J. Acceptance, efficacy and preference of sildenafil in patients on long term auto-intracavernosal therapy: a study with follow-up at one year. *Int J Impot Res* 2002 Dec;14(6):483-6.
<http://www.ncbi.nlm.nih.gov/pubmed/12494282>
119. Mulhall JP, Daller M, Traish AM, et al. Intracavernosal forskolin: role in management of vasculogenic impotence resistant to standard 3-agent pharmacotherapy. *J Urol* 1997 Nov;158(5):1752-8; discussion 1758-9.
<http://www.ncbi.nlm.nih.gov/pubmed/9334594>
120. Buvat J, Costa P, Morlier D, et al. Double-blind multicentre study comparing alprostadil alpha-cyclodextrin with moxislyte chlorhydrate in patients with chronic erectile dysfunction. *J Urol* 1998 Jan;159(1):116-9.
<http://www.ncbi.nlm.nih.gov/pubmed/9400450>
121. Bechara A, Casabé A, Chélez G, et al. Comparative study of papaverine plus phentolamine versus prostaglandin E1 in erectile dysfunction. *J Urol* 1997 Jun;157(6):2132-4.
<http://www.ncbi.nlm.nih.gov/pubmed/9146599>
122. Bennett AH, Carpenter AJ, Barada JH. An improved vasoactive drug combination for a pharmacological erection program. *J Urol* 1991 Dec;146(6):1564-5.
<http://www.ncbi.nlm.nih.gov/pubmed/1719248>
123. McMahon CG. A comparison of the response to the intracavernosal injection of papaverine and phentolamine, prostaglandin E1 and a combination of all three agents in the management of impotence. *Int J Impot Res* 1991;3:113-21.
124. Levine SB, Althof SE, Turner LA, et al. Side effects of self administration of intracavernous papaverine and phentolamine for the treatment of impotence. *J Urol* 1989 Jan;141(1):54-7.
<http://www.ncbi.nlm.nih.gov/pubmed/2908954>
125. McMahon CG, Samali R, Johnson H. Treatment of intracorporeal injection nonresponse with sildenafil alone or in combination with triple agent intracorporeal injection therapy. *J Urol* 1999 Dec;162(6):1992-7; discussion 1997-8.
<http://www.ncbi.nlm.nih.gov/pubmed/10569554>
126. Padma-Nathan H, Hellstrom WJ, Kaiser FE, et al. Treatment of men with erectile dysfunction with transurethral alprostadil. Medicated Urethral System for Erection (MUSE) Study Group. *N Engl J Med* 1997 Jan;336(1):1-7.
<http://www.ncbi.nlm.nih.gov/pubmed/8970933>
127. Guay AT, Perez JB, Velásquez E, et al. Clinical experience with intraurethral alprostadil (MUSE) in the treatment of men with erectile dysfunction. A retrospective study. Medicated urethral system for erection. *Eur Urol* 2000 Dec;38(6):671-6.
<http://www.ncbi.nlm.nih.gov/pubmed/11111182>
128. Fulgham PF, Cochran JS, Denman JL, et al. Disappointing initial results with transurethral alprostadil for erectile dysfunction in a urology practice setting. *J Urol* 1998 Dec;160(6 Pt 1):2041-6.
<http://www.ncbi.nlm.nih.gov/pubmed/9817319>
129. Mulhall JP, Jahoda AE, Ahmed A, et al. Analysis of the consistency of intraurethral prostaglandin E(1) (MUSE) during at-home use. *Urology* 2001 Aug;58(2):262-6.
<http://www.ncbi.nlm.nih.gov/pubmed/11489714>
130. Lewis RW, Weldon K, Nemo K; the MUSE-ACTIS Study Group. Combined use of transurethral alprostadil and an adjustable penile constriction band in men with erectile dysfunction: results from a multicentre trial. *Int J Impot Res* 1998;10:S49 (365).
131. Shabsigh R, Padma-Nathan H, Gittleman M, et al. Intracavernous alprostadil alfadex is more efficacious, better tolerated, and preferred over intraurethral alprostadil plus optional actis: a comparative, randomized, crossover, multicentre study. *Urology* 2000 Jan;55(4):109-13.
<http://www.ncbi.nlm.nih.gov/pubmed/10654905>
132. Montague DK, Angermeier KW. Penile prosthesis implantation. *Urol Clin North Am* 2001 May;28(2):355-61, x.
<http://www.ncbi.nlm.nih.gov/pubmed/11402587>
133. Holloway FB, Farah RN. Intermediate term assessment of the reliability, function and patient satisfaction with the AMS700 Ultrex penile prosthesis. *J Urol* 1997 May;157(5):1687-91.
<http://www.ncbi.nlm.nih.gov/pubmed/9112506>

134. Tefilli MV, Dubocq F, Rajpurkar A, et al. Assessment of psychosexual adjustment after insertion of inflatable penile prosthesis. *Urology* 1998 Dec;52(6):1106-12.
<http://www.ncbi.nlm.nih.gov/pubmed/9836564>
135. Wilson SK, Cleves MA, Delk JR 2nd. Comparison of mechanical reliability of original and enhanced Mentor Alpha I penile prosthesis. *J Urol* 1999 Sep;162(3 Pt 1):715-8.
<http://www.ncbi.nlm.nih.gov/pubmed/10458350>
136. Montorsi F, Rigatti P, Carmignani G, et al. AMS three-piece inflatable implants for erectile dysfunction: a long-term multi- institutional study in 200 consecutive patients. *Eur Urol* 2000 Jan;37(1):50-5.
<http://www.ncbi.nlm.nih.gov/pubmed/10671785>
137. Goldstein I, Newman L, Baum N, et al. Safety and efficacy outcome of mentor alpha-1 inflatable penile prosthesis implantation for impotence treatment. *J Urol* 1997 Mar;157(3):833-9.
<http://www.ncbi.nlm.nih.gov/pubmed/9072580>
138. Carson CC 3rd. Efficacy of antibiotic impregnation of inflatable penile prostheses in decreasing infection in original implants. *J Urol* 2004 Apr;171(4):1611-4.
<http://www.ncbi.nlm.nih.gov/pubmed/15017233>
139. Wolter CE, Hellstrom WJ. The hydrophilic-coated inflatable penile prosthesis: 1-year experience. *J Sex Med* 2004 Sep;1(2):221-4.
<http://www.ncbi.nlm.nih.gov/pubmed/16429621>
140. Mulcahy JJ. Long-term experience with salvage of infected penile implants. *J Urol* 2000 Feb;163(2):481-2.
<http://www.ncbi.nlm.nih.gov/pubmed/10647660>
141. Montorsi F, Dehò F, Salonia A, et al. Penile implants in the era of oral drug treatment for erectile dysfunction. *BJU Int* 2004 Sep;94(5):745-51.
<http://www.ncbi.nlm.nih.gov/pubmed/15329092>

