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Collaborative Review – Benign Prostatic Hyperplasia

Phosphodiesterase Type 5 Inhibitors in the Management of Non-neurogenic Male Lower Urinary Tract Symptoms: Critical Analysis of Current Evidence

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Abstract

Context: A large body of epidemiologic data suggests a causal relationship between lower urinary tract symptoms (LUTS) and erectile dysfunction (ED). Recently reported studies on phosphodiesterase type 5 inhibitors (PDE5-Is) and LUTS have further contributed to the understanding of mechanisms involved in this relationship and of potential treatment options.
Objective: A nonsystematic descriptive review was performed to summarize the literature concerning the role of PDE5-Is in men with LUTS, particularly looking at data derived from clinical trials in relation to the different PDE5-Is or their association with α-blockers.
Evidence acquisition: A comprehensive electronic search was conducted in October 2010 using the Medline database to identify all publications relating to ED and BPH and treatment with sildenafil, vardenafil, tadalafil, udenafil, UK-369003, and combination therapy with alfuzosin and tamsulosin.
Evidence synthesis: In studies in which either ED or LUTS was the entry criterion, sildenafil appears to improve both erectile function and LUTS in subjects with ED. Placebo-controlled trials of tadalafil and vardenafil showed improvement of LUTS secondary to benign prostatic hyperplasia (BPH), but none of the studies showed a significant effect on urodynamic measures. Exploratory studies with UK-369003 showed improvements in LUTS and ED. Sildenafil or tadalafil associated with alfuzosin or tamsulosin showed greater benefits for the combination therapy for both LUTS and ED. The coadministration of udenafil and an α-blocker in patients with BPH and ED also appeared to improve both LUTS and ED severity.
Conclusions: Consistent evidence of improvements in LUTS has been shown with PDE5-Is, either alone or in combination with α-blockers. However, effects on urodynamics or objective measures of urinary flow are lacking. Further areas of research include investigation of mechanism of PDE5-Is, urodynamic studies, identification of new efficacy end points, head-to-head comparison with standard of care, potential benefit of add-on treatment, and long-term outcomes.

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1. Introduction

A large body of epidemiologic evidence supports a causal relationship between lower urinary tract symptoms (LUTS) and erectile dysfunction (ED) [1–10] (Table 1), including (1) a consistent dose–response association between increased frequency of LUTS and ED, (2) a significantly higher prevalence of LUTS in men suffering from ED as compared with men with normal erections, and (3) a statistically significant increase on multivariable models of the risk of ED for increasing urinary complaints after adjusting for age and comorbidities.

The association between ED and LUTS also has biologic plausibility given the interrelationships of the known pathophysiologic mechanisms of these disease states [11,12]. The four pathophysiologic mechanisms [13] include the roles of nitric oxide synthase [14,15], autonomic hyperactivity and the metabolic syndrome [16–18], the Rho-kinase activation/endothelin pathway [19], and pelvic atherosclerosis [1]. These processes are not mutually exclusive and may overlap substantially [20,21].

In relation to preclinical data, numerous studies have investigated the effects of phosphodiesterase type 5 inhibitors (PDE5-Is) in the prostate, bladder, urethra, and lower urinary vasculature [22–47]. These agents can be classified according to their preference of affinity for cyclic adenosine monophosphate (cAMP) and/or cyclic guanosine monophosphate (cGMP). The 21 human phophodiesterase (PDE) genes are divided into 11 families based on their protein sequences, regulatory considerations, and sensitivity to inhibitors, as well as their cAMP and/or cGMP affinity [22,23]. Alternative splicing of PDE messenger RNAs (mRNAs) occurs at the 50- and/or 30-ends of the transcripts for most of the 21 genes, which yields at least 80 different PDE proteins. Further, at least 6 of the 11 isoenzyme families (PDE types 1–5 and 11) have proved to be of functional importance in the management of LUTS [3]. Francis et al [45] published an excellent review of the effects of cGMP on cellular targets (cGMP-dependent protein kinases, cGMP-gated cation channels, and PDEs). Dorsey et al [46] carried out an extensive review of basic science articles published between 1990 and 2009 examining the pharmacologic effects of PDE5-Is for the treatment of ED.

The objective of this nonsystematic descriptive review was to summarize the literature concerning the role of PDE5-Is in the management of men with LUTS, particularly looking at data derived from clinical trials in relation to the different PDE5-Is or their association with α-blockers.

