



## Platinum Priority – Review – Benign Prostatic Hyperplasia

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# The Relationship between Erectile Dysfunction and Lower Urinary Tract Symptoms and the Role of Phosphodiesterase Type 5 Inhibitors

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### Abstract

**Context:** The relationship between lower urinary tract symptoms (LUTS) and erectile dysfunction (ED) and the potential interplay of phosphodiesterase type 5 inhibitors (PDE5-I) have clinical implications for both patient screening and treatment.

**Objective:** To describe the current literature assessing the LUTS–ED relationship and the role of PDE5-I from both a basic science and clinical intervention perspective.

**Evidence acquisition:** We focused on data recently published (1990–2008) describing epidemiologic and mechanistic manuscripts of the LUTS–ED relationship with emphasis on papers involving PDE5-I—particularly those using level 1 evidence clinical trials. Base key words used included BPH, LUTS, ED, and *phosphodiesterase inhibitors* in combination with such secondary key words as *nitric oxide*, *autonomic hyperactivity*, *Rho-kinase*, *atherosclerosis*, and *mechanism*. We abstracted >200 articles and reviewed >100.

**Evidence synthesis:** The large overlap of elderly men with both LUTS and ED likely stems from a cause-and-effect relationship. Thus far, four proposed mechanisms attempt to explain the relationship between LUTS and ED. Multiple studies showing that PDE5-I improved LUTS have been performed. Understanding the role of PDE5-I in the LUTS and ED relationship affects patient screening and treatment but also raises further research questions.

**Conclusions:** The future use of phosphodiesterase inhibitors as either prophylaxis or as a primary treatment for LUTS looms as a possibility and may not be limited to men.

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## 1. Introduction

Erectile dysfunction (ED) and lower urinary tract symptoms (LUTS) are two highly prevalent diseases in aging men that frequently coassociate and adversely affect quality of life (QoL). A large body of epidemiologic data supports a causal relationship between LUTS and ED. Thus far, four mechanisms with varied degrees of overlap have been proposed: alteration in nitric oxide (NO) levels, autonomic hyperactivity (AH), the Rho-kinase pathway, and pelvic atherosclerosis. An understanding of these complex and incompletely understood mechanisms begins to elucidate how phosphodiesterase type 5 inhibitors (PDE5-I) may play a role in the treatment of LUTS and is essential for health care professionals to optimize both patient screening and treatment.

## 2. Evidence acquisition

### 2.1. Epidemiologic evidence of causality between lower urinary tract symptoms and erectile dysfunction

In the 1990s, numerous publications began to emphasize the common overlap of LUTS and ED in elderly men. Since then, the preponderance of well-designed longitudinal studies highlights a cause-and-effect relationship between LUTS and ED (Table 1). When viewed together, these studies demonstrate reliable strength of association among study consistency, dose-response effect, and temporality (although further studies are needed). The studies in Table 1 also consistently account for alternative explanations of bias, confounding, and randomness through the use of well-powered multivariate analyses.

### 2.2. Mechanisms of interaction between lower urinary tract symptoms and erectile dysfunction

To date, biologically plausible possible interrelationships between LUTS and ED fall into four categories: alteration in NO levels, AH, the alternate pathway through Rk, and pelvic atherosclerosis. These theories are not mutually exclusive and may overlap substantially. Risk factors for one often are risk factors for another, and second messenger cascades ultimately leading to smooth muscle contraction and relaxation for either prostatic/bladder neck tissue or erectile tissue may be shared. Fig. 1 graphically demonstrates the interplay of the four theories. Areas in which PDE5-I may be relevant are emphasized below.

#### 2.2.1. Alteration in nitric oxide levels

The NO system (both NO and NO synthase [NOS]) is well characterized as the main regulator of penile corporal smooth muscle relaxation and resultant erection. However, the presence and role of NO and phosphodiesterase (PDE) isoenzymes in organs contributing to LUTS—the prostate, bladder, and urethra—continue to be elucidated. The presence and functional relevance of both PDE type 4 (PDE4) and PDE type 5 (PDE5) in the human prostate has been established [1]. The NO system has been shown to be down-regulated in the transition zone of the prostate in benign prostatic hyperplasia (BPH) when compared with normal controls [2].