4. PREMATURE EJACULATION (PE)

4.1 Introduction

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

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

4.2 Definition of PE

4.2.1 Overview

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

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

Recently, two more definitions have been proposed:

- The Second International Consultation on Sexual and Erectile Dysfunction defined PE as '*ejaculation with minimal stimulation and earlier than desired, before or soon after penetration, which causes bother or distress, and over which the sufferer has little or no voluntary control*' (5).
- The International Society for Sexual Medicine (ISSM) has adopted a completely new definition of

PE which is the first evidence-based definition, '*Premature ejaculation is a male sexual dysfunction characterized by ejaculation which always or nearly always occurs prior to or within about one minute of vaginal penetration; and inability to delay ejaculation on all or nearly all vaginal penetrations; and negative personal consequences, such as distress, bother, frustration and/or the avoidance of sexual intimacy*'. It must be noted that this definition is limited to men with lifelong PE who engage in vaginal intercourse since there are insufficient objective data to propose an evidence-based definition for acquired PE (6).

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

4.2.2 **Classifications**

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

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

- 'Natural variable PE' is characterised by inconsistent and irregular early ejaculations, representing a normal variation in sexual performance.
- 'Premature-like ejaculatory dysfunction' 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 (13).

4.3 **Epidemiology of PE**

4.3.1 **Prevalence**

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

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

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

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

4.3.2 Pathophysiology and risk factors

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

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

According to the NHLS, the prevalence of PE is not affected by age (16,17), unlike ED, which increases with age. Premature ejaculation is not affected by marital or income status (16). However, PE is more common in blacks, Hispanic men and men from Islamic backgrounds (28,29) and may be higher in men with a lower educational level (15,16). Other risk factors may include a genetic predisposition (30), poor overall health status and obesity (16), prostate inflammation (31,32), thyroid hormone disorders (33), emotional problems and stress (16,34), and traumatic sexual experiences (1516).

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

4.4 Impact of PE on QoL

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

Despite the serious psychological and QoL consequences of PE, few men seek treatment. In the GSSAB survey, 78% of men who self-reported a sexual dysfunction sought no professional help or advice for their sexual problems (15), with men more likely to seek treatment for ED than for PE (15). In the PEPA survey, only 9% of men with self-reported PE consulted a doctor (17).

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

4.5 Diagnosis of PE

Diagnosis of PE is based on the patient's medical and sexual history (43,44). History should classify PE as lifelong or acquired and determine whether PE is situational (under specific circumstances or with a specific partner) or consistent. Special attention should be given to the duration time of ejaculation, degree of sexual stimulus, impact on sexual activity and QoL, and drug use or abuse. It is also important to distinguish PE from ED.

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

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

Table 7: Common factors in different definitions of ED

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

4.5.1 Intravaginal ejaculatory latency time (IELT)

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

In everyday clinical practice, self-estimated IELT is sufficient. Self-estimated and stopwatch-measured

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

4.5.2 PE assessment questionnaires

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

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

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

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

4.5.3 Physical examination and investigations

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

4.6 Recommendations

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

4.7 References

1. Rosenberg MT, Sadovsky R. Identification and diagnosis of premature ejaculation. *Int J Clin Pract* 2007 Jun;61(6):903-8.
<http://www.ncbi.nlm.nih.gov/pubmed/17504352>
2. Oxford Centre for Evidence-based Medicine Levels of Evidence (May 2001). Produced by Bob Phillips, Chris Ball, Dave Sackett, Doug Badenoch, Sharon Straus, Brian Haynes, Martin Dawes since November 1998.
<http://www.cebm.net/index.aspx?o=1025> [access date January 2011].
3. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 4th Ed. Text Revision. Washington, D.C., American Psychiatric Publishing, Inc, 2000.
4. International Classification of Diseases and Related Health Problems. 10th Ed. Geneva, World Health Organization, 1994.

