Expert Opinion on Drug Metabolism & Toxicology

ISSN: 1742-5255 (Print) 1744-7607 (Online) Journal homepage: http://www.tandfonline.com/loi/iemt20

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To cite this article: Tan V. Le, Peter Tsambarlis & Wayne J. G. Hellstrom (2018): Pharmacodynamics of the agents used for the treatment of erectile dysfunction, Expert Opinion on Drug Metabolism & Toxicology, DOI: 10.1080/17425255.2019.1560421

To link to this article: https://doi.org/10.1080/17425255.2019.1560421

Published online: 22 Dec 2018.

EXPERT OPINION ON DRUG METABOLISM & TOXICOLOGY
https://doi.org/10.1080/17425255.2019.1560421

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REVIEW

Pharmacodynamics of the agents used for the treatment of erectile dysfunction

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ABSTRACT

Introduction: Erectile dysfunction (ED) is one of the most common complaints encountered by the practicing urologist, particularly when treating older men. The last 20 years have represented a pivotal time in the treatment of ED.

Areas covered: Several pharmacologic agents have been approved by regulatory agencies, including phosphodiesterase type 5 (PDE5) inhibitors, intraurethral suppositories, and vasoactive injectable agents. This review will focus on the pharmacodynamic properties of these agents and the clinical consequences of those properties.

Expert opinion: The decision on which agent to use should be individualized and based on the patient's goals and likelihood of success with the chosen treatment. The selection is also often driven by side-effect profiles that can be minimized by understanding the interplay between the individual patient and the medication. A thorough knowledge of the metabolism and pharmacologic properties of the available therapies will aid the urologist in selecting an individualized treatment plan for each patient.

ARTICLE HISTORY
Received 27 August 2018
Accepted 12 December 2018

KEYWORDS
Erectile dysfunction; phosphodiesterase type 5 inhibitors; intracavernosal injection; intraurethral suppository; pharmacodynamics; toxicity profiles

1. Introduction

Erectile dysfunction (ED) is a frequent ailment encountered in the urology office. Prevalence estimates can reach as high as 64% in some subgroups [1]; with the seminal 1994 study of American men revealing that 52% of men aged 40–79 have some degree of ED [2]. There also exists a myriad of treatment options for these men, ranging from oral therapies to the inflatable penile prosthesis. Each of the drugs presented in this review offer unique pharmacokinetic and pharmacodynamic properties. While many of these properties are similar, nuances between these medications can make a drug more suitable for one man over another. This review will examine the route of administration, metabolism, mechanism of action, pharmacodynamic properties, and toxicity profiles of the ED therapies currently approved by the Food and Drug Administration (FDA).

Oral therapies consist of the phosphodiesterase type 5 (PDE5) inhibitors. The only approved medication which is delivered via a urethral suppository is alprostadil or prostaglandin (PGE1). The compounded intracavernosal injection therapies (alprostadil, phentolamine, papaverine, and atropine) will be assessed in the setting of the combinations in which they are available. A brief discussion of the relevant mechanical therapies is included, as these therapies remain the optimal choice for certain populations. Finally, the authors will offer a discussion of the circumstances under which certain treatments offer advantages or disadvantages over other therapies.

2. Phosphodiesterase type 5 inhibitors

2.1. Overview

Supported by level 1 evidence, PDE5 inhibitors represent the first-line treatment recommendation of both the American Urological Association and the European Association of Urology for ED [3,4]. Overall, there are currently seven globally available PDE5 inhibitors (sildenafil, tadalafil, vardenafil, avanafil, lodenafil, mirodenafil, and udenafil) with different dosages and formulations. Among these, the PDE5 inhibitors approved by the United States FDA include: sildenafil (approved in 1998) [5], vardenafil, tadalafil (both approved in 2003) [6,7], and avanafil (approved in 2012) [8]. This review focuses on these four FDA-approved PDE5 inhibitors, as udenafil, mirodenafil and lodenafil are only available outside of the United States.

2.2. Mechanism

Penile erection is a neurovascular phenomenon that requires dilation of the penile vasculature, relaxation of cavernosal smooth muscle, increased intracavernosal blood flow and normal veno-occlusive function [9]. It is primarily mediated by the neurotransmitter nitric oxide (NO) through the cyclic guanosine monophosphate (cGMP) pathway [9]. (Figure 1)

Sexual stimulation leads to the synthesis and release of NO from nerve endings and vascular endothelial cells in the penis. NO rapidly diffuses in the corpora cavernosa and stimulates guanylyl cyclase, an enzyme that catalyzes the conversion of guanosine triphosphate to cGMP. Elevated cGMP stimulates the

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Article highlights

- Pharmacologic treatments for men with ED can be offered orally, intraurethrally, or intracavernosally
- The PDE5 inhibitors are separated largely by their selectivity for PDE5 and duration of action with tadalafil representing the only approved long acting option.
- Intraurethral and intracavernosal options bypass the nervous system and act locally to produce penile erection.
- Mechanical therapies are non-pharmacologic alternatives that can be offered to appropriately selected patients
- A complete knowledge of patients' goals, comorbidities, and willingness to accept the associated side effects of each therapy is necessary to provide the optimal treatment regimen for a man with ED.

Table 1. PDE isoenzymes expression [12].

