Ruolo del trattamento con i5PDE nelle patologie prostatiche benigne
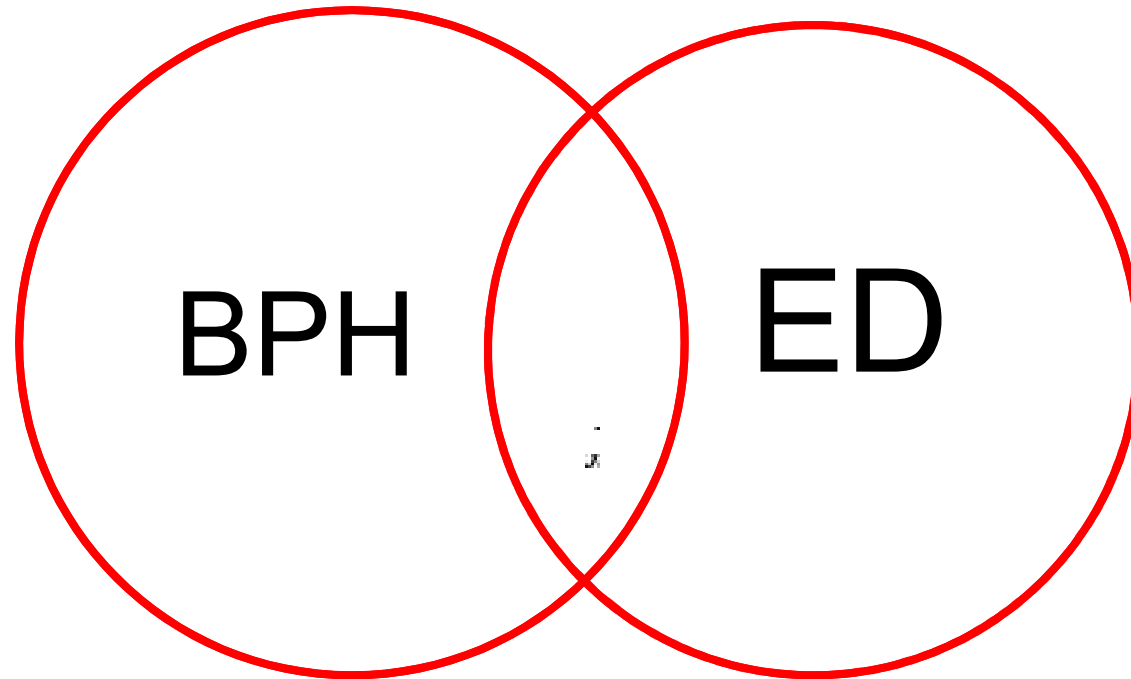
Federico Deho' MD

Università Vita-Salute San Raffaele, Milano
IRCCS Ospedale San Raffaele, Milano

BPH & ED

- Simply **coexisting conditions**?

- Share **common physiopathologic mechanisms**?

- Share **common subtended risk factors**?

"***a cause of a disease*** (ED) is an event, condition (LUTS) or characteristic that preceded the disease that without which it would have never occurred or occurred at a later time"

Rothman K et al. Philadelphia PA: Lippincot-Raven 1998

Continuum of relationships between medical conditions

Least Stringent				Most Stringent
Unrelated	Observational Association	Common Risk Factor/s	Common Initiator	Causality

BPH & ED: Epidemiological Surveys

• Several trials have analysed the association between LUTS and ED

• A **causal association** between LUTS and ED **cannot be established** on the basis of the ever-increasing number of **epidemiological studies**

The Environment and Disease: Association or Causation?

by Sir Austin Bradford Hill CBE DSC FRCP(hon) FRS
(*Professor Emeritus of Medical Statistics, University of London*)

ED prevalence as a function of age - ITALY

Random sample from non-randomly selected general practices
Question only (type: dissatisfied with ability to achieve and maintain erection
sufficient for sexual performance)   Response: 82% (n=2010)

