Is there a true association between BPH/LUTS and ED?

Anthony J. Bella MD, FRCSC
Greta and John Hansen Chair in Men’s Health Research
Division of Urology, Department of Surgery
University of Ottawa
ACKNOWLEDGEMENTS

Research Funding

Prostate Cancer Research Foundation of Canada
Canadian Male Sexual Health Council
Canadian Foundation for Innovation Infrastructure Grant
Northeastern Section of the American Urological Association
American Medical Systems PROPPER Study
(ClinicalTrials.gov Identifier: NCT01383018)

Greta and John Hansen Chair in Men’s Health Research
Speakers Bureau/Honoraria/Consulting Fees:

Eli Lilly Inc, Pfizer, Abbott, American Medical Systems, Coloplast, Actavis Specialty Pharmaceuticals
Session type/Title: Point counterpoint 1 - Is there a true association between BPH/LUTS and ED?

Chairs:
Edgardo Becher – Argentina
Archimedes Nardoza – Brazil

The scientific committee has scheduled your session as follows:
Date: Thursday 9 October 2014
Time: 10:30 – 11:00 hrs
Room: Comandatuba Ballroom

The titles/topics and speakers of the presentations are:
Pro: Anthony Bella – Canada
Con: Andrea Salonia – Italy
Session type/ Title: Point counterpoint 14: Is there a true association between BPH/LUTS and ED?

Chairs:
Edgardo Becher – Argentina
Archimedes Nardozza – Brazil

The scientific committee has scheduled your session as follows:
Date: Thursday 9 October 2014
Time: 10:30 – 11:00 hrs
Room: Comandatuba Ballroom

The titles/topics and speakers of the presentations are:
Pro: Anthony Bella – Canada
Con: Andrea Salonia – Italy
WHAT IS BEHIND THIS VERY DISTINGUISHED DOOR?
A VERY DISTINGUISHED HALLWAY, OF COURSE.
GIANTS OF THE UROLOGICAL FIELD
1. Much smarter than Dr. Bella
2. Better looking than Dr. Bella
2. Better looking than Dr. Bella – with or without a lab coat
3. Professor Salonia hates to lose – he will do what it takes
THERE WILL ONLY BE ONE MAJOR FLAW IN HIS ARGUMENTS......
He will use “evidence” to create a LIE.
There will only be one major flaw in his arguments......

He will use "evidence" to create a lie.
Session type/ Title:  Point counterpoint 1- Is there a true association between BPH/LUTS and ED?

Chairs:
Edgardo Becher – Argentina
Archimedes Nardozza – Brazil

The scientific committee has scheduled your session as follows:
Date: Thursday 9 October 2014
Time: 10:30 – 11:00 hrs
Room: Comandatuba Ballroom

The titles/topics and speakers of the presentations are:
Pro: Anthony Bella – Canada
Con: Andrea Salonia – Italy
WHAT IS AN ASSOCIATION?

In statistics, an **association** is any relationship between two measured quantities that renders them **statistically dependent**.

It is important to note that association does not establish **causality**.
Session type/ Title:  Point counterpoint 1- Is there a true association between BPH/LUTS and ED?

Chairs:
Edgardo Becher – Argentina
Archimedes Nardozza – Brazil

The scientific committee has scheduled your session as follows:
Date: Thursday 9 October 2014
Time: 10:30 – 11:00 hrs
Room: Comandatuba Ballroom

The titles/topics and speakers of the presentations are:
Pro: Anthony Bella – Canada
Con: Andrea Salonia – Italy
Silodosin and tadalafil have synergistic inhibitory effects on nerve-mediated contractions of human and rat isolated prostates

Roberta Buono a,*, Alberto Briganti a, Massimo Freschi b, Luca Villa a, c, Giovanni La Croce a, d, Marco Moschini a, Fabio Benigni a, Fabio Castiglione c, d, Francesco Montorsi a, c, Petter Hedlund a, e

A R T I C L E   I N F O

Article history:
Received 12 May 2014
Received in revised form 9 September 2014
Accepted 14 September 2014

Keywords:
Alfa-1A-adrenoceptor
Phosphodiesterase 5
Inhibition
Contraction
Prostate
Smooth muscle

