Lower Urinary Tract Symptoms, Benign Prostatic Hyperplasia, Erectile Dysfunction, and Phosphodiesterase-5 Inhibitors

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Many patients who present to their healthcare provider with lower urinary tract symptoms (LUTS) due to benign prostatic hyperplasia (BPH) will also have erectile dysfunction (ED), and vice versa. Although α-adrenergic receptor blockers and 5-α-reductase inhibitors are highly effective in treating BPH-associated LUTS, these agents have sexual adverse effects that cause many men to discontinue therapy. The discovery of nitric oxide as a major factor in the mechanism of erection has led to the development of new drugs for ED, including the phosphodiesterase (PDE) inhibitors. Preliminary data support the theory that inhibition of PDE isoenzymes in the prostate may improve LUTS due to BPH through relaxation of prostatic smooth muscle. Further studies of PDE inhibitors in men with ED and BPH-associated LUTS are indicated.
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Key words: Benign prostatic hyperplasia • Erectile dysfunction • Lower urinary tract symptoms • Phosphodiesterase

Two conditions that occur with relatively high frequency in aging men have received a great deal of attention over the past decade: lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH), and erectile dysfunction (ED), also referred to as impotence. There are several reasons for the recent interest in these conditions. Both are common disorders for which prevalence increases with advancing age. Thus, at a time when life expectancy is rising steadily in industrialized countries, an increasing number of aging men will

be affected by one of these two conditions and a larger patient reservoir will present with the associated symptoms. In addition, before 1990, surgical intervention was the only therapy for these conditions. The standard treatment of LUTS associated with BPH consisted of a transurethral resection of the prostate; in the case of ED, not many treatments were available other than penile implants. Lastly, the past decade has witnessed an unprecedented explosion of knowledge regarding the pathophysiology and natural history of LUTS and BPH,[1] followed by a rapid development of several highly effective medical interventions for these conditions. Similarly, our understanding of the mechanisms underlying ED and thereby its pathophysiology has also significantly increased,[2] leading to a variety of innovative treatments, such as vacuum constriction devices, injection of vasoactive substances, and a new class of drugs known as phosphodiesterase (PDE) inhibitors.[3]

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LUTS and ED: Two Common Conditions in Aging Men or Common Etiology?

Histologic hyperplasia of the prostate typically occurs in men older than 40 years, with the prevalence increasing with advancing age.[1] As the prevalence of histologic stromoglandular hyperplasia increases, so does the incidence of moderate to severe LUTS.[4]

Similarly, the prevalence of ED also increases with advancing age.[5,6] Therefore, it is no surprise that, when queried, many patients presenting to their health care provider with complaints of LUTS will also have ED, and vice versa. This interrelationship has been substantiated in multiple studies demonstrating not only that patients with BPH and associated LUTS have ED but also that the severity of LUTS corresponds with the severity of ED.[7]

In an epidemiologic study conducted in Germany by Braun and colleagues,[8] a validated questionnaire on ED was mailed out to men aged 30 to 80 years; 4489 replies were received. Regular sexual activity was reported by 96% of men in the youngest group and up to 71.3% of those in the oldest group. Thirty-one percent to 44% of the responders were dissatisfied with their current sex life, and the overall prevalence of ED was 19.2%, with a steep age-related increase from 2.3% to 53.4%. Of interest, high comorbidity was found between ED and hypertension, diabetes, and pelvic surgery, as well as LUTS.

The Olmsted County Study of Urinary Symptoms and Health Status Among Men has provided some of the most significant insights over the past decade into the epidemiology and natural history of LUTS. In a recent abstract presented at the 2003 meeting of the American Urological Association, Chung and colleagues[9] reported epidemiologic evidence correlating LUTS to ED in the Olmsted County population. The investigators found that, overall, the sexual domains queried were inversely related to the severity of LUTS, with correlation coefficients ranging from −0.15 to −0.30 ($P < .001$) in the 1541 men who reported regular sexual partners. Although the correlation of LUTS with difficulty in getting an erection and the level of sexual drive decreased with age, it remained significant within all age decades. Difficulty in getting an erection demonstrated the strongest correlation with LUTS, whereas the remaining questions in the erectile function domain and the degree of difficulty ejaculating correlated with LUTS within each decade for men younger than 60 and 70 years, respectively. The investigators concluded from these cross-sectional data that sexual dysfunction appears to be associated with LUTS independent of the effects of age.