Rat bladder PDE5 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 [3]. The same research conversely revealed that PDE5 mRNA is found in greatest quantity in human corpora cavernosa (approximately 10-fold higher) but was also found in order of decreasing magnitude over the vas deferens, prostate, epididymis, bladder (vascular endothelium and muscle fibers only), testis, and kidney. The same authors used rat models to test multiple PDE5-I. The study demonstrated a reduction of cyclic guanosine monophosphate (cGMP)-catabolizing activity in human bladder cells and rat bladder strips and induced a consistent antiproliferative and relaxant effect. Next, an *in vivo* bladder outlet obstruction (BOO) model in which rat urethras were narrowed with a silk ligature was used. Chronic treatment with 10 mg/kg per day of vardenafil significantly reduced bladder nonvoiding contractions by 47% compared with placebo ( $p < 0.05$ ). Tamsulosin demonstrated a comparable 51% reduction in nonvoiding contractions in the same study. Other researchers utilized a rat model that demonstrated a PDE inhibitor dose-dependent reduction in smooth muscle contraction of bladder, urethral, and prostate strips [4]. A reduction in bladder nonvoiding contractions was also noted in the rat BOO model after administration of intravenous (IV) sildenafil and vardenafil. The same study demonstrated inhibition of human prostate stromal cell proliferation with vardenafil *in vivo*. Other *in vitro* human prostatic smooth muscle cell models demonstrated an antiproliferative as well as a down-regulated signal transduction pathway (through protein kinase C) effect through the use NO donors (sodium nitroprusside [SNP]) [5]. This research also revealed an increased *in vitro* prostate cell proliferation with NO antagonists.

**Table 1 – Summary of epidemiologic studies associating lower urinary tract symptoms (LUTS) and erectile dysfunction (ED)**

Study	Study design/name	n	Findings
Braun et al [38]	Cologne Male Survey	4000	LUTS in 72.2% of patients with ED vs 37.7% without ED; prevalence risk highly significant
Blanker et al [39]	Krimpen Community Cohort	3924	ED RR: 1.8–7.5 for increasing urinary complaints; risk of ED greater with LUTS than with smoking or cardiac symptoms
Moreira et al [33]	Brazilian Cohort Study	428	ED incidence RR: 3.67 if self-reported BPH—2-yr follow-up; addresses temporality of BPH → ED
Boyle et al [40]	UrEpik Study	4800	IPSS >7 showed odds ratio of 1.39 of having ED in a weighted multiple regression model, including age; similar odds ratios: heart attack, hypertension, and smoking
Vallancien et al [41]	Cross-sectional European Survey	1274	55% of patients with mild LUTS had ED vs 70% with severe LUTS; significance maintained after multiple regression analyses
Rosen et al [42]	Multinational Survey of the Aging Male	12815	RR 3.7–7.6; IPSS correlated with IIEF, sexual activity, and ejaculatory parameters; controlled for age and comorbidities; older men still sexually active
Braun et al [43]	Cologne Male Survey	4489	Prevalence of LUTS in men suffering from ED was about 72.2% (n = 621) vs 37.7% (n = 1367) in men with normal erections; the odds ratio was 2.11, even after controlling for age
Chung et al [44]	Cross-sectional Community Survey	2115	LUTS correlated with ED; sexual satisfaction and libido inversely correlated with LUTS
Ponholzer et al [45]	Austrian Study	2858	RR for ED in men with LUTS (IPSS >7) was 2.2; controlled for age, vascular risk factors, and predominance of obstructive or irritative symptoms
Hansen et al [46]	Danish Study	3442	LUTS predicted ED after multiple regression; RR 2.3–3.4; overall LUTS prevalence 39% and ED prevalence 29%
Elliott et al [47]	US Veterans Administration Survey	181	ED correlated with obstructive LUTS after controlling for age, depression, hypertension, and coronary artery disease on multivariate analysis
Terai et al [48]	Japanese Cross-sectional Survey	2084	RR: 1.5; ED correlated with LUTS (IIEF vs IPSS); correlation remained after controlling for age
McVary et al [49]	MTOPS Secondary Analysis	3000	AUASS correlated with ED and other domains; included correlation with maximum flow rate (multivariate analysis controlled for confounders)
Shiri et al [34]	Finish Cohort Study	1126	RR of ED incidence with DAN-PSS score 7–11 was 2.7, RR was 3.1 for DAN-PSS >12 over a 5-yr period; addresses temporality of BPH → ED
Paick et al [50]	PLESS Study and Questionnaire	2981	2% increase in ED risk for unit increase in PLESS LUTS survey, significant after controlling for age
Brookes et al [36]	BACH Study Subset Analysis	2301	Multivariable regression model of ED found strong association of AUASS and ED independent of age; nocturia, incontinence, and prostatitis strongest factors; no differences found across race or ethnicity

