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Role of Phosphodiesterase Type 5 Inhibitor on Benign Prostatic Hyperplasia/Lower Urinary Tract Symptoms

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= Abstract =

There is strong evidence from multiple epidemiological studies that benign prostate hyperplasia (BPH) induced lower urinary tract symptoms (LUTS) are correlated with erectile dysfunction (ED). Although a direct causal relationship is not established yet, four pathophysiological mechanisms can explain the relationship. These include alteration in activity of nitric oxide (NO)-cyclic GMP signal pathway, autonomic hyperactivity, increased Rho kinase/Rho A pathway and pelvic atherosclerosis. Androgens have been suggested to have an important role in the maintenance of the functional and structural integrity of the urinary tract. Sexual function should be assessed and discussed with the patient when choosing the appropriate management strategy for LUTS, as well as when evaluating the patient's response to treatment. Multiple large clinical trials have shown an improvement in LUTS after phosphodiesterase-5 (PDE5)-inhibitor treatment. Sildenafil is a pioneer of this clinical trial and appears to improve both erectile function and LUTS in subjects with ED. Basically PDE5 I with long half life is an appropriate candidate, therefore tadalafil and undenafil had been used to evaluate both diseases. Placebo-controlled trials of tadalafil showed improvement of LUTS secondary to BPH, but none of the studies showed a significant effect on urodynamic measures. PDE5 Is, such as sildenafil and tadalafil, increase the concentration of cGMP in plasma and smooth muscle, facilitating erection of the penis, relaxation of the bladder neck and prostate and subsequent bladder emptying. And theses PDE5 Is increase cAMP and cGMP levels and are more highly distributed in the prostate than plasma. These findings may help in the assessment of the feasibility of using PDE5 Is to concurrently treat both LUTS and ED.

Key Words: Phosphodiesterase type 5 inhibitor (PDE5 I), Sexual function, erectile dysfunction (ED), Lower urinary tract symptoms (LUTS)

Introduction

Benign prostate hyperplasia (BPH) associated with lower urinary tract symptoms (LUTS) and erectile dysfunction (ED) is highly prevalent in men ＞50 years of age.[1,2] The prevalence of BPH is very high; 40% of men have BPH by 50 years of age, increasing to ＞80% by 80 years of age.[3] The prostate, bladder, urethra and central nervous system can be a etiological organs for LUTS caused by BPH, although it is not clear that prostate hypertrophy is a source of LUTS.[4] The prevalence of ED is similarly high and also increases with age; 40% of 40-year-old men experience some degree of ED, and the rate is as high as 70% in 70-year-old men.[5] The severity of BPH induced

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LUTS is proportional to the severity of ED. Both BPH and ED have a significant negative impact on health-related quality of life measures for ageing men.[6]

There has been increasing interest in the nitric oxide (NO) pathway as a potential pharmacological target for treating BPH/LUTS. The presence of nitric oxide synthase (NOS) has been described in the human prostate by biochemical, immunohistochemical and molecular biological methods.[7] In the human prostate, endothelial NOS is related to the maintenance of local vascular perfusion, whereas neuronal NOS is mainly involved in the initiation of the relaxation of smooth muscle and in the control of glandular function, including the proliferation of epithelial and subepithelial cells.[8] Inducible NOS has not been detected in normal prostate tissue, although there is evidence that inducible NOS is expressed in hyperplastic and malignant tissues.[9]

Uckert et al[10] described the expression of phosphodiesterase (PDE) isoenzymes in the human prostate by means of molecular biology and protein chemistry. They found mRNA transcripts encoding for PDE 1, 2, 4, 5, 7, 8, 9 and 10 in different anatomic regions of the human prostate, and demonstrated hydrolytic activities of PDE isoenzymes 4 and 5 in cytosolic fractions of prostatic tissue.[10]

NO mediates smooth muscle relaxation in the corpus cavernosum, prostate and bladder.[10-12] Phosphodiesterase 5 inhibitors (PDE5 Is), such as sildenafil, tadalafil and udenafil increase the concentration of cGMP in smooth muscle by blocking the PDE 5, facilitating erection of the penis, relaxation of the bladder neck and prostate leading to bladder emptying.