A B S T R A C T

Lower urinary tract symptoms (LUTS) in men with benign prostatic hyperplasia (BPH) are associated with erectile dysfunction. Alpha-1-adrenoceptor antagonists are effective drugs for treating symptomatic BPH. Clinical data show improvements in LUTS by phosphodiesterase 5 inhibitors. This study aimed to evaluate effects of silodosin, a highly selective α1A-adrenoceptor antagonist, alone or in combination with the phosphodiesterase 5 inhibitor tadalafil on contractions of isolated human and rat prostates. In organ bath studies, effects of increasing concentrations of silodosin (1 nM–1 μM) and tadalafil (100 nM–100 μM) on contractions by electrical field stimulation or phenylephrine of human and rat prostate strip preparations were investigated. The combination silodosin and tadalafil reduced electrically-induced contractions of human prostate preparations better than single drugs alone. At any frequencies (1–32 Hz), inhibitory effects of combined therapy (P-values vs single drug) in human tissue were 26–42% (1 nM silodosin+100 nM tadalafil; P < 0.05), 40–58% (10 nM silodosin+1 μM tadalafil; P < 0.001–0.05), 56–67% (100 nM silodosin+10 μM tadalafil; P < 0.01–0.05), and 33–55% (1 μM silodosin+100 μM tadalafil P < 0.01–0.05).
Silodosin and tadalafil have synergistic inhibitory effects on nerve-mediated contractions of human and rat isolated prostates

Roberta Buono a,*, Alberto Briganti b, Massimo Freschi b, Luca Villa a, Luca La Croce a, d, Giovanni La Croce a, d, Marco Moschini a, Fabio Benigni a, Fabio Castiglione c, d, Francesco Montorsi a, c, Petter Hedlund a, e

a Division of Oncology/Unit of Urology, Urological Research Institute, IRCCS Ospedale San Raffaele, Milan, Italy
b Division of Oncology/Unit of Pathology, IRCCS Ospedale San Raffaele, Milan, Italy
c Universita Vita-Salute San Raffaele, Milan, Italy
d Department of Clinical and Experimental Pharmacology, Lund University, Lund, Sweden
e Department of Clinical Pharmacology, Linköping University, Linköping, Sweden

ABSTRACT

Lower urinary tract symptoms (LUTS) in men with benign prostatic hyperplasia (BPH) are associated with erectile dysfunction. Alpha-1-adrenoceptor antagonists are effective drugs for treating symptomatic BPH. Clinical data show improvements in LUTS by phosphodiesterase 5 inhibitors. This study aimed to evaluate effects of silodosin, a highly selective α1A-adrenoceptor antagonist, alone or in combination with the phosphodiesterase 5 inhibitor tadalafil, on contractions of isolated human and rat prostates. In organ bath studies, effects of increasing concentrations of silodosin (1 nM–1 μM) and tadalafil (100 nM–100 μM) on contractions by electrical field stimulation or phenylephrine of human and rat prostate strip preparations were investigated. The combination silodosin and tadalafil reduced electrically-induced contractions of human prostate preparations better than single drugs alone. At any frequencies (1–32 Hz), inhibitory effects of combined therapy (P-values vs single drug) in human tissue were 26–42% (1 nM silodosin+100 nM tadalafil; P < 0.05), 40–58% (10 nM silodosin+1 μM tadalafil; P < 0.001–0.05), 56–67% (100 nM silodosin+10 μM tadalafil; P < 0.001–0.05), and 33–55% (1 μM silodosin+100 μM tadalafil P < 0.01–0.05).
Silodosin and tadalafil have synergistic inhibitory effects on nerve-mediated contractions of human and rat isolated prostates

Roberta Buono a,*, Alberto Briganti a, Massimo Freschi b, Luca Villa a,c, Giovanni La Croce a,d, Marco Moschini a, Fabio Benigni a, Fabio Castiglione c,d, Francesco Montorsi a,c, Petter Hedlund a,e

a Division of Oncology/Unit of Urology, Urological Research Institute, IRCCS Ospedale San Raffaele, Milan, Italy
b Division of Oncology/Unit of Pathology, IRCCS Ospedale San Raffaele, Milan, Italy
c Università Vita-Salute San Raffaele, Milan, Italy
d Department of Clinical and Experimental Pharmacology, Lund University, Lund, Sweden
e Department of Clinical Pharmacology, Linköping University, Linköping, Sweden

