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EAU Guidelines

EAU Guidelines on Erectile Dysfunction: An Update

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Article info

Article history:

Accepted January 23, 2006

Published online ahead of
print on February 9, 2006

Keywords:

Diagnosis and treatment
EAU guidelines
Erectile dysfunction
Impotence

Abstract

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

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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). A panel of experts in this field was established by the Guidelines Office of the European Association of Urology (EAU) to update the previously published guidelines [1] for the clinical evaluation and treatment of ED based on a review of available scientific information, as well as on current research and clinical practice.

1.2. Epidemiology and risk factors

A recent review of the current epidemiologic literature on ED suggests that approximately 5–20% of men complain of moderate to severe ED [2].

Several risk factors (smoking, hypertension, diabetes, lipidemia, atherosclerosis, pelvic surgery) have been identified based on the knowledge of the pathophysiology of erection [3,4]. Lifestyle risk factors may be modified. In the Massachusetts Male Aging Study, men who initiated physical activity in midlife had a 70% reduced risk for ED relative to those who remained sedentary, whereas in its longitudinal results, regular exercising showed a significantly lower incidence of ED over an 8-yr

follow-up period [5]. A multicenter, randomized, open-label study compared 2 yr of intensive exercise and weight loss with an educational control in obese men with moderate ED [6]. Significant improvements in body mass index (BMI), physical activity scores, and erectile function were observed in the lifestyle intervention group. These changes were highly correlated with both weight loss and activity levels.

1.3. *Managing ED: implications in the everyday clinical practice*

The current availability of effective and safe oral drugs for ED, in conjunction with the tremendous media interest for the condition, has increased the number of men seeking help for ED.

2. **Diagnosis**

2.1. *Basic work-up*

A detailed medical history that includes determining the presence of hypertension, diabetes mellitus, myocardial disease, lipidemia, hypercholesterolemia, renal insufficiency, hypogonadism, neurologic and psychiatric disorders, and indeed any chronic illness of patients must always be the first step in the evaluation of ED [7]. It is desirable to involve the partner although this may not be possible on the first visit. This has to be performed in a relaxed atmosphere that will facilitate communication between the physician, the patient, and his partner. Detailed descriptions should be obtained of the quality of morning and erotic or masturbation-induced erections, in terms of rigidity and duration, as well as arousal, ejaculation, and orgasmic problems. If differences in these events between partners exist, they should be discussed.

Lower urinary tract symptoms and ED are common in older men with an overall prevalence of >50% in men aged ≥ 50 yr. However, their relationship is independent of comorbidities such as diabetes, hypertension, cardiac disease, and hypercholesterolemia [8].

Genitourinary (mainly radical prostatectomy) and rectal surgery, as well as many drugs, particularly antihypertensive and psychotropic drugs may cause ED. Other drug groups and substance abuses are well-documented causes of ED [3].

The chronic use of alcohol, marijuana, codeine, meperidine, methadone, and heroin is associated with a high percentage of ED [9].

The use of validated questionnaires, such as the International Index for Erectile Function (IIEF), may be helpful to assess all sexual function domains (erectile function, orgasmic function, sexual desire, ejaculation, intercourse, and overall satisfaction) and also the impact of a specific treatment modality [10].

A focused physical examination must be performed on every patient, with particular emphasis on the genitourinary, endocrine, vascular, and neurologic systems. The physical examination may reveal unsuspected findings, such as Peyronie disease, prostatic enlargement, or cancer as well as signs and symptoms indicative of hypogonadism (small testes, alterations in secondary sexual characteristics, diminished sexual desire, changes in mood, fatigue syndrome, reduced physical performance) [7]. Blood pressure and heart rate should be measured if not assessed in the previous 3–6 mo. Particular attention must be given to patients with cardiovascular disease (see Section 2.2). 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 mo. Hormonal testing must include a morning sample of total testosterone (bioavailable or calculated-free testosterone is more reliable to establish the presence of hypogonadism, ie, these tests are preferable to total testosterone if available). Further laboratory tests must be considered only in selected patients (eg, prostate-specific antigen [PSA] for detection of prostate cancer). Additional hormonal tests (eg, prolactin, follicle-stimulating hormone [FSH], luteinizing hormone [LH]) must be carried out when low testosterone levels are detected. If any abnormality is observed, further investigation by referral to another specialist may be necessary [11]. Minimal diagnostic evaluation (basic work-up) in patients with ED is presented in Fig. 1.

