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DRUG EVALUATION

Tadalafil for the treatment of benign prostatic hyperplasia

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ABSTRACT

Introduction: In men, lower urinary tract symptoms (LUTS) are primarily attributed to benign prostatic hyperplasia (BPH). Therapeutic options are targeted to relax prostate smooth muscle and/or reduce prostate enlargement.

Areas covered: This article reviews the major preclinical and clinical data on PDE5 inhibitors with a specific focus on tadalafil. It includes details of the role of the nitric oxide (NO)-cyclic guanosine monophosphate (cGMP) – PDE5 pathway in the LUT organs (bladder and prostate) in addition to the available data on tadalafil in patients with LUTS secondary to BPH with or without erectile dysfunction (ED).

Expert opinion: Preclinical and clinical data have clearly demonstrated that PDE5 inhibitors induce bladder and prostate relaxation, which contributes to the improvement seen in storage symptoms in both animal models of bladder and prostate hypercontractility. Tadalafil is effective both as a monotherapy and add-on therapy in patients with LUTS secondary to BPH. Furthermore, as LUTS-BPH and ED are urological disorders that commonly coexist in aging men, tadalafil is more advantageous than α1-adrenoceptors and should be used as the first option. Tadalafil is a safe and tolerable therapy and unlike α1- adrenoceptors and 5-alpha reductase inhibitors, which can cause sexual dysfunctions, tadalafil improves sexual function.

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KEYWORDS
Tadalafil; benign prostatic hyperplasia; lower urinary tract; prostate; bladder; phosphodiesterase type 5; erectile dysfunction; cyclic GMP

1. Introduction

The cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5) is ubiquitous enzyme expressed in several cells and tissues. The inhibition of PDE5 amplifies the NO-cGMP pathway, thus leading to vascular [1] and non-vascular smooth muscle relaxation [2,3], lower leucocyte adhesion [4,5], reduced platelet activation and inhibition of cell proliferation [6,7].

In the early 1980s, zaprinast was introduced as the first-in-class PDE5 inhibitor. Later, Viagra (sildenafil citrate) was launched on the market in 1998 as the first oral treatment for male erectile dysfunction (ED). Although sildenafil was first developed for treating patients with hypertension [8] and angina pectoris [9], its efficacy was not demonstrated in these conditions. The impact of sildenafil has stimulated academic, clinical and industrial research to better understand the NO-cGMP-PDE5 pathway in several organs and systems and the pathophysiology of ED. In 2003, two other PDE5 inhibitors named vardenafil, a closely related structural analog of sildenafil and tadalafil, a tetrahydro-β-carboline derivative were approved by the Food and Drug Administration (FDA) for treating patients with ED. In 2012, avanafil, a PDE5 inhibitor was also approved by FDA. Although other PDE5 inhibitors are commercially available as lodenafil carbonate [2,10], udenafil [11] and mirodenafil [12,13] they have not been approved by FDA. In 2011, the therapeutic indication of tadalafil was expanded by FDA to treating patients with lower urinary tract symptoms secondary with benign prostatic hyperplasia (LUTS-BPH) with or without ED. This review highlights major preclinical and clinical studies of tadalafil (Box 1) in the treatment of LUTS-BPH. We decided to also focus on the preclinical data to understand the rationale of repurposing tadalafil in the treatment of BPH even in patients without ED.

A PubMed search was performed. Articles were selected on the basis of preclinical and clinical data regarding the main mediators and risk factors responsible for BPH. As for preclinical data, we focused on the role of PDE5 inhibitors, including tadalafil as anti-inflammatory, antiproliferative and relaxant in the prostate in animal models of benign prostate hyperplasia. As for clinical trials, we focused on data from randomized controlled trials conducted in patients with LUTS secondary to BPH with or without ED who have received tadalafil alone or in combination with other therapies. Only studies published in English were considered. Articles published within the past 10 years were prioritized; however, older studies were included owing to their historical scientific relevance. The terms LUTS, BPH, LUTS-BPH, ED, PDE5, PDE5 inhibitors, sildenafil, vardenafil, tadalafil were used.

1.1. Overview of the market

Benign prostatic hyperplasia (BPH) is an anatomopathological diagnosis and refers to the proliferation of the epithelial and the smooth muscle layers of the prostate. Anatomically, these processes can result in an increase in the volume of the prostate. The clinical presentation of BPH is a result from the dynamic (the

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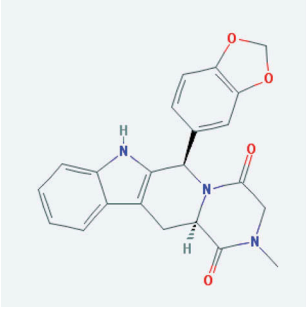
Box 1. Drug summary.

