UPDATES IN THE MANAGEMENT OF BENIGN PROSTATIC HYPERPLASIA (BPH)*

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LUTS Due to BPH and ED: A Hypothetical Link, Convenient Histological Construct, or Common Biology?

A link between lower urinary tract symptoms (LUTS) due to benign prostatic hyperplasia (BPH) and erectile dysfunction (ED) is common medical knowledge, substantiated not only by patient accounts but by a large body of published evidence. Yet the relative contributions of their underlying causes and intertwined effects, as well as underlying related pathophysiologies, remain only partially understood.

“We know that LUTS and ED coexist, but is it a hypothetical link, a convenient histologic construct, or a common biology?” asked Kevin McVary, MD, Professor of Urology at Northwestern University, in a master lecture on the state of understanding the relationship between LUTS and ED. Dr. McVary, a major contributor to the urology and sexual medicine literature, spoke at the 2012 World Meeting on Sexual Medicine in Chicago, Illinois, last August.

Advancing Age: A Common Factor, But Not a Cause

LUTS and BPH occur typically in men over age 40 and the prevalence increases with age, as does the prevalence of ED. Patients with BPH and LUTS often have ED as well, and both clinical observation and clinical trials show the severity of LUTS and ED correspond. Similar to the manner by which smoking and lung cancer are related—by epidemiologic consistency—so do LUTS and ED appear to be related, Dr. McVary said.

But while age is a prevailing commonality in LUTS and ED, it is likely not causal. Several large studies, while noting the increase in incidence by age, point to more complex underpinnings. In a large, nationwide, community-based study of the relationship between sexual life and urinary symptoms involving over 2,000 French men between 50 and 80 years old, overall urinary symptoms were inversely related to sexual life satisfaction. The association persisted after regression analysis to control for other factors such as age, number of sexual relations, comorbidities, and previous prostate surgeries.

Unsurprisingly, in 2003, the large Multinational Survey of the Aging Male (MSAM-7) provided reinforcing evidence that as men age, the incidence and prevalence of LUTS rises? What was surprising was that the results pointed in another direction. According to Dr. McVary, “When [the investigators] controlled for age, and looked at LUTS severity by decade, it was clear that something much more fundamental was affecting both ED and LUTS” (Fig 1).

The Medical Therapy of Prostatic Symptoms (MTOPS) study, which was started in the mid-1990s, helped to reveal the complex biologic foundations of LUTS and ED. MTOPS was designed to evaluate the long-term effects of alpha-blockers on progression of BPH. In addition to establishing the efficacy and safety of doxazosin and finasteride, and confirming the superiority of combination over single-agent therapy, MTOPS clarified a relationship between prostate volume and lower urinary tract symptoms, “perhaps because of the cohort or very complete clinical phenotyping,” McVary said.

The story remains incomplete. One provocative concept asks whether the negative impact of LUTS on quality of life—poor sleep, reduced physical activity, depressed mood—could contribute to the development of ED as “collateral damage.”

Separate Common Conditions or Biologically Linked?

LUTS and ED may be inextricably bound by shared regulatory and functional pathways among the prostate gland, the bladder, and the penis. Dr. McVary and other urologic experts, but not all, believe that a common pathophysiology underlies LUTS and ED. “This view may be controversial,” he said, “but the complexity of the relationship [between LUTS and ED] is not.”

Of several pathophysiologic hypotheses of the origins of LUTS and ED that have been proposed and defended, some are not mutually exclusive.

• Reduced nitrous oxide (NO) cyclic guanosine monophosphate (cGMP) signaling is plausible, although controversial, as a factor in the development of ED, and may also apply in the LUTS population. As NO synthase decreases, there is upregulation of RhoA/Rho-kinase signaling. In animal models with reduced NO synthase, smooth muscle contraction is followed by evidence of LUTS.

• Autonomic hyperactivity, which is also tightly linked to the metabolic syndrome, mood—could contribute to the development of ED as “collateral damage.”

