



European Association of Urology

GUIDELINES ON ERECTILE DYSFUNCTION

**E. Wespes, E. Amar, D. Hatzichristou,
F. Montorsi, J. Pryor, Y. Vardi**

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1 BACKGROUND

1.1 Introduction

The introduction of new oral therapies has completely changed the diagnostic and therapeutic approach to erectile dysfunction (ED) (impotence). A panel of experts in this field have developed guidelines for clinical evaluation and treatment based on the review of available scientific information.

Male erectile dysfunction has been defined as the persistent (lasting for at least 6 months) 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 psychological health, and has a significant impact on the quality of life of both sufferers and their families. Recent epidemiological data have shown a high prevalence and incidence of ED. The Massachusetts Male Aging Study reported a combined prevalence of 52% for minimal, moderate, and complete ED in non-institutionalized 40 to 70-year-old men in the Boston area [1]. In this study, the individual prevalences were 17.2, 25.2 and 9.6 for minimal, moderate and complete ED, respectively [1]. The same study found that the incidence of ED was 24 new cases per 1000 men.

Erection is a neurovascular phenomenon under hormonal control, and includes arterial dilatation, trabecular smooth muscle relaxation and activation of the corporeal veno-occlusive mechanism [2,3]. The advances in basic and clinical research during the last 15 years has led to the development of several new treatment options for ED, including new pharmacological agents for intracavernosal, intraurethral and oral use. The recent advent of medical therapy and the poor results of long-term follow-up in reconstructive vascular surgery, have significantly modified the medical management of this disorder [4-6].

The current availability of an effective and safe oral therapy for ED and the future availability of other oral drugs, awaiting final approval, in conjunction with the tremendous media interest for the condition, have resulted in an increasing number of men seeking help for ED. As a consequence, many physicians without background knowledge and clinical experience in the diagnosis and treatment of ED are involved in making decisions concerning the evaluation and treatment of these men. The results of this is that some men with ED may undergo little or no evaluation before treatment is initiated, or that men without ED may seek treatment in order to enhance their sexual performance with anti-ED drugs. In such circumstances, the disease causing the symptom (ED) may remain untreated. Such observations made the development of guidelines for the diagnosis and treatment of ED, a necessity. The European Association of Urology formed an expert panel to address the shortcomings and problems associated with the diagnosis and treatment of ED. The overall objective of the project was to develop guidelines for clinical evaluation and treatment, based on the evaluation and review of available scientific information, as well as on current research and clinical practice in the field. Moreover, the panel identified critical problems and knowledge gaps, setting priorities for future clinical research.

2 DIAGNOSIS

During the first visit, the essential step in the management of ED is the taking of a comprehensive medical and psychological history of the patients and his partner when possible [7,8]. A detailed medical history is critical as many common disorders are associated with ED, including hypertension, diabetes mellitus, myocardial disease, lipidaemia, hypercholesterolemia, renal insufficiency, hypogonadism, neurological and psychiatric disorders, and indeed any chronic illness. Genitourinary and rectal surgery, as well as many drugs, particularly anti-hypertensive and psychotropic drugs may cause ED. Other drug groups and substance abuses are well-documented causes of ED. The chronic use of alcohol, marijuana, codeine, meperidine, methadone and heroin is associated with a high percentage of ED [9]. The influence of radiation therapy on ED is well known. Evaluation has revealed vasculogenic alteration to be the most consistent organic erectile abnormality in radiotherapy [10].

The initial enquiry about medical history allows a more relaxing atmosphere to be established and permits questions about erectile function and other aspects of sexual history to be asked more easily, even when men do not volunteer to describe their problem. The sexual history may include information about previous and current sexual relationships, current emotional status, onset and duration of the erectile problem and possible previous consultations and treatments. Detailed descriptions of the quality of both erotic and morning erections, in terms of rigidity and duration, as well as arousal, ejaculation and orgasmic problems should be discussed. The use of validated questionnaires, such as the international index for erectile function, may be helpful in order to assess objectively not only the present status but also the impact of a specific treatment [11].

A focused physical examination must be performed on every patient, with particular emphasis on the genitourinary, endocrine, vascular and neurological systems [7]. The physical examination may reveal unsuspected findings, such as Peyronie's disease, small testes and prostatic cancer. A rectal examination should be performed in every patient older than 50 years. Laboratory testing (blood glucose and testosterone) should be carried out in the majority of the patients and selectively in other patients when lipid profile, prolactin and prostate-specific antigen (PSA) assessment should be considered [12-14].