ARTICLE INFO

Article history:
Received 12 May 2014
Received in revised form 9 September 2014
Accepted 14 September 2014

Keywords:
Alpha-1A-adrenoceptor Phosphodiesterase 5 Inhibition Contraction Prostate Smooth muscle

ABSTRACT

Lower urinary tract symptoms (LUTS) in men with benign prostatic hyperplasia (BPH) are associated with erectile dysfunction. Alpha-1A-adrenoceptor antagonists are effective drugs for treating symptomatic BPH. Clinical data show improvements in LUTS by phosphodiesterase 5 inhibitors. This study aimed to evaluate effects of silodosin, a highly selective α1A-adrenoceptor antagonist, alone or in combination with the phosphodiesterase 5 inhibitor tadalafil on contractions of isolated human and rat prostates. In organ bath studies, effects of increasing concentrations of silodosin (1 nM–1 μM) and tadalafil (100 nM–100 μM) on contractions by electrical field stimulation or phenylephrine of human and rat prostate strip preparations were investigated. The combination silodosin and tadalafil reduced electrically-induced contractions of human prostate preparations better than single drugs alone. At any frequencies (1–32 Hz), inhibitory effects of combined therapy (P-values vs single drug) in human tissue were 26–42% (1 μM silodosin + 100 nM tadalafil; P < 0.05), 40–58% (10 nM silodosin + 1 μM tadalafil; P < 0.001–0.05), 56–67% (100 nM silodosin + 10 μM tadalafil; P < 0.001–0.05), and 33–55% (1 μM silodosin + 100 μM tadalafil; P < 0.01–0.05).
Considering the physiological basis for micturition, parasympathetic nerve activity of the lower urinary tract, including NO-synthase-containing nerves of the outflow region, reaches a peak during emptying of the bladder (Fowler et al., 2008). Dense staining for NOS has been identified in nerves of the outflow region and prostate of animals and humans, and experimental data show that NO is an important inhibitory neurotransmitter and its release relaxes the outflow region during voiding (Fowler et al., 2008; Giuliano et al., 2013). As such, and similar to the mode of action in the therapy for erectile dysfunction, tadalafil may be considered to have a main effect on motor-related signals of the outflow region during voiding when the NO/cGMP system is presumed to be functionally active. This is also proposed for the prostate, where phosphodiesterase 5 inhibitors in vitro appear to be more effective during simultaneous activity of the soluble guanylyl cyclase to produce cGMP (Giuliano et al., 2013).
A review of the use of tadala treatment of benign prostatic men with and without erectile function.

Konstantinos Hatzimouraditi in *Ther Adv Urol*
2014, Vol. 6(4) 135–147
Lower urinary tract symptoms in men

John M Hollingsworth, Timothy J Wilt

1 Department of Urology, University of Michigan Medical School, Ann Arbor, MI, USA
2 Center for Healthcare Outcomes and Policy, University of Michigan Medical School, Ann Arbor, MI, USA
3 Minneapolis VA Center for Chronic Diseases Outcomes Research, Minneapolis, MN 55417, USA
4 University of Minnesota School of Medicine, Minneapolis, MN, USA

Correspondence to: TJ Wilt tijwilt@va.gov

Cite this as: BMJ 2014;349:g4474
doi: 10.1136/bmj.g4474

Phosphodiesterase type 5 inhibitors

Tadalafil is the latest drug to be approved for the treatment of BPH related lower urinary tract symptoms. Commonly used as an erectile aid, it targets the phosphodiesterase type 5 (PDE5) enzyme, and 55-70% of men with mild to severe lower urinary tract symptoms report erectile dysfunction. Although the mechanisms underlying the association are not clear, lower urinary tract symptoms and erectile dysfunction have common links (for example, the nitric oxide-cGMP pathway) that are potential targets for PDE5 inhibitors. Moreover, the PDE5 enzyme is highly expressed in the bladder neck, prostatic urethra, and prostate tissue.
THE CLINICAL PICTURE
PDE5-Is for the Treatment of Concomitant ED and LUTS/BPH

M. Gacci • A. Sebastianelli • M. Salvi • L. Vignozzi •
G. Corona • K. T. McVary • S. A. Kaplan • M. Oelke •
M. Maggi • M. Carini