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Tadalafil Attenuates Cell Growth in Human Prostate Hyperplasia in Human BPH Xenograft Model

Using a novel xenograft model, researchers from Japan transplanted human benign prostatic hyperplasia (BPH) tissue into nude-scid mice, and then treated the animals with oral tadalafil. Following 2 months of tadalafil, or nothing (control), along with sustained-release testosterone pellets, BPH tissues were collected from the mice and a range of immunohistochemical studies were performed. Among the investigators’ findings was that tadalafil attenuated cell growth and induced apoptosis of BPH cells through nitric oxide signaling, confirming results from a number of other studies. These data help to elaborate the therapeutic action of tadalafil in reducing prostate volume in patients with BPH, and extend understanding of the mechanism of action of phosphodiesterase type 5 inhibition, which has not yet been fully explained.8

IN A CONTEST OF ORAL TABLET VERSUS CHEWABLE SILDENAFIL, THE TABLET WINS BY A NONSIGNIFICANT MARGIN

Oral sildenafil in tablet form was preferred over a chewable form of the medication by 54% to 46% of men with mild-to-moderate and severe erectile dysfunction (N=61) who took part in a qualitative and quantitative study to assess patient perceptions of the new chewable formulation (Viagra® Jet). Positive reports from subjects testing the chewable form included a perception of greater efficacy, higher speed of onset, longer duration of therapeutic effect, more prolonged erections, and rapid absorption. Negative perceptions included unpleasant flavor, need to drink water, blue coloration of the tongue, and large tablet size. No difference between the oral and chewable sildenafil forms were found by the International Index of Erectile Function-Erectile Function domain and Erection Hardness Score.8
LUTS due to BPH and ED (continued from front page)

- Pelvic ischemia is now on the forefront as a potential common causality, with evidence supporting it.

No Improvement in Flow Rates?

Along the way to better understanding LUTS and ED, investigators encountered a bump in the road when studies showed flow rates were not changing following treatment with phosphodiesterase type 5 (PDE5) inhibitors or alpha-blocking agents. Dr. McVary and other experts first proposed PDE5 inhibition as a check on a potential temporal relationship between the 2 diseases. “PDE5 inhibitors relax the prostate, detrusor, and cavernous tissue,” Dr. McVary said. “Patients treated with PDE5 inhibitors consistently report improvements in voiding symptoms and irritative symptoms, with responses varying only by the frequency of voiding.” PDE5 inhibitors were effective, to a degree. “In studies with PDE5 inhibitors, the International Prostate Symptom Score changed and patients reported improvement in symptoms, but flow rates did not change,” Dr. McVary said. Sildenafil, tadalafil, and vardenafil each reported improvement in symptoms, but maximum urinary flow rates did not change, Dr. McVary said. “Perhaps the real importance is that these studies open a window onto better understanding of the etiology of LUTS.”

Addressing Patient-Reported Outcomes

One valuable lesson has emerged from trials with PDE5 inhibitors and alpha-blockers for the treatment of LUTS secondary to BPH and ED: Patients place different emphasis on the importance of their symptoms, and patient considerations should be important, not only to clinical care, but also in the design of studies, Dr. McVary said (Fig 3). Accordingly, the National Institute of Diabetes and Digestive and Kidney Diseases, with leadership from Dr. McVary and others, will undertake a prospective trial focusing on patient-reported outcomes (PROs) in early 2013. Measurement of Male Urologic Symptoms will seek to quantify early, late, transient, and persistent symptoms of lower urinary tract symptoms and to develop a measurement tool for PRO as an alternative or supplement to American Urological Association symptom scores. As studies continue to measure the effects of pharmaceutical agents on symptoms and anatomic structures, patient care may thus be improved by identifying and treating symptoms of LUTS and ED that most trouble individual patients.

According to another theory, based on human data, an increase in autonomic tone is associated with a worsening of LUTS. “From our own work, men with lower urinary tract symptoms who were entered into the MTOPS study [and underwent assessment of their autonomic nervous systems] had an increase in sympathetic tone,” Dr. McVary said. Animal models of LUTS also show that along with increases in sympathetic tone, both prostate growth and voiding patterns are altered.