2.2. *Cardiovascular system and sexual activity: the patients at risk*

There is a high prevalence of cardiovascular disease among patients seeking treatment for sexual dysfunction and the potential cardiac risks associated with sexual activity are well established [4,12]; the latter comes well before with a mean time interval of almost 3 yr [13]. The proposed management recommendations are adapted by a consensus conference on sexual dysfunction and cardiac risks [14].

Patients with ED requiring initiating or resuming sexual activity are stratified into three risk categories.

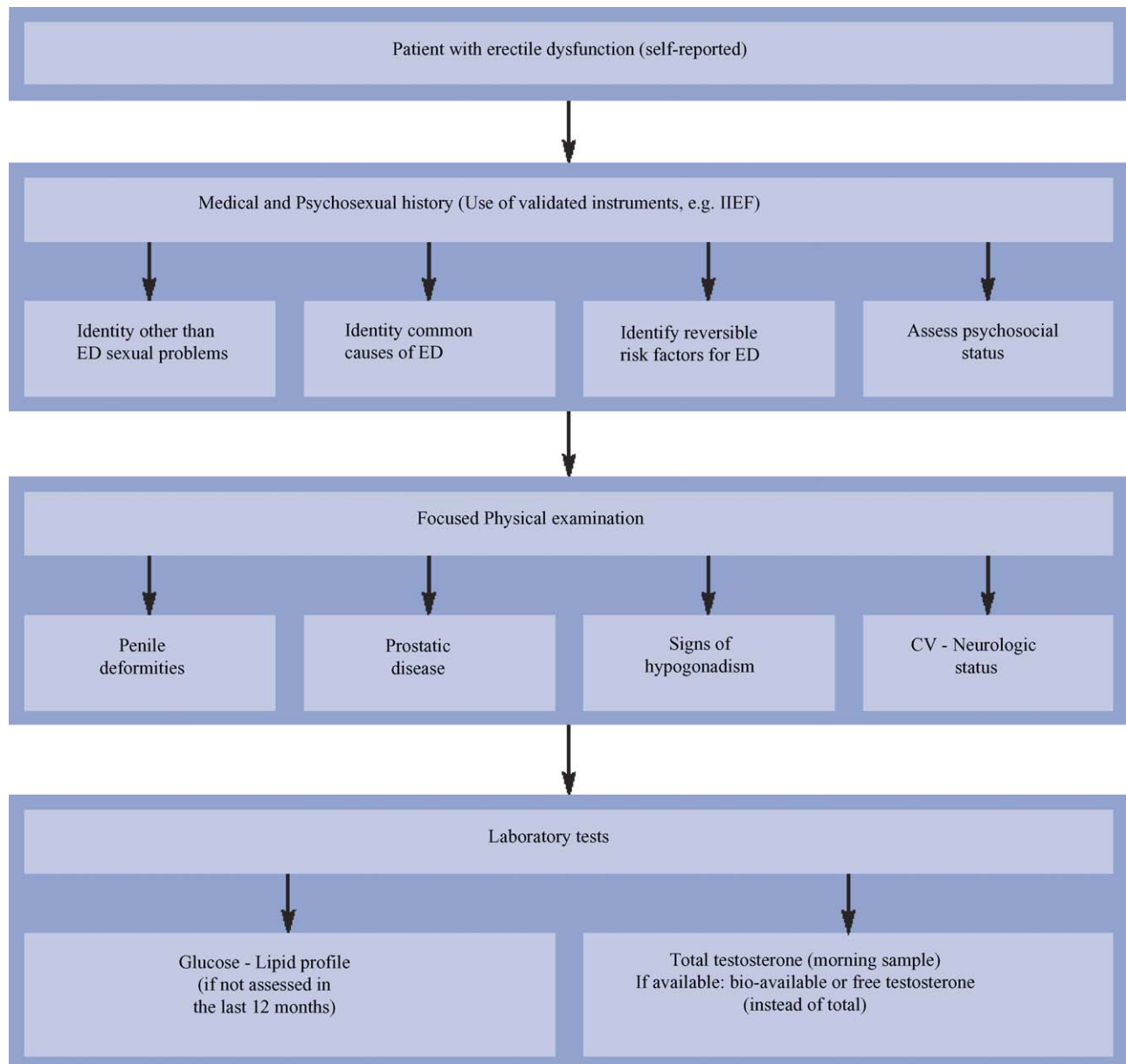


Fig. 1 – Minimal diagnostic evaluation (basic work-up) in patients with erectile dysfunction (ED). IIEF = International Index of Erectile Function; CV = cardiovascular.

The low-risk category includes patients who do not have any significant cardiac risk associated with sexual activity. The ability to perform exercise of modest intensity (eg, 6 or more metabolic equivalents of energy expenditure in resting state [METs]) without symptoms typically implies low risk.

The intermediate- or indeterminate-risk category includes patients whose cardiac condition is uncertain or whose risk profile is such that further testing or evaluation is indicated before the resumption of sexual activity. Based on the results of testing, these patients may be subse-

quently assigned to either the high- or low-risk group.

The high-risk category consists of patients whose cardiac condition is sufficiently severe or unstable that sexual activity may constitute a significant risk. Most patients are moderately to severely symptomatic. High-risk individuals should be referred for cardiologic assessment and treatment. Sexual activity should be deferred until the patient's cardiac condition has been stabilized by treatment or a decision has been made by the cardiologist or internist that sexual activity may be safely resumed.

Table 1 – 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 (eg, Peyronie disease, congenital curvature) that might require surgical correction
- 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 (eg, implantation of penile prosthesis, cases of sexual abuse)

2.3. Specialized diagnostic tests