Considering the high incidence of ED and BPH in aging men, the ability to treat both disorders with a single agent, such as a PDE5 I, would be in valuable.[13] Recently, several studies on PDE5 Is have yielded statistically significant improvements in various measures of sexual function and urinary symptoms.[14,15] Accordingly, we examined the inter-relationship between BPH/LUTS and ED and also the role of PDE5 I on BPH/LUTS.

Inter-relationships between LUTS and ED

To date, the following four biologically plausible inter-relationships between BPH/LUTS and ED have been proposed: (i) an alteration in NO levels; (ii) autonomic hyperactivity; (iii) the increased Rho kinase/Rho A signaling; and (iv) pelvic atherosclerosis.[16] These four hypotheses are partially overlaped, each with a variable amount of supporting data to explain the BPH/LUTS-ED relationship which has been demonstrated in multiple studies.[17]

1. Alteration in NO levels

NO has been identified as the capital signaling molecule for penile erection. In recent years, it has been recognized that reduced NO availability is linked to the development of prostate gland hyperplasia and the subsequent development of LUTS. As a logical result, there is an increasing interest in the NO-cGMP pathway as a potential pharmacological target to treat male BPH induced LUTS. NOS is found in the normal prostate in two isoforms: endothelial NOS (eNOS) in the endothelial cells and under the form of neuronal NOS (nNOS) not only in nerve fibers transversing the fibromuscular prostatic stroma, but also, interestingly, in the cytoplasm of the basal cells.[18,19] It has been reported that NOS expression, and thus NO production, of the prostate is reduced in the transition zone of the prostate in BPH, compared with normal prostate tissue.[20] The proposed reduction in expression of NOS isoforms resulted in increased smooth muscle cell contractile forces at the bladder neck and prostatic urethra. Additionally, the NO bioavailability results in prostatic smooth muscle cell proliferation, which further contributes to increased outlet resistance. A recent discovery was made of PDE5 expression in the striated muscle of the urethra and levator ani in rats.[21] This finding was surprising, as it was previously believed that PDE5 was not expressed, or not of relevance, in striated muscle fibers. The discovery of PDE5 expression in striated muscle of the urethra and levator ani could lead to better understanding of urethral relaxation and pelvic floor disorders, both of which can manifest as LUTS.

2. Autonomic hyperactivity

Rat models have demonstrated an effect on prostatic growth and differentiation through manipulation of autonomic activity.[22] A recent study trying to explain the epidemiological relationship between the metabolic syndrome and LUTS hypothesized that the metabolic syndrome is associated with an overactivity of the autonomic nervous system for which hyperinsulinemia, a key element of the metabolic syndrome might be responsible.[23,24] Autonomic hyperactivity and a component of the metabolic syndrome refer to a dysregulation of sympathetic and parasympathetic tones. Increased sympathetic tone results in penile flaccidity and antagonizes penile erections and contraction of prostate smooth muscle. PDE5 Is can attenuate the contracted prostatic tissue through norepinephrine and elevated cGMP levels.[25]

3. The Rho kinase/Rho A pathway

Contraction of smooth muscle is stimulated by the inhibition of myosin light chain phosphatase by Rho kinase, and, therefore, provides a calcium-independent mechanism for smooth muscle contraction. Thus, an abnormally upregulated Rho-kinase/Rho A pathway could contribute to a lack of smooth muscle relaxation, changes in bladder compliance and thus LUTS. Upregulation of Rho kinase/Rho A has indeed been linked to both ED and LUTS in various studies.[26,27] Furthermore, the relaxant and anti-proliferative effect of Rho-kinase inhibitors corroborated this finding.[28] The suggestion that bladder outlet obstruction (BOO) induces ED via an upregulation of Rho kinase in the penis has experimental merit.[29] There is also a possibility that a multisystem dysfunction of Rho kinase exists and leads to both ED and LUTS.[30] Rho kinase has further been shown to have a role in hypertension and its expression correlates to aging, which provides a partial explanation not only for the relationship between LUTS and ED, but also for the connection of LUTS, ED and hypertension.[31]