Parazzini F. et al. Eur Urol 2000
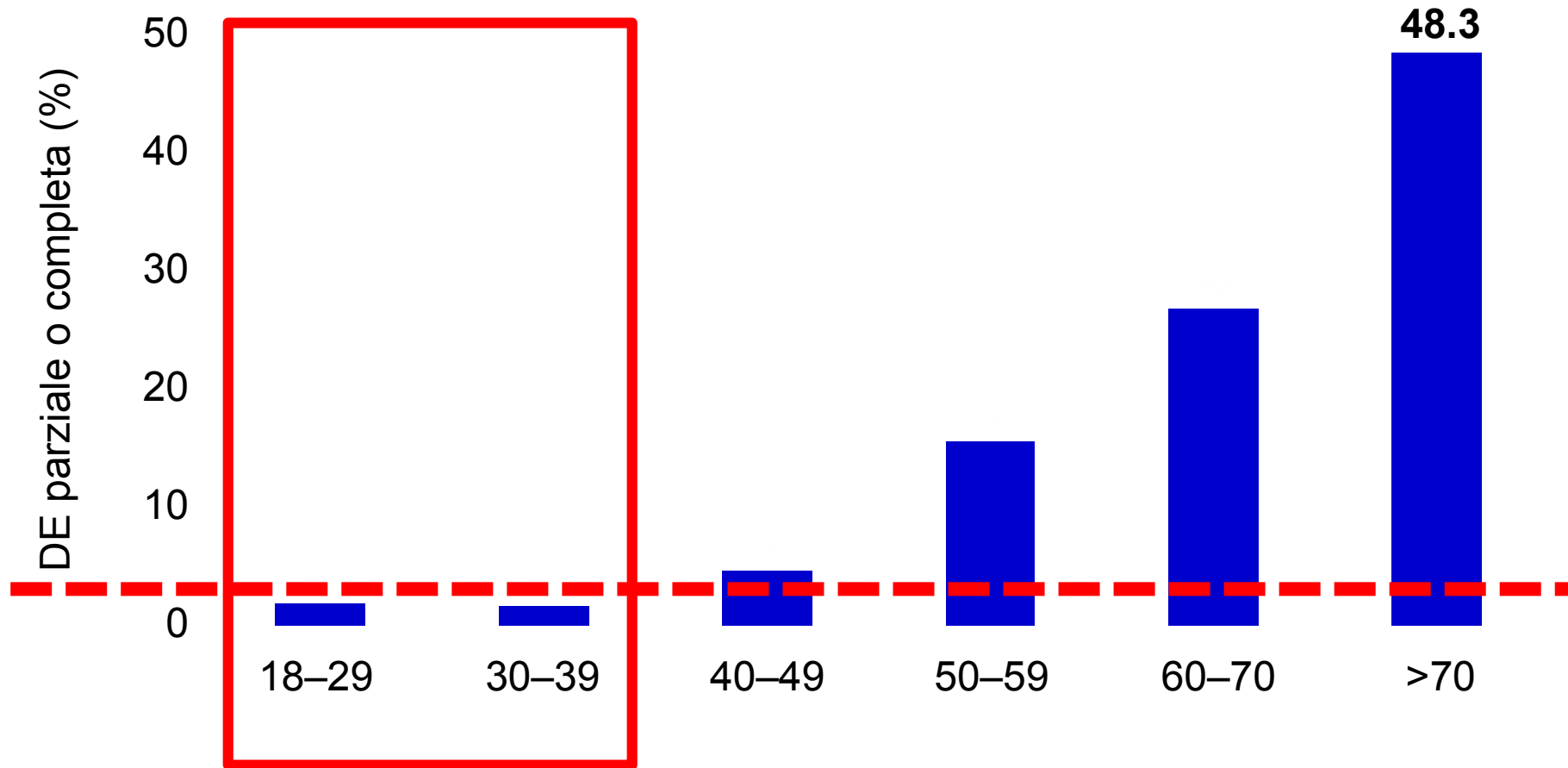
Lower Urinary Tract Symptoms and Male Sexual Dysfunction: The Multinational Survey of the Aging Male (MSAM-7)