5. McMahon CG, Abdo C, Incrocci L, et al. Disorders of orgasm and ejaculation in men. *J Sex Med* 2004 Jul;1(1):58-65.
<http://www.ncbi.nlm.nih.gov/pubmed/16422984>
6. McMahon CG, Althof SE, Waldinger MD, et al. An evidence-based definition of lifelong premature ejaculation: report of the International Society for Sexual Medicine (ISSM) ad hoc committee for the definition of premature ejaculation. *J Sex Med* 2008 Jul;5(7):1590-606.
<http://www.ncbi.nlm.nih.gov/pubmed/18466262>
7. Balon R, Segraves RT, Clayton A. Issues for DSM-V: sexual dysfunction, disorder, or variation along normal distribution: toward rethinking DSM criteria of sexual dysfunctions. *Am J Psychiatry* 2007 Feb;164(2):198-200.
<http://www.ncbi.nlm.nih.gov/pubmed/17267778>
8. Waldinger MD, Schweitzer DH. The DSM-IV-TR is an inadequate diagnostic tool for premature ejaculation. *J Sex Med* 2007 May;4(3):822-3.
<http://www.ncbi.nlm.nih.gov/pubmed/17498112>
9. Waldinger MD, Schweitzer DH. The use of old and recent DSM definitions of premature ejaculation in observational studies: a contribution to the present debate for a new classification of PE in the DSM-V. *J Sex Med* 2008 May;5(5):1079-87.
<http://www.ncbi.nlm.nih.gov/pubmed/18331260>
10. Waldinger MD, Schweitzer DH. Changing paradigms from a historical DSM-III and DSM-IV view toward an evidence-based definition of premature ejaculation. Part I-validity of DSM-IV-TR. *J Sex Med* 2006 Jul;3(4):682-92.
<http://www.ncbi.nlm.nih.gov/pubmed/16839325>
11. Waldinger MD, Schweitzer DH. Changing paradigms from a historical DSM-III and DSM-IV view toward an evidence-based definition of premature ejaculation. Part II-proposals for DSM-V and ICD-11. *J Sex Med* 2006 Jul;3(4):693-705.
<http://www.ncbi.nlm.nih.gov/pubmed/16839326>
12. Godpodinoff ML. Premature ejaculation: clinical subgroups and etiology. *J Sex Marital Ther* 1989 Summer;15(2):130-4.
<http://www.ncbi.nlm.nih.gov/pubmed/2769774>
13. Waldinger MD. Premature ejaculation: state of the art. *Urol Clin North Am* 2007 Nov;34(4):591-9, vii-viii.
<http://www.ncbi.nlm.nih.gov/pubmed/17983899>
14. Waldinger MD. The neurobiological approach to premature ejaculation. *J Urol* 2002 Dec;168(6):2359-67.
<http://www.ncbi.nlm.nih.gov/pubmed/12441918>
15. Laumann EO, Nicolosi A, Glasser DB, et al; GSSAB Investigators' Group. Sexual problems among women and men aged 40-80 y: prevalence and correlates identified in the Global Study of Sexual Attitudes and Behaviors. *Int J Impot Res* 2005 Jan-Feb;17(1):39-57.
<http://www.ncbi.nlm.nih.gov/pubmed/15215881>
16. Laumann EO, Paik A, Rosen RC. Sexual dysfunction in the United States: prevalence and predictors. *JAMA* 1999 Feb;281(6):537-44.
<http://www.ncbi.nlm.nih.gov/pubmed/10022110>
17. Porst H, Montorsi F, Rosen RC, et al. The Premature Ejaculation Prevalence and Attitudes (PEPA) survey: prevalence, comorbidities, and professional help-seeking. *Eur Urol* 2007 Mar;51(5):816-23; discussion 824.
<http://www.ncbi.nlm.nih.gov/pubmed/16934919>
18. Dunn KM, Croft PR, Hackett GI. Sexual problems: a study of the prevalence and need for health care in the general population. *Fam Pract* 1998 Dec;15(6):519-24.
<http://www.ncbi.nlm.nih.gov/pubmed/10078790>
19. Spira A, Bajos N, Giami A, et al. Cross-national comparisons of sexual behavior surveys--methodological difficulties and lessons for prevention. *Am J Public Health* 1998 May;88(5):730-1.
<http://www.ncbi.nlm.nih.gov/pubmed/9585733>
20. Fugl-Meyer AR, Sjogren Fugl-Meyer K. Sexual disabilities, problems and satisfaction in 18-74 year old Swedes. *Scan J Sexol* 1999;2:79-105.
21. Solstad K, Hertoft P. Frequency of sexual problems and sexual dysfunction in middle-aged Danish men. *Arch Sex Behav* 1993 Feb;22(1):51-8.
<http://www.ncbi.nlm.nih.gov/pubmed/8435039>

22. Basile Fasolo C, Mirone V, Gentile V, et al; Andrology Prevention Week centers; Italian Society of Andrology (SIA). Premature ejaculation: prevalence and associated conditions in a sample of 12,558 men attending the andrology prevention week 2001—a study of the Italian Society of Andrology (SIA). *J Sex Med* 2005 May;2(3):376-82.
<http://www.ncbi.nlm.nih.gov/pubmed/16422869>
23. Blanker MH, Bosch JL, Groeneveld FP, et al. Erectile and ejaculatory dysfunction in a community-based sample of men 50 to 78 years old: prevalence, concern, and relation to sexual activity. *Urology* 2001 Apr;57(4):763-8.
<http://www.ncbi.nlm.nih.gov/pubmed/11306400>
24. Giuliano F, Patrick DL, Porst H, et al; 3004 Study Group. Premature ejaculation: results from a five-country European observational study. *Eur Urol* 2008 May;53(5):1048-57.
<http://www.ncbi.nlm.nih.gov/pubmed/17950985>
25. Patrick DL, Althof SE, Pryor JL, et al. Premature ejaculation: an observational study of men and their partners. *J Sex Med* 2005 May;2(3):358-67.
<http://www.ncbi.nlm.nih.gov/pubmed/16422867>
26. Jern P, Santtila P, Witting K, et al. Premature and delayed ejaculation: genetic and environmental effects in a population-based sample of Finnish twins. *J Sex Med* 2007 Nov;4(6):1739-49.
<http://www.ncbi.nlm.nih.gov/pubmed/17888070>
27. Waldinger MD, Quinn P, Dilleen M, et al. A multinational population survey of intravaginal ejaculation latency time. *J Sex Med* 2005 Jul;2(4):492-7.
<http://www.ncbi.nlm.nih.gov/pubmed/16422843>
28. Richardson D, Goldmeier D. Premature ejaculation—does country of origin tell us anything about etiology? *J Sex Med* 2005 Jul;2(4):508-12.
<http://www.ncbi.nlm.nih.gov/pubmed/16422845>
29. Carson C, Gunn K. Premature ejaculation: definition and prevalence. *Int J Impot Res* 2006 Sep-Oct;18(Suppl 1):S5-13.
<http://www.ncbi.nlm.nih.gov/pubmed/16953247>
30. Waldinger MD, Rietschel M, Nöthen MM, et al. Familial occurrence of primary premature ejaculation. *Psychiatr Genet* 1998 Spring;8(1):37-40.
<http://www.ncbi.nlm.nih.gov/pubmed/9564687>
31. Screponi E, Carosa E, Di Stasi SM, et al. Prevalence of chronic prostatitis in men with premature ejaculation. *Urology* 2001 Aug;58(2):198-202.
<http://www.ncbi.nlm.nih.gov/pubmed/11489699>
32. Shamloul R, el-Nashaar A. Chronic prostatitis in premature ejaculation: a cohort study in 153 men. *J Sex Med* 2006 Jan;3(1):150-4.
<http://www.ncbi.nlm.nih.gov/pubmed/16409229>
33. Carani C, Isidori AM, Granata A, et al. Multicenter study on the prevalence of sexual symptoms in male hypo- and hyperthyroid patients. *J Clin Endocrinol Metab* 2005 Dec;90(12):6472-9.
<http://www.ncbi.nlm.nih.gov/pubmed/16204360>
34. Dunn KM, Croft PR, Hackett GI. Association of sexual problems with social, psychological, and physical problems in men and women: a cross sectional population survey. *J Epidemiol Community Health* 1999 Mar;53(3):144-8.
<http://www.ncbi.nlm.nih.gov/pubmed/10396490>
35. El-Nashaar A, Shamloul R. Antibiotic treatment can delay ejaculation in patients with premature ejaculation and chronic bacterial prostatitis. *J Sex Med* 2007 Mar;4(2):491-6.
<http://www.ncbi.nlm.nih.gov/pubmed/17367444>
36. Rowland D, Perelman M, Althof S, et al. Self-reported premature ejaculation and aspects of sexual functioning and satisfaction. *J Sex Med* 2004 Sep;1(2):225-32.
<http://www.ncbi.nlm.nih.gov/pubmed/16429622>
37. Rowland DL, Patrick DL, Rothman M, et al. The psychological burden of premature ejaculation. *J Urol* 2007 Mar;177(3):1065-70.
<http://www.ncbi.nlm.nih.gov/pubmed/17296413>
38. Symonds T, Roblin D, Hart K, et al. How does premature ejaculation impact a man's life? *J Sex Marital Ther* 2003 Oct-Dec;29(5):361-70.
<http://www.ncbi.nlm.nih.gov/pubmed/14504007>
39. Riley A, Segraves RT. Treatment of premature ejaculation. *Int J Clin Pract* 2006 Jun;60(6):694-7.
<http://www.ncbi.nlm.nih.gov/pubmed/16805755>
40. Byers ES, Grenier G. Premature or rapid ejaculation: heterosexual couples' perceptions of men's ejaculatory behavior. *Arch Sex Behav* 2003 Jun;32(3):261-70.
<http://www.ncbi.nlm.nih.gov/pubmed/12807298>