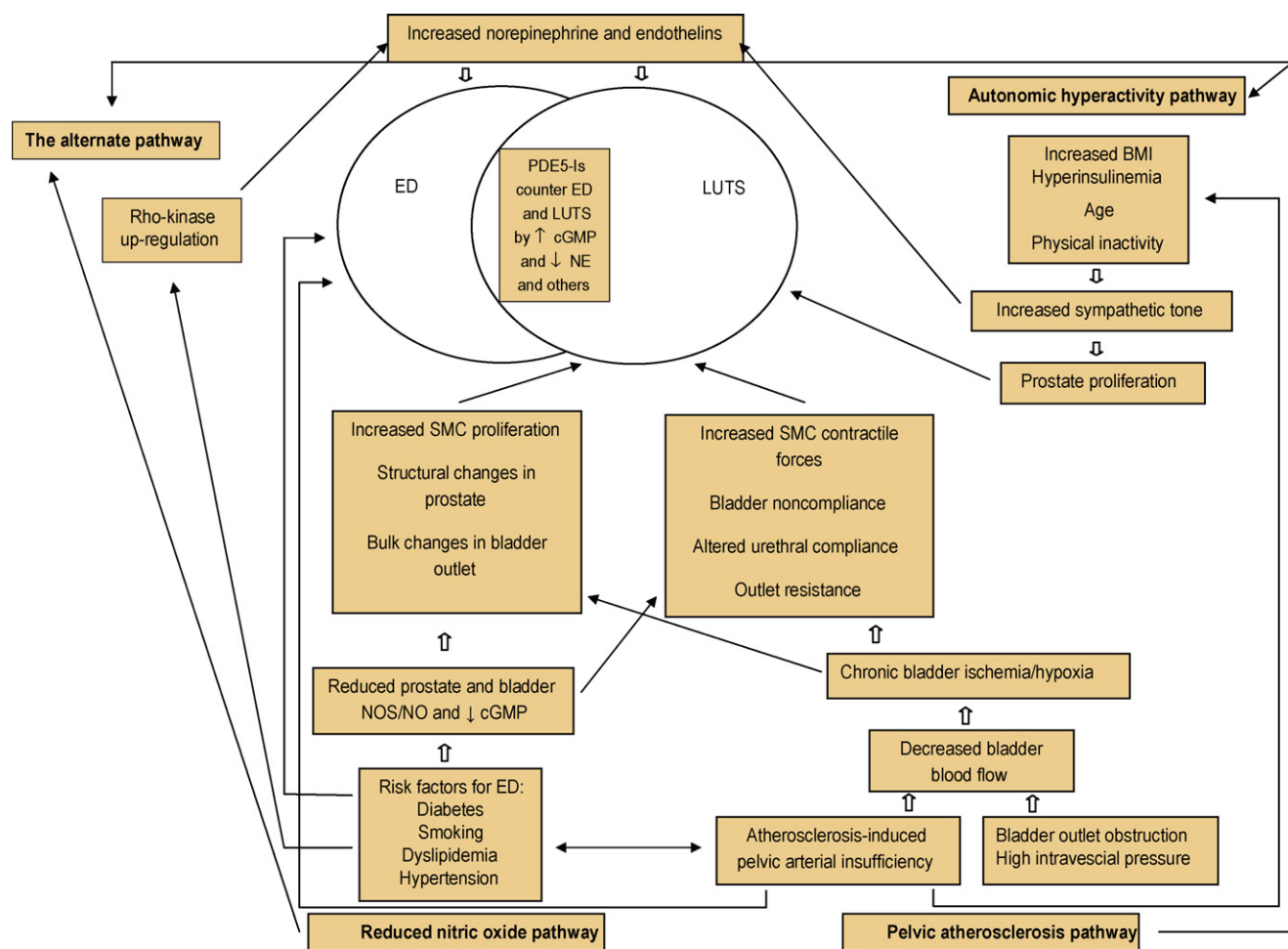
RR = relative risk; BPH = benign prostatic hyperplasia; MTOPS = Medical Therapy of Prostatic Symptoms trial; AUASS = American Urological Association Symptom Score; DAN-PSS = Danish Prognostic Symptom Score; PLESS = Proscar Long-Term Efficacy and Safety Study; BACH = Boston Area Community Health Survey.

NO activates soluble guanylate cyclase (sGC) of smooth muscle cells, which in turn increases cGMP. Increased cellular cGMP is responsible for smooth muscle cell relaxation and resultant tumescence. PDE5-I prevented degradation and hydrolysis of cGMP, thereby exerting effects on erectile and other tissues. However, the exact mechanism by which cGMP elicits smooth muscle relaxation remains uncertain and is the subject of much study. The commonly accepted pathway involves activation of potassium channels by cGMP and cGMP-specific protein kinase (as well as by NO itself), leading to hyperpolarization and closure of voltage-dependent

calcium (Ca) channels. This elicits a decrease in intracellular Ca, the dissociation of calmodulin from myosin light chain (MLC) kinase, its phosphorylation and inactivation, the subsequent dephosphorylation of myosin (by MLC phosphatase), and detachment from actin. Further research is required to elucidate the exact effect and mechanism PDE5-I has on prostate tissue.

