Phosphodiesterase Type 5 Inhibitors for Lower Urinary Tract Symptoms Associated With Benign Prostatic Hyperplasia

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1. Introduction
Lower urinary tract symptoms (LUTS) are defined by the International Continence Society as all urinary symptoms which occur during the phases of storage (increased daytime frequency, nocturia, urgency, and/or urinary incontinence), voiding (terminal dribble, hesitancy, intermittency, straining, and/or splitting/spraying/slow stream), and post-micturition (incomplete emptying or post-micturition dribble). A population-based epidemiologic study using the 2002 International Continence Society definition showed that the prevalence of storage LUTS (men, 51.3%; women, 59.2%) was greater than that of voiding (men, 25.7%; women, 19.5%) and post-micturition (men, 16.9%; women, 14.2%) symptoms combined. LUTS in men may be related to bladder dysfunction or bladder outlet obstruction, which is often associated with benign prostatic hyperplasia (BPH). Although α1-adrenergic receptor antagonists (α-blockers) and 5α-reductase inhibitors are helpful in treating LUTS associated with BPH (LUTS/BPH), some storage symptoms such as nocturia or urgency may be refractory to standard treatment. The benefit of antimuscarinics in alleviating these symptoms should be weighed against the risks of urinary retention or treatment-related side effects such as dry mouth and constipation.

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There are 2 CME questions based on this article
Since the launch of sildenafil citrate in 1998, phosphodiesterase type 5 (PDE5) inhibitors are extensively used as the first-line drug of choice for treating male erectile dysfunction (ED). With increasing evidence to support the close relationship between LUTS/BPH and ED, PDE5 inhibitors were used to treat LUTS in some preliminary studies with favorable outcomes. This mini review focuses on the rationale for using PDE5 inhibitors for LUTS/BPH treatment, updates clinical results regarding all three PDE5 inhibitors for LUTS/BPH treatment, and reviews the safety profiles of their concomitant use with $\alpha$-blockers based on a literature review.

2. ED and LUTS Associated With BPH

2.1. Close Links Between ED and LUTS/BPH—Epidemiologic Evidence

Since the 1990s, several population- or community-based epidemiologic studies have shown that urinary symptoms might have direct impact on sexual dysfunction and satisfaction with one’s sexual life.3–5 In a large, community-based study conducted in France involving 2011 men aged 50–80 years, Macfarlane et al.3 found that the severity of overall urinary symptoms was inversely related to satisfaction with one’s sexual life, and the association persisted after adjusting for various factors of age and frequency of sexual relations.5 In a multinational study involving 423 men aged ≥40 years in a community population in the UK and 1271 people visiting a urology clinic aged ≥45 years in 12 countries, the authors found that patients with LUTS, especially those with storage symptoms associated with incontinence had a higher odds ratio for sexual dysfunction.4 Braun et al.5 found that the prevalence of LUTS in men suffering from ED was about 72.2% ($n=621$) versus 37.7% ($n=1367$) in men with normal erections. The occurrence of LUTS can be considered an age-independent risk factor for the development of ED with an odds ratio of 2.11 ($p<0.001$).5 In a multinational survey involving 12,825 men aged 50–80 years, sexual disorders and their impact on quality of life were strongly related to both age and the severity of LUTS. The relationship between sexual disorders and LUTS was independent of comorbidities including diabetes, hypertension, cardiac disease, and hypercholesterolemia.6 Recently, a population-based, cross-sectional internet survey enrolling 30,000 men and women aged >40 years was conducted in the US ($n=20,000$), the UK ($n=7500$), and Sweden ($n=2500$). Among 11,834 men with a mean age of 56.1 years, 71% reported being currently sexually active, and 26% of these sexually active men had mild to severe ED, 7% had ejaculation disorders, and 16% had premature ejaculation. ED was associated with an older age, hypertension, diabetes, depression, and LUTS including urgency with fear of leaking, a weak stream, a split stream, leaking during sexual activity, and dysuria.7 A population-based data survey study conducted in the UK also showed that men with a diagnosis of LUTS had a significantly increased prevalence of all kinds of sexual dysfunction compared with men without LUTS, and a diagnosis of LUTS even preceded the diagnosis of sexual dysfunction in a majority of men.8

