# GUIDELINES ON ERECTILE DYSFUNCTION

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## Definition and epidemiology

Male erectile dysfunction (ED) 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 is related to physical and psychosocial health, and has a significant impact on the quality of life of both sufferers and their partners and families.

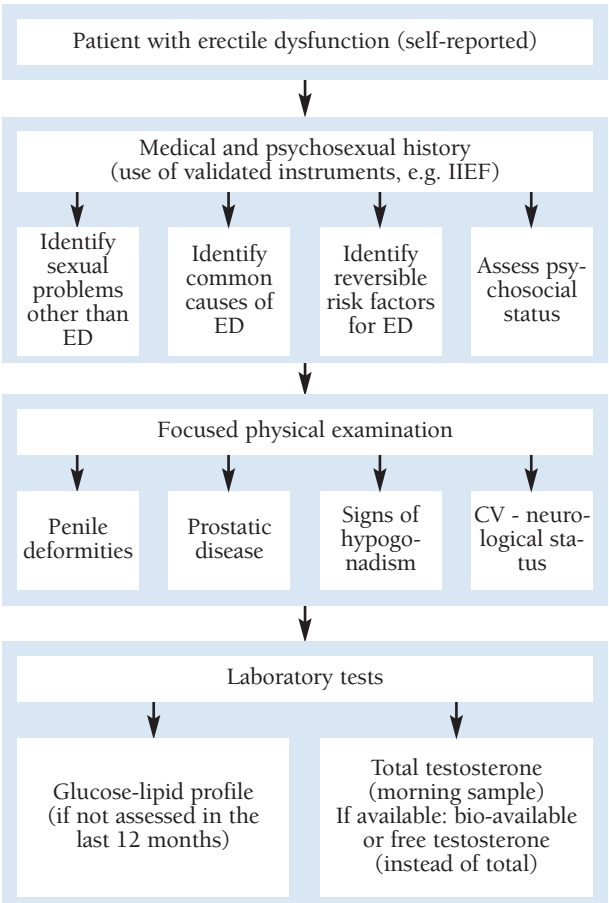
A recent review of the current epidemiological literature on ED suggest that approximately 5-20% of men have moderate to severe ED. ED shares common risk factors with cardiovascular disease such as lack of exercise, obesity, smoking, hypercholestaeremia and metabolic syndrome. Modification of risk factors (predominantly initiation of exercise or weight loss) may reduce the risk of ED.

## Diagnosis and work-up

### Basic work-up

The basic work-up (minimal diagnostic evaluation, Figure 1) must be performed in every patient with ED.

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



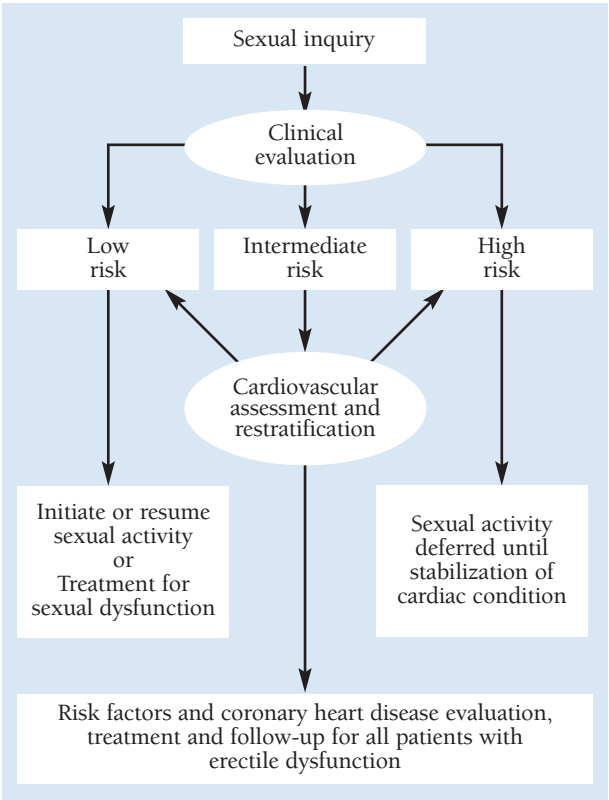
Due to the potential cardiac risks associated with sexual activity, the 2nd Princeton Consensus Conference stratified patients with erectile dysfunction requiring initiating or resuming sexual activity into three risk categories (Figure 2). The low-risk group includes asymptomatic patients with fewer than 3 risk factors for coronary artery disease (excluding gender), mild or stable angina (evaluated and/or being treated), uncomplicated past myocardial infarction, left ventricular dysfunction/congestive heart failure (NYHA class I), post-successful coronary revascularization, controlled hypertension and mild valvular disease. All other patients are included in the intermediate or high-risk categories and need cardiology consultation.