#### 2.2.2. Autonomic hyperactivity

AH, a component of the metabolic syndrome, refers to a dysregulation of sympathetic and parasympathetic tone. Increased sympathetic tone results in



**Fig. 1 – Four proposed theories linking erectile dysfunction (ED) and lower urinary tract symptoms (LUTS).** The arrows demonstrate the interplay of the four theories, as they share many common pathways and etiologies. Note that risk factors for one mechanism often are similar for another. The theory of atherosclerosis and pelvic ischemia asserts that risk factors for ED affect pelvic arterial blood flow, resulting in loss of smooth muscle from the bladder detrusor, with loss of bladder compliance. At the same time, prostate fibrosis increases urethral resistance, resulting in LUTS. A similar process results in smooth muscle loss in the penis with resultant ED. Atherosclerosis can lead to reduced nitric oxide (NO) levels, autonomic hyperactivity (AH), and Rho-kinase activation. The AH theory asserts that increased AH results from increased body mass index (BMI), hyperinsulinemia, increased age, and decreased physical activity. The resulting increased sympathetic tone encourages benign prostatic hyperplasia (BPH) growth, LUTS, and vasoconstrictive forces that result in ED through norepinephrine, endothelin, and other secondary messenger systems. The Rho-kinase system, when activated from atherosclerosis or decreased NO, uses similar pathways to result in LUTS and BPH. The theory of pelvic reduction in NO synthase (NOS) and NO and decreased cyclic guanosine monophosphate (cGMP) from various systemic diseases that also promote ED results in increased smooth muscle cell (SMC) contractile forces at the bladder neck and prostatic urethra. Additionally, the reduced NOS/NO results in prostatic SMC proliferation and increased outlet resistance. Both forces worsen LUTS. Note that atherosclerosis results in similar SMC alterations. PDE5-I can improve both LUTS and ED by targeting various points in the different pathways by increasing cGMP or blocking the effects of norepinephrine and other secondary messengers.

penile flaccidity and antagonizes penile erection. Epidemiologic studies that did not account for confounding showed increased risk of LUTS with components of metabolic syndrome and AH, including type 2 diabetes,  $\beta$ -blocker requirements, sedentary lifestyle, hypertension, and obesity [6,7].

Rat models have demonstrated an effect on prostatic growth and differentiation through manipulation of autonomic activity [8]. Special strains of rats that are spontaneously hypertensive (SHR) and develop increased autonomic activity, prostate hyperplasia, and ED show improvement in their

ED after brief aggressive treatment of their hypertension [9]. In a different model, hyperlipidemic rats developed simultaneous prostatic enlargement, bladder overactivity, and ED after being fed a high-fat diet [10]. 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 the result of a central increase in sensitivity to peripheral signals.

AH commonly manifests mood into a brief physiologic event (for example, performance anxiety can lead to ED, or fear leads to dry mouth). AH also has been shown to lead to LUTS and subjective dysfunctional voiding [11]. In this study, increased American Urological Association (AUA) symptom scores, BPH Impact Index (BII) scores, and even prostate size significantly correlated with markers for AH such as increased serum norepinephrine levels or abnormal hypertensive response to tilt table testing. This relation remained significant after controlling for confounders (body mass index [BMI], insulin level, physical inactivity, and age).

The degree of smooth muscle relaxation at any given time is determined by the balance between sympathetic and parasympathetic tone in the smooth muscle of the bladder or prostate. Norepinephrine released from sympathetic nerve endings as well as endothelins [12] and prostaglandin (PG) F<sub>2</sub>-alpha [13] from the endothelium activate receptors on smooth muscle cells. This initiates a cascade of molecular signaling that leads to an increase in intracellular levels of Ca. Ca binds to calmodulin, activating MLC kinase, which phosphorylates MLC. The phosphorylated MLC then interacts with alpha-actin, leading to cycling of myosin cross-bridges (heads) and development of force. It is believed that other molecules are involved in modulating the contractile state. For example, the protein caldesmon may create a latch state, allowing the force of contraction to be maintained at a low level of myosin phosphorylation with low energy expenditure [14]. PDE5-I has recently been shown to be able to attenuate prostatic tone developed in isolated tissue by norepinephrine and elevate cGMP levels [15]. Second messengers such as prostaglandin F<sub>2</sub>-alpha and endothelins have also been shown to be effected by PDE5-I [16].

### 2.3. The alternate pathway: Rho-kinase activation

Smooth muscle relaxation and contraction are typically discussed through a Ca-dependent mechanism of action, whereas the alternate pathway through Rk activation is Ca independent. Recent

