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A review on pharmacological options for the treatment of erectile dysfunction: state of the art and new strategies

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Abstract

Introduction: Erectile dysfunction (ED) affects between 12.9% and 28.1% of men worldwide, presenting a strong aged-correlated prevalence. Several pharmacological treatments are currently available for ED which can be classified into oral, injection and topical/intraurehtral therapy.

Areas covered: An extensive research on PubMed/MEDLINE until February 2023 was performed. For each of the aforementioned drug-classes, available molecules and formulations, their efficacy and most common adverse events as well as general guidelines on prescription were investigated and extensively described. A glimpse into future directions regarding ED pharmacotherapy is also present.

Expert opinion: In recent years, there have been significant developments in pharmacological treatments for ED. It's essential for physicians to identify the best treatment option for patients based on their preferences and sexual habits. The treatment approach for ED has shifted from a sequential to a parallel paradigm, where all treatment options are available as first-line therapies. While there are promising regenerative therapies for ED, such as shockwaves and platelet-rich plasma injections, pharmacological treatment is still the most effective option for most patients.

Keywords: erectile dysfunction, pharmacotherapy, PDE5 inhibitors, prostaglandin, intracavernous injections

Article highlights

- Current pharmacological strategies to the treatment of erectile dysfunction (ED) are based on three classes of drugs: oral, injections and intrauretral/topical therapy.
- Four oral inhibitors of PDE5 (PDE5Is) are currently available. Whereas no differences in terms of efficacy have been found, higher PDE5-selectivity is correlated with less systemic side effects.
- To date, only alprostadil is approved for intraurethral/topical therapy. This formulation permits the desired erection avoiding the most common systemic effects of oral PDE5Is.
- Intracavernous injections (ICIs) consists of prostaglandin E1 (alprostadil), which can also be used in different "mixtures" containing papaverine, phentolamine and atropine in order to reduce the risk of priapism and penile fibrosis.
- Oral, intracarnosal and intraurethral/topical therapy may be used simultaneously in patients non-responders to monotherapy.
- Emerging pharmacological approaches consists of soluble guanylate cyclase (sGC) stimulators and activators, maxi-potassium channel activators, NO donors, melanocortin agonist, botulinum toxin and topical PDE5Is.
- As most recent guidelines suggest, the therapeutic choice should rely on patient's characteristics and comorbidities as well as specific needs.

1. Introduction

Erectile dysfunction (ED) is a common and vexing clinical problem that leads to the substantial disruption of quality of life and relationships [1]. Although the true prevalence of this condition is difficult to evaluate, most studies report an estimated prevalence ranging from 12.9% to 28.1% [2], depending on the definition used for of ED and the median age of the study-cohort. As the world population ages, the prevalence of ED, which has shown a steep correlation with age [3], will also be likely to feature an upward trend.

Erectile dysfunction is defined as the persistent (at least 6 months) inability to achieve and maintain penile erection sufficient to allow a satisfactory sexual performance [4,5]. It is classified as organic or psychogenic according to the underlying aetiology [5,6]; organic causes of ED include hormonal dysregulations, vasculogenic and neurological impairments [5]

Despite centuries of interest in ED, it is only within the past 40 years that demonstrably and consistently effective pharmacologic treatments have been available for this common disease [7]. However, understanding the pharmacology of ED treatment requires some knowledge of the molecular mechanisms that regulate erectile function (EF) [7].

During sexual stimulation, nerve impulses release neurotransmitters from cavernous nerve terminals and relaxing factors from the endothelial cells, resulting in the relaxation of vascular smooth muscle at the level of the corpora cavernosa and an increase of blood flow to the penis [8]. In particular, the sacral parasympathetic divisions (S2-S4) regulate penile tumescence, and inputs of the thoracolumbar sympathetic divisions (T11-L2) mediate penile detumescence [9].

The nitric oxide (NO) pathway has emerged as a fundamental and essential element of penile vasodilation; upon sexual stimulation, the cavernous nerves release directly nitric oxide (NO) and acetylcholine, generating a more sustained release of NO [10]. Nitric oxide activates soluble guanylate cyclase, an enzyme that catalyzes the conversion of Guanosine Triphosphate (GTP) to cyclic Guanosine Monophosphate (cGMP). The increased levels of cGMP plays a critical role in the activation of Protein Kinase G (PKG) [7], thus leading to cytosolic free calcium depletion. As a consequence of free cytosolic Calcium drop in smooth muscle cells of penile arteries and corporal erectile tissue, the actin–myosin cross-bridge formation occurs, leading to muscular relaxation and subsequent vasodilation. With vasodilation, penile blood flow increases, and the corporal bodies become engorged with blood [7].

The cessation of the sexual arousal causes NO production decrease and the consequent cGMP intracellular levels reduction, leading to corporal vasodilatation interruption. The activation of mainly type 5 phosphodiesterase (PDE5) as well as type 6 and 9 phosphodiesterase (PDE6, PDE9) [7], that is responsible for hydrolysing cGMP, causes a further reduction of cGMP level.

Since ED and CVD share common risk factors, some lifestyle adjustments, such as weight loss, sodium dietary restriction, physical activity, moderate alcohol consumption and smoking cessation, are usually recommended. Despite the well-known correlation between ED and cardiovascular disease (CVD), current strategies to ED treatment for most men are based on pharmacotherapy [11]. The pharmacological options for ED may be classified in three main categories: oral pharmacotherapy, intracavernosal injection therapy and topical therapy; all currently available and effective drugs act peripherally within the penis.