PDE	Organ
PDE1	Testes, heart, olfactory cilia, central nervous system
PDE2	Central nervous system, adrenal cortex
PDE3	Adipose tissue, cardiac muscle, vascular smooth muscle, liver, platelets
PDE4	Neural and endocrine tissues
PDE5	Vascular smooth muscle, corpus cavernosum, lung, kidney, platelets
PDE6	Retina (rods & cones)
PDE7	Skeletal and cardiac muscle, lymphoid tissue
PDE8	Testes, ovary, colon, small intestine
PDE9	Spleen, intestine, kidney, heart, brain
PDE10	Central nervous system, testes
PDE11	Prostate, testes, liver, pituitary, heart

PDE: phosphodiesterase.

relaxation of penile smooth muscle and a several-fold increase in arterial inflow augmented by a decrease in venous outflow. This process is terminated by the degradation of cGMP by PDE5, an enzyme that breaks the phosphodiester bond in biological molecules, returning the penis to the flaccid state [10], (Figure 1) Notably, phosphodiesterase (PDE) is present throughout the body (Table 1) and is categorized into at least 11 different isoenzymes and 53 isoforms, with PDE5 being the most important for the penile erection process [11,12]. PDE5, which was identified by Francis et al. in 1980, contains two identical subunits and each has catalytic and regulatory domains [13].

PDE5 inhibitors, which are similar to cGMP in structure, can bind to PDE5 competitively and inhibit the degradation of cGMP. Therefore, cGMP levels remain high and facilitate the maintenance of penile erection. It is important to recognize that PDE5 inhibitors are not erectogenic drugs. They require the release of NO from penile nerve endings and vascular endothelium under the influence of sexual stimulation in order to produce an erection [14].

2.3. Pharmacological profiles

While the PDE5 inhibitors share a mechanism of action, they have different pharmacological profiles (Table 2). Sildenafil, vardenafil and avanafil have similar times to reach maximum plasma concentration (Tmax) values; while tadalafil has the longest Tmax. In clinical practice, Tmax reflects the onset of action and describes the shortest time to initiation of erection [15]. Therefore, clinicians should consider PDE5 inhibitors with shorter Tmax values for on-demand use [3,4].

The half-life (T1/2) value of tadalafil is greater than the other PDE5 inhibitors. Clinically, this produces a longer duration of action, especially in terms of therapeutic effect (up to 36 hours) [7].

There are 11 subtypes of PDE enzymes, located in different regions throughout the body. The most common adverse events of PDE5 inhibitors (headaches, flushing, dizziness, and nasal congestion) are likely caused by PDE5 inhibition in smooth muscle tissue outside of the penile cavernosum [3,4].

Biochemical selectivity for PDE5 also has a profound effect on the toxicities associated with the oral therapies [15]. A PDE5 inhibitor should ideally inhibit only PDE5, but one with 100% selectivity does not exist. The inhibition of PDE subtypes 1, 6, and 11 are responsible for many of the adverse effects associated with PDE5 inhibitors [16]. PDE1 is responsible for smooth muscle contraction, and its inhibition is correlated with vasodilation, flushing, tachycardia, and other cardiovascular effects [16]. Co-administration of a PDE5 inhibitor and nitrates may result in serious vascular reactions, such as severe hypotension. Therefore, PDE5 inhibitors are

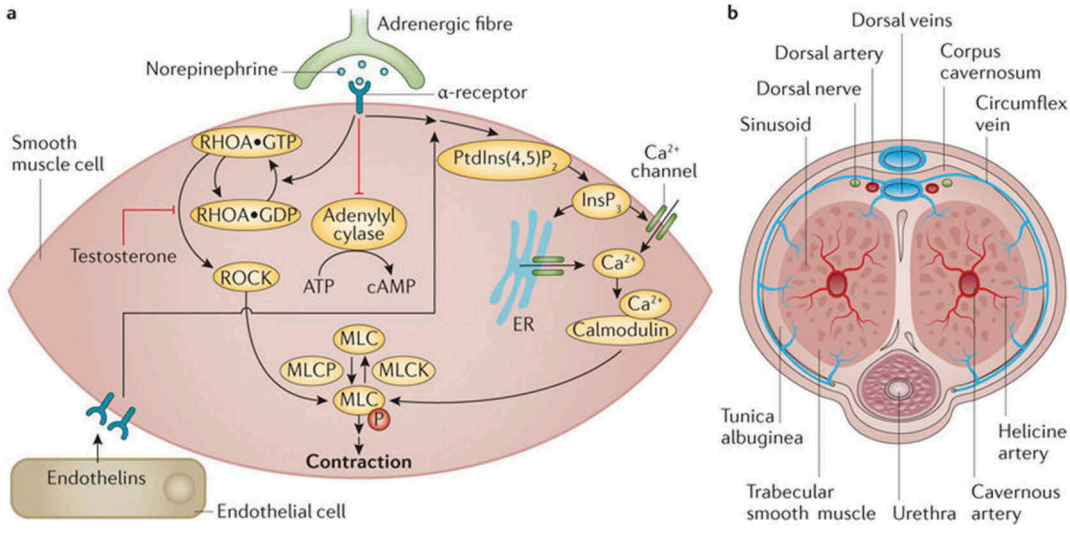

Figure 1. Mechanism of penile erection and effect of PDE5 inhibitors [10].

Table 2. Comparison of PDE5 inhibitors.

