Update on Phosphodiesterase Type 5 Inhibitors for the Treatment of Lower Urinary Tract Symptoms due to Benign Prostatic Hyperplasia

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Many aging men will experience both erectile dysfunction (ED) and benign prostatic hyperplasia (BPH), resulting in lower urinary tract symptoms (LUTS). Basic and clinical evidence suggests common pathogenic mechanisms underlying both LUTS and ED. Decreases in the nitric oxide-cyclic guanosine monophosphate (NO-cGMP) pathway with age result in decreased levels of intracellular cGMP and calcium, leading to diminished smooth muscle relaxation of the bladder and prostate and worsening LUTS. Phosphodiesterase type 5 inhibitors as monotherapy in combination with α-blockers have shown efficacy in treating both LUTS and ED. Tadalafil has recently been approved by the US Food and Drug Administration for the treatment of LUTS secondary to BPH, with or without concomitant ED.

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KEY WORDS

Lower urinary tract symptoms • Benign prostatic hyperplasia • Phosphodiesterase inhibitors • Erectile dysfunction • Tadalafil • Sildenafil • Vardenafil

The aging man faces many health challenges. The constellation of hypertension, diabetes, androgen deficiency, depression, and cardiovascular disease all pose serious threats to the longevity of men. Many of these ailments manifest themselves in the domains of urinary and sexual function. Approximately 40% of men by age 50 and 80% of men by age 80 will have benign prostatic hyperplasia (BPH).[1] The prevalence of erectile dysfunction (ED) also increases concomitantly with

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age. By age 40, 40% of men will experience some form of ED.[2] That risk increases twofold by age 50 and fivefold by age 60.[3] Several studies have demonstrated the comorbid occurrence of lower urinary tract symptoms (LUTS) and ED. Laumann and colleagues showed, in the National Health and Social Life Survey, that LUTS posed significant risk factors for ED.[4] Similarly, in the Multinational Survey of the Aging Male, LUTS were identified as risk factors for ED in the 12,815 evaluable men. The Dutch survey on aging men demonstrated severe LUTS were associated with ED (odds ratio [OR], 7.5 [95% confidence interval (CI), 2.5-22.5]; $P < .01$) and ejaculatory dysfunction (OR, 4.2 [95% CI, 1.4-12.9]; $P < .01$). These symptoms were 10 times higher in men in their 70s compared with men in their 50s.[5] The aging man faces significant insults to his quality of life given the high prevalence of these two entities together. The significant overlap in sexual dysfunction and LUTS has led to the proposal that a common pathophysiology may account for the symptoms. Subsequently, it has been proposed that if there is a shared underlying process, then a single common agent may be a feasible treatment for both. Hence, there has been a surge in research of phosphodiesterase type-5 inhibitors (PDE5-I) for the cotreatment of LUTS and ED.

Pathophysiology and Pharmacology

There is substantial evidence that the pathogenic mechanisms underlying LUTS and ED share many common pathways. The nitric oxide-cyclic guanosine monophosphate (NO-cGMP) pathway has been proposed as the main shared mechanism of LUTS and ED.[6] It is thought that LUTS result from increased smooth muscle tension mediated by NO.[7-10] NO is released by neuronal NO synthase (nNOS) and endothelial NO synthase (eNOS) found within the urothelium, smooth muscle, prostatic stroma and glandular epithelium, blood vessels, bladder nerves, and outlet. NO activates the enzyme guanylate cyclase that generates cGMP, causing a downstream decrease in intracellular calcium levels and ultimately smooth muscle relaxation.[6,11] Decreases in the NO-cGMP pathway with age would result in decreased levels of intracellular cGMP and calcium, leading to less smooth muscle relaxation of the bladder and prostate, thus worsening LUTS. Erections are mediated in a similar fashion. Following stimulation of the penile erectile nerves, nNOS and eNOS produce NO, which is released into the vascular smooth muscle lining, the corpora cavernosa, and its vessels. This results in increased blood flow and vascular dilatation. On a cellular level, NO diffuses into the vascular smooth muscle cell where it binds to a heme moiety on the NO-guanylyl cyclase (GC). It activates the GC enzyme resulting in increased conversion of guanosine triphosphate (GTP) to cGMP. Cyclic GMP binds to protein kinase Gs and activates the phosphotransferase activity to cause phosphorylation of several cellular proteins, resulting in reduced intracellular calcium and desensitization to calcium signaling. This results in the vasodilatation, smooth muscle relaxation, and increased blood flow for an erection.

