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REVIEW

Phosphodiesterase 5 inhibitors: preclinical and early-phase breakthroughs for impotence treatments

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ABSTRACT

Introduction: Erectile dysfunction (ED) is a condition that affects millions of men worldwide and is characterized by the inability to achieve or maintain an erection for satisfactory sexual performance. There are numerous treatment options for ED, including medications, mechanical assist devices, and surgical management; however, first-line treatment is usually a phosphodiesterase 5 (PDE5) inhibitor. There is a growing interest in developing novel, efficacious PDE5 inhibitors that provide better quality, safety, and tolerability profiles with less adverse effects. Our review of udenafil, mirodenafil, youkenafil, lodenafil, and SLx-2101 analyzes the safety, efficacy, and pharmacokinetic properties of these new ED drugs.

Areas covered: Clinical trials demonstrated improved scores in questionnaires, such as the International Index of Erectile Function and Sexual Encounter Profile, for udenafil, mirodenafil, and lodenafil, while youkenafil and SLx-2101 revealed enhanced safety and tolerability in early pharmacokinetic studies.

Expert opinion: It is our opinion that more robust clinical trials are required before these medications can be made available in the United States. Additionally, the field of urology may benefit from pursuing other avenues of pharmacotherapy, such as injections, tablets with a different mechanism of action, or stem cell therapy, to restore the integrity of the endothelium within the penis.

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Erectile dysfunction; phosphodiesterase inhibitors; adverse events; novel drugs; pharmacokinetics

1. Introduction

Erectile dysfunction (ED) is a common condition that affects millions of men worldwide and is characterized by the inability to achieve or maintain an erection for satisfactory sexual performance [1]. The prevalence of ED is estimated to affect between 10–20% of adult males worldwide. Known risk factors for ED include various chronic diseases, such as hypertension, diabetes, and dyslipidemia, all of which disrupt the architecture of cavernosal tissues and functional components of the neurovascular bundle in the penis. Despite its complexity, the mechanism of an erection is well delineated. During sexual arousal, parasympathetic activity stimulates smooth muscle (SM) relaxation and vasodilation via cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) signaling [2]. Postganglionic parasympathetic cavernous nerves release acetylcholine (ACh) from their nerve terminals. ACh binds to muscarinic receptors in endothelial cells, stimulating endothelial nitric oxide synthase (eNOS) to produce nitric oxide (NO) from 1-arginine [2]. NO is released from the endothelial cells and diffuses across vascular SM membranes to stimulate cGMP production in the cytosol. cGMP signaling promotes opening of K^+ channels, closing of Ca^{2+} channels, and sequestering of intracellular Ca^{2+}. The subsequent decrease in cytosolic Ca^{2+} concentrations promotes SM relaxation and vasodilation. This signaling cascade is terminated by phosphodiesterase 5 (PDE5), which breaks down cGMP [2] [Figure 1].

For decades, urologists and primary care providers have used a range of treatment options for ED, including first-line oral PDE5 inhibitors, such as sildenafil, vardenafil, avanafil, and tadalafil [3]. PDE5 inhibitors prevent the breakdown of cGMP in corpus cavernosum, corpus spongiosum, and glans penis, contributing to increased SM relaxation and stronger, prolonged erections. These drugs facilitate erections rather than induce erections, because they still require sexual stimulation, NO synthesis, and sufficiently functioning SM cells [3]. Within the genital tract, PDE5 is expressed in a multitude of locations, including the prostate, vas deferens, epididymis, and testes. Outside of the genital tract, PDE5 is expressed in the lung, skeletal muscle, and endocrine glands (thyroid and adrenal); however, all expression levels are much lower than in the corpus cavernosum [3]. This distribution in expression is important when trying to comprehend the increased rates of adverse effects experienced by some patients and subsequent discontinuation of current PDE5 inhibitors. Overall, there are a total of 11 established PDE enzyme families with distinct properties and various side effects.

Detrimental effects on auditory, cardiovascular, ocular, and reproductive systems are among the more serious side effects of PDE inhibitors. For example, there have been multiple documented cases linking sensorineural hearing loss with sildenafil [4]. Skeith et al. demonstrated that the risk of ototoxicity was greatest in combination with loop diuretics and CYP3A4 inhibitors [4]. Due to the lack of selectivity of current PDE inhibitors, the expression of

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Article highlights

- Erectile dysfunction (ED) is a common patient complaint worldwide.
- First-line treatment therapies for ED may lead to adverse effects that cause intolerance or nonadherence
- Novel phosphodiesterase 5 (PDE5) inhibitors have recently been developed and trialed to assess their efficacy, safety, and tolerability in men
- Our review covers current literature on new PDE5 inhibitors, including udenafil, mirodenafil, youkenafil, lodenafil, and SLx-2101
- We review their pharmacokinetic properties and the results of clinical trials for these novel agents

PDE6 in the retina can lead to short-term ophthalmologic adverse effects, such as blurred vision, disturbed color vision, and photophobia. Regarding reproductive safety, tadalafil's increased selectivity for PDE11, which is highly expressed in the testes, was a concern for detrimental effects on the structure and function of testes in a rat model [5]. Fortunately, this has not been observed in human trials [5].

