EAU GUIDELINES ON MALE SEXUAL DYSFUNCTION: Erectile Dysfunction and Premature Ejaculation

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ERECTILE DYSFUNCTION
Introduction

Erectile dysfunction (ED) is defined as the persistent inability to attain and maintain an erection sufficient to permit satisfactory sexual performance. Erectile dysfunction may affect physical and psychosocial health and may have a significant impact on the quality of life (QoL) of sufferers and their partners. There is increasing evidence that ED can also be an early manifestation of coronary artery and peripheral vascular disease; therefore, ED should not be regarded only as a QoL issue, but also as a potential warning sign of cardiovascular disease (CVD).
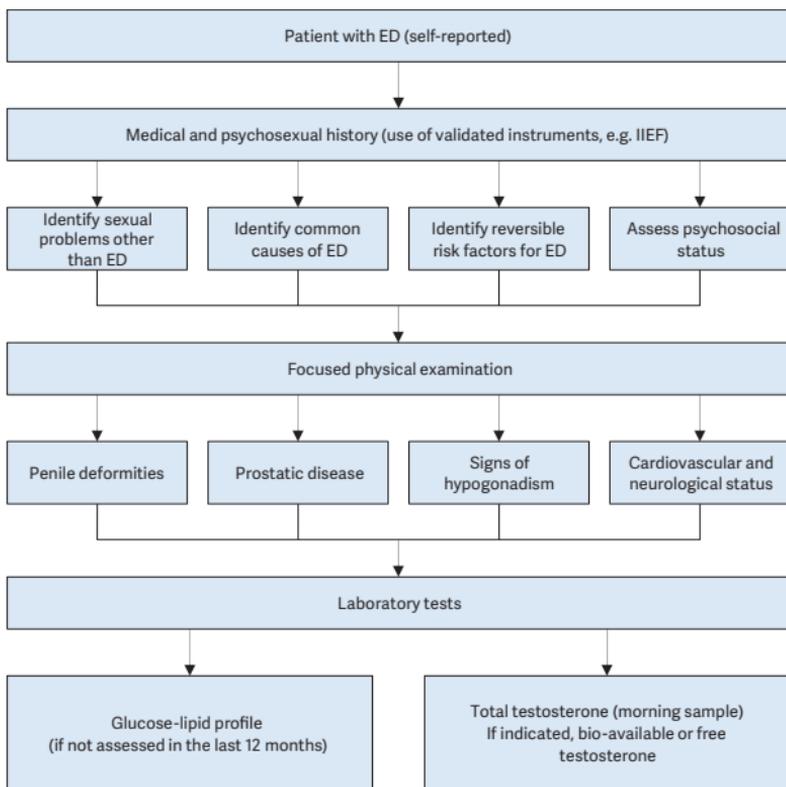
Table 1: Pathophysiology of erectile dysfunction

Vasculogenic
Cardiovascular disease (hypertension, coronary artery disease, peripheral vasculopathy, etc.)
Diabetes mellitus
Hyperlipidaemia
Smoking
Major pelvic surgery (RP) or radiotherapy (pelvis or retroperitoneum)
Neurogenic
Central causes
Degenerative disorders (multiple sclerosis, Parkinson's disease, multiple atrophy, etc.)
Spinal cord trauma or diseases
Stroke
Central nervous system tumours
Peripheral causes
Type 1 and 2 diabetes mellitus
Chronic renal failure
Polyneuropathy
Surgery (major surgery of pelvis/retroperitoneum)
Surgery of the urethra (urethral stricture, urethroplasty, etc.)
Anatomical or structural
Hypospadias, epispadias
Micropenis
Peyronie's disease
Penile cancer
Phimosis

Hormonal
Hypogonadism
Hyperprolactinaemia
Hyper- and hypothyroidism
Hyper- and hypocortisolism (Cushing's disease, etc.)
Panhypopituitarism and multiple endocrine disorders
Drug-induced
Antihypertensives (thiazide diuretics, etc.)
Antidepressants (selective serotonin reuptake inhibitors, tricyclics)
Antipsychotics (neuroleptics, etc.)
Antiandrogens (GnRH analogues and antagonists)
Recreational drugs (alcohol, heroin, cocaine, marijuana, methadone, synthetic drugs, anabolic steroids, etc.)
Psychogenic
Generalised type (e.g., lack of arousability and disorders of sexual intimacy)
Situational type (e.g., partner-related, performance-related issues or due to distress)
Trauma
Penile fracture
Pelvic fractures