	Parameter	Sildenafil, 100 mg	Tadalafil, 20 mg	Vardenafil, 20 mg	Avanafil, 200 mg
Characteristic	Trade Name (Company)	Viagra (Pfizer)	Cialis (Eli Lilly)	Levitra (Bayern)	Stendra (Mitsubishi Tanabe)
	Approved year	1998	2003	2003	2012
	Dose	25, 50, 100 mg	5, 10, 20 mg	5, 10, 20 mg	50, 100, 200 mg
	Generic (Company)	2016 (Teva)	No	No	No
Pharmaco-logical	Cmax	560 µg/L	378 µg/L	18.7 µg/L	5.2 µg/L
	Tmax	0.8–1 hours	2 hours	0.9 hours	0.5–0.75 hours
	T1/2	2.6–3.7 hours	17.5 hours	3.9 hours	6–17 hours
	AUC	1,685 µg.h/L	8,066 µg.h/L	56.8 µg.h/L	11.6 µg.h/L
	Protein binding	96%	94%	94%	99%
	Bioavailability	41%	NA	15%	8–10%
	Fatty food	Reduced absorption	No effect	Reduced absorption	Reduced absorption
	PDE selectivity	Low against PDE6, Very low against PDE1	Low against PDE11, Very low against PDE6	Low against PDE6, Very low against PDE1	Highly PDE5
Adverse event	Headache	12.8%	14.5%	16%	9.3%
	Flushing	10.4%	4.1%	12%	3.7%
	Dyspepsia	4.6%	12.3%	4%	Uncommon
	Nasal congestion	1.1%	4.3%	10%	1.9%
	Dizziness	1.2%	2.3%	2%	0.6%
	Abnormal vision	1.9%		<2%	None
	Back pain		6.5%		<2%
	Myalgia		5.7%		<2%

Cmax: maximal concentration, Tmax: time-to-maximum plasma concentration; T1/2: plasma elimination halftime, AUC: area under curve or serum concentration time curve

absolutely contraindicated in men taking nitrates [3,4]. PDE6 is involved with photo transduction in the retina [12]. Sildenafil and vardenafil cross-react with PDE6. This explains the complaint of some patients that sildenafil and vardenafil produce visual disturbances such as blurred vision, sensitivity to light, and inability to discriminate between blue and green color [5,6,16]. PDE11 inhibition has been associated with myalgias and lower back pain. Tadalafil cross-reacts with PDE11 to some extent, but the consequences of this effect are unknown. Many randomized, controlled trials have concluded that flushing and visual side effects are more common in patients receiving sildenafil or vardenafil, whereas back pain/myalgia is more common in patients receiving tadalafil [17,18]. Avanafil is up to 100-fold more selective for PDE5 than for PDE1, PDE6, or PDE11 as compared to sildenafil, tadalafil, and vardenafil [8,16]. The high selectivity and low cross-reactivity exhibited by avanafil is likely the reason for the reduced rates of visual disturbances, hemodynamic changes, and musculoskeletal effects seen as compared to the other PDE5 inhibitors [16].

2.4. Sildenafil

When it was approved in 1998, sildenafil became the first selective PDE5 inhibitor to hit the market [5]. It is rapidly absorbed after oral administration and reaches peak plasma concentrations within 30–60 minutes. The plasma half-life of sildenafil is approximately 4 hours, and the duration of action is nearly 12 hours [5]. Sildenafil is administered in doses of 25, 50, and 100 mg. Its efficacy is reduced after a heavy, fatty meal due to impaired absorption. The recommended starting dose is 50 mg and should be adapted according to the patient's response and toxicities [5].

Many studies concluded that sildenafil was efficacious (based on International Index for Erectile Function [IIEF] and Sexual Encounter Profile [SEP] scores) in the treatment of ED [3,4,19,20]. Several years ago, a novel formulation of an orally disintegrating tablet (ODT) became available at the dosage of 50mg [21,22]. ODT formulations rapidly disintegrate in the mouth, making them easier to swallow. They remain highly portable and do not need to be taken with water [23]. Sildenafil ODT provides equivalent systemic exposure compared with sildenafil film-coated oral tablets [24,25], thus offering a convenient alternative method of administration. A recent study concluded that sublingual and supralingual administration of sildenafil ODTs resulted in remarkably similar pharmacokinetic profiles [26].

2.5. Tadalafil

Tadalafil was approved for the treatment of ED in February 2003 and is effective 30 minutes after administration, with peak efficacy at approximately two hours. Oral bioavailability is estimated to be at least 36% of the administered dose, and the T1/2 is 17.5 hours. Erectile capacity is maintained for up to 36 hours and is not affected by food [7]. Tadalafil can be administered in on-demand doses of 10 and 20 mg or a daily dose of 5 mg [7]. Back pain and myalgia are reported to be more common in men treated with tadalafil then the other PDE5 inhibitors [17,18].

Tadalafil significantly improved patient scores for IIEF, SEP [3,4] and treatment satisfaction, both on-demand [27,28] and with daily use [29,30]. The efficacy of tadalafil has been successfully established in difficult-to-treat subgroups such as: patients with diabetes mellitus [31,32], prostate cancer treated with radical prostatectomy [33], and prostate cancer treated with external beam radiotherapy [34].

Notably, several studies have reported on the efficacy of daily tadalafil on ED in men with lower urinary tract symptoms (LUTS) [35,36]. Daily tadalafil has been shown to improve erectile function in men with LUTS and ED when treated with a combination of tadalafil and finasteride [37,38]. Recently, daily tadalafil has also been approved for the treatment of LUTS secondary to benign prostatic hyperplasia.