41. Sotomayor M. The burden of premature ejaculation: the patient's perspective. *J Sex Med* 2005 May;2(Suppl 2):110-4.
<http://www.ncbi.nlm.nih.gov/pubmed/16422797>
42. Solursh DS, Ernst JL, Lewis RW, et al. The human sexuality education of physicians in North American medical schools. *Int J Impot Res* 2003 Oct;15(Suppl 5):S41-5.
<http://www.ncbi.nlm.nih.gov/pubmed/14551576>
43. Sharlip I. Diagnosis and treatment of premature ejaculation: the physician's perspective. *J Sex Med* 2005 May;2(Suppl 2):103-9.
<http://www.ncbi.nlm.nih.gov/pubmed/16422796>
44. Shabsigh R. Diagnosing premature ejaculation: a review. *J Sex Med* 2006 Sep;3(4):318-23.
<http://www.ncbi.nlm.nih.gov/pubmed/16939476>
45. Rowland DL, Slob AK. Premature ejaculation: psychophysiological considerations in theory, research, and treatment. *Annu Rev Sex Res* 1997;8:224-53.
<http://www.ncbi.nlm.nih.gov/pubmed/10051895>
46. Althof SE. Prevalence, characteristics and implications of premature ejaculation/rapid ejaculation. *J Urol* 2006 Mar;175(3 Pt 1):842-8.
<http://www.ncbi.nlm.nih.gov/pubmed/16469562>
47. Althof SE, Symonds T. Patient reported outcomes used in the assessment of premature ejaculation. *Urol Clin North Am* 2007 Nov;34(4):581-9, vii.
<http://www.ncbi.nlm.nih.gov/pubmed/17983898>
48. Patrick DL, Rowland D, Rothman M. Interrelationships among measures of premature ejaculation: the central role of perceived control. *J Sex Med* 2007 May;4(3):780-8.
<http://www.ncbi.nlm.nih.gov/pubmed/17419817>
49. Rosen RC, McMahon CG, Niederberger C, et al. Correlates to the clinical diagnosis of premature ejaculation: results from a large observational study of men and their partners. *J Urol* 2007 Mar;177(3):1059-64; discussion 1064.
<http://www.ncbi.nlm.nih.gov/pubmed/17296411>
50. Symonds T, Perelman M, Althof S, et al. Further evidence of the reliability and validity of the premature ejaculation diagnostic tool. *Int J Impot Res* 2007 Sep-Oct;19(5):521-5.
<http://www.ncbi.nlm.nih.gov/pubmed/17568761>
51. Symonds T, Perelman MA, Althof S, et al. Development and validation of a premature ejaculation diagnostic tool. *Eur Urol* 2007 Aug;52(2):565-73.
<http://www.ncbi.nlm.nih.gov/pubmed/17275165>
52. Arafa M, Shamloul R. Development and evaluation of the Arabic Index of Premature Ejaculation (AIPE). *J Sex Med* 2007 Nov;4(6):1750-6.
<http://www.ncbi.nlm.nih.gov/pubmed/17970977>
53. McMahon CG. Ejaculatory latency vs. patient-reported outcomes (PROs) as study end points in premature ejaculation clinical trials. *Eur Urol* 2007 Aug;52(2):321-3.
<http://www.ncbi.nlm.nih.gov/pubmed/17445975>
54. Althof S, Rosen R, Symonds T, et al. Development and validation of a new questionnaire to assess sexual satisfaction, control, and distress associated with premature ejaculation. *J Sex Med* 2006 May;3(3):465-75.
<http://www.ncbi.nlm.nih.gov/pubmed/16681472>
55. Rosen RC, Catania JA, Althof SE, et al. Development and validation of four-item version of Male Sexual Health Questionnaire to assess ejaculatory dysfunction. *Urology* 2007 May;69(5):805-9.
<http://www.ncbi.nlm.nih.gov/pubmed/17482908>

4.8 Treatment

In many relationships, PE causes few if any problems. In such cases, treatment should be limited to psychosexual counselling. Before beginning treatment, it is essential to discuss patient expectations thoroughly. Erectile dysfunction, in particular, or other sexual dysfunction or genitourinary infection (e.g. prostatitis), should be treated first or at the same time as PE.