2.2. Nitric Oxide/Cyclic Guanosine Monophosphate—A Common Mechanism of ED and LUTS

Although there are strong links between ED and LUTS based on epidemiologic evidence, the exact mechanisms are still unclear. Smooth muscle tone and function may play important roles in both erection function and urinary bladder physiology. Since the discovery of nitric oxide (NO) as the major nonadrenergic noncholinergic neurotransmitter in penile erection, the NO/cyclic guanosine monophosphate (cGMP) pathway with an inhibitory effect on smooth muscles and nerves of the lower urinary tract (LUT) was postulated as one of the major component in urination control.9–11 NO-mediated smooth muscle relaxation was also demonstrated in the human bladder neck, trigone, sphincter, and prostate.12,13 LUT smooth muscles can be relaxed by drugs that increase the intracellular concentrations of cyclic adenosine monophosphate (cAMP) and cGMP. In LUT smooth muscles, increases in cAMP seem to play a major role in bladder relaxation, whereas cGMP is more important for urethral relaxation.14,15 Furthermore, NO released from the urothelium was implicated in suppressing excitatory signals from adjacent afferent nerves. On the other hand, overexpression of NO synthase and increased release of NO from the urothelium were found in an animal model with interstitial cystitis, which might be attributed to bladder overactivity induced by inflammation.16,17 Interestingly, systemic administration of 20 mg of isosorbide dinitrate as an NO donor sublingually in 11 healthy volunteers in a pressure flow study produced a decreased in the average detrusor pressure during micturition of 57 to 52 cmH$_2$O, while the average uroflow rate increased from 16.7 to 20.2 mL/s. The authors concluded that systemic NO administration can lower the functional bladder outlet resistance in men, and the NO/cGMP pathway might be a promising target for medical treatment of LUTS.18 In addition to the NO/cGMP pathway, there are other possible mechanisms, including pelvic atherosclerosis/ischemia, the autonomic hyperactivity/metabolic syndrome hypothesis and the Rho-kinase activation/endothelin pathway, which might explain the relationship between ED and LUTS/BPH.19,20

3. Distribution of Phosphodiesterases (PDEs) in the LUT

PDEs, a heterogeneous group of hydrolytic enzymes, inactivate the cAMP and cGMP intracellular signals and are
involved in smooth muscle tone regulation. In total, 11 distinct families with 21 human genes were identified based on their amino acid sequences, cyclic nucleotide substrates, and catalytic considerations.21

PDE1, -2, -3, -4, -5 and -9 were identified in the human urinary bladder.22 Werkstrom et al.23 characterized the distributions of PDE5 and cGMP in the human urethra, and the smooth muscle relaxant effect was associated with increased levels of cGMP.

Almost all of the PDEs found in the human prostate are highly expressed as the PDE9A and PDE11A isoforms.14 Secondary messengers including cGMP and cAMP were found to be involved in the control of the normal function of the prostate. Uckert et al.24 further demonstrated by an immunohistologic method the presence of PDE4 in the fibromuscular stroma of the prostate as well as in glandular structures of the transition zone. In contrast to the distribution of PDE4, the presence of PDE5 and PDE11 was mainly observed in glandular and stromal regions.24 The presence and functional relevance of PDE isoenzymes 1, 4, and 5 in human prostatic tissue support the possible use of inhibitors of PDE1, -4, and -5 to treat urinary obstruction secondary to BPH.11,25-27

An in vitro prostate tissue study also confirmed that PDE4 and -5 inhibitors can reverse the tension induced by norepinephrine, and the most prominent enhancement in tissue cGMP levels could be significantly elevated by tadalafil, vardenafil and sildenafil to different degrees (28-fold, 12-fold and threefold, respectively).28 Treatment with selective PDE4 inhibitors showed their ability to reduce bladder overactivity and to suppress experimental bladder inflammation in animal studies.29,30 Recently, Bittencourt et al.13 further confirmed that sildenafil was effective in inducing bladder neck smooth muscle relaxation in vitro, and this effect could be abolished by Nω-nitro-L-arginine methyl ester (L-NAME), which further indicated the dependence of the NO/cGMP pathway in the bladder neck.

4. Clinical Results of PDE5 Inhibitors for LUTS Treatment

Different kinds of PDE1, -4 and -5 inhibitors were used to verify their effectiveness in treating LUTS. In a pilot study using the PDE1 inhibitor, vinpocetine, 11 of 19 patients (57.9%) with urge incontinence and a low-compliance bladder and who were nonresponders to standard pharmacologic therapy showed improvements in clinical symptoms and/or urodynamic parameters.31

With the extensive use of PDE5 inhibitors in the treatment of male ED since 1998, more clinical data show that PDE5 inhibitors appear to improve erectile function as well as urinary symptom scores. In an observational, nonrandomized study conducted in 2002 which enrolled 112 male patients for ED treatment, concomitant International Prostate Symptom Score (IPSS) evaluations after 1–3 months of sildenafil treatment showed a trend towards improvements in the IPSS. A lower IPSS at the baseline appeared to predict a better response to sildenafil.32 In another open-label study, 48 men (with a mean age of 62 years) with ED and an IPSS of ≥ 10 were enrolled to receive on-demand sildenafil citrate treatment for 3 months. About 60% of these men showed an improvement in their IPSS with a mean 4.6-point reduction, but only 35% of them had more than a 4-point improvement.33 In a double-blind, placebo-controlled trial in 25 patients with spinal cord injury who had ED and micturition disorders, a urodynamic study done 1–3 hours after the oral administration of 20 mg of vardenafil showed an increased bladder capacity (253 vs. 296 mL; p = 0.004) and reduced maximal detrusor pressure (57 vs. 52 cmH2O; p = 0.039).34