Affix nerve activity is another emerging concept. “We know that NO is active in the urethra of the bladder and that this can be uncoupled, and as it is uncoupled the bladder may create its own ‘pacemaker’ activity and affect sensory enervation of the bladder,” Dr. McVary said. Hence the novel idea that LUTS may actually originate in the spinal cord and not so much in the prostate.
Both tadalafil and tamsulosin significantly improved lower urinary tract symptoms (LUTS) suggestive of benign prostatic hyperplasia (BPH) versus placebo as early as 1 week in a 12-week, international, double-blind, placebo-controlled trial in men with moderate to severe LUTS, some of whom also had erectile dysfunction (ED). Tadalafil alone improved International Prostate Symptom Score (IPSS) quality of life (QoL) Index, global improvement, and treatment satisfaction. Tadalafil, but not tamsulosin, also improved ED.10

Mathias Oelke, PhD, on behalf of a research group from Hannover Medical School, Hannover, Germany, presented the results of this study to the 2012 annual meeting of the American Urological Association (AUA).

Over 500 men 45 years of age and older with moderate-to-severe LUTS/BPH were randomized to once-daily tadalafil 5 mg (n=171), tamsulosin 0.4 mg (n=168), or placebo (n=172) for 12 weeks, following a 4-week placebo run-in. The primary efficacy outcome was IPSS change at 12 weeks or last measurement, using analysis of covariance. Other measures included BPH Impact Index, IPSS QoL index, BPH Treatment Satisfaction Scale (TSS-BPH), Patient and Clinician Global Impression of Improvement scales, International Index of Erectile Function-Erectile Function domain (IIEF-EF), maximum urinary flow rate (Qmax), and treatment emergent adverse events (TEAEs). (The study was not powered to directly compare tadalafil and tamsulosin.)10

Total IPSS was significantly improved versus placebo with both tadalafil (-2.1; P<0.001) and tamsulosin (-1.5; P=0.023) through 12 weeks. Treatment with both agents also resulted in significant improvements in the BPH Impact Index versus placebo at 4 weeks and at endpoint. Qmax increased significantly versus placebo at endpoint with both tadalafil (2.4 mL/s; P=0.009) and tamsulosin (2.2 mL/s; P=0.014) versus placebo, and the incidence of TEAEs was similar between tadalafil (23.4%) and tamsulosin (23.8%), as compared to placebo (20.3%) (Table 1).10

Differences between the 2 agents emerged in secondary measures. The IPSS QoL index and the TSS-BPH both improved significantly with tadalafil versus placebo (both P<0.05) but not with tamsulosin (both P>0.4). IIEF-EF domain improved versus placebo with tadalafil (4.0; P=0.001) but not with tamsulosin (0.4; P=0.699).10

In discussions following the presentation of these data at AUA 2012, and in an exchange of letters to the editor in European Urology, where the study was published in the spring of 2012,11 a question was raised about the choice of a 5-mg daily dose of tadalafil for the study: “As the standard dosage of tadalafil for ED is 10 mg and 20 mg in non-responding cases, it is unclear how the authors explain the significant improvement of ED at a suboptimal dose”.12

Once-daily doses of tadalafil 2.5 mg and 5 mg have both been licensed in the European Union to treat ED since 2007, Dr. Oelke responded, and in the United States since 2008, as well as in other countries around the world. He added that once-daily tadalafil 5 mg provides patients and physicians with a treatment alternative to as-needed therapy with 10 mg or 20 mg tadalafil, and acknowledged that results of this study may prompt further evaluation of lower doses of tadalafil for ED not associated with LUTS or BPH.

Note: Tadalafil 5 mg daily has also been approved in the United States to treat signs and symptoms of BPH since 2011 (CIALIS [package insert], Indianapolis, IN: Eli Lilly; 2010. http://pi.lilly.com/us/cialis-pi.pdf).