We here report a comprehensive narrative review of the published literature regarding the pharmacological armamentarium for ED, focusing on the available drugs and formulations, their efficacy, common adverse events and indications, as well as emerging therapies and new biochemical targets.

2. Oral PDE5 inhibitors

Inhibitors of PDE5 (PDE5Is) endorsed a revolution in ED treatment, improving the quality of life of many patients and they are still considered the mainstay of oral pharmacotherapy for ED. Selective inhibitors of PDE5 are potent facilitators for penile erection that primarily promote the erection maintenance rather than its attainment, by prolonging the vasodilatory effects of cGMP in the penis. Reliance on initial NO activity for efficacy also makes clear how these agents are less effective in men with neurogenic etiologies for ED (eg, postpelvic surgery, severe diabetes) [12], because these drugs are not able to induce an erogenous stimulus [13]. The erection, in fact, occurs only in presence of a sexual stimulation and adequate NO production [11].

There are currently seven available PDE5Is world-wide: sildenafil, vardenafil, tadalafil, avanafil, udenafil, mirodenafil, lodenafil carbonate. However, only the first four have been approved by FDA and EMA (**Table 1**). All of these drugs have proven efficacy. There are only limited published data, mainly industry-sponsored, comparing the advantages of one drug over the others, without a clear and ultimate evidence regarding the superiority of a specific molecule [14]. In clinical practice, the choice of a specific PDE5I is ultimately based on patients' preferences and profile [5].

Physicians should inform patients about different molecules' therapeutic effect duration and their disadvantages (**Table 1**) [5], and carefully assess patient sexual profile [11]. A close follow-up must be taken into account, in order to identify any issues related to treatment [15]. Nevertheless, this strategy aims to improve patients' compliance and satisfaction; indeed, up to 50% of patients prescribed with PDE5Is stop treatment due to issues such as costs, inadequate efficacy or adverse events [16–18].

2.1. Comparative efficacy

A meta-analysis including more than 31.000 patients in which the efficacy of different PDE5Is was compared, showed that all the compounds endorse a mean improvement ranging from 5.6 to 7.4 points in the International Index of Erectile Function (IIEF)-EF domain score, which is significantly higher as compared to placebo [14]. In this study, tadalafil reported only a small advantage in terms of efficacy in comparison to other drugs, even if with low grade of evidence. A more recent meta-analysis, that included two groups of 47.626 and 20.325 patients in order to provide a comprehensive evaluation of efficacy and safety, respectively, confirmed the well-known higher efficacy of PDE5Is compared to placebo, suggesting higher efficacy for sildenafil 50 mg and higher tolerability for tadalafil 10 mg[19]. Of note, in another clinical trial, tadalafil 5 mg once daily intake resulted to improve EF among men who have a partial response to on-demand PDE5I therapy [20].

Although many differences in terms of chemical structure, dosages, formulations and pharmacokinetic profiles can be identified among PDE5Is, there is no strong evidence supporting the superiority of one molecule toward the other [5]. Despite the wide use of the available PDE5Is, in fact, there are no randomized multicenter studies comparing the efficacy for different molecules. In conclusion, the choice of drugs is mainly based on frequency of intercourse (occasional use or regular therapy) and patient's personal experience [5,11].

2.2. Common adverse effects

Over the past two decades, PDE5Is have accrued a very favorable safety profile [21]. The principal class-specific medical contraindication is the use of concomitant daily dose nitrate therapy (eg, nitroglycrine, isosorbide mononitrate and isosorbide dinidtrate) or other nitric oxide donors drugs, as the combination of these compounds and PDE5Is may lead to a sustained vasodilatation, causing a precipitous and dangerous drop in blood pressure [5,22]. Moreover, following the Princeton III Consensus Recommendations, patients with high cardiovascular risk associated with sexual activity, namely men with unstable or refractory angina pectoris, uncontrolled hypertension, congestive heart failure (NYHA class IV), recent MI without intervention (<2 weeks), high-risk arrhythmia, obstructive hypertrophic cardiomyopathy with severe symptoms, and moderate to severe valve disease (particularly aortic stenosis), should be referred to a cardiologist and any ED therapy deferred until the cardiac condition has been stabilized [23].

As PDE5Is are degraded by cytochrome P450 CYP3A4, patients taking cytochrome CYP3A4 inhibitors, such as antifungals (e.g., ketoconazole, itraconazole), macrolides and HIV protease inhibitors (e.g., ritonavir), may need lower doses of PDE5I [24].

PDE5 inhibitors have different biochemical selectivity, that is the key factor in determining its side effects profile [25]. Phosphodiesterase, in fact, consist of at least 11 subtypes of enzymes implicated in various cellular functions [26]. The ideal PDE inhibitor should be able to inhibit only PDE5. However, such a compound does not exist, and this explains the onset of adverse reactions, which are attributable to the inhibition of the other isoforms of PDE in tissues outside the penis [1,11]. Common adverse reactions associated with PDE5Is include headaches (12% – 15%), flushing (4% – 14%), indigestion (<1% – 10%), stuffy nose /congestion (4% – 10%), vision disturbances (0% – 5%), and myalgias (rare 4%).