## Specific examinations and tests

While the majority of patients with ED can be managed within the sexual care setting, some circumstances may dictate the need for specific diagnostic testing:

- The patient with 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 (e.g. Peyronie's disease, congenital curvature) that might require surgical correction.
- Patients with complex psychiatric or psychosexual disorders.
- Patients with complex endocrine disorders.
- Specific tests may also be indicated at the request of the patient or his partner.
- For medico-legal reasons (e.g. implantation of penile prosthesis, cases of sexual abuse).

**Figure 2. Treatment algorithm according to cardiac risk (2nd Princeton Consensus Conference)**



Specific diagnostic tests include:

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

The NPTR should take place for at least two nights. The presence of an erectile event of at least 60% rigidity recorded on the tip of the penis, lasting for 10 minutes or more, should be considered as indicative of a functional erectile mechanism.

The intracavernous injection test offers limited information regarding vascular status. Duplex ultrasound is the simplest diagnostic method to assess vascular status. There is no need to continue vascular investigation when the duplex examination is normal (peak systolic blood flow higher than 30 cm/sec and a resistance index higher than 0.8). When it is abnormal, arteriography and DICC should be performed only for patients who are considered potential candidates for vascular reconstructive surgery.

## Treatment

Only psychogenic erectile dysfunction, post-traumatic arteriogenic erectile dysfunction in young patients, and hormonal causes can be potentially cured with specific treatment modalities. The majority of men with erectile dysfunction will be treated with no cause-specific treatment options. This fact leads to a structured treatment strategy that depends on efficacy, safety, invasiveness and cost as well as patient and partner satisfaction. A treatment algorithm for ED is presented in Figure 3.

## First-line therapy
## Phosphodiesterase (PDE) inhibitors

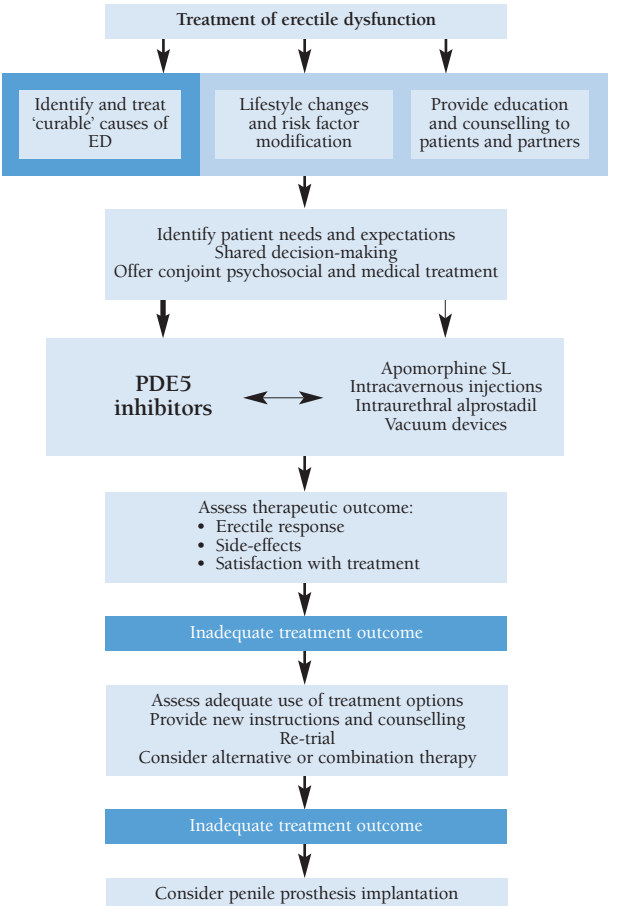
Three potent selective PDE5 inhibitors are currently on the market with European Medicines Agency (EMEA) approval and with proven efficacy and safety for the treatment of ED. They are not initiators of erection but they require sexual stimulation in order to facilitate an erection.