Table 1: Results of a 12-week Study of Tadalafil and Tamsulosin

<table>
<thead>
<tr>
<th></th>
<th>PLA</th>
<th>TAD 5 mg</th>
<th>TAM 0.4 mg</th>
<th>P-Value TAD vs PAL</th>
<th>P-Value TAM vs PLA</th>
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<td></td>
<td></td>
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</tr>
<tr>
<td>Endpoint</td>
<td>-4.2 +/- 0.5</td>
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<td>-5.7 +/- 0.5</td>
<td>0.001</td>
<td>0.023</td>
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<td>1-week</td>
<td>-2.5 +/- 0.4</td>
<td>-4.0 +/- 0.4</td>
<td>-4.0 +/- 0.4</td>
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<td>0.005</td>
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<tr>
<td>4-weeks</td>
<td>-3.3 +/- 0.4</td>
<td>-5.5 +/- 0.4</td>
<td>-5.7 +/- 0.4</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
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<td><strong>BII</strong></td>
<td></td>
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<tr>
<td>Endpoint</td>
<td>-0.9 +/- 0.2</td>
<td>-1.7 +/- 0.2</td>
<td>-1.5 +/- 0.2</td>
<td>0.003</td>
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<tr>
<td>4-weeks</td>
<td>-0.4 +/- 0.2</td>
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<td>-1.3 +/- 0.2</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
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<td><strong>IPSS-QoL</strong></td>
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<td>-1.1 +/- 0.1</td>
<td>0.022</td>
<td>0.546</td>
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<td><strong>CGI-I</strong></td>
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<tr>
<td>Better</td>
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<td>–</td>
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<td>19.6%</td>
<td>26.1%</td>
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<td>Worse</td>
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<td>4.3%</td>
<td>5.1%</td>
<td>–</td>
<td>–</td>
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<tr>
<td><strong>PGI-I</strong></td>
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<td>Better</td>
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</tr>
<tr>
<td>Worse</td>
<td>5.0%</td>
<td>4.4%</td>
<td>5.1%</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td><strong>TSS-BPH</strong></td>
<td>28.9</td>
<td>22.2</td>
<td>28.9</td>
<td>0.005</td>
<td>0.457</td>
</tr>
<tr>
<td><strong>IIEF-EF</strong></td>
<td>2.1 +/- 0.8</td>
<td>6.0 +/- 0.8</td>
<td>1.7 +/- 0.8</td>
<td>&lt;0.001</td>
<td>0.699</td>
</tr>
</tbody>
</table>

PLA, placebo; TAD, tadalafil; TAM, tamsulosin; IPSS, International Prostate Symptom Score; QoL, quality of life; BII, BPH Impact Index; CGI-I, Clinician Global Impression of Improvement; PGI-I, Patient Global Impression of Improvement; TSS-BPH, treatment Satisfaction Scale-BPH; IIEF-EF, International Index of Erectile Function-Erectile Function.

T-test compares mean changes from baseline. *-standard error; p-value is from analysis of covariance for treatment difference in LS means. **Percentage of subjects in each response category at endpoint; p-value from Cochran-Mantel-Haenszel test for distribution of response across categories. ^Median score at endpoint, lower scores indicate higher satisfaction; p-value from Van Elteren test comparing medians.

Is the Effect of Tadalafil on LUTS Linked to ED Severity, and Is the Drug’s Effect on ED Related to the Severity of LUTS?

Lower urinary tract symptoms (LUTS) and benign prostatic hyperplasia (BPH) often coexist, but the pathophysiology of LUTS is complex and not completely understood. Phosphodiesterase type 5 (PDE5) inhibitors affect smooth muscle relaxation, smooth muscle and endothelial cell proliferation, nerve activity, and tissue perfusion, all of which may impact LUTS. But these actions and their interactions remain unclear.