Therefore, it is an appealing option in patients with concomitant ED and LUTS [4].

2.6. Vardenafil

Vardenafil became commercially available in March 2003 and is effective 30 minutes after administration [6]. It is rapidly absorbed following oral administration, with peak plasma levels detected within 1 hour. The T1/2 of vardenafil is approximately 4 hours and its effect is reduced when taken with a heavy, fatty meal [6].

More recently, an ODT form of vardenafil has been released, which dissolves in the patient's mouth and can be taken without water. Vardenafil is available in two different formulations, the film-coated tablet (FCT) at 5, 10, 20 mg and the ODT at 10 mg [39]. Absorption with ODT is unrelated to food intake and exhibits higher bio-availability compared to FCT [40]. Doses of 5, 10 and 20 mg have been approved for on-demand treatment of ED. The recommended starting dose is 10 mg and should be titrated based on the patient's response and side-effects [41].

Vardenafil significantly improved patient scores for IIEF, SEP and treatment satisfaction [42]. The efficacy of vardenafil ODT has been demonstrated in multiple randomized controlled trials and does not seem to differ from the non-ODT formulation [43,44].

2.7. Avanafil

Avanafil is the most recent PDE5 inhibitor to become available, gaining approval in 2013 [8]. It is available as a 50, 100, or 200 mg tablet. Avanafil, which has a higher selectivity for PDE5 as compared to other PDE subtypes, is used for the treatment of ED while minimizing adverse effects [8,16].

In comparison with other PDE5 inhibitors, avanafil is the most rapidly absorbed following oral administration, with a median Tmax of 30 to 45 minutes after dosing [4,8]. A high-fat meal delays its absorption, reducing maximum concentrations. The recommended starting dose is 100 mg taken as needed approximately 15 to 30 minutes before sexual activity; the dosage may be adapted according to efficacy and tolerability [4].

Avanafil is efficacious (based on IIEF, SEP scores) in the treatment of ED at doses of 50, 100, and 200 mg taken in an on-demand fashion, with rapid onset of action, excellent tolerability, and a reassuring safety profile [45,46]. The safety and efficacy of avanafil has also been investigated in two special difficult-to-treat populations: men with diabetes and ED [47] and men with ED secondary to radical retropubic prostatectomy; it was shown to be efficacious in both groups [48].

2.8. Clinical use

PDE5 inhibitors are recommended as first-line therapy in the treatment of ED with an overall grade A recommendation [3,4,49]. All PDE5 inhibitors have an excellent efficacy and safety profile. In clinical practice, a physician should distinguish between two kinds of side effects: those strictly related to PDE5 inhibition, such as headache, flushing, and dyspepsia, and those associated to residual inhibitory activity of drugs on other PDEs, such as vasodilation and tachycardia (PDE1), visual disturbances (PDE6), and back pain (PDE11) [5,6,16].

Before considering PDE5 inhibitors for men with ED, a thorough assessment of the cardiovascular risk profile should be made [3,4]. All PDE5 inhibitors are currently contraindicated in: i) patients who have suffered from a myocardial infarction, stroke, or have experienced a life-threatening arrhythmia within the last six months; ii) patients with resting hypotension (blood pressure < 90/50 mmHg) or hypertension (blood pressure > 170/100 mmHg); iii) patients with unstable angina, angina with sexual intercourse, or congestive heart failure categorized as New York Heart Association Class IV [3,4]. In addition, the co-administration of specific drugs with PDE5 inhibitors must be recorded. An absolute contraindication to PDE5 inhibitor use is mandated in patients who are using any form of organic nitrate (nitroglycerine, isosorbide mononitrate, and isosorbide dinitrate) or NO donor (such as amyl nitrate 'poppers,' which are used for recreation) [3,4,12]. Besides cardiovascular comorbidity, functional impairment of the liver or kidney needs to be carefully considered when determining the starting dose for each PDE5 inhibitor [3,4,12].

The basic work-up of the patient must identify reversible risk factors for ED. Lifestyle changes and risk factor modification must precede or accompany any physical or/and pharmacological treatment [3,4]. Major potential clinical benefits associated with lifestyle changes are frequently seen in men with specific comorbid cardiovascular or metabolic disorders, such as diabetes or hypertension. The clinician must emphasize the importance of a healthy lifestyle to both the patient and his partner at the critical moment a patient is motivated to make a change [4].

In addition, psychosocial factors can influence every aspect of sexual function. Psychogenic ED is generally driven by a man's anxiety related to the ability to achieve or maintain an erection. For men with predominantly psychogenic ED, physicians may offer a referral to psychotherapy as either an alternative or an adjunct to medical treatment [3]. Pharmacological treatments are often effective in these situations, but the addition of psychotherapy or psychosexual counseling may help reduce the anxiety associated with being treated for ED and ultimately transition off medical therapies for ED. Psychotherapy and psychosexual counseling aim to help patients and their partners improve communication about sexual concerns, reduce anxiety related to entering a sexual situation, and discuss strategies for integrating ED treatments into their sexual relationship [3].

