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A review of the use of tadalafil in the treatment of benign prostatic hyperplasia in men with and without erectile dysfunction

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***Abstract*:** Epidemiological data link erectile dysfunction (ED) and benign prostatic hyperplasia (BPH)-associated lower urinary tract symptoms (LUTS), two highly prevalent conditions in aging men, assuming common pathophysiological pathways. Tadalafil 5 mg once daily has been approved for the treatment of men with LUTS with or without comorbid ED. The aim of this review is to provide an overview of current knowledge on the epidemiological and pathophysiological links between ED and LUTS and to focus on tadalafil as a new treatment option in men with BPH-associated LUTS.

A Medline search was completed using the Medical Subject Headings (MESH® keywords) 'prostatic hyperplasia' and 'phosphodiesterase inhibitors'. This search revealed 125 relevant references (entire Medline database up to 11 March 2014). The efficacy of tadalafil 5 mg once daily for the treatment of LUTS has been reported by several well-designed studies. Tadalafil improves significantly the total International Prostate Symptom Score (IPSS), the voiding and storage subscores, the IPSS Quality of Life (QoL) and the BPH Impact Index (BII). Its efficacy is irrelevant to the erectile function status of the patients. However, in the majority of these studies tadalafil is not associated with improvement in maximum urine flow or post-void residual volume (PVR). Its safety profile is well established and no new or unexpected adverse events other than those reported in ED studies have been recorded. Tadalafil is today a new treatment alternative to other established drugs for LUTS such as the α-adrenergic antagonists or 5α-reductase inhibitors. However, it is not just an alternative, since sexual adverse events associated with these drugs are avoided and tadalafil is the only drug that can treat both ED and LUTS at the same time.

Keywords: erectile dysfunction, lower urinary tract symptoms, phosphodiesterase inhibitors, prostatic hyperplasia

Introduction

Erectile dysfunction (ED) and lower urinary tract symptoms (LUTS) are highly prevalent conditions associated with a significant negative impact on patients' quality of life [Rosen *et al.* 2003, Robertson *et al.* 2007]. For a long time, ED and LUTS were considered to be two distinct clinical entities with an increasing prevalence in aging men despite the fact that almost all treatment modalities for benign prostatic hyperplasia (BPH)-associated LUTS have some negative impact on patients' sexual function [Gacci *et al.* 2011]. This common belief has been rejected by several epidemiological studies showing a strong relationship between them and that they share several comorbidities and lifestyle factors [Rosen *et al.* 2005; Roehrborn *et al.* 2007]. While it is not clear how they are associated, there are emerging data supporting common pathophysiological mechanisms [McVary, 2005].

Phosphodiesterase type 5 inhibitors (PDE5i) are the current first-line treatment option for the majority of men with ED due to their excellent efficacy and safety profile [Hatzimouratidis *et al.* 2010]. Early clinical research showed that all PDE5i are also beneficial for the treatment of LUTS [McVary *et al.* 2007a, 2007b; Stief *et al.*

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2008]. However, only tadalafil 5 mg once daily has been approved for the treatment of BPH-associated LUTS in men with or without ED. These new data provided new treatment options in the urologic armamentarium but also further promoted clinical research aiming to better understand the pathophysiology of LUTS.

The aim of this review is to provide an update on the current knowledge on the rationale for the use of tadalafil for the treatment of BPH-associated LUTS, and its efficacy and safety. A Medline (http://www.ncbi.nlm.nih.gov) search was completed using the Medical Subject Headings (MESH® keywords) 'prostatic hyperplasia' and 'phosphodiesterase inhibitors' in the English language only. This search revealed 125 relevant references (entire Medline database up to 11 March 2014).

The rationale for the use of tadalafil in the treatment of BPH-associated LUTS

Epidemiological data on the association of ED and LUTS

Several epidemiological studies have reported a strong correlation between ED and LUTS. The National Health and Social Life Survey (NHSLS) [Laumann *et al.* 1999] demonstrated an increasing prevalence of ED in men with age, ranging from 7% to 18%. In the Cologne Male Survey [Braun *et al.* 2000, 2003] the overall prevalence of ED was 19.2%. The EDEM study [Martin-Morales *et al.* 2001] reported an ED prevalence rate of 12.1%. The Krimpen study [Blanker *et al.* 2001a, 2001b] showed that the overall prevalence of significant (severe) ED was 11%. The UrEpik study [Boyle *et al.* 2003] reported that the overall prevalence of ED was 21%. The Cross National Study on the Epidemiology of ED and its Correlates [Nicolosi *et al.* 2003a, 2003b] reported an overall prevalence of moderate or complete ED of 16%. The Multinational Survey of the Aging Male (MSAM-7) [Rosen *et al.* 2003] reported an overall prevalence of ED (difficulty achieving an erection) of 48.7% with 10% of men reporting complete absence of erections. In a population-based study in Denmark, the prevalence of ED was 28.8% while the prevalence of LUTS was 39.1% [Hansen, 2004]. Finally, in the Boston Area Community Health (BACH) study [Brookes *et al.* 2008] the overall prevalence of ED was 47% (less than 10% reported moderate or severe dysfunction) while the overall prevalence of LUTS was 81% (only 19% reported moderate or severe symptoms). In all of these studies LUTS were a significant risk factor for ED, but in the majority of them, LUTS were also an independent risk factor [Blanker *et al.* 2001; Braun *et al.* 2003; Nicolosi *et al.* 2003a; Rosen *et al.* 2003; Hansen, 2004]

These studies can be criticized due their cross-sectional design which cannot address the temporal relationship between LUTS and ED. Therefore, it is not possible to establish a definite causal association between LUTS and ED. There are only two longitudinal, prospective studies assessing the causal relationship between LUTS and ED. Shiri and colleagues [Shiri *et al.* 2005b], in a population-based study in Tampere (Finland), reported that the 5-year incidence of ED was greater in men reporting LUTS at baseline. Compared with men with no LUTS (IPSS: 0), the incidence of ED was 2.7 times higher among men with IPSS 7–11, and 3.1 times higher in men with IPSS 12 or more. Men with mild bother scores were at higher risk of ED than those with mild symptoms scores [Shiri *et al.* 2005a] while the incidence of LUTS was higher in men with moderate or severe ED than in those free of ED at baseline [Shiri *et al.* 2007]. In the Health Professionals Follow-Up Study (HPFS) [Mondul *et al.* 2008], men with severe LUTS in 1994 or earlier had a statistically significant 40% higher risk of ED subsequently compared with men without LUTS when assessed in year 2000. The risk of ED increased with increasing LUTS severity and the positive association between LUTS and ED was stronger in younger than in older men.

Common pathophysiological pathways

While the common pathophysiological pathways between ED and LUTS are not clear, four theories have been described and reviewed in the literature [McVary, 2005; Ponholzer and Madersbacher, 2007; Kohler and McVary, 2009; Gacci *et al.* 2011]. The first hypothesis includes impaired nitric oxidase synthase (NOS) in the endothelium of the pelvis including the prostate, bladder and penis. The second hypothesis is based on increased Rho-kinase activation resulting in decreased smooth muscle relaxation with consecutive increased bladder outlet resistance and impaired erection. The third hypothesis is based on the autonomic hyperactivity and metabolic syndrome effects on LUTS, prostate growth and ED. Finally, the fourth hypothesis illustrates

atherosclerosis as a common mechanism for LUTS and ED. These theories are compatible and may overlap substantially [Kohler and McVary, 2009]. The theories of impaired NOS and reduced NO levels, increased Rho-kinase activation and atherosclerosis and pelvic ischemia are linked by common vascular risk factors. Atherosclerosis may reduce NO levels and Rho-kinase activation and may result in loss of smooth muscle from the bladder detrusor and prostate fibrosis associated with loss of bladder compliance and increased urethral resistance, respectively.