In a post hoc, integrated analysis involving over 800 men with a mean age of 63 years and coexisting LUTS/BPH and erectile dysfunction (ED), Hartmut Porst and colleagues from Germany asked whether the severity of ED or LUTS/BPH had an impact on the response to tadalafil. Sexually active men with ED from 3 placebo-controlled trials were included in the analysis. All had total International Prostate Symptom Scores (IPSS) >7 and maximum urinary flow rates (Qmax) of 4 to 5 mL/s. Each trial launched with a 4-week placebo run-in, followed by randomization to 12 weeks of treatment with placebo (n=400) or tadalafil 5 mg once daily (n=415). Changes from baseline to endpoint (12 weeks or last postbaseline observation) were compared to placebo using analysis of covariance.

Baseline characteristics between placebo and tadalafil-treated groups were generally similar, including mean age (63.2 and 62.8 years, respectively), International Index of Erectile Function-Erectile Function (IIEF-EF) score, IPSS, and Qmax. Results indicated that the improvements following treatment with tadalafil 5 mg were independent of BPH/LUTS and ED severity, and vice versa. IPSS improvements in men with mild, moderate, or severe ED at baseline were statistically significant versus placebo (all P<0.005, Fig 4) and comparable across groups.

IIEF-EF improvements in men with mild-moderate or severe LUTS at baseline were significant versus placebo (both P<0.001, Fig 5) and comparable across groups.

Improvements were also significant for both IPSS and IIEF-EF when investigators assessed these parameters in men with baseline prostate-specific antigen (PSA) of < or ≥2 ng/mL (all P<0.01), and were comparable across PSA subgroups.

“The severity of erectile dysfunction has no impact at all on the improvement of the IPSS score and prostate volume as a surrogate for PSA,” Dr. Porst said. When asked whether the IIEF-EF score improved in patients who at baseline had an IIEF-EF greater than 17, Dr. Porst said it did improve. The question was then asked, “How do you know [whether], in the group of men who didn’t complain of erectile dysfunction, or who had minimal erectile dysfunction but their erections got better following treatment, the result was not an artifact of the study design?” Dr. Porst responded that his group had analyzed this in a separate trial and determined that there was no real impact on improvement in IPSS score in patients with or without ED.

“Even if the men who were mildly symptomatic got better erections, I think you could expect that some differences [occurred] among men who were most symptomatic,” one audience member said, stimulating discussion.

The placebo effect is historically an issue with agents that treat ED, a member of the audience commented. Two placebo effects occur: one on voiding, and one on erectile function. How is it possible to tease these two out? “If a group of men claim not to have erectile dysfunction, but on taking a pill, have erections like they are 20 years old, this is almost like an unblinding,” said the audience member. It is known that PDE5 inhibitors cause improvements in men who do not claim to have erectile dysfunction.

Dr. Porst explained that in an earlier study he and colleagues conducted an analysis of the correlation between the changes in the IIEF and changes in the IPSS. The results generated a plot with 2 central lines. The key issue, he said, is whether there is a correlation between the mapping of changes in both dimensions, and the data show that there is not. Thus the take-home message is, those effects are indeed independent. However, he admitted that the placebo effect “is a problem.”

Laser prostatectomy, the BPH Treatment Most Likely to Benefit Elderly, Infirm Patients, Is Not Likeliest Procedure to Be Used

Laser prostatectomy has advantages over transurethral resection of the prostate (TURP) that may be of particular significance to elderly and ill patients, including shorter hospital stay, decreased risk of bleeding, and no transurethral resection syndrome. However, in a large population-based analysis of patient and provider factors associated with choice of benign prostatic hyperplasia (BPH) procedure, elderly, infirm patients were least likely to receive laser prostatectomy even as use of the procedure increased overall in the near-decade analyzed (2001 to 2009).

Florian R. Schroeck, MD, on behalf of colleagues from the University of Michigan, reported these results at the 2012 annual meeting of the American Urological Association from an analysis of all payer data for the state of Florida in that time frame. From this database, the investigators identified patients who had undergone laser prostatectomy or TURP, then calculated surgery rates over time for each procedure. Multilevel models were used to evaluate patient and provider factors associated with choice of laser prostatectomy or TURP (patient age, race, Charlson comorbidity index, surgeon volume of procedures).