An increase in the Rho-Rho-associated protein kinase (ROCK) calcium sensitizing pathway may also contribute to impaired smooth muscle relaxation and bothersome LUTS and ED. Increased Rho-ROCK signaling has been demonstrated in penile and bladder pathology, such as ED and overactive bladder in men with diabetes.[12,13] Autonomic hyperactivity resulting in increased sympathetic activity has also been shown as a causative agent in LUTS and ED.[14] The corpus cavernosum, prostate (subtype α_{1A}), and detrusor muscle (subtype α_{1D}) demonstrate high concentrations of α_1-adrenergic receptors. Derangements in their autonomic activity have led to ED and bladder overactivity, as demonstrated in rat models.[14,15] The final pathogenic mechanism shared between ED and LUTS relates to pelvic atherosclerosis, which decreases NO signaling, increases Rho-ROCK pathways, and forms a constituent of autonomic hyperactivity. Arterial insufficiency has been shown in animal and human models to result in bladder and penile ischemia, resulting in fibrosis and reduced NOS (Figure 1).[16,17]

PDE5-I Effect on Prostate and Bladder

PDEs function by hydrolyzing and inactivating cyclic nucleotides such as cGMP. There are 11 PDE isoenzymes, with PDE5 found mainly in the penis. PDE5 has three isoforms (A1-A3), with A3 mainly expressed in the penis, bladder, prostate, urethra, and aorta. PDE5 and PDE11 are both expressed in the glandular and stromal areas of the prostate.[10,18] During sexual stimulation, NO is released from penile smooth muscle causing an increase in intracellular cGMP and a cascade of intracellular second-messengers to raise intracellular calcium, resulting in smooth muscle relaxation. For the penis to return to the flaccid state, cGMP is hydrolyzed to GMP by PDE5. PDE5-I block the degradation of cGMP by PDE5 resulting in persistently elevated intracellular cGMP and prolonged relaxation of smooth muscle. PDE5-I, including tadalafil, sildenafil, and vardenafil, increase NO/cGMP concentrations

