Curr Urol Rep (2013) 14:585–594
DOI 10.1007/s11934-013-0373-2

The use of PDE-5 Inhibitors in the Treatment of Lower Urinary Tract Symptoms Due to Benign Prostatic Hyperplasia

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Published online: 18 October 2013

Abstract The relationship between lower urinary tract symptoms secondary to BPH and ED has recently been the subject of significant research due to the prevalence of both conditions concomitantly existing in older men. Many large-scale studies have demonstrated an association between erectile dysfunction and lower urinary tract symptoms. Although the mechanisms underlying the relationship between LUTS and ED are not fully elucidated, several theories are currently proposed in literature: the nitric oxide/cGMP pathway, RhoA/Rho-kinase signaling, pelvic atherosclerosis associated with chronic hypoxia, and autonomic adrenergic hyperactivity. The mechanisms by which these pathways affect the bladder, prostate, pelvic vasculature and spinal cord are also the subject of current research. In this chapter, we examine the randomized, placebo-controlled trials that have evaluated the use of PDE-5Is in LUTS, as well as randomized, controlled trials (RCTs) researching combination PDE-5Is and alpha blockers.

Keywords PDE-5 INHIBITORS · Benign Prostatic Hyperplasia · AUA Symptom Index (AUA-SI) · Lower Urinary Tract Symptoms (LUTS)

Introduction

The relationship between lower urinary tract symptoms (LUTS) secondary to benign prostatic hyperplasia (BPH) and erectile dysfunction (ED) have been frequently investigated due to the high prevalence of both conditions in older men. This large body of epidemiologic data supports a causal relationship between LUTS and ED [1]. The level of concern for this association between LUTS and sexual dysfunction has grown among patients, government agencies, investigators and the healthcare providers who treat such men. It is well-established that both LUTS and ED independently reduce quality of life. In combination, these two clinical entities logically compound life distress. The association between these two diseases has also garnered attention, as investigators have hypothesized a common pathophysiology to explain the idea that they are causally linked. This common-theme hypothesis has taken on a life of its own, as pharmaceutical companies have expanded the indications for their drugs for both diseases.

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Epidemiology

The first large-scale study reporting on an age-independent association between LUTS and male sexual dysfunction was presented by Macfarlane et al [2]. Based on data from a study of 5,849 men who underwent a 1-year observational trial with alfuzosin, baseline LUTS were strongly correlated with different aspects of sexual dysfunction. Additional studies were published in the last decade, involving more than 35,000 men who contributed data on ED and LUTS. Based on these results, there is, on average, an increase of approximately 100 % in ED rates in men with concomitant moderate or severe LUTS. The results are consistent overall across studies [1].

The largest and most widely cited study to date is the multinational survey of the aging male (MSAM-7) by Rosen et al. [3], in which the relationship between LUTS and both ED and Ejaculatory Dysfunction (EjD) was studied, as measured by the IIEF, IPSS and Danish Prostate Symptom Score (Dan-PSS), a validated measure of ejaculation, low desire, and ejaculation-related concern in aging men [4]. Data from 12,815 men aged 50–80 years from the United States and six European countries were analyzed. Thirty-one percent of respondents had moderate-to-severe LUTS and 48.7 %

reported difficulties achieving an erection, with 10 % noting a complete absence of erection. Within each age category, the frequency of ED was strongly related to the severity of LUTS with a relative risk (RR) increasing from 3.1 (moderate LUTS) to 5.9 (severe LUTS) regardless of the coexistence of comorbid conditions, such as diabetes, hypertension, cardiac disease, or hyperlipidemia (Fig. 1).

The impact of LUTS on men's sexual health was evaluated as part of a cross-sectional epidemiological study (the EPILUTS study) to assess the prevalence of LUTS among men and women aged 40 years or older in the USA, the UK, and Sweden [5••]. The analysis included 11,834 men with a mean age of 56.1 years, 71 % of whom reported being currently sexually active. Twenty-six percent had mild to severe ED, 7 % had ejaculatory dysfunction, and 16 % experienced premature ejaculation. This problem (premature ejaculation) had not previously been assessed. However, a strong, dose-related relationship between LUTS and male sexual dysfunction was again observed (Fig. 2).

Men with multiple LUTS had more severe ED and experienced more frequent ejaculatory dysfunction and premature ejaculation. In the logistic regression analysis, greater age, hypertension, diabetes, depression, urgency with fear of leaking, and leaking during sexual activity were significantly associated with ED. More frequent LUTS were associated with most of the common sexual dysfunctions in men, highlighting again the importance of assessing the sexual health of *all* men presenting with LUTS.