Over the 9-year period, the data confirmed a significant increase in use of laser prostatectomy had occurred, from 12 to 53 per 100,000 men (P=0.01), along with a corresponding significant decrease in TURP, from 103 to 58 per 100,000 men (P=0.01). Patients were less likely to undergo laser prostatectomy if they received care from a low- versus high-volume surgeon (odds ratio 0.30, 95% confidence interval 0.29 to 0.31), were older (≥80 years), and were more infirm (Fig 6).

“When we found that…older and sick patients are less likely to receive laser prostatectomy, this raised a concern about underuse in a population that could potentially benefit the most from it,” Dr. Schroeck said. For example, in 2005 an elderly, infirm patient had only a 26% chance of receiving laser prostatectomy compared with a 53% chance for a young, healthy patient. Physician practice style, or perhaps habit, appeared to explain most use of laser prostatectomy. “We thought certain providers may have more older patients or more patients with comorbidities that might explain these results, but what we found is that this effect was independent of patient age or comorbidity composition of a specific physician patient group,” Dr. Schroeck said.

Other studies have not reported similar findings. One audience member noted that a Medicare study had found higher use of laser prostatectomy in the elderly population. Dr. Schroeck responded that for his study, the data set was not limited to the Medicare population, but included all surgeries. Nor was the age of the surgeon relevant to the results, although the results were adjusted for this.
PDE5 Inhibitor Therapy for LUTS Secondary to BPH, With or Without ED: New Evidence from AUA 2012

Several abstracts from the 2012 American Urological Association (AUA) meeting contributed to evidence for the usefulness of (phosphodiesterase type 5) PDE5 inhibitor therapy for lower urinary tract symptoms (LUTS) as well as erectile dysfunction (ED).

- PDE5 inhibitor therapy is effective for LUTS secondary to BPH with or without ED. Combining PDE5 inhibitors with alpha-1-adrenergic blockers improves maximum urinary flow rate (Qmax) as well as International Index of Erectile Function (IIEF) and International Prostate Symptom Score (IPSS) scores. A meta-analysis analyzed all available prospective and cross-sectional studies on use of PDE5 inhibitors alone or in combination with alpha-1-adrenergic blockers in patients with LUTS/BPH. A Medline search using the terms “silidenafil,” “tadalafil,” “vardenafil,” “ udenafil,” “alpha-blockers,” and “alpha-1-adrenergic blockers” resulted in 12 studies meeting the investigators’ criteria for complete data and appropriate methodology. A total of 3,492 patients were included in the analysis. Seven studies (n=3214) compared PDE5 inhibitors to placebo, and five (n=216) compared combination PDE5 inhibitor plus alpha-blocker therapy with alpha-blocker therapy alone. Median follow-up of all randomized controlled trials was 12 weeks.16

When results of all 12 trials were combined, the use of PDE5 inhibitors alone was found to be associated with a significant improvement in the IIEF score (+5.5; \( P < 0.0001 \)) and the IPSS (-2.8; \( P = 0.0001 \)), but not in the Qmax (0; \( P = \text{not significant} \)), compared to placebo. However, the combination of PDE5 inhibitor plus alpha-blocker therapy did significantly improve all of these measures—IEF (+3.6; \( P = 0.0001 \)), IPSS (-1.9; \( P = 0.05 \)), and Qmax (1.5; \( P = 0.0001 \))—when compared to alpha-blocker therapy alone (Fig 7).17