Unfortunately, over 50% of patients who initially respond to PDE5 inhibitors discontinue treatment within 2–3 years [2]. Patients with suboptimal response to PDE5 inhibitors may benefit from alternative treatments, such as intraurethral suppositories, intracavernosal injections, penile vacuum erectile devices, low-intensity shockwave therapy (LiSWT), or penile prosthetic surgery. In recent years, there has been a growing interest in developing more efficacious PDE5 inhibitors that are safe and tolerable without adverse side effects. Several novel drugs, including udenafil, mirodenafil, youkenafil, lodenafil, and SLx-2101, are currently being evaluated for their safety, efficacy, and biochemical profiles in clinical trials [6]. This review aims to provide clinicians and researchers with a comprehensive overview of these drugs from both clinical and pharmacokinetic perspectives.

2. Experimental drugs

2.1. Udenafil

2.1.1. Background

Udenafil, brand name Zydena®, is an oral reversible PDE5 inhibitor developed by Dong-A Pharmaceutical Co., Ltd. in Seoul, Korea, which was approved in 2005 for the treatment of ED [7]. Structurally, udenafil is a pyrazolopyrimidine derivative with a molecular structure similar to sildenafil citrate [8]. Additionally, the isoenzyme selectivity profile of udenafil is comparable to sildenafil regarding PDE5 but inhibits PDE1, PDE2, PDE3, and PDE6 far less than sildenafil, which may explain its more favorable side-effect profile, as demonstrated by the pivotal trials discussed below [7].

2.1.2. Clinical trials

Several clinical trials have demonstrated the efficacy and safety of oral administration of udenafil in treating ED. In a study by Paick et al., on-demand treatment with 100 mg or 200 mg udenafil resulted in significantly greater improvement in International Index of Erectile Function-Erectile Function Domain (IIEF-EFD) scores from baseline (0.2 for placebo, 7.52 for 100 mg udenafil, 9.93 for 200 mg udenafil) [9,10]. A higher percentage of patients treated with 100 mg udenafil (88.8%) and 200 mg udenafil (92.4%) reported successful penetration on Sexual Encounter Profile (SEP) question 2 (Q2), compared with placebo (53.4%). Per the scores in SEP question 3 (Q3), the udenafil groups (70.1% for 100 mg, 75.7% for 200 mg) also more frequently reported maintenance of erection for successful intercourse, as compared to the placebo groups (15.4%) [10]. At the end of 12 weeks, a significantly greater proportion of patients in the 100 mg and 200 mg udenafil groups (81.5% and 88.5%, respectively) responded positively to the Global Assessment Questionnaire (GAQ), as compared to the placebo groups (25.9%). Furthermore, a greater percentage of patients in the 100 mg and 200 mg udenafil groups (25.2% and 48.1%, respectively) achieved normal IIEF-EFD scores compared to the