Although the majority of patients with ED can be managed within the sexual care setting, some circumstances may dictate the need for specific diagnostic testing (Table 1). Specific diagnostic tests are summarized in Table 2.

The nocturnal penis tumescence and rigidity (NPTR) test 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 min, should be considered as indicative of a functional erectile mechanism [15]. A positive test is defined as a rigid erectile response (unable to bend the penis) that appears within 10 min after the intracavernous injection and lasts at least for 30 min. Such a response may indicate a functional but not necessarily normal erection because it may coexist with arterial insufficiency or veno-occlusive dysfunction [16]. Its clinical implication is that the patients will respond to the intracavernous injection program. In all other cases, the test is inconclusive, and a duplex ultrasound of the penile arteries should be requested.

A peak systolic blood flow >30 cm/s and a resistance index >0.8 are generally considered as normal [17]. There is no need to continue vascular investigation when the duplex examination is normal. When it is abnormal, however, arteriography and dynamic infusion cavernosometry and

cavernosography (DICC) should be performed only for patients who are considered potential candidates for vascular reconstructive surgery.

Patients with psychiatric disorders must be referred to a psychiatrist particularly interested in ED.

Patients with ED due to penile abnormalities, such as hypospadias, congenital curvature, or Peyronie disease with preserved rigidity may require surgical correction, which has high success rates.

2.4. Patient education

The physician should consider the expectations and needs of the patient and his partner and their education is essential in the management of ED.

3. Treatment

3.1. Treatment options

The primary goal of the management strategy for a patient with ED is to cure the patient's symptoms by adopting a holistic approach. Because ED may be associated with modifiable or reversible factors, including lifestyle or drug-related factors, these may be modified prior to or in conjunction with specific therapeutic options.