Diagnostic evaluation

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

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│              Patient with ED (self-reported)                 │
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                              │
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│  Medical and psychosexual history (use of validated          │
│                instruments, e.g. IIEF)                        │
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      │              │                │               │
┌───────────┐ ┌───────────┐ ┌───────────────┐ ┌──────────────┐
│ Identify  │ │ Identify  │ │ Identify      │ │ Assess       │
│ sexual    │ │ common    │ │ reversible    │ │ psychosocial │
│ problems  │ │ causes of │ │ risk factors  │ │ status       │
│ other     │ │ ED        │ │ for ED        │ │              │
│ than ED   │ │           │ │               │ │              │
└───────────┘ └───────────┘ └───────────────┘ └──────────────┘
                              │
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│              Focused physical examination                    │
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      │              │                │               │
┌───────────┐ ┌───────────┐ ┌───────────────┐ ┌──────────────┐
│ Penile    │ │ Prostatic │ │ Signs of      │ │ Cardio-      │
│ deformities│ │ disease  │ │ hypogonadism  │ │ vascular and │
│           │ │           │ │               │ │ neurological │
│           │ │           │ │               │ │ status       │
└───────────┘ └───────────┘ └───────────────┘ └──────────────┘
                              │
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│                    Laboratory tests                          │
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           │                             │
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│ Glucose-lipid profile  │   │ Total testosterone (morning    │
│ (if not assessed in    │   │ sample)                        │
│ the last 12 months)    │   │ If indicated, bio-available or │
│                        │   │ free testosterone              │
└────────────────────────┘   └────────────────────────────────┘
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ED = erectile dysfunction; IIEF = International Index of Erectile Function.

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

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

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

Table 3: Indications for specific diagnostic tests

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

Table 4: Specific diagnostic tests

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

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

Disease management

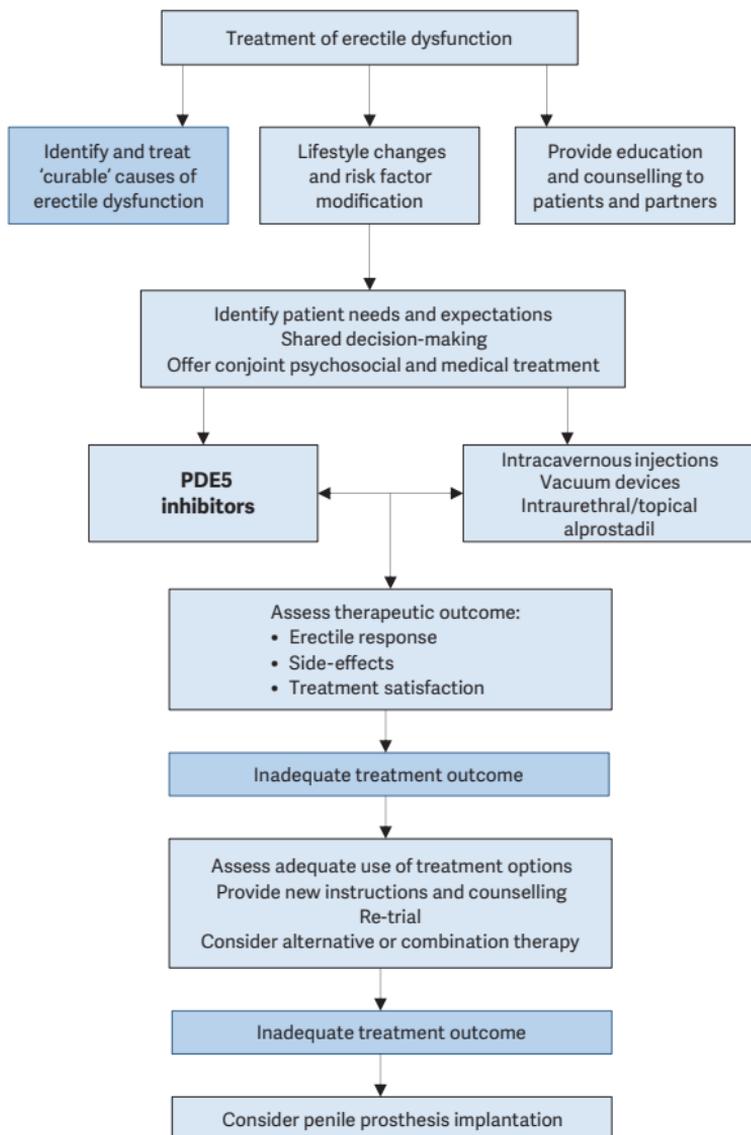## Figure 2: Treatment algorithm for erectile dysfunction

Treatment of erectile dysfunction

Identify and treat 'curable' causes of erectile dysfunction

Lifestyle changes and risk factor modification

Provide education and counselling to patients and partners

Identify patient needs and expectations
Shared decision-making
Offer conjoint psychosocial and medical treatment

PDE5 inhibitors

Intracavernous injections
Vacuum devices
Intraurethral/topical alprostadil

Assess therapeutic outcome:
- Erectile response
- Side-effects
- Treatment satisfaction

Inadequate treatment outcome

Assess adequate use of treatment options
Provide new instructions and counselling
Re-trial
Consider alternative or combination therapy

Inadequate treatment outcome

Consider penile prosthesis implantation

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

Parameter	Sildenafil, 100 mg	Tadalafil, 20 mg	Vardenafil, 20 mg	Avanafil 200mg
C_{max}	560 µg/L	378 µg/L	18.7 µg/L	5.2 µg/L
T_{max} (median)	0.8-1 hours	2 hours	0.9 hours	0.5-0.75 hours
T1/2	2.6-3.7 hours	17.5 hours	3.9 hours	6-17 hours
AUC	1,685 µg.h/L	8,066 µg.h/L	56.8 µg.h/L	11.6 µg.h/L
Protein binding	96%	94%	94%	99%
Bioavailability	41%	NA	15%	8-10%

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

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

Table 6: Common adverse events of the four PDE5Is currently EMA-approved to treat ED*

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

* Adapted from EMA statements on product characteristics.