work has identified RhoA, a small G-protein, and its downstream target, Rk, as possible mediators of the  $\alpha$ -adrenergic (norepinephrine) and endothelin-1 (ET-1) triggered smooth muscle contraction [17]. This is thought to occur by way of Rk inhibition of MLC phosphatase. MLC phosphatase dephosphorylates MLC, stopping MLC from interacting with  $\alpha$ -actin and promoting smooth muscle relaxation and erection. Inhibition of MLC phosphatase by Rk means that there will be more active (phosphorylated) MLC available at the same level of MLC kinase activity (without requiring an increase in cytosolic Ca), effectively “sensitizing” the smooth muscle, and so contributes to the tonic phase of agonist-induced penile smooth muscle contraction and flaccidity. In human endothelial cells, the RhoA/Rk pathway was found to inhibit the Akt-dependent phosphorylation and activation of endothelial nitric oxide synthase (eNOS). Thus, an abnormally up-regulated RhoA/Rk pathway could contribute to a lack of smooth muscle relaxation, changes in bladder compliance, and thus LUTS. This also means that inhibition of this pathway presents a potential avenue for LUTS treatment development. Other studies confirm that Rk likely potentiates smooth muscle tone through the use of norepinephrine and endothelin pathways [18]. One study reported that corpus cavernosum smooth muscle from rabbits with partial BOO showed a broad range of molecular and functional differences, including increased penile smooth muscle contractility, reduced relaxation, modest alterations in total smooth muscle myosin, decreased innervation, and increased smooth muscle bundle size compared to controls [19]. These data are supported by evidence of Rk dysfunction in the bladder following BOO [20]. A recent rat model found differences in erectile response with ganglionic stimulation when comparing old and young rats [21]. Differences in erectile function between young and old rats were markedly attenuated after administration of an Rk inhibitor. A synergistic effect and greater improvement of ED was noted when the elderly rats were given a combination of an Rk inhibitor with a PDE5-I. The role of PDE5-I to help alleviate Rk-induced dysfunction thus may involve multiple pathways: NO activation of eNOS and countering of norepinephrine and endothelin changes, as demonstrated for AH.

### 2.4. Pelvic atherosclerosis

Diffuse atherosclerosis of the prostate, penis, and bladder serves an additional hypothesis linking LUTS with ED [22]. The theory asserts that known

**Table 2 – Summary of level 1 clinical trials of lower urinary tract symptoms (LUTS) and phosphodiesterate inhibitors (PDE-I)**

Study	Agent dose duration	n PDEI n	Inclusion	Exclusion	Placebo Run-in	IPSS Δ: PDE-I vs placebo (p value)	Other findings
McVary et al [26]	Sildenafil 50–100 mg qday 12 wk	369 189	Age ≥45, history of ED: ≤25 IIEF (EF domain), IPSS ≥12	PCa (or suspected); urinary symptom from causes other than BPH, hypotension, retinitis pigmentosa, hepatic/liver failure, use of 5-ARI within 6 mo; use of α-blocker/PDE5-I within last month	No	6.3 vs 1.9 (p < 0.0001)	No change in Q <sub>max</sub> ; IIEF, BII, mean IPSS QoL score, and GAQ all significantly improved
Stief et al [27]	Vardenafil 10 mg bid 8 wk	222 109	Age 45–64, IPSS ≥12, no history of ED required	Vardenafil contraindications: spinal cord injury, prostatitis, history of stricture, urinary retention, bladder or prostate cancer, history of cancer with ≤3 yr life expectancy; use of nitrates, androgens, anticoagulants, ED treatments, or α-blocker use during the study	No	5.9 vs 3.6 (p = 0.0013)	No change in Q <sub>max</sub> or PVR; IIEF, QoL, irritative and obstructive IPSS subscores all significantly improved
McVary et al [28]	Tadalafil 5 mg → 20 mg qday 4-wk run-in +12 wk (6 → 6)	281 138	Age ≥45, IPSS ≥12 from BPH for 6 mo, no history of ED required	Elevated PSA, recent 5-ARI use, BPH medication use during the study, history of pelvic surgery, hepatic/liver failure, causes of LUTS other than from BPH, uncontrolled diabetes, nitrate use, chemotherapy	Yes	5 mg 2.8 vs 1.2 (p = 0.003) <b>20 mg 3.8 vs 1.7 (p = &lt;0.001)</b> 7.1 vs 4.5 (p = <0.001): includes run-in	No change in Q <sub>max</sub> ; IIEF, irritative and obstructive IPSS subscores, mean IPSS QoL score all significantly improved
Roehrborn et al [29]	Tadalafil 2.5, 5, 10, 20 mg qday 4-wk run-in +12 wk	1058 ~212/ group	Age ≥45, IPSS >12 from BPH for 6 mo, Q <sub>max</sub> : 4–15 ml/s	Elevated PSA, recent 5-ARI use, BPH medication use during the study, history of pelvic surgery, hepatic/liver failure, causes of LUTS other than from BPH, uncontrolled diabetes, nitrate use, chemotherapy	Yes	2.5 mg 3.9 vs. 2.3 (p < 0.05) <b>5 mg 4.9 vs 1.8 (p &lt; 0.05)</b> 10 mg 5.2 vs 4.5 (p < 0.05) 20 mg 5.3 vs 4.5 (p < 0.05)	No change in Q <sub>max</sub> ; IIEF, mean IPSS QoL score, BII, LUTS GAQ all significantly improved (≥5 mg); dose >5 mg minimal Δ improvement but ↑ side effects

IPSS = International Prostate Symptom Score; ED = erectile dysfunction; IIEF = International Index of Erectile Function; EF = erectile function; PCa = prostate cancer; BPH = benign prostatic hyperplasia; PDE5-I = phosphodiesterase type 5 inhibitor; BII = BPH Impact Index; QoL = quality of life; GAQ = Global Assessment Question; PVR = postvoid residual.