Various behavioural techniques have demonstrated benefit in treating PE and are indicated for patients uncomfortable with pharmacological therapy. In lifelong PE, behavioural techniques are not recommended for first-line treatment. They are time-intensive, require the support of a partner and can be difficult to do. In addition, long-term outcomes of behavioural techniques for PE are unknown.

Pharmacotherapy is the basis of treatment in lifelong PE. Since no drug for PE has been approved by the EMEA or FDA, all medical treatments are off-label indications. Only chronic selective serotonin reuptake inhibitors (SSRIs) and on-demand topical anaesthetic agents have consistently shown efficacy in PE. Again, long-term outcomes for pharmacological treatments are unknown.

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

4.8.1 **Psychological/behavioural strategies**

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

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

Both these procedures are typically applied in a cycle of three pauses before proceeding to orgasm. Behavioural strategies are based on the hypothesis that PE occurs because the man fails to appreciate the sensations of heightened arousal and 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 many 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 'start-stop' programme (2).

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

4.8.1.1 *Guideline recommendation*

Treatment of PE	LE	GR
Psychological/behavioural therapies	3	C

4.8.2 **Topical anaesthetic agents**

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

4.8.2.1 *Lidocaine-prilocaine cream*

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

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

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

4.8.2.2 SS-cream

SS-cream is a topical anaesthetic agent made from the extracts of nine herbs. It is applied to the glans penis 1 h before and washed off immediately prior to coitus. SS-cream increased the vibratory threshold in a dose-dependent fashion, as well as the latency and amplitude of somatosensory-evoked potentials measured at the glans penis (17,18). In a double-blind, randomised, placebo-controlled study (19), application of 0.2 g SS-cream improved IELT from 1.37 min to 10.92 min in the treatment group versus 2.45 min in the placebo group. Sexual satisfaction improved by 82% in the treatment group versus 20% in the placebo group. Mild local burning and mild pain were reported by 18.5% of patients. No adverse effects on sexual function or partner or systemic side-effects were observed.

4.8.2.3 Guideline recommendation

Topical therapy for PE	LE	GR
Lidocaine-prilocaine cream	1B	A
SS-cream	1B	A

4.8.3 Selective serotonin reuptake inhibitors

Ejaculation is mediated by a spinal ejaculation generator (20, 21) and by descending supraspinal modulation from several brain regions. The neurotransmitter 5-hydroxytryptamine (5-HT, serotonin) is also involved in ejaculatory control. The retarding effect of 5-HT on ejaculation is probably due to central activation (i.e. spinally and supraspinally) of 5-HT_{1B} and 5-HT_{2C} receptors, while stimulation of 5-HT_{1A} receptors precipitates ejaculation.

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

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

Based on this meta-analysis, SSRIs were expected to increase the geometric mean IELT by 2.6-fold to 13.2-fold. Paroxetine was found to be superior to fluoxetine, clomipramine and sertraline. Sertraline was superior to fluoxetine, whereas the efficacy of clomipramine was not significantly different from fluoxetine and sertraline. Paroxetine was evaluated in doses of 20–40 mg, sertraline 25–200 mg, fluoxetine 10–60 mg and clomipramine 25–50 mg; there was no significant relationship between dose and response among the various drugs. There is limited evidence that citalopram may be less efficacious compared to other SSRIs, while fluvoxamine may not be effective (27,28).

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

Common side-effects of SSRIs include fatigue, drowsiness, yawning, nausea, vomiting, dry mouth, diarrhoea and perspiration; they are usually mild and gradually improve after 2 to 3 weeks (24). Decreased libido, anorgasmia, anejaculation and ED have been also reported.

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

4.8.3.1 Dapoxetine

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

An integrated analysis of two, double-blind, randomised, controlled trials (1,958 patients) with dapoxetine was published (32). Dapoxetine, 30 and 60 mg, was administered 1 to 3 h before intercourse.

Intravaginal ejaculatory latency time improved from a baseline of 0.9 min to 1.75 min, 2.78 min and 3.32 min in the patient groups treated with placebo, 30 mg dapoxetine, and 60 mg dapoxetine, respectively. Improved ejaculation control was reported by 51% and 58% of patients in the 30 mg and 60 mg groups, respectively. Both dapoxetine doses were effective on the first dose. Common adverse events for 30 mg and 60 mg doses of dapoxetine, respectively, were nausea (8.7%, 20.1%), diarrhoea (3.9%, 6.8%), headache (5.9%, 6.8%), and dizziness (3.0%, 6.2%).

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

In another randomised, double-blind, parallel-group, placebo-controlled, phase II trial including 1,162 men in 22 countries (34), mean average IELT increased from 0.9 min at baseline (all groups) to 1.9 min, 3.2 min, and 3.5 min with placebo and dapoxetine 30 mg and dapoxetine 60 mg, respectively, at study end point. The geometric mean IELT increased from 0.7 min at baseline to 1.1 min, 1.8 min, and 2.3 min, respectively, at study end point. All PEP measures and IELTs improved significantly with dapoxetine versus placebo at week 12 and week 24 ($p < 0.001$ for all). The most common adverse effects were nausea, dizziness, diarrhea, and headache. Adverse effects led to discontinuation in 1.3%, 3.9%, and 8.2% of subjects with placebo and dapoxetine 30 mg. Finally, in a randomised, double-blind, placebo controlled, phase III trial (1,238 men in USA and Canada), dapoxetine reduced the personal distress and interpersonal difficulty associated with PE (35).

Dapoxetine has been approved (December 2008) for the on-demand treatment of PE in seven European countries (Sweden, Austria, Finland, Germany, Spain, Italy and Portugal). This is currently the first and only drug approved for such an indication.

4.8.3.2 Guideline recommendation

Treatment for PE	LE	GR
Selective serotonin receptor inhibitors (SSRIs)	1A	A

4.8.4 Phosphodiesterase type 5 inhibitors

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

There is only one well-designed, randomised, double-blind, placebo-controlled study comparing sildenafil to placebo (39). Although IELT was not significantly improved, sildenafil increased confidence, the perception of ejaculatory control and overall sexual satisfaction, reduced anxiety and decreased the refractory time to achieve a second erection after ejaculation.