What is the evidence on tadalafil based on these four theories? The upregulation of the NO/cGMP activity is probably the most important. Preclinical studies reported partial reversal of norepinephrine- and endothelin-1-reduced prostatic tissue contraction [Kedia *et al.* 2009] and an antiproliferative effect on cultured prostate and bladder smooth muscle cells [Filippi *et al.* 2007]. These mechanisms may decrease smooth muscle tension in the prostatic stroma and capsule and attenuate cellular proliferation associated with prostate/bladder hypertrophy, respectively. An assessment of the activity of PDE5i on endothelin-1-induced contraction of human prostatic tissue (mediated by ROCK pathway) showed that tadalafil had greater activity when compared with sildenafil or vardenafil and among PDE5i, only tadalafil achieved >50% relaxation of the precontracted strips [Kedia *et al.* 2009]. Evidence on the efficacy of tadalafil in the modulation of autonomic nervous system overactivity and afferent nerve activity is very limited. PDE5i cause an inhibitory effect of NO on ion channels in afferent neurons and on afferent nerve activity in the bladder. Calcium channels in bladder afferent neurons are inhibited by NO [Yoshimura *et al.* 2001]. Moreover, vardenafil reduces nonvoiding contractions associated with bladder afferent nerve firing [Behr-Roussel *et al.* 2011]. Tadalafil inhibits *in vitro* PDE5 activity, prominently expressed in the human vesicular-deferential arteries and increases prostate tissue oxygenation in spontaneously hypertensive rats [Morelli *et al.* 2011]. Moreover, tadalafil increased prostatic blood perfusion in a preliminary evaluation of men using contrast-enhanced ultrasound [Bertolotto *et al.* 2009]. Finally, tadalafil attenuates the expression of various inflammatory markers (tumor necrosis factor [TNF]-α, interleukin [IL]-1β and IL-8) and therefore may reduce atherosclerotic damage and overall inflammation by reducing leukocyte recruitment [Roumeguere *et al.* 2010]. Tadalafil's proposed mechanism of action based on current data is presented in Figure 1 [Andersson *et al.* 2011].

Clinical data on the efficacy and safety of tadalafil in men with BPH-associated LUTS

Efficacy data of PDE5i in the treatment of LUTS

McVary and colleagues [McVary *et al.* 2007b] reported on the first double-blind, placebo-controlled trial with tadalafil in men with both ED and LUTS. A total of 281 men were randomized in a 1:1 ratio to receive 5 mg of tadalafil daily (138 men, mean age: 61 years) followed by dose escalation to 20 mg for 6 weeks or 12 weeks of placebo (143 men, mean age: 62 years). Tadalafil significantly improved the mean change from baseline in IPSS at 6 weeks (5 mg tadalafil −2.8 *versus* placebo -1.2) and at 12 weeks (5/20 mg tadalafil −3.8 *versus* placebo −1.7). Larger changes were observed with inclusion of the placebo run-in at 12 weeks (5/20 mg tadalafil −7.1 *versus* placebo −4.5). Mean irritative and obstructive IPSS subscores, the IPSS QoL index, a question about urinary symptom improvement and the BPH Impact Index (BII) significantly improved *versus* placebo. IPSS and International Index of Erectile Function (IIEF) scores significantly improved in the 56% of men with LUTS who were sexually active and had ED. No differences in uroflowmetry parameters were recorded in the placebo and tadalafil groups. Moreover, no change in PVR was recorded in the tadalafil group.

Roehrborn and colleagues [Roehrborn *et al.* 2008] reported data from a dose finding study with tadalafil in men with ED and LUTS. A total of 1058 patients were included in a randomized, double-blind, placebo-controlled, parallel design, 12-week study (211 in the placebo group, 208 in the tadalafil 2.5 mg daily group, 212 in the tadalafil 5 mg daily group, 216 in the tadalafil 10 mg daily group and 209 in the tadalafil 20 mg daily group). The IPSS least-squares mean change from baseline to end point was significantly improved for 2.5 (−3.9, $p = 0.015$), 5 (−4.9, $p < 0.001$), 10 (−5.2, $p < 0.001$) and 20 mg (−5.2, $p < 0.001$) tadalafil compared with placebo (−2.3). IPSS improvements at 4, 8 and 12 weeks were significant for all tadalafil doses and they demonstrated a dose–response relationship. Tadalafil (2.5 mg) significantly improved the IPSS obstructive subscore and the IIEF erectile function domain, the latter in sexually active men with a history of ED. Statistically significant

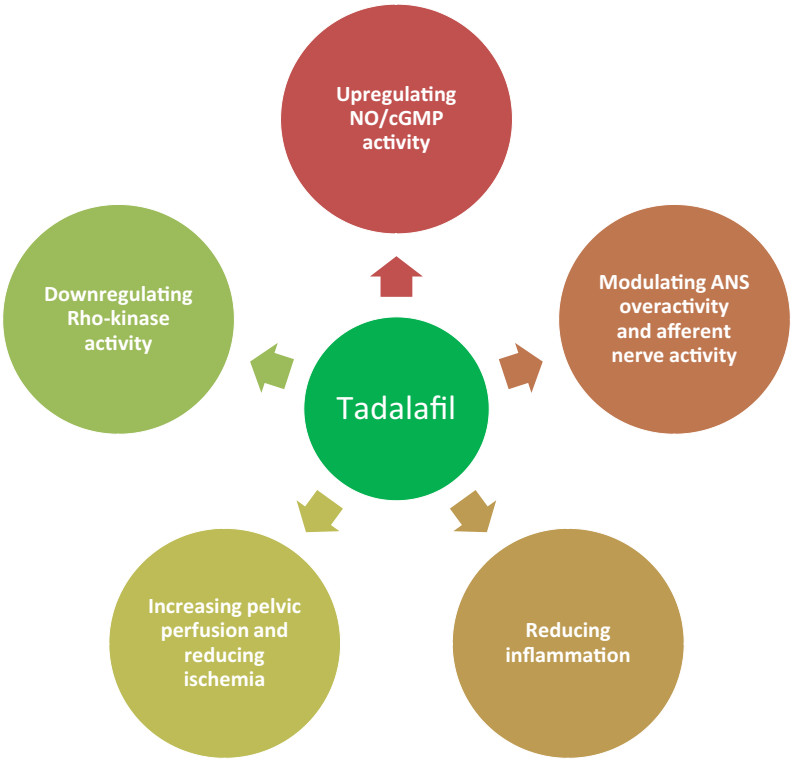

Figure 1. Mechanisms by which tadalafil may reduce benign prostatic hyperplasia (BPH)-associated lower urinary tract symptoms.

improvements were noted for 5, 10 and 20 mg tadalafil compared with placebo, as assessed by the IPSS irritative and obstructive subscores, IPSS QoL, BII (nonsignificant for 10 mg), Global Assessment Question and IIEF erectile function domain. No statistically significant effect of treatment compared with placebo was noted for peak flow at any tadalafil dose. Furthermore, no clinically relevant changes were noted in PVR or prostate-specific antigen (PSA) values. In this study, tadalafil 5 mg appeared to provide a positive risk–benefit profile and it is the only dose approved for this indication.