ED may be treated successfully with the current treatment options, but they do not cure the underlying problem. The only exceptions to this are psychogenic ED dysfunction, posttraumatic arteriogenic ED in young patients, and hormonal causes (eg, hypogonadism, hyperprolactinemia) that may be cured with specific interventions. This fact leads to a structured treatment strategy that depends on efficacy, safety, invasiveness, and cost as well as patient preferences [18]. A treatment algorithm for ED is presented in Fig. 2.

3.2. Lifestyle management in ED with concomitant risk factors

Potential benefits of lifestyle changes may be of special relevance in individuals with ED and specific comorbid cardiovascular or metabolic diseases, such as diabetes or hypertension [19,20].

3.3. "Curable" causes of ED

3.3.1. Hormonal causes

Testosterone deficiency is a result of primary testicular failure or secondary to pituitary/hypothalamic causes. Hyperprolactinemia may result from

Table 2 – Specific diagnostic tests

- Nocturnal penile tumescence and rigidity (NPTR) using Rigiscan®
- Vascular studies
 - Intracavernous vasoactive drug injection
 - Duplex ultrasound of the cavernous arteries
 - Dynamic infusion cavernosometry or cavernosography (DICC)
 - Internal pudendal arteriography
- Neurologic studies (eg, bulbocavernosus reflex latency, nerve conduction studies)
- Endocrinology studies
- Specialized psychodiagnostic evaluation

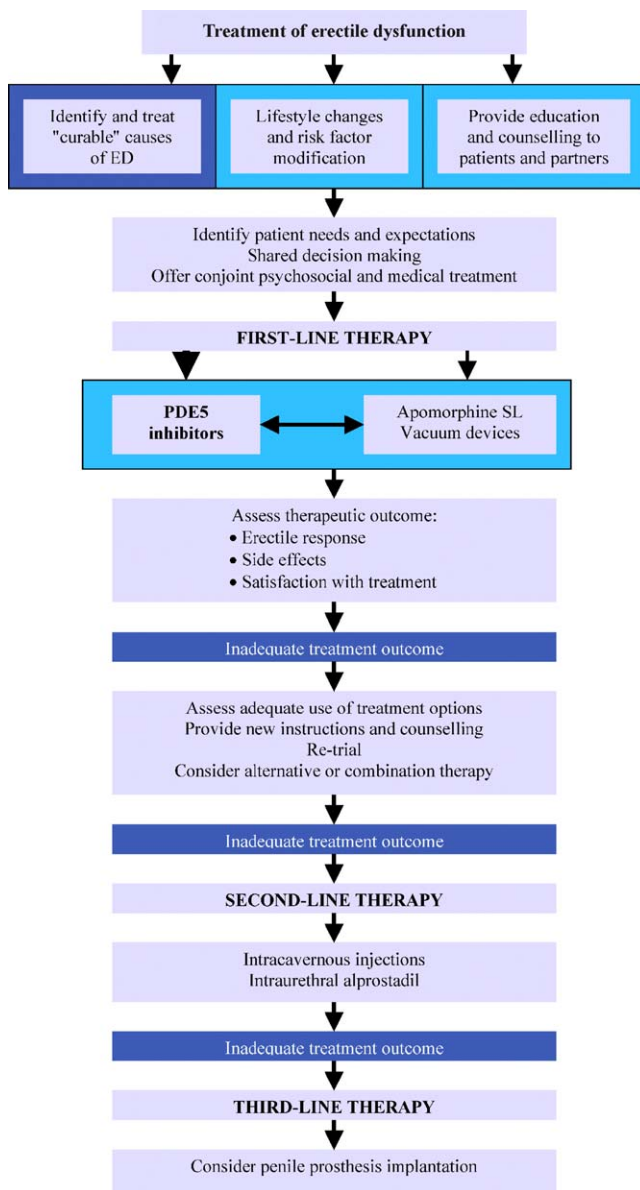


Fig. 2 – Treatment algorithm for erectile dysfunction.