A large cross-sectional assessment of sexual function and LUTS was also conducted in 3230 men in Europe, Russia, the Middle East, Latin America, and Asia.[10] Multiple logistic regression confirmed that patients with severe LUTS were approximately twice as likely to experience ED (odds ratio [OR], 2.0; 95% confidence interval [CI], 1.4-2.8), as well as reduced ejaculate (OR, 1.8; 95% CI, 1.3-2.5). In addition, men with severe LUTS were 6 times as likely to complain of pain and discomfort on ejaculation.

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A strong age-independent relationship between severity of ED and severity of LUTS was also found in an epidemiologic study conducted in France by Macfarlane and colleagues.[11]

Perhaps the most important cross-sectional data are those from the Multinational Survey of the Aging Male (MSAM-7), a survey of more

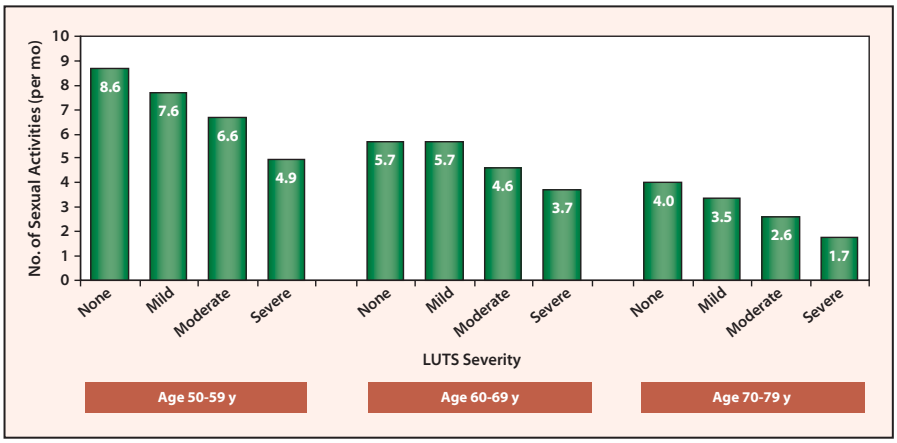

Figure 1. *Multinational Survey of the Aging Male (MSAM-7): Average occurrences of sexual intercourse or activity per month by decade of life, stratified by lower urinary tract symptom (LUTS) severity. Data from Rosen R et al.*[12]

than 14,000 men, ages 50 to 80 years, that confirmed a high prevalence of BPH associated with LUTS in aging men in the United States and Europe.[12] The majority of men surveyed in this questionnaire demonstrated mild to moderate-to-severe LUTS, with 30% to 35% having moderate-to-severe symptoms. Based on responses to the Danish Prostatic Symptom Score sex questionnaire, approximately 60% of the men were bothered by ejaculatory dysfunction as well. Ejaculatory problems were almost as prevalent as erection problems and, with patients stratified by age group, an increased prevalence of ejaculatory dysfunction with increasing severity of LUTS was clearly evident. When controlling for age and other comorbidities, the association between LUTS and ejaculatory dysfunction was maintained (Figure 1).

The Prospective European Doxazosin and Combination Therapy (PREDICT) study was a multicenter trial conducted in 5 European countries and enrolling more than 1000 patients ages 50 years or older with peak flow rates between 5 mL/s and 15 mL/s and symptom scores of 12 points or greater.[13,14] Subjects were asked general questions regarding their sexual activity (eg, Are you sexually active? Do you wish to be sexually active? Do you have a regular sex partner?) and specific questions regarding 5 domains of sexual dysfunction, that is, decreased interest in sex, problems getting an erection, problems keeping an erection, problems completing the sex act, and problems deriving satisfaction. Subjects were queried about both frequency and bothersomeness of each of the 5 domains of sexual dysfunction, and results were analyzed by country and other parameters.

Table 1 outlines the ORs for patients to respond positively to each of the 5 sexual dysfunction domains, stratified by the severity of LUTS as well as by age. There was a strong relationship between advancing age and the odds of having each of the 5 sexual dysfunction conditions. There was also a relationship between increasing symptom severity as measured by the International Prostate Symptom Score (IPSS) and 3 of the 5 sexual dysfunction conditions. When controlling for IPSS, age was significantly related to the frequency of 4 of the 5 sexual dysfunction domains, as well as the bothersomeness of one of the domains. When controlling for age, however, IPSS was significantly related to the frequency of 2, and the bothersomeness of 3, of the 5 sexual dysfunction domains: IPSS was significantly correlated to the frequency of gaining an erection, completing the sexual act, and deriving satisfaction from it, and to the bother associated with decreases in interest in sexual activity, gaining an erection, and deriving satisfaction from it.[13,14]

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Medical Therapies for LUTS/BPH and Their Adverse Effects

Medical therapies for BPH-associated LUTS are highly effective. Two classes of drugs are available: α-adrenergic receptor blockers (alfuzosin, doxazosin, tamsulosin, and terazosin) and inhibitors of the 5-α-reductase isoenzyme(s) (dutasteride and finasteride). Although highly effective in improving symptom severity and bother, both classes of drugs have side effects that occasionally prompt patients to discontinue therapy.