Drug name	Tadalafil
Phase	Launched
Indication	Lower urinary tract symptoms secondary to benign prostatic hyperplasia with or without erectile dysfunction
Pharmacology description	Phosphodiesterase type 5 inhibitor
Route of administration	Oral
Chemical structure	
Pivotal trial(s)	References# [14,63–67]

tension of the prostate smooth muscle into the prostatic urethra) and static (anatomic obstruction due to prostate enlargement) pathways thus resulting in urinary symptoms. The prevalence of BPH increases as men get older. Treating BPH is of high importance, due to the fact that it impacts the quality of life due to the appearance of LUTS.

Regarding the pharmacological management of BPH, medications were developed to target the dynamic phase such as α1-adrenoceptor blockers (terazosin, doxazosin, tamsulosin, and alfuzosin) and tadalafil and the static phase such as 5-alpha reductase inhibitors (finasteride and dutasteride).

The α1-adrenoceptor blockers and 5-alpha-reductase inhibitors are the oldest therapies for treating patients with BPH, but many patients do not tolerate them due to their adverse effects such as dizziness, postural hypotension, retrograde or reduced ejaculation (alpha-1 adrenoceptor blockers) and male infertility, ejaculatory dysfunction and loss of libido (5-alpha reductase inhibitors). PDE5 is an ubiquitous enzyme expressed in the lower urinary tract organs including vessels, bladder, bladder neck, prostate, urethra and corpus cavernosum. The inhibition of PDE5 by tadalafil promotes vascular and non-vascular smooth muscle relaxation, leading to prostate smooth muscle relaxation and hence relieving the urinary symptoms. Tadalafil has been developed by Elli Lilly and was first approved for the treatment of ED. In 2011, tadalafil 5 mg once daily has been licensed for the treatment of LUTS secondary to BPH with or without ED by the US food and Drug Administration. As ED and LUTS-BPH are common urologic conditions of aging men associated with decreased quality of life, tadalafil constitutes a more advantageous therapy over α1-adrenoceptor blockers.

2. Chemistry

Tadalafil acts by preventing the binding of cGMP to the catalytic domain of PDE5. This makes the hydrolysis reaction impossible in producing the inactive metabolite 5′-GMP [15,16]. The blockade occurs by hydrogen bonding to the indole ring and the side chain of the 817 glutamine residue of PDE5, thereby stabilizing the ligand in the catalytic pocket [17–19]. In addition, other interactions carried out by specific groups of the molecule (with some residues in subdomains of the enzyme catalytic site) are also important. For instance, the methylenedioxyphenyl group, which represents a group with greater conformational mobility, allows interactions with residues in the H pocket [17]. It is noteworthy that interaction with H pocket is one of the reasons why tadalafil maintains high affinity when compared to sildenafil [17].

3. Pharmacodynamics

The action of cGMP is terminated by cGMP-specific 3′,5′-cyclic phosphodiesterase (PDE5) [20], retinal rod rhodopsin-sensitive cGMP 3′,5′-cyclic phosphodiesterase (PDE6) [21], and high affinity cGMP-specific 3′,5′-cyclic phosphodiesterase 9 (PDE9) [22]. Tadalafil inhibits the PDE5 enzyme with greater selectivity thus enhancing intracellular levels of cGMP to promote smooth muscle relaxation [20].

4. Pharmacokinetics and selectivity

While PDE5 is expressed in several organs including prostate [23], bladder [24], testis [25], corpus cavernosum [26], vascular smooth muscle [24,27] and platelets [28], and others, the PDE6 isoform is mainly found in the mammalian eye to control phototransduction in the rod and cone segments of retina [29]. Due to the amino acid sequence homology between PDE5 and PDE6 and the similarity of their catalytic domains, the first generation of PDE5 inhibitors (sildenafil and vardenafil) can also inhibit PDE6 [30]. On the other hand, the PDE5/PDE6 ratio (780) makes tadalafil [31] a more selective PDE5 inhibitor than sildenafil and vardenafil. Visual disturbances such as functional blindness, blurred vision, and greater light sensitivity have been linked to PDE6 inhibition [32]. With respect to the cross-reactivity with the isoform PDE11, in cells overexpressing human PDE11, the PDE5/PDE11 ratios for tadalafil, vardenafil, and sildenafil are 40, 9300 and 1000-fold [33]. However, the physiological role of PDE11 is poorly studied. To date, there are no studies that evaluated whether sildenafil, vardenafil or tadalafil interfere with PDE9 activity, an enzyme that preferentially degrades cGMP.