More serious and rare side effects include angina, sudden decrease or loss of vision, serious skin reactions, and seizures [27]. The administration of PDE5Is in patients affected by diabetes, hypertension and dyslipidemia may be associated with non-arteritic anterior ischemic optic neuropathy, without a well-established causal relationship [9]. The incidence of priapism with the use of PDE5Is, while frequently mentioned in advertising, seems to be lower than for some other common medications that are not explicitly given with the intention of inducing erections (eg, trazodone, second generation antipsychotics) [28]. Patients should be counseled on this potential but may be reassured that the likelihood of prolonged erection is low.

2.3. Sildenafil

Sildenafil is the first PDE5I approved (1998) for the treatment of ED and it was originally synthesized as an effective drug for angina. This agent binds the core of the catalytic domain of PDE5 reducing the hydrolyzation of cGMP and allowing a more sustained corporal vasodilation [29].

Administered orally, at doses of 25, 50, or 100 mg, sildenafil is rapidly absorbed with a half-life of 3 to 5 hours; it reaches the maximum plasma concentrations after 60 minutes, when the onset of action typically occurs [30]. It is advised to take sildenafil without meal at least 30 minutes before sexual intercourse. Recently, a new oro-dispersible formulation (at doses of 25, 50 and 75 mg) has been introduced in several countries [11]. It is metabolized by the liver, mainly by the cytochrome isoenzymes CYP3A4 (primary route) and CYP2C9 (secondary route), to an active metabolite; avoiding the association with strong inhibitors of these cytochromes (e.g., ritonavir, erythromycin, ketoconazole) is fundamental [31]. The administration of sildenafil should be avoided in case of severe cardiovascular disorders. It is also strictly contraindicated in the following conditions: hypotension (Blood pressure < 90/50 mmHg), severe hepatic impairment, retinitis pigmentosa, recent myocardial infarction or stroke.

2.4. *Vardenafil*

Vardenafil, approved by FDA in 2003, is a structural modification of the parent molecule sildenafil, with similar pharmacokinetic and molecular action. Administered orally, at dosages of 5 to 20 mg, induces an erection within 30 minutes of oral dosing in fifty percent of users [32]. It is advised to take vardenafil without meal at least 30 minutes before sexual intercourse. This agent is also available in a sublingually administered 10 mg formulation [7]. It has been demonstrated that vardenafil has beneficial effects, with a good profile of tolerability and safety, in men with premature ejaculation [33].

The dosing should be adjusted to lower concentration in case of concomitant assumption of inhibitors of CYP3A4, by which vardenafil is predominantly metabolized [7]. Similarly, to sildenafil, vardenafil should be taken without meal, as its absorption is slowed by dietary lipid intake. The administration of vardenafil should be avoided in patients with congenital QT syndrome and patient using Type IA or III antiarrhythmics [34]. Hemodialysis and severe hepatic failure represent absolute contraindications against vardenafil assumption.

2.5. *Tadalafil*

Tadalafil came on the market in 2003, after FDA Approval. Because of its particular rigid chemical structure, it has a highly selective action on PDE5, leading to a lower risk of adverse events related to cross-binging of other PDE isoforms in other tissues, such as the cardiovascular system or the liver [7,9,35]. Tadalafil is typically administered orally, at doses of 5 to 20 mg on-demand or 2.5 to 5 mg daily, reaching its therapeutic within 30 minutes following administration, with peak efficacy after two hours [7].

Tadalafil is the only PDE5I approved with a daily dosing, thus representing the ideal treatment for patients who desire to avoid scheduling sexual intercourse and regaining spontaneity which could be a concern when using on demand PDE5Is [36–38]. Unlike sildenafil and vardenafil, it has a long half-time of 17.5 hours with a maintained efficacy up to 36 hours and its absorption [39]. When used on demand, it is advised to take tadalafil 10-20 mg at least 1 hour before intercourse.

Tadalafil daily has been also approved for the treatment of lower urinary tract symptoms, associated with benign prostatic hyperplasia [40]. Like other PDEIs, tadalafil in metabolized by the cytochrome CYP3A4 [39].

2.6. *Avanafil*

Avanafil is one of the most recently developed PDE5I, approved for the treatment of ED in 2012 at dosages of 50, 100 or 200 mg [41]. Administered orally, this agent reaches the maximum plasma

concentration 30-45 minutes within of oral administration, after a rapid absorption from the gastrointestinal tract [9] with a half-life of approximately 6 hours. Therefore, it is recommended to take avanafil on-demand about 30 minutes before intercourses. Avanafil produces a potent inhibition of PDE5 (IC50 5.2 mmol/L) with high enzyme-subtype selectivity compared to other PDE5Is, thus resulting in lower rate of visual disturbances, myalgia, lower back pain, tachycardia, and flushing [42]. Even at the highest dose, this drug has shown great tolerability with mild adverse effects, making it a good choice for proper on-demand patient-treatment [42]. Unfortunately, as data regarding the use of avanafil in patients with severe hepatic (Child-Pugh class C) or renal impairment (estimated creatinine clearance < 30 mL/min) are lacking, it is not recommended in these particular populations [43].