4. Pelvic atherosclerosis

An additional mechanism is diffuse atherosclerosis of blood vessels supplying pelvic organ such as prostate, penis and bladder.[32] 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 significant higher the International Prostate Symptom Score (IPSS) compared with subjects with one or no risk factors.[33] Another epidemiologic study showed that men with risk factors for vascular disease are more likely to have a higher IPSS and a lower International Index of Erectile Function (IIEF) score than men without risk factors.[34] Animal models mimicking pelvic ischemia and hypercholesterolemia show a striking similarity in the smooth muscle alterations of the detrusor muscle and corpora cavernosa. In the rabbit, chronic ischemia resulted in fibrosis, smooth muscle atrophy and decreased compliance of the bladder.[35] Chronic ischemia is associated with an increased production of profibrotic and proapoptotic cytokines, such as transforming growth factor-b1 (TGF β1), which correlates with the severity of fibrosis.[35] TGF β1further impairs neurogenic relaxation in the prostate, which appears to involve the NO pathway, and may result in a loss of elasticity and an increase in smooth muscle tone of the prostate.[36] Penile ischemia leads to smooth muscle loss in the penis, resulting in ED. Loss of smooth muscle in the bladder decreases compliance and worsens LUTS.

Testosterone in LUTS

Androgens have been suggested to have an important role in the maintenance of the functional and structural integrity of the urinary tract. It is possible that declining testosterone production with aging contributes to the development of BPH induced LUTS.[37] Androgen receptors have been found to be expressed in the epithelial cells of the urethra and the bladder of rabbits and in the urothelium, bladder smooth muscle, striated muscle cells of the proximal urethra and in the neurons in the autonomic ganglia of the prostatic plexus of the male rat.[38,39]

The role of testosterone and its metabolites on maintaining the reflex activity in the pelvic part of the auto-

nomic nervous system has been demonstrated in rats.[40] The effects of testosterone can be partially explained by the fact that NO production is androgen dependent in the urinary tract. NOS in an earlier study had appeared to be androgen dependent in the urogenital tract of the rat.[41] It suggested that LUTS may be related with low level of testosterone.[42,43]

Activity of Phosphodiesterase Type 5 Inhibitors in Patients with Lower Urinary Tract Symptoms

PDE5 mRNA is expressed in the bladder, urethra and prostate. PDE5 Is has also been shown to inhibit the contraction of isolated bladder, urethra and prostate

Table 1. Clinical evidence of sildenafil and lower urinary tract symptoms

Study	Subjects and entry/ baseline data	Study design	Treatment	Effects
Sairam et al[46]	112 men with ED 18% with LUTS IPSS <7: 67%, 8~9: 26%, 20~35: 6%	Prospective open-label (evidence level 2b)	On demand	- Improved erections: 81% - Changes in IPSS correlated with sexual function scores - A lower IPSS at baseline predicted higher sexual function scores after treatment
Chang et al[47]	108 men with ED IPSS and IIEF assessed at 3 mo	Retrospective (evidence level 2b)	On demand	- IPSS decreased from 15.8 to 13.3 - Significant inverse correlation between IIEF and IPSS
Mulhall et al[48]	48 men with IPSS >10	Open label (evidence level 2b)	100 mg	- Mean improvement in ED: 7; IPSS: 4.6 points; quality of life: 1.4 - Improvement of IPSS in 60% of patients (35% >4 points); mild LUTS in 17%
McVary et al[49]	189 sildenafil 180 placebo IIEF ≤25, IPSS ≥12	12-wk, double-blind, placebo-controlled (evidence level 1a)	50 mg increased to 100 mg	- Sildenafil group: significantly greater improvements in IPSS and IPSS quality of life than placebo - Greater improvements in patients with severe/moderate LUTS than in those treated with placebo - Adverse events and study discontinuation due to adverse events greater in sildenafil group
McVary et al[50]	Equal previous study. BMI: obese ≥30, overweight ≥25, normal <25 kg/m^2	Ad hoc analysis previous study (evidence level 1a)	50 mg increased to 100 mg	- Significantly greater improvements in IPSS and IIEF observed in sildenafil-treated patients versus placebo were independent of BMI

ED: erectile dysfunction, LUTS: lower urinary tract infection, IPSS: International Prostate Symptom Score, IIEF: International Index of Erectile Function, BMI: body mass index.

strips in an in vitro study.[44] These results serve as an impetus to attempt PDE5 Is in patients with BPH induced LUTS. Multiple studies indicate that PDE5 Is improve BPH induced LUTS.