(a)
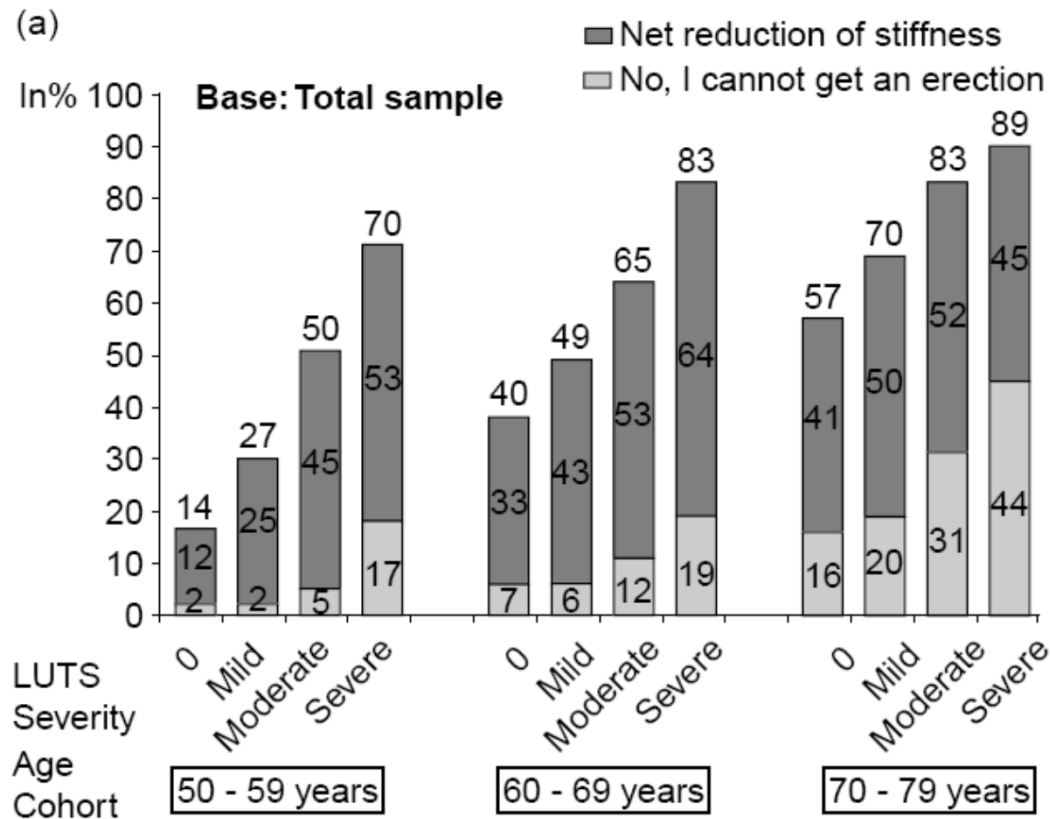
DAN-PSS-SEX
ED according to age & LUTS severity

Rosen RC, et al. Eur Urol 2003

How Can We Best Characterize the Relationship Between Erectile Dysfunction and Benign Prostatic Hyperplasia?

Raymond A. Costabile, MD, and William D. Steers, MD

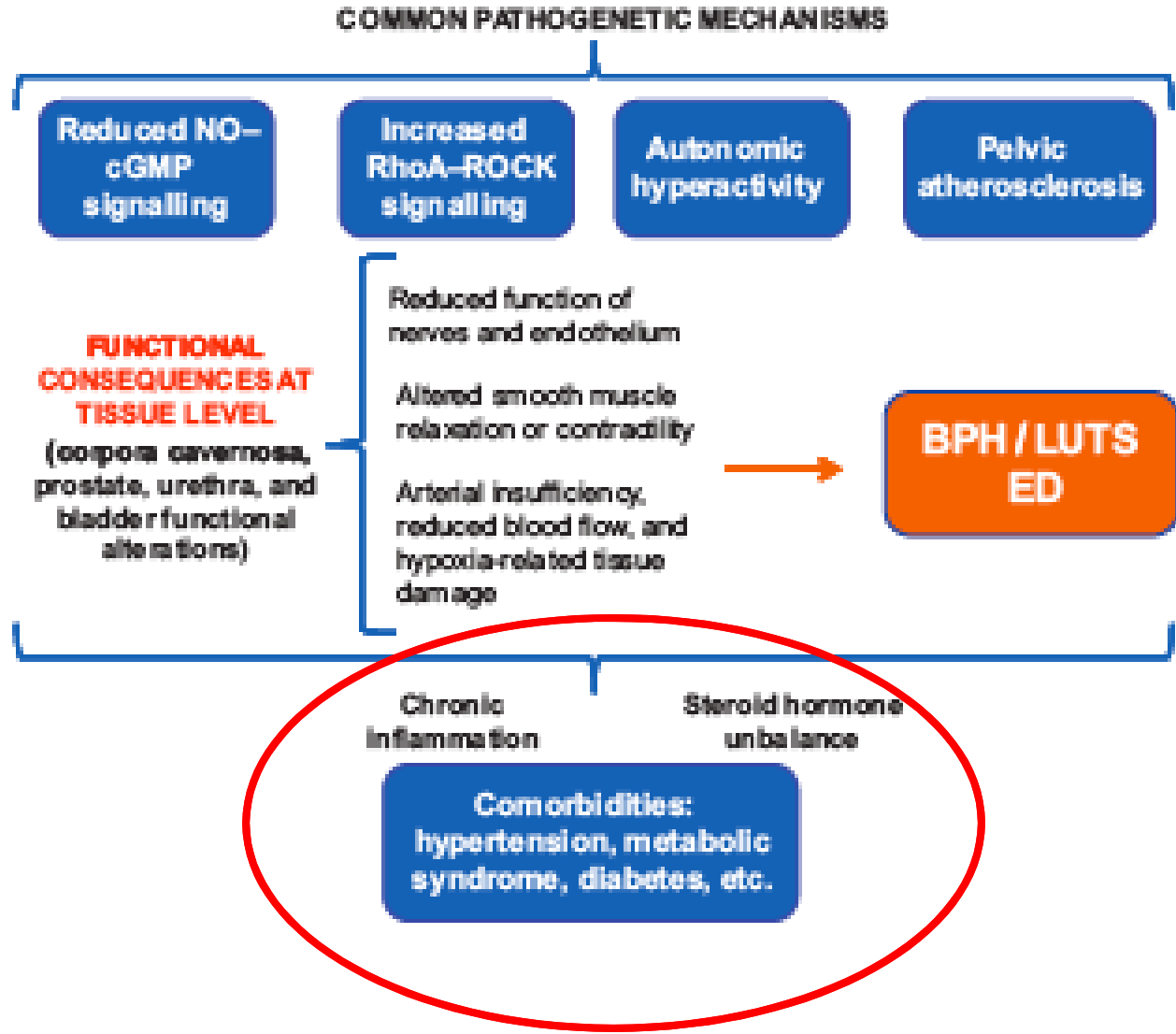Urology Department, University of Virginia Health System, Charlottesville, VA, USA