3. Intraurethral therapy

Among different treatment protocols available for ED (from traditional medicine to surgery), intraurethral treatment may be considered a desirable choice in facing the most frequent patients' complaints about ED pharmacotherapy, such as drug interactions, treatment inefficiency, multiple contraindications, undesirable side effects or treatment intrusiveness [40,41].

Several compounds such as alprostadil [44], testosterone [45], papaverine [46] and PDE5Is, including sildenafil and tadalafil, have been evaluated for topical treatment, although only the first one has entered clinical practice.

3.1. Intraurethral prostaglandin E-1 (alprostadil)

The vasoactive agent alprostadil can be administered per urethra with two different formulations: intraurethral (IU) injection or topical application.

Intraurethral alprostadil, introduced in 1994 and commercially promoted as MUSE (Medicated Urethral System for Erection), is a treatment option for men for whom PDE5Is are contraindicated, for men or partners who prefer to avoid oral medication, and/or for men or partners who prefer not to use the needles required for intracavernous injections (ICIs) [47,48]. According to a randomized clinical trial [49], direct delivery of the drug within the urethral meatus guarantees an adequate treatment efficacy and confidence among patients, without increasing the incidence of side effects. The application of alprostadil is performed by using a small catheter passed into urethral meatus, depositing a single dose of alprostadil into the urethral mucosa; the drug transfuses into the corpora cavernosa to elicit pharmacotherapeutic effect [11]. Among the four concentrations (125, 250, 500 and 1000 μg) evaluated in dose-escalation studies, the 500 micrograms concentration was identified as the adequate dose for satisfactory erectile response in most cases [47,50,51], with the onset of

action within 30 to 60 minutes. Although IU alprostadil has not proved to be as effective as intracavernosal injection of alprostadil [52], the effective dose of PGE-1 endorses a significantly higher number of successful intercourses at home (the main outcome measurement) compared with placebo [47,50]. Despite the currently limited clinical role, intraurethral PGE-1 application might be successfully recommended to non-responders to PDE5Is as a combination therapy (IU alprostadil plus PDE5Is) [11]. Several local side effects, such as local pain, burning sensation or minor urethral bleeding have been frequently reported. Less frequent systemic side effects consist of hypotensive spells (up to 5%), potentially associated with blurred vision, confusion, dizziness, sweating, and fatigue, or an occasional syncope (1 – 3%) [53]. MUSE should be used with caution in patients with acute/chronic urethritis, known urethral strictures, balanitis, severe hypospadias and curvature [7]. A vaginal intercourse with a pregnant partner unless a condom represents an absolute contraindication to IU alprostadil application, because of the possible transfer of prostaglandin and subsequent induction of labor [7].

Alprostadil cream was proposed in the previous decade as non-invasive treatment option; the combination of alprostadil, at dosages of 200 to 300 μg, with a cutaneous permeation enhancer, in fact, allows to increase local absorption of the agent from the site of application [54]. Topical administration of alprostadil in the penis meatus before intercourse has been evaluated in terms of safety and efficacy with promising outcomes in a Multicenter, open-label, long-term study in more than one thousand patients with ED [55]. In successful phase II and phase III, a satisfactory erectile response was recorded by 74% to 83% of patients, associated with a rapid onset of pharmacological action; the application of alprostadil cream endorses penis full rigidity attainment in approximately 10 to 12 minutes, with an average duration of 60 minutes [55,56]. The novel formulation (Vitaros), that consists of 300 micrograms of alprostadil and 2.5% of w/w dodecyl-2-n,n-dimethylaminopropionate hydrochloride (a chemical enhancer), has shown such promising results that Canada and Europe has approved it for clinical use [57,58]. Although the probability of systemic side effects is very low, thanks to the elevated rate of drug absorption (98%) from the fossa navicularis, several local adverse events have been reported: burning sensation and erythema (12.2%), pain and tenderness (4.4%), prolonged erections (1.3%), and erections lasting at least 4 hours (0.4%) [56]. Rare systemic adverse reactions consist of occasional dizziness or fainting and, in female partners, vaginal burning or itching. Couples planning for pregnancy and penis abnormalities represent contraindications to topical alprostadil.

Although evidence-based data indicate that PDE5Is and IC alprostadil are more effective, topical cream could represent a suitable alternative to other treatment options or as a combination therapy, because of the convenience of its application [11].

4. Intracavernosal therapy

4.1. Intracavernosal prostaglandins

Prostaglandin E1 (PGE1, also known as alprostadil), is the first and only drug approved for intracavernous (IC) injection for the management of ED (**Table 2**) [59]. As other intracavernosal agents, its mechanism of action does not rely on an intact nerve supply. Therefore, whenever penile vascularization is preserved, an erection could occur. After binding with G-protein-coupled receptors (mainly EP2 and EP4), PGE1 induces relaxation of smooth muscle in the corpora cavernosa and subsequent vasodilatation by increasing cyclic adenosine monophosphate (cAMP) synthesis [8]. In addition, PGE1 causes an α-adrenoceptor-mediated inhibition of noradrenaline release, reinforcing vasodilatation and inducing veno-occlusion [60]. The erection generally appears after 5 – 15 minutes and lasts according to the dose injected, but with substantial discrepancy among patients [55].