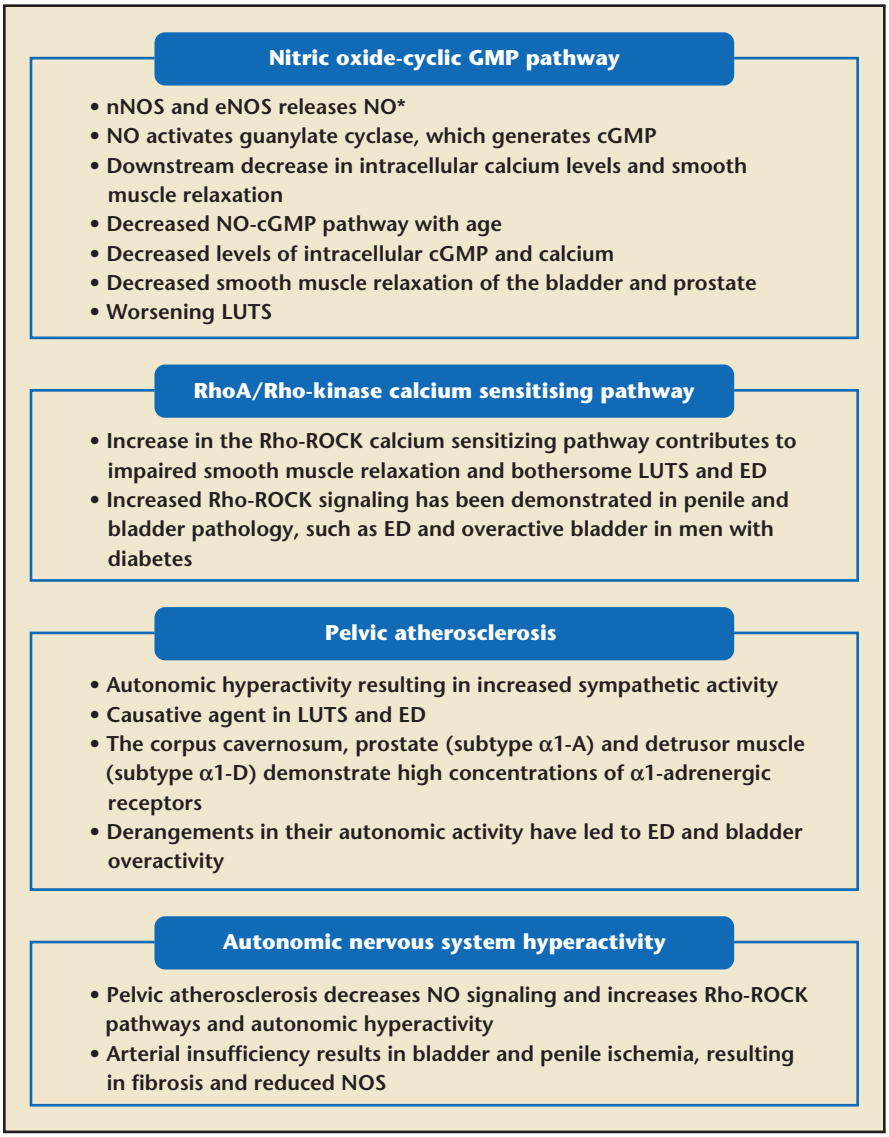

Figure 1. Pathogenic mechanisms. *Urothelium, smooth muscle, prostatic stroma and glandular. cGMP, guanosine monophosphate; ED, erectile dysfunction; eNOS, endothelial NO synthase; LUTS, lower urinary tract symptoms; nNOS, neuronal NO synthase; NO, nitric oxide; Rho-ROCK, Rho-associated protein kinase.

in the smooth muscle of the penis, urethra, and bladder neck, resulting in enhanced bladder emptying and prostatic relaxation (Table 1).

PDE5-I for the Treatment of LUTS and ED

If LUTS and ED share a common pathophysiology, PDE5-I may potentially be able to treat both entities. PDE5-I would theoretically relax prostatic smooth muscle, resulting in lower urethral pressures; inhibit dose-dependent contraction of bladder, urethra, and prostate; and reduce prostatic stromal proliferation.[19,20] A series of early clinical studies demonstrated the clinical benefit of PDE5-I for the treatment of LUTS. Open-label studies by Sairam and colleagues[21] and Ying and associates[22] examined men who had both LUTS and ED. Sairam and co-authors treated 112 men attending an andrology outpatient clinic with on-demand sildenafil. At 1- and 3-month follow-up visits, International Prostate Symptom Score (IPSS) and International Index of Erectile Function (IIEF) questionnaires were completed. At baseline, 32% of men had moderate-severe LUTS (IPSS $>$ 7). At 3 months, 100% of men with severe LUTS became moderate, and 60% of men with moderate LUTS became mild ($P < .01$).[21] Ying and coworkers assessed 32 patients with ED and BPH. They were offered on-demand sildenafil and were evaluated with the IPSS and IIEF at baseline and 6 months. The results demonstrated IPSS scores declined by 20.1% and IIEF scores increased by 42.7% ($P < .01$).[22] In both studies, lower IPSS at baseline predicted a better response to PDE5-I therapy for ED.

Mulhall and colleagues assessed 48 men with ED who also had mild-moderate LUTS (IPSS $\geq$ 10). They were treated with on-demand sildenafil, 100 mg, and were followed with the IPSS and IIEF validated questionnaires. After a minimum of 3 months, 60% of men had an improvement in IPSS, with 35% of those men showing an improvement $\geq$ 4 points.[23] These three preliminary, open-label, nonrandomized studies demonstrated that treatment of men with ED and mild-moderate LUTS would benefit from treatment with PDE5-I. Next, a series of randomized, placebo-controlled, double-blind trials provided more substantive evidence of the efficacy of PDE5-I for the treatment of LUTS.

McVary and associates reported on a 12-week, double-blind, placebo-controlled trial of sildenafil in 369 men diagnosed with both ED (IIEF $\leq$ 25) and moderate LUTS (IPSS $\geq$ 12). Men who received sildenafil had statistically significant improvements in IPSS (-6.32 vs -1.93 points; $P < .01$). There were also improvements seen in IIEF domains, quality of life (QoL) scores, and self-esteem questionnaires. There was no statistical difference in urinary flow rates (Q_{max}, $P = .08$) seen between the sildenafil and placebo groups.[24] McVary and colleagues next reported on

TABLE 1

Phosphodiesterase Types[41-43]