Porst and colleagues [Porst *et al.* 2009] reported on the efficacy of tadalafil in a subset of patients included in the previous study with ED. Overall, 581 men were included (115 in the placebo group, 113 in the tadalafil 2.5 mg group, 117 in the tadalafil 5 mg group, 120 in the tadalafil 10 mg group and 116 in the tadalafil 20 mg group). IPSS improvements from baseline to end point with tadalafil were −3.6 (2.5 mg), –4.2 (5 mg), –4.7 (10 mg) and −4.7 (20 mg) *versus* –2.1 with placebo (all p values < 0.05). Similarly, the changes in peak urinary flow (Q_{max}) and PVR were small and not clinically meaningful. Therefore, the efficacy of tadalafil in the treatment of BPH-associated LUTS is similar in men with or without ED. In this context, Broderick and colleagues [Broderick *et al.* 2010] reported on another paper again based on the same database of patients that changes in BPH–LUTS after 12 weeks of treatment with placebo or various doses of once-daily tadalafil were similar in men with or without comorbid ED. After 12 weeks, changes in IPSS in men with ED (change from baseline, placebo −2.4; tadalafil 2.5, 5, 10, 20 mg −4.3, –4.8, –5.3, –5.6) and without ED (–2.4, –3.2, –5.3, –5.1, –4.5) were not significantly different (subgroup/interaction p values: 0.352/0.644). Similar effects were observed for IPSS QoL (with ED: –0.6, –0.9, –0.9, –1.0, –1.1; without ED: –0.6, –0.7, –0.9, –0.8, –0.8; 0.090/0.773) and BII (with ED: –0.7, –0.9, –1.3, –1.3, –1.4; without ED: –1.0, –0.7, –1.3, –1.3, –1.2; 0.753/0.852).

Porst and colleagues [Porst *et al.* 2011] reported also on the efficacy of tadalafil 5 mg *versus* placebo in a randomized, double-blind, placebo-controlled, 12-week study including 325 men with BPH-associated LUTS. Tadalafil 5 mg significantly improved IPSS *versus* placebo (–5.6

versus –3.6; $p = 0.004$) and this improvement was apparent after 1 week and significant after 4 weeks (–5.3 *versus* –3.5; $p = 0.003$). The BII improvement was apparent at 4 weeks (–1.8 *versus* –1.2; $p = 0.029$) and continued at 12 weeks (–1.8 *versus* –1.3; $p = 0.057$). Tadalafil 5 mg significantly improved the IIEF erectile function domain score in sexually active men with ED (6.7 *versus* 2.0; $p < 0.001$) at 12 weeks. Finally, tadalafil 5 mg did not significantly improve Q_{max} or PVR.

Egerdie and colleagues [Egerdie *et al.* 2012] assessed the effects of tadalafil 2.5 or 5 mg once daily on ED and BPH-associated LUTS in 606 men with both conditions in a multinational, double-blind, placebo-controlled study. Tadalafil 2.5 and 5 mg significantly improved IIEF erectile function domain scores *versus* placebo (both $p < 0.001$). However, IPSS improvements were significant with tadalafil 5 mg ($p < 0.001$), but not 2.5 mg (mean change −3.8 ± 0.5 for placebo, –4.6 ± 0.4 for tadalafil 2.5 mg, and 6.1 ± 0.4 for tadalafil 5 mg). Tadalafil 5 mg also significantly improved BII ($p < 0.001$). This study also supported tadalafil 5 mg as the selected dose for BPH-associated LUTS.

Recently, three papers provided analysis of pooled data from four randomized, double-blind, placebo-controlled, 12-week, parallel-design, multinational LUTS/BPH studies assessing the efficacy and safety of tadalafil once-daily for LUTS/BPH [Roehrborn *et al.* 2008; Porst *et al.* 2011; Oelke *et al.* 2012] or LUTS/BPH and ED [Egerdie *et al.* 2012].

Porst and colleagues [Porst *et al.* 2013b] reported that tadalafil significantly improved total IPSS *versus* placebo (mean changes −6.0 and −3.6, respectively; $p < 0.001$). Improvements in the IPSS storage and voiding subscores, IPSS QoL, BII and the IIEF erectile function domain score were also significant *versus* placebo (all $p < 0.001$). Nonsignificant impact of baseline ED severity or PSA category on IPSS response was observed (interaction p values, 0.463 and 0.149, respectively) while the IIEF erectile function domain score was not significantly impacted by baseline LUTS/BPH severity or PSA category (interaction p values, 0.926 and 0.230, respectively). Finally, improvements in IPSS and IIEF scores during treatment were weakly correlated ($r = –0.229$).

Porst and colleagues [Porst *et al.* 2013a] also presented subgroup analyses demonstrating that IPSS improvements were significant regardless of baseline LUTS severity (IPSS <20/≥20), age (≤65/>65 years), recent previous use of α-adrenergic antagonists or PDE5i, total testosterone level (<300/≥300 ng/dl) or PSA predicted prostate volume (≤40/>40 ml). The rates of treatment emergent adverse events were comparable between all subgroups but were somewhat higher in patients with recent previous α-adrenergic antagonists use.

Finally, Brock and colleagues [Brock *et al.* 2013] reported that tadalafil significantly reduced BPH-associated LUTS compared with placebo in men without ED (IPSS −5.4 *versus* −3.3, $p < 0.01$; IPSS voiding subscore −3.5 *versus* −2.0, $p < 0.01$; IPSS storage subscore −1.9 *versus* −1.3, $p < 0.05$). Tadalafil also significantly improved QoL (IPSS QoL −1.0 *versus* −0.7; BII −1.4 *versus* −1.0; both $p < 0.05$).

Based on these analyses of the pooled data the improvements of tadalafil in IPSS, IPSS storage and voiding subscores, BII and IPSS QoL in all patients and in patients stratified by their erectile function status are presented in Figures 2, 3, 4, 5 and 6, respectively [Brock *et al.* 2013; Porst *et al.* 2013b].

Finally, Brock and colleagues [Brock *et al.* 2014] using unidirectional and bidirectional path analysis models reported that tadalafil 5mg once daily directly improved urinary tract symptoms secondary to BPH regardless of underlying ED. Therefore, tadalafil's effect is not due to indirect effects including psychological benefits of improved erectile function in men with both conditions.

Analysis and interpretation of the urodynamic data

Despite the fact that all placebo-controlled trials showed clearly a positive effect on LUTS including both obstructive and irritative scores and QoL scores, none of these studies shows any efficacy in terms of uroflowmetry parameters (Q_{max}) or PVR. These parameters are considered an important outcome measure in clinical trials, assessing the impact of drugs on LUTS including α-adrenergic receptor antagonists and 5α-reductase inhibitors.

Following the dose-finding study, Roehrborn and colleagues [Roehrborn *et al.* 2010], provided a *post hoc* analysis on the effects of tadalafil on Q_{max}, bladder capacity (voided urine plus PVR) and

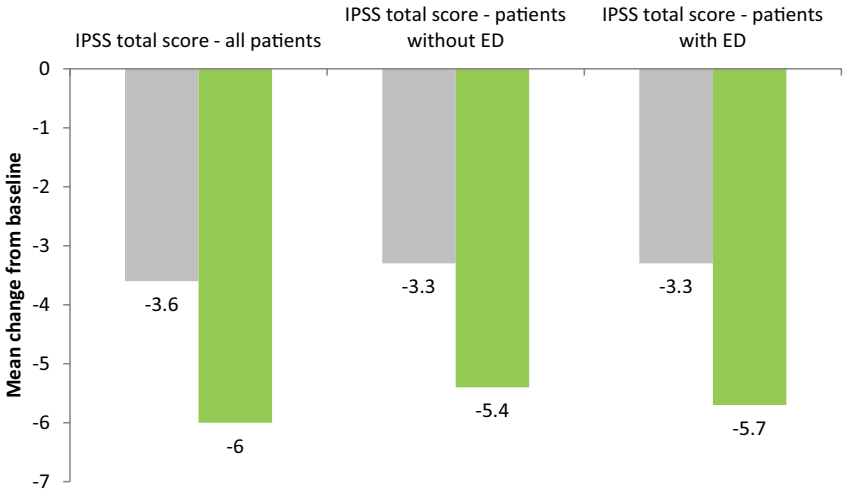

Figure 2. Improvement in International Prostate Symptom Score (IPSS) in all patients treated with tadalafil 5 mg *versus* placebo ($p < 0.001$), in patients without erectile dysfunction (ED; $p < 0.05$) and in patients with ED ($p < 0.001$). Improvement was similar between men without ED and with ED (p value for treatment-by-ED-status interaction was insignificant for total IPSS, $p = 0.73$). Data from Brock *et al.* [2013] and Porst *et al.* [2013b].