IC alprostadil, at a therapeutic dose ranging between 1 and 40 μg, has been demonstrated to be safe and effective, obtaining sexual satisfaction in more than 70% of cases and a significant increase in rigidity scores in 90% of ED patients [61–63]. In some cases, escalation of the dose up to 60 μg is still well tolerated [11]. In a comparative study, alprostadil monotherapy had also the lowest discontinuation rate (27.5%) compared to overall drug combinations (37.6%) [63]. No differences in terms of efficacy have been found between "slow" or "bolus" injection of the drug [64].

Self-administration of alprostadil is generally safe, with penile hematoma and local pain reported in 33.3% and 11.7% of the patients, respectively [62,65]. Pain gradually decreases after prolonged use and could be relieved with add-on sodium bicarbonate or local anaesthesia [53,66]. Penile fibrosis presenting with corporal nodule/plaques (0.8%) and priapism (0.36%) are the two most serious adverse events described in IC alprostadil users, although being more common with the use of combination therapy [67]. Fibrotic changes caused by alprostadil alfadex and alprostadil sterile powder showed a spontaneous healing in the 33-47% of the cases [62,65].

Although being introduced as the first available therapy for ED in the 1980s [68], as of today IC injections of PGE1 represent a second-line treatment in those patients with contraindications, intolerability, or poor-response to PDE5Is or during early rehabilitation after prostatectomy [1,5,11]. Contraindications include men with a history of hypersensitivity to alprostadil, men at risk of priapism, and men with bleeding disorders [5]. Since self-administration has proved to be affected by a higher incidence of fibrosis [69], an office-training program for men or their partners when limited manual dexterity is present, and the use of automatic injection pens, could improve efficacy and reduce treatment dropouts [1,5,70].

4.2. *Intracavernosal "combination" therapies*

Various IC drugs have been tested as an alternative to alprostadil. Papaverine, an enzylisoquinoline alkaloid obtained from the opium poppy (*Papaver somniferum*), promotes relaxation of smooth muscle in the sinusoids of corpora cavernosa and dilatation of helicine arterioles through a non-selective PDE5 inhibition that results in increased intracellular cAMP and decreased intracellular calcium concentrations [71,72]. Papaverine-induced erections may require a long time to reverse, frequently resulting in priapism (6 – 7%) [60,73]. For this reason and the elevated risk of penile fibrosis/curvature in prolonged usage (5.7 – 11%) [74], papaverine monotherapy is not recommended [11].

To prevent untoward events, lower concentrations of papaverine are combined with other vasoactive drugs that are not able to promote erection alone, obtaining a strategic therapeutic synergy of both safety and efficacy, hence the definition of "combination therapy". Most common combination formulations include papaverine + phentolamine, referred as "Bimix" and papaverine + phentolamine + alprostadil, also known as "Trimix". Furthermore, atropine may be added to the latter three molecules to form "Quadmix" (**Table 2**) [11].

Phentolamine is a non-selective α-adrenergic antagonist that decreases arterial resistance and promotes vasodilatation by inhibiting smooth muscle cells contraction [75]. The commercial preparation of Bimix, approved for clinical use in some European countries, contains papaverine hydrochloride (15 mg/mL) and phentolamine mesylate (0.5 mg/mL) in 2-mL vials [76]. The combination of these two drugs has shown the same efficacy and equal rate of prolonged erection compared to PGE1 30 μg alone, whereas it caused significantly less injection pain (15% vs 35%, $p<0.05$) [77]. The addition of alprostadil (Trimix) provides the highest efficacy rates, reaching up to 92% [78,79]. This three-drug combination has similar adverse effects as alprostadil monotherapy, although fibrosis is more common when higher dose of papaverine is used (5 – 10%) [78] . Noteworthy, hypotension could potentially occur with higher concentration of the compounds [53]. In a randomized clinical trial, the combination of papaverine 17.64 mg + phentolamine 0.58 mg + PGE1 5.8 μg had a two-fold efficacy rate compared to PGE1 40 μg monotherapy (50% vs 22%), with very low pain (12.5% vs 22%) due to the reduced dose of alprostadil being used [80]. Therefore, Trimix could be a suitable option for patients who underwent radical pelvic surgery as pain or tenderness after PGE1 is accentuated by an underlying cavernous nerve injury [53,63]. Unfortunately, no commercially marketed preparation for Trimix is available, due to the low stability of the combined agents.

The added value of atropine is expressed by its anti-cholinergic effect on the corpora cavernosa, enhancing the activity of the non-adrenergic, non-cholinergic and endothelium-derived relaxing factor pathways in the erection mechanism [81]. In a clinical study including 60 diabetic patients with pure neurogenic, pure vasculogenic or mixed ED, a "full" dose mixture of papaverine hydrochloride 12.1 mg/mL, phentolamine mesylate 1.01 mg/mL, PGE1 10.1 μg/mL and atropine sulphate 0.15 mg/mL has proven to be effective in 80% of the patients at 18-month follow-up, with minimal unfavorable effects. Moreover, a "reduced" dose of the same mixture corresponding to one-third of the original concentrations was effectively used by 10% of the patients [71]. However, in another randomized clinical trial, the addition of atropine sulfate did not improve subjective and objective erectile response when combined with 50 mg papaverine hydrochloride, PGE1 10 μg, and phentolamine mesylate 0.2 mg [82]. Ultimately, patients' subjective preference, tolerability and satisfaction with the sexual outcome will be the prevalent deciding factor in choosing which multi-drug formulation to use [11].