Family	Genes	Substrate	Tissue Distribution	Inhibitors	Clinical Application
PDE1	1A, 1B, 1C	cAMP/cGMP	Brain, heart, lung, smooth muscle	Vinpocetine, nimodipine, nicardipine	Dementia, memory loss
PDE2	2A	cAMP/cGMP	Heart, lung, liver, adrenal, platelets, endothelial cells	EHNA, Bay 60-7550, IC933	Sepsis, ARDS, memory loss
PDE3	3A, 3B	cAMP	Heart, lung, liver, platelets, smooth muscles, adipocytes	Lixazinone, cilostamide, milrinone, ciolstazol, siguazodan	Glomerulonephritis, congestive heart failure thrombosis, intermittent claudication, pulmonary hypertension
PDE4	4A, 4B, 4C, 4D	cAMP	Brain, heart, lung, liver, kidney, smooth muscles, endothelial cells	Rolipram, denbufylline, roflumilast, cilomast	Glomerulonephritis, asthma, COPD, bipolar depression, organ transplant
PDE5	5A	cGMP	Brain, heart, smooth muscles, endothelial cells	Sildenafil, vardenafil, tadalafil, zaprinast, dipyridamole, ariflo, DMPPO	ED, chronic renal failure, pulmonary hypertension, organ transplantation
PDE6	6A, 6B, 6C	cGMP	Lung, pineal gland, photoreceptors	Vardenafil, tadalafil, zaprinast, dipyridamole, DMPPO	Unknown
PDE7	7A, 7B	cAMP	Brain, heart, kidney, pancreas, skeletal muscle, T lymphocytes	Dipyrimadole, IC242, BRL 50481	Unknown
PDE8	8A, 8B	cAMP	Brain, heart, liver, eye, kidney, ovary, testes, T lymphocytes, thyroid	Dipyrimadole	Unknown
PDE9	9A	cGMP	Brain, lung, liver, kidney	Zaprinast, SCH 51866	Unknown
PDE10	10A	cAMP/cGMP	Brain, testes, thyroid	Dipyridamole, papaverine	Unknown
PDE11	11A	cAMP/cGMP	Heart, liver, prostate, skeletal muscle, pituitary gland	Tadalafil, zaprinast, dipyridamole	Unknown

ARDS, acute respiratory distress syndrome; cAMP, cyclic adenosine monophosphate; cGMP, cyclic guanosine monophosphate; COPD, chronic obstructive pulmonary disease; DMPPO, 1,3-dimethyl-6-(2-propoxy-5-methanesulfonylamidophenyl)pyrazol[3,4d]-pyrimidin-4-(5H)-one; ED, erectile dysfunction; EHNA, erythro-9-(2-hydroxy-3-nonyl)-adenine.

the efficacy and safety of once-daily tadalafil in a multicenter, randomized, double-blind, placebo-controlled trial. There was a single-blind, placebo run-in period of 4 weeks followed by randomization of the 281 men with moderate-severe LUTS (IPSS) to either placebo for 12 weeks or tadalafil, 5 mg, once daily for 6 weeks, then dose-escalated to 20 mg once daily for the next 12 weeks. At both 6 and 12 weeks, tadalafil significantly improved the mean change from baseline of IPSS. Treatment effects (difference between change from baseline IPSS for tadalafil and placebo) were 1.7 (95% CI, 0.5-2.9; $P = .003$) at 6 weeks and 2.1 (95% CI, 0.9-3.3; $P = < .001$) at 12 weeks. Also observed were significant improvements in IPSS QoL domain, BPH impact index (BII), and IIEF. Again, there were numerical improvements in tadalafil and placebo groups at 6 and 12 weeks compared with baseline for uroflowmetry parameters but no statistical differences observed. Also, there was no statistically significant change in postvoid residual volume when comparing the tadalafil group with placebo.[25]

