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REVIEW

Phosphodiesterase inhibitors for treatment of voiding dysfunction: An overview of experimental and clinical evidence

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Abstract

Recently, the focus of the origin of lower urinary tract symptoms (LUTS) has change from the prostate to the bladder. Regardless of the underlying mechanism associated with the origin of LUTS, alpha-blockers continue to be the most common medicine prescribed to treat LUTS due to benign prostatic obstruction (BPO). The newest class of drug introduced to treat LUTS/BPO is phosphodiesterase inhibitors (PDEi) and the aim of this study was to review the role of PDEi in the treatment of LUTS/BPO. In this review, the first evidence was evaluated based on epidemiological studies followed by randomized clinical trials which provide evidence on the administration of PDEi in patients with LUTS/BPO. Experimental studies were also assessed to tentatively elucidate the association between LUTS and erectile dysfunction, and to elucidate the underlying mechanism. There is still controversy regarding the administration of PDEi due to the fear of detrusor impairment, response to acute administration, and the effects of PDEi combined with alpha-blockers. Following this review, we conclude that treatment of BPO/LUTS with PDEi is beneficial, based on experimental studies, strong evidence and the large number of randomized clinical trials confirming their efficiency.

Key words: Benign prostatic hyperplasia; Lower urinary tract symptoms; Phosphodiesterase inhibitor; Mechanism of action; Urodynamics

Core tip: In this study, an extensive review was performed on the use of phosphodiesterase inhibitors to treat lower urinary symptoms due to benign prostatic obstruction. This study explored experimental and recent clinical evidence in order to assist in the decision-making process in daily practice.

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INTRODUCTION

The population is ageing worldwide and consequently the prevalence of lower urinary tract symptoms (LUTS) is increasing and becoming a public health problem. As men grow older the prevalence of histologic benign prostatic hyperplasia (BPH) also increases. BPH is observed in approximately 8% of men aged 31-40 years, 42% of men aged 51-60 years, 71% of men aged 61-70

Table 1 Initial evidence based in epidemiological studies of a common pathophysiology between lower urinary tract symptoms and erectile dysfunction

Ref.	Number of participants	Major conclusion
Cologne Male Survey Braun *et al*[6]	4000	72.2% of patients with ED had concomitant LUTS Only 37.7% had LUTS without ED
Population-based cohort study in Brazil Moreira *et al*[7]	602	Incidence of ED was 65.5 cases per 1000 person-years Relative risk of ED was 1.8-7.5 in patients with LUTS
Sexual dysfunction in European men Vallancien *et al*[8]	1274	Prevalence ED-Mild (55%), severe (70%) LUTS Prevalence of ED was 55% in men with mild LUTS and increased to 70% in severe LUTS
Association of LUTS in Japanese men with erectile dysfunction Terai *et al*[9]	3189	Severity of ED was significantly associated with moderate to severe IPSS, RR = 1.5 which persisted after adjustment for age
Boston Area Community Health survey Brookes *et al*[10]	2301	Strong association was observed between the AUA-SI associated to ED and ED after adjusting for age

ED: Erectile dysfunction; LUTS: Lower urinary tract symptoms; RR: Relative risk; IPSS: International Prostatic Score Symptoms; AUA-SI: American Urological Association Symptom Index.

years, and 88% of men aged 81 years and older[1]. BPH may result in enlargement of the prostate, also defined as benign prostatic enlargement and may be associated with bladder outlet obstruction (BOO). BOO in this case is defined as a benign prostatic obstruction (BPO). Permanent BPO may result in adaptive changes of the detrusor muscle causing storage LUTS, if BPO progresses and persists this may lead to a failure of the detrusor resulting in emptying LUTS. Due to these observations the focus of the origins of LUTS has changed from the prostate to the bladder. As the pathophysiology of LUTS is not totally understood it has been hypothesized that possible LUTS/BPO arises due to local alterations in detrusor smooth muscle cells, local receptors, neural signalization, blood flow and changes in the extracellular matrix. Regardless of the underlying mechanism associated with the origin of LUTS, alpha-blockers are the most common medicine prescribed to treat LUTS/BPO[2]. Alpha-blockers decrease urethral resistance and improve the urinary flow by relaxation of smooth muscle of the prostate and bladder neck.