In addition to that, an alternative combination therapy may comprise of intracavernosal injection of aviptadil, a synthetic vasoactive intestinal polypeptide (VIP), and phentolamine [83]. VIP increases the activity of adenosine cyclase, leading to smooth muscle relaxation with subsequent filling of cavernosal sinuses and causing erection through a phentolamine-complementary mechanism [84]. A prepared mixture of aviptadil 25 μg plus phentolamine mesylate 1-2 mg has been clinically tested and approved in Denmark, the United Kingdom and New Zealand. This combination is different from other ICIs as it only facilitates an erection rather than producing full rigidity on its own, meaning that a patient still needs physical or visual stimulation in order to gain a full effect [85]. Clinical research has established that treatment outcomes achieved with the injection of aviptadil/phentolamine remain consistent when compared to placebo over a 6- and 12-month follow-up, with a 74% rate of grade 3 erections [86,87]. Moreover, a favorable side-effect profile was reported, as the incidence of priapism, pain and fibrosis was 0.06, 0.5 and 0%, respectively. As aviptadil/phentolamine has been proved effective also as mono-therapy in unresponsive patients, with efficacy rates of 67 – 73% [88], this combination therapy could be proposed to those who had unsuccessful results from other ICIs [5].

5. Association of oral and intracavernosal, intraurethral or topical pharmacotherapy

Combination of an oral PDE5I with an ICI (generally alprostadil) has been considered as a second-line therapeutic approach in patients non-responders to monotherapy. When combined, the effects of PDE5Is and PGE1, acting through the NO-cGMP pathway and the cAMP pathway, respectively, are synergic and complementary, producing a more intense relaxation of corpora cavernosa smooth

muscle [8]. Indeed, compared to ICI alone, the association of sildenafil and alprostadil or Trimix has shown increased response in men who had failed previous IC therapy [89]. In patient with ED after nerve-sparing radical prostatectomy (NS-RP), the addition of an IC agent to oral therapy with PDE5I showed an improvement of erections in 68% of men as assessed with the SHIM score [90]. Moreover, when combination therapy is used in a "rehabilitation" program after RP, the return of spontaneous erection may be successfully achieved with less penile discomfort, due to the lower dose of IC injections [90]. Despite these promising results, the concurrent use of PDE5Is and ICIs has raised safety worries. Reported adverse events are more common when combination therapy is used (49% vs 31 – 37%), namely penile pain, headache, facial flushing, nasal congestion, dizziness and syncope [89]. Three cases of priapism were also reported with concurrent use of PDE5I drugs and ICIs, thus it is important for patients to know that when taking these medications together or in a specific sequence over a certain period of time, they can expect this adverse effect [91].

Intraurethral alprostadil has also been used in association with PDE5Is, resulting in improved erections. In 214 patients dissatisfied with the results of oral or intraurethral therapy alone, the IIEF-5 scores were significantly greater after treatment with the combination therapy as compared with either single therapy [92]. Similarly, sildenafil plus intraurethral alprostadil combination resulted in a 100% rate of erections sufficient for vaginal penetration among 28 men who had failed monotherapy [93]. In addition to that, also patients with ED following NS-RP had improvements in IIEF-5 scores, rigidity and spousal satisfaction with combination therapy compared to sildenafil alone [94]. Common adverse effects are urethral burning and urethral bleeding, although they are unlikely to cause discontinuation, whereas no cases of priapism were reported [92–94]. Overall, this particular combination therapy is well tolerated.

The association of PDE5Is and alprostadil cream has also been considered. This combination has been evaluated in an open-label protocol including 68 patients with an incomplete response to PDE5Is monotherapy [95]. An oral PDE5I of choice taken 1 h before intercourse plus 300 μg of topical alprostadil applied 30 min before intercourse resulted in a 72% response rate. Overall, 29% of patients experienced an adverse event, especially penile burning or pain (24%), though they were of short duration, and none caused discontinuation of therapy.

In conclusion, oral plus IC or intraurethral or topical combination therapy is currently considered off-label and should be undertaken with caution and meticulous selection of patients.

6. Hormonal treatment

Testosterone deficiency is associates with ED, low sexual desire and dissatisfaction derived from overall sexual life [5]. Total testosterone plays a pivotal role in how the penis responds to sexual

stimulation and maintains libido. Indeed, testosterone replacement therapy leads to EF improvement in hypogonadal men [96,97]. Therefore, testosterone supplementation (intramuscular or transdermal) is considered a valid option in men presenting ED with low testosterone levels [5,98]. Moreover, the combination of testosterone with other pharmacological treatments for ED has been associated with better results in terms of EF improvement [1].

7. Emerging pharmacological approaches

7.1. Soluble guanylate cyclase (sGC) stimulators and activators: BAY 60-4552

In case of poor response to PDE5is, direct stimulation of sGC may represent an alternative therapeutic approach. BAY 60-4552 is a heme-dependent stimulator which has shown promising results in preclinical studies. Safety and efficacy of the combination of BAY 60-452 (1 mg) and vardenafil (10 mg) versus vardenafil (20 mg) have been evaluated in a phase II study; the combination therapy has proved to be effective compared to placebo, but not superior to vardenafil alone [99].