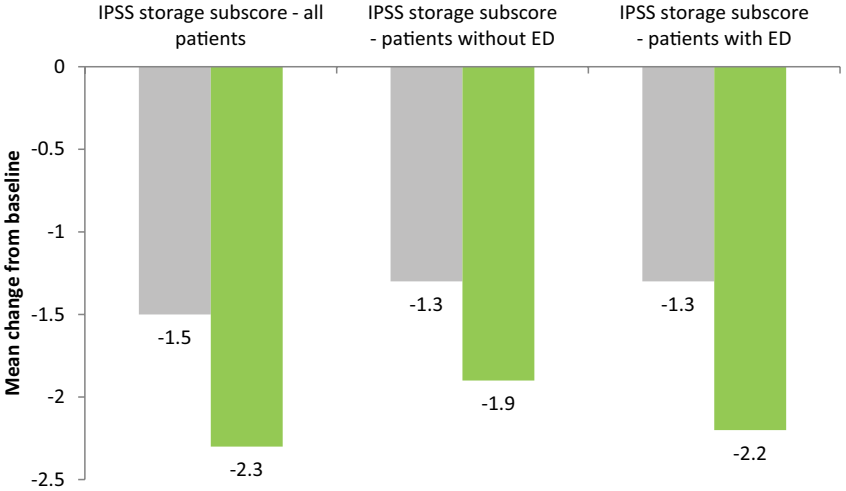

Figure 3. Improvement in International Prostate Symptom Score (IPSS) storage subscore in all patients treated with tadalafil 5 mg *versus* placebo ($p < 0.001$), in patients without erectile dysfunction (ED; $p < 0.05$) and in patients with ED ($p < 0.001$). Improvement was similar between men without ED and with ED (p value for treatment-by-ED-status interaction was insignificant for IPSS storage subscore, $p = 0.78$). Data from Brock *et al.* [2013] and Porst *et al.* [2013b].

voiding efficiency (voided urine/bladder capacity). None of these parameters improved statistically significant. Tadalafil had its greatest effects on bladder capacity and voiding efficiency in men with a Q_{max} of <10 ml/s at baseline, but these changes were not significantly different from placebo responses.

Dmochowski and colleagues [Dmochowski *et al.* 2010] presented data from a 12-week, multicenter, randomized, double-blind, placebo-controlled clinical trial comparing tadalafil 20 mg once daily *versus* placebo in men with BPH-associated LUTS. Invasive and noninvasive urodynamics were done in order to identify the possible effect of tadalafil at its maximal dose in the lower urinary tract system. Urodynamic measures remained largely unchanged during the study with no statistically significant or clinically adverse difference between tadalafil and placebo in change in detrusor pressure at maximum urinary flow rate (mean difference between treatments −2.2 cm H_2O, $p = 0.33$) or any other

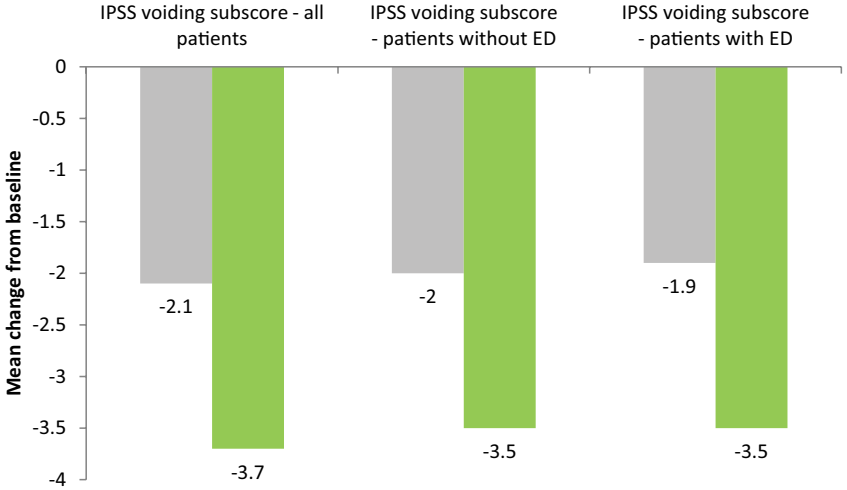

Figure 4. Improvement in International Prostate Symptom Score (IPSS) voiding subscore in all patients treated with tadalafil 5 mg *versus* placebo ($p < 0.001$), in patients without erectile dysfunction (ED; $p < 0.05$) and in patients with ED ($p < 0.001$). Improvement was similar between men without ED and with ED (p value for treatment-by-ED-status interaction was insignificant for IPSS voiding subscore, $p = 0.69$). Data from Brock *et al.* [2013] and Porst *et al.* [2013b].

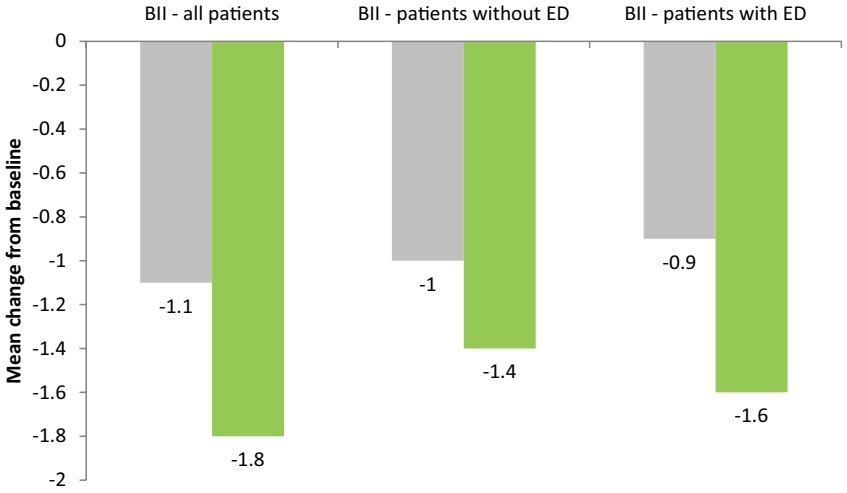

Figure 5. Improvement in Benign Prostatic Hyperplasia Impact Index (BII) in all patients treated with tadalafil 5 mg *versus* placebo ($p < 0.001$), in patients without erectile dysfunction (ED; $p < 0.05$) and in patients with ED ($p < 0.001$). Improvement was similar between men without ED and with ED (p value for treatment-by-ED-status interaction was insignificant for BII, $p = 0.81$). Data from Brock *et al.* [2013] and Porst *et al.* [2013b].

urodynamic parameter assessed including maximum urinary flow rate, maximum detrusor pressure, bladder outlet obstruction index or bladder capacity (all measures $p \geq 0.13$) despite the fact that tadalafil significantly improved IPSS.