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

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

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

4.8.4.1 Guideline recommendation

Treatment for PE	LE	GR
PDE5 inhibitors	2B	C

4.8.5 Other drugs

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

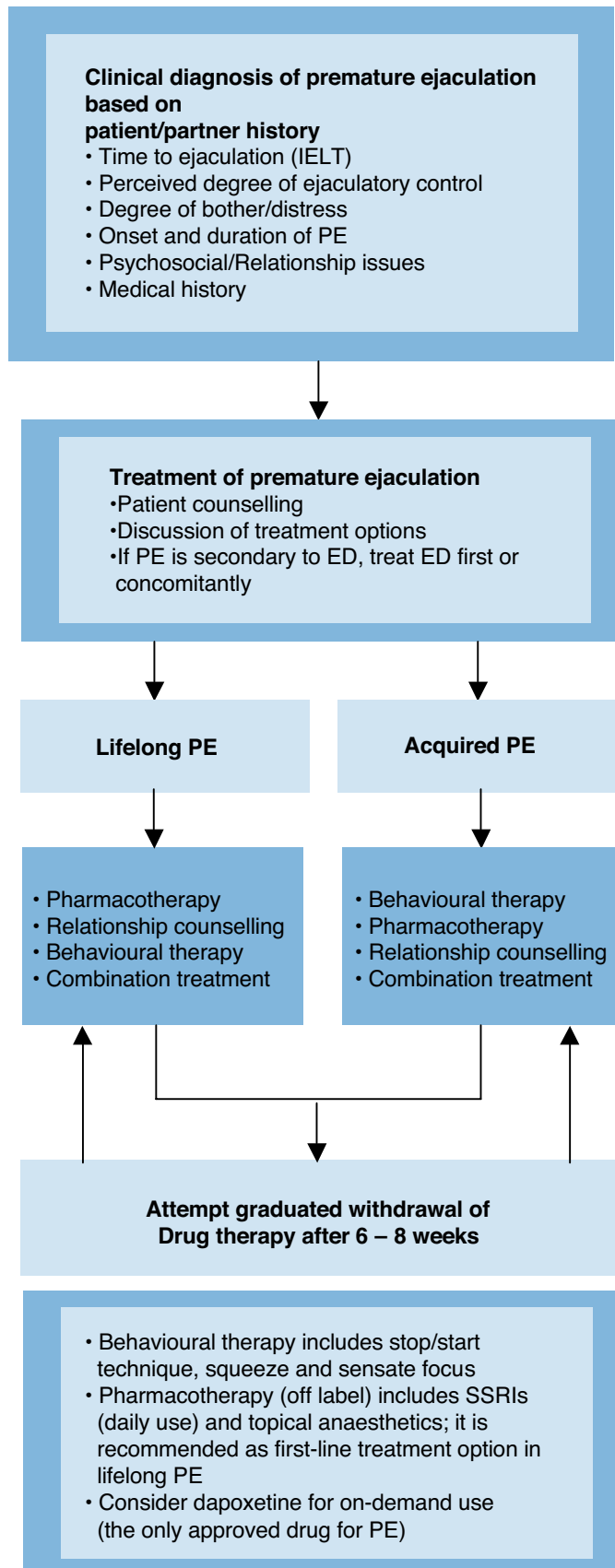
Research suggests that the alpha-1 adrenergic antagonists, terazosin and alfuzosin (45,46), and tramadol (47,48) may have some efficacy in PE. However, further research is needed to investigate their role fully. Currently they are not recommended in clinical practice (49).

4.8.6 Guidelines on treatment of PE

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

ED = erectile dysfunction; PE = premature ejaculation; SSRI = selective serotonin reuptake inhibitor; pm = on-demand administration.