In summary, the major epidemiologic findings to date include: (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 in the risk of ED for increasing urinary complaints in logistic regression models after controlling for age and comorbidities. According to these reproducible and robust data, considering the strength of association, internal consistency, and dose-response effects, a causal link between LUTS and ED is strongly supported [6]. Moreover, the association between ED and LUTS has biologic plausibility given the interrelationships of the known pathophysiological mechanisms of these disease states.

LUTS Treatment

The treatment of LUTS secondary to BPH underwent a major paradigm shift with the advent of alpha-blockers in the 1990s. Used alone or in combination with 5-alpha reductase inhibitors, medical treatment soon became the standard of care for LUTS/BPH. Unfortunately, these medications can be associated with bothersome sexual side effects that vary between different classes of medications, different medications within the same classes and different combinations of drugs.

The primary purpose of treating LUTS is to improve symptoms and reduce bother, while at the same time causing as few side effects as possible. Ideally, there should be few adverse events, including those related to sexual function. In fact, almost all therapies for BPH-related LUTS are associated with some sexual side effects, although they differ in type, frequency and severity.

Surprisingly, even in active surveillance of LUTS there is some alteration of sexual function. The impact on ED in men with LUTS undergoing active surveillance is variable during a short period, with some men finding that their sexual function improves and others finding that it deteriorates. However, in the long run, sexual function tends to deteriorate. The effect of alpha-blockers (AB) on ED in men with LUTS is variable during a short period, with men reporting either no change or a modest improvement of unknown significance. However, the effect of ABs on EjD in men with LUTS is significantly affected by two agents (tamsulosin and silodosin). The other ABs have little or no impact on EjD. The effect of 5-alpha-

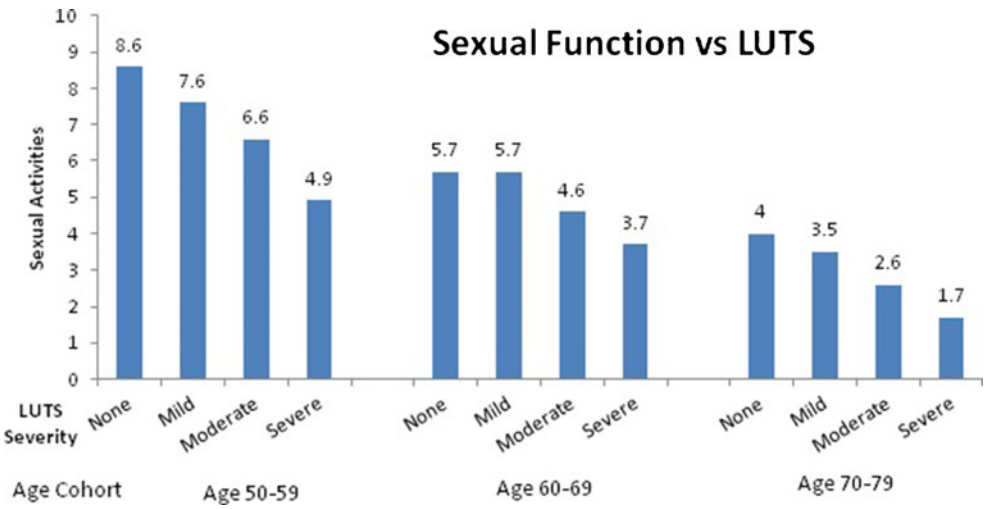

Fig. 1 Sexual function declines as the severity of LUTS increases and with age. Severity of LUTS assessed by IPSS score: None 0, Mild 1–7, Moderate 8–19, Severe 20–35 [3]