*Sildenafil (Viagra™)*

Sildenafil is the first PDE5 inhibitor, with > 20 million men treated over a 6 year post-marketing experience. It is effective (erection with rigidity sufficient for vaginal penetration) after 30-60 minutes from administration. A heavy fatty meal may reduce or prolong absorption. It is administered in 25, 50 and 100 mg doses. The recommended starting dose is 50 mg and this should be adapted according to the response and side effects. Efficacy may be maintained for up to 12 hours.

In pre-marketing studies, after 24 weeks of treatment in a dose-response study, improved erections were reported by 56%, 77% and 84% of the men taking 25, 50 and 100 mg of

Figure 3. Treatment algorithm for ED



sildenafil respectively, compared with 25% by those taking placebo. The efficacy of sildenafil in almost every subgroup of patients with ED is more than established.

*Tadalafil (Cialis™)*
Tadalafil is effective from 30 minutes after administration but its peak efficacy is expected after about 2 hours. Efficacy is maintained for up to 36 hours. Its efficacy is not influenced by food. It is administered in 10 and 20 mg doses. The recommended starting dose is 10 mg and this should be adapted according to the response and side effects.

In pre-marketing studies, after 12 weeks of treatment and in a dose-response study, improved erections were reported by 67% and 81% of the men taking 10 mg and 20 mg of tadalafil compared with 35% in the control placebo group. These results are confirmed in post-marketing studies. Tadalafil also improved erections in difficult-to-treat subgroups.

*Vardenafil (Levitra™)*
Vardenafil is effective 30 minutes after administration. Its effect is reduced by a heavy fatty meal (> 57% in fat). It is administered in 5, 10 and 20 mg doses. The recommended starting dose is 10 mg, adapted according to the response and side effects. *In vitro*, it is 10-fold more potent than sildenafil. However, this does not necessarily imply greater clinical efficacy.

In pre-marketing studies, after 12 weeks of treatment and in a dose-response study, improved erections were reported by 66%, 76% and 80% of the men taking 5 mg, 10 mg and 20 mg

of vardenafil respectively, compared with 30% by those taking placebo. Efficacy is confirmed in post-marketing studies. Vardenafil also improved erections in difficult-to-treat subgroups.

### Safety issues for PDE5 inhibitors

*Adverse events*

Common adverse events include headache, flushing, dizziness, dyspepsia and nasal congestion. Sildenafil and vardenafil are associated also with visual abnormalities in fewer than 2% of patients, while tadalafil is associated with back pain/myalgia in 6% of patients. However adverse events are generally mild in nature, self-limited by continuous use and the drop-out rate due to adverse events is similar to placebo.

*Cardiovascular safety*

Clinical trials and post-marketing data of all PDE5 inhibitors demonstrated no increase in myocardial infarction rates. None of the PDE5 inhibitors adversely affects total exercise time or time to ischaemia during exercise testing in men with stable angina. In fact they may actually improve exercise tests.

Nitrates are totally contraindicated with all PDE5 inhibitors due to unpredictable hypotension. The duration of interaction between organic nitrates and PDE5 inhibitors is dependent upon the PDE5 inhibitor and nitrate under study. If a patient develops angina while on a PDE5 inhibitor, other agents may be administered instead of nitroglycerine or until the appropriate time has passed (24 hours for sildenafil/vardenafil and 48 hours for tadalafil).

In general, the adverse event profile of the PDE5 inhibitor will not worsen even when the patient is on multiple antihypertensive agents.

*Alpha blocker interactions*
All PDE5 inhibitors appear to have some interaction with alpha blockers, which under some conditions may result in orthostatic hypotension. Sildenafil labelling currently describes a precaution advising that 50 or 100 mg (not 25 mg) dosages should not be taken within a four-hour window of an alpha blocker. The concomitant use of vardenafil with alpha blockers is not recommended. However, co-administration of vardenafil with tamsulosin is not associated with clinically significant hypotension. Tadalafil is contraindicated in patients taking alpha blockers with the exception of tamsulosin.

*Dose adjustments*
Lower doses of PDE5 inhibitors may be required in patients taking ketoconazole, itraconazole, erythromycin, clarithromycin and HIV protease inhibitors (ritonavir, saquinavir). Higher doses of the PDE5 inhibitors may be required in patients taking rifampicin, phenobarbital, phenytoin and carbamazepine. Kidney or hepatic dysfunction may require dose adjustments or warnings.

In patients with hypogonadism, androgen supplementation improves erectile responses and provokes arterial cavernous dilatation.