It is important that the physician facilitates communication with the patient and his partner and explains the strategy behind the diagnostic and therapeutic approach. It may not often be possible to involve the partner on the first visit, but an effort should be made to involve the partner during the second visit. On that occasion the physician examines the results of the blood tests. If any abnormality is observed, further investigation by referral to another specialist may be necessary.

The discussion considers patient's expectations and needs, and should involve the physician, the patient and his partner. It should cover the understanding of the disorder, interpretation of the diagnostic tests and rational selection of treatment options. Patient and partner education are essential components in the management of ED [15].

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.
- Specific tests may be indicated at the request of the patient or his partner.
- For medico-legal reasons.

Among the specific tests used are: assessment of nocturnal penile tumescence and rigidity (NTPR) using Rigiscan-NTPR; vascular studies, such as intracavernous vasoactive drug injection and duplex ultrasound completed with arteriography or cavernosometry; neurological studies, such as bulbocavernous reflex latency and nerve conduction; endocrinological studies and specialized psychodiagnostic evaluation. The NTPR 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 [16].

The intracavernosal injection test offers limited information regarding vascular status. A positive test is defined as a rigid erectile response (unable to bend the penis) that appears within 10 minutes after the intracavernosal injection and lasts for 30 min. Such a response may be considered to be associated with normal arterial and veno-occlusive haemodynamics [16]. In all other cases, the test is inconclusive, and a duplex ultrasound of the penile arteries should be requested. A peak systolic blood flow higher than 30 cm/sec and a resistance index higher than 0.8 are generally considered as normal [16]. If the result of the duplex examination is normal, the vascular investigation stops. When it is abnormal, arteriography and cavernosometry should be performed only for patients who are considered potential candidates for vascular reconstructive surgery. Patients with psychiatric disorders will be sent to a psychiatrist particularly interested in ED. Patients with penile abnormalities, such as hypospadias, congenital curvature or Peyronie's disease with preserved rigidity, may require surgical correction with very good success.

3 TREATMENT

The first objective of every doctor is to cure the medical condition. Therefore, the primary goal in the management strategy for a patient with ED is to determine the aetiology of the disease and treat it when possible, and not to treat the symptom alone. It is clear that ED may be associated with modifiable or reversible factors, including lifestyle or drug-related factors, that may be modified prior to or in conjunction with the employment of specific therapeutic operations.

Testosterone deficiency is potentially reversible and is a result of primary testicular failure or secondary to pituitary/hypothalamic causes [12]. Patients with hormone abnormalities need to take the advice of an endocrinologist. Testosterone replacement is effective but can only be used when other possible endocrinological causes for the testicular failure have been excluded. Testosterone replacement therapy is contraindicated in men with a history of prostate carcinoma or with symptoms of prostatism. Prior to initiating testosterone replacement, a digital rectal examination (DRE) and serum PSA test should be performed. Patients receiving androgen therapy should be monitored for clinical response as well as the development of hepatic or prostatic disease [12]. However, it should be mentioned that this treatment is not always effective in the management of ED associated with hypogonadism.

In young patients with pelvic or perineal trauma, a surgical penile revascularization procedure is often associated with good results; there is a 60-70% long-term success rate [5]. The lesion must be demonstrated by duplex ultrasound and confirmed by penile pharmaco-arteriography. A corporeal veno-occlusive dysfunction must be excluded by pharmaco-cavernosometry.

When no specific therapies for ED are required, a strategic approach should be followed. Again the patient and his partner, when possible, must be informed on the route of administration, the invasiveness, the cost and the reversibility of the treatment. In other cases, such as older patients without traumatic lesions or in patients with secondary cavernovenous leakage, vascular surgery is no longer recommended due to poor results at long-term follow-up.

3.1 First-line therapy

The phosphodiesterase type I (PDE₅) is an enzyme which 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 [17].

Three potent selective PDE₅ inhibitors are currently on the market approved by the U.S. Food and Drug Administration (FDA) with proven efficacy and safety for the treatment of ED.