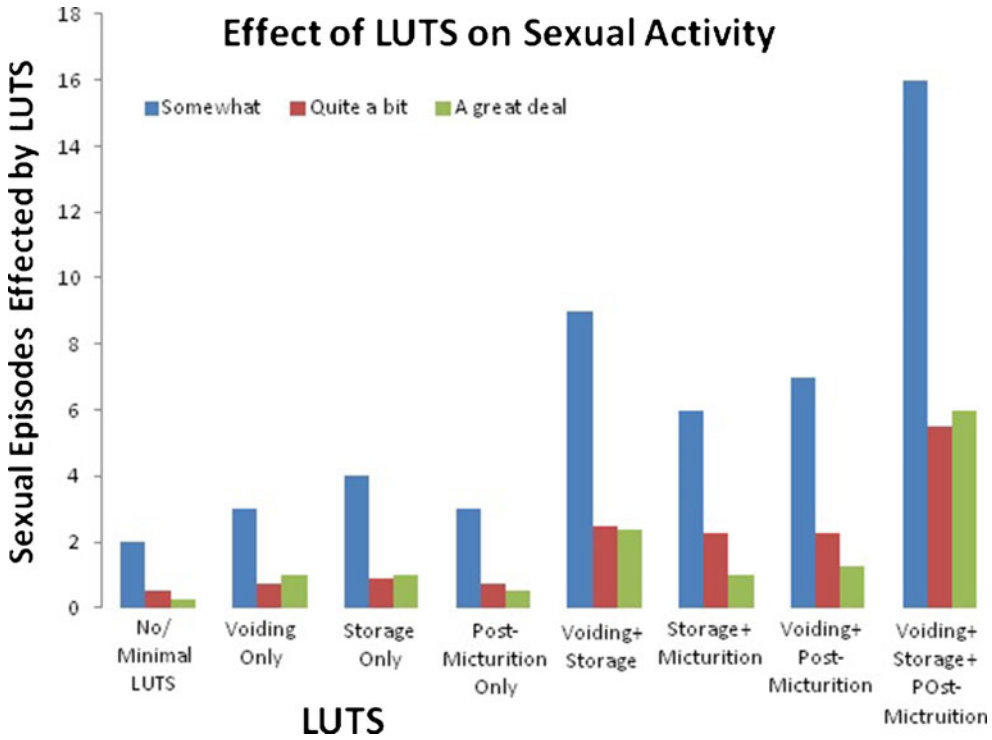

Fig. 2 Decreased enjoyment of sexual activity due to LUTS; EpiLUTS study [5••]

reductase inhibitors (5ARI) on sexual function in men with LUTS is modest but global, with effects on penile erection, ejaculation and sexual desire. It was originally thought that the effects were fully reversible, yet there have been reports of persistence of the sexual side effects following cessation of therapy when these drugs have been used to treat male pattern baldness. The veracity of this finding is unclear at present.

Pathophysiology of Luts and the PDE-5 Signal Pathway

Although the mechanisms underlying the relationship between LUTS and ED are not fully elucidated, several pathophysiological theories are currently proposed in the literature, while the possible common links between these pathways are still under investigation. Sexual dysfunction is frequently found in aging men with LUTS secondary to BPH, and is linked to LUTS/BPH via the nitric oxide/cGMP pathway, RhoA/Rho-kinase signaling, pelvic atherosclerosis associated with chronic hypoxia, and autonomic adrenergic hyperactivity.

NOS/cGMP Pathway

The NOS/cGMP pathway in erectile function has been well characterized, however, investigations have recently focused on the link between BPH/LUTS and ED using the NOS pathway as a common link between the two entities (Fig. 3) [7].

Investigators have suggested that BPH may result from proliferation of prostatic stroma and epithelium and/or from increased prostatic smooth muscle tone. A critical regulator of prostate innervation and smooth muscle tone is nitric oxide (NO), derived from nitric oxide synthase (NOS). Since NO is a key regulator of proliferation and smooth muscle relaxation, and NOS signaling is altered in patients with BPH, investigators have proposed that decreased NO in patients leads to increased severity of LUTS [8]. NOS is found in endothelial and neuronal forms in nerves within the prostate, as well as in the basal cells of the glandular epithelium [9]. Also, nitric oxide synthase expression of both forms is reduced in the transition zone of the prostate in BPH [10]. The subsequent reduction in bioavailable NO results in increased smooth muscle cell contraction at the bladder neck and smooth muscle cell proliferation within the stroma of the prostate, resulting in worsening of bladder outlet obstruction [11]. Further, in vitro models have demonstrated an antiproliferative effect on prostatic smooth muscle cells by NO donors, such as sodium nitroprusside, via a negative effect on the proliferation of the protein kinase C signal transduction pathway [12]. Phosphodiesterase (PDE) mRNA and protein have been localized across the whole human urogenital tract, with different patterns of expression and concentrations [13]. The hypothesis that impaired NO/cGMP signaling contributes to the pathophysiology of BPH has provided further background for a potential role of NO donor drugs and PDE5-i in the management of BPH-associated LUTS [7]. In this respect, PDE5-i increased the levels of cAMP and cGMP in the human prostate and plasma, and the distribution of PDE5-i was found to be higher in the prostate than in the plasma of treated men [11]. In addition, PDE5-is have shown antiproliferative effects in the prostatic stroma [14].