2. Evidence acquisition

A comprehensive electronic literature search was performed in October 2010 using the Medline database, through either PubMed or Ovid as a search engine, to identify all publications relating to benign prostatic hyperplasia (BPH), LUTS, ED, and PDE5-Is. Both experimental and clinical research studies were considered. English-language articles were included for review, and non-English articles were included if they provided additional relevant information. The search was conducted using a free-text protocol that included the following terms: *lower urinary tract symptoms, benign prostatic hyperplasia, bladder neck, PDE receptors, phosphodiesterase inhibitors, cavernous tissue, erectile dysfunction, sildenafil, vardenafil, tadalafil, udenafil, alfuzosin, tamsulosin,* and *UK-369003*. These terms were arranged by variable combinations of the Boolean operators AND and OR.

Attention was given only to published studies pertaining to the field of urology as based on the journal, authorship, and/or manuscript content. Review articles and case reports were considered if they were relevant. Studies published as abstracts only and reports from meetings were not included unless the interest of the study was considered to be high. Other significant studies cited in the reference lists of the selected papers were evaluated. Publications reporting on the same cohort group from the same institution were limited to the most recent publication. The panel of authors discussed the list of source items, and the articles considered more relevant were selected.

3. Evidence synthesis

3.1. Sildenafil and lower urinary tract symptoms

The most common form of management of ED is pharmacotherapy with PDE5-Is [48]. Table 2 presents a summary of clinical studies of sildenafil and LUTS.

In a prospective open-label study by Sairam et al [49] in 147 men attending an andrology clinic with ED as their main complaint, 112 men used sildenafil on demand before sexual intercourse. Subjects completed the International

Table 1 – Relevant epidemiologic studies of the relationship between lower urinary tract symptoms and erectile dysfunction

Study	Country	Patients	Range,yr	ED,%	LUTS, %	Risk ratio for ED
Braun et al [3]	Germany	4489	30–80	19.2	72.2	2.11
Nicolosi et al [4]	Brazil, Italy, Japan, Malaysia	2412	40–70	16.1	–	2.2–4.9
Rosen et al [5]	USA and six European countries	12 815	50–80	48.9	30.8	3.7–7.6
Vallancien et al [6]	Five European countries	1274	36–92	62	91	1.2–1.9
Boyle et al [7]	Korea and three European countries	4800	40–79	21.1	–	1.1–1.7
Hansen [8]	Denmark	3700	40–65	28.2	39.1	2.3–3.4
Terai et al [9]	Japan	2084	> 40	29.9	27.1	1.5

ED = erectile dysfunction; LUTS = lower urinary tract symptoms.

Table 2 – Clinical evidence of sildenafil and lower urinary tract symptoms

Study	Subjects and entry/ baseline data	Study design	Treatment	Effects
Sairam et al [49]	112 men with ED 18% with LUTS IPSS <7: 67%, 8–9: 26%, 20–35: 6%	Prospective open-label (evidence level 2b)	On demand	• Improved erections: 81% • Changes in IPSS correlated with sexual function scores • A lower IPSS at baseline predicted higher sexual function scores after treatment
Chang et al [52]	108 men with ED IPSS and IIEF assessed at 3 mo	Retrospective (evidence level 2b)	On demand	• IPSS decreased from 15.8 to 13.3 • Significant inverse correlation between IIEF and IPSS
Mulhall et al [53]	48 men with IPSS >10	Open label (evidence level 2b)	100 mg	• Mean improvement in ED: 7; IPSS: 4.6 points; quality of life: 1.4 • Improvement of IPSS in 60% of patients (35% >4 points); mild LUTS in 17%
McVary et al [54]	189 sildenafil 180 placebo IIEF ≤25, IPSS ≥12	12-wk, double-blind, placebo-controlled (evidence level 1a)	50 mg increased to 100 mg	• Sildenafil group: significantly greater improvements in IPSS and IPSS quality of life than placebo • Greater improvements in patients with severe/moderate LUTS than in those treated with placebo • Adverse events and study discontinuation due to adverse events greater in sildenafil group
McVary et al [55]	Equal previous study. BMI: obese ≥30, overweight ≥25, normal <25 kg/m^2	Ad hoc analysis previous study (evidence level 1a)	50 mg increased to 100 mg	• Significantly greater improvements in IPSS and IIEF observed in sildenafil-treated patients versus placebo were independent of BMI

ED = erectile dysfunction; LUTS = lower urinary tract infection; IPSS = International Prostate Symptom Score; IIEF = International Index of Erectile Function; BMI = body mass index.