a functional pituitary tumor. Patients with hormone abnormalities need to take the advice of an endocrinologist. Testosterone supplementation (intramuscular, oral, or transdermal) is effective but can only be used when other possible endocrinologic causes for the testicular failure have been excluded. Testosterone supplementation therapy is contraindicated in men with a history of prostate carcinoma. Prior to initiating testosterone supplementation, 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. There is no contraindication of testosterone therapy in men with

coronary artery disease (CAD) with a properly diagnosed hypogonadism or ED. Caution should be exercised regarding the occasional increase in hematocrit, especially in those with congestive heart failure. However, it should be mentioned that this treatment is not always effective in the management of ED associated with hypogonadism [21].

3.3.2. Posttraumatic arteriogenic ED in young patients

In young patients with pelvic or perineal trauma, a surgical penile revascularization procedure is associated with a 60–70% long-term success rate. The lesion must be demonstrated by duplex ultrasound and confirmed by penile phacoarteriography. The presence of corporeal veno-occlusive dysfunction is a contraindication to revascularization [6,22].

Vascular surgery for the treatment of veno-occlusive dysfunction is no longer recommended because of poor results at long-term follow-up [23].

3.3.3. Psychosexual counseling and 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 [24].

3.4. First-line therapy

3.4.1. Oral pharmacotherapy

Phosphodiesterase type 5 (PDE5) is an enzyme that hydrolyzes 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. Three potent selective PDE5 inhibitors are currently licensed with proven efficacy and safety for the treatment of ED.

3.4.1.1. Sildenafil. Sildenafil was the first PDE5 inhibitor and >20 million men have been treated in the 6 yr since its launch (over a 6-yr post-marketing experience). It is effective (erection with rigidity sufficient for vaginal penetration) after 30–60 min from administration [25].

Its efficacy is reduced after a heavy fatty meal (reduced, ie, prolonged absorption). It is administered in doses of 25, 50, and 100 mg. The recommended starting dose is 50 mg and adapted according to the response and side effects. Efficacy may be maintained for up to 12 h [26]. Pharmacokinetic data of sildenafil are presented in Table 3. Adverse events (Table 4) are generally mild in nature and self-limited by continuous use; the drop-out

Table 3 – Summary of the key pharmacokinetic data for the three PDE5 inhibitors

Parameter	Sildenafil 100 mg	Tadalafil 20 mg	Vardenafil 20 mg
C _{max}	560 µg/l	378 µg/l	18.7 µg/l
T _{max}	0.8–1 h	2 h	0.9 h
T _{1/2}	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%

Data based on fasted state, higher recommended dose, and information from the European Medicine Evaluation Association statements on product characteristics.
C_{max} = maximal concentration; T_{max} = time to maximum plasma concentration; T_{1/2} = plasma elimination half-time; AUC = area under curve – serum concentration time curve.

rate due to adverse events is similar to that for placebo.

In pre-marketing studies, after 24 wk 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 sildenafil, respectively, compared with 25% reported by those taking placebo [25]. The efficacy of sildenafil in almost every subgroup of patients with ED is more than established.

3.4.1.2. Tadalafil. Tadalafil is effective from 30 min after administration, but its peak efficacy is expected in about 2 h [27]. Efficacy is maintained for up to 36 h [28]. Its efficacy is not influenced by food. It is administered in 10- and 20-mg doses. The recommended starting dose is 10 mg and is adapted according to the response and side effects. Pharmacokinetic data of tadalafil are presented in Table 3. Adverse events (Table 4) are generally mild in nature and self-limited by continuous use; the drop-out rate due to adverse events is similar to that for placebo.

Table 4 – Common adverse events of the three PDE5 inhibitors

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%	–

Data are from the European Medicine Evaluation Association statements on product characteristics.