1. Sildenafil and lower urinary tract symptoms

The most common form of management of ED is pharmaco-therapy with PDE5 Is.[45] Table 1 presents a summary of clinical studies of sildenafil and BPH/LUTS.[46-50] Mulhall et al[48] found that sildenafil has a positive effect in men presenting to a sexual dysfunction clinic with mild-to-moderate LUTS and ED. Kaplan et al[51] recently reported the results obtained in a pilot study designed to ascertain the safety and efficacy of the combination of the α-blocker, alfuzosin SR and sildenafil versus monotherapy for the treatment of BPH/LUTS and ED. They concluded that combination treatment was a safe and effective therapy for enhancing both voiding and sexual function in men at high risk for BPH/LUTS and ED.

2. Tadalafil and lower urinary tract symptoms

The efficacy of tadalafil to relieve LUTS secondary to BPH has been reported in a number of clinical trials (Table 2).[52-54] In a recently completed phase II proof of concept study, the PDE5 I, tadalafil, was effective in treating LUTS due to BPH. The primary efficacy endpoint was a change in IPSS at 6 and 12 weeks. Responses to 5 mg of tadalafil for 6 weeks, followed by dose escalation to 20 mg for 6 weeks, were compared with 12 weeks of placebo.[52] At both 6 and 12 weeks, tadalafil produced greater improvements over baseline measures in the IPSS, IPSS health-related quality of life index and bladder impact index compared to placebo. The peak flow rate changes were similar in the placebo- and tadalafil-treated groups.

3. Vardenafil and lower urinary tract symptoms

In a randomized and placebo-controlled study, vardenafil 10 mg taken twice a day was used as a treatment for LUTS (IPSS >12) in men with BPH.[55] A

Table 2. Clinical evidence of tadalafil and lower urinary tract symptoms derived from clinical trials

Study	Subjects and entry/ baseline data	Study design	Treatment/duration	Effects
McVary et al[52]	138 tadalafil 143 placebo Stratified by IPSS <20 or ≥20 and prior a-blocker therapy	Prospective, randomized, double-blind, placebo-controlled (evidence level 1a)	5 mg increased to 20 mg after 6 wk; 12 wk	- At 6 and 12 wk, IPSS improvements significantly higher in tadalafil than placebo groups - Withdrawal due to adverse events: placebo 1.4%, tadalafil 3.6%; no changes in urodynamic parameters
Roehrborn et al[53]	1058 (approximately 200 per group): placebo, four tadalafil doses, stratified by IPSS <20 or ≥20	Prospective, randomized, double-blind, placebo-controlled (evidence level 1a)	2.5, 5, 10, 20 mg; 12 wk	- Significant improvement in the 5-mg group - IPSS increased from 4.9 to 1.8 - Higher doses associated with IPSS improvements but more adverse events
Dmochowski et al[54]	99 tadalafil 101 placebo IPSS 13	Prospective, randomized, double-blind, placebo-controlled (evidence level Ia)	20 mg; 12 wk	- Significant improvement of IPSS (mean difference between treatments: 4.2). - No change in urodynamic measures (detrusor pressure at maximal urinary low rate)

IPSS: International Prostate Symptom Score.

total of 247 men were randomized, and 225 completed the 8-wk intention-to-treat study. The mean change in total IPSS in this study was 5.9 in the vardenafil arm and 3.6 in the placebo arm. Although the difference in total score was statistically significant, it is of interest that the placebo arm experienced what would be considered a clinically significant improvement in total IPSS score. There were neither significant changes in flow rate nor changes in post-voiding residual (PVR) urine volume.