Index of Erectile Function (IIEF) [50] and the International Prostate Symptom Score (IPSS) [51] (IPSS; range 0–35 points, with higher score reflecting more symptoms) at baseline ($n = 112$) and at 1 mo ($n = 98$) and 3 mo ($n = 81$). Only 20 patients (18%) complained of bothersome LUTS despite the fact that 67%, 26%, and 6% of patients had mild (IPSS < 7), moderate (8–19), and severe (20–35) LUTS, respectively, at baseline. At the 3-mo assessment, IPSS scores were generally improved, although not uniformly. Of interest, all severe cases reverted to moderate ED, and 60% of moderate cases became mild; 18% of mild cases progressed to moderate ED. Improvements in LUTS and quality of life (QoL) were associated with improvements in overall sexual function, not solely erectile function. Older patients tended to have more residual LUTS, worse QoL, and ED throughout the study. This study was significantly biased by a number of methodological flaws, including patient self-selection (attendees of an andrology clinic) and an uncontrolled design. In this context, inclusion and exclusion criteria, patient demographics, medical history, and 1-mo data were not reported. The study also lacked data regarding sildenafil dosage, use frequency, or sexual activity frequency and any correlation with the IPSS psychometric assessment. The incidence of adverse drug reactions, discontinuation reasons, and actual IPSS were not reported either.

Chang et al [52] reported the results of a retrospective study including 108 patients with ED treated by on-demand sildenafil with a 3-mo follow-up assessment of both the IIEF and IPSS questionnaires. The IIEF increased from 26.2 to 39, whereas the IPSS decreased from 15.8 to 13.3, with a significant inverse correlation of the two parameters after treatment ($p < 0.05$). The increase of the IIEF score was lower in older patients ($p = 0.01$), and there was no correlation between decreasing extent of IPSS and age. A larger and significant decrease of the IPSS score was found in patients with a greater increase of the IIEF score ($p = 0.048$). Sildenafil appears to improve both erectile function and LUTS in patients with ED.

It should be noted that in these two studies, ED was an essential criterion for inclusion, whereas in the studies discussed later, LUTS and ED or only LUTS were the entry criterion. Thus men without ED may have been included.

In a study reported by Mulhall et al [53], 48 men with ED and LUTS, which was documented by a pretreatment IPSS >10, were enrolled in an exploratory nonrandomized, non–placebo-controlled study. Patients were treated with 100 mg sildenafil as needed (mean number [plus or minus standard deviation (SD)] of pills of sildenafil per week was 2.0 ± 0.6) and completed the IIEF and IPSS questionnaires at least 3 mo following treatment initiation. At the end of the study, scores had improved so that no patient had severe ED, 17% had moderate ED, 42% had mild ED, and 41% had normalized the IIEF-Erectile Function (IIEF-EF) domain score. Considering that reductions in IPSS of ≥3 points are patient perceivable and defined as clinically relevant, interestingly enough Mulhall et al [53] showed that both the mean IPSS (-4.6 ± 1.6 points; $p = 0.013$) and the IPSS-QoL (-1.4 ± 0.2; $p = 0.025$) scores significantly improved. Likewise, LUTS severity improved in 60% of patients (35% >4 points) and became mild in only 17%. Improvements in LUTS were independent of baseline IPSS, ED severity, or improvement in ED. This finding suggested a positive impact of sildenafil on men with mild to moderate LUTS, although the magnitude of improvement in the IPSS scores was modest. Study limitations include patient self-referral and uncontrolled design. Minimal demographic and no adverse reaction or patient discontinuation data were presented. All patients received sildenafil doses of 100 mg without a dose titration. The relationship between frequency of sildenafil use and/or sexual intercourse and associated LUTS was not explored. In contrast with previous studies, LUTS improvement was evenly distributed between patients with all severities of LUTS and ED.