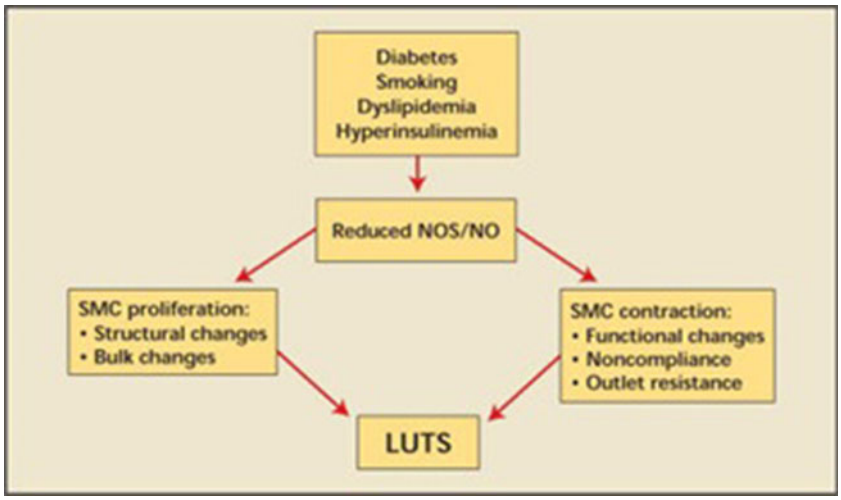

Fig. 3 The nitric oxide synthase/nitric oxide (NOS/NO) theory of erectile dysfunction and lower urinary tract symptoms (LUTS). SMC=smooth muscle cell [27]

RhoA/Rho-KINASE (Rock) Signaling

It is theorized that smooth muscle relaxation in the penis and prostate and the NO pathway may be mitigated by pathways that circumvent the relaxing effects of NO. The Rho kinase pathway is one such pathway in which RhoA is activated by GTP, and translocated to the cell membrane where it acts as a kinase to maintain the phosphorylated state of myosin light chain by inhibition of myosin phosphatase. Actin and myosin cross-bridging and contraction then ensue, independent of intracellular calcium levels [15]. Upregulation of RhoA/ROCK has been established in diabetes-related ED [16–18], and may provide further insight into the multifactorial nature of BPH/LUTS and ED. Despite the seemingly independent mechanism of ROCK signaling, some evidence suggests that the Rho kinase pathway is also involved in the inhibition of eNOS, which may lead to decreased smooth muscle relaxation, thus providing a way for PDE-5 inhibitors to overcome smooth muscle contraction and bladder outlet obstruction (BOO) resultant from the ROCK pathway [19].

Pelvic Atherosclerosis and Chronic Hypoxia

Pelvic atherosclerosis is thought to affect voiding function via fibrosis and contraction of smooth muscle cells in the prostate and bladder, through alterations in the NOS pathway and inhibitory effects on vascular endothelial growth factor (VEGF). These induce a state of chronic hypoxia in the bladder and prostate that is associated with ED and LUTS [20]. Investigators demonstrated in rabbits that chronic hypoxia due to pelvic arterial disease resulted in significant detrusor fibrosis, and increased bladder pressures. This fibrosis was also associated with significantly higher levels of TGF-Beta1 in the bladder tissue (Fig. 4) [21].

Increased levels of TGF-beta1 are inhibitory to NOS function and NO production [23], which results in impaired prostatic smooth muscle relaxation [24], potentially contributing to bladder outlet obstruction. Prostate smooth muscle isolated from rabbits with pelvic atherosclerosis showed significant contraction on isometric tension measurements, as well as structural damage [25]. Chronic pelvic ischemia secondary to atherosclerosis is also associated with prostatic glandular atrophy, resulting in decreased levels of VEGF. VEGF is also an important regulator of the NOS pathway [26] and is therefore associated with the PDE-5 mechanism.

Autonomic Hyperactivity

Autonomic hyperactivity (AH), a component of the metabolic syndrome, refers to a dysregulation of sympathetic and parasympathetic tone. While the relationship between autonomic hyperactivity and the PDE-5 pathway is unclear, animal models have shown clearly that prostatic hyperplasia and ED are induced by autonomic hyperactivity [27]. Increased sympathetic tone results in penile flaccidity and antagonizes penile erection. Several epidemiologic studies that did not account for confounding showed increased risk of LUTS with components of metabolic syndrome and AH, including type II diabetes, beta blocker requirements, sedentary lifestyle, hypertension, and obesity [28, 29].

AH has been shown to lead to LUTS and subjective dysfunctional voiding [30]. In this study, increased AUA symptom scores, BPH Impact Index Scores, and even prostate size were significantly correlated with markers for autonomic hyperactivity, such as increased serum norepinephrine levels or abnormal hypertensive response to tilt table testing. This relation remained significant after controlling for confounders (BMI, insulin level, physical inactivity and age).