In addition to the greater selectivity of tadalafil for PDE5 relative to PDE6, another advantage of tadalafil is related to its pharmacokinetic properties. The higher half-life and duration of action of tadalafil (17.5 and 36 h, respectively) in comparison to sildenafil (3.8 and 8 h) and vardenafil (3.9 and 12 h) [31], its dose linearity and no interference of food in bioavailability [34] makes tadalafil a more attractive therapeutic choice. Tadalafil has an apparent volume of distribution (V/F) of 60–70 l and is predominantly metabolized by cytochrome P450 (CYP) 3A4. As tadalafil is mainly metabolized by CYP 3A4, all inducers and inhibitors of 3A4 have the potential to reduced or increase systemic exposure, respectively [35]. Administration of tadalafil is contraindicated in patients taking nitrates as it potentiates their associated hypotensive effect [36].

5. Preclinical data

5.1. Nitric oxide-cGMP pathway

Nitric oxide (NO) is the main mediator that relaxes vascular and non-vascular smooth muscle of the lower urinary tract (LUT) organs including bladder, prostate, urethra and corpus cavernosum [37]. Nitric oxide activates the intracellular receptor named soluble guanylate cyclase (sGC), which converts guanosine triphosphate (GTP) into 3′,5′-cyclic guanosine monophosphate (cGMP). In the LUT, the intracellular levels of cGMP are controlled by its rate of formation, mainly due to soluble guanylate cyclase (sGC) activity [37] and by its degradation in virtue of phosphodiesterase (PDE) activities [38]. In the prostate and urethra from mice, it was observed that the levels of cGMP can also be modulated nonenzymatically by multidrug resistance proteins type 4 and 5 (MRP4 and MRP5), which pump cGMP out of the cell [39]. Although MRPs are expressed in human prostate and bladder [40], its physiological role has not been studied yet. The physiological effects of cGMP are exerted through the activation of cGMP-dependent protein kinases (PKG), cyclic nucleotide-gated ion channels and the activation and/or inhibition of PDEs.

5.2. Role of PDE5 inhibitors in the lower urinary tract

The nitric oxide signaling pathway plays a key role in relaxing smooth muscle from the bladder, bladder neck, prostate, urethra and corpus cavernosum smooth muscle. The density of neuronal nitric oxide synthase (nNOS), evaluated by immunohistochemistry, has been found to be greater in nerve terminals from the bladder neck, urethra, and prostate than in the detrusor smooth muscle from several species [38]. In the prostate, nNOS is mainly localized in the stroma and in the glandular epithelium [23,41]. In humans and animals (rats, mice, and rabbits), the levels of NO and/or cGMP are associated with impaired function of the bladder [42], prostate [43], urethra [44] and corpus cavernosum [45,46], thus contributing to smooth muscle hypercontractility, or in the case of humans to LUTS. Therefore, substances that increase or restore the intracellular levels of cGMP are of great value to ameliorate the hypercontractility seen in the smooth muscle from bladder, prostate, and urethra, hence alleviating the LUTS symptoms.

In the LUT, PDE5 is widely distributed in the bladder, bladder neck, prostate, vasculature, and external urethral sphincter. A study carried out in rat bladder showed that the relative expression of PDE5 mRNA was greater in the bladder and urethra than in the prostate and corpus cavernosum [47]. Conversely, in human bladder, the PDE5 gene is expressed similarly in other portions of the male genital tract including seminal vesical, vas deferens, urethra, and prostate with the exception of the corpus cavernosum, in which mRNA PDE5 is 10-fold greater than in the bladder [48]. (Table 1)

In prostatic tissue obtained from patients, cDNA fragments encoding PDE1, 2, 4, 5, 7, 8, 9, and 10 were detected and the PDE inhibitors; papaverine, rolipram, zaprinast and sildenafil-induced concentration-dependent relaxation with maximal response values of 58%, 32%, 28%, and 19%, respectively [49]. The PDE5 distribution in prostatic urethra and prostate derived from male patients who underwent adenomectomy for BPH [24] or benign tissues from prostatectomy procedure [50] was also assessed. While an intense PDE5 positivity was observed on smooth muscle cells from the urethra wall and on the endothelial and smooth cells from blood vessels, a scanty distribution was found on the fibromuscular stroma of prostate [24,50].