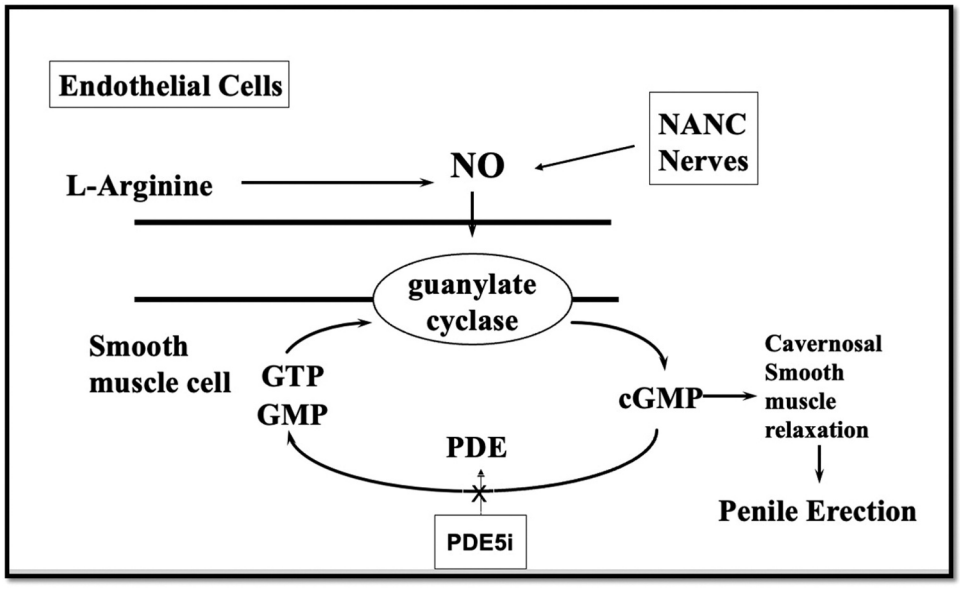

Figure 1. Mechanism of phosphodiesterase type 5 inhibitors during a penile erection.

placebo groups (3.7%) [10]. A phase III study by Park et al., which compared the on-demand treatment of 100 mg udenafil to placebo, also reported improved rates of successful penetration (SEP Q2, 73.22% for placebo vs 82.27% for 100 mg udenafil); ability to maintain erection for successful intercourse (SEP Q3, 28.3% for placebo vs 54.7% for 100 mg udenafil); and IIEF-EFD scores (15.8 for placebo vs 19.77 for 100 mg udenafil) [11]. Udenafil 100 mg was demonstrated to be effective for up to 12 hours after treatment [11].

Once-daily treatment with udenafil has also been investigated as a potential treatment for ED, which may enable more spontaneous sexual activity. A clinical trial conducted by Zhao et al. reported that patients who received 50 or 75 mg once-daily dosing of udenafil for 12 weeks, compared to those who received a placebo, had significantly greater improvements in IIEF-EFD scores (3.14 for placebo, 6.59 for 50 mg udenafil, 8.34 for 75 mg udenafil); intercourse satisfaction (0.93 for placebo, 2.14 for 50 mg udenafil, 3.48 for 75 mg udenafil); sexual desire (0.33 for placebo, 1.77 for 50 mg udenafil, 1.42 for 100 mg udenafil); and overall satisfaction (0.74 for placebo, 2.17 for 50 mg udenafil, 2.84 for 75 mg udenafil) [12]. A phase III, open-label, fixed-dose extension study by Moon et al. evaluated the long-term efficacy and safety of once-daily oral administration of 75 mg udenafil for ED. At the conclusion of the 48-week extension point, nearly half (45.1%) of the subjects recovered normal erectile function (EF), as measured by an IIEF-EFD score higher than 26 [13]. Positive GAQ responses (95.4%) were also observed at the 48-week extension point [13]. Patients demonstrated improvements in IIEF-EFD scores (23.98 ± 5.44) compared to baseline (14.6 ± 4.57) [13]. Of note, after a 4-week, treatment-free period following 24 weeks of once-daily, fixed dosing of udenafil 75 mg, 14.2% subjectively reported normal EF, as measured by an IIEF-EFD score higher than 26. The most frequently reported adverse effects associated with udenafil were flushing, nasal congestion, and headaches [13]. However, in contrast to tadalafil and sildenafil, treatment with udenafil did not result in myalgia or abnormalities in color vision [13].

Paick et al. investigated the safety and efficacy of udenafil 100 mg and 200 mg in patients who were also receiving antihypertensive drugs [9]. Compared to the placebo groups, the udenafil groups reported significant improvements in IIEF-EFD scores (18.0 for placebo, 22.9 for 100 mg udenafil, 24.3 for 200 mg udenafil) from baseline (16.0 for placebo, 14.2 for 100 mg udenafil, 14.3 for 200 mg). The mean changes in response for IIEF Q3 (0.1 for placebo, 1.3 for 100 mg udenafil, and 1.4 for 200 mg udenafil); IIEF Q4 (0.7 for placebo, 2.0 for 100 mg udenafil, and 2.5 for 200 mg udenafil); SEP Q2* (3.13 for placebo, 25.85 for 100 mg udenafil, and 29.82 for 200 mg udenafil); and SEP Q3* (change of 20.59 for placebo, 57.88 for 100 mg udenafil, and 71.11 for 200 mg udenafil) demonstrated greater improvement in the udenafil groups compared to the placebo groups [9]. Forty-four point two percent and 54.5% of patients achieved normal EF, as measured by an IIEF-EFD score higher than 26, in the 100 mg and 200 mg udenafil groups, respectively. The percentage of positive GAQ responses were also significantly higher in the 100 mg udenafil (78.8%) and 200 mg udenafil groups (85.2%) compared to the placebo groups (41.2%) [9]. The most common adverse events were transient headache and flushing, which were mild or moderate in severity [9].