Epidemiology Data Concerning Comorbidity of ED and LUTS/BPH

Several national or cross-national studies, based on an unselected population of LUTS/BPH or ED patients, demonstrated a tight correlation between LUTS/BPH and ED. We analyzed the results of the most important single center and cross sectional trials.
<table>
<thead>
<tr>
<th>Authors/Country</th>
<th>Name of study</th>
<th>Sample and assessment</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>LUTS</td>
</tr>
<tr>
<td><strong>Single center trials</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laumann et al. [14] (USA)</td>
<td>National Health and Social Life Survey</td>
<td>1410 men (aged 18–59)</td>
<td>Self-report of LUTS, 1 question on ED</td>
</tr>
<tr>
<td>Braun et al. [15] (Germany)</td>
<td>Cologne Male Survey</td>
<td>4477 men (aged 30–80)</td>
<td>IPSS, 18 questions KEEED</td>
</tr>
<tr>
<td>Shiri et al. [16] (Finland)</td>
<td>Tampere Aging Male Urological Study</td>
<td>1126 men (aged 50–70)</td>
<td>DAN-PSS, 2 ED questions</td>
</tr>
<tr>
<td>Morant et al. [17] (UK)</td>
<td>Health Improvement Network database in 333 general practices in UK</td>
<td>11,327 men with LUTS and ED, aged &gt;18 years questionnaire assessing voiding and storage LUTS</td>
<td>-</td>
</tr>
<tr>
<td>McVary et al. [18] (USA)</td>
<td>Retrospective US claims data analysis (1999–2004)</td>
<td>81,659 men with ED (mean age 57 years)</td>
<td>IPSS</td>
</tr>
<tr>
<td>Antunes et al. [19] (Brazil)</td>
<td>Prostate cancer screening program in São Paulo (Brazil)</td>
<td>1008 men screened for PCA (mean age 61 years)</td>
<td>IPSS, IIEF</td>
</tr>
<tr>
<td><strong>Multicenter trials</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nicolosi et al. [20] (international)</td>
<td>ED Epidemiology Cross National Study (Brazil, Italy, Japan, Malaysia)</td>
<td>2412 men (aged 40–70)</td>
<td>IPSS, 1 question on ED</td>
</tr>
<tr>
<td>Boyle et al. [21] (international)</td>
<td>UrEpi Study Group, UK, Netherlands, France, Korea</td>
<td>4800 men (aged 40–79)</td>
<td>IPSS, O‘Leary’s Sexual Function Inventory</td>
</tr>
<tr>
<td>Rosen et al. [22] (international)</td>
<td>Multinational survey of the aging male (MSAM-7) USA/Europe</td>
<td>12,815 men (aged 50–80)</td>
<td>IPSS, DAN-PSSsex, IIEF</td>
</tr>
<tr>
<td>Holden et al. [23] (Australia)</td>
<td>Men in Australia Telephone Survey (MATeS)</td>
<td>5900 men (aged ≥40)</td>
<td>IPSS, 1 question on ED</td>
</tr>
<tr>
<td>Wein et al. [24] (international)</td>
<td>Epidemiology of LUTS (EpiLUTS) study USA, UK, Sweden</td>
<td>11,834 men (mean age 56.1)</td>
<td>SF-12, IPSS, IIEF, Male Sexual Health Questionnaire,</td>
</tr>
<tr>
<td>Frankel et al. [25] (international)</td>
<td>12 countries: Community population and Urology clinic</td>
<td>423 (aged 40) community 1271 (aged &gt; 55) with LUTS/BPH</td>
<td>ICSmale and ICSsex questionnaires</td>
</tr>
<tr>
<td>Li et al. [26] (international)</td>
<td>Asian multinational registry (Hong Kong, Malaysia, Philippines, Singapore, Thailand)</td>
<td>994 men (aged 40–88 years) with BPH</td>
<td>IPSS, DAN-PSS, IIEF-5</td>
</tr>
</tbody>
</table>
Phosphodiesterase Type 5 Inhibitors in the Management of Non-neurogenic Male Lower Urinary Tract Symptoms: Critical Analysis of Current Evidence