The 2 available 5-α-reductase inhibitors, dutasteride and finasteride, have similar adverse-event spectrums. Both induce ED, decrease libido, and decrease volume of ejaculate about twice as often as placebo.[15,16] Overall, between 5% and 15% of patients, depending on the study, report one or several of these sexually related adverse events within the first year of study participation.

α-Adrenergic receptor blockers induce sexually related adverse events less often, with one notable exception.

Table 1
PREDICT Study: Odds Ratios for Various Domains of Sexual Dysfunction by Lower Urinary Tract Symptom Severity and Age

	Odds Ratio for Domain of Sexual Dysfunction				
	Decreased Interest	Gaining Erection	Keeping Erection	Completing Sex Act	Deriving Satisfaction
IPSS					
14-19	0.875	0.965	0.807	0.986	0.951
>19	1.332*	1.285	1.519†	1.132	1.486†
Age, y					
55-59	1.165	1.099	1.853†	0.802	1.760*
60-64	1.695†	1.422	2.136†	1.581*	2.698‡
65-69	2.054‡	2.069‡	3.371‡	2.207†	3.180‡
≥ 70	1.681‡	2.506‡	3.445‡	3.320†	4.625‡

IPSS, International Prostate Symptom Score.
*.05 < *P* < .1; †*P* < .05; ‡*P* < .001.
Data from Sweeney M et al.[14]

Tamsulosin has been reported to induce retrograde or anejaculation in an average of 8.4% of patients receiving a 0.4 mg/d dosage and 18.1% receiving a 0.8 mg/d dosage.[17,18] In an open-label extension of pivotal US trials, up to 30% of patients complained of some ejaculatory abnormalities.[19] The clinical relevance of ejaculatory dysfunction secondary to tamsulosin therapy is minimal, since even in long-term studies, subjects rarely discontinued therapy because of this occurrence.

Not unexpectedly, the rate of sexually related adverse events with combination therapy represents the total of all sexually related adverse events likely to be encountered with either α-receptor blockers or 5-α-reductase inhibitors. Men with BPH should be counseled about the potential sexual adverse events associated with medical therapy.

PDEs and Their Inhibitors

Our understanding of the mechanism of penile erection has increased significantly over the past 10 to 15 years.[2] Penile erection is now understood as being the result of trabecular smooth muscle relaxation. This process is mediated by cholinergic and nonadrenergic/noncholinergic (NANC) nerves containing nitric oxide (NO), atrial natriuretic factor, vasoactive intestinal polypeptide, and calcitonin gene-related peptide as neurotransmitters.[20] The release of NO from NANC nerve terminals initiates dilation of the cavernous trabecular smooth muscle via stimulation of cyclic guanosine monophosphate (cGMP) synthesis. The discovery of NO as a major factor in penile smooth muscle relaxation and thus in the mechanism of erection has resulted in the development of drugs that elevate intracellular levels of cGMP. Among these agents are NO donors and inhibitors of the PDE enzymes, such as sildenafil, vardenafil, and tadalafil. These PDE inhibitors exert their effect by preventing the breakdown of cGMP to its inactive metabolic product, thereby elevating the available intracellular levels of cGMP that are crucial to the initiation and maintenance of the erectile process.

To date, 11 PDE groups have been identified, numbered accordingly from PDE-1 to PDE-11 (Table 2). These groups may be further differentiated into 21 subgroups and approximately 53 variants.[21] PDE-5 is most prevalent in the corpus cavernosum, vascular and visceral muscles, and blood platelets and is most important in the erectile process. Other PDE isoenzymes are distributed throughout other tissues in the body and account for side effects attributed to PDE inhibitors. Whereas the functional significance of some isoenzymes is recognized, it is presently unknown for others.