Roehrborn and colleagues[26] conducted a dose-finding study using tadalafil 2.5, 5, 10, or 20 mg. After a 4-week placebo run-in period, 1058 men with LUTS were randomized to the different doses or placebo for 12 weeks. Significant improvements in IPSS and IIEF were seen with all doses, with the 5-mg dose providing the best risk-benefit profile.[26] Stief and associates[27] also evaluated the efficacy of vardenafil for the treatment of LUTS secondary to BPH. A sample of 222 men was randomized to receive either vardenafil, 10 mg, twice daily or placebo.[27] Again, there was significant improvement in IPSS total score in the vardenafil group. Porst and colleagues[28] recently reported on their international randomized, double-blind, placebo-controlled trial assessing tadalafil in men with LUTS. This multinational study randomized 325 men over age 45 with IPSS $\geq$ 13 to either tadalafil, 5 mg, daily or placebo for 12 weeks. This followed a 4-week wash-out period and 4-week placebo lead-in period. Compared with placebo, tadalafil significantly improved IPSS voiding and storage subscores ($P = .02$ and .002, respectively). The QoL index also improved ($P = .013$) but no difference was observed with the nocturia question ($P = .233$). IPSS questions for frequency (question 2) and urgency (question 3) improved significantly compared with placebo ($P < .001$ and $P = .035$, respectively). Tadalafil improved IIEF-EF domain at 12 weeks (least squares treatment difference [95% CI, 2.5-6.9], $P < .001$). Few treatment emergent adverse events (TEAEs) were reported and the proportion of reporting at least one TEAE was similar between the placebo and treatment groups (tadalafil 26% vs placebo 22%). For tadalafil, most TEAEs were mild to moderate in severity with the most common being headache (3.7%) and back pain (3.1%). Small increases in Q_{max} (tadalafil 1.6 mL/s [4.6] vs placebo 1.1 mL/s [4.6]; $P = .30$) and in postvoid residual volume (PVR) (tadalafil 8.8 mL [56.4] vs placebo 4.5 mL [66.7]; $P = .50$) were observed in both treatment groups.[27]

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Several other studies assessing tadalafil administered once daily in men with LUTS and ED have demonstrated significantly improved ED and BPH outcomes with sustained benefits and excellent tolerability.[29,30] Based on these randomized, placebo-controlled, double-blind trials, the US Food and Drug Administration (FDA) approved tadalafil in October 2011 for the treatment of LUTS secondary to BPH, as well as for the treatment of concurrent LUTS and ED.

Combination α-Blocker and PDE5-I

α_1-Adrenergic blockers (α-blockers) are considered the first-line monotherapy for LUTS secondary to BPH. Concerns regarding the coadministration of α-blockers and PDE5-I are related to potential drug-drug interactions leading to hemodynamic changes and significant lowering of blood pressure. Kloner and colleagues assessed the safety of combining tadalafil with two different α-blockers. In the first study, healthy volunteers took doxazosin, 8 mg, for 7 days, followed by coadministration of either tadalafil, 20 mg, or placebo for a single dose. Although there was a greater decrease in mean maximal systolic blood pressure in the doxazosin plus tadalafil group, symptoms of dizziness experienced by three patients did not correlate to measurable changes in blood pressure. The second study had healthy subjects take tamsulosin, 0.4 mg, for 7 days, followed by a single dose of tadalafil (10 or 20 mg) or placebo given 2 hours after the α-blocker. There were no statistically significant differences seen in standing systolic blood pressure between groups.[31]

Giuliano and associates[32] also demonstrated no clinically relevant hemodynamic interactions between tadalafil, 20 mg, and alfuzosin, 10 mg, daily. The product labeling for tadalafil now states that

caution be advised when PDE5-I are coadministered with α-blockers. Patients should be stabilized on α-blockers prior to the initiation of PDE5-I therapy for ED or LUTS and physicians should discuss with patients the potential for PDE5-I to augment the effect of α-blockers on their blood pressure. The only contraindication to all three PDE5-I is the use of nitrates.[32]

An early pilot study by Kaplan and associates demonstrated that combination alfuzosin and sildenafil was superior to monotherapy for treating LUTS and ED.

Dual therapy with an α-blocker and PDE5-I has also been explored to verify if combination therapy would be superior to α-blocker therapy alone for LUTS. An early pilot study by Kaplan and associates[33] demonstrated that combination alfuzosin and sildenafil was superior to monotherapy for treating LUTS and ED. Patients were given alfuzosin, 10 mg, daily, sildenafil, 25 mg, daily, or both. Improvement of IPSS was significant with all three treatments but greatest with combination (−24.1%) compared with alfuzosin (−15.6%) and sildenafil (−16.9%) alone ($P < .03$). IIEF improved greatest with combination therapy (58.6%) compared with alfuzosin (16.7%) and sildenafil (49.7%) alone ($P = .002$).[33] Bechara and colleagues[34] assessed the safety and efficacy of tamsulosin 0.4 mg/d versus tamsulosin 0.4 mg/d plus tadalafil 20 mg/d in 30 men with LUTS. A randomized, double-blind, crossover study was performed at a single institution. Each randomized group received tamsulosin or tamsulosin plus tadalafil for 45 days, and then switched to the other treatment regimen for the following 45 days. Although both groups had improvements in IPSS and IPSS-QoL compared with baseline ($P < .001$), the combination group had greater improvement (mean IPSS: tamsulosin alone 12.7 vs tamsulosin/tadalafil 10.2; $P < .05$) and IPSS-QoL (mean IPSS QoL: tamsulosin alone 2.3 vs tamsulosin/tadalafil 1.6; $P < .05$). IIEF was better in the arm receiving tadalafil (mean IIEF: tamsulosin alone 16.9 vs tamsulosin/tadalafil 23.2; $P < .001$), but there were no differences in improvements seen in both uroflowmetry Q_{max} (mean Q_{max} [mL/s]: tamsulosin alone 11.7 vs tamsulosin/tadalafil 12.5; $P > .05$), and PVR (mean PVR [mL]: tamsulosin alone 24.8 vs tamsulosin/tadalafil 21.3; $P > .05$).[34] These studies and others demonstrate the efficacy of combination PDE5-I and α-blockers for the treatment of LUTS, especially in men who also have ED.[35,36]