risks for ED (hypertension, smoking, hypercholesterolemia, and diabetes mellitus) also affects LUTS. In a recent epidemiologic study that supports this notion, both men and women who had two risk factors of atherosclerosis (diabetes mellitus, hypertension, hyperlipidemia, and nicotine use) had a statistically significantly higher International Prostate Symptom Score (IPSS) compared with subjects with one or no risk factors [23]. Smooth muscle alterations in the bladder, prostate, and penis of animal models of hypercholesterolemia and pelvic ischemia show similarities [22]. Hypoxia-induced overexpression of TGF $\beta$ 1 and altered prostanoid production have been proposed as potential mechanisms. Penile ischemia leads to smooth muscle loss in the penis, resulting in ED. Loss of smooth muscle in the bladder would decrease compliance and worsen LUTS. Similarly, bladder ischemia from either BOO or pelvic vascular disease can induce bladder smooth muscle loss with resultant replacement of collagen deposition and fibrosis as well as loss of compliance, hyperactivity, and impaired contractility. Loss of smooth muscle in the prostate would result in a less distensible urethra, increased flow resistance, a decreased urinary flow rate, and worsening LUTS. Pelvic atherosclerosis ties in elegantly with all the previously described theories, as pelvic ischemia/atherosclerosis is a component of the metabolic syndrome/AH, up-regulates Rk activity, and reduces NOS expression.

### 2.5. Clinical trials of phosphodiesterase-inhibitor effects on lower urinary tract symptoms

In 2002, a small, uncontrolled study of 112 men demonstrated an improvement in IPSS from baseline that failed to reach statistical significance in men who were on sildenafil over a 3-mo period [24]. In 2006, another small, uncontrolled study of 48 men on sildenafil for a 3-mo period and a baseline IPSS score >10 noted a reduction in American Urological Association Symptom Score (AUASS) of 4.6 points ( $p = 0.013$ ) [25]. These initial uncontrolled studies set the stage for further research on the effects of PDE inhibitors on LUTS through randomized clinical trials (level 1 evidence).

Four randomized, placebo-controlled studies sought to elucidate the relationship between PDE inhibitors and LUTS using sildenafil, vardenafil, and tadalafil twice, respectively (Table 2). The study with sildenafil used a 12-wk, double-blinded, placebo-controlled approach in 369 men  $\geq 45$  yr who had International Index of Erectile Function (IIEF) scores <26 (on erectile function [EF] domain) and IPSS

scores >11 [26]. Exclusion criteria included history or suspicion of prostate cancer (PCa), urinary symptom causes other than from BPH (eg, stones, urinary tract infection [UTI]), hypotension, retinitis pigmentosa, hepatic/liver failure, use of anitmuscarinics or 5- $\alpha$  reductase inhibitors within 6 mo of the study, or use of  $\alpha$ -blockers/PDE5-I within 1 mo of the trial. No placebo run-in was employed. The 189 men receiving sildenafil had significant improvement in IPSS versus the 180 men on placebo ( $-6.32$  vs  $-1.93$ ,  $p < 0.0001$ ) and in IIEF scores ( $9.17$  vs  $1.86$ ;  $p < 0.0001$ ). BPH index, mean IPSS QoL score, total self-esteem and relationship questionnaire scores, and overall treatment satisfaction were all significantly improved in the treatment arm. However, no difference in urinary flow rates was noted between the treatment and placebo arms ( $Q_{\max} -0.31$  vs  $Q_{\max} -0.16$  ml/s;  $p = 0.8$ ).

The vardenafil study included 222 men aged 45–64 who had an IPSS >11 at the time of randomization between 8 wk treatment of 10 mg bid versus placebo [27]. No history of ED was required for inclusion in the study. Exclusion criteria included contraindications to use of vardenafil; spinal cord injury; prostatitis, bladder or urethra stricture; urinary retention (postvoid residual [PVR] >100 ml); pelvic surgery or trauma; history of prostate or bladder cancer; history of any malignancies, life expectancy <3 yr; concomitant use of nitrates, androgens, anticoagulants, cytochrome P-450 3A4 inhibitors; and any treatment for ED or  $\alpha$ 1-adrenoceptor antagonists at the time of the study. No placebo run-in was used for this study. Vardenafil treatment resulted in a significantly higher IPSS versus placebo, with a decrease in IPSS of 2.3 greater than placebo (16.8 to 11 in the treatment arm and 16.8 to 13.2 in the placebo arm;  $p = 0.0013$ ). Significant improvement was noted in QoL, irritative and obstructive IPSS subscores, and IIEF scores in the treatment group. As in the sildenafil trial, no statistically significant improvement in  $Q_{\max}$  was found in comparison to placebo. PRV also did not significantly change in the treatment group. Although the results of the above two studies are provocative, a methodologic lack of a single blind run-in with placebo tempers their findings.

