Phosphodiesterase Type 5 Inhibitors for the Treatment of Male Lower Urinary Tract Symptoms

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Both lower urinary tract symptoms due to benign prostatic hyperplasia (BPH) and erectile dysfunction have a very high prevalence among aging men, and there is some clinical evidence that they may share a common pathophysiology. Consequently, several preliminary studies of phosphodiesterase type 5 inhibitors—sildenafil and tadalafil—have recently been conducted in men with concomitant erectile dysfunction and lower urinary tract symptoms to determine whether these agents are effective for the treatment of symptomatic BPH. These studies have demonstrated efficacy, both alone and in combination with an α-blocker, in treating lower urinary tract symptoms along with sexual dysfunction. However, larger-scale randomized studies are necessary to determine long-term safety, efficacy, and cost effectiveness.
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Key words: Benign prostatic hyperplasia • Lower urinary tract symptoms • Sildenafil • Tadalafil • Phosphodiesterase type 5 inhibitors • Erectile dysfunction

The rationale for using phosphodiesterase 5 (PDE-5) inhibitors such as sildenafil (Viagra®; Pfizer Inc, New York, NY) and tadalafil (Cialis®; Lily ICOS LLC, Indianapolis, IN) for treating symptomatic benign prostatic hyperplasia (BPH) stems from the following 2 observations: (1) the prevalence of lower urinary tract symptoms (LUTS), BPH, and erectile dysfunction (ED) increases with age,[1-3] and (2) early clinical evidence suggests that PDE-5 inhibitors are effective

in treating LUTS and ED. The prevalence of BPH is very high: 40% of men have BPH by age 50, and this has increased to more than 80% by age 80.[2] The prevalence of ED is similarly high and increases with age: 40% of 40-year-old men experience some degree of ED, and the rate is as much as 70% in 70-year-olds.[4,5] Not surprisingly, both BPH and ED have a significant negative impact on quality-of-life measures for aging men.[6]

In a large-scale study in the United States and multiple European countries entitled the Multinational Survey of the Aging Male, more than 34,800 men were surveyed, with 12,815 responses deemed evaluable. Rosen and colleagues[1] reported that LUTS was clearly identified as a risk factor for sexual dysfunction in aging men. In that study, sexual dysfunction was defined as ED and ejaculatory dysfunction, and both were strongly related to the severity of LUTS independent of other comorbidities. These observations have led to the question of whether the concomitant increase in LUTS and ED in aging men is due to coincidence or shared pathophysiology.

Considering the high incidence of both erectile dysfunction and BPH in aging men, the ability to treat both disorders with a single agent—such as a PDE-5 inhibitor—would be valuable.

Coincidence or Common Pathophysiology?

It is reasonable to suspect that ED and LUTS due to BPH share a common pathophysiology that has been proposed by multiple studies. There is clinical and basic science evidence that the following play a role in the relationship between LUTS and sexual dysfunction: α-adrenoreceptors,[7] endothelin-1,[8] nitric oxide,[8-10] Rho-kinase activity,[11-13] and metabolic syndrome (ie, glucose intolerance, hypertension, hyperlipidemia, and central obesity).[14,15] It should be stressed that these observations do not establish causation. Moreover, causation by any given factor is difficult to prove.

Nitric oxide is a promising therapeutic target, as it mediates smooth muscle relaxation in the corpus cavernosum and bladder.[8-10,16,17] PDE-5 inhibitors such as sildenafil and tadalafil increase nitric oxide concentration in smooth muscle, facilitating both erection of the penis and bladder neck and prostatic relaxation and subsequent bladder emptying. Considering the high incidence of both ED and BPH in aging men, the ability to treat both disorders with a single agent—such as a PDE-5 inhibitor—would be valuable. At this time, however, PDE-5 inhibitors are approved by the Food and Drug Administration only for the treatment of ED.

PDE-5 Inhibitors Improve Lower Urinary Tract Symptoms

There is preliminary clinical evidence that PDE-5 inhibitors may improve LUTS. A study by Hopps and Mulhall examined the effects of sildenafil on LUTS in men presenting to a sexual dysfunction clinic.[18] Men who were candidates and opted for treatment with sildenafil for ED completed both the International Prostate Symptom Score (IPSS) and the International Index of Erectile Function (IIEF) inventories. A total of 48 men with a mean age of 64 ± 11 years with moderate LUTS (IPSS ≥ 10) met inclusion criteria and completed the IPSS and IIEF before and at least 3 months after treatment with sildenafil. After treatment with sildenafil, 60% of those studied improved their IPSS, with 35% reporting an improvement of 4 points or more. The mean number of uses of sildenafil per week was 2 ± 0.6. The investigators concluded that sildenafil has a positive effect on men with mild to moderate LUTS and ED.