Other drugs have been used to treat LUTS related to BPO such as 5-alpha-reductase inhibitors. These are taken alone or with alpha-blockers to decrease progression of the disease or to avoid urinary retention[3,4]. Anticholinergics have also been administered to patients with predominant storage LUTS/BPO with a low risk of urinary retention regardless of obstruction[5]. The newest class of drug introduced to treat BPO is phosphodiesterase inhibitors (PDEi) and the aim of this study was to review the role of PDEi in the treatment of LUTS/BPO.

INITIAL EVIDENCE

The use of PDEi in patients with LUTS/BPO was proposed initially based on observational epidemiological studies specially designed to evaluate erectile dysfunction (ED). It was observed in these studies that demographic data showed a similar prevalence of ED and LUTS/BPO in men as they aged, raising the possibility of a common underlying mechanism contributing to both conditions.

The pioneering work carried out in 2000 to study the prevalence of ED in Germany in the Cologne Male Survey evaluated 4000 patients[6]. LUTS/BPO was present in 72.2% of patients with ED, however, only 37.7% had LUTS/BPO without ED. It was also observed in a Brazilian Cohort Study that an epidemiological association existed between LUTS/BPO and ED. In this particular study, the relative risk of ED was 1.8-7.5 in patients complaining of LUTS and this risk was greater than smoking or cardiac symptoms[7]. In Europe a demographic study evaluating 1274 European men showed that 55% of patients with mild LUTS/BPO had ED, however, the prevalence of ED increased to 70% in patients with severe LUTS/BPO[8]. In a Japanese Cross-Sectional Survey, a correlation between ED and LUTS/BPO was observed and the relative risk was 1.5 which persisted after adjustment for age[9]. In the United States of America, multivariate regression of the Boston Area Community Health Survey data found an association between the American Urological Association Symptom Index and ED without differences in race or ethnicity[10]. Therefore, in different parts of the world several studies showed an epidemiological correlation between ED and BPO/LUTS (Table 1).

Clinical use of phosphodiesterase inhibitors to treat BPO/LUTS

Following and during these observational studies, a proof-of-concept clinical study to evaluate improvement in BPO/LUTS in men taking sildenafil for ED was performed in 2002[11]. Patients taking sildenafil were evaluated using the International Index of Erectile Function (IIEF) and International Prostate Symptoms Score (IPSS) instruments at baseline, one and three months. During

the treatment period, an improvement in the IPSS and quality of life (QoL) was observed. An inverse relationship between IPSS and IIEF during treatment with sildenafil was also noted. The major limitations of this study were its open label and uncontrolled design. In other uncontrolled studies, a similar impact of sildenafil in BPO/LUTS and ED was observed[12,13]. Different from the uncontrolled design of the papers reported above, the next generation of studies included randomized and placebo-controlled trials.

In 2007, the first multicenter, randomized, placebo-controlled, double-blind trial was reported[14]. The end point was defined as change from baseline of erectile function assessed with the IIEF instrument. Secondary end points were changes in LUTS from baseline evaluated with the IPSS, QoL question of the IPSS, Benign Prostatic Hyperplasia Impact Index (BPHII), peak flow rate (Qmax), Self-Esteem And Relationship (SEAR) scores and end of treatment satisfaction using Erectile Dysfunction Inventory of Treatment Satisfaction Index Score. Compared with placebo, sildenafil significantly improved the IIEF, IPSS, BPHII, IPSS QoL and SEAR score. Significant improvement in Qmax was not observed in the sildenafil group compared with placebo. The limitations of this study were lack of a placebo run-in period and determination of correlations between LUTS and ED improvements.

In 2007, another multicenter, randomized, placebo-controlled, double-blind trial assessed the efficacy of tadalafil once daily for BPO/LUTS[15]. Inclusion criteria were age greater than 45 years and IPSS > 12 for at least six months. Exclusion criteria were elevated prostatic score antigen (PSA), recent use of 5∝-reductase inhibitors, use of BPH medication during study, history of pelvic surgery, liver failure, other causes of LUTS, uncontrolled diabetes, and nitrate use or chemotherapy. Different from previous studies, a placebo run-in period was included in the study design. After a four-week placebo run-in period, 281 men with BPO/LUTS were randomized to 5 mg tadalafil daily for six weeks, followed by dose escalation to 20 mg for six weeks or placebo for a total of 12 wk. Tadalafil significantly improved the mean change from baseline IPSS compared with placebo. Improvement was also seen in the IPSS QoL, BPHII and IIEF. No significant change was observed in Qmax. Based on these results, the authors concluded that daily tadalafil caused a significant improvement in BPO/LUTS and ED.