4. The impact and distribution of a single phosphodiesterase type 5 inhibitor dose in prostate tissue and plasma in patients with BPH

PDE5 Is with short (sildenafil) and long (tadalafil) half-lives have been demonstrated to significantly improve symptoms in men with LUTS. In a study reported by Zhao et al,[56] evaluated the single dose effects of tadalafil or udenafil, comprising novel PDE5 Is with intermediate half-lives of 7.3～12.1 h. Udenafil and tadalafil significantly increased the levels of cGMP and cAMP in the prostate and plasma (Fig. 1).[56] These results suggest that PDE5 Is enhanced the production of cyclic nucleotides in the plasma and prostate. In addition, the amount produced was not dependent on the trauma of the TURP but rather the type of PDE5 Is, although the source of the cyclic nucleotides remains unknown (Fig. 2).[56] The commonly accepted pathway involves activation of potassium channels by cGMP- and cGMP-specific protein kinases (as

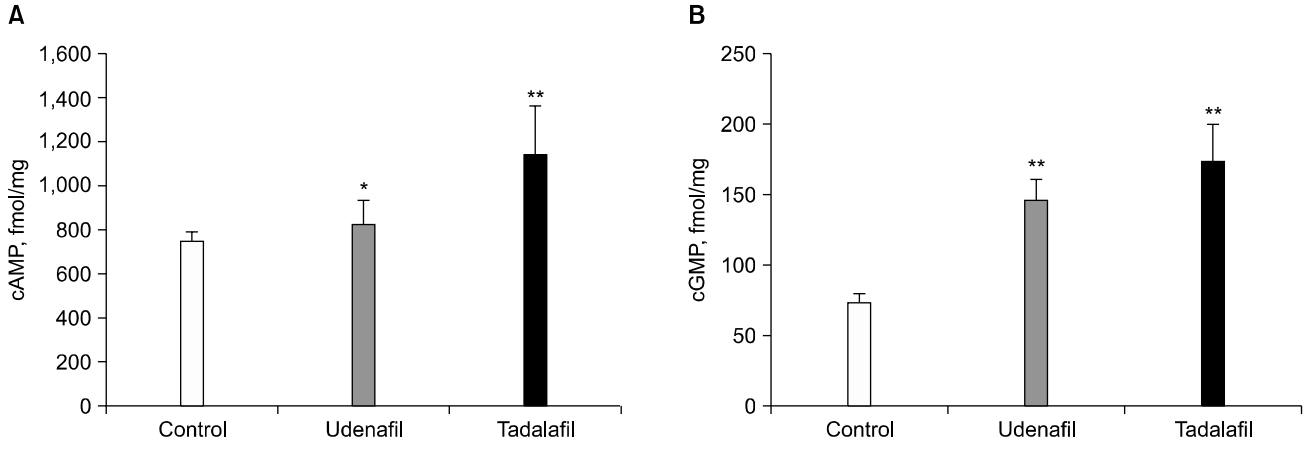

Fig. 1. cAMP and cGMP levels in prostate tissue. (A) cAMP and (B) cGMP levels were significantly higher in prostate tissues of groups 2 (udenafil, 200 mg) and 3 (tadalafil, 20 mg) than group 1 (control). *p＜0.05, **p＜0.01.