The potential roles for PDE-5 inhibitors in treating voiding dysfunction and α-adrenergic blockers (ABs) in enhancing sexual function are a fertile area of research. However, the combination of these 2 agents in treating both sexual dysfunction and LUTS has not been previously reported. Kaplan and colleagues recently reported on the results of a pilot study designed to ascertain the safety and efficacy of the combination of an AB, alfuzosin SR (Uroxatral®; Sanofi-Aventis, Bridgewater, NJ), and sildenafil versus monotherapy in the treatment of LUTS and sexual dysfunction.[19] A total of 62 consecutive men with a mean age of 63.4 years (range, 50–76 years) with previously untreated LUTS and sexual dysfunction were randomized into 1 of 3 treatment arms—alfuzosin 10 mg/day, sildenafil 25 mg/day, or a combination of both—for a 12-week trial. Efficacy was evaluated by means of the following: IPSS, peak urinary flow rate (Q_{max}), postvoid residual urine, voiding diary, and IIEF and ejaculatory function; adverse events were also recorded. Of the 62 subjects, a total of 55 (89%) completed the 12-week trial. Changes from baseline in efficacy parameters for each group are shown in Table 1.

Improvements at 12 weeks in IPSS, Q_{max}, frequency, nocturia, and IIEF were significant for all 3 groups but greatest for the combination group. Both the sildenafil and combination arms had significantly improved scores for IIEF questions 3 (frequency

Table 1
Results of the Use of Alfuzosin, Sildenafil, or a Combination of Both on Lower Urinary Tract Symptoms and Erectile Dysfunction Measures

	Alfuzosin Baseline (n = 20)	Alfuzosin at 12 Weeks	Sildenafil Baseline (n = 21)	Sildenafil at 12 Weeks	Combination Baseline (n = 21)	Combination at 12 Weeks
IPSS	17.3	14.6	17.8	14.9	17.3	13.5
Q_{max} (mL/s)	9.4	10.5	9.7	10.3	9.5	11.5
PVR (mL)	54	31	46	34	53	32
Frequency (voids/day)	8.7	6.4	9.1	7.8	9.3	6.1
Nocturia (voids/night)	2.9	1.8	2.6	2.1	3.1	1.8
IIEF	17.4	20.3	14.3	21.4	16.2	25.7

IPSS, International Prostate Symptom Score; Q_{max}, peak urinary flow rate; PVR, postvoid residual urine; IIEF, International Index of Erectile Function. Reproduced from Kaplan SA et al,[19] with permission from the American Urological Association.

of penetration) and 4 (frequency of maintained erections). Self-reported ejaculatory function improved in all 3 groups. Adverse events included dizziness (n = 3), dyspepsia (n = 3), and flushing (n = 1). Investigators concluded that treatment with the combination of an AB and a PDE-5 inhibitor was a safe and effective therapy to enhance both voiding and sexual function in men at risk. However, larger-scale, placebo-controlled studies are needed to further elucidate the role of combination therapy to treat these 2 conditions.

Investigators concluded that treatment with the combination of an α-blocker and a PDE-5 inhibitor was a safe and effective therapy to enhance both voiding and sexual function in men at risk.

In a recently completed phase II proof-of-concept study, tadalafil was shown to be effective in treating LUTS due to BPH. The efficacy and safety of tadalafil dosed once daily was assessed in men with moderate to severe LUTS secondary to BPH in a randomized, double-blind, placebo-controlled, parallel-group, dose-escalation, US study.[20]

Patients were treated with placebo for 4 weeks (single-blind) to evaluate treatment compliance and establish baseline IPSS and uroflowmetry values. After stratification by baseline IPSS (13–19, moderate LUTS; 20–35, severe LUTS), geographic region, and prior AB therapy; 281 men were randomly assigned to tadalafil (5 mg for 6 weeks followed by dose escalation to 20 mg for 6 weeks) or placebo (12 weeks). The primary efficacy endpoint was change in IPSS at 6 and 12 weeks. Secondary efficacy endpoints included changes in IPSS quality of life (QOL) index, BPH Impact Index (BII), uroflowmetry values, and a LUTS global assessment question (GAQ; ie, "Has the treatment you have been taking since your last visit improved your urinary symptoms?"). Responses to tadalafil 5 mg (6 weeks) or tadalafil 5 mg followed by 20 mg (5/20 mg; 12 weeks total) were compared with placebo using analysis of covariance (IPSS, BII, uroflowmetry values) and logistic linear regression (LUTS GAQ) models.