In 2008, in an 8-wk randomized, double-blind, placebo-controlled study, vardenafil 10 mg was administered to 222 men with BPO/LUTS with or without ED. Inclusion criteria were age 45-64 years and IPSS score ⩾ 12[16]. Exclusion criteria were vardenafil contraindications, spinal cord injury, prostatitis, urethral stricture, urinary retention, bladder or prostate cancer, past cancer with low life expectancy, use of androgens, anticoagulants, ED treatments, or alpha-blockers during the treatment period. The IPSS score, Qmax, postvoid residual urine volume (PVR), and the erectile dysfunction domain of the IIEF were assessed. Vardenafil significantly improved the mean change in the IPSS from baseline compared with placebo. It also improved ED and QoL. However, no changes in Qmax or PVR were noted. A weak point of this study was the lack of a placebo run-in phase.

A dose-finding study was reported in 2008[17]. In this study, after a 4-wk placebo run-in period, 1058 men with BPO/LUTS were randomized to receive daily tadalafil (2.5, 5, 10 or 20 mg) or placebo. Inclusion criteria were age greater than 45 years, IPSS score ⩾ 12 for at least 6 mo, and Qmax between 4 and 15 mL/s. Exclusion criteria were elevated PSA, recent use of 5∝-reductase inhibitors, use of BPH medication during study, history of pelvic surgery, liver failure, other causes of LUTS, uncontrolled diabetes, and nitrate use or chemotherapy. IPSS change from baseline to endpoint was improved with all tadalafil doses compared with placebo. In the Global Assessment Questionnaire, LUTS also improved at all doses, however, doses greater than 5 mg had minimal improvement with more side effects. As a consequence, this improvement demonstrated a dose-response relationship and 5 mg tadalafil once daily had a positive risk-benefit profile. No significant change in Qmax was observed.

It is possible to conclude with a high level of evidence that PDEi clearly improves BPO/LUTS based on the results presented in these four clinical trials.

Following these randomized controlled trials (RCTs), more recent systematic reviews and meta-analyses have emerged[18-20].

In 2013, a study that aimed to evaluate the efficacy and safety of tadalafil 5 mg once daily compared to placebo over 12 wk for the treatment of both LUTS/BPO and ED in sexually active men was performed. The data were pooled from four multinational, randomized studies of men ⩾ 45 years with LUTS/BPO. The randomization and placebo run-in period were strong points in this study. Principal end-points were change in the IPSS, QoL, BPHII, and IIEF. Tadalafil (n = 505) significantly improved total IPSS *vs* placebo (n = 521); mean changes from baseline were -6.0 and -3.6, respectively ($P < 0.001$). Improvements in the IIEF Domain score (tadalafil, 6.4; placebo, 1.4) were also significant *vs* placebo, as were the IPSS, IPSS QoL, and BPHII (all $P < 0.001$). The authors concluded that tadalafil was efficacious and well tolerated in the treatment of ED and LUTS/BPO[20].

In one of these meta-analyses, the use of PDEi alone or in combination with alpha-blockers was summarized to identify the best candidates for this treatment based on clinical features and LUTS severity[18]. Trials included in this review were selected using the following inclusion criteria: (1) They were RCTs; (2) The subject of the study was a PDEi for LUTS/BPO; (3) Control groups received placebo for PDEi alone or alpha-blockers alone and PDEi plus alpha-blockers; and (4) The primary outcomes were the IPSS, IIEF, and Qmax. Of 508 retrieved studies, 497 articles were excluded; leaving only 11 studies. More than 6000 men evaluated in these 11 studies were includ-

Table 2 Randomized clinical trials and meta-analyses with strong evidence for the use of phosphodiesterase inhibitors in patients with lower urinary tract symptoms due to benign prostatic obstruction