There is a paucity of data from head-to-head clinical trials on PDE5 inhibitors, making it difficult for clinicians to differentiate among these agents to select the most appropriate treatment for their ED patients [3,4,49]. Tadalafil has a longer duration of action, with a Tmax that is twice as long as the other PDE5 inhibitors. Notably, avanafil can be taken as needed approximately 15–30 minutes before sexual activity with a lower incidence of side effects than sildenafil, vardenafil, and tadalafil [50]. Therefore, choosing the optimal PDE5

inhibitor depends on the expected frequency of intercourse and the patient's personal experience. Their needs and expectations must be considered, and close follow-up is important to identify any issues related to treatment. In addition, the patients need to know whether a drug is short or long-acting, its possible disadvantages, and how to properly use it [3,4,49]. Imparting this knowledge is the responsibility of the prescribing physician.

Several studies have demonstrated treatment with tadalafil 5 mg once daily in men complaining of ED to be well-tolerated and effective [27–30]. Porst et al. presented an interesting post hoc analysis of six previously published, larger, double-blind, randomized studies of tadalafil once-daily versus placebo. The authors concluded that a daily dosing regimen proves to be well tolerated and effective in improving erectile function across clinical subpopulations regardless of age, lifestyle, comorbidities, and concomitant medications [51]. Interestingly, once-daily tadalafil tends to be preferred by patients due to greater improvements in sexual self-confidence, time concerns, and spontaneity. The 5 mg daily regimen provides an alternative to on-demand dosing for couples who prefer spontaneous rather than scheduled sexual activity, as the dosing no longer needs to be temporally linked to sexual activity [4].

Notably, many authors have recorded the role of tadalafil in restoring morning erections. Aversa et al. indicated that long-term use of tadalafil improved endothelial function with a dramatic increase in morning erections with sustained effects after its discontinuation due to improved oxygenation to the penis [52]. A randomized controlled trial by Brock et al. documented a significant protective effect of daily tadalafil treatment on penile length, erectile function, and recovery of morning erections in patients after bilateral nerve-sparing radical prostatectomy [53].

3. Intraurethral alprostadil

Intraurethral alprostadil, marketed as MUSE® (Meda Pharmceuticals, Somerset New Jersey), is an FDA-approved urethral suppository that offers an alternative to oral therapy in men with ED. Approved in 1997, alprostadil predated the approval of PDE5 inhibitors for ED [54]. It offers a local penile application of vasoactive drug without requiring a penile injection. Chemically, alprostadil is identical to prostaglandin E_1 (PGE_1) which is a known vasodilator [55]. The vasodilation initiates the cascade previously described and ultimately results in an erection. This is augmented by stimulation of cyclic adenosine monophosphate (cAMP) and results in intracellular calcium trapping and smooth muscle relaxation, with resultant erection [54].

Alprostadil delivered via intraurethral suppository is absorbed directly through the urothelium into the corpus spongiosum and reaches the corpora cavernosa via venous channels [56]. The drug is rapidly absorbed and metabolized both locally in the penis, and systemically in the lungs. Ultimately, excretion of the inactive metabolite, 15-keto-PGE_1, is 90% renal [57]. Alpostadil is completely cleared within 24 hours [56]. Due to its pharmacokinetic properties, erection is typically noted about 10–15 minutes after application and can last anywhere between 30 minutes and 12 hours [58].

The efficacy of intraurethral alprostadil has been confirmed in multiple studies [59–61]. The dose comparison studies have consistently shown an increase in efficacy up to a dose of 1000 micrograms [59,60]. For this reason, a starting dose of 500 micrograms is recommended with the ability to titrate up if needed and tolerated. Using this method, up to 69% of men can be expected to achieve an erection satisfactory for penetration [59–62].

In terms of safety, intraurethral alprostadil is well tolerated. The most common side effect is penile pain which is reported between 7%[62] and 32.7%[60] of patients. The most serious side effect is hypotension, which is dose dependent. This was initially reported in the clinic, but not at home, in the largest study evaluating the efficacy and safety of intraurethral alprostadil [60]. This reinforces the importance of using the lowest efficacious dose and should encourage the clinician to use caution when prescribing intraurethral alprostadil to men already on antihypertensives. It should be noted that no cases of priapism have been identified in the literature on intraurethral alprostadil monotherapy [59–62].

4. Intracavernosal injections

In the early 1980s, Virag [63] and Brindley [64] first described intracavernosal injections (ICI) as the administration of a vasoactive substance directly into the corpus cavernosa of the penis to produce an erection. The four substances commonly used in clinical practice are alprostadil, papaverine, phentolamine, and atropine. ICI therapy is recommended in most men with ED who fail to respond to PDE5 inhibitors as the second-line therapy with a grade A recommendation [3,4].

Men who have contraindications to PDE5 inhibitors, men who prefer not to use an oral medication, or men who find that PDE5 inhibitors are inadequate, ineffective, or have adverse effects may choose ICI to treat their ED [3,4]. In addition, ICI therapy is beneficial in facilitating the recovery of spontaneous erections during early penile rehabilitation after radical prostatectomy [65,66]. ICI are also utilized to assess cavernosal relaxation and arterial dilatation during penile duplex Doppler ultrasonagraphy studies in the evaluation of vasculogenic ED [67]. Contraindications to ICI include: a history of hypersensitivity to alprostadil, increased risk of priapism, and bleeding diatheses [3,4]. Importantly, reported drop-out rates during treatment of ED with ICI have been relatively high, about 41–68% [68,69], with most drop-outs occurring within the first two to three months. Therefore, careful counseling of patients during the office-training phase, as well as close follow-up, are of the utmost importance [70,71].

Presently, ICI therapy can be prescribed as monotherapy (alprostadil), bimixture (phentolamine and papaverine), trimixture (phentolamine, papaverine, and alprostadil) or quadmixture (phentolamine, papaverine, alprostadil and atropine) [3,4].