**Table 2 – Clinical evidence of sildenafil and lower urinary tract symptoms**

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects and entry/baseline data</th>
<th>Study design</th>
<th>Treatment</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sairam et al [49]</td>
<td>112 men with ED; 18% with LUTS; IPSS &lt;7: 67%, 8-9: 26%, 20-35: 6%</td>
<td>Prospective open-label (evidence level 2b)</td>
<td>On demand</td>
<td>• Improved erections: 81%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Changes in IPSS correlated with sexual function scores</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• A lower IPSS at baseline predicted higher sexual function scores</td>
</tr>
<tr>
<td>Chang et al [52]</td>
<td>108 men with ED; IPSS and IIEF assessed at 3 mo</td>
<td>Retrospective (evidence level 2b)</td>
<td>On demand</td>
<td>• IPSS decreased from 15.8 to 13.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Significant inverse correlation between IIEF and IPSS</td>
</tr>
<tr>
<td>Mulhall et al [53]</td>
<td>48 men with IPSS &gt;10</td>
<td>Open label (evidence level 2b)</td>
<td>100 mg</td>
<td>• Mean improvement in ED: 7; IPSS: 4.6 points; quality of life: 1.4</td>
</tr>
<tr>
<td>McVary et al [54]</td>
<td>189 sildenafil; 180 placebo; IIEF ≤25, IPSS ≥12</td>
<td>12-wk, double-blind, placebo-controlled (evidence level 1a)</td>
<td>50 mg increased to 100 mg</td>
<td>• Sildenafil group: significantly greater improvements in IPSS and IPSS quality of life than placebo</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Greater improvements in patients with severe/moderate LUTS than in those treated with placebo</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Adverse events and study discontinuation due to adverse events greater in sildenafil group</td>
</tr>
<tr>
<td>McVary et al [55]</td>
<td>Equal previous study; BMI: obese ≥30, overweight ≥25, normal &lt;25 kg/m²</td>
<td>Ad hoc analysis previous study (evidence level 1a)</td>
<td>50 mg increased to 100 mg</td>
<td>• Significantly greater improvements in IPSS and IIEF observed in sildenafil-treated patients versus placebo were independent of BMI</td>
</tr>
</tbody>
</table>

ED = erectile dysfunction; LUTS = lower urinary tract infection; IPSS = International Prostate Symptom Score; IIEF = International Index of Erectile Function; BMI = body mass index.
Phosphodiesterase Type 5 Inhibitors in the Management of Non-neurogenic Male Lower Urinary Tract Symptoms: Critical Analysis of Current Evidence

Juan I. Martínez-Salamanca \textsuperscript{a,}\textsuperscript{*}, Joaquin Carballido \textsuperscript{a}, Ian Eardley \textsuperscript{b}, Francois Giuliano \textsuperscript{c}, Christian Gratzke \textsuperscript{d}, Raymond Rosen \textsuperscript{e}, Andrea Salonia \textsuperscript{f}, Christian Stief \textsuperscript{d}

Table 3 – Clinical evidence of tadalafil and lower urinary tract symptoms derived from clinical trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects and entry/baseline data</th>
<th>Study design</th>
<th>Treatment/duration</th>
<th>Effects</th>
</tr>
</thead>
</table>
| McVary et al \textsuperscript{[56]} | 138 tadalafil 143 placebo 143 placebo Stratified by IPSS <20 or ≥20 and prior α-blocker therapy, (evidence level 1a) | Prospective, randomized, double-blind, placebo-controlled | 5 mg increased to 20 mg after 6 wk; 12 wk | • At 6 and 12 wk, IPSS improvements significantly higher in tadalafil than placebo groups  
• Withdrawal due to adverse events: placebo 1.4%, tadalafil 3.6%; no changes in urodynamic parameters |
| Roehrborn et al \textsuperscript{[57]} | 1058 (approximately 200 per group); placebo, four tadalafil doses, stratified by IPSS <20 or ≥20 | Prospective, randomized, double-blind, placebo-controlled (evidence level 1a) | 2.5, 5, 10, 20 mg; 12 wk | • Significant improvement in the 5-mg group  
• IPSS increased from 4.9 to 1.8  
• Higher doses associated with IPSS improvements but more adverse events |
| Dmochowski et al \textsuperscript{[63]} | 99 tadalafil 101 placebo IPSS ≥13 | Prospective, randomized, double-blind, placebo-controlled (evidence level 1a) | 20 mg; 12 wk | • Significant improvement of IPSS (mean difference between treatments: –4.2).  
• No change in urodynamic measures (detrusor pressure at maximal urinary low rate) |