Figure 4: Management of PE*



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

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

4.9 References

1. Semans JH. Premature ejaculation: a new approach. *South Med J* 1956 Apr;49(4):353-8.
<http://www.ncbi.nlm.nih.gov/pubmed/13311629>
2. de Carufel F, Trudel G. Effects of a new functional-sexological treatment for premature ejaculation. *J Sex Marital Ther* 2006 Mar-Apr;32(2):97-114.
<http://www.ncbi.nlm.nih.gov/pubmed/16418103>
3. Grenier G, Byers ES. Rapid ejaculation: a review of conceptual, etiological, and treatment issues. *Arch Sex Behav* 1995 Aug;24(4):447-72.
<http://www.ncbi.nlm.nih.gov/pubmed/7661658>
4. Metz ME, Pryor JL, Nesvacil LJ, et al. Premature ejaculation: a psychophysiological review. *J Sex Marital Ther* 1997 Spring;23(1):3-23.
<http://www.ncbi.nlm.nih.gov/pubmed/9094032>
5. Abdel-Hamid IA, El Naggar EA, El Gilany AH. Assessment of as needed use of pharmacotherapy and the pause-squeeze technique in premature ejaculation. *Int J Impot Res* 2001 Feb;13(1):41-5.
<http://www.ncbi.nlm.nih.gov/pubmed/11313839>
6. De Amicis LA, Goldberg DC, LoPiccolo J, et al. Clinical follow-up of couples treated for sexual dysfunction. *Arch Sex Behav* 1985 Dec;14(6):467-89.
<http://www.ncbi.nlm.nih.gov/pubmed/4084048>
7. Hawton K, Catalan J, Martin P, et al. Long-term outcome of sex therapy. *Behav Res Ther* 1986; 24(6):665-75.
<http://www.ncbi.nlm.nih.gov/pubmed/3800838>
8. Morales A, Barada J, Wyllie MG. A review of the current status of topical treatments for premature ejaculation. *BJU Int* 2007 Sep;100(3):493-501.
<http://www.ncbi.nlm.nih.gov/pubmed/17608824>
9. Sachs BD, Liu YC. Maintenance of erection of penile glans, but not penile body, after transection of rat cavernous nerves. *J Urol* 1991 Sep;146(3):900-5.
<http://www.ncbi.nlm.nih.gov/pubmed/1875517>
10. Wieder JA, Brackett NL, Lynne CM, et al. Anesthetic block of the dorsal penile nerve inhibits vibratory-induced ejaculation in men with spinal cord injuries. *Urology* 2000 Jun;55(6):915-7.
<http://www.ncbi.nlm.nih.gov/pubmed/10840108>
11. Atikeler MK, Gecit I, Senol FA. Optimum usage of prilocaine-lidocaine cream in premature ejaculation. *Andrologia*. 2002 Dec;34(6):356-9.
<http://www.ncbi.nlm.nih.gov/pubmed/12472618>
12. Busato W, Galindo CC. Topical anaesthetic use for treating premature ejaculation: a double-blind, randomized, placebo-controlled study. *BJU Int* 2004 May;93(7):1018-21.
<http://www.ncbi.nlm.nih.gov/pubmed/15142155>
13. Henry R, Morales A, Wyllie MG. TEMPE: Topical Eutectic-Like Mixture for Premature Ejaculation. *Expert Opin Drug Deliv* 2008 Feb;5(2):251-61.
<http://www.ncbi.nlm.nih.gov/pubmed/18248322>
14. Dinsmore WW, Hackett G, Goldmeier D, et al. Topical eutectic mixture for premature ejaculation (TEMPE): a novel aerosol-delivery form of lidocaine-prilocaine for treating premature ejaculation. *BJU Int* 2007 Feb;99(2):369-75.
<http://www.ncbi.nlm.nih.gov/pubmed/17129234>
15. Henry R, Morales A. Topical lidocaine-prilocaine spray for the treatment of premature ejaculation: a proof of concept study. *Int J Impot Res* 2003 Aug;15(4):277-81.
<http://www.ncbi.nlm.nih.gov/pubmed/12934056>
16. Atan A, Basar MM, Tuncel A, et al. Comparison of efficacy of sildenafil-only, sildenafil plus topical EMLA cream, and topical EMLA-cream-only in treatment of premature ejaculation. *Urology* 2006 Feb; 67(2):388-91.
<http://www.ncbi.nlm.nih.gov/pubmed/16461091>
17. Xin ZC, Choi YD, Seong DH, et al. Sensory evoked potential and effect of SS-cream in premature ejaculation. *Yonsei Med J* 1995 Nov;36(5):397-401.
<http://www.ncbi.nlm.nih.gov/pubmed/8545998>
18. Xin ZC, Choi YD, Lee WH, et al. Penile vibratory threshold changes with various doses of SS-cream in patients with primary premature ejaculation. *Yonsei Med J* 2000 Feb;41(1):29-33.
<http://www.ncbi.nlm.nih.gov/pubmed/10731916>
19. Choi HK, Jung GW, Moon KH, et al. Clinical study of SS-cream in patients with lifelong premature ejaculation. *Urology* 2000 Feb;55(2):257-61.
<http://www.ncbi.nlm.nih.gov/pubmed/10688090>

20. Truitt WA, Coolen LM. Identification of a potential ejaculation generator in the spinal cord. *Science* 2002 Aug;297(5586):1566-9.
<http://www.ncbi.nlm.nih.gov/pubmed/12202834>
21. Borgdorff AJ, Bernabé J, Denys P, et al. Ejaculation elicited by microstimulation of lumbar spinothalamic neurons. *Eur Urol* 2008 Aug;54(2):449-56.
<http://www.ncbi.nlm.nih.gov/pubmed/18394782>
22. Giuliano F. 5-Hydroxytryptamine in premature ejaculation: opportunities for therapeutic intervention. *Trends Neurosci* 2007 Feb;30(2):79-84.
<http://www.ncbi.nlm.nih.gov/pubmed/17169440>
23. Olivier B, van Oorschot R, Waldinger MD. Serotonin, serotonergic receptors, selective serotonin reuptake inhibitors and sexual behaviour. *Int Clin Psychopharmacol* 1998 Jul;13(Suppl 6):S9-14.
<http://www.ncbi.nlm.nih.gov/pubmed/9728669>
24. Waldinger MD. Premature ejaculation: definition and drug treatment. *Drugs* 2007;67(4):547-68.
<http://www.ncbi.nlm.nih.gov/pubmed/17352514>
25. Waldinger MD, Hengeveld MW, Zwinderman AH. Paroxetine treatment of premature ejaculation: a double-blind, randomized, placebo-controlled study. *Am J Psychiatry* 1994 Sep;151(1):1377-9.
<http://www.ncbi.nlm.nih.gov/pubmed/8067497>
26. Waldinger MD, Zwinderman AH, Schweitzer DH, et al. Relevance of methodological design for the interpretation of efficacy of drug treatment of premature ejaculation: a systematic review and meta-analysis. *Int J Impot Res* 2004 Aug;16(4):369-81.
<http://www.ncbi.nlm.nih.gov/pubmed/14961051>
27. Waldinger MD, Zwinderman AH, Olivier B. SSRIs and ejaculation: a double-blind, randomized, fixed-dose study with paroxetine and citalopram. *J Clin Psychopharmacol* 2001 Dec;21(6):556-60.
<http://www.ncbi.nlm.nih.gov/pubmed/11763001>
28. Waldinger MD, Hengeveld MW, Zwinderman AH, et al. Effect of SSRI antidepressants on ejaculation: a double-blind, randomized, placebo-controlled study with fluoxetine, fluvoxamine, paroxetine, and sertraline. *J Clin Psychopharmacol* 1998 Aug;18(4):274-81.
<http://www.ncbi.nlm.nih.gov/pubmed/9690692>
29. Waldinger MD, Zwinderman AH, Olivier B. On-demand treatment of premature ejaculation with clomipramine and paroxetine: a randomized, double-blind fixed-dose study with stopwatch assessment. *Eur Urol* 2004 Oct;46(4):510-5; discussion 516.
<http://www.ncbi.nlm.nih.gov/pubmed/15363569>
30. McMahon CG, Touma K. Treatment of premature ejaculation with paroxetine hydrochloride as needed: 2 single-blind placebo controlled crossover studies. *J Urol* 1999 Jun;161(6):1826-30.
<http://www.ncbi.nlm.nih.gov/pubmed/10332446>
31. Kim SW, Paick JS. Short-term analysis of the effects of as needed use of sertraline at 5 PM for the treatment of premature ejaculation. *Urology* 1999 Sep;54(3):544-7.
<http://www.ncbi.nlm.nih.gov/pubmed/10475369>
32. Pryor JL, Althof SE, Steidle C, et al; Dapoxetine Study Group. Efficacy and tolerability of dapoxetine in treatment of premature ejaculation: an integrated analysis of two double-blind, randomised controlled trials. *Lancet* 2006 Sep;368(9539):929-37.
<http://www.ncbi.nlm.nih.gov/pubmed/16962882>
33. Shabsigh R, Patrick DL, Rowland DL, et al. Perceived control over ejaculation is central to treatment benefit in men with premature ejaculation: results from phase III trials with dapoxetine. *BJU Int* 2008 Sep;102(7):824-8.
<http://www.ncbi.nlm.nih.gov/pubmed/18647300>
34. Buvat J, Tesfaye F, Rothman M, et al. Dapoxetine for the treatment of premature ejaculation: results from a randomized, double-blind, placebo-controlled phase 3 trial in 22 countries. *Eur Urol* 2009 Apr;55(4):957-67.
<http://www.ncbi.nlm.nih.gov/pubmed/19195772>
35. Kaufman JM, Rosen RC, Mudumbi RV, et al. Treatment benefit of dapoxetine for premature ejaculation: results from a placebo-controlled phase III trial. *BJU Int* 2009 Mar;103(5):651-8.
<http://www.ncbi.nlm.nih.gov/pubmed/19021601>
36. Chen J, Keren-Paz G, Bar-Yosef Y, et al. The role of phosphodiesterase type 5 inhibitors in the management of premature ejaculation: a critical analysis of basic science and clinical data. *Eur Urol* 2007 Nov;52(5):1331-9.
<http://www.ncbi.nlm.nih.gov/pubmed/17728050>
37. McMahon CG, McMahon CN, Leow LJ, et al. Efficacy of type-5 phosphodiesterase inhibitors in the drug treatment of premature ejaculation: a systematic review. *BJU Int* 2006 Aug;98(2):259-72.
<http://www.ncbi.nlm.nih.gov/pubmed/16879663>