Rat models have demonstrated an effect on prostatic growth and differentiation through manipulation of autonomic activity. The SHR rats that develop increased autonomic

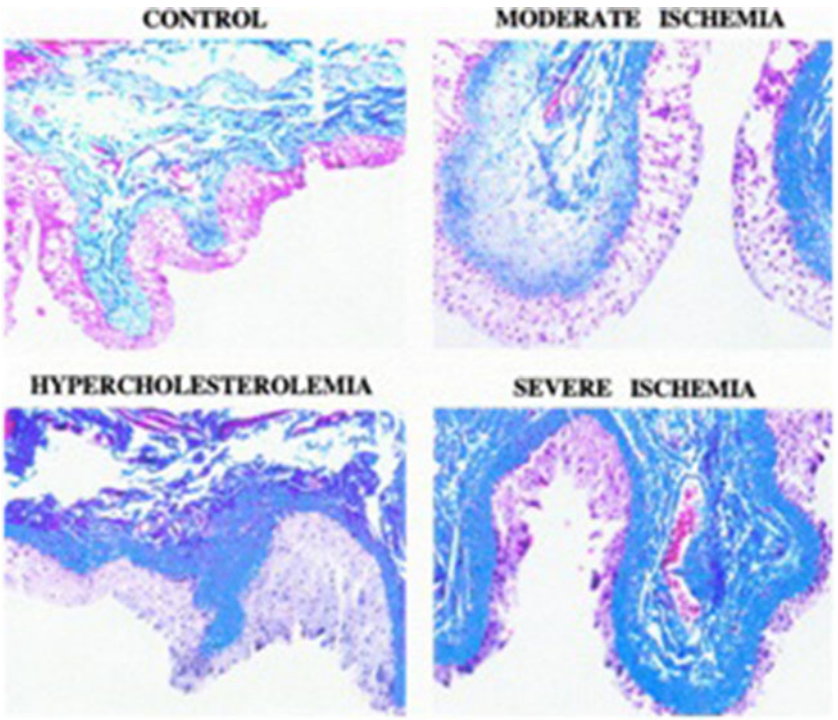

Fig. 4 Masson's trichrome stain of urothelium in bladder tissues from control, hypercholesterolemia, moderate bladder ischemia and severe bladder ischemia groups. Chronic moderate bladder ischemia (MBI) produces marked structural damage in urothelium causing thickening, disruption of mucosa, vacuolization and dense fibrosis of suburothelial layer. Severe bladder ischemia (SBI) produced more extensive changes causing thickening of urothelium, distortion of mucosa and more extensive fibrosis in suburothelial layer. Hypercholesterolemia (Hch) produced only mild regional thickening of urothelium but did not produce destructive changes or fibrosis of suburothelial layer [22]

activity, prostate hyperplasia and ED show improvement in their ED after brief, aggressive treatment of their hypertension [31]. In a different model, hyperlipidemic rats developed simultaneous prostatic enlargement, bladder over activity and ED after being fed a high-fat diet. It remains unclear whether the increase in LUTS or ED is a consequence of an alteration in the function of the bladder/penis itself that generates increased central activation, or is the result of a central increase in sensitivity to peripheral signals.

Studies using SHR, which were shown to develop increased autonomic activity, prostatic hyperplasia, LUTS, and ED, further support a significant role of the autonomic nervous system in promoting the common pathophysiology of these disorders. SHR had an overabundance of sympathetic fibers innervating the bladder, prostate, and penis, and showed improvement in erectile function after antihypertensive therapy.

Mechanism of Action of PDE-5 Inhibitors in BPH/LUTS

Bladder

PDE5 is widely expressed in human bladder tissue and modulates proliferative and smooth muscle relaxant effects through cGMP. A PDE-resistant cGMP analog demonstrated consistent antiproliferative and relaxant effects in human bladder cells. All PDE-5 inhibitors showed similar activities, however, vardenafil had activity levels similar to that of the cGMP analog. Also vardenafil significantly reduced non-voiding contractions of smooth muscle at a level comparable to that of tamsulosin [14].

The RhoA/Rho kinase (ROCK) pathway has been shown to have an important role in the regulation of human bladder muscle tone [7]. As emerging data demonstrated a link between bladder dysfunction and the PDE-5 pathway, it seemed plausible that a link existed between PDE-5 and the RhoA/Rho kinase pathway. Morelli et al. investigated the relationship between the PDE-5 pathway and RhoA/Rho kinase, and the effect of vardenafil-induced cGMP accumulation on RhoA/ROCK signaling in the bladder. In this study, vardenafil prevented RhoA membrane translocation and activation, which decreased ROCK activity in rats genetically prone to overactive bladder. Vardenafil dosing led to an accumulation of cGMP, which interrupted the RhoA/ROCK signaling pathway. These results suggested that improvement in OAB symptoms in rats may be at least partially due to cGMP-dependent RhoA/ROCK inhibition [15].