4.1. Monotherapy ICI

Intracavernosal alprostadil induces an erection via the identical method described above for intraurethral alprostadil. The drug is self-administered directly into the corpora cavernosa with a fine gauge needle and does not require systemic

absorption [58]. As such, the doses for intracavernosal alprostadil are significantly lower than intraurethral administration.

Several trials have demonstrated intracavernosal alprostadil to be superior to intraurethral administration [72–74]. In a study of 60 men, 87% were able to participate in penetrative sexual intercourse using intracavernosal alprostadil (20 micrograms) compared to 53% of men who used 1000 micrograms of intraurethral alprostadil, $p < 0.05$ [73]. These rates of efficacy were similar to those demonstrated by Porst in a study of 103 men [74]. In this study, 70% of the men were able to participate in penetrative intercourse at home using up to 20 micrograms of intracavernosal alprostadil vs 43% using up to 1000 micrograms of intraurethral alprostadil[74]. A third study of 111 men that allowed crossover also allowed increased doses of intracavernosal alprostadil, up to 40 micrograms [72]. In this study, 92.6% were able to obtain an erection satisfactory for intercourse at home using intracavernosal alprostadil vs 63% in the intraurethral group [72]. All three studies demonstrated superior efficacy of intracavernosal therapy over the transurethral approach.

In terms of safety, the side effects of intracavernosal alprostadil are similar to intraurethral alprostadil. The most common complaint is pain, which occurred in up to 50.2% of men administering intracavernosal alprostadil [75]. The largest study on the safety of intracavernosal alprostadil included 683 men from 51 sites. In this large, multi-center, study, penile pain was reported in 50.2% of men. Hematoma was the second most common adverse event, occurring 8.3% of the time. An erection lasting between 4 and 6 hours occurred in 5.1% of men in the study, and priapism, defined in the study as an erection lasting over 6 hours, occurred in 0.7%. Hypotension was suspected in 1.3% of men due to reported lightheadedness, irregular pulse, vasovagal reaction, or other symptoms associated with hypotension [75].

4.2. Bimix ICI (papaverine + phentolamine)

Papaverine, which is a non-opiate derivative of the poppy plant (Papaver somniferum), was first described for intracavernosal use by Virag in 1982 [63]. This agent is a non-specific PDE inhibitor that causes an increase in intracellular cAMP and cGMP, leading to corporal smooth muscle relaxation and penile erection [63]. Papaverine is currently not licensed for the treatment of ED as monotherapy. It is most commonly used in combination therapy with phentolamine in ICI [4]. Phentolamine is a competitive alpha adrenergic receptor blocker which induces an increase in corporal blood flow. The addition of phentolamine decreases arterial resistance and promotes vasodilatation in synergy with papaverine. Bimix is approved for clinical use under the name Androskat in some European countries. It contains papaverine hydrochloride (15 mg/mL) and phentolamine mesylate (0.5 mg/mL) in 2 mL ampoules [4]. Bimix improves erectile capacity and increases sexual satisfaction in men with ED undergoing ICI therapy [76].

4.3. Trimix (phentolamine + papaverine + alprostadil)

Trimix ICI therapy was first introduced in 1991 by Bennett, with a reported success rate of 92% in 116 patients [77]. This combination has a side effect profile similar to alprostadil monotherapy, but a lower incidence of penile pain due to the lower dose of alprostadil used. Fibrosis, however, is more common (5–10%) when papaverine is used [77].

In a randomized study, Trimix was twice as effective as alprostadil monotherapy at achieving erections rigid enough for penetration (50% vs 22%), with a lower proportion of subjects reporting pain (12.5% vs 41%) [78]. Currently, trimix is suitable for poor responders to monotherapy, for severe veno-occlusive dysfunction, or in men who are post radical pelvic surgery [18]. Patients should be trained in the office regarding self-injection before home injection is undertaken. This also presents an opportunity to titrate the medication to the lowest dosage that safely yields an erection of sufficient rigidity for sexual intercourse [3,4]. Currently, no standardized mixture is approved by the FDA; these combinations must be titrated by the physician [3]. Concentrations of each component vary widely in the literature, but ratios of 12–30 mg papaverine: 10–20 µg alprostadil: 1–2 mg phentolamine are common. A common dosing regimen includes a mixture of 30 mg papaverine + 10 µg alprostadil + 1 mg phentolamine per 1 mL with a starting dose of 0.1–0.5 mL^3. Clinicians should start with a small dose of medication, especially in patients with nonvasculogenic forms of ED [3,4].

4.4. Quadmix (phentolamine + papaverine + alprostadil + atropine)

Adding atropine to trimixture significantly increases the effectiveness in terms of improving erection and minimizing side effects [49]. The value of atropine in the combination remains unclear. Adaikan hypothesized that the anti-erectile arm of the cholinergic pathway in the human cavernosum might be blocked by atropine [79]. A full-dose quadmixture which has been recommended consists of papaverine hydrochloride 12.1 mg/mL, phentolamine mesylate 1.01 mg/mL, alprostadil 10.1 mg/mL, and atropine sulfate 0.15 mg/mL [49]. Notably, 95% to 100% of patients with ED achieved sustained rigidity after dose titration with quadmix [49]. As with all ICI therapy, patients should receive in-office training regarding self-injection. The optimal dose of quadmix is dependent on a man's subjective preference, tolerability, and sexual satisfaction [49].