PDEs and the Prostate

In 2000, Fawcett and colleagues[22] reported the molecular cloning and characterization of a distinct human PDE gene family—PDE-11A. Tissue distribution studies indicate that expression of PDE-11 mRNA is relatively high in prostate and skeletal muscles. In addition to mRNA distribution, the expression of PDE-11 protein was examined by Western blotting in human tissue extracts by using 3 separate anti–PDE-11A antisera. Results demonstrated that

Table 2
Distribution and Function of Phosphodiesterase (PDE)

PDE Isoenzyme/ Substrate	Tissue Distribution	Possible Functional Significance of PDE
PDE-1/ cGMP cAMP	Brain, heart, skeletal muscles, liver, vascular muscles, visceral muscles	Vascular muscular weakness, taste, olfaction
PDE-2/ cGMP cAMP	Adrenal cortex, corpus cavernosum, heart, visceral muscles, brain, skeletal muscles	Olfaction, adrenocorticosteroid production
PDE-3/ cGMP cAMP	Corpus cavernosum, heart, vascular and visceral muscles, blood platelets, liver, adipose tissue, kidneys	Myocardial contractility, insulin secretion, lipolysis, glucose production, platelet aggregation
PDE-4/ cAMP	Brain, testes, thyroid gland, lung, mast cells, skeletal muscles, vascular and visceral muscles	Inflammation, vascular and visceral muscle tone, depression, thyroid gland secretion, reproduction
PDE-5/ cGMP	Corpus cavernosum, vascular and visceral muscles, blood platelets	Erection, smooth muscle tone, platelet aggregation
PDE-6/ cGMP	Retina (cones, rods)	Signal transduction in vision
PDE-7/ cAMP	Skeletal muscles, heart, lymphocytes	T cell activation, skeletal muscles, metabolism
PDE-8/ cAMP	Widespread; eg, testes, ovaries, bowel	T cell activation
PDE-9/ cGMP	Widespread; most strongly expressed in the spleen, small intestine, and brain	?
PDE-10/ cGMP cAMP	Brain (putamen and caudal nerve), testes, thyroid gland	Dopamine signal transmission
PDE-11/ cGMP cAMP	Skeletal muscles, heart, vascular and visceral muscles (corpus cavernosum, prostate), pituitary gland, testes, liver, and kidneys	?

cGMP, cyclic guanosine monophosphate; cAMP, cyclic adenosine monophosphate.
Reprinted with permission from Gresser and Gleiter.[21]

the human prostate contains a single protein of approximately 56 kDa that co-migrates with recombinant human PDE-11A and is in close agreement with the predictive molecular weight of human PDE-11A1. Functional studies demonstrate that the partially purified full-length recombinant in human PDE-11A1 is capable of hydrolyzing both cGMP and cyclic adenosine monophosphate (cAMP), which is in stark contrast to the most closely related PDE—namely, PDE-5—which is highly specific for cGMP. The authors concluded that the potential physiologic role of PDE-11 in the tissues in which it was identified requires further investigation.

In 1995, Takeda and colleagues[23] demonstrated that NO plays a role not only in mediating erectile function but also in mediating the contractile function of human and canine prostates. The investigators performed pharmacologic experiments using electrical field stimulation on strips of human and canine prostates. Results demonstrated that sodium nitroprusside, a known donor of NO, causes relaxation of both human and canine prostates, with the mean magnitude of the relaxant response per cross-sectional area in human prostates being significantly greater than in the canine prostate.[23,24]

Extending the similarities between the relaxation of the smooth muscle in the prostate and the erectile process, it seems reasonable to assume that an inhibition of the PDE isoenzymes in the prostate would also, through a similar mechanism as observed in the trabecular muscles of the penis, lead to a relaxation of the muscles and thus, analogous to the effect of α-receptor blockers, cause an improvement of LUTS associated with clinical BPH.

To this end, two sources can be examined. In a study by Hopps and Mulhall,[25] men presenting to a sexual dysfunction clinic were given both the International Index of Erectile Function (IIEF) and the IPSS questionnaires. Thirty-two men with an IPSS of greater than 10 were enrolled and queried before and 3 months after commencement of therapy with the PDE-5 inhibitor sildenafil citrate. Erectile function was normalized in 75% of subjects; IPSS improved in 62% of subjects, 37% of whom had an improvement of at least 5 points. The investigators found no correlation between improvement in erectile function domains and IPSS score. They concluded that these data indicate a positive impact of sildenafil on men with mild to moderate LUTS, presumably mediated through the relaxation of the prostatic smooth muscle.