2.1.3. Pharmacokinetics and safety

Regarding its action toward PDE5, udenafil has a PDE1 selectivity ratio of 1262 compared to 41 for sildenafil and a greater PDE11 selectivity ratio of 96 compared to 7.1 for tadalafil [14]. The function of PDE11 is not currently well understood, but it is widely expressed in the skeletal muscle, testes, heart, prostate, kidney, liver, and pituitary [15]. While optimal dosage times have yet to be established through clinical trials, studies have demonstrated that udenafil reaches peak plasma concentrations (Tmax) at 0.8–1.3 hours and has a half-life of 7.3–12.1 hours, suggesting relatively quick onset and long duration [16]. A summary of the findings from clinical trials on the novel agents as well as the pharmacokinetics of the currently approved agents can be found in Tables 1 and 2, respectively. Udenafil has a longer half-life than sildenafil or vardenafil and a shorter Tmax than tadalafil [22,23]. In a multiple-dose study conducted by Kim et al., udenafil displayed a longer half-life (7–12 hours) than sildenafil (4 hours) but a similar Tmax after 7 weeks [8]. Importantly, another Kim et al. study evaluated the

Table 1. Summary of clinical trial findings of the novel agents.

	Udenafil	Mirodenafil	Lodenafil	Youkenafil	SLx-2101
Time to Onset	0.8–1.3 hours	1.25 hours	1.2 hours	0.8–1.4 hours	1 hour
Half-life	7.3–12.1 hours	2.5 hours	2.36 hours	2.1 hours	8–13 hours
Change in International Index of Erectile Function	+3.14 for placebo +6.59* for 50 mg +8.34* for 75 mg	+3.4 for placebo +7.6 for 50 mg +11.6 for 100 mg	+14.8 for placebo +18.6 for 40 mg +20.6 80 mg	Not available	Not available
Side Effects	Flushing, headache, nausea, congestion	Flushing, headache, eye redness, nausea, dizziness	Rhinitis, headache, flushing, visual disorder, and dizziness	Flushing, dizziness, headache, visual disturbances, hypotension, abdominal discomfort, chest discomfort, bilirubin elevation	Headache, visual disturbances
Contraindications	Nitrates	Nitrates	Nitrates	Nitrates	None identified
Type of Clinical Trial	Randomized, double-blind, placebo-controlled trial [11]	Multicenter, randomized, double-blind, placebo-controlled trial [17]	Randomized, placebo-controlled trial [19]	Randomized, placebo-controlled trial [18]	Randomized, double-blinded, placebo-controlled trial [20]

Table 2. Pharmacokinetics of currently approved phosphodiesterase 5 inhibitors [21].

	Sildenafil	Tadalafil	Vardenafil	Avanafil
Time to Onset	0.5 to 4 hours	Up to 36 hours	1 hour	0.5 hours
Half-life	4 hours	17.5 hours	4–6 hours	5 hours
Side Effects	Headache, flushing, dyspepsia, nasal congestion, nasopharyngitis, visual abnormalities	Headache, flushing, dyspepsia, nasal congestion, nasopharyngitis, back pain, myalgia	Headache, flushing, dyspepsia, nasal congestion, nasopharyngitis, visual abnormalities	Headache, flushing, dyspepsia, nasal congestion, nasopharyngitis
Contraindications	Nitrates	Nitrates	Nitrates	Nitrates

DISCLAIMER: This table is adapted from reference [21]: Huang SA, Lie JD. Phosphodiesterase-5 (PDE5) Inhibitors In the Management of Erectile Dysfunction. P T. 2013 Jul;38(7):407–19. The copyright for this table is attributed © 2013, MediMedia U.S.A., Inc. The Pharmacy and Therapeutics journal has ceased publication as of 2019. We have tried to contact the rights holder for permission. please contact the Expert Opinion on Investigational Drugs Editorial Office if you have any queries.

effect of food on the pharmacokinetics of udenafil and determined that the Tmax was delayed under fed conditions. The mean Tmax values after low-fat and high-fat meals were 2.1 hours and 2.6 hours, respectively. Although the oral bioavailability was not altered by food intake, the maximum serum concentration (Cmax) in the low-fat state was reduced by 21% [24]. This information suggests that tadalafil remains superior in its ability to maintain linear pharmacokinetics irrespective to food intake [25].