Results demonstrated that at 6 weeks (5 mg) and 12 weeks (5/20 mg) tadalafil improved baseline scores for IPSS, IPSS QOL, BII, and LUTS GAQ compared with placebo (Table 2). Peak flow rate changes were similar in the placebo and tadalafil treatment groups. The subset of men with LUTS/BPH who were sexually active and also had ED showed a significant increase in IIEF erectile dysfunction domain scores (6.0 with 5 mg vs 0.6 with placebo; 7.7 with 5/20 mg vs 1.4 with placebo).[20] The only treatment-emergent adverse event with an incidence of 5% or more in any group was erection increase (5.1%, tadalafil 5/20 mg). Tadalafil dosed once daily was well tolerated and demonstrated statistically significant and clinically meaningful efficacy in the treatment of LUTS secondary to BPH and

Table 2
Efficacy Results for Use of Daily-Dosed Tadalafil 5 mg, Tadalafil 5/20 mg, and Placebo at 6 and 12 Weeks

	Placebo 6 wk	Tadalafil 5 mg 6 wk	*P* Value	Placebo 12 wk	Tadalafil 5/20 mg 12 wk	*P* Value
n	143	138		143	138	
IPSS*	−1.2 ± 0.47	−2.8 ± 0.48	.003	−1.7 ± 0.49	−3.8 ± 0.50	< .001
IPSS QOL*	−0.2 ± 0.11	−0.5 ± 0.11	.017	−0.3 ± 0.12	−0.7 ± 0.12	.008
BII*	−0.4 ± 0.21	−0.7 ± 0.22	.107	−0.6 ± 0.23	−1.3 ± 0.23	.008
LUTS GAQ, endpoint (% yes)	32.6	55.9	< .001	37.7	57.4	< .001

*Change from baseline, least-squares mean ± standard error.
IPSS, International Prostate Symptom Score; QOL, quality of life; BII, Benign prostatic hyperplasia Impact Index; LUTS GAQ, lower urinary tract symptoms global assessment question. Reproduced from Roehrborn C et al.[20] with permission from the American Urological Association.

improved erectile function in men with both LUTS and ED.

Sildenafil has also been evaluated for the treatment of LUTS. In a randomized, double-blind, placebo-controlled study, similar findings were noted. In this 12-week study, 366 men more than 45 years of age with an IIEF score less than 25 and an IPSS greater than 12 points were given sildenafil 50 or 100 mg or placebo, either at bedtime or before sexual activity. The results indicate that IPSS decreased 6.32 points in the sildenafil group versus 1.93 in the placebo group. Significant changes in the IPSS subscores for storage and voiding were also noted in the sildenafil arm compared with placebo. Finally, the erectile function domain scores of the IIEF improved by 9.17 points with sildenafil, compared with 1.86 points with placebo ($P < .0001$), and there were no changes in Q_{max} compared with placebo.[21]

Conclusions

Clinical evidence suggests that PDE-5 inhibitors may be useful in treating LUTS. The best evidence thus far comes from randomized, placebo-controlled phase II trials of both tadalafil and sildenafil for the treatment of symptomatic BPH.[20,21]

What advantages do PDE-5 inhibitors have over current therapies for BPH? No medication currently approved for symptomatic BPH can also successfully treat ED. The ability to treat both BPH and ED with 1 medication is noteworthy given the significant negative impact on quality-of-life measures these disorders have in aging men.

Not all men with BPH are candidates for treatment with PDE-5 inhibitors, in particular those with

Main Points

- Both lower urinary tract symptoms (LUTS) due to benign prostatic hyperplasia (BPH) and erectile dysfunction (ED) have a very high prevalence among aging men, and their occurrence increases at a similar rate. A large-scale study has shown that sexual dysfunction is strongly related to the severity of LUTS, independent of other comorbidities.
- Because of this association, researchers are now investigating whether the concomitant increase in LUTS and ED in aging men is due to a shared pathophysiology, and whether phosphodiesterase type 5 (PDE-5) inhibitors, which have proven highly effective in the treatment of ED, may also be useful in the treatment of symptomatic BPH.
- Two recently completed phase II studies, 1 with sildenafil and 1 with tadalafil, both showed statistically significant improvements versus placebo in various measures of sexual function and urinary symptoms.
- In another study, which compared the use of sildenafil, alfuzosin (an α-blocker), or a combination of the 2 for treating LUTS and sexual dysfunction, the combination was found to be safe and superior to either monotherapy.
- Large-scale, randomized, placebo-controlled studies of PDE-5 inhibitors, alone and in combination with α-blockers, are needed to further assess the long-term safety and effectiveness of these agents in treating men with symptomatic BPH and ED.

significant coronary artery disease, a recent myocardial infarct, unstable angina, or those who are taking organic nitrates. To date, the effects of sildenafil and tadalafil on urodynamically proven bladder outlet obstruction have not been demonstrated. Similarly, the safety of long-term daily treatment of BPH with sildenafil or tadalafil has not been investigated.

Basic science and early clinical evidence support the use of PDE-5 inhibitors in treating both BPH and ED. However, long-term studies are needed to further assess the safety, efficacy, and cost-effectiveness of such treatment. Future trials should be randomized and include comparison arms with ABs. Treatment success with these agents for symptomatic BPH and ED will likely rely on proper patient selection. ■

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