Ref.	Design of study	Placebo run-in	Participant/inclusion criteria	End point	Major conclusion
Sairam *et al*[11]	Not RCT	No	112 male patients All taking sildenafil Inclusion criteria was presence ED	Assess relationship between ED and LUTS; if sildenafil influences LUTS in patients with ED	No relation between ED score and LUTS before treat ED Sildenafil improves ED and LUTS
McVary *et al*[14]	Open-label, randomized, double-blind, placebo-controlled	No	369 patients were randomized to sildenafil 100 mg (n = 189) or placebo (n = 180) during 12 wk/Men with ED and LUTS	Change IPSS, QoL,BPHII, Qmax, SEAR, and EDITS	Sildenafil improve IIEF, IPSS, BPHII, IPSS QoL and SEAR score Qmax not altered
McVary *et al*[15]	Randomized, double-blind, placebo-controlled	Yes	281 men randomized to tadalafil 5 mg daily, followed by dose escalation to 20 mg/Men aged 45 yr or higher and IPSS > 12	Change IPSS, QoL, BPHII, Qmax, and IIEF	Tadalafil improve IPSS, QoL, BPHII, and IIEF Qmax not altered
Stief *et al*[16]	Randomized, double-blind, placebo-controlled	No	222 men were randomized to vardenafil 10 mg twice daily or placebo/age 45-64 yr, IPSS ⩾ 12, with or without ED	Change in IPSS, Qmac, PVR, and IIEF	Vardenafil improve IPSS, IIEF, and QoL Qmax and PVR not altered
Roehrborn *et al*[17]	Randomized, double-blind, placebo-controlled	Yes	1058 men were randomized to receive daily tadalafil 2.5, 5, 10 or 20 mg/age greater than 45 yr, IPSS ⩾ 12, and Qmax between 4-15 mL/s	Change in IPSS, IIEF, QoL, BPHII, GAQ, and Qmax	Tadalafil improve IPSS and GAQ in all doses But, dose higher than 5 mg had minimal improvement with higher side effects Qmax not altered
Porst *et al*[20]	Meta-analysis		1026 men, tadalafil (n = 505) compared to placebo (n = 521). Data pooled from four multinational study/age ⩾ 45 yr, presence of LUTS/BPO	Change in IPSS, QoL, BPHII, and IIEF	Tadalafil improve IPSS, QoL, BPHII, and IIEF compared with placebo
Gacci *et al*[18]	Meta-analysis		Twelve studies, been seven studies (n = 3214) comparing PDEi *vs* placebo, and five (n = 216) on the combination of PDEi with ∝-blockers *vs* ∝-blockers alone/Men with LUTS/BPO	Change in IPSS, IIEF, and Qmax Identify best candidates for treatment with PDEi based on clinical features	PDEi alone improve IPSS, IIEF, but not Qmax Association of PDEi with ∝-blockers improve IPSS, IIEF, and Qmax
Yan *et al*[19]	Meta-analysis		515 patients (seven studies)/ patients with LUTS/BPO and ED	Compare combination of PDEi with ∝-blockers *vs* ∝-blockers alone. Change IPSS, QoL, BPHII, Qmax, and IIEF	Combination of PDEi with ∝-blockers has additive favorable effects compared with PDEi monotherapy

RCT: Randomized control trial; ED: Erectile dysfunction; LUTS: Lower urinary tract symptoms; IPSS: International prostatic symptoms score; QoL: Quality of life; BPHII: Benign Prostatic Hyperplasia Impact Index; Qmax: Peak flow rate; SEAR: Self-esteem and relationship; EDITS: Erectile Dysfunction Inventory of Treatment Satisfaction Index Score; IIEF: International Index of Erectile Function; PVR: Postvoid residual urine volume; GAQ: Global Assessment Question; BPO: Benign prostatic obstruction; PDEi: Phosphodiesterase inhibitors.

ed in this meta-analysis, with seven evaluating PDEi *vs* placebo in 3214 men, and five evaluating the combination of PDEi with alpha-blockers *vs* alpha-blockers alone in 216 men. Median follow-up in all RCTs was 12 wk. The IIEF score (5.5; $P < 0.0001$) and IPSS (-2.8; $P < 0.0001$) were significantly different, but not the Qmax (-0.00; P = not significant) at the end of the study as compared with placebo. The association of PDEi and alpha-adrenergic blockers improved the IIEF score (3.6; P <0.0001), IPSS score (-1.8; $P = 0.05$), and Qmax (1.5; $P < 0.0001$) at the end of the study as compared with a-blockers alone. Therefore, the meta-analysis suggested that PDEi can significantly improve LUTS and EF in men with BPO.