A recent meta-analysis [Dong *et al.* 2013] reported that after pooling four doses (2.5, 5, 10 and 20 mg), tadalafil failed to produce a significant outcome in Q_{max} although it was improved (mean difference = +0.26 ml/s, $p = 0.14$), but 5 mg of tadalafil significantly improved Q_{max} (mean difference = +0.63 ml/s, $p = 0.04$).

Is there any explanation for these findings? The answer is currently no. McVary commented that it might be a potential new basic pathophysiology paradigm in which the impact of PDE5 activity on LUTS symptoms may reveal an alternate explanation for the etiology of LUTS not involving relaxation of prostatic smooth muscle but bladder compliance changes, improvement in

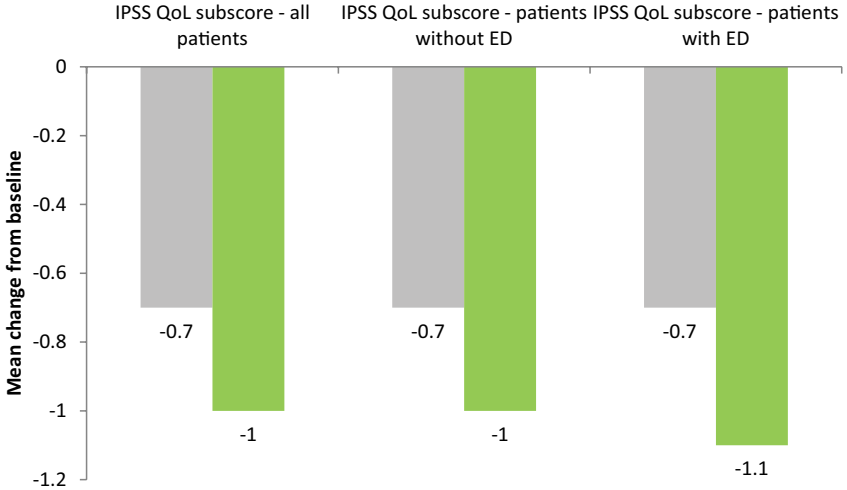

Figure 6. Improvement in International Prostate Symptom Score (IPSS) quality of life (QoL) subscore in all patients treated with tadalafil 5 mg *versus* placebo ($p < 0.001$), in patients without erectile dysfunction (ED; $p < 0.05$) and in patients with ED ($p < 0.001$). Improvement was similar between men without ED and with ED (p value for treatment-by-ED-status interaction was insignificant for IPSS QoL, $p = 0.89$). Data from Brock *et al.* [2013] and Porst *et al.* [2013b].

bladder wall perfusion or central nervous system impact [McVary, 2006]. While the answer to this question is of the highest importance in understanding the mechanisms of LUTS and the effect of new treatments, its importance from a clinical point of view may be less significant since symptom alleviation is the primary treatment target in the majority of patients.

Long-term efficacy of tadalafil

While the efficacy of tadalafil was established from placebo-controlled studies, it is unknown whether this positive effect is maintained through time. This is important to know since LUTS are a chronic condition and treatments must be efficacious also in the long-term. In this context, Donatucci and colleagues [Donatucci *et al.* 2011] reported on the long-term efficacy of tadalafil. A total of 427 men who completed the 12-week, placebo-controlled, dose-finding study assessing once-daily tadalafil (2.5, 5, 10 or 20 mg) or placebo elected to continue into the open-label extension period using tadalafil 5 mg. Changes in the total IPSS, IPSS irritative and obstructive subscores, IPSS health-related QoL and BII were maintained after 1 year and were similar despite the tadalafil dose administered during the double-blind study. During the open-label extension period, mean PSA increased from 1.6 ± 1.3 to 1.8 ± 1.4 ng/ml. Mean PVR was 61.1 ± 60.4 ml at study entry and 42.2 ± 64.1 ml after the open-label extension period. Therefore, it can be concluded that the efficacy of tadalafil is maintained for at least 1 year.

Comparative data on the efficacy of tadalafil and tamsulosin

Another important question that rises up is the efficacy of tadalafil compared with an established treatment for BPH-associated LUTS such as an α-adrenergic antagonist. In this context, Oelke and colleagues [Oelke *et al.* 2012], reported on a randomized, double-blind, international, placebo-controlled, parallel-group study including tamsulosin as an active control. A total of 511 men with BPH/LUTS were randomized to placebo ($n = 172$), tadalafil 5 mg ($n = 171$) or tamsulosin 0.4 mg ($n = 168$) once daily for 12 weeks following a 4-week run-in period. This study was not designed for statistical testing of noninferiority or superiority between tadalafil and tamsulosin but it was adequately powered for the comparison of each active treatment with placebo. IPSS scores significantly improved *versus* placebo with tadalafil (–2.1; $p = 0.001$) and tamsulosin (–1.5; $p = 0.023$). This improvement was evident as early as 1 week (tadalafil and tamsulosin both −1.5; $p < 0.01$). BII significantly improved *versus* placebo (tadalafil −0.8, $p = 0.003$; tamsulosin −0.6, $p = 0.026$). The IPSS QoL index and the Treatment Satisfaction Scale-BPH improved significantly *versus* placebo with

tadalafil (both $p < 0.05$) but not with tamsulosin (both $p > 0.1$). Surprisingly, given the data from previously published studies, Q_{max} increased significantly *versus* placebo with both tadalafil (2.4 ml/s; $p = 0.009$) and tamsulosin (2.2 ml/s; $p = 0.014$). PVR decrease was higher with tamsulosin but statistical significance was not reached by either treatment *versus* placebo.

As expected, the IIEF erectile function domain improved *versus* placebo with tadalafil (4.0; $p < 0.001$) but not tamsulosin (–0.4; $p = 0.699$). Giuliano and colleagues [Giuliano *et al.* 2013], reported on the effects of tadalafil or tamsulosin on sexual function, including ejaculation and orgasm, satisfaction and erectile function based on sexually active men from the same patient cohort. Of 511 study participants, 310 (60.7%) had ED and were sexually active. The IIEF orgasmic function domain (IIEF-OF; including IIEF questions 9 and 10) increased significantly with tadalafil *versus* placebo ($p = 0.048$), as did IIEF-Q9 ($p = 0.045$) but not IIEF-Q10 ($p = 0.100$). Compared with placebo, IIEF-OF, IIEF-Q9 and IIEF-Q10 decreased significantly with tamsulosin (all $p < 0.05$). These data reflect the ejaculation disorders associated with tamsulosin in a certain subgroup of patients. The IIEF intercourse satisfaction domain (IIEF-IS) and the IIEF-overall satisfaction domain (IIEF-OS) increased significantly with tadalafil (both $p < 0.001$). For tamsulosin, the change was not significant for IIEF-IS, while IIEF-OS decreased significantly ($p = 0.009$).

These are the only studies published so far showing that tadalafil improves LUTS to a similar extent as tamsulosin, an α-adrenergic antagonist that is widely prescribed for this condition. These are also the only studies showing a statistically significant increase in Q_{max} that is similar for both active treatments. Although these studies cannot give an answer comparing the two active treatments directly, tadalafil seems to be at least as efficient as tamsulosin while having an extra benefit in improving all aspects of sexual life.