Recommendations for the treatment of erectile dysfunction (ED)	LE	GR
Enact lifestyle changes and risk factor modification prior to or accompanying ED treatment.	1a	A
Start pro-erectile treatments at the earliest opportunity after radical prostatectomy.	1b	A
Treat a curable cause of ED first, when found.	1b	B
Use phosphodiesterase type 5 inhibitors (PDE5Is) as first-line therapy.	1a	A
Assess all patients for inadequate/incorrect prescriptions and poor patient education, since they are the main causes of a lack of response to PDE5Is.	3	B

Use vacuum erection devices as a first-line therapy in well-informed older patients with infrequent sexual intercourse and comorbidity requiring non-invasive, drug-free management of ED.	4	C
Use intracavernous injections as second-line therapy.	1b	B
Use implantation of a penile prosthesis as third-line therapy.	4	C

PREMATURE EJACULATION (PE)
Introduction
Although PE is a common male sexual dysfunction, it is poorly understood. Patients are often unwilling to discuss their symptoms and many physicians do not know about effective treatments. As a result, patients may be misdiagnosed or mis-treated.

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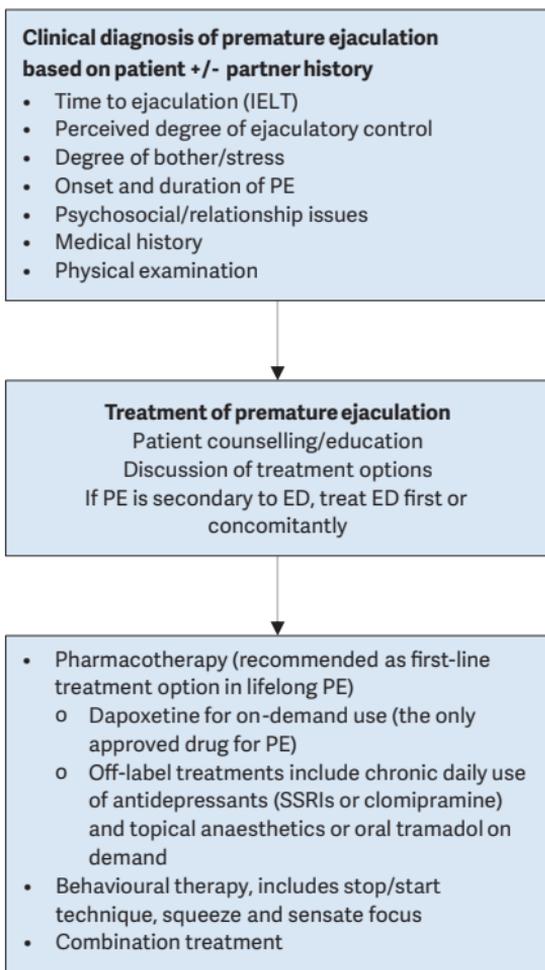
Diagnostic evaluation

Recommendations for the diagnostic evaluation of premature ejaculation (PE)	LE	GR
Perform the diagnosis and classification of premature ejaculation (PE) based on medical and sexual history, which should include assessment of intravaginal ejaculatory latency time (IELT) (self-estimated), perceived control, distress and interpersonal difficulty due to the ejaculatory dysfunction.	1a	A
Do not use stopwatch-measured IELT in clinical practice.	2a	B
Do not use patient-reported outcomes in clinical practice.	3	C
Include physical examination in the initial assessment of PE to identify anatomical abnormalities that may be associated with PE or other sexual dysfunctions, particularly erectile dysfunction.	3	C
Do not perform routine laboratory or neuro-physiological tests. They should only be directed by specific findings from history or physical examination.	3	C

Disease management

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

Figure 3: Management of premature ejaculation*

**Clinical diagnosis of premature ejaculation
based on patient +/- partner history**
- Time to ejaculation (IELT)
- Perceived degree of ejaculatory control
- Degree of bother/stress
- Onset and duration of PE
- Psychosocial/relationship issues
- Medical history
- Physical examination

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Treatment of premature ejaculation
Patient counselling/education
Discussion of treatment options
If PE is secondary to ED, treat ED first or
concomitantly

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- Pharmacotherapy (recommended as first-line
  treatment option in lifelong PE)
    o Dapoxetine for on-demand use (the only
      approved drug for PE)
    o Off-label treatments include chronic daily use
      of antidepressants (SSRIs or clomipramine)
      and topical anaesthetics or oral tramadol on
      demand
- Behavioural therapy, includes stop/start
  technique, squeeze and sensate focus
- Combination treatment

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

This short booklet text is based on the more comprehensive
EAU Guidelines (ISBN 978-90-79754-91-5), available to all members of
the European Association of Urology at their website,
http://www.uroweb.org/guidelines.