In a study by Kang et al., administration of udenafil in rats with hypocholesterolemia resulted in decreased plasma levels of endothelin 1, a vasoconstrictive peptide, and dimethylarginine, a natural endogenous inhibitor of both neuronal and endothelial isoforms of NO synthase [26]. These results suggest that udenafil may play a beneficial role in treating ED caused by endothelial dysfunction secondary to hypercholesterolemia.

2.2. Mirodenafil

2.2.1. Background

Mirodenafil, brand name Mvix®, is a second generation PDE5 inhibitor manufactured by SK Chemical Life Science in Seongnam, Korea, and approved in 2007. This compound is potent, reversible, and selective for PDE5 [27]. An orally disintegrating film was later developed in 2011 for patients who had difficulty swallowing tablets [27]. Early preclinical studies demonstrated a 10-fold higher selectivity for PDE5 than sildenafil, while the inhibitory effects on other PDEs are lower than sildenafil [27]. This promising data prompted the initiation of clinical trials to test the compound's efficacy.

2.2.2. Clinical trials

An evaluation on the efficacy and safety of mirodenafil in treating men with ED was first reported by Paick et al. in 2008 [27]. They observed improved scores in IIEF Q3 (0.68 ± 1.61 for placebo, 1.16 ± 1.66 for 50 mg mirodenafil, 1.64 ± 1.63 for 100 mg mirodenafil) and IIEF Q4 (0.80 ± 1.58 for placebo, 1.84 ± 1.71 for 50 mg mirodenafil, 2.62 ± 1.51 for 100 mg mirodenafil) from baseline for the on-demand 50 mg or 100 mg mirodenafil groups after 12 weeks, compared to the placebo groups [27]. Following treatment, 17.3%, 46.6%, and 62.2% of the placebo, 50 mg mirodenafil, and 100 mg mirodenafil groups, respectively, achieved normal EF, as measured by an IIEF-EFD score higher than 26 [28]. Mirodenafil treatment was generally well tolerated, with the most frequent adverse effects being mild or moderate facial flushing, nausea, headache, and eye redness. No color vision changes were reported, and side effects resolved spontaneously [28].

Clinical trials have also revealed mirodenafil to have benefits on lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH) [17]. Chung et al. investigated the safety and efficacy of once-daily dosing of 50 mg mirodenafil in patients with ED and LUTS and observed significant improvements in IIEF and International Prostate Symptom Score (IPSS) scores as well as improvements in maximum urine flow rate (Qmax) and postvoid residual volume (PVR) after 12 weeks, compared to placebo [17]. The mirodenafil group reported greater improvement changes from baseline in IPSS scores (−3.17), IIEF scores (4.39), and Qmax (2.26 mL/s) compared to the placebo group [29]. The most common adverse effects were facial flushing and headaches [17]. The mechanism by which mirodenafil improves urinary symptoms is not well understood and is currently under study.

Mirodenafil has demonstrated safety and efficacy in treating ED in patients with comorbidities and in combination with other medications. In a phase III study conducted by Park et al., on-demand treatment with 100 mg mirodenafil, compared to placebo, led to significant improvements in IIEF-EFD (9.3 vs 1.4), IIEF Q3 (1.7 vs 0.4), and IIEF Q4 (1.7 vs 0.3) scores, with mild and spontaneously resolving adverse effects [30]. In a prospective, multicenter, open-label study, Bang et al. also reported that daily use of 50 mg mirodenafil was safe and effective in patients on alpha-blocker therapy for BPH-LUTS after 8 weeks of treatment [29]. They observed that the total IPSS score decreased from an average of 23.7 to 13.7, Qmax increased from an average of 12.82 to 16.80, and PVR decreased from an average of 42.60 to 24.67 after 8 weeks of treatment. Paick et al. demonstrated that 100 mg mirodenafil was effective in treating ED in Korean men taking at least one antihypertensive medication, without causing any serious adverse effects [30]. Furthermore, all treatment-related adverse effects resolved spontaneously without discontinuation of treatment. In this study, the mirodenafil group, in comparison to the placebo group, had more significant increased scores in IIEF-EFD (9.35 ± 6.86 vs 2.66 ± 6.44), IIEF Q3 (1.37 ± 1.66 vs 0.31 ± 1.64), SEP Q2 (30.18 ± 37.45% vs 6.50 ± 43.20%), and SEP Q3 (55.30 ± 40.44 vs 16.48 ± 36.05%) as well as increased positive responses to the GAQ (84.31% vs 26.00%). After the 12-week treatment period, 40.7% of the mirodenafil group achieved normal EF, as measured by an IIEF-EFD score higher than 26, compared to only 7.5% of the placebo group [30].