A recent meta-analysis was carried out to evaluate the efficacy of PDEi alone or in combination with alpha-blockers for the treatment of ED and LUTS/BPO. The databases MEDLINE, EMBASE, PubMed, the Cochrane Controlled Trial Register of Controlled Trials, and the Chinese Biological Medical Database were searched to identify RCTs that referred to the use of a combination of PDE5 inhibitors and alpha-blockers for the treatment of ED and LUTS associated with BPH. The principal objectives were to evaluate the IPSS, Qmax, and IIEF. Seven publications involving 515 patients were included in the meta-analysis. PDE5 inhibitors and alpha-blockers significantly improved the IIEF, IPSS, and Qmax values compared with PDE5 inhibitors alone ($P = 0.04$, 0.004, 0.007, respectively). The major conclusion was that the combined use of PDEi and alpha-blockers results in additive favorable effects in men with ED and LUTS/BPO compared with PDEi monotherapy[19] (Table 2).

It is important to note that although many of these studies evaluated men with ED and LUTS/BPO, some studies reported an improvement in LUTS/BPO inde-

pendently of ED[21,22].

Experimental studies

Due to the particular course presented above, the clinical use of PDEi to treat BPO/LUTS began before the mechanism of action of these drugs was known. Therefore, because the mechanism of action was not understood, a common pathophysiological link between ED and BPH was investigated, and an increasing number of experimental studies have emerged in subsequent years[23,24].

To explain the mechanism involved, several theories have been proposed. The four principal hypotheses are: ischemia due to pelvic atherosclerosis, autonomic hyperactivity, a calcium-independent Rho-kinase activation pathway, and reduced nitric oxide (NO) levels[25,26].

The ischemia hypothesis is based on blood flow to the lower urinary tract (LUT) being affected by smooth muscle cell (SMC) contraction, thus decreasing oxygenation leading to chronic ischemia of LUT tissue and contributing to LUTS. Atherosclerosis is associated with remodeling of SMCs in the pelvic vasculature[27,28], penis[29,30], and bladder[28] also associated with LUTS. Therefore PDEi may act by increasing perfusion of the bladder through relaxation of SMCs resulting in increased oxygenation.

It has also been postulated in experimental studies that overactivity of terminal afferent nerves (autonomic) within LUT may be associated with contraction of SMCs[31-33]. Again PDEi might be associated with relaxation of SMCs thus improving LUTS.

Rho-kinase/RhoA activation has been shown to mediate detumescence and maintain flaccidity. Rho kinase inhibits the regulatory subunit of myosin phosphatase within SMCs and maintains contractile tone under low-cytosolic calcium concentration. Upregulated Rho-kinase activity has been reported in ED, as a consequence Rho-kinase inhibitors have been examined to treat ED[34].

Despite the candidate mechanisms mentioned above, it is likely that there is an overlap between the roles of these mechanisms. The reduced NO hypothesis seems to be the best one.

The cornerstone of the process seems to be cyclic nucleotide monophosphate, cyclic adenosine monophosphate and cyclic guanosine monophosphate (cGMP). Cyclic nucleotides are synthesized from the corresponding nucleoside triphosphates by the activity of adenylyl and guanylyl cyclases. Soluble guanylyl cyclase is a widely distributed signal transduction enzyme that, under activation by NO, converts GTP into the second messenger, cGMP, which exerts its effect by activating cyclic guanylyl kinase I (cGK Ⅰ) and cGK Ⅱ, cGMP-gated ion channels, and/or cGMP-regulated phosphodiesterases (PDE). The accumulation of intracellular cGMP triggers a cascade, leading to decreased intracellular calcium level and subsequent relaxation of SMCs[35,36]. The amount of cGMP results from the balance between production (NO) and degradation due to PDE isoenzymes which can hydrolyze and inactivate cyclic nucleotides[24]. Therefore, increased smooth muscle tension may play a central role in the pathophysiology of LUTS.

An *in vitro* study revealed that 4 wk of treatment with the NO synthase (NOS) blocker, N^{ω}-nitro-L-arginine methyl ester hydrochloride (L-NAME), caused *in vitro* detrusor muscle supersensitivity to muscarinic agonists *via* increases in the levels of [H^3]-inositol-phosphate[23]. This finding was corroborated by in vivo experimental studies which showed that administration of L-NAME resulted in a significant increase in non-voiding contractions (NVC) in rats[24].