7.2. Maxi-potassium channel activators

Potassium channel contribution to penile erection is a well-known concept [100]. Andolast is the only maxi-potassium channel activating drug in clinical development for the treatment of rhinitis, asthma and chronic obstructive pulmonary disease [101]. The effect of a single-dose corpus cavernosum injection of naked DNA sequence of the alpha-unit of maxi-potassium channel in 11 patients affected by moderate-severe ED has recently been evaluated in a phase I trial. Although no data about efficacy can be drawn from these early results, because of the lack of a control group, the maxi-potassium channel activator has proved primary safety outcomes and preliminary evidence of effectiveness. Among future therapeutic options for ED, maxi-potassium gene transfer can be considered a viable approach, even though further studies are needed for an adequate investigation of its efficacy [102].

7.3. NO donors

The on-demand administration of 0.2% glyceryl trinitrate topical gel (MED2005) has recently been evaluated. Modification of IIEF score was considered the primary outcome; after MED2005 treatment, 23.1% of patients showed a clinically relevant increase in IIEF-EF scores (> 3 points) compared to 14.5% of patients treated with placebo [103]. Topical glyceryl trinitrate, therefore, can represent a valid treatment option in mild ED, but further studies are needed for an accurate assessment of clinical significance in case of patients affected by moderate and severe ED.

7.4. *Melanocortin agonist*

The contribution of the melanocortin system to sexual function is well known and pro-erectile functions of spinal melanocortin receptors, such as MC4R, have been proposed in multiple studies [104,105]. Indeed, intrathecal injection of melanocortin agonist (i.e. MT-II) to male rats' lumbar spinal cord increases spontaneous erections [106]. Differently from "peripherical" molecular pathways targeted by conventional drugs, MT-II manipulation of melanocortinergic receptors elicits a centrally-mediated erection by modulating the sympathetic efferent nerves to the pelvis, with little effect on the parasympathetics [107]. In a double-blind placebo-controlled study, MT-II peptide (0.025 mg/Kg) subcutaneous injection to 20 patients affected by psychogenic and organic ED was able to elicit significant erection in 17/20 men without video sex stimulation. Therefore, contrary to PDE5Is, MT-II agonist seems to induce spontaneous erection in absence of sexual stimulation [108]. Further clinical studies led to the development of PT-141, a cyclic heptapeptide melanocortin analog with improved tolerability, a more rapid onset of action compared to MT-II, and equal efficacy. In the phase IIA study, PT-141 intranasal administration induced a clinically significant erectile response compared to placebo [109,110]. Finally, in a pilot study the administration of a selective melanocortin-4 receptor agonist displayed a similar number of clinical responses to sildenafil [111]. Despite these preliminary promising results, which indicate melanocortin system as a novel target for ED treatment, further studies are needed.

7.5. *Botulinum toxin*

Botulinum neurotoxin (BoNT), produced by *Clostridium botulinum*, is one of the most potent toxins to humans. Among the seven distinct biochemical forms, BoNT-A is the most commonly used form in medicine. Recently, BoNT-A administration within corpora cavernosa has been evaluated as a pro-erectile agent, given its muscle relaxing action and the ability to reduce the sympathetic tone. To date, a phase I RCT of 24 patients and a phase II RCT of 160 patients who were non-responders to other pharmacotherapy options, are the only two human studies available [112,113]. The BoNT-A administration has shown promising efficacy, evaluated in terms of penile henodynamic parameters, Erection Hardness Score (EHS), SHIM and Sexual Encounter Profile questions 2 and 3 [114]. As a consequence of the fact that BoNT-A treatment seems to improve vascular parameters and SHIM scores, it could be a promising therapy for patients who are non-responders to PDE5Is and/or IC therapies.

7.6. *Topical PDE5 inhibitors*

Topical application of PDE5Is can avoid the issue of systemic absorption, minimizing interactions and contraindications even in case of patients affected by cardiovascular diseases, renal or hepatic impairment. PDE5 formulations used in treatment of ED include sildenafil gel [115], tadalafil gel [116], sildenafil cream [117] and tadalafil cream [118]. Although there is no approved topical medication in USA/Europe for ED, many studies have been performed on topical sildenafil, showing good penetration and few side effects [119–122]. Despite the lower success rate in inducing erection than oral formulations (35% vs 70%), sildenafil gel has advantages such as fewer side effects, shorter onset time, and sustainable outcomes for more extended periods [123].

Along with sildenafil, tadalafil is one of the most studied PDE5Is as topical drug, as it faces serious problems of low dissolution and poor absorption through biological membranes [24,116]. However, further studies about transdermal delivery of tadalafil are required to verify its effectiveness [124].

8. Conclusion

The pharmacological armamentarium of ED counts numerous approved drugs, that can be also combined to achieve maximum efficacy. In order to reduce common side effects present efforts are focused on finding different pathways of administration. Moreover, new molecules and new classes are being studied and evaluated in terms of efficacy and safety. Finally, the therapeutic choice should rely on patient's characteristics and comorbidities as well as specific needs.