In the prostate from spontaneously hypertensive rats, which present bladder and prostate hypercontractility and hypoxic areas (evaluated by hypoxyprobe staining), the expression of hypoxia-related proteins, such as HIF-1α were significantly increased in comparison to control animals. Long-term treatment with tadalafil (2 mg/kg/day, by oral gavage) for seven or twenty-eight days completely restored expression levels to match the controls, thus implying that inhibition of PDE5 by tadalafil improved prostate oxygenation and restored tissue structure [50]. In adult rats with pelvic ischemia (induced by endothelial injury of iliac artery followed by a 2% cholesterol-rich diet), both an increase in smooth muscle α-actin and collagen deposition in the stroma from ventral prostate, accompanied by greater contractile responses induced by α1-adrenoceptor agonists and transmural stimulation were observed. Chronic treatment with tadalafil (2 mg/kg) for 8 weeks prevented the histological and functional alterations seen in untreated rats. These results led the authors to conclude, that besides aging and androgen impairment, pelvic ischemia seems to contribute to the development of BPH and PDE5 inhibitors could reverse arterial insufficiency due to atherosclerosis [51].

The role of PDE5 inhibitors in bladder relaxation was also assessed. Sildenafil, at 10 μM, produced a relaxation of 40% (of maximum response) in isolated human bladder tissue from men who underwent prostatectomy. The mechanism involved also showed a role for local production of hydrogen sulfide [52]. In spinal cord-injured rats, which display neurogenic detrusor overactivity and non-void contractions (NVCs) thus leading to greater bladder afferent nerve firing (BANF), intravenous administration of vardenafil (1 mg/kg, for 45 min) reduced both NVCs and BANF, thus improving storage symptoms [53]. In the human bladder, an NO-donor caused a concentration-dependent relaxation (36%) and vardenafil (100 nM) significantly potentiated (62%) SNP-induced relaxation [48].

With respect to the role of PDE5 inhibitors in the proliferation of smooth muscle from the LUT, most of the studies focused on the prostate. In human prostatic smooth muscle cells obtained from patients underwent prostatectomy, the NO-donors SIN-1 and SNAP produced a weak anti-proliferative effect, evaluated by [^{3}H]- thymidine and [^{35}S]-methionine, while the co-incubation with the PDE5 inhibitor, sildenafil greatly reduced [^{3}H]-thymidine incorporation in a concentration-dependent manner. This reduction was greater in cells stimulated with the endogenous substance, lysophosphatidic acid, in comparison with cells treated alone with sildenafil [54]. In human prostate stromal cells, the PDE5 inhibitors sildenafil, tadalafil, and vardenafil inhibited cell viability (in a concentration-dependent manner), evaluated by tetrazolium assay, with maximal inhibition obtained at 10 μM (20%, 60%, and 90%, respectively) after 24 h of incubation [47]. Another study showed that tadalafil inhibited 5-bromo-2-deoxyuridine (BrDU) incorporation in primary prostate stromal cells (again in a concentration-dependent manner) and this effect was

Table 1. Major preclinical findings linking the role of PDE5 enzyme and its inhibitors in the prostate and bladder.