Safety issues

All of these studies reported that tadalafil is not only efficacious but also a safe treatment. As in the classic ED trials, the most common side effects were headache, dyspepsia, nasal congestion, flushing and back pain. In the pooled analysis of data from four randomized, double-blind, placebo-controlled, 12-week, parallel-design, multinational LUTS/BPH studies, the incidence of headache, back pain and dyspepsia was 3.8%, 2.5%, 2.1% and 2.6%, 1.2%, 0.2% for the tadalafil 5 mg and placebo group, respectively. Treatment discontinuation rates due to adverse events were 2.7% and 1.2% for the tadalafil 5 mg and placebo group, respectively [Porst *et al.* 2013b]. Brock and colleagues [Brock *et al.* 2013] reported similar findings without any significant difference in adverse events between patients with or without ED. In the open-label extension study, no new or unexpected adverse event was recorded while treatment discontinuation due to adverse events was 5.2% without significant differences between placebo and all tadalafil doses used [Donatucci *et al.* 2011].

For several years, well before data became available, concerns were raised in terms of combining an α-adrenergic antagonist with a PDE5i. Giuliano and colleagues [Giuliano *et al.* 2006], in a randomized, double-blind, placebo-controlled, crossover study in 18 healthy middle-aged men who received alfuzosin 10 mg daily for 7 days and either a single 20 mg dose of tadalafil or placebo on day 7 reported that tadalafil 20 mg showed no clinically relevant hemodynamic interactions with alfuzosin 10 mg daily. Goldfischer and colleagues [Goldfischer *et al.* 2012], reported on the safety of daily coadministration of alpha-blockers with tadalafil 5 mg in men with BPH-associated LUTS. All patients were stable on α-adrenergic antagonists for 4 weeks as recommended by US Food and Drug Administration (FDA) and European Medicines Agency (EMA) precautions [Hatzimouratidis *et al.* 2010]. The proportion of patients who reported treatment-emergent dizziness (due to orthostatic hypotension) was not significantly different between the two treatment groups (tadalafil 7%; placebo 5.7%; $p = 0.403$). No difference between treatment groups was observed with respect to patients meeting the criteria for a positive orthostatic test (30 per treatment group, $p = 1.00$). However, consistent with the results of previous clinical pharmacology studies of healthy subjects, a trend was seen for increased hemodynamic signs and symptoms in men taking nonuroselective alpha-blockers, most notably those taking doxazosin.

Is there still a role for combination therapy?

Since the coadministration of tadalafil and α-adrenergic antagonists is safe when following the

proper instructions, another question that arises is the possible role of combination treatment in patients with BPH-associated LUTS, especially using the new more uroselective α-adrenergic antagonists.

Animal and clinical data have provided preliminary evidence for the benefits of combining α-adrenergic antagonists and PDE5i [Giuliano, 2008; Oger *et al.* 2008]. Bechara and colleagues [Bechara *et al.* 2008] reported on the combination of tadalafil (20 mg/day) plus tamsulosin (0.4 mg/day) to tamsulosin alone in 20 men with LUTS. This was a randomized, double-blind, crossover design, 12-week study. Improvements of IPSS score and IPSS QoL were significant with both treatments but greater with the drug combination. Both regimens similarly improved the maximum flow rate and decreased the PVR from baseline ($p < 0.001$) with no significant differences between tamsulosin alone *versus* tamsulosin and tadalafil ($p > 0.05$). The IIEF improved with tamsulosin plus tadalafil ($p < 0.001$) but not with tamsulosin alone ($p > 0.05$). The General Assessment Question (GAQ) showed that all patients preferred the combination scheme. No serious adverse events were recorded while only two patients (one in each group) discontinued treatment due to an adverse event (headache and cutaneous rash, respectively). Regadas and colleagues [Regadas *et al.* 2013], compared the combination therapy of tamsulosin/tadalafil taken daily to tamsulosin/placebo. A total of 40 men with BPH-associated LUTS were randomized to tamsulosin 0.4 mg/tadalafil 5 mg or tamsulosin 0.4 mg/placebo once daily for 30 days. The primary end point was to demonstrate changes in urodynamic variables in the voiding phase, detrusor pressure at maximum flow ($P_{det}Q_{max}$) and maximum flow rate (Q_{max}). $P_{det}Q_{max}$ showed a significant reduction in tamsulosin/tadalafil group (13 ± 17.0) compared with tamsulosin/placebo (–1.2 ± 14.35) group ($p = 0.03$). Q_{max} increased in both groups, tamsulosin/tadalafil (1.0 ± 2.4) and tamsulosin/placebo (1.4 ± 2.4), but the difference was not significant between treatment groups ($p = 0.65$).

Recently, data on the combination of tadalafil with finasteride (a 5α-reductase inhibitor) have been published [Casabe *et al.* 2014]. This study was an international, randomized, double-blind, parallel study including men with prostate volumes 30 ml or greater. The combination of tadalafil 5 mg and finasteride 5 mg improved IPSS significantly compared with finasteride monotherapy at all time points (4, 8 and 16 weeks; $p \leq 0.022$). IPSS improved by 1.7, 1.4 and 1 more in the combination group compared with the finasteride-only group at the above time points, respectively. As expected, IIEF improved significantly in the combination group ($p < 0.001$). Combination therapy was well tolerated and most adverse events were mild/moderate. Interestingly, almost no sexual adverse event has been reported in the combination group.

While these preliminary data show that combination therapy may provide additional efficacy benefits, it is questionable whether these benefits are of clinical importance. In addition to significantly increasing the treatment cost, new data are required and combination therapy currently should be considered only in clinical trials.

Conclusions

ED and BPH-associated LUTS are epidemiologically linked and share common pathophysiological pathways. Tadalafil 5 mg once daily is approved for the treatment of LUTS in men with or without ED. Its efficacy is well established, its safety profile is well known and it can provide a treatment alternative to currently established treatments for LUTS. In addition to these facts, tadalafil is an established treatment for ED and is the only drug available today that can treat simultaneously two conditions that are highly prevalent in aging men. Moreover, sexual adverse events commonly associated with α-adrenergic antagonists or 5α-reductase inhibitors are avoided. While the efficacy of tadalafil is irrelevant to concomitant ED, men having both conditions seem to benefit the most from this new treatment.

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Conflict of interest statement

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References

Andersson, K., De Groat, W., McVary, K., Lue, T., Maggi, M., Roehrborn, C. *et al.* (2011) Tadalafil for the treatment of lower urinary tract symptoms secondary to benign prostatic hyperplasia: pathophysiology and mechanism(s) of action. *Neurourol Urodyn* 30: 292–301.

Bechara, A., Romano, S., Casabe, A., Haime, S., Dedola, P., Hernandez, C. *et al.* (2008) Comparative efficacy assessment of tamsulosin vs. tamsulosin plus tadalafil in the treatment of LUTS/BPH. Pilot study. *J Sex Med* 5: 2170–2178.

Behr-Roussel, D., Oger, S., Caisey, S., Sandner, P., Bernabe, J., Alexandre, L. *et al.* (2011) Vardenafil decreases bladder afferent nerve activity in unanesthetized, decerebrate, spinal cord-injured rats. *Eur Urol* 59: 272–279.

Bertolotto, M., Trincia, E., Zappetti, R., Bernich, R., Savoca, G. and Cova, M. (2009) Effect of tadalafil on prostate haemodynamics: preliminary evaluation with contrast-enhanced US. *Radiol Med* 114: 1106–1114.

Blanker, M., Bohnen, A., Groeneveld, F., Bernsen, R., Prins, A., Thomas, S. *et al.* (2001a) Correlates for erectile and ejaculatory dysfunction in older Dutch men: a community-based study. *J Am Geriatr Soc* 49: 436–442.