9. Expert opinion

In the last three decades several pharmacological options have been developed for the treatment of ED with a significant improvement of patients' care. As we have summarized in this narrative review, each pharmacological treatment is characterized by a peculiar efficacy and safety profile and, as such, it is of paramount importance for the treating physician to identify and counsel patients on the best drug according to his will, expectations and sex life. In details, oral therapy with PDE5is should be tailored according to patients profile taking into account age, the relationship status and the frequency of intercourses: young men in a stable sexual relationship for instance may be good candidates for a once daily treatment; conversely, older men with infrequent intercourses may be better treated with an on-demand compound. Moreover, although solid comparative data demonstrating the superiority of one PDE5i toward the other are lacking, shifting from one compound to the other could improve the outcome: previous studies have shown that a once-daily administration, for instance, may succeed where an on-demand therapy has failed [125]. Finally, safety profile and pharmacological formulation should be also considered: some patients could be less compliant to one compound due to side effects while they may report any issues with another;

likewise, novel oro-dispersible formulations of sildenafil and vardenafil could be appealing for patients looking for a discrete drug with a rapid onset of the effect.

Beside oral therapy, ICI therapy should be considered in patients non-responding to oral treatments or as first-line in those with absolute contraindication to PDE5is. To date, this treatment is mainly dedicated to patients suffering from ED after pelvic surgery or radiotherapy or those with severe and uncontrolled diabetes; in some of these cases, a combination of both oral PDE5I and alprostadil ICI may be needed to achieve a satisfactory erection. The concept of combination of multiple treatments has been recently expanded in the context of ED. Indeed, the current treatment paradigm of ED has shifted from a "vertical" consequential algorithm to an "horizontal" parallel one, where all treatment options may be used as a first-line therapy or in combination according to the profile of the patient. With the advent of novel regenerative therapies for ED, such as shockwaves and ICIs of platelet-rich plasma (PRP), both patients and physicians have been more focused in looking for a restorative treatment rather than only treating the symptom of impotence. However, as of today, these promising regenerative therapies have not been proved to be more effective than conventional pharmacotherapy neither to provide a long-lasting improvement of EF [1,5,11]. Moreover, data from randomized trials have demonstrated that combining oral treatment with PDE5is to shockwaves in patients with vasculogenic ED could lead to a more significant improvement of EF as compared to shockwaves alone [126].

For all these reasons, pharmacological treatment of ED still represents the best option for the large majority of patients. Further research should be directed on developing novel compounds which could succeed where current treatments have failed; in this context, few encouraging data have shown that treatment with BoNT-A may result effective in rescuing non-responders to both PDE5is and alprostadil [112,113]. That said, due to their excellent efficacy and safety profile, we foresee that PDE5is will remain as the most prescribed treatment for ED in the next decades.

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Table 1. Pharmocological characteristics of available PDE5Is *

	Sildenafil (100mg)	Tadalafil (20mg)	Vardenafil (20mg)	Avanafil (200mg)
C_{max}	560 µg/L	378 µg/L	18.7 µg/L	5.2 µg/L
T_{max}	0.8-1 hours	2 hours	0.9 hours	0.5-0.75 hours
$T_{1/2}$	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%
PDE5 vs PDE6 selectivity [35]	16-fold	550-fold	21-fold	121-fold
Adverse events	Headache 12.8% Flushing 10.4% Dyspepsia 4.6% Nasal congestion 1.1% Dizziness 1.2% Abnormal vision 1.9%	Headache 14.5% Flushing 4.1% Dyspepsia 12.3% Nasal congestion 4.3% Dizziness 2.3% Back pain 6.5% Myalgia 5.7%	Headache 16% Flushing 12% Dyspepsia 4% Nasal congestion 10% Dizziness 2% Abnormal vision <2%	Headache 9.3% Flushing 3.7% Nasal congestion <2% Dizziness <2% Back pain <2% Myalgia <2%

*Adapted from EAU guidelines on Sexual and Reproductive Health (2023)
C_{max} = maximal concentration; T_{max} = time-to-maximum plasma concentration; $T_{1/2}$ = plasma elimination halftime; AUC = area under curve or serum concentration time curve.

Table 2. Summary of available ICIs characteristics*

	Caverject™ or Edex/Viridal™	Bimix	Trimix	Quadmix	Invicorp™
Substance	Alprostadil	Papaverine + Phentolamine	Papaverine + Phentolamine + Alprostadil	Papaverine + Phentolamine + Alprostadil + Atropine	Vasoactive intestinal peptide (VIP) + Phentolamine
Dosage	5-40 pg/mL	30 mg/mL + 0.5 mg/mL	30 mg/mL + 11 mg/mL + 10 ug/mL	12.1 mg/mL + 1.01 mg/mL + 10.1 µg/mL + 0.15 mg/mL	25 ug + 1-2 mg
Efficacy	~ 70%	~ 90%	~ 92%	~ 80%	~ 80%
Adverse events	Penile pain 12.77% Priapism 1.78% Fibrosis 4.92% Haematoma 10.17%	Penile pain 14.06% Priapism 5.5% Fibrosis 13.02% Haematoma 14.46%	Priapism 3.15% Fibrosis 4.53% Haematoma 14.83%	Priapism 4.8% Fibrosis 6.26% Haematoma 26.03%	Penile pain 0.5% Priapism 0.06%
Availability	Easily available	Not licensed for the treatment of ED	Not licensed for the treatment of ED	Not licensed for the treatment of ED	Easily available

*Adapted from EAU guidelines on Sexual and Reproductive Health (2021)