In a 12-wk prospective, multicenter, double-blind, randomized, placebo-controlled trial, the efficacy of treatment with daily sildenafil on ED (IIEF ≤25) and LUTS (IPSS ≥12) was examined in 189 men as compared with 180 men treated with placebo [54]. Sildenafil (50 mg) or placebo was administered daily either before bedtime or sexual activity. After 2 wk, sildenafil was increased to 100 mg daily, being well tolerated by 90% of patients. Patients were instructed to attempt sexual activity at least weekly. Decreases in IPSS scores were greater in the sildenafil group (6.3 points; 95% confidence interval [CI], 4.5–8.1) than in the placebo group (1.9 points; 95% CI, 0.2–3.7) ($p < 0.0001$). Sildenafil patients with severe and moderate LUTS experienced greater improvement in IPSS than patients receiving placebo (−8.6 vs −2.4 for severe LUTS; −2.4 vs −1.7 for moderate LUTS). IPSS quality-of-life scores were statistically ($p < 0.0001$) and clinically improved with sildenafil (0.97; 95% CI, 0.62–1.32 vs 0.29; 95% CI, 0.05–0.64). Small insignificant increases in maximum flow rate (Q_{max}) were seen in both groups. Total (191 vs 121 events; p value not reported) and treatment-associated adverse events (86 vs 25 events; p value not reported) were higher in the sildenafil than in the placebo group. Study discontinuations due to treatment-related adverse reactions were more common in the sildenafil arms (5% vs 3%), although total study discontinuations were more common (14% vs 11%) in patients receiving placebo (14% vs 11%). These findings are important as the first prospective controlled trial of a PDE5-I used for treatment of LUTS in men with ED and LUTS at baseline, supporting the concept that daily sildenafil may improve LUTS outcomes in addition to ED. Unfortunately, associations between patient's age, frequency of LUTS, frequency of sexual activity, ED severity, ED improvements, and other potential mediating factors were not examined. Another limitation of the study was the lack of a baseline placebo-controlled run-in phase. The 50-mg starting dose of sildenafil and forced dose titration further limited the study's ability to determine the efficacy of lower daily doses. This study found that sildenafil administered daily decreased the frequency of LUTS. However, these findings did not shed light on those patients with LUTS who may respond best to PDE5 therapy, the presence of a dose–response effect, or whether changes in LUTS are independent from ED amelioration.

Moreover, a post hoc analysis of the results to assess the response to treatment according to body mass index (BMI) categories (namely, obese, ≥30 kg/m^2; overweight, ≥25 kg/m^2; and normal weight, <25 kg/m^2) found that significantly greater improvements in IPSS and IIEF observed in sildenafil-treated patients versus placebo were independent of BMI stratification [55].

3.2. *Tadalafil and lower urinary tract symptoms*

The efficacy of tadalafil to relieve LUTS secondary to BPH has been reported in a number of clinical trials (Table 3).

Daily tadalafil for BPH-related LUTS (IPSS ≥13), regardless of ED, was studied in a prospective double-blind, placebo-controlled, multicenter parallel-arm trial [56]. Patients were randomized to receive either tadalafil 5 mg (n = 138) or placebo (n = 143) daily; patients were stratified by IPSS (<20 or ≥20), prior α-blocker therapy, and geographic distribution. Patients were evaluated after 6 wk of treatment, and the tadalafil dose was increased to 20 mg daily. IPSS was <20 in 64% of patients. The IPSS change at 6 wk was significantly greater in the tadalafil 5 mg group than in the group receiving placebo (2.8 ± 0.5 vs 1.2 ± 0.5; p = 0.003). More patients taking tadalafil reported a clinically relevant improvement in IPSS than those men receiving placebo (49.3% vs 36.4%; p = 0.03). Patients receiving placebo and dose-escalated tadalafil tended to experience further LUTS improvement during weeks 6–12. At week 12, the IPSS improvement was greater in the tadalafil group than the placebo group (3.8 ± 0.5 vs 1.7 ± 0.5; $p < 0.001$), and more tadalafil-treated patients experienced a perceivable IPSS improvement (60.9% vs 42.7%; $p < 0.01$). Adverse events led to discontinuation in 1.4% of patients receiving placebo and 3.6% of tadalafil patients. Most of the tadalafil-associated adverse event discontinuations (grades 4/5) occurred during the 5-mg period. Neither group experienced significant changes in urodynamic parameters.