5. Mechanical therapy

Certain patients are not candidates for pharmacological intervention, but still desire treatment for their ED. Other men try and fail with pharmacological intervention and are seeking third- or fourth-line options. These men stand to benefit from mechanical therapy. The two available mechanical therapies at this time are the vacuum erection device (VED) and the penile prosthesis (PP).

The VED is an FDA-approved option for men with ED that predates oral therapies. The device creates negative pressure in the penis drawing venous and arterial blood into the corpora [80]. A constricting band is then placed at the base of the penis to trap the blood and thus maintain the erection [81]. The mechanical nature of the device prevents it from having true pharmacokinetic properties, but the onset of action is essentially immediate.

The penile prosthesis represents an option for men who fail the previously described therapies or are unwilling to continue with their current treatment regimen due to intolerance of side effects, unreliability, or diminished response. The device requires surgical implantation, is available in 1, 2, and 3-piece models, and should be offered to men meeting the above criteria [82]. The device is somewhat outside of the scope of this review, but should be included as option for men with ED.

6. Erectile dysfunction in post radical prostatectomy (RP) and post radiotherapy (RT)

Approximately 25–75% of men experience post RP ED [4]. In addition, ED is a common sequela after external beam radiotherapy for prostate cancer. The mechanisms contributing to ED in post RP and post RT involve injury to the neurovascular bundles, penile vasculature, and cavernosal structural tissue. A variety of treatments have been introduced as penile rehabilitation strategies, with various recommendations for their implementation which consider timing, schedule, and delivery of treatment [3,4].

PDE5 inhibitors have been recommended as first line for the purpose of penile rehabilitation because of their non-invasiveness, ease of administration, good tolerability and positive impact on quality of life [3,4]. While all PDE5 inhibitors offer potential benefit, tadalafil appears to be the most effective in improving erectile function in men with ED following post RP or post RT [53]. Moreover, taking tadalafil once daily significantly shortened the time to erectile function recovery versus placebo over the nine-month double/blind treatment period [83]. Likewise, tadalafil once daily improved quality of life post-operatively, during both the double-blind treatment and open-label treatment periods [84].

Historically, the treatment options for post RP ED have included ICI, intraurethral alprostadil, VED and PP implantation. ICI and penile prostheses are frequently still seen as second and third-line treatments, respectively [3,4]. Importantly, psychotherapeutic regimens have been prescribed with reported rehabilitative benefits. Clinicians should educate men regarding the sexual effects of prostate cancer treatments and set realistic expectations regarding functional recovery. Moreover, a treatment plan for male sexual health after prostate cancer treatment should include monitoring of the sexual function. Overall, these efforts, including combining psychosocial support and somatic erectogenic treatments, may motivate men and their partners to maintain intimacy during sexual function recovery [3].

7. Conclusion

PDE5 inhibitors are typically the first-line treatment for ED due to their high levels of efficacy and tolerability. Before considering PDE5 inhibitors, the cardiovascular risk profile and the function of the liver and kidney must be thoroughly assessed. Choosing the optimal PDE5 inhibitor will depend on the frequency of intercourse and the patient's sexual profile. Tadalafil has a longer duration of action and can be used for daily treatment, while avanafil is absorbed the most rapidly. In addition, sildenafil ODT and vardenafil ODT remain highly portable and do not need to be administered with water. Intraurethral alprostadil and ICI are second-line therapies in patients who do not respond to PDE5 inhibitors, but represent options that do not require sexual stimulation or an intact nervous system. Both require patient counseling to ensure that the drug is administered properly.

8. Expert opinion

PDE5 inhibitors have revolutionized the treatment of ED since their approval in 1998. The evidence base for the current PDE5 inhibitors is strong, and thus they represent first-line therapy for the majority of men. It is important to remember that these drugs are not initiators of erection, and sexual stimulation is required to achieve penile rigidity. To the best of our knowledge, there have been no unsponsored randomized controlled trials comparing the efficacy and safety of the currently available PDE5 inhibitors. Therefore, the choice of one specific PDE5 inhibitor over another must rely on drug pharmacokinetics and the patient's personal goals and expectations. Differences between sildenafil and vardenafil are relatively small. Vardenafil is a less potent inhibitor of PDE6 than sildenafil and is less likely to produce the ocular side effects associated with this cross reactivity. Both are administered on-demand due to their short half-lives in plasma. The package insert suggests that these agents be initiated at a low dose, then titrated upwards depending on the patient's response and/or side effects. In cases with low frequency of sexual intercourse, sildenafil or vardenafil on-demand are the optimal choices. The authors prefer on-demand formulation for any man who expects to engage in sexual intercourse two or fewer times per week. The advantage of ODTs are ease of transport without the need for water for administration. Tadalafil has the longest half-life among the PDE5 inhibitors. It can be administered two different ways: on-demand or daily. Tadalafil is often used when sildenafil or vardenafil are not as effective as the patient desires. In addition, tadalafil on-demand is effective in cases of ED concomitant with other conditions such as diabetes mellitus, or after radical prostatectomy. Daily administration of tadalafil is usually indicated in cases of men who have a higher expected frequency of sexual intercourse per week. In these cases, the prolonged duration of action of tadalafil provides a degree of spontaneity which is not provided by the other PDE5 inhibitors at a similar or lower cost. Notably, daily tadalafil has also been reported to be efficacious in alleviating LUTS associated with benign prostatic hyperplasia.