3.1.1 Sildenafil (Viagra)

Sildenafil the first PDE₅ inhibitor, with > 20 million men treated over a 5 year post-marketing experience, is effective after 30-60 minutes in the presence of sexual stimulation but its effect is reduced by a heavy fatty meal. Its half-life is approximately 4h (Table 1) [17]. The dosages are 25, 50 and 100mg. The starting dose should be 50mg and adapted according to the response and side effects.

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 100mg of Sildenafil, respectively compared with 25% by those taking placebo [4].

3.1.2 Vardenafil (Levitra)

Vardenafil is available in 5, 10 and 20mg doses. In vitro it is 10-fold more potent than Sildenafil, however, this does not necessarily imply greater clinical efficacy [18].

It is effective after 30 minutes in the presence of sexual stimulation but its effect is reduced by a heavy fatty meal. Its half-life is approximately 4h (Table 1) [17]. The starting dose should be 10mg and adapted 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 66%, 76% and 80% of the men taking 5 mg, 10mg and 20mg of Vardenafil respectively compared with 30% by those taking placebo [19].

3.1.3 Tadalafil (Cialis)

Tadalafil is available in 10 and 20mg doses.

It is effective after 30 minutes in the presence of sexual stimulation. Its efficacy is not influenced by food and alcohol. Its half-time is 17.5h (Table 1) [17].

The starting dose should be 10mg and adapted 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 10mg and 20mg of Tadalafil compared with 35% in the control placebo group [20].

Table 1: Comparison of key pharmacokinetic parameters of three PDE₅ inhibitors, Vardenafil, Sildenafil and Tadalafil

| | Sildenafil (100mg) | Vardenafil (20 mg) | Tadalafil (20 mg) |
|--------------------------|--------------------|--------------------|-------------------|
| T _{max} (h) | 1.16 | 0.75 | 2 |
| T _{1/2} (h) | 3.82 | 4.7 | 17.5 |
| C _{max} (ng/ml) | 327 | 31.8 | 378 |
| AUC (ng/ml/h) | 1963 | 96.3 | 8066 |

AUC: area under the plasma concentration versus time curve; C_{max}: peak plasma concentrations; T_{max}: time to peak plasma concentration; t_{1/2}: half-life.

The most common side effects of PDE₅ inhibitors include headaches, flushing, dyspepsia and nasal congestion (Table 2). All PDE₅ inhibitors act in a similar way via the NO/cGMP mechanism. They are formally

contraindicated in patients who take long-acting nitrates or who use short-acting, nitrate-containing medications [17]. It may be hazardous to prescribe PDE₅ inhibitors in patients with [22]:

- active coronary ischaemia;
- congestive heart failure and borderline low blood pressure;
- borderline low cardiac volume status;
- a complicated multi-drug anti-hypertensive program;
- drug therapy that can prolong the half-life of PDE₅ inhibitors.

Table 2: Treatment-related adverse events reported by patients using the maximum dosis of PDE₅ inhibitors, Sildenafil, Vardenafil and Tadalafil

| Adverse events | Sildenafil (%) [21] (100 mg) | Vardenafil (%) [19] (20 mg) | Tadalafil (%) [20] (20 mg) |
|--------------------|---------------------------------|--------------------------------|-------------------------------|
| Headache | 19 | 15 | 11 |
| Flushing | 19 | 11 | 5 |
| Rhinitis | 5 | 7 | 5 |
| Dyspepsia | 6 | 7 | 17 |
| Back pain | | | 9 |
| Visual disturbance | 3 | | |

Since all 3 substances are metabolized mainly via cytochrome P450 CYP3A4, a dose adjustment should be considered when given in combination with CYP3A4 inhibitors (e.g. HIV protease inhibitors, ketoconazole, erythromycin) [17].

In patients with hypogonadism, androgen supplementation improves erectile responses and provokes arterial cavernous dilatation [23].

3.1.4 Apomorphine sublingual (*Uprima, Ixense, Taluvian*)

Apomorphine sublingual (SL) is a dopamine agonist that acts to enhance proerectile stimuli through the hypothalamic neural pathways [24-25]. (It is not accepted by the FDA in USA). The sublingual formulation produces a rapid circulating plasma concentration resulting in a quick onset of action, producing an erection in a median time of 18-19 min.