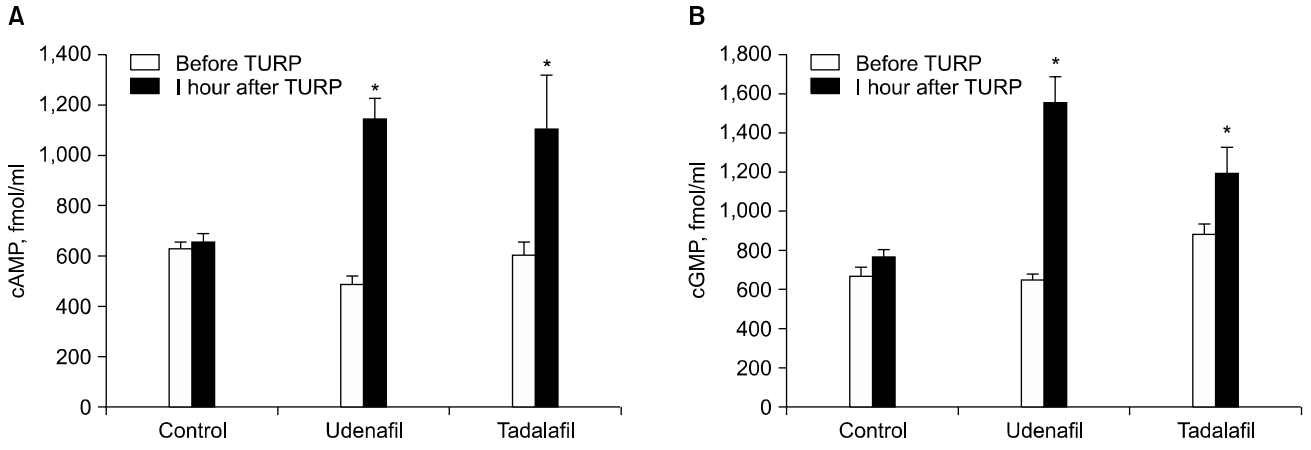

Fig. 2. cAMP and cGMP levels in plasma. (A) cAMP and (B) cGMP levels increased significantly 1 h after TURP in the plasma of groups 2 (udenafil, 200 mg) and 3 (tadalafil, 20 mg), but not group 1 (control). *p＜0.01.

well as by NO itself), leading to hyperpolarization and closure of voltage-dependent calcium channels. This change elicits a decrease in intracellular calcium, the dissociation of calmodulin from myosin light chain (MLC) kinase, phosphorylation and inactivation of MLC, and the subsequent dephosphorylation of myosin (by MLC phosphatase), and detachment from actin. Most tissues contain multiple forms of PDEs but, in tissues (including the penile corpus cavenosum), PDE5 is the major cGMP hydrolyzing PDE.[57] PDE5 Is act by inhibiting the PDE5 enzyme in the tissue/organ. The physiological activity of the tissue is regulated by cGMP and the cellular cGMP level is dictated by the balance between the rates of synthesis by guanylate cyclase and breakdown by PDE. PDEs cleave the cyclic phosphate ring that is required for the action of cGMP.[58] Therefore, the administration of PDE5 I results in an equivalent pharmacological effect at the site or the organ where the enzyme exists. It is also known that the PDE5 enzyme is expressed in the prostate.[25] Therefore, the high T/P ratio in the prostate indicates a longer duration of action at the relevant tissue, and udenafil has a longer influence than the PDE5 Is with a shorter half-life (p=0.0001) (Fig. 3).[56] However, the role of cGMP in the plasma is unclear. Further research is needed to elucidate the exact effects of PDE5 Is on prostate tissues and the underlying mechanisms of action.

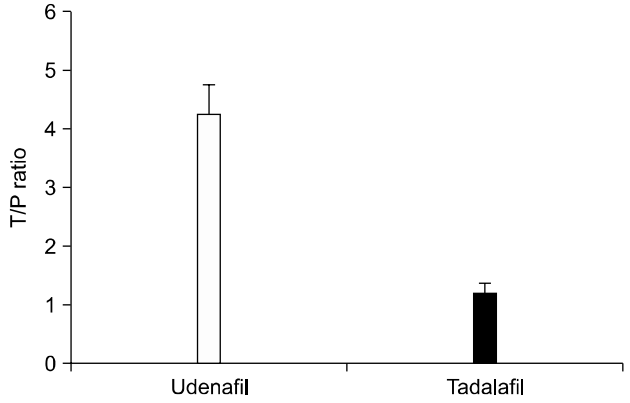

Fig. 3. The prostate tissue-to-plasma (T/P) ratio of the phosphodiesterase type 5 inhibitor (PDE5 I) concentration. The ratio was significantly higher in group 2 (udenafil, 200 mg) than in group 3 (tadalafil, 20 mg).

Conclusion

BPH/LUTS and ED are common disorders in aging men, which are independently associated to one another. The two disorders share certain pathophysiologic mechanisms and this association has many clinical implications. These four pathophysiologic mechanisms are alteration in NO bioavailability, Rho kinase/Rho A pathway, autonomic hyperactivity, and pelvic atherosclerosis. Androgens have been suggested to have an important role in the maintenance of the functional and structural integrity of the urinary tract. Nocturia may be related with cause of low testosterone. Multiple large clinical trials have shown an improvement in BPH/LUTS after PDE5 I treatment. PDE5 mRNA is expressed in the bladder, urethra and prostate. PDE5 Is has also been shown to inhibit the contraction of isolated bladder, urethra and prostate. PDE5 Is significantly increased the levels of cAMP and cGMP in the human prostate and plasma, and the distribution of PDE5 Is in the prostate was higher than in the plasma. These findings may facilitate the feasibility of PDE5 Is for the simultaneously treatment of BPH-induced LUTS and ED.

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