The study performed using tadalafil likely yields more reliable findings given its trial design [28]. Following a 4-wk, single-blind, placebo run-in, 281 men were randomly assigned (1:1) to 5 mg tadalafil for 6 wk, followed by dose escalation to 20 mg for 6 wk or 12 wk of placebo. Subjects were aged  $\geq 45$  and had IPSS  $\geq 12$  secondary to BPH for at least 6 mo. Study exclusion criteria included elevated prostate-specific antigen (PSA); recent finasteride (prior 3 mo)

or dutasteride (prior 12 mo) treatment; a history of pelvic surgery; neurologic conditions affecting bladder function; recent lower urinary tract instrumentation; urinary retention (PVR >200) or bladder stones; a history of urethral obstruction; detrusor-sphincter dyssynergia; urinary tract inflammation or infection; intravesical obstruction secondary to the prostate median lobe; PCa; certain cardiovascular diseases; clinically significant renal or hepatic insufficiency; recent history of stroke or spinal cord injury; current treatment with nitrates, cancer chemotherapy, antiandrogens, or a potent cytochrome P450 3A4 inhibitor; or uncontrolled diabetes (glycosylated HbA1c >9%). Tadalafil significantly improved the mean change of IPSS at 6 wk over placebo (5 mg  $-2.8$  vs  $-1.2$  placebo), at 12 wk (5/20 mg  $-3.8$  vs  $-1.8$ ), and with inclusion of the placebo run-in at 12 wk ( $-7.1$  vs placebo  $-4.5$ ). No differences were seen in uroflow parameters between the placebo and treatment groups. Significant improvements were seen in obstructive and irritative IPSS domains, IPSS/QoL index, and IIEF scores.

A recent well-designed and powered study presented at the 2008 AUA found similar results [29]. In this randomized, double-blind, placebo-controlled, parallel-group, global study, 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. Subjects were aged  $\geq 45$ , had IPSS >12 from BPH for 6 mo, and a  $Q_{max}$  4–15 ml/s. Exclusion criteria included elevated PSA; recent 5ARI use; BPH medication use during the study; history of pelvic surgery; hepatic/liver failure; causes of LUTS other than from BPH; uncontrolled diabetes; nitrate use; and chemotherapy use. After a 4-wk, single-blind placebo run-in, men were stratified by baseline IPSS (<20 vs  $\geq 20$ ), baseline uroflow parameters, ED history (<3 mo vs  $\geq 3$  mo), and geographic region. The subjects had IPSS, irritative and obstructive IPSS subscores, IPSS QoL, BII, peak flow ( $Q_{max}$ ), Global Assessment Question (LUTS GAQ—Has the treatment you have been taking since your last visit improved your urinary symptoms?), and IIEF assessed before and after the 12-wk treatment. The study's main end point revealed a significant improvement in IPSS in the 5 mg group, with a change of 4.9 versus 1.8 ( $p < 0.05$ ). Mean IPSS QoL score, BII, and LUTS GAQ all significantly improved with at least a 5-mg dose. Peak flow ( $Q_{max}$ ) 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 side effects. The subset of men who

were sexually active (55%) showed a significant improvement in IIEF scores (+2.38 placebo vs +7.15 in the 5 mg tadalafil treatment group;  $p \leq 0.001$ ).

All four studies consistently demonstrated that PDE5-I significantly improved IPSS compared with placebo. The magnitude of IPSS improvement observed was comparable with results reported in previous  $\alpha$ -blocker studies. For example, a non-blinded study using 10 mg of alfuzosin showed a mean change in IPSS at 12 wk of 3.8 compared with 1.7 for placebo [30]. However, a head-to-head trial is required to definitively state that treatment effects are truly comparable.

Importantly, none of the studies demonstrated a significant effect of PDE5-I on peak flow ( $Q_{max}$ ). A previous small study of 32 patients undergoing urologic screening prior to initiating isorbide dinitrate demonstrated conflicting results [31]. 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  $Q_{max}$ , PVR volumes, and IPSS. The 17 patients without complaint did not have significant improvement in micturition parameters. The discrepancy of this study can help conceptualize the statistical concept of regression toward the mean. This is a phenomenon in which members of a population with extreme values for an observation (in this case, subjective voiding complaints) will likely give less extreme measurements for purely statistical reasons on other occasions when they are observed (in this case, follow-up measurements). Using the same rationale, it can be argued that allowing subjects with LUTS without a reduced  $Q_{max}$  as an entry criterion into the PDE5-I trials artificially reduces the treatment effect upon  $Q_{max}$ . Although it is possible that PDE5-I may truly exert an effect on  $Q_{max}$ , the most recent PDE5-I trial in which a  $Q_{max}$  inclusion criterion of 4–15 ml/s was used (thereby eliminating the regression toward the mean possibility) and in which no change in  $Q_{max}$  was observed makes this seem very unlikely [29].