In pre-marketing study, the percentage of attempts resulting in erection firm enough for intercourse (46.9%) was significantly higher with 3mg apomorphine SL than with placebo (32.3%) [25]. It is well tolerated and there is no interactive action with other medications, food and alcohol. The main side effect is nausea in 7% of the cases [25].

3.1.5 Vacuum device

A vacuum device could be used in patients in stable relationships in whom the mechanism of ED is easily understood [26]. 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.

3.1.6 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 [27].

3.2 Second-line therapy

Intracavernosal injection or intraurethral therapy can be used according to the patient's wishes.

3.2.1 Intracavernosal injection

Several drugs have been proposed for intracavernosal injection, alone or in combination (prostaglandin E₁, phentolamine-vasointestinal polypeptide, phentolamine-papaverine, maxisilitrimx); however, only two are approved by the FDA-alprostadil sterile powder and alprostadil alfadex [28]. Patient comfort and education are essential elements of the practice of intracavernosal injection therapy. The use of an automatic special pen that avoids the needle view can resolve the fear of the penile puncture.

Injection therapy is effective in most cases of ED, but it is contraindicated in men with a history of hypersensitivity to the drug employed and in men at risk of priapism. It is not advised in men with limited manual dexterity but their partners may be taught the technique. Intracavernosal therapy is effective in 60-90%

of cases. The erection appears after 5-15 minutes and lasts according to the dose injected. Side-effects include prolonged erections or priapism, penile pain and fibrosis.

After 4 h 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 at a dose starting at 200µg every 5 minutes and increasing to 500µg, if necessary, is required. 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. The patient must be carefully observed for systemic effects of the treatment used.

3.2.2 Intraurethral therapy

Prostaglandin E₁ may be administered intraurethally 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 [29]. Side-effects include penile pain and hypotension, and the clinical success rate is lower than that achieved with intracavernosal therapy [29].

3.3 Third-line therapy

3.3.1 Prosthesis

For patients who fail pharmacological therapy or who prefer a permanent solution to their problem, surgical implantation of a prosthesis may be considered. Two types of prosthesis exist: malleable and inflatable. The inflatable penile prosthesis provides not only a more cosmetic erection but also a more satisfying one. Penile growth is usually better with an inflatable rather than a semi-rigid erection, although the former is associated with an increased rate of mechanical failure and complications. There is also a difference in price. The inflatable prosthesis is much more expensive. In several countries, patients are reimbursed for the cost of the prosthesis, but an organic cause has to be determined for the ED and the patient has to undergo a complete impotence assessment.

Prosthetic infection is the most problematic complication following surgery as the combination of infection and a foreign body requires removal of the prosthesis. The patients most commonly affected by infection problems are diabetics [30].

Exact intra-operative length measurement is mandatory. If the device is too long postoperative pain and eventually prosthesis erosion may result. If too short a device is used, the "concorde" deformity with leaking of the glans during intercourse may occur, and lateral perforation may result.

4 CONCLUSION

It must be emphasized that the physician should warn the patient that sexual intercourse is considered to be 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.

A great deal of progress has been made in the pharmacological treatment of ED. In the past, the most effective therapy required intracavernosal injections, but an increasing number of oral agents have been introduced with very good success rates. 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 at fulfilling the following characteristics: good efficacy, easy administration, freedom from toxicity and side-effects, with a rapid onset and a possible long-acting effect.

Clinical trials performed in multiple countries have shown strong efficacy and good safety of PDE₅ inhibitors in the general populations as well as in a difficult to treat population such as patients with diabetes mellitus and as patients having undergone a post-radical prostatectomy.

There have been no published head to head clinical trials comparing Sildenafil, Vardenafil and Tadalafil. Patients should be encouraged to try all PDE₅ inhibitors and develop their own opinion. They will choose the compound that is perceived by them to have the best efficacy as well as other features such as time of onset, duration of action, window of opportunity and their own individual experience with side effects. Apomorphine in post-marketing studies seems to be effective mainly in patients with psychogenic and a mild organic impotence and should be reserved in patients contraindicated for PDE₅ inhibitors.

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6 ABBREVIATIONS USED IN THE TEXT

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| DRE | digital rectal examination |
| ED | erectile Dysfunction |
| FDA | U.S. Food and Drug Administration |
| cGMP | cyclic guanosine monophosphate |
| NPTR | nocturnal penile tumescence and rigidity |
| PDE | phosphodiesterase |
| PSA | prostate specific antigen |