Table 3 – Clinical evidence of tadalafil and lower urinary tract symptoms derived from clinical trials

Study	Subjects and entry/ baseline data	Study design	Treatment/ duration	Effects
McVary et al [56]	138 tadalafil 143 placebo Stratified by IPSS <20 or ≥20 and prior α-blocker therapy,	Prospective, randomized, double-blind, placebo-controlled (evidence level 1a)	5 mg increased to 20 mg after 6 wk; 12 wk	• At 6 and 12 wk, IPSS improvements significantly higher in tadalafil than placebo groups • Withdrawal due to adverse events: placebo 1.4%, tadalafil 3.6%; no changes in urodynamic parameters
Roehrborn et al [57]	1058 (approximately 200 per group): placebo, four tadalafil doses, stratified by IPSS <20 or ≥20	Prospective, randomized, double-blind, placebo-controlled (evidence level 1a)	2.5, 5, 10, 20 mg; 12 wk	• Significant improvement in the 5-mg group • IPSS increased from 4.9 to 1.8 • Higher doses associated with IPSS improvements but more adverse events
Dmochowski et al [63]	99 tadalafil 101 placebo IPSS ≥13	Prospective, randomized, double-blind, placebo-controlled (evidence level Ia)	20 mg; 12 wk	• Significant improvement of IPSS (mean difference between treatments: −4.2). • No change in urodynamic measures (detrusor pressure at maximal urinary low rate)

IPSS = International Prostate Symptom Score.

This large controlled study [56] again showed that PDE5-Is can significantly improve LUTS severity regardless of ED. The interpretation of the results is limited by a statistical analysis that used one-sided tests without corrections for multiple comparisons. Prestudy use of α-blocker therapy was relatively low (only 24% of patients), and patients with mild LUTS were included in the active treatment phase. In both groups, outcome measure improvements during the 4-wk placebo run-in phase exceeded those of the initial 6 wk of active therapy. At 12 wk, the mean tadalafil-attributable (tadalafil vs placebo response) IPSS improvement was approximately 2 points, with about 18% more patients experiencing perceivable improvement. At the end of the study, IPSS scores remained in the moderate symptom severity range in both groups. Attempts were again not made to correlate the symptom improvements with sexual activity. Furthermore, forced dose titration limited the ability of the study to identify a dose–response relationship or to analyze the durability of the effects seen during the 6 wk of low-dose tadalafil. This is of particular interest because some outcome measures continued to improve in the placebo group throughout the 12-wk trial. Quadrupling the tadalafil dose resulted in clinically insignificant additional reductions in IPSS scores (approximately 1 point).

Similar results were reported in a randomized double-blind, placebo-controlled, parallel-group, multinational study, where 1058 men were randomly assigned to placebo or one of four tadalafil daily dosing regimens (2.5, 5, 10, or 20 mg) for 12 wk [57]. At baseline, patients had IPSS >12 due to BPH for 6 mo and a peak flow (Q_{max}) of 4–15 ml/s. After a 4-wk single-blind placebo run-in phase, men were stratified by baseline IPSS (<20 vs ≥20), baseline uroflow parameters, ED history (<3 vs ≥3 mo), and geographic region. The study's main end point revealed a significant improvement of the IPSS in the 5-mg tadalafil group, with a change of 4.9 versus 1.8 points ($p < 0.05$). Mean IPSS quality-of-life score, BPH Impact Index, and LUTS Global Assessment Question all significantly improved with at least a 5-mg daily dose. Q_{max} was not significantly different from the placebo treatment group for any treatment arm. An increase in tadalafil dose >5 mg showed similar improvements in IPSS but had a higher incidence of adverse effects. The subset of men who were sexually active (55%) showed a significant improvement in IIEF-EF domain scores (+2.38 placebo vs +7.15 in the 5-mg tadalafil treatment group; $p = 0.001$).

Taken together, these studies confirmed that tadalafil significantly improved IPSS scores as compared with placebo. Of note, the magnitude of the observed IPSS improvement was comparable with results reported in previous α-blocker studies. For example, a nonblinded study using 10 mg of alfuzosin showed a mean change in IPSS at 12 wk of 3.8 points compared with 1.7 for placebo [58]. However, a head-to-head trial is required to state that treatment effects are truly comparable.