Prostate

While PDE-5 inhibitors have demonstrable effects on bladder musculature, the effect of PDE-5 inhibitors locally in prostatic smooth muscle tissue has also proven to be an important part of the physiologic activity of these medications in the treatment of LUTS. Zhao et al. found that PDE-5 inhibitors increased plasma levels of cyclic nucleotides as well as in prostatic tissue. The elevated ratio of cyclic nucleotides in prostatic tissue to plasma levels indicated a longer duration of action in the prostate [11]. The cyclic nucleotide cGMP has also been implicated in the function of the prostate via the NO-cGMP signal pathway. Nitric oxide synthase that exists in the

prostate in its neuronal and endothelial forms has been found in prostatic basal cells as well [9]. In addition, its expression is reduced in the transition zone of the prostate in BPH. In rat models, reduced expression of NOS resulted in increased smooth muscle cell proliferation and contraction of the prostatic urethra contributing to bladder outlet obstruction [11].

Vasculature

Morelli et al. found that PDE 5 is highly expressed in human vesicular-deferential arteries, and investigated the effect of PDE-5 inhibitors on prostatic blood flow. PDE-5 activity in the arteries, as measured by cGMP breakdown, was significantly reduced by tadalafil, resulting in increased relaxation response to NO donors, as well as improvement in prostate tissue oxygenation comparable to controls [32]. Similarly, Morelli's study of the PDE-5 inhibitor effect on bladder hypoxia showed significant reductions in hypoxia-related induction of smooth muscle-specific genes by administration of vardenafil. Together, these data provide strong support for a common link between pelvic vasculature dysfunction and LUTS, as well as objective data regarding the usefulness of PDE-5 inhibitors in the bladder and prostate via improved blood flow and reduced hypoxia to these organs [15].

Spinal cord

Recently, investigators demonstrated the presence of PDE5 in the lumbosacral spinal cord in a rat model [33]. In addition, the authors showed that sildenafil had no urodynamic effects in normal rats, but pronounced effects in rats obstructed at the bladder outlet. The obstructed rats also had changes in afferent neurons primarily residing in the dorsal root ganglia, suggesting the PDE5I might affect their sensitivity to cGMP and, consequently, toward PDE5I. Sildenafil administered in a small dose (1 μg) directly to the sacral spinal cord had urodynamic effects that cannot be explained by a peripheral site of action. The urodynamic effects of PDE5I in bladder-obstructed rats may thus be mediated at least in part via effects on the sacral spinal cord.

Summary of Randomized Controlled trials of PDE5 Inhibitors vs Placebo

Lower urinary tract symptoms associated with benign prostatic hyperplasia are a common condition of middle-aged and older men. Interestingly, sexual dysfunction is also highly prevalent among this group of men, yet current therapies for the treatment of LUTS/BPH (i.e., alpha blockers, 5-alpha-reductase inhibitors and phytotherapies) are associated with bothersome sexual side effects. This combination of disease- and treatment-associated side effects set the stage for the discovery for a treatment modality that could help both LUTS and ED. It was suggested for the first time in 2002 that PDE5Is could improve urinary symptom scores in men [34•]. In 2006, Mulhall et al. demonstrated in a cohort of men with IPSS scores of >10 and erectile dysfunction that PDE5Is can improve LUTS [35]. After these uncontrolled studies, several clinical trials have investigated the use of PDE5Is in LUTS/BPH men. McVary et al. performed a systematic review and meta-analysis to determine the relative efficacy and safety of PDE5Is alone or in combination with alpha-blockers, and to define the best candidates for this treatment based on clinical feature and LUTS severity. In this review, 107 publications were reviewed, however only seven met criteria as randomized controlled trials of PDE5 inhibitors vs. placebo for the study. Ultimately, data from 2,749 patients were included in the studies that were reviewed in this analysis. The following is a summary of these trials.

McVary et al. examined the treatment response to sildenafil in men with moderate to severe LUTS associated with BPH in a double-blind, placebo-controlled trial. The sildenafil group (n= 189) showed an improvement in IPSS scores of 8.6 points, while the placebo group's IPSS scores improved by only 2.4 points. No change in maximal flow rate (Qmax) was observed in either group. This study also examined the effect of BMI with regards to treatment and improvement of LUTS with PDE5 inhibitor, and found improvement in iPSS scores regardless of BMI, with no change in Qmax regardless of BMI [36•].