Avanafil is a second generation PDE5 inhibitor and is the most selective among the available PDE5 inhibitors. Notably, avanafil can be administered as needed approximately 15–-30 minutes before sexual activity. It is commonly prescribed as an alternative in cases when sildenafil, vardenafil, or tadalafil treatment have failed to produce an adequate erection or are producing intolerable side effects. Of note, avanafil is currently the most expensive oral therapy, which can be a barrier for many patients.

Regardless of which PDE5 inhibitor is being prescribed, a thorough assessment of the cardiovascular risk profile should be undertaken. Patient needs, and expectations, must

be considered, and close follow-up is important to identify any issues related to treatment. In addition, the patients need to be educated as to the duration of action, their possible disadvantages, and how to administer each medication to achieve the highest efficacy.

There are two main reasons why patients fail to respond to PDE5 inhibitors: incorrect drug use or the drug's lack of efficacy. The management of non-responders depends upon identifying the underlying cause [4]. Importantly, the physician must verify that the patient has been using a licensed medication. There is a large counterfeit market in PDE5 inhibitors, especially Viagra. The three most common causes of incorrect drug use are failure of sexual stimulation, failure to use an adequate dose, and failure to wait an adequate amount of time between taking the medication and attempting sexual intercourse [4]. Once these three possibilities have been ruled out, the physician should consider testosterone deficiency concomitant with ED in cases not responding to PDE5 inhibitors [3,4]. Testosterone deficiency is defined as total testosterone <300 ng/dl with the presence of symptoms and signs of hypogonadism. In this population, patients should be counseled that concomitant use of testosterone supplementation to achieve a eugonadal level and PDE5 inhibitors may be more likely to restore sexual function than PDE5 inhibitors alone [3,4]. Importantly, these men should be advised that testosterone therapy is not an effective mono-therapy. The combination of long-acting injectable testosterone undecanoate and tadalafil 5 mg once daily produced a significant improvement in IIEF scores when compared to testosterone combined with on-demand tadalafil [85]. Moreover, the improvement in erectile function was well maintained, even after the cessation of treatment. In patients with severe ED, it has been suggested that a combination of tadalafil daily and a short acting PDE5 inhibitor (such as sildenafil) may improve erectile quality, without a significant increase in side effects. Cui et al. evaluated the efficacy of long-term 5mg once daily tadalafil combined with 50 mg sildenafil on demand in the early stage of ED treatment. Improvement in patients with moderate and severe ED in the combined medication group were significantly higher than in the tadalafil alone group [86].

Men who do not respond to PDE5 inhibitors can be offered second-line options such as transurethral medications and/or ICI. The efficacy of intraurethral alprostadil has been well established. However, as the dose is increased, the likelihood that patients will experience an adverse event such as penile pain and dysuria increases as well. All patients should be educated about priapism and instructed on safe responses and maneuvers should a prolonged erection occur, but episodes of priapism are exceedingly rare with intraurethral alprostadil. ICI therapy remains an important tool in treating and diagnosing ED. Moreover, ICI was introduced as an adjunct in penile rehabilitation, in men who are post radical prostatectomy. There may be a superior option for men who have inherent damage to their cavernous nerves from radical prostatectomy. Moreover, patients do not require sexual stimulation when using ICI. The dropout rate for ICI therapy is relatively high, and can be associated with priapism, ecchymosis, hematoma formation, and possible penile fibrosis. Some men also find the penile injections to be uncomfortable both physically and psychologically and discontinue therapy for this reason. Patients need to be educated on the benefits and limitations of ICI therapy prior to beginning treatment in order to improve compliance and reduce dropout rates. In men who do not respond to or cannot tolerate pharmacologic agents, mechanical therapy with either VED or penile prosthesis should be offered.

PDE5 inhibitors may also be combined with ICI in cases of severe ED. McMahon et al. reported on 93 men with mixed etiology ED who failed high-dose trimix ICI therapy. This combination of sildenafil with trimix ICI may salvage as many as 31% of men who do not respond to the trimix ICI alone [87]. Another study by Nandipati et al. combined ICI alprostadil and nightly sildenafil in 22 men immediately after nerve-sparing RP. At an average follow-up of 6 months, 50% had return of spontaneous partial erections and 96% were sexually active [88].

In addition, intraurethral alprostadil and PDE5 inhibitors may be combined to treat oral monotherapy failures. This combination maintains the minimally invasive nature of therapy because the alprostadil does not need to be injected. Raina et al. evaluated the sildenafil-intraurethral alprostadil combination in 23 men at least 6 months post RP who were unsatisfied with sildenafil monotherapy of 100 mg [89]. Nineteen of these 23 men (83%) reported improvement in rigidity and sexual satisfaction. Another study using combination therapy reported an improvement in erections in 28 patients, who had failed either sildenafil or intraurethral alprostadil monotherapy [90].

Currently, low-intensity extracorporeal shock wave therapy (ESWT) should be considered as an investigational therapy for men with ED, as there is a lack of evidence from the available randomized control trials regarding the efficacy of ESWT on men with ED.

It should be noted that the pharmacological options for ED treatment do not influence the underlying pathophysiology and do not cure the condition. Thus, further research into ED, with gene, stem cell therapies or ESWL may, in theory, be beneficial in correcting the underlying cause of a man's ED rather than just treating the symptoms.

Funding

This paper was not funded.

Declaration of interest

W Hellstrom is a consultant for Pfizer. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

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