- Men with LUTS/BPH and ED receiving tadalafil 5 mg once daily had significantly improved ejaculatory function and sexual satisfaction versus tamsulosin 0.4 mg and placebo comparators in a 12-week double-blind study with over 500 subjects. When compared to placebo, tadalafil significantly improved the IIEF orgasmic function (OF) domain (0.8; \( P = 0.048 \)) as well as the IIEF-Q9 (proportion of attempts achieving ejaculation) (0.4; \( P = 0.045 \)), but not the IIEF-Q10 (orgasm). Responses to tamsulosin were significantly less than placebo for these domains: OF (-1.1; \( P = 0.006 \)), Q9 (-0.5, \( P = 0.011 \)), and Q10 (-0.6, \( P = 0.009 \)). The percentage of men with improvement in ejaculation was 24% with placebo, 39.8% with tadalafil (P = 0.011 vs placebo), and 18.3% with tamsulosin (P = 0.333 vs placebo). Orgasmic function improved for 26% of men with placebo, 40.8% with tadalafil (P = 0.026 vs placebo), and 19.4% with tamsulosin (P = 0.273 vs placebo).18

- In the combination of tamsulosin and daily tadafalil safe (and effective)? Do PDE5 inhibitors work during storage, emptying, or both? Both questions were evaluated in a randomized, double-blind, placebo-controlled trial conducted between October 2010 and September 2011 by investigators from Brazil. Patients with LUTS associated with ED (N=40), who were evaluated by IPSS and urodynamic studies at baseline and 30 days after treatment, were randomized into 2 groups: treatment with daily tadalafil 5 mg and tamsulosin 0.4 mg (n=20, group 1), or tamsulosin 0.4 mg and placebo (n=20, group 2). Results showed the combination of tamsulosin and tadafalil was more effective on measures of total IPSS and voiding subscore, but no significant between-group differences were seen in domains of filling subscore, quality of life subscore, maximum flow, or detrusor pressure at maximum flow.18

Urodynamic studies indicated that 65%, or 13 patients, receiving the combination of daily tadafalil and tamsulosin, and 40% (8 patients) receiving tamsulosin and placebo had detrusor overactivity (DO). After treatment, DO resolved in 54% and 37% of patients, respectively. With the active combination, no cardiovascular side effects, such as hypotension and dizziness, resulted in discontinuation of treatment.18

- Daily tadafalil was shown to be better than PRN PDE5 inhibitor therapy for return-to-normal erectile function in an assessment by 2 identical, double-blind, randomized, placebo-controlled studies with a total of 590 men, average age 58 years, with ED. Following 1 month of the maximum dose of PDE5 inhibitor treatment and 1 month of no-drug treatment, subjects were randomized to once-daily tadafalil 2.5 mg to 5 mg, tadalafil 5 mg, or placebo for 12 weeks. When results of the 2 studies were combined, investigators found a significantly higher percentage of men treated with tadafalil 2.5 mg to 5 mg (39%) and tadalafil 5 mg (40%) had IIEF-ED domain scores at or above 26 at endpoint, compared to placebo (12%; both \( P < 0.001 \)). Both tadafalil groups also had 8-point improvements from baseline in IIEF-ED domain scores versus a 2-point improvement for placebo (\( P < 0.001 \)). Tadalafil was generally well-tolerated and consistent with other reports of tolerability with the once-daily form.18

## Figure 7: Results of meta-analysis on the use of PDE5 inhibitors alone or in combination with alpha-blockers in patients with LUTS/BPH.

<table>
<thead>
<tr>
<th>treatments</th>
<th>studies</th>
<th>ΔIIEF, P&lt;0.001</th>
<th>ΔIPSS, P&lt;0.001</th>
<th>ΔQmax, not significant</th>
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<tr>
<td>PDE5 inhibitors</td>
<td>7 RCTs</td>
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<tr>
<td>PDE5 inhibitors + α-blockers</td>
<td>5 RCTs</td>
<td>+3.6</td>
<td>-1.8</td>
<td>+1.5</td>
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## Figure 8: Results of meta-analysis on the use of PDE5 inhibitors alone or in combination with α-blockers in patients with LUTS/BPH.