Preclinical data	Protocol design	Relevant effects	Study
Prostate			
In vitro	Gene expression for PDE5 in rat organs	In rat, the relative expression of PDE5 is greater in the bladder and urethra than in the prostate and corpus caversoum.	[47]
In vitro	Gene expression for PDE5 in human organs	In human genital tract, the mRNA PDE5 expression in seminal vesicle, vas deferens, urethra and prostate was similar.	[48]
In vitro	Functional assays	Inhibitors of PDEs as zaprinast, sildenafil, rolipram, and papaverine induced isolated prostate from human.	[49]
In vivo	Chronic administration of tadaladil (2 mg/kg) for 7 or 28 days in spontaneously hypertensive rats (SHR)	SHR presents prostate hypercontractility. The expression of HIF1-alfa, a marker of hypoxia was increased in these organs. Chronic administration of tadalafil improved prostate oxygenation and restored tissues alterations.	[50]
In vivo	Chronic treatment with tadalafil (2 mg/kg) for 8 weeks in rat underwent pelvic ischemia and fed with a cholesterol-rich diet.	The prostate from these animals presented an increase of alpha-actin and collagen and great contractile response. Tadalafil prevented both the histological and functional alterations.	[51]
In vitro	Cell proliferation in primary cells from human prostatic smooth muscle	The NO-donors, SIN-1 and SNAP produced weak antipriliferative effect and this response was greatly potentiated in the presence of sildenafil.	[54]
In vitro	Cell viability in human prostate stroma cells	The PDE5 inhibitors, sildenafil, tadalafil and vardenafil concrentration-dependent inhibited cell viability (20%, 60%, and 90%, respectively).	[54]
In vitro	Proliferation determination in human prostate stroma cells	The antiproliferative effect of tadalafil was reversed by the protein kinase G inhibitor, KT 2358.	[47]
In vitro	Treatment with vardenafil (10 nM, 1 h) and tadalafil (100 nM, 1 h) in human myofibroblast prostatic cells exposed to TNF-alpha and ox-LDL to induce induce inflammation.	Tadlafil and vardenafil reduced prostate inflammation and this effect was reversed by the PKG inhibitor, KT 5823.	[54]
In vitro	The gene and protein expression of PDE5 were determined in testosterone – treat rat and in hyperplasic prostate from patients.	The gene and protein expression of PDE5 were increased in hyperplasic prostate from rat and human.	[23]
Bladder			
In vitro	Concentration-response curves to sildenafil in isolated bladder from human.	Sildenafil relaxed by 40% at 10 μM isolated human bladder in a mechanism dependent on hydrogen sulfide release.	[52]
In vivo	Treatment with vardenafil (1 mg/kg, 45 min, i.v) In spinal-cord injured rats.	Detrusor overactivity is seen in this animal model and vardenafil reduced the on-void contractions and bladder nerve affrent firing, thus improving storage symptoms.	[53]
In vitro	Functional assays	In human bladder, the NO-donor, sodium nitroprusside relaxed and vardenafil increased this response.	[48]

reversed by the PKG inhibitor, KT 2358 (200 nM), thus showing that the antiproliferative effect induced by tadalafil involves the activation of PKG by cGMP [55]. In human myofibroblast prostatic cells exposed to TNF-alpha and ox-LDL to induce inflammation, in vitro treatment with vardenafil (10 nM, 1 h) and/or tadalafil (100 nM, 1 h) reduced the levels of IL-8, a marker of prostate inflammation and the co-incubation with the PKG inhibitor, KT5823, reversed this effect, thus suggesting the involvement of cGMP-PKG in blunting the inflammation [56].

Interestingly, in a testosterone-induced rat model of BPH and in human hyperplastic prostate, a 2.5 fold increase on mRNA PDE5 was observed in comparison with respective controls, accompanied by greater protein expression [23]. Although Zhang et al., 2015 [23] did not evaluate whether PDE5 inhibitors could interfere on prostate proliferation, considering that PKG activation by cGMP interferes on cell cycle, we can speculate that the greater PDE5 expression seen in the rat and human prostate, the lower the cGMP levels would be, thus favoring prostate proliferation to induce prostatic hyperplasia (Table 1)

Another potential beneficial effect of the accumulation of cGMP in the prostate is its anti-inflammatory effect. In human prostate cells incubated with TNF-alpha or metabolic factors (including oxidized low-density protein (oxLDL)), higher levels of IL-8 were observed. In vitro treatment with tadalafil or vardenafil reduced the secretion of IL-8 and suppressed the expression of the oxLDL receptor in mechanisms dependent on PKG activation [56]. A more recent study showed that all PDE5 inhibitors, tadalafil (2 and 10 mg/kg), vardenafil (10 and 30 mg/kg) and sildenafil (10 and 30 mg/kg) administered in rats with autoimmune prostatitis promoted a substantial reduction on pelvic pain. However, in this study, the authors did not quantify whether these inhibitors reduced pro-inflammatory cytokines [57].

6. Pivotal clinical trials of tadalafil in patients with benign prostatic hyperplasia

Lower urinary tract symptoms (LUTS) secondary to BPH is a condition that impacts the quality of life in elderly men and characterized by increased frequency of urination and urgency with or without nocturia [58]. Benign prostatic hyperplasia refers to the noncancerous proliferation of smooth muscle, connective tissues and glandular epithelium of the prostate. Aging [59], diabetes [60], obesity [61] and elevated markers of inflammation [62] constitute an important risk factor for BPH development.