38. Wang WF, Minhas S, Ralph DJ. Phosphodiesterase 5 inhibitors in the treatment of premature ejaculation. *Int J Androl* 2006 Oct;29(5):503-09.
<http://www.ncbi.nlm.nih.gov/pubmed/16573707>
39. McMahon CG, Stuckey BG, Andersen M, et al. Efficacy of sildenafil citrate (Viagra) in men with premature ejaculation. *J Sex Med* 2005 May;2(3):368-75.
<http://www.ncbi.nlm.nih.gov/pubmed/16422868>
40. Salonia A, Maga T, Colombo R, et al. A prospective study comparing paroxetine alone versus paroxetine plus sildenafil in patients with premature ejaculation. *J Urol* 2002 Dec;168(6):2486-9.
<http://www.ncbi.nlm.nih.gov/pubmed/12441946>
41. Zhang XS, Wang YX, Huang XY, et al. [Comparison between sildenafil plus sertraline and sertraline alone in the treatment of premature ejaculation]. *Zhonghua Nan Ke Xue*. 2005 Jul;11(7):520-525. [article in Chinese]
<http://www.ncbi.nlm.nih.gov/pubmed/16078671>
42. Chen J, Mabjeesh NJ, Matzkin H, et al. Efficacy of sildenafil as adjuvant therapy to selective serotonin reuptake inhibitor in alleviating premature ejaculation. *Urology* 2003 Jan;61(1):197-200.
<http://www.ncbi.nlm.nih.gov/pubmed/12559295>
43. Tang W, Ma L, Zhao L, et al. [Clinical efficacy of Viagra with behavior therapy against premature ejaculation]. *Zhonghua Nan Ke Xue*. 2004 May;10(5):366-7, 370. [article in Chinese]
<http://www.ncbi.nlm.nih.gov/pubmed/15190831>
44. Hsieh JT, Chang HC, Law HS, Hsieh CH, Cheng JT. In vivo evaluation of serotonergic agents and alpha-adrenergic blockers on premature ejaculation by inhibiting the seminal vesicle pressure response to electrical nerve stimulation. *Br J Urol* 1998 Aug;82(2):237-40.
<http://www.ncbi.nlm.nih.gov/pubmed/9722759>
45. Basar MM, Yilmaz E, Ferhat M, Basar H, Batislam E. Terazosin in the treatment of premature ejaculation: a short-term follow-up. *Int Urol Nephrol* 2005;37(4):773-7.
<http://www.ncbi.nlm.nih.gov/pubmed/16362597>
46. Cavallini G. Alpha-1 blockade pharmacotherapy in primitive psychogenic premature ejaculation resistant to psychotherapy. *Eur Urol* 1995;28(2):126-30.
<http://www.ncbi.nlm.nih.gov/pubmed/8529737>
47. Safarinejad MR, Hosseini SY. Safety and efficacy of tramadol in the treatment of premature ejaculation: a double-blind, placebo-controlled, fixed-dose, randomized study. *J Clin Psychopharmacol* 2006 Feb;26(1):27-31.
<http://www.ncbi.nlm.nih.gov/pubmed/16415702>
48. Salem EA, Wilson SK, Bissada NK, Delk JR, Hellstrom WJ, Cleves MA. Tramadol HCL has promise in on-demand use to treat premature ejaculation. *J Sex Med* 2008 Jan;5(1):188-93.
<http://www.ncbi.nlm.nih.gov/pubmed/17362279>
49. Lue TF, Giuliano F, Montorsi F, Rosen RC, Andersson KE, Althof S, Christ G, Hatzichristou D, Hirsch M, Kimoto Y, Lewis R, McKenna K, MacMahon C, Morales A, Mulcahy J, Padma-Nathan H, Pryor J, de Tejada IS, Shabsigh R, Wagner G. Summary of the recommendations on sexual dysfunctions in men. *J Sex Med* 2004 Jul;1(6):6-23.
<http://www.ncbi.nlm.nih.gov/pubmed/16422979>

5. CONCLUSION

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

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

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

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

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

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

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

6. ABBREVIATIONS USED IN THE TEXT

This list is not comprehensive for the most common abbreviations

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

Conflict of interest

All members of the Male Sexual Dysfunction guidelines working group have provided disclosure statements of all relationships which they have and which may be perceived as a potential source of conflict of interest. This information is kept on file in the European Association of Urology Central Office database. This guidelines 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.