Based on experimental studies which have shown that rat PDE expression is highest in the bladder, approximately 10-fold higher than in rat corpora cavernosa followed in decreasing prevalence by vas deferens, prostate, kidney, testis, and epididymis[37], further experimental studies evaluated the action of PDEi on LUT. One of these studies demonstrated that administration of sildenafil in rats improved detrusor overactivity and bladder outlet obstruction (lack of urethral relaxation) caused by the NOS inhibitor, L-NAME, in a urodynamic study (UDS)[24]. In another study, with similar methodology, it was also demonstrated that tadalafil decreased NVC and frequency of micturition (FM) in rats in a UDS[38].

As a consequence of these experimental studies, there is good support for the use of PDEi in the treatment of BPO/LUTS.

CONTROVERSIES IN ADMINISTRATION OF PHOSPHODIESTERASE INHIBITORS TO TREAT BPO/LUTS

Impairment detrusor

It has been observed in several clinical trials that PDEi improved the IPSS without changing Qmax in uroflowmetry[14,16,17,39]. If a PDEi caused relaxation of the bladder neck, urethra, and prostatic relaxation in human and animals[24,37,40], it was expected to increase Qmax. Thus, these findings have raised the theoretical possibility that administration of PDEi cause impairment in detrusor function with unknown long-term effects[41].

As a consequence, an experimental study was performed with the endpoint of determining whether tadalafil caused detrusor muscle impairment. In this study, it was reported that chronic depletion of NO caused an increase in NVC, volume threshold (VT) and FM in rats and treatment with tadalafil reduced VT and FM. However, tadalafil did not decrease threshold pressure or peak pressure (PP) in rats with chronic NO deficiency. Tadalafil which increased cGMP probably explains the reduction in VT (decrease in urethral resistance) and MC (relaxation of detrusor) observed in this study. As tadalafil did not decrease detrusor pressure (threshold pressure or PP) it is evident that PDE5i do not cause impairment in detrusor muscle[38].

A clinical trial assessed the impact of tadalafil treatment (20 mg once daily) compared to placebo on detru-

sor pressure and maximum flow (pdetQmax) in men with BPO/LUTS with or without bladder outlet obstruction at baseline. In this study, tadalafil was not associated with a negative impact on detrusor function as the change of pdetQmax was not significant compared with the placebo arm[42].

Acute effects of phosphodiesterase inhibitors on BPO/LUTS

There are few reports of the acute effects of PDEi on BPO/LUTS. The vast majority of studies have evaluated chronic administration of PDEi.

In one clinical trial, 68 patients were randomized to the placebo (n = 32) or sildenafil arm (n = 36). All patients were evaluated at baseline with free uroflowmetry. Uroflowmetry was repeated two hours after administration of placebo or sildenafil. The authors concluded that sildenafil caused a significant improvement in Qmax 15.6 ± 6.8 mL/s from baseline to end point 19.3 ± 7.2 mL/s (P < 0.001), and compared with the placebo arm 15.8 mL/s (P < 0.0001). The increase in Qmax was attributed to urethral relaxation[43].

An experimental study was performed to observe the effect of acute infusion of sildenafil in rats with detrusor overactivity. It was observed that sildenafil decreased the number of micturition cycles from baseline to end point (-0.93 ± 0.34, P = 0.031)[24].

Combination of phosphodiesterase inhibitors with alpha-blockers

According to the American Urological Association guidelines, a1-adrenergic blockers are considered to be the most effective monotherapy for the treatment of LUTS secondary to BPH[2]. PDE5 inhibitors are the first-line treatment for erectile ED. Due to the strong association between BPO/LUTS and ED, the coprescription of PDE5 inhibitors and a1-adrenergic blockers is likely to increase. Thus, one of the most frequently asked questions by physicians is whether to combine or replace alpha-blockers with PDEi in patients with BPO/LUTS and ED.