2.2.3. Pharmacokinetics and safety

To reiterate, mirodenafil is highly selective for PDE5 and has fewer inhibitory effects on other PDEs, compared to sildenafil [18,27]. Mirodenafil has a Tmax of 1.25 hours and a half-life of 2.5 hours [27]. For a 100 mg mirodenafil dose, the Cmax is 373.4 ng/mL; however, mirodenafil's bioavailability is relatively low and rapidly undergoes breakdown by CYP450 enzymes, CYP3A4 and CYP2C [31]. The data regarding the effect of food on the pharmacokinetics of mirodenafil is minimal, thereby highlighting a direction for future studies.

2.3. Youkenafil

2.3.1. Background

Youkenafil®, an analog of sildenafil and vardenafil, developed by Yangtze River Pharmaceutical Group in Taizhou (Jiangsu Province), China, is another selective PDE5 inhibitor, which is currently undergoing clinical trials for eventual authorization by the Chinese Food and Drug Administration [19]. Early preclinical data determined that youkenafil is pharmacologically more active than sildenafil and possesses fewer gastrointestinal side effects [19]. The efficacy of the clinical trials and the pharmacokinetics of youkenafil are detailed in the following sections.

2.3.2. Clinical trials

As reported by Liang et al., the safety and tolerability of youkenafil up to a 200 mg dose was demonstrated in the study population [32]. Safety was determined through adverse event monitoring and laboratory analysis, including blood chemistry, urinalysis, electrocardiogram monitoring, and ocular fundus examination [32]. Adverse effects reported in patients receiving youkenafil included dizziness, headache, nasal congestion, hypotension, abdominal discomfort, bilirubin elevation, and chest discomfort [32]. *In vitro* studies suggest that youkenafil is metabolized by CYP3A4/5 [32]. However, further clinical trials are needed to determine the safety, tolerability, and efficacy of youkenafil in human subjects. While the study by Liang et al. suggests that youkenafil is safe up to 200 mg, without randomized, placebo-controlled trials to compare its efficacy to current PDE5 inhibitors, no recommendations can be made regarding its efficacy. To our knowledge, there are no scheduled clinical trials to determine youkenafil's efficacy.

2.3.3. Pharmacokinetics and safety

Youkenafil has a chemical structure similar to sildenafil but with stronger inhibition of PDE5 and milder gastrointestinal side effects [32]. In a rat model conducted by Yangtze River Pharmaceutical Group, youkenafil significantly increased sexual behavior and reversed paroxetine-induced ED [32]. This group also determined several pharmacokinetic parameters, including a half-life of 2.1 hours, an oral clearance of 32.5 mL/min/kg, and a volume of distribution of 6.5 L/kg [32]. Youkenafil was mainly distributed in the intestine, lung, liver, and kidney of rats after oral administration [32]. A previous study suggested that youkenafil is heavily metabolized by CYP450 enzymes and that its efficacy may be affected by inducers, inhibitors, and polymorphisms of these enzymes [32]. In this previous study, the authors also investigated the effect of fed vs fasted state on the pharmacokinetic parameters of youkenafil and observed that food did not affect its bioavailability but could decrease Cmax and increase Tmax [32]. Further studies are needed to determine the safety, efficacy, and pharmacokinetic profile of youkenafil in humans.

2.4. Lodenafil

2.4.1. Background

Lodenafil, brand name HELLEVA®, developed by Cristalia Productos Quimicos Farmaceuticos in Sao Paulo, Brazil, is a unique PDE5 inhibitor with a dimeric structure consisting of two lodenafil molecules connected by a carbonate bridge [6]. The oral bioavailability is higher in this formulation than the prodrug [33]. The efficacy of novel clinical trials and resulting pharmacokinetic parameters are discussed in detail below.