Importantly, none of the studies demonstrated a significant effect of the PDE5-I on Q_{max}. A previous small study regarding 32 patients undergoing urologic screening before initiating isosorbide dinitrate demonstrated conflicting results [59]. Upon follow-up at 2 wk and 3 mo after therapy, the subset of patients ($n = 15$) who had reported subjective complaints with micturition achieved significant improvement in Q_{max}, postvoiding residual (PVR) volume, and IPSS. The 17 patients without complaint did not have significant improvement in micturition parameters. It should be noted that allowing subjects with LUTS without a reduced Q_{max} as an entry criterion into the PDE5-I trials artificially reduces the treatment effect on Q_{max}. Although it is possible that PDE5-Is may truly exert an effect on Q_{max}, the most recent PDE5-I trial where a Q_{max} inclusion criterion of 4–15 ml/s was used (thereby eliminating the possibility of regression toward the mean) and in which no change in Q_{max} was observed makes this seem very unlikely [57]. In contrast, it has been recently recommended that additional standardized urodynamic protocols (equipment calibration, a detailed procedure manual and centralized training, and implementation of a central reader) are needed to limit intersite variability when urodynamic studies are incorporated in large randomized, placebo-controlled, multicenter trials in men with LUTS [60]. Measurement variability may have obscured small changes in Q_{max} following treatment.

A recent post hoc analysis in men with LUTS secondary to BPH with ($n = 716$) or without ($n = 340$) comorbid ED at baseline showed that changes in IPSS score after 12 wk of treatment with placebo or various doses of once-daily tadalafil were similar [61]. It has also been reported that treatment with 20 mg of tadalafil (once every 3 d) had beneficial effects on LUTS and ED beyond treatment cessation (16 and 20 wk after treatment commencement) in patients with moderate to severe ED and LUTS [62].

Finally, a multicenter randomized, double-blind, placebo-controlled clinical trial was conducted to compare tadalafil 20 mg once daily versus placebo for 12 wk in men with LUTS secondary to clinical BPH with or without bladder outlet obstruction. In this study, invasive and noninvasive urodynamics, IPSS scores, and general safety measures were assessed [63]. The primary study end point was change in detrusor pressure at maximum urinary flow rate. Urodynamic measures remained largely unchanged during the study; in this context, no statistically significant or clinically adverse difference between tadalafil and placebo in change in detrusor pressure at maximum urinary flow rate (mean difference between treatments: −2.2 cm H_2O ($p = 0.33$) or any other urodynamic parameter (maximum urinary flow rate, maximum detrusor pressure, bladder outlet obstruction index, or bladder capacity) were observed. Treatment with tadalafil resulted in significant improvements in IPSS scores (mean difference between treatments: −4.2; $p < 0.001$). Tadalafil was generally well tolerated with most of the adverse events mild to moderate in severity. Few patients discontinued the therapy due to adverse events (tadalafil: 2.0%; placebo: 1.0%). Treatment with tadalafil for LUTS due to BPH improved symptoms with no urodynamic changes.

3.3. *Vardenafil and lower urinary tract symptoms*

In a randomized and placebo-controlled study, vardenafil 10 mg taken twice a day was used as a treatment for LUTS

(IPSS >12) in men with BPH [64]. A total of 247 men were randomized, and 225 completed the 8-wk intention-to-treat study. The mean change in total IPSS in this study was 5.9 in the vardenafil arm and 3.6 in the placebo arm. Although the difference in total score was statistically significant, it is of interest that the placebo arm experienced what would be considered a clinically significant improvement in total IPSS score. There were neither significant changes in flow rate nor changes in PVR urine volume. A possible explanation for the marked placebo effect in this study is the absence of a placebo run-in phase, as in previous studies. Given that the mean difference in IPSS decline between placebo and treatment groups was 2.3 points, the clinical efficacy of the drug at reaching the "3-point cut-off" is unclear.

In another study, 80 men with LUTS-BPH, IPSS ≥12, and without concomitant ED were randomized to receive 10 mg vardenafil or placebo twice a day. In this study, significant improvements were observed in the IPSS total score (−6.14 vs −3.2; $p = 0.001$), irritative and obstructive IPSS subscores, and QoL, without observable difference again in urinary flow [65]. Significant improvements on IIEF domain scores in the vardenafil group as compared with placebo were also observed, as in previous studies.