Therapeutic management for LUTS-BPH is aimed at relaxing the bladder and/or prostate smooth muscle and inhibiting prostatic cell growth. There is an increasing interest in agents that increase cGMP levels for the treatment of LUTS-BPH, since the enzymes involved on NO and cGMP biosynthesis are presented on the bladder and in the transition zone of the human prostate, fibromuscular stroma, glandular epithelium and blood vessels [63].

The efficacy of tadalafil as monotherapy or in combination with α1-adrenoceptor blockers for the treatment of LUTS-BPH has been demonstrated in several randomized, placebo-controlled clinical trials. The majority of the studies evaluated efficacy with subjective parameters as total International Prostate Symptom Score (IPSS), IPSS irritative domain, IPSS obstructive domain, IPSS quality of life (IPSS-QoI) and non-invasive urodynamics parameters such as maximum flow rate (Qmax) and post-void residual volume (PVR).

In a single-blind, placebo-controlled trial study, men 45 years or older with a history of LUTS-BPH of 6 months or longer (N = 251) were randomly assigned to receive dose escalation of tadalafil (5 and 20 mg and 6 weeks interval between dose) or placebo. Tadalafil significantly improved the mean change from baseline in International Prostate Symptom Score (IPSS) at 6 (5 mg −2.8 vs placebo −1.2) and 12 (20 mg −3.8 vs placebo −1.7) weeks. Tadalafil also improved responses on secondary evaluation as IPSS irritative and obstructive index. The International Index of Erectile Function was also improved in 56% of men with LUTS-BPH with ED. No difference in the Qmax and PVR parameters between the tadalafil-treated group in comparison with placebo was observed [63]. In a randomized pilot, double-blind, crossover study conducted in men older than 50 years with a history of LUTS-BPH (N = 30 patients) for at least 6 months were grouped to receive tamsulosin (0.4 mg/day) or tamsulosin (0.4 mg/day) plus tadalafil (20 mg/day) for 45 days. Both tadalafil plus tamsulosin and tamsulosin alone significantly improved IPSS (mean: 10.2 and 12.7, $P < 0.001$, respectively), IPSS-QOL (mean: 1.6 and 2.3, $P < 0.001$, respectively), Qmax (mean:12.6 vs 11 L mL/sec) and PVR (mean: 21.3 and 24.8 mL) compared to baseline (mean: 19.4, 4.1, 9.6 mL/sec and 60 ml, respectively) [64]. In a parallel, multinational, randomized, double-blind, placebo-controlled, group study, men with ED and moderate to severe LUTS secondary to BPH were assigned to receive either placebo (N = 115), tadalafil 2.5 mg (N = 113), 5 mg (N = 117), 10 mg (N = 120) and 20 mg (N = 116) for 12 weeks. The IPSS score (2.5 mg: −3.6, 5 mg: −4.2, 10 mg: −4.7 and 20 mg: −4.7 versus placebo: −2.1, $P < 0.05$) showed a significant improvement from baseline in all tadalafil doses versus placebo. The Qmax and PVR scores did not show any statistical difference between tadalafil groups versus placebo [65].

Two other clinical trials with similar study design (placebo-controlled, double-blind, a screening/washout period and a placebo lead-in of 4 weeks) evaluated the efficacy of increasing dose of tadalafil in comparison with placebo, in men with BPH-LUTS. Roehrborns et al., 2008 showed that the IPSS score from baseline was significantly improved for 2.5 mg (−3.0, $P = 0.015$), 5 mg (−4.9, $P < 0.001$), 10 mg (−5.2, $P < 0.001$) and 20 mg (−5.2, $P < 0.001$) of tadalafil when compared to placebo (−2.3) [66]. In another study tadalafil 5 mg, but not 2.5 mg significantly improved IPSS (−6.1 ± 0.4) in comparison to baseline (−3.8 ± 0.5) [67] (Table 2)

7. Safety and tolerability

Overall, in the clinical trials mentioned above, there were no reports of increased post-void volume. Tadalafil is well tolerated, and the proportion of patients reporting at least one treatment-emergent adverse event (TEAE) did not differ from placebo. The most common treatment-related adverse effects report in these trials were headache, followed by flushing, dyspepsia and myalgia/back pain [63–67].

8. Conclusion

Tadalafil represents a well-tolerated and effective treatment option in men with LUTS-BPH with or without ED. As LUTS-BPH and ED can appear concomitantly in aging men, a drug that improves the signs and symptoms of both conditions is of therapeutic relevance.