2.4.2. Clinical trials

A phase II, double-blind, placebo-controlled study conducted in Brazil, which enrolled 72 men over the age of 18 who had been experiencing ED for more than 6 months and were in a stable sexual relationship, was the pivotal trial for lodenafil [34]. Participants were randomized to placebo, lodenafil 20 mg, lodenafil 40 mg, or lodenafil 80 mg for a 4-week observation period, and the ascending doses were well tolerated. A significant improvement in IIEF-EFD and SEP Q2 and Q3 scores for lodenafil dosing, compared to placebo, were noted [34]. Building upon this early data, a larger phase III clinical trial was conducted in Brazil, where 350 men with ED were randomized to placebo and lodenafil dosing of 40 mg or 80 mg and followed for 4 weeks [35]. The primary endpoints were IIEF-EFD outcome scores, SEP Q2 and Q3 scores, and adverse events. IIEF-EFD scores were 14.8 for placebo, 18.6 for lodenafil 40 mg, and 20.6 for lodenafil 80 mg. Increased scores in SEP Q2 with the use of lodenafil or placebo demonstrated 52.1% for placebo, 63.5% for lodenafil 40 mg, and 80.8% for lodenafil 80 mg (analysis of variance (ANOVA) p value: <0.01) [32]. Finally, increased scores in SEP Q3 with the use of lodenafil or placebo demonstrated 29.7% for placebo, 50.8% for lodenafil 40 mg, and 66.0% for lodenafil 80 mg (ANOVA p value: <0.01) [35]. Adverse reactions were mild and included headache, flushing, rhinitis, dyspepsia, and fluctuations in color vision [35]. However, the incidence of multiple adverse effects was significantly higher in the lodenafil groups compared to the placebo groups. The incidence of rhinitis, headache, and flushing in patients treated with lodenafil 80 mg was 35%, 32%, and 27%, respectively, which was significantly higher compared to the placebo groups who experienced those events at 9%, 10%, and 5%, respectively [35]. Further trials are needed to determine the comparative efficacy and safety of lodenafil versus currently approved PDE5 inhibitors.

2.4.3. Pharmacokinetics and safety

Following ingestion of lodenafil, the carbonate bridge is cleaved to yield two active lodenafil molecules [34,35]. Clinical trials have demonstrated a Tmax of 1.2 hours and a half-life of 2.36 hours [36]. Studies have documented that the compound enhances NO-dependent relaxation induced by ACh or electrical stimulation in isolated rat and human penile tissue [35,36]. Additionally, lodenafil was noted to be twice as potent as sildenafil in inhibiting the hydrolysis of cGMP in human platelet extracts [37]. However, it is important to note that increased potency was observed in an *in vitro* investigation involving different tissue from humans, dogs, and rats, thus raising concerns about the drug's pharmacological profile [37]. The current studies on lodenafil fail to incorporate data regarding the effect of food on the pharmacokinetics of this drug, an interaction which directly influences patients' adherence and satisfaction with drug therapy.

2.5. SLx-2101

2.5.1. Background

SLx-2101® is a novel compound developed by Surface Logix in Brighton, Massachusetts, United States, for the treatment of ED, endothelial dysfunction, and hypertension [38]. It is our opinion that due to the lack of recent literature and very little preclinical data on the compound, drug companies have abandoned initiating further research on SLx-2101.

2.5.2. Clinical trials

In a double-blind, randomized, single-dose, phase II study, SLx-2101 was investigated for its safety, tolerability, and efficacy in men with ED who responded to PDE5 inhibitors [39]. The study enrolled 40 healthy male volunteers who were given single doses of 5, 10, 20, 40, or 80 mg, with 6 subjects receiving an active compound and 2 receiving a placebo at each dosing level. The study demonstrated that SLx-2101 was well tolerated up to 40 mg, with headache being the most reported adverse effect and with no clinically significant cardiac abnormalities observed, per assessment of heart rate, blood pressure, and electrocardiogram monitoring [39]. At the highest dosing of 80 mg, subjects reported visual disturbances. RigiScan data demonstrated positive effects on erectile rigidity at 0–6 hours after dosing of 10, 20, 40, and 80 mg (without visual sexual stimulation) and at 24–24.5 hours after dosing of 20, 40, and 80 mg (with visual sexual stimulation). In addition, SLx-2101 demonstrated some erectile activity 36–48 hours after a single dose of 10 mg while maintaining good safety and tolerability profiles [39].

2.5.3. Pharmacokinetics and safety

Following oral administration, SLx-2101 is metabolized into its active form, SLx-2081, which can extend the clinical viability of the compound and offer a longer duration of benefit to men with ED [6]. The Tmax for SLx-2101 is 1 hour, whereas the Tmax for SLx-2081 is 2.8 hours. The half-life of SLx-2101 is 8–13 hours, whereas the half-life of SLx-2081 is 9–14 hours [39].

3. Conclusion

Our communication provides a comprehensive review of several novel drugs currently being evaluated for their safety, efficacy, and biochemical profiles in clinical trials for treating men with ED. Our analysis of the clinical trials conducted on these drugs reveals that they have demonstrated clear efficacy and safety in treating ED and have different pharmacokinetic effects on PDE isoenzyme families, which may benefit patients with specific underlying conditions.