<table>
<thead>
<tr>
<th>treatments</th>
<th>studies</th>
<th>ΔIIEF, P&lt;0.001</th>
<th>ΔIPSS, P&lt;0.001</th>
<th>ΔQmax, not significant</th>
</tr>
</thead>
<tbody>
<tr>
<td>α-blockers</td>
<td>10 RCTs</td>
<td>-2.8</td>
<td>-1.9</td>
<td>0.0</td>
</tr>
<tr>
<td>PDE5 inhibitors + α-blockers</td>
<td>10 RCTs</td>
<td>+5.5</td>
<td>-2.8</td>
<td>0.0</td>
</tr>
</tbody>
</table>

## Figure 10: Results from autopsy studies reported from 1941 to 1991 show a striking worldwide similarity in increases of BPH by decade.

<table>
<thead>
<tr>
<th>Location</th>
<th>Year</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Holland</td>
<td>1989</td>
<td>5.0%</td>
</tr>
<tr>
<td>Vancouver</td>
<td>1972</td>
<td>4.0%</td>
</tr>
<tr>
<td>Spain</td>
<td>1944</td>
<td>4.0%</td>
</tr>
<tr>
<td>France</td>
<td>1954</td>
<td>4.0%</td>
</tr>
<tr>
<td>China</td>
<td>1960</td>
<td>4.0%</td>
</tr>
<tr>
<td>Brazil</td>
<td>1975</td>
<td>4.0%</td>
</tr>
<tr>
<td>France</td>
<td>1981</td>
<td>4.0%</td>
</tr>
</tbody>
</table>

FINASTERIDE LABEL CHANGES

In April 2012, the US Food and Drug Administration (FDA) announced changes to the labeling for finasteride 1 mg (Propecia®) and finasteride 5 mg (Proscar®). These changes were based on a history of reported sexual adverse events concurrent with the drugs’ use, and some reports of adverse events persisting after discontinuation (see box below). An analysis of controlled clinical trials revealed that following treatment with Propecia, 3.8% of men reported 1 or more adverse sexual experiences versus 2.1% of men who were randomized to placebo in the trials. The FDA reviewed 421 postmarketing reports of sexual dysfunction related to the use of Propecia. Of these, 59 instances of reported sexual dysfunction continued for at least 3 months after discontinuation of the drug. The sexual adverse events included erectile dysfunction (ED), decreased libido, problems with ejaculation, and orgasm disorders.

With Proscar, the FDA reviewed reports of 131 cases of ED and 68 cases of decreased libido. When information about duration of these adverse events was included in the reports (sometimes it was not), it appeared the events continued for at least several weeks after drug discontinuation.

In a discussion at the 2012 World Meeting on Sexual Medicine, Francois Giuliano, MD, PhD, from France, and Arthur (Bud) Burnett, MD, MBA, of Johns Hopkins University, discussed the quality of evidence (pro and con) for underreporting of sexual adverse events, and ways in which adverse event reporting may be improved in preapproval clinical studies and in post-marketing surveillance.

“You get what you ask for,” Dr. Giuliano said, referring to the fallibility of adverse event reporting that is based on subjective patient referrals, or students—of clinical trial personnel. Physicians, nurses or other healthcare professionals, or students—may well be taking other medications that are themselves associated with sexual side effects.

The issue of sexual side effects with finasteride, especially in post-marketing surveillance, was raised by James Saunders, MD, in a similar uncertainty is revealed by results from the CombAT (Combination of Avodart and Tamsulosin) study, a 4-year randomized, double-blind, parallel-group trial in almost 5,000 men age 50 years and over with moderate to severe benign prostatic hyperplasia, suggested that the occurrence of irreversible adverse events related to treatment remains unclear.12 Some clinical trial evidence suggests that reports of sexual adverse events diminish with time, while other limited data indicate that sexual side effects may persist despite discontinuation of the finasteride.13 There are clear criteria for causality, the speakers agreed, and satisfying these criteria represents a tall hurdle.

Apart from this specific issue, both speakers also agreed there is a vital need to improve the system of adverse event reporting, documentation, and coding.

REFERENCES & FURTHER READING