9. Expert opinion

The disorders LUTS-BPH and ED present in older men and can also coexist as pathways in the bladder, prostate and corpus cavernosum are similar. Considering preclinical studies, tadalafil plays an important role in the pathophysiology of LUTS-BPH as it (i) relaxes vascular and non-vascular smooth muscle, (ii) increases tissues oxygenation, (iii) reduces afferent nerve activity, (iv) reduces bladder and prostate smooth muscle cell proliferation and (v) inflammation. Although the three PDE5 inhibitors sildenafil-Viagra, vardenafil-Levitra and tadalafil-Cialis approved by FDA share the same mechanism of action, the longer duration of action of tadalafil, its safety and tolerability makes it more advantageous than sildenafil and vardenafil and hence tadalafil is the only representative of PDE5 inhibitors approved to treating patients with LUTS secondary to BPH with or without ED. The enhanced prostate and bladder smooth muscle relaxation induced by long-term treatment with PDE5 inhibitors seen in animal models of bladder and prostate hypercontractility are translated into the clinic as patients with LUTS secondary to BPH with or without ED showed significant improvement on the IPSS, IPSS-QoI and IIEF-EF scores.

Several preclinical trials have shown pleiotropic effects of PDE5 inhibitors including anti-inflammatory, antiproliferative, anti-oxidant effects. This is in addition to its relaxing effects in the bladder outlet, prostate and corpus cavernosum due to cGMP accumulation, which was not observed with other available therapies for BPH. As substances that increase the levels of cGMP are shown to have antiproliferative effects in several cancer cell lines such as breast [68,69] glioma [70], colon [71,72] and prostate [73], tadalafil should be first option treatment in patients with LUTS-BPH with or without and ED, although clinical trials have not assessed these effects yet.

In our opinion, the evaluation of the efficacy of drugs that interfere with LUTS-BPH has some limitations. Firstly, most studies define efficacy as an improvement in subjective symptoms. As far as we know only two studies used objective parameters (urodynamic analysis) to evaluate the effect of tadalafil on voiding and storage symptoms. A recent clinical trial (designed as a one-armed, prospective study) recruited 105 untreated outpatients with LUTS-BPH who received tadalafil (5 mg) for 12 months. With respect to the urodynamic parameters evaluated, that is the first desire to void, maximum cystometric capacity, maximum flow rate, detrusor pressure at Qmax, post-void residual volume, bladder outlet obstruction index and detrusor overactivity, tadalafil significantly improved these parameters at short (3 months)- and long (12 months)-term [72]. The second limitation of the studies is that clinical trials were

Table 2. Major clinical data regarding the efficacy of tadalafil in patients with lower urinary tract symptoms secondary to benign prostatic hyperplasia with or without erectile dysfunction.