McVary et al. studied the efficacy of tadalafil once daily for LUTS/BPH. This study was a single-blind, placebo-controlled trial with 281 men taking 5 mg tadalafil for 6 weeks followed by dose escalation to 20 mg for 6 weeks or 12 weeks of placebo. IPSS scores at 6 weeks showed significant improvements for the tadalafil group vs. placebo (-2.8 vs. -1.2). At 12 weeks, the improvements in the IPSS scores persevered (-3.8 vs. -1.7). Of note, when post-void residual was measured, no significant change was seen. Similarly, there were no changes in uroflometry across groups [37••].

Vardenafil dosed twice-daily at 10 mg for the treatment of BPH/LUTS was studied by Stief et al. in a randomized, double-blind, placebo-controlled study. Men with IPSS scores greater than or equal to 12 were assessed with IPSS, Qmax and PVR after 8 weeks of treatment. Vardenafil showed significant improvement in the mean IPSS score compared to placebo (-5.9 vs. 3.6), although only nominal improvements were seen in irritative and obstructive IPSS subscores, EF, and Urolife QoL-9 scores. Qmax and PVR did not change significantly [38•].

In an effort to delineate the dose of PDE5 inhibitor needed to treat BPH/LUTS, Roehrborn and McVary assigned patients to 12-week treatments of placebo or tadalafil at doses of 2.3, 5, 10, or 20 mg. Mean IPSS scores showed improvements at all dosages compared to placebo. Interestingly, improvements in IPSS scores were documented at 4, 8 and 12 weeks for patients taking tadalafil. Tadalafil showed significant improvements in

IPSS obstructive subscore for the 2.5-mg dose, while the 5-, 10-, and 20-mg dosages showed improvements in both IPSS obstructive and irritative subscores. Qmax did not improve at any tadalafil dose. The authors concluded that the 5-mg dosage appeared to provide a positive risk-benefit profile [39•].

In a similar study evaluating the effect of once-daily tadalafil on BPH/LUTS, Porst and McVary evaluated 581 men in a multinational randomized, double-blind, placebo-controlled study. Statistically significant improvements in patient IPSS scores were noted at each dose: -5.4 (2.5 mg), 6.8 (5 mg), 7.9 (10 mg) and 8.2 (20 mg) versus 2.0 for placebo. All p-values were <0.05. There were no significant changes in Qmax or PVR [40•].

Tamimi et al. evaluated the PDE5 inhibitor UK-369,003 in a multicenter, double-blind, placebo- and active-controlled study with 418 men over the age of 40 and with IPSS scores of 13 or higher. The initial Qmax rate was 5–15 mL/s. Patients were given doses of 10, 25, 50 or 100 mg in a modified release formulation, and 40 mg in an immediate release formulation for 12 weeks. They found an increasing efficacy with increasing dose of the MR medication. The 100-mg MR and 4-mg IR dose IPSS improvements were -2.91 and -2.50 times better than placebo, respectively. Interestingly, in contrast to the other studies reviewed in this chapter, UK-369,003 improved Qmax significantly by 2.1 mL/s, as compared to 0.84 for placebo [41•].

In continued analysis of Tadalafil, Porst et al. investigated the efficacy and onset of tadalafil on BPH/LUTS, as well as patient and clinician perception of changes in urinary symptoms. Once again, Tadalafil improved IPSS results compared to placebo (-5.6 vs. -3.6), and IPSS results were apparent after 1 week and statistically significant at 4 weeks. As with many of the other studies investigating the effect of PDE5 inhibitors on Qmax and PVR, no significant change was seen in this study [42•].

In another RCT, there were no differences from baseline in men randomized to placebo versus tadalafil 20 mg daily for 12 weeks in either noninvasive or invasive urodynamics. This study was conducted to demonstrate the safety of tadalafil daily in terms of negative impact on bladder contractility, and found no such effect. Notably, it also did not find any positive effect on contractility or the bladder outlet condition [43].

A systematic review of published material regarding the use of PDE5 inhibitors for LUTS due to BPH was recently published, synthesizing the results of several articles involving a total of 3,214 patients enrolled in trials of PDE inhibitors [44••]. In this review, 107 publications were reviewed, however only seven met criteria as randomized controlled trials of PDE5 inhibitors versus placebo. It is clear from this analysis that the relationship between ED and LUTS and the effect of PDE5Is on these conditions has been thoroughly studied. Nearly 2,800 patients have been studied in RCTs comparing PDE5Is against a placebo. IPSS scores were significantly improved for all treatment groups compared to placebo with a mean difference of almost three points on the IPSS scale. This is an improvement that is clinically relevant for symptomatic men and is perceived by patients. The efficacy seems to be quite similar across the different classes of PDE5Is and the different dosages.