\textsuperscript{a}IPSS = International Prostate Symptom Score.
A third possibility is that, in fact, these drugs do not work to improve LUTS. The purported changes in symptoms may be driven by trial design rather than by actual physiologic effect. Given that these agents improve erectile function, there may be a compromise to patients being unblinded, that is, when a man notices that his erections improve, he would be more likely to suspect that he is on the active drug. Moreover, a clinical trial giving free tadalafil for a minimum of 3 mo may be a powerful force for creating new-onset LUTS.
Finally, Kaplan asserts that a clinical study that provides free tadalafil for a minimum of 3 mo may be a powerful inducement for creating new-onset “LUTS” in patients who simply have ED [1]. We consider it very unlikely that these 1000 subjects with and without ED would falsely, and convincingly, report to approximately 100 independent investigators that they have had at least 6 mo of BPH-related urinary symptoms and successfully manipulate uroflowmetry measures so that they might participate in a BPH study with a 4- to 5-mo duration (including washout of BPH medication, placebo run-in period, and seven clinic visits) for a 50% chance of receiving a “free” ED medication.
Finally, Kaplan asserts that a clinical study that provides free tadalafil for a minimum of 3 mo may be a powerful inducement for creating new-onset "LUTS" in patients who simply have ED [1]. We consider it very unlikely that these 1000 subjects with and without ED would falsely, and convincingly, report to approximately 100 independent investigators that they have had at least 6 mo of BPH-related urinary symptoms and successfully manipulate uroflowmetry measures so that they might participate in a BPH study with a 4- to 5-mo duration (including washout of BPH medication, placebo run-in period, and seven clinic visits) for a 50% chance of receiving a "free" ED medication.

We believe the MOA of PDE5-I as discussed in our article provides further understanding of how tadalafil may improve both ED and BPH-LUTS. Inhibition of the phosphodiesterase type 5 isoenzymes increases the intracellular level of cyclic guanosine monophosphate, with a multifaceted effect on both the penile and lower urinary tract tissue [2]. The current understanding of the MOA for PDE5-I in the treatment of BPH-LUTS is evolving, and while the exact MOA is not yet fully established, several recent research efforts (both in animals and humans) have added to the body of knowledge. The authors agree that further mechanistic investigations in men are necessary.
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

Gerald B. Brock,*,† Kevin T. McVary,‡ Claus G. Roehrborn,§ Steven Watts,§ Xiao Ni,§ Lars Viktrup,§ David G. Wong§ and Craig Donatucci§

Purpose: Tadalafil has regulatory approval for the treatment of men with signs/symptoms of benign prostatic hyperplasia with and without erectile dysfunction. We assessed whether the effects of treatment with tadalafil for lower urinary tract symptoms/benign prostatic hyperplasia are independent of improvements in erectile dysfunction.

Materials and Methods: Four separate analyses used integrated data from 4 randomized, double-blind, placebo controlled studies in men with lower urinary tract symptoms/benign prostatic hyperplasia with and without erectile dysfunction to test whether total I-PSS (International Prostate Symptom Score) improvement was due to improvement in IIEF-EF (International Index of Erectile Function-Erectile Function domain score). Unidirectional and bidirectional path analysis models determined direct and indirect treatment effects mediated by improvements in lower urinary tract symptoms/benign prostatic hyperplasia and erectile dysfunction symptoms.
Benign prostatic hyperplasia suggestive of lower urinary tract symptoms and erectile dysfunction are chronic comorbid conditions that share a common epidemiological association.\textsuperscript{1-3} There is a strong interconnection between the conditions in that men with LUTS suggestive of BPH are more likely to experience ED, the severity of LUTS corresponds to the severity of ED and increasing severity of either condition is associated with a decreased quality of life.\textsuperscript{3} While it is widely recognized that BPH is not the exclusive cause of LUTS and clinical drug trials often enroll men based in part on a clinical diagnosis of nonneurogenic LUTS suggestive of BPH (LUTS/BPH), the term has been considered meaningful to clinicians.\textsuperscript{4}
Benign prostatic hyperplasia suggestive of lower urinary tract symptoms and erectile dysfunction are chronic comorbid conditions that share a common epidemiological association. There is a strong interconnection between the conditions in that men with LUTS suggestive of BPH are more likely to experience ED, the severity of LUTS corresponds to the severity of ED and increasing severity of either condition is associated with a decreased quality of life. While it is widely recognized that BPH is not the exclusive cause of LUTS and clinical drug trials often enroll men based in part on a clinical diagnosis of nonneurogenic LUTS suggestive of BPH (LUTS/BPH), the term has been considered meaningful to clinicians.