Blanker, M., Bosch, J., Groeneveld, F., Bohnen, A., Prins, A., Thomas, S. *et al.* (2001b) Erectile and ejaculatory dysfunction in a community-based sample of men 50 to 78 years old: prevalence, concern, and relation to sexual activity. *Urology* 57: 763–768.

Boyle, P., Robertson, C., Mazzetta, C., Keech, M., Hobbs, R., Fourcade, R. *et al.* (2003) The association between lower urinary tract symptoms and erectile dysfunction in four centres: the UREPIK study. *BJU Int* 92: 719–725.

Braun, M., Sommer, F., Haupt, G., Mathers, M., Reifenrath, B. and Engelmann, U. (2003) Lower urinary tract symptoms and erectile dysfunction: co-morbidity or typical "aging male" symptoms? Results of the "Cologne Male Survey". *Eur Urol* 44: 588–594.

Braun, M., Wassmer, G., Klotz, T., Reifenrath, B., Mathers, M. and Engelmann, U. (2000) Epidemiology of erectile dysfunction: results of the 'Cologne Male Survey'. *Int J Impot Res* 12: 305–311.

Brock, G., Broderick, G., Roehrborn, C., Xu, L., Wong, D. and Viktrup, L. (2013) Tadalafil once daily in the treatment of lower urinary tract symptoms (LUTS) suggestive of benign prostatic hyperplasia (BPH) in men without erectile dysfunction. *BJU Int*, in press.

Brock, G., McVary, K., Roehrborn, C., Watts, S., Ni, X., Viktrup, L. *et al.* (2014) Direct effects of tadalafil on lower urinary tract symptoms versus indirect effects mediated through erectile dysfunction symptom improvement: integrated data analyses from 4 placebo controlled clinical studies. *J Urol* 191: 405–411.

Broderick, G., Brock, G., Roehrborn, C., Watts, S., Elion-Mboussa, A. and Viktrup, L. (2010) Effects of tadalafil on lower urinary tract symptoms secondary to benign prostatic hyperplasia in men with or without erectile dysfunction. *Urology* 75: 1452–1458.

Brookes, S., Link, C., Donovan, J. and McKinlay, J. (2008) Relationship between lower urinary tract symptoms and erectile dysfunction: results from the Boston Area Community Health Survey. *J Urol* 179: 250–255; discussion 255.

Casabe, A., Roehrborn, C., Da Pozzo, L., Zepeda, S., Henderson, R., Sorsaburu, S. *et al.* (2014) Efficacy and safety of the coadministration of tadalafil once daily with finasteride for 6 months in men with lower urinary tract symptoms and prostatic enlargement secondary to benign prostatic hyperplasia. *J Urol* 191: 727–733.

Dmochowski, R., Roehrborn, C., Klise, S., Xu, L., Kaminetsky, J. and Kraus, S. (2010) Urodynamic effects of once daily tadalafil in men with lower urinary tract symptoms secondary to clinical benign prostatic hyperplasia: a randomized, placebo controlled 12-week clinical trial. *J Urol* 183: 1092–1097.

Donatucci, C., Brock, G., Goldfischer, E., Pommerville, P., Elion-Mboussa, A., Kissel, J. *et al.* (2011) Tadalafil administered once daily for lower urinary tract symptoms secondary to benign prostatic hyperplasia: a 1-year, open-label extension study. *BJU Int* 107: 1110–1116.

Dong, Y., Hao, L., Shi, Z., Wang, G., Zhang, Z. and Han, C. (2013) Efficacy and safety of tadalafil monotherapy for lower urinary tract symptoms secondary to benign prostatic hyperplasia: a meta-analysis. *Urol Int* 91: 10–18.

Egerdie, R., Auerbach, S., Roehrborn, C., Costa, P., Garza, M., Esler, A. *et al.* (2012) Tadalafil 2.5 or 5 mg administered once daily for 12 weeks in men with both erectile dysfunction and signs and symptoms of benign prostatic hyperplasia: results of a randomized, placebo-controlled, double-blind study. *J Sex Med* 9: 271–281.

Filippi, S., Morelli, A., Sandner, P., Fibbi, B., Mancina, R., Marini, M. *et al.* (2007) Characterization and functional role of androgen-dependent PDE5 activity in the bladder. *Endocrinology* 148: 1019–1029.

Gacci, M., Eardley, I., Giuliano, F., Hatzichristou, D., Kaplan, S., Maggi, M. *et al.* (2011) Critical analysis of the relationship between sexual dysfunctions and lower urinary tract symptoms due to benign prostatic hyperplasia. *Eur Urol* 60: 809–825.

Giuliano, F. (2008) Lower urinary tract symptoms and sexual dysfunction: a common approach. *BJU Int* 101(Suppl. 3): 22–26.

Giuliano, F., Kaplan, S., Cabanis, M. and Astruc, B. (2006) Hemodynamic interaction study between the

alpha1-blocker alfuzosin and the phosphodiesterase-5 inhibitor tadalafil in middle-aged healthy male subjects. *Urology* 67: 1199–1204.

Giuliano, F., Oelke, M., Jungwirth, A., Hatzimouratidis, K., Watts, S., Cox, D. *et al.* (2013) Tadalafil once daily improves ejaculatory function, erectile function, and sexual satisfaction in men with lower urinary tract symptoms suggestive of benign prostatic hyperplasia and erectile dysfunction: results from a randomized, placebo- and tamsulosin-controlled, 12-week double-blind study. *J Sex Med* 10: 857–865.

Goldfischer, E., Kowalczyk, J., Clark, W., Brady, E., Shane, M., Dgetluck, N. *et al.* (2012) Hemodynamic effects of once-daily tadalafil in men with signs and symptoms of benign prostatic hyperplasia on concomitant alpha1-adrenergic antagonist therapy: results of a multicenter randomized, double-blind, placebo-controlled trial. *Urology* 79: 875–882.

Hansen, B. (2004) Lower urinary tract symptoms (LUTS) and sexual function in both sexes. *Eur Urol* 46: 229–234.

Hatzimouratidis, K., Amar, E., Eardley, I., Giuliano, F., Hatzichristou, D., Montorsi, F. *et al.* (2010) Guidelines on male sexual dysfunction: erectile dysfunction and premature ejaculation. *Eur Urol* 57: 804–814.

Kedia, G., Uckert, S., Kedia, M. and Kuczyk, M. (2009) Effects of phosphodiesterase inhibitors on contraction induced by endothelin-1 of isolated human prostatic tissue. *Urology* 73: 1397–1401.

Kohler, T. and McVary, K. (2009) The relationship between erectile dysfunction and lower urinary tract symptoms and the role of phosphodiesterase type 5 inhibitors. *Eur Urol* 55: 38–48.

Laumann, E., Paik, A. and Rosen, R. (1999) Sexual dysfunction in the United States: prevalence and predictors. *JAMA* 281: 537–544.

Martin-Morales, A., Sanchez-Cruz, J., Saenz De Tejada, I., Rodriguez-Vela, L., Jimenez-Cruz, J. and Burgos-Rodriguez, R. (2001) Prevalence and independent risk factors for erectile dysfunction in Spain: results of the Epidemiologia De La Disfuncion Erectil Masculina Study. *J Urol* 166: 569–574; discussion 574–565.

McVary, K. (2005) Erectile dysfunction and lower urinary tract symptoms secondary to BPH. *Eur Urol* 47: 838–845.

McVary, K. (2006) Unexpected insights into pelvic function following phosphodiesterase manipulation - what's next for urology? *Eur Urol* 50: 1153–1156.