Udenafil, for example, has a longer half-life than sildenafil or vardenafil and reaches Tmax quickly, which may be beneficial for patients with endothelial dysfunction secondary to hypercholesterolemia. Mirodenafil has been determined to be effective in treating ED and LUTS associated with BPH. Youkenafil has shown promise via *in vitro* studies and requires further clinical trials to determine its safety and efficacy. Lodenafil has demonstrated significant improvement in outcome scores in IIEF and in SEP Q2 and Q3, with mild adverse reactions. Lastly, SLx-2101, albeit seemingly abandoned, indicated promise in preclinical studies. Importantly, a thorough review of more robust data is warranted before any of these drugs can be made openly available in the United States.

4. Expert opinion

The pursuit of innovative PDE5 inhibitors for the treatment of ED presents a promising opportunity for advancement in the field. However, there are substantial obstacles and challenges that need to be addressed to ensure the successful development of these novel compounds. Existing medications, such as sildenafil, tadalafil, avanafil, and vardenafil, have proven to be effective in treating ED, but they are accompanied by common side effects, including headaches, nasal congestion, myalgia, and facial flushing. These side effects may render the drugs unsuitable for some patients, therefore necessitating alternative options.

Moreover, there is a pressing need for additional pharmaceutical options for patients who may not respond well to traditional PDE5 inhibitors and who may require noninvasive treatment alternatives, including those with diabetes and spinal cord injuries as well as those treated with prostatectomy and radiation therapy. Additionally, the interactions of the novel drugs with alpha-blocking medications, nitrates, and other common prescriptions need to be elucidated before making further recommendations. Developing treatments specifically tailored to nonresponders and to those with contraindications could vastly improve their quality of life and overall health outcomes.

The investigational drugs discussed in this review have demonstrated promising results in preclinical and early-phase clinical studies. Nevertheless, to solidify their position as viable treatment options, their safety, efficacy, and tolerability require further validation through more rigorous and larger-scale clinical trials. One of the primary challenges in this process is designing and executing well-controlled, randomized clinical trials that offer conclusive evidence of the benefits and safety profiles of these novel compounds, particularly when compared to the widely prescribed drugs in clinical practice. These trials are often difficult to conduct because of

the paucity of PDE5 inhibitor-naïve study subjects and because of the investigational drugs being compared to agents controlled by large pharmaceutical companies, thus making it difficult to market a new product.

Comparing the duration and dosage of these drugs may prove difficult due to variations in their chemical structures and mechanisms of action. The execution of such trials necessitates extensive planning, funding, and involving a large patient population to ensure a statistically significant result. Collaborative efforts between researchers, pharmaceutical companies, and regulatory agencies will be crucial in overcoming these challenges.

In the coming years, research efforts may shift toward developing more effective and safer drugs for ED treatment. This could entail a deeper comprehension of the intricate mechanisms underlying ED and the creation of drugs that more precisely target these mechanisms. These future research directions may also involve exploring new technologies and methodologies, such as LiSWT, gene therapy, stem cell therapy, platelet-rich plasma, or umbilical cord-derived Wharton's jelly, which could revolutionize the treatment and management of ED. A systematic review by Ezzet et al. compared many of the novel technologies under investigation. Of these, the utilization of adipose-derived stem cells (ADSCs) in rat models showed significant promise [40]. More specifically, several studies noted that ADSCs improved ED secondary to a multitude of etiologies, including cavernosal nerve injury, penile fibrosis, and endothelial compromise secondary to diabetes [40]. In addition, several studies demonstrated the beneficial effects of LiSWT as treatment of ED in patients. One study reported that LiSWT improved EF for up to 6 months in patients with vasculogenic ED [40]. The data regarding the efficacy of gene therapy are controversial, but some of the techniques mentioned in the literature include introducing genes within viral vectors that upregulate the production of endothelial NO. These therapies aim to improve the patient's ability to obtain organic erections, without the need for further therapies. This could revolutionize the treatment of ED, and we feel more research will be focused on these treatments in the future.

In conclusion, the development of novel PDE5 inhibitors offers hope for improved and patient-specific treatment of ED. Additional research is required to confirm their safety, efficacy, and tolerability as well as to compare them with existing drugs and in combination with some of the aforementioned alternative treatments. Despite these challenges, the potential benefits of developing new medications to treat ED are substantial, and continued research in this field is both necessary and justified. The future of ED treatment hinges on the collaborative efforts of researchers, healthcare professionals, and patients working together to pave the way for more effective, safer, and personalized therapies.

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Author contributions

Z Melchiode, T Nguyen, O Dawood, and GA Bobo performed literature searches, Z Melchiode, T Nguyen, O Dawood, and GA Bobo drafted the manuscript, and Z Melchiode, O Dawood, GA Bobo, and WJG Hellstrom revised and finalized the manuscript for publication.

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