In this study we tested the hypothesis that the impact of tadalafil on LUTS/BPH improvement is mediated through ED changes in men with both conditions.
Benign prostatic hyperplasia suggestive of lower urinary tract symptoms and erectile dysfunction are chronic comorbid conditions that share a common epidemiological association. There is a strong interconnection between the conditions in that men with LUTS suggestive of BPH are more likely to experience ED, the severity of LUTS corresponds to the severity of ED and increasing severity of either condition is associated with a decreased quality of life. While it is widely recognized that BPH is not the exclusive cause of LUTS and clinical drug trials often enroll men based in part on a clinical diagnosis of nonneurogenic LUTS suggestive of BPH (LUTS/BPH), the term has been considered meaningful to clinicians. Improvement in IIEF-EF. Although path analysis suggested that improvement of erectile dysfunction by tadalafil might indirectly improve LUTS suggestive of BPH to a small degree, the predominant treatment response (approximately 70%) was a direct effect on voiding function.
A review of the use of tadalafil in the treatment of benign prostatic hyperplasia in men with and without erectile dysfunction

Konstantinos Hatzimouratidis

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 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.
CONCLUSIONS
• There is an association between BPH/LUTS and Erectile Dysfunction
• There is an association between BPH/LUTS and Erectile Dysfunction

• Professor Salonia will now do his best to “muddy the waters” and take a clear association that many of you in the audience have researched, published, and lectured about......
• There is an association between BPH/LUTS and Erectile Dysfunction

• Professor Salonia will now do his best to “muddy the waters” and take a clear association that many of you in the audience have researched, published, and lectured about......and create confusion
Please remember.....
Please remember…..

Professor Salonia hates to lose – he will do what it takes
Please remember.....
Please remember.....
Phosphodiesterase Type 5 Inhibitors in the Management of Non-neurogenic Male Lower Urinary Tract Symptoms: Critical Analysis of Current Evidence

Juan I. Martínez-Salamanca \textsuperscript{a,}\textsuperscript{,}*, Joaquin Carballido \textsuperscript{a}, Ian Eardley \textsuperscript{b}, Francois Giuliano \textsuperscript{c}, Christian Gratzke \textsuperscript{d}, Raymond Rosen \textsuperscript{e}, Andrea Salonia \textsuperscript{f}, Christian Stief \textsuperscript{d}
Phosphodiesterase Type 5 Inhibitors in the Management of Non-neurogenic Male Lower Urinary Tract Symptoms: Critical Analysis of Current Evidence

EUROPEAN UROLOGY 60 (2011) 527–535

Juan I. Martínez-Salamanca a,a,*, Joaquin Carballido a, Ian Eardley b, Francois Giuliano c, Christian Gratzke d, Raymond Rosen e, Andrea Salonia f, Christian Stief d

A large body of epidemiologic evidence supports a causal relationship between lower urinary tract symptoms (LUTS) and erectile dysfunction (ED) [1–10] (Table 1), including (1) a consistent dose–response association between increased frequency of LUTS and ED, (2) a significantly higher prevalence of LUTS in men suffering from ED as compared with men with normal erections, and (3) a statistically significant increase on multivariable models of the risk of ED for increasing urinary complaints after adjusting for age and comorbidities.
The association between ED and LUTS also has biologic plausibility given the interrelationships of the known pathophysiologic mechanisms of these disease states [11,12]. The four pathophysiologic mechanisms [13] include the roles of nitric oxide synthase [14,15], autonomic hyperactivity and the metabolic syndrome [16–18], the Rho-kinase activation/endothelin pathway [19], and pelvic atherosclerosis [1]. These processes are not mutually exclusive and may overlap substantially [20,21].
There is a true association between BPH/LUTS and ED

Anthony J. Bella MD, FRCSC
Greta and John Hansen Chair in Men’s Health Research
Division of Urology, Department of Surgery
University of Ottawa