3.4. UK-369003

The modified-release (MR) formulation of UK-369003 is a highly selective and potent inhibitor of PDE5 that provides 24-h drug coverage as once-daily administration. Treatment with UK-369003 has been investigated for treatment of storage LUTS in men with and without ED [66]. A total of 310 men with a clinical diagnosis of overactive bladder were stratified into two groups (with or without ED) and randomized to one of five treatment groups (10, 25, 50, or 100 mg UK-369003 or placebo once a day) for 12 wk. Overall, there were no clinically relevant treatment differences in voiding frequency, mean voided volume, urgency episode frequency, or nocturia frequency for any dose of UK-369003 MR as compared with placebo. In the subset of patients with ED there were improvements in IIEF-EF domain score and for the Quality of Erection Questionnaire scores in all UK-369003 treatment groups as compared with placebo.

In a placebo-controlled study investigating the efficacy and safety of UK-369003 for the treatment of men with LUTS, 418 men with IPSS ≥13 and maximum Q_{max} of 15 ml/s were randomized to one of seven treatment groups for 12 wk [67]. Treatments included UK-369003 10, 25, 50, or 100 mg MR, UK-369003 40 mg immediate release (IR), tamsulosin 0.4 mg prolonged release, or placebo. Differences for change from baseline at week 12 in Q_{max} for UK-369003 mg MR and placebo were 2.10 ml/s and 0.84 ml/s, respectively. The mean change in the IPSS from baseline at week 12 for UK-369003 100 mg MR and 40 mg IR was −2.91 and −2.50 improvement over placebo, respectively. The Bayesian statistical analysis gave high posterior probabilities for true differences between UK-369003 100 mg MR and placebo.

3.5. Combination therapy

These are small trials, unsponsored, and of limited value because of their limited size and lack of adequate controls (level of evidence 2b).

3.5.1. Alfuzosin and sildenafil

The effect of sildenafil 25 mg ($n = 21$), the α_1-blocker alfuzosin 10 mg ($n = 20$), or sildenafil 25 mg plus alfuzosin 10 mg ($n = 21$) daily was explored in a randomized, open-label, 12-wk, parallel-group pilot study in men with moderate to severe LUTS and ED [68]. Baseline IPSS (mean ± SD) was 17.4 ± 3.4 (45% moderate and 55% severe LUTS). As compared with baseline, IPSS improved significantly in all groups (alfuzosin: 17.3 ± 4.3 vs 14.6 ± 3.7 points; $p = 0.01$; sildenafil: 16.9 ± 4.1 vs 14.9 ± 4.2 points; $p = 0.03$; combination: 17.8 ± 4.7 vs 13.5 ± 4.2; $p = 0.002$). Mean IPSS remained in the moderate LUTS category for all groups. Alfuzosin significantly ($p < 0.05$) improved Q_{max} (11.7%), whereas sildenafil alone did not. Combination therapy produced near-additive improvements in IPPS (24.1%), Q_{max} (21.1%), and ED measures. Seven patients (two on alfuzosin, two on sildenafil, and three on the combination) withdrew due to adverse events. Dizziness and gastrointestinal symptoms were the most common side effects. Combination therapy produced greater improvements than either monotherapy, although the beneficial effects of sildenafil on LUTS were small, as were the benefits of alfuzosin on ED. The study was limited due to an open-label design, small sample size, and no placebo control. The number of patients experiencing a clinically significant improvement in IPSS (>3 points) was not reported; neither were correlations between baseline demographics, ED, and LUTS severity or increases in sexual activity with response. The fixed low dose also prevented assessment of a potential dose–response relationship.

3.5.2. Alfuzosin and tadalafil

Tadalafil as an adjunctive therapy to alfuzosin was studied in a 12-wk open-label trial of 66 men with ED and LUTS (IPSS >8); 58 completed the study, with 6 dropouts secondary to medication-related adverse events [69]. Men were randomized to monotherapy with alfuzosin 10 mg daily, tadalafil 20 mg every other day, or a combination of the two compounds. At follow-up, IIEF-EF scores were improved in all groups (increase of 15%, 36%, and 37% from baseline for the alfuzosin, tadalafil, and combination group, respectively). It is apparent that α-blockers had little additive benefit when used as an adjunct to tadalafil with respect to the treatment of ED symptoms. Interestingly, all groups had an increase in peak urine flow (increase of 22%, 10%, and 29.6% from baseline for the alfuzosin, tadalafil, and combination group, respectively), as well as a significant decrease in IPSS score (decrease of 27%, 8%, and 42% from baseline, respectively). All changes were statistically significant compared with baseline values ($p < 0.05$), with the exception of the change in IPSS score in the tadalafil-only group. The small sample size, open-label nature, and the absence of a placebo control group limited the value of this study.