In pre-marketing studies, after 12 wk of treatment and in a dose-response study, improved erections were reported by 67% and 81% of the men taking 10 and 20 mg tadalafil compared with 35% in the control placebo group [27]. These results were confirmed in post-marketing studies. Tadalafil also improved erections in difficult to treat subgroups [29].

3.4.1.3. Vardenafil. Vardenafil is effective after 30 min from administration. Its effect is reduced by a heavy fatty meal (>57% in fat). It is administered in 5-, 10-, and 20-mg doses [30]. The recommended starting dose is 10 mg and is 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 [31]. Pharmacokinetic data of vardenafil are presented in Table 3. Adverse events (Table 4) are generally mild in nature and self-limited by continuous use; the drop-out rate due to adverse events is similar to that for placebo.

In pre-marketing studies, after 12 wk of treatment and in a dose-response study, improved erections were reported by 66%, 76%, and 80% of the men taking 5, 10, and 20 mg vardenafil, respectively, compared with 30% by those taking placebo [30]. Efficacy is confirmed in post-marketing studies. Vardenafil also improved erections in difficult to treat subgroups [32].

3.4.1.4. Choice or preference among the different PDE5 inhibitors. In the absence of any controlled studies comparing the efficacy or tolerability among the three drugs it is necessary to discuss with the patient the relative merits of each of them. It is important that the patient be well educated on how to use the drug and that an adequate dose be prescribed. Each drug has to be taken at least four times before it is considered noneffective. The patient will choose the final drug after his own experience.

3.4.1.5. Safety issues for PDE5 inhibitors.

3.4.1.5.1. Cardiovascular safety. Clinical trials and post-marketing data of sildenafil, tadalafil, and vardenafil have demonstrated no increase in myocardial infarction rates in patients who received these agents as part of either double-blind, placebo-controlled trials or open-label studies or compared to expected rates in aged-matched populations of men [33]. Organic nitrates (eg, nitroglycerin, 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 drops in blood pressure and symptoms of hypotension. The duration of interaction between organic nitrates and PDE5 inhibitors is dependent on the PDE5 inhibitor and nitrate under study.

3.4.1.5.2. Antihypertensive drugs. In general, the adverse event profile of the PDE5 inhibitor is not worsened by a background of antihypertensive medicines, even when the patient is taking multiple antihypertensive agents.

3.4.1.5.3. α -Blocker interactions. All PDE5 inhibitors appear to have some interaction with α -blockers, which under some conditions may result in orthostatic hypotension. Since the 31 March 2005 warning, caution in the use of PDE5 inhibitors with α -blocking agents is advised.

3.4.1.5.4. Visual safety. In recent published articles, several reported cases of nonarteritic anterior ischemic optic neuropathy (NAION) have been reported after ingestion of PDE5 inhibitors for erectile dysfunction [34]. NAION is characterized by acute ischemia of the anterior portion of the optic nerve in the absence of provable arteritis. The ischemia may result in infarction of all or a portion of the optic nerve head, and finally visual field defect or in rare cases vision loss.

The onset symptom is sudden painless monocular visual loss that may progress over hours to weeks. It is characterized by early, generalized, or segmental optic disc edema that resolves after weeks to months and optic disc pallor ensues. No effective treatment is available and prevention is limited to the treatment of risk factors mainly aiming at decreasing the risk of a similar event in the fellow eye [35].

Numerous risk factors have been reported for NAION, mainly cardiovascular risk factors, including hypertension, diabetes, cigarette smoking, and hypercholesterolemia [36]. However, the potential relationship between NAION and PDE5 inhibitors is uncertain.

Patients taking or considering taking PDE5 inhibitors should inform their health care professionals if they have ever had severe loss of vision, which might reflect a prior episode of NAION, because such patients are at an increased risk of developing NAION again and they should be referred to the ophthalmologist.