To address this issue a randomized, double-blind, placebo- and active-controlled (tamsulosin 0.4 mg), and parallel design trial was carried out to compare the effects of daily tadalafil 5 mg in patients with LUTS/BPO. The IPSS, BPH Impact Index, and IIEF-Erectile Function Domain (IIEF-EF) were assessed at baseline and end point (12 wk or end of therapy). The Patient and Clinician Global Impression of Improvement (PGI-I and CGI-I, respectively) instruments and the subject-rated Treatment Satisfaction Scale-BPH (TSS-BPH), evaluated from 0% (greater) to 100% (lower) satisfaction, were administered at end point. Uroflowmetry and postvoid residual were also assessed at screening, baseline, and end of visits. Tadalafil and tamsulosin caused an improvement in the IPSS from baseline to endpoint. However, for the IPSS QoL a significant improvement compared with placebo was only reported in the tadalafil arm, but not the tamsulosin arm. The TSS-BPH overall satisfaction score at endpoint was significantly lower (indicating higher satisfaction) in the tadalafil group compared with placebo, driven by greater satisfaction with efficacy. There was no significant difference between tamsulosin and placebo in TSS-BPH overall satisfaction or satisfaction with efficacy. Tadalafil resulted in an improvement in IIEF-EF, but tamsulosin did not change this index. Tadalafil and tamsulosin caused a significant increase in Qmax. For PVR, both active treatments caused reductions, but these were not statistically significant. The strong point of this study was the wash-out and placebo run-in periods. The principal limitation was that it was not powered to assess noninferiority or superiority between tadalafil and tamsulosin. The author concluded that tadalafil or tamsulosin resulted in significant improvements in IPSS and Qmax related to BPO/LUTS. However, only tadalafil had a significant impact on the IPSS QoL and erectile function[44].

A randomized, double-blind, placebo-controlled study was performed to compare the effect of tamsulosin 0.4 mg/daily and tadalafil 5 mg daily with tamsulosin 0.4 mg/placebo on the lower urinary tract in a UDS. All patients underwent a baseline UDS before randomization to tamsulosin 0.4 mg/tadalafil 5 mg or tamsulosin 0.4 mg/placebo once daily for 30 d. An end of study UDS was performed on completion of treatment. The UDS assessed pdetQmax, Qmax during voiding, bladder outlet obstruction index calculated as pdetQmax-2Qmax, and detrusor overactivity (assessed as incidence). The primary end points were a change in urodynamic variables in the voiding phase, pdetQmax and Qmax, from baseline to week four. The secondary endpoint of this study was improvement in the IPSS. A total of 40 men were randomized to receive tamsulosin 0.4 mg/tadalafil 5 mg (n = 20) or tamsulosin 0.4 mg/placebo (n = 20) once daily for four weeks. When the groups were compared, pdetQmax decreased significantly in the tamsulosin/tadalafil group compared with the tamsulosin/placebo group. In both groups, Qmax increased from baseline to endpoint, however, the difference in Qmax at endpoint was not significant between the groups. Significant improvements were observed in total IPSS, IPSS filling and voiding subscore in the tamsulosin/tadalafil group compared with the tamsulosin/placebo group. The limitations of this study were lack of placebo run-in period and the small number of participants. A strong point was that this was the first study to define the action of tadalafil in LUT using a computerized UDS. The principal conclusion of this study was that only the combination of tamsulosin/tadalafil decreased after-load (pdetQmax) and had the potential to protect detrusor smooth muscle. In addition, the combination significantly improved the IPSS compared with tamsulosin/placebo[45].

In another clinical trial similar to the above study, tadalafil 20 mg in combination with tamsulosin 0.4 mg was compared to tamsulosin 0.4 mg in patients with LUTS. Improvement in the IPSS was greater with the combination treatment. No difference was observed in

Table 3 Studies evaluating the combination of phosphodiesterase inhibitors and alpha-blockers in patients with lower urinary tract symptoms