McVary, K., Monnig, W., Camps, J., Jr, Young, J., Tseng, L. and Van Den Ende, G. (2007a) Sildenafil citrate improves erectile function and urinary symptoms in men with erectile dysfunction and lower urinary tract symptoms associated with benign prostatic hyperplasia: a randomized, double-blind trial. *J Urol* 177: 1071–1077.

McVary, K., Roehrborn, C., Kaminetsky, J., Auerbach, S., Wachs, B., Young, J. *et al.* (2007b) Tadalafil relieves lower urinary tract symptoms secondary to benign prostatic hyperplasia. *J Urol* 177: 1401–1407.

Mondul, A., Rimm, E., Giovannucci, E., Glasser, D. and Platz, E. (2008) A prospective study of lower urinary tract symptoms and erectile dysfunction. *J Urol* 179: 2321–2326.

Morelli, A., Sarchielli, E., Comeglio, P., Filippi, S., Mancina, R., Gacci, M. *et al.* (2011) Phosphodiesterase type 5 expression in human and rat lower urinary tract tissues and the effect of tadalafil on prostate gland oxygenation in spontaneously hypertensive rats. *J Sex Med* 8: 2746–2760.

Nicolosi, A., Glasser, D., Moreira, E. and Villa, M. (2003a) Prevalence of erectile dysfunction and associated factors among men without concomitant diseases: a population study. *Int J Impot Res* 15: 253–257.

Nicolosi, A., Moreira, E., Jr, Shirai, M., Bin Mohd Tambi, M. and Glasser, D. (2003b) Epidemiology of erectile dysfunction in four countries: cross-national study of the prevalence and correlates of erectile dysfunction. *Urology* 61: 201–206.

Oelke, M., Giuliano, F., Mirone, V., Xu, L., Cox, D. and Viktrup, L. (2012) Monotherapy with tadalafil or tamsulosin similarly improved lower urinary tract symptoms suggestive of benign prostatic hyperplasia in an international, randomised, parallel, placebo-controlled clinical trial. *Eur Urol* 61: 917–925.

Oger, S., Behr-Roussel, D., Gorny, D., Charles Tremeaux, J., Combes, M., Alexandre, L. *et al.* (2008) Combination of alfuzosin and tadalafil exerts in vitro an additive relaxant effect on human corpus cavernosum. *J Sex Med* 5: 935–945.

Ponholzer, A. and Madersbacher, S. (2007) Lower urinary tract symptoms and erectile dysfunction; links for diagnosis, management and treatment. *Int J Impot Res* 19: 544–550.

Porst, H., Kim, E., Casabe, A., Mirone, V., Secrest, R., Xu, L. *et al.* (2011) Efficacy and safety of tadalafil once daily in the treatment of men with lower urinary tract symptoms suggestive of benign prostatic hyperplasia: results of an international randomized, double-blind, placebo-controlled trial. *Eur Urol* 60: 1105–1113.

Porst, H., McVary, K., Montorsi, F., Sutherland, P., Elion-Mboussa, A., Wolka, A. *et al.* (2009) Effects of once-daily tadalafil on erectile function in men

with erectile dysfunction and signs and symptoms of benign prostatic hyperplasia. *Eur Urol* 56: 727–735.

Porst, H., Oelke, M., Goldfischer, E., Cox, D., Watts, S., Dey, D. *et al.* (2013a) Efficacy and safety of tadalafil 5 mg once daily for lower urinary tract symptoms suggestive of benign prostatic hyperplasia: subgroup analyses of pooled data from 4 multinational, randomized, placebo-controlled clinical studies. *Urology* 82: 667–673.

Porst, H., Roehrborn, C., Secrest, R., Esler, A. and Viktrup, L. (2013b) Effects of tadalafil on lower urinary tract symptoms secondary to benign prostatic hyperplasia and on erectile dysfunction in sexually active men with both conditions: analyses of pooled data from four randomized, placebo-controlled tadalafil clinical studies. *J Sex Med* 10: 2044–2052.

Regadas, R., Reges, R., Cerqueira, J., Sucupira, D., Josino, I., Nogueira, E. *et al.* (2013) Urodynamic effects of the combination of tamsulosin and daily tadalafil in men with lower urinary tract symptoms secondary to benign prostatic hyperplasia: a randomized, placebo-controlled clinical trial. *Int Urol Nephrol* 45: 39–43.

Robertson, C., Link, C., Onel, E., Mazzetta, C., Keech, M., Hobbs, R. *et al.* (2007) The impact of lower urinary tract symptoms and comorbidities on quality of life: the BACH and UREPIK studies. *BJU Int* 99: 347–354.

Roehrborn, C., Kaminetsky, J., Auerbach, S., Montelongo, R., Elion-Mboussa, A. and Viktrup, L. (2010) Changes in peak urinary flow and voiding efficiency in men with signs and symptoms of benign prostatic hyperplasia during once daily tadalafil treatment. *BJU Int* 105: 502–507.

Roehrborn, C., McVary, K., Elion-Mboussa, A. and Viktrup, L. (2008) Tadalafil administered once daily for lower urinary tract symptoms secondary to benign prostatic hyperplasia: a dose finding study. *J Urol* 180: 1228–1234.

Roehrborn, C., Nuckolls, J., Wei, J. and Steers, W. Benign Prostatic Hyperplasia Registry and Patient Survey Steering Committee (2007) The Benign Prostatic Hyperplasia Registry and Patient Survey: study design, methods and patient baseline characteristics. *BJU Int* 100: 813–819.

Rosen, R., Altwein, J., Boyle, P., Kirby, R., Lukacs, B., Meuleman, E. *et al.* (2003) Lower urinary tract symptoms and male sexual dysfunction: the Multinational Survey of the Aging Male (MSAM-7). *Eur Urol* 44: 637–649.

Rosen, R., Giuliano, F. and Carson, C. (2005) Sexual dysfunction and lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH). *Eur Urol* 47: 824–837.

Roumeguere, T., Zouaoui Boudjeltia, K., Babar, S., Nuyens, V., Rousseau, A., Van Antwerpen, P. *et al.* (2010) Effects of phosphodiesterase inhibitors on the inflammatory response of endothelial cells stimulated by myeloperoxidase-modified low-density lipoprotein or tumor necrosis factor alpha. *Eur Urol* 57: 522–528.

Shiri, R., Hakkinen, J., Koskimaki, J., Hakama, M., Tammela, T. and Auvinen, A. (2007) Erectile dysfunction influences the subsequent incidence of lower urinary tract symptoms and bother. *Int J Impot Res* 19: 317–320.

Shiri, R., Hakkinen, J., Koskimaki, J., Huhtala, H., Auvinen, A., Hakama, M. *et al.* (2005a) Association between the bothersomeness of lower urinary tract symptoms and the prevalence of erectile dysfunction. *J Sex Med* 2: 438–444.

Shiri, R., Hakkinen, J., Hakama, M., Huhtala, H., Auvinen, A., Tammela, T. *et al.* (2005b) Effect of lower urinary tract symptoms on the incidence of erectile dysfunction. *J Urol* 174: 205–209; discussion 209.

Stief, C., Porst, H., Neuser, D., Beneke, M. and Ulbrich, E. (2008) A randomised, placebo-controlled study to assess the efficacy of twice-daily vardenafil in the treatment of lower urinary tract symptoms secondary to benign prostatic hyperplasia. *Eur Urol* 53: 1236–1244.

Yoshimura, N., Seki, S. and De Groat, W. (2001) Nitric oxide modulates Ca(2+) channels in dorsal root ganglion neurons innervating rat urinary bladder. *J Neurophysiol* 86: 304–311.