Urodynamics and PDE5-I

The acute effects of PDE5-I have been assessed using uroflowmetry as a marker of drug effect on BPH tissue. Two studies assessed maximum and average flow rates in men given sildenafil either 30 or 120 minutes before uroflowmetry. The maximum and average flow rates were significantly higher in the sildenafil-treated groups compared with those who did not receive medication.[37,38] Dmochowski and colleagues[39] conducted a multicenter, randomized, double-blind, placebo-controlled trial comparing once daily tadalafil, 20 mg, versus placebo over 12 weeks in 200 men with LUTS secondary to BPH using invasive and noninvasive urodynamics (UDS). No statistically significant UDS changes were seen between the study and control arms, indicating tadalafil has no negative impact on bladder function. Patients taking tadalafil did report significantly improved IPSS ($P < .001$).[39]

As PDE5-I are thought to reduce smooth muscle tone in the prostate thereby improving LUTS, Bertolotto and colleagues performed transrectal contrast-enhanced ultrasound to detect hemodynamic changes in the prostates of patients before and 90 minutes after receiving tadalafil, 20 mg. After tadalafil was given the enhancement peak and area under the curve increased significantly ($P < .01$) demonstrating vascular changes in the prostate.[40] This lent further evidence to the effect, much like in corporal tissue, that PDE5-I cause hemodynamic changes within the prostate.

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Conclusions

ED and LUTS frequently coexist in older men. There appears to be a common pathophysiology to both conditions, whereby PDE5-I block the degradation of cGMP, allowing increased levels of smooth muscle relaxation in the bladder, prostate, and urethra. The emergence of PDE5-I for the treatment of ED and LUTS as monotherapy or in combination with an α-blocker has broadened our therapeutic approach to

these patients. It is hoped that the recent FDA approval of tadalafil and more widespread use of PDE-Is for the dual treatment of ED and LUTS will lead to larger clinical trials of longer duration. Key questions still remain such as the need to reconcile the discrepancy between subjective symptom improvement, as measured by IPSS, and lack of improvement seen in objective parameters, such as Q_{max} and PVR. ■

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MAIN POINTS

- Erectile dysfunction (ED) and lower urinary tract symptoms (LUTS) frequently coexist in older men. If LUTS and ED share a common pathophysiology, phosphodiesterase inhibitors (PDE5-I) may potentially be able to treat both entities.
- PDE5-I theoretically would block the degradation of cyclic guanosine monophosphate and relax prostatic smooth muscle, which would result in lower urethral pressures; inhibit dose-dependent contraction of bladder, urethra, and prostate; and reduce prostatic stromal proliferation.
- α_1-adrenergic blockers (α-blockers) are considered the first-line monotherapy for LUTS secondary to BPH. Concerns regarding the coadministration of α-blockers and PDE5-I are related to potential drug-drug interactions leading to hemodynamic changes and significant lowering of blood pressure.
- The emergence of PDE5-I for the treatment of ED and LUTS as monotherapy or in combination with an α-blocker has broadened our therapeutic approach to these patients. It is hoped that the recent US Food and Drug Administration approval of tadalafil and the more widespread use of PDE-Is for the dual treatment of ED and LUTS will lead to larger clinical trials of longer duration.
- Questions remain such as the need to reconcile the discrepancy between subjective symptom improvement, as measured by International Prostate Symptom Score, and lack of improvement seen in objective parameters, such as Q_{max} and postvoid residual volume.

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