Another interpretation of the phenomenon of no change in  $Q_{max}$  with subjective improvement in IPSS with PDE5-I is that detrusor activity is the main target for their palliative effect, with BOO-related phenomena being less important. Apropos, a recent study of men with neurogenic bladders showed statistically significant improvement of maximum detrusor pressure, total capacity, and volume triggering bladder spasm in spinal cord injury patients who were given vardenafil 1–3 hr before urodynamics when compared to themselves without vardenafil dosing [32].

### 3. Evidence synthesis

Numerous epidemiologic studies as described in Table 1 assessing LUTS and ED implicate a causal relationship between LUTS and ED with advancing age. However, only a few studies have addressed the temporality of this relationship, and further longitudinal research on ED incidence in men with LUTS is required [33,34]. The four previously discussed mechanisms explaining the LUTS–ED relationship are biologically plausible, and an understanding of their basic mechanisms helps clarify the potential role of PDE-I in amelioration of LUTS. PDE5-I facilitates the NO–cGMP pathway essential for smooth muscle relaxation in tissues in the bladder, bladder neck, and prostate. The importance of the NO theory has become more intuitive with the publication of consistent findings from multiple well-designed studies that show PDE5-I improves LUTS [26–29]. AH leads to heightened sympathetic activity and increased norepinephrine, endothelins, and other second messengers—pathways that have been demonstrated to be opposed by PDE5-I. The Rk system uses the same pathways of norepinephrine and endothelins that can be addressed by PDE5-I. Further synergistic improvement in ED models is found when combining PDE5-I with Rk inhibitors. Pelvic atherosclerosis up-regulates Rk systems, is directly responsible for AH as part of the metabolic syndrome, and down-regulates NO synthesis. Further research of each mechanism and their interrelation is essential.

It is important to note that none of the studies demonstrates a significant effect of PDE5-I on peak flow ( $Q_{max}$ ). This may implicate detrusor activity as the main target for the palliative effect of PDE-I on LUTS, with BOO-related phenomena being less important. Worthy of further research is the emergence of storage LUTS and detrusor activity versus obstructive emphasis of a prostate source. Studies from the early 1990s have demonstrated an equivalent age-related increase in LUTS affecting both men and women [35]. This refutes prostatic changes as the sole cause for LUTS and forces one to consider a more critical role of the central nervous system and the bladder in the etiology of LUTS. Another study demonstrated vascular risk factors related to LUTS in both men and women [23]. A separate study implicated nocturia (but no other AUASS question), incontinence, and prostatitis-like symptoms as the strongest predictors of ED in men [36]. The study is also unique in that its diverse subject sampling was able to show that there were no differences in results across race or ethnicity. Further, basic science data using PDE inhibitors have

shown a reduction in nonvoiding bladder contractions in human tissue and rat obstructive models [3,4]. Finally, a study showed improved urodynamics parameters in spinal cord patients given PDE inhibitors [32]. Although further research is required, given the current literature on the LUTS–ED relationship, one can consider PDE-I as primary treatment for LUTS in men with concurrent ED. The role of PDE-I in the treatment of LUTS in women or men without ED should also be pondered. Combination therapy with 5 alpha-reductase inhibitors also has a potential role.

As the LUTS–ED relationship is established, further insight into the etiology of LUTS will be determined. Clarification of this relationship is essential in an increasingly aged population, as it affects both patient screening and treatment. A recent study analyzed rates of BPH screening among men seeking care for ED [37]. Screening for BPH was less likely for men with ED who saw a primary care provider as opposed to a urologist. When screening did occur, the time from ED diagnosis to BPH screening was much longer amongst primary care physicians. Paradoxically, patients were less likely to be screened if older, though they were five times more likely to be diagnosed and treated for BPH.

### 4. Conclusions

LUTS and sexual dysfunction are highly prevalent in aging men. It is well established that both LUTS and ED independently reduce QoL. In combination, these two clinical entities logically compound life distress. Four explanations that partially overlap, each with a variable amount of supporting data, have been proposed to explain the LUTS–ED relationship demonstrated in multiple studies. These include altered NO levels, AH, Rk activation, and pelvic atherosclerosis. PDE5-I has demonstrated the ability to improve LUTS in multiple studies. Sexual problems related to LUTS are not necessarily limited to ED, and many currently available treatments (medical and surgical) for one disease affect the other. PDE5-I seems to exert positive effects to a greater degree on detrusor activity rather than directly on the prostate. The future use of PDE-I as prophylaxis for LUTS or as primary treatments for LUTS/overactive bladder looms as a possibility, especially in those who have concurrent ED. Further, treatment of LUTS with PDE5-I may not necessarily be limited to the treatment of men but could be used for the treatment of LUTS in women.

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*Study concept and design:* Köhler, McVary.

*Acquisition of data:* Köhler, McVary.

*Analysis and interpretation of data:* Köhler, McVary.

*Drafting of the manuscript:* Köhler.

*Critical revision of the manuscript for important intellectual content:* Köhler, McVary.

*Statistical analysis:* Köhler, McVary.

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