Study design	Treatment	*N*	Total IPSS	IPSS storage subscore	IPSS voiding subscore	Urodynamics parameters	Patients with erectile dysfunction
Men 45 years old or older with LUTS-BPH of at least 6 months or longer, single-blind, placebo-controlled.[62]	Tadalafil 5 mg for 6 weeks Tadalafil 20 mg for 6 weeks	281	−2.8 ± 0.5 vs. −1.2 ± 0.5 (placebo) P < 0.05 −3.8 ± 0.5 vs. −1.7 ± 0.5 (placebo) P < 0.05	−0.4 ± 0.2 vs. −1.1 ± 0.2 (placebo) P < 0.05 −0.7 ± 0.3 vs. −1.7 ± 0.3 (placebo) P < 0.05	−0.8 ± 0.3 vs. −1.7 ± 0.3 (placebo) P < 0.05 −2.2 ± 0.3 vs. −1.0 ± 0.3 (placebo) P < 0.05	No significant changes of Qmax	No
Men of 50 years old or older with history of LUTS-BPH of at least 6 months, randomized, double-blind, crossover, placebo-controlled, 45 days [63].	Tamsulosin 0.4 mg/day plus tadalafil 20 mg/day Tamsulosin 0.4 mg/day Placebo	30	10.2 12.7 19.4	NA	NA	Qmax: 12.6 mL/s P < 0.05 Qmax: 11.7 mL/s P < 0.05 Qmax: 9.6 mL/s	Yes patients who received tadalafil had significant improvements of IIEF-Ef when compared to placebo.
Men with 45 years or older with LUTS-BPH history of at least 6 months, double-blind, placebo-controlled, parallel-design, phase 2–3, multicenter, 12 weeks [64].	Tadalafil 2.5 mg Tadalafil 5 mg Tadalafil 10 mg Tadalafil 20 mg Placebo	581	−3.6 ± 0.8 vs. placebo -4.2 ± 0.8 vs. placebo -4.7 ± 0.8 vs. placebo -4.7 ± 0.8 vs. placebo -2.1 ± 0.8	NA	NA	No significant changes of Qmax.	No
Men with 45 years or older with LUTS-BPH for at least 6 months or longer, double-blind, randomized, placebo-controlled, parallel-design, multicenter, 12 weeks [65].	Tadalafil 2.5 mg Tadalafil 5 mg Tadalafil 10 mg Tadalafil 20 mg Placebo	1058	−3.88 ± 0.5 vs. placebo -4.87 ± 0.49 vs. placebo -5.17 ± 0.49 vs. placebo -5.21 ± 0.5 vs. placebo -2.27 ± 0.49	−1.58 ± 0.23 vs. placebo -1.89 ± 0.23 vs. placebo -1.96 ± 0.23 vs. placebo -2.07 ± 0.23 vs. placebo -0.99 ± 0.23	−2.23 ± 0.33 vs. placebo -2.94 ± 0.33 vs. placebo -3.13 ± 0.32 vs. placebo -3.12 ± 0.33 vs. placebo -1.26 ± 0.33	No significant changes of Qmax.	Yes patients who received tadalafil had significant improvements of IIEF-Ef when compared to placebo.
Men with 45 years old or older with a history of LUTS-BPH for at least 6 months and ED >3 months, randomized, double-blind, placebo-controlled, parallel-design, phase 3, multicenter, 12-weeks[66].	Tadalafil 2.5 mg Tadalafil 5 mg Placebo	606	−4.6 ± 0.4 vs. placebo NS -6.1 ± 0.4 vs. placebo P < 0.05 −3.8 ± 0.5	−1.9 ± 0.2 vs. placebo NS -2.5 ± 0.2 vs. placebo P < 0.05 −1.6 ± 0.2	−2.7 ± 0.3 vs. placebo NS -3.6 ± 0.3 vs. placebo P < 0.05 −2.2 ± 0.3	Qmax: 1.7 ± 4.5 mL/s P = 0.027 1.6 ± 4.2 mL/s P = 0.186 1.2 ± 4.5 mL/s	Yes patients who received tadalafil had significant improvements of IIEF-EF when compared to placebo.
Treatment naïve men who visited the hospital with complaints of both voiding and storage LUTS, single-center, open-label, prospective study, 12 months, not placebo-controlled.[73]	Tadalafil 5 mg	94	12.1 ± 5.7 vs. 19 ± 5.9 (baseline) P < 0.05	5.1 ± 2.5 vs. 7.8 ± 2.9 (baseline) P < 0.05	7.0 ± 4.1 vs. 11.2 ± 4.4 (baseline) P < 0.05	All urodynamic parameters as FDV (mL), MCC (mL), Qmax (mL/s), PdetQmax (cmH_2O), PVR (mL) BOOI and DO were significantly improved after 3 and 12 months of tadalafil treatment.	No

IPSS: International Prostate Symptom Score; IIEF: International Index of Erectile Function; LUTS: Lower Urinary Tract Symptoms; BPH: Benign Prostatic Hyperplasia, ED: erectile dysfunction; FDV: First Desire to Void; MCC: Maximum Cystometric Capacity; Qmax: Maximum Flow Rate; PdetQmax: Detrusor Pressure at Qmax; PVR: Post-Void Residual Urine; BOOI: Bladder Outlet Obstruction Index: DO: Detrusor Overactivity.

not powered to assess superiority or non-inferiority of tadalafil in comparison with other therapies. In relation to this, more clinical trials comparing the association of tadalafil and other pharmacological agents used in LUTS-BPH as 5-alpha reductase inhibitors, β3- adrenoceptor agonists and muscarinic receptor antagonists are needed in order to personalize the therapeutic strategies for patients with LUTS-BPH.

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Declaration of interest

G De Nucci is the CSO of Galeno Clinical Research Ltd (a contract research organization) which conducts clinical trials. Over the past three years, Galeno Clinical Research Ltd has conducted two phase I trials and two phase II trials, as well as one phase III trial for Biolab Farmaceutica. Professor De Nucci has received speaker's fees from EMS Farmaceutica. 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.

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