3.4.1.6. Dose adjustments and chronic use. Certain drugs can inhibit the metabolic breakdown of PDE5 inhibitors and, on the other hand, some agents enhance the breakdown of PDE5 inhibitors, requiring higher doses of the PDE5 inhibitors [1]. In

patients with hypogonadism, androgen supplementation improves erectile responses and provokes arterial cavernous dilatation [37]. Chronic use of PDE5 inhibitors seems to improve endothelial function and could be the future treatment for curing the patient [38].

3.4.1.7. Apomorphine sublingual. 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. Apomorphine has been approved for ED treatment in many countries but not in the United States.

Efficacy rates (erections hard enough for intercourse) range from 28.5% to 55% [39]. 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%). 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 [40]. Today, the use of apomorphine is limited to patients with mild to moderate ED or psychogenic causes due to reduced efficacy rates. It also may represent a first-line treatment in patients with certain contraindications (eg, use of nitrates) for the use of PDE5 inhibitors.

3.4.2. Topical pharmacotherapy

Several vasoactive drugs (2% nitroglycerin, 15–20% papaverine gel, and 2% minoxidil solution or gel) have been used for topical application to the penis [41]. Adverse events include skin and glans erythema, burning sensation, allergic reactions, and side effects to the partner (hypotension, headache) due to absorption from the vagina. No topical therapy has been approved and their role in the treatment of ED is currently unknown.

3.4.3. Vacuum constriction devices

Vacuum constriction devices (VCDs) provide passive engorgement of the corpora cavernosa in conjunction with a constrictor ring placed in the root of the penis to retain blood within the corpora. Thus, erections with these devices are not normal because they do not use physiologic erection pathways. Efficacy, in terms of erections satisfactory for intercourse, is as high as 90% regardless of ED etiology and satisfaction rates range between 27% and 94% [42].

3.5. Second-line therapy

3.5.1. Intracavernous injections

Patients not responding to oral drugs may be offered intracavernous injections with high success rates [43]. The erection appears after 5–15 min and lasts according to the dose injected. An office training program is required for the patient or his partner to learn the correct injection process.

Efficacy rates for intracavernous alprostadil of >70% are presented in general ED populations as well as patient subgroups (eg, 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. Complications of intracavernous alprostadil include penile pain (50% of patients, after 11% of injections), prolonged erections (5%), priapism (1%), and fibrosis (2%).

After 6 h of erection, patients are advised to consult the doctor to avoid any damage to the intracavernous muscle, which would provoke permanent impotence. When this problem occurs, the dose is usually reduced for the next injection under blood pressure monitoring.

3.5.2. Intraurethral therapy

Prostaglandin E₁ may be administered intraurethally in the form of a semisolid 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 administered route seems to be less invasive [44]. Side effects include penile pain and hypotension, and the clinical success rate is lower than that achieved with intracavernosal therapy.

3.6. Penile prosthesis

The surgical implantation of a penile prosthesis may be considered in patients in whom pharmacotherapy fails or for those who prefer a permanent solution to their problem [45]. Two types of prosthesis exist: malleable (semirigid) and inflatable (two- or three-piece). Most patients prefer the three-piece inflatable devices due to the more “natural” erections.

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

The two main complications of penile prosthesis implantation are mechanical failures and infection. Although diabetes is considered as one of the main risk factors for infection, current data do not support this fact. Infections as well as erosion in

patients with spinal cord injuries are significantly higher (9%). Infection requires removal of the prosthesis, antibiotic administration, and reimplantation after 6–12 mo. However, a salvage therapy with removal and reimplantation at the same time after copious irrigation of the corpora with multidrug solutions is associated with 82% success rates.

4. Conclusion

A great deal of progress has been made in the pharmacologic treatment of ED. Today the worldwide availability of the three PDE5 inhibitors for oral use associated with high efficacy and safety rates even in difficult to treat populations (eg, diabetes mellitus, radical prostatectomy) has revolutionized ED treatment. 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. Treatment options for patients not responding to oral drugs (or contraindicated) include intracavernous injections, intraurethral alprostadil, VCDs, and implantation of penile prosthesis.

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