3.5.3. Tamsulosin and tadalafil or sildenafil

In a randomized double-blind crossover pilot study, Bechara et al [70] assessed the efficacy and safety of tamsulosin versus tamsulosin and tadalafil in patients with LUTS. Thirty men with BPH/LUTS were randomized to receive tamsulosin 0.4 mg/d versus tamsulosin 0.4 mg/d and tadalafil 20 mg/d for 45 d, and then they switched to the other treatment mode for 45 d. Improvements in IPSS and IPSS-QoL were significant with both treatments but greater with the drug combination. Both regimens similarly improved Q_{max} and decreased the PVR volume from baseline with no significant differences between tamsulosin alone versus tamsulosin and tadalafil. The IIEF domain score improved with tamsulosin and tadalafil but not with tamsulosin alone. Both treatments were well tolerated. This pilot study showed that tamsulosin with tadalafil was more effective than tamsulosin alone for both LUTS and ED.

In another study, 60 men with BPH-related LUTS were randomized to receive sildenafil (25 mg) monotherapy ($n = 20$), tamsulosin (0.4 mg once daily) monotherapy ($n = 20$), or the combination of both ($n = 20$) for 8 wk [71]. IPSS, Q_{max}, PVR volume, Sexual Health Inventory for Male (SHIM) scores, and questions number 3 and 4 of the IIEF significantly improved in each group. Improvement in the symptom score was more evident in both the combination (40.1%) and the tamsulosin-only (36.2%) groups as compared with the sildenafil-only group (28.2%) ($p < 0.001$). Improvement of Q_{max} and PVR volume were greater in both the tamsulosin-only and in the combination group as compared with the sildenafil-only group. SHIM scores had a significantly greater improvement in both the sildenafil-only (65%) and in the combination (67.4%) group than in patients who received tamsulosin only (12.4%; $p < 0.001$), and increases in the IIEF scores were greater in the sildenafil-only and combination group than tamsulosin only. This study showed that treatment with the combination of tamsulosin and sildenafil was not superior to monotherapy with tamsulosin to decrease voiding symptoms.

3.5.4. α-Adrenergic blockers and udenafil

In an open, prospective, and noncomparative study, Chung et al [72] evaluated the clinical efficacy and safety of administering udenafil, a relatively novel PDE5-I, in patients with LUTS and ED who had been undergoing stable α-blocker therapy for BPH. This trial was open, prospective, and noncomparative. LUTS and ED improved significantly compared with baseline. The authors concluded that the coadministration of udenafil and an α-blocker in patients with BPH and ED was well tolerated and significantly improved both LUTS and ED severity. However, this trial had limitations in regard to the unique nature of the study design and inclusion criteria. The results should be cautiously interpreted given other limitations of the study, including absence of the placebo group, the fact that enrolled patients were undergoing stable α-blocker therapy without limitation to the individual kind of α-blocker prescribed earlier, udenafil was not taken regularly, and only the subjective parameter of IPSS score was evaluated. However, this study was the first trial on the coadministration of udenafil and α-blockers in patients with BPH/LUTS and ED.

In summary, the implications for clinicians are clear. Men with LUTS frequency present with symptoms of ED and vice versa. A variety of treatment options are available, including treating with daily dosing of a PDE5-I, use of combination therapy, or other options. These common problems in men have a marked impact on QoL, and urologists and other clinicians should manage them appropriately.

4. Conclusions

Consistent evidence of improvements in symptoms of LUTS has been shown with PDE5-Is, either alone or in combination with α-blockers. Despite evidence of symptom improvement, there is surprisingly no evidence across multiple studies and different PDE5 agents of any effect on urodynamics or objective measures of urinary flow. No evidence of improvement in ED with α-blockers was observed, but they do consistently produce improvements in urinary symptoms and flow. Various combinations of PDE5-Is and α-blockers have been tested. These do effectively improve both ED and LUTS although not convincingly better than either alone.

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Acquisition of data: Martínez-Salamanca
Analysis and interpretation of data: Martínez-Salamanca, Carballido, Eardley, Giuliano, Gratzke, Rosen, Salonia, Stief.
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