In a similar trial conducted by Sairam and colleagues,[26] 112 men attending an ED clinic received sildenafil therapy. One third of the patients had an initial IPSS of greater than 7, that is, moderate to severe LUTS. Ninety-one men (81%) reported improved erections after sildenafil utilized "on demand," that is, before planned sexual intercourse. Interestingly enough, at the 3-month follow-up, the IPSS and LUTS-specific quality-of-life scores also improved. All patients who initially had severe LUTS improved to a moderate disease state, and 60% of those with moderate LUTS converted to mild symptomatology. Differences in IPSS between 3 months and baseline, however, had no correlation with improved erections after therapy. Patients who complained of concomitant LUTS had fewer erections after sildenafil therapy than did those who had no such complaints. These investigators also stipulate that the improvement in LUTS after sildenafil therapy is a result of the smooth muscle relaxant properties of sildenafil via the NO donor mechanism.

Table 3
Selectivity of Sildenafil, Vardenafil, and Tadalafil with Reference to the Various Phosphodiesterase (PDE) Groups

	IC_{50} Value, nmol (x-fold selectivity)		
PDE Group	Sildenafil	Vardenafil	Tadalafil
PDE-1	281 (80)	70 (500)	> 30,000 (> 4450)
PDE-2	> 30,000 (> 8570)	6200 (44,290)	> 100,000 (> 14,800)
PDE-3	16,200 (4630)	> 1000 (> 7140)	> 100,000 (> 14,800)
PDE-4	7680 (2190)	6100 (43,570)	> 100,000 (> 14,800)
PDE-5	3.5 (1)	0.14 (1)	6.7 (1)
PDE-6 (rods)	37 (11)	3.5 (25)	1260 (187)
PDE-6 (cones)	34 (10)	0.6 (4)	1300 (193)
PDE-7A	21,300 (6090)	> 30,000 (> 214,000)	> 100,000 (> 14,800)
PDE-8A	29,800 (8510)	> 30,000 (> 214,000)	> 100,000 (> 14,800)
PDE-9A	2610 (750)	581 (4150)	> 100,000 (> 14,800)
PDE-10A	9800 (2800)	> 3000 (> 21,200)	> 100,000 (> 14,800)
PDE-11A	2730 (780)	162 (1160)	37 (5)

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Although all 3 PDE inhibitors currently available for the treatment of ED exhibit significant inhibition of the PDE-5 isoenzyme—most prevalent in the corpus cavernosum—the selectivity regarding other PDE isoenzymes differs significantly (Table 3).[21] As is evident in Table 3, the PDE inhibitor with the highest selectivity against PDE-11A is tadalafil. This agent shows 5 times greater selectivity with respect to PDE-5 against PDE-11, which indicates a strong inhibition of PDE-11 at clinically utilized doses. Sildenafil and vardenafil have selectivities of 780- and 1160-fold, respectively, with respect to PDE-5. Although no formal study has been conducted to date, the Eli Lilly Australia subsidiary has received several reports of improvement of BPH associated with LUTS in men receiving tadalafil for ED. These data suggest that a formal study of tadalafil—with its relatively greater selectivity against PDE-11—in men with ED and BPH-associated LUTS is indicated.

If, in fact, the smooth muscle relaxant effect of tadalafil were to mimic the efficacy of α-receptor blockers, it would provide the opportunity for a different combination therapy for men with enlarged prostates, BPH, and LUTS—namely, the combination of a 5-α-reductase inhibitor, with its inherent risk of sexually related adverse events, and a PDE inhibitor, with its positive effect on erectile function as well as its smooth muscle relaxing effect on the prostate. ■

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Main Points

- Many patients who present to their healthcare provider with complaints of lower urinary tract symptoms (LUTS) will also have erectile dysfunction (ED), and vice versa. This interrelationship has been substantiated in multiple studies demonstrating not only that patients with benign prostatic hyperplasia (BPH) and associated LUTS have ED but also that the severity of LUTS corresponds with the severity of ED.
- Medical therapies for BPH-associated LUTS are highly effective. Two classes of drugs are available: α-adrenergic receptor blockers and 5-α-reductase inhibitors.
- The discovery of nitric oxide (NO) as one of the major factors in penile smooth muscle relaxation and thus in the mechanism of erection has led to the development of drugs that are able to elevate the intracellular levels of cyclic guanosine monophosphate. Among these agents are NO donors and inhibitors of the phosphodiesterase (PDE) enzymes, such as sildenafil, vardenafil, and tadalafil.
- Preliminary studies have shown that men receiving sildenafil therapy for ED experience an improvement in LUTS, presumably mediated through the relaxation of the prostatic smooth muscle.