Summary of Randomized Controlled Trials of pde5 Inhibitors and Urodynamics

Measurement of improvement in symptoms secondary to BPH and BOO after treatment can be difficult, given that the main tools to do so are validated questionnaires such as the IPSS score. While these questionnaires provide a platform from which we may study and compare the effect of treatment for BPH/LUTS, it

Trial	PVR	Qmax	Qave	Vcomp
McVary,Monnig et al.	-	No Change	-	-
McVary, Roehrborn et al.	No Change	No Change	No Change	No Change
Steif, Porst et al.	No Change	No Change	-	-
Roehrborn, McVary et al.	No Change	No Change	No Change	-
Porst, McVary et al.	No Change	No Change	-	-
Tamimi Mincik et al.	-	No Change	-	-
Porst, Kim et al.	No Change	No Change	-	-

Fig. 5 Table summarizing comparison of urodynamic parameters measured in placebo vs. PDE5 inhibitor RCTs [44••]

does not provide empiric data for analysis. Urodynamics represent the best current method for obtaining data that is not influenced by patient perception. The previously mentioned randomized controlled trials included some urodynamic parameters, such as Qmax, PVR and uroflowmetry (Fig. 5).

Despite significant symptomatic improvement in the PDE5 inhibitor arms, no urodynamic changes were found in these studies, suggesting that PDE5Is alone must exert their clinical activity differently than alpha-blockers. Alpha-blockers act mainly to relieve prostatic obstruction, while PDE5Is may relieve LUTS via a relaxation effect on the bladder smooth muscle tone [44••].

Safety

An overall rate of adverse events was calculated to be 16 % in the treatment group while only 6 % in the placebo group. Common side effects of the medications including flushing, gastroesophageal reflux, headache, and dyspepsia are consistent with those noted in the RCT of PDE5i for erectile dysfunction [44••].

Limitations

The information provided by the studies involving PDE5Is contributes to a growing database of information from which clinicians can draw recommendations with regards to PDE-5 inhibitors I the treatment of BPH/LUTS. The nature of these studies, however, reduces the overall value due to small sample size, inconsistent recording of safety data, and short duration. One recent long-term study showed that patients randomized to placebo that were switched to 5 mg of tadalafil also showed improvement. Patients who were switched to higher dosages of medication (i.e., 2.5 mg to 5 mg) experienced improvement in IPSS scores, while those maintained on one dose did not experience any additional improvement at one year, but did not deteriorate either [45]. Unfortunately, no data exists yet with regard to ejaculation or global sexuality improvement, which would be useful in the context of the treatment of BPH/LUTS and ED with PDE5Is. Also, there are no RCTs comparing different classes of PDE5Is, nor are there studies reporting side effect profiles such as sexual outcomes for combination therapy of PDE5Is and 5-alpha-reductase inhibitors. Finally, cost effectiveness of PDE5I therapy has not been addressed satisfactorily.

Key Points

PDE5Is are a safe and effective treatment for men over the age of 45 with LUTS due to BPH alone or in combination with alpha-blockers.

PDE5Is consistently improve IPSS scores, however, Qmax and PVR are unlikely to be effected by this medication.

Side effects most commonly include flushing, gastroesophageal reflux, headache, and dyspepsia.

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Further research into the long-term effectiveness of PDE5Is is warranted, along with cost effectiveness studies.

DO'S AND DON'TS

DO'S

Treatment with PDE5Is can be a useful therapy in men with LUTS secondary to BPH

PDE5I/alpha-blocker combination therapy can significantly improve symptoms related to BPH

DON'Ts

Do not use PDE5Is in combination with other drugs that may induce vasodilation such as nitroprusside, nitroglycerine, or isosorbide.

Do not use PDE5Is in patients with NYHA class 2 or worse, heart disease, history of CVA in the last 6 months, unstable angina, or hypotension.

Do caution patients against the concurrent use of PDE5Is and alcohol.

Compliance with Ethics Guidelines

Conflict of Interest Dr. Casey Lythgoe reported no potential conflicts of interest relevant to this article.

Dr. Kevin McVary received consultancies and honoraria from Allergan, Lilly/ICOS, NxThera, and Watson Pharmaceuticals. Dr. McVary received honoraria and payment for the development of educational presentations including service on speakers' bureaus from GSK.

Dr. McVary serves as a Section Editor for Current Urology Reports.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of outstanding importance

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