Ref.	Design of study	Placebo run-in	Participant /Inclusion criteria	End point	Major conclusion
Oelke *et al*[44]	Randomized, multicentric, placebo controlled, and parallel-group	Yes	Men ⩾ 45 yr of age with BPO/LUTS, IPSS ⩾ 13, and Qmax between 4-15 mL/s 512 men were randomized to placebo (n = 172), tadalafil 5 mg (n = 171) or tamsulosin 0.4 mg (n = 168); Men ⩾ 45 yr of age with BPO/LUTS, IPSS ⩾ 13, and Qmax between 4-15 mL/s	Compare effect of tadalafil 5 mg once daily with placebo on BPO/LUTS	Tadalafil 5 mg and tamsulosin 0.4 mg had similar improvement in BPO/LUTS and Qmax compared with placebo However, only tadalafil caused a significant improvement in QoL, treatment satisfaction, and erectile function
Regadas *et al*[45]	Randomized, double-blind, and placebo controlled	No	Men ⩾ 45 yr of age, BOOI ⩾ 20 and IPSS ⩾ 14 A total of 40 men were randomized to tadalafil 5 mg/tamsulosin 0.4 mg (n = 20) or tamsulosin 0.4 mg /placebo (n = 20) Men ⩾ 45 yr of age, BOOI ⩾ 20 and IPSS ⩾ 14	Observe changes in urodynamic variables (Qmax and PdetQmax)	Combination of tamsulosin/tadalafil decrease after-load (pdetQmax) and has potential to protect detrusor smooth muscle Additionally, the combination resulted in a significant improvement in IPSS compared with tamsulosin/placebo
Bechara *et al*[46]	Randomized, double-blind, and crossover study	No	History of LUTS/BPO of at least six months Thirty men were randomized to tamsulosin 0.4 mg or tamsulosin 0.4 mg/tadalafil 20 mg daily History of LUTS/BPO of at least six months	Acess efficacy and safety of combination of tamsulosin with tadalafil compared with tamsulosin alone	Combination therapy had more significative impact in IPSS and ED compared with tamsulosin alone
Kaplan *et al*[39]	Randomized, double-blind study	No	Men aged 50-76 yr with untreated LUTS and ED Sixty two patients were randomized to receive alfuzosin 10 mg (n = 20), sildenafil 25 mg (n = 21), or a combination of both (n = 20) Men aged 50-76 yr with untreated LUTS and ED	Acess efficacy and safety of combination of alfuzosin with sildenafil	Only sildenafil or combination improve ED Improvement in IPSS was observed with three treatments
Gacci *et al*[47]	Randomized, double-blind placebo-controlled trial	Yes	Men with persistent storage LUTS Sixty men were randomized to tamsulosin 0.4 mg or tamsulosin 0.4 mg/vardenafil 10 mg Men with persistent storage LUTS	Acess efficacy and safety of combination of tamsulosin with vardenafil	Combination therapy had more significative impact in IPSS and ED compared with tamsulosin alone

BPO/LUTS: Benign prostatic hyperplasia/lower urinary tract symptoms; Qmax: Peak flow rate; QoL: Quality of life; IPSS: International Prostatic Symptoms Score; PdetQmax: Detrusor pressure at maximum flow; ED: Erectile dysfunction; BOOI: Bladder outlet obstruction index.

Qmax or PVR between the groups. The IIEF improved in the combination group, but not in the tamsulosin group. The authors concluded that tamsulosin with tadalafil was more effective than tamsulosin alone in improving LUTS and ED. Small sample size was the principal limitation of this study[46].

In 2007, a pilot study was carried out to assess the efficacy of alfuzosin 10 mg, sildenafil 25 mg daily, and the combination of both on LUTS and ED. Improvements in the IPSS and IIEF were significant with the three treatments, but were greatest with the combination of alfuzosin and sildenafil. An improvement in the IIEF was only observed in the sildenafil and combination groups. The authors concluded that the combination of sildenafil and alfuzosin was more effective than monotherapy in improving both voiding and sexual dysfunction in men. Weak points of this study were no placebo arm in the study design, small sample size, and the experimental dose of sildenafil (25 mg once daily)[39].

Tamsulosin 0.4 mg/d was compared with the combination of tamsulosin 0.4 mg/d plus vardenafil 10 mg/d. After a 2-wk run-in period, tamsulosin patients were randomized to a 12-wk treatment period. The IPSS, IPSS-bother, IIEF-5 and Over Active Bladder questionnaire scores, uroflowmetry data (Qmax, Qave), and postvoiding residual urine were recorded after run-in (baseline), and 2 and 12 wk after treatment. Significant differences from baseline to 12 wk were observed in the following: Qmax (placebo: 0.07, vardenafil: 2.56, P = 0.034); Qave (placebo: -0.15, vardenafil: 1.02, P = 0.031); filling-IPSS subscores (placebo: -1.67, vardenafil: -3.11, P = 0.039); and IIEF (placebo: 0.06, vardenafil: 2.61, P = 0.030). The authors concluded that the combination of tamsulosin and vardenafil was more effective in improving both LUTS and erectile function, as compared with tamsulosin alone[47] (Table 3).

CONCLUSION

Treatment of BPO/LUTS with phosphodiesterase inhibitors is beneficial, based on experimental studies, strong evidence and a large number of randomized clinical trials confirming their efficiency.

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