## Apomorphine sublingual (Uprima™, Ixense™)

Apomorphine is a centrally acting drug (dopamine agonist, mainly D2) that improves erectile function by enhancing the natural central erectile signals that normally occur during sexual stimulation. It is administered sublingually on demand in 2 or 3 mg doses. Efficacy rates (erections sufficient for intercourse) range from 28.5 to 55%. Due to rapid absorption, 71% of erections are achieved within 20 minutes. The most common adverse events are nausea (7%), headache (6.8%) and dizziness (4.4%). Apomorphine is not contraindicated in patients taking nitrates or antihypertensive drugs of all classes, and it does not affect vital signs.

Comparative studies clearly show that apomorphine is associated with significantly lower efficacy and satisfaction rates than sildenafil.

## Vacuum device

A vacuum device could be used in patients in stable relationships in whom the mechanism of ED is easily understood. It is also better accepted in older patients. The device applies a negative pressure to the penis, thus drawing venous blood into the penis, which is then retained by the application of a visible constricting band at the base of the penis. The adverse effects associated with vacuum therapy are penile pain, numbness and delayed ejaculation.

## Psychosexual therapy

For patients with a significant psychological problem, psychosexual therapy may be given either alone or in combination

with another therapeutic approach. Psychosexual therapy takes time and has been associated with variable results.

## Second-line therapy
## Intracavernosal injection

Alprostadil (Caverject®, Edex/Viridal®) is the first and only drug approved for intracavernous erectile dysfunction treatment. It is the more efficacious monotherapy for intracavernous treatment in 5-40 µg doses. Drug combinations (mainly alprostadil-papaverine-phentolamine, tri-mix) may increase efficacy. The erection appears after 5-15 minutes 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.

Efficacy rates for intracavernous alprostadil of more than 70% are presented, with sexual activity reported after 94% of the injections and satisfaction rates of 87-93.5% in patients and 86-90.3% in partners. Complications of intracavernous alprostadil include penile pain (50% of patients, after 11% of injections), prolonged erections (5%), priapism (1%) and fibrosis (2%).

After 4h of erection, patients are advised to consult the doctor to avoid any damage to the intracavernous muscle, which would provoke permanent impotence. A 19-gauge needle is used to aspirate blood and therefore to decrease the intracavernous pressure. This simple method is usually sufficient to make the penis flaccid. However, if the penis becomes rigid again after this, phenylephrine intracavernous injection is required at a dose starting of 200 µg every 5 min, increasing to

500 µg if necessary. When this problem occurs, the dose is usually reduced for the next injection.

## Intraurethral therapy

Prostaglandin E1 may be administered intraurethrally in the form of a semi-solid pellet. A band placed at the base of the penis seems to improve the resulting rigidity. About 70% of patients have been satisfied or very satisfied. Even the administrated route seems to be less invasive. Side-effects include penile pain and hypotension, and the clinical success rate is lower than that achieved with intracavernosal therapy.

## Third-line therapy
## Penile prosthesis

The surgical implantation of a penile prosthesis may be considered in patients who fail 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, but they are much more expensive. Satisfaction rates of 70-87% are reported from patients after appropriate consultation.

The two main complications of penile prosthesis implantation are mechanical failures (fewer than 5% after 5 year follow-up with current three-piece prosthesis) and infection (2-3% with proper antibiotic prophylaxis - may be further reduced with the implantation of antibiotic impregnated or hydrophilic coated prosthesis). Infection requires removal of the prosthesis, antibiotic administration and reimplantation after 6-12 months. However, salvage therapy with removal and reim-

plantation at the same time after copious irrigation of the corpora with multi-drug solutions is associated with 82% success rates.

## Conclusion

The worldwide availability of the three PDE5 inhibitors for oral use associated with high efficacy and safety rates even in difficult-to-treat populations (e.g. diabetes mellitus, radical prostatectomy) has revolutionized erectile dysfunction treatment. Treatment options for patients not responding to oral drugs (or contraindicated) include intracavernous injections, intraurethral alprostadil, vacuum constriction devices and implantation of penile prostheses. 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. The search for the ideal pharmacological therapy for erectile failure aims at fulfilling the following characteristics: good efficacy, easy administration, freedom from toxicity and side-effects, a rapid onset and a possible long-acting effect.

*This short booklet text is based on the more comprehensive EAU guidelines (ISBN 90-70244-29-2), available to all members of the European Association of Urology at their website - http://www.uroweb.org.*