Furthermore significant improvements in LUTS were demonstrated in several large, multicenter, randomized, placebo-controlled trials (Table 1).35-41 However, most of those studies showed that PDE5 inhibitors could only improve the irritative or obstructive symptoms based on IPSS reduction but had little effect on uroflowmetric parameters or the post-voiding residual volume. The combined use of PDE5 inhibitors and α-blockers seems to have more-promising results than monotherapy alone in terms of IPSS reduction or mean maximal uroflow rate (Qmax) improvement. One possible explanation for this poor uroflow rate response with PDE5 inhibitors alone may be the predominant effects of non-voiding contractions by these PDE5 inhibitors.27 Aging, the static component of the prostate in bladder outlet obstruction, sympathetic tone overactivity, and androgen-dependent PDE5 inhibitor activity were cited as possible factors influencing the responses.11,42-45

5. Safety Concerns About Combined Therapy With α-Blockers

The concurrent reduction of the sympathetic tone within the LUT by α-blockers and inhibition of prostate growth by 5α-reductase inhibitors are still the main strategy in medical management of LUTS/BPH.

Although early clinical results showed the potential of using PDE5 inhibitors to improve LUTS/BPH, the safety profiles of the combined use of α-blockers and PDE5 inhibitors in LUTS/BPH treatment are not well established. According to the label information, none of the three PDE5 inhibitors should be taken with α-blockers other than tamsulosin because of the risk of adverse vasodilatory events.46 However, a randomized placebo-controlled study confirmed the safety and efficacy of the combined use of 4 mg of doxazosin daily and 100 mg of sildenafil on-demand for treating non-organic ED men who were sildenafil nonresponders.47 A similar hemodynamic evaluation was conducted in 16 men with BPH, and the blood pressure was measured in both the supine and passive orthostatic positions after 0.4 mg of tamsulosin daily for
14 days and a single dose of 100 mg of sildenafil or a placebo. The authors confirmed that the combined use of tamsulosin and sildenafil decreased the systemic blood pressure and vascular resistance index in the supine position.48

The safety of the combined use of alfuzosin and tadalafil was evaluated in a randomized, double-blind, placebo-controlled, crossover study. Eighteen healthy volunteers who received 10 mg of alfuzosin daily for 7 days were randomized to receive on-demand 20 mg of tadalafil or a placebo on the 7th day. Only a 4-mmHg difference in the standing systolic blood pressure was noted between the tadalafil and placebo groups.49 Recently, in a randomized, double-blind, placebo-controlled, crossover study, 38 patients with BPH and ED, who were treated with 4 mg of doxazosin (67.6%) daily or 8 mg (32.4%) on a regular basis, were enrolled. The standing and supine blood pressures were measured 1 hour before and 6 hours after the administration of 10 mg of vardenafil. A maximal decrease in systolic pressure of 6.18 mmHg in the standing position was found with the combined use of doxazosin and vardenafil. The authors concluded that a single dose of 10 mg of vardenafil had no hypotensive effects on patients receiving regular doxazosin treatment.50 Although there are usually small additive reductions in blood pressure without significant adverse events, some patients may still develop orthostatic hypotension when these PDE5 inhibitors are used in patients receiving regular \(\alpha\)-blocker treatment. Precautions are necessary for all three PDE5 inhibitors regarding this potential interaction.51

### 6. Conclusion

Men with a diagnosis of LUTS have a significantly increased prevalence of all kinds of sexual dysfunction compared with those men without LUTS. The NO/cGMP pathway, which has an inhibitory effect on smooth muscles and nerves of the LUT, is postulated to be one of the major components in their regulation. Early randomized clinical studies showed that daily dosing with PDE5 inhibitors could improve the irritative or obstructive symptoms based on IPSS reduction but had little effect on uroflowmetric parameters or post-voiding residuals. The combined use of PDE5 inhibitors and \(\alpha\)-blockers showed more-promising results, but the safety concerns of this combined use should be further evaluated and confirmed by additional randomized and comparative clinical studies.

### Table 1  Summary of recent randomized clinical studies for phosphodiesterase type 5 inhibitors in treating lower urinary tract symptoms associated with benign prostatic hyperplasia

<table>
<thead>
<tr>
<th>Author (publication year)</th>
<th>Arm/drug (no. of patients)</th>
<th>Mean IPSS</th>
<th>Qmax (mL/s)</th>
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<tr>
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<td>Sildenafil 50 or 100 mg qd (189)</td>
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*p < 0.05. IPSS = International Prostate Symptom Score; Qmax = mean maximal uroflow rate; – = not available; qd = everyday; bid = twice a day; qod = every other day.
References