- A **significant variability** exists in many studies looking at a relationship between ED and BPH

- None examining a **temporal relationship**

- In Several studies, the **statistical association is either weak or nonexistent**

- This **variability weakens the argument for causality** based on the consistency criterion

Table 2 – Evidence of association between male lower urinary tract symptoms and erectile dysfunction in uro/andrologic (benign prostatic hyperplasia/erectile dysfunction) population-based studies: monocentric and cross-sectional

Author (country)	Level of evidence	Name of study	Sample	Assessment	Prevalence	Associations
Schou et al, 1996 [20] (Denmark)	2b	Scandinavian Survey	401 men with BPH (<50 to >69 yr of age)	DAN-PSS questionnaire: 3 questions concerning sexuality	EJD: 44% Pain during ejaculation: 15%	EJD and age
Namasivayam et al, 1998 [21] (UK)	2b	Prostate-Assessment Clinic in UK	168 men with LUTS	IPSS BPHII	ED: 56% (46% according to NIH) EJD: 38%	LUTS: age, sexual drive, ED, EJD
Baniel et al, 2000 [22] (Israel)	2b	BPH before prostatectomy	131 men with severe LUTS (55–74 yr of age)	IPSS, PBI, NPT	ED: 67%	ED: severe LUTS
Tubaro et al, 2001 [23] (Italy)	2b	QOL in Italian Patients with LUTS Suggestive of BPH	877 men with LUTS/BPH	IPSS, ICS-BPH, ICS-Sex	ED: 58% EJD: 56% Delayed ejaculation: 20%	ED: LUTS, in particular, with urinary loss
Sak et al, 2004 [24] (UK)	2b	Men with LUTS to a nurse-led assessment clinic	1420 men with LUTS (mean: 63 yr of age)	IPSS, BPHII O'Leary Sexual Questionnaire	ED: 47%	ED: age, LUTS, Q_{max}, and PVR
Hoesl et al, 2005 [25] (Germany)	2a	500 office-based urologists in Germany	8768 men (≥40 yr of age) with LUTS/BPH	IPSS KEED QoL mediated	ED: 62%	ED: LUTS with impact on QoL
Morant et al, 2009 [26] (UK)	2a	Health Improvement Network database in 333 general practices in the UK	11 327 men with LUTS and ED >18 yr of age)	Questionnaire assessing voiding and storage LUTS	ED range: 1.7% in 2000 to 4.9% in 2007	ED: Overall LUTS, both voiding and storage LUTS Storage LUTS-ED OR: 3.0 Voiding LUTS-ED OR: 2.6
El-Sakka et al, 2006 [27] (Egypt)	2b	Prospective study on ED patients	476 men with ED (mean: 55 yr of age)	IPSS IIEF	LUTS: 27.6% mild, 30% moderate, 42.4% severe	LUTS: ED risk factors (age, obesity, diabetes, hypertension, and IHD)
McVary et al, 2008 [28] (USA)	2b	Retrospective US claims data analysis (1999–2004)	81 659 men with ED (mean: 57 yr of age)	IPSS	LUTS at baseline: 1.5% LUTS after 2 yr: 7.6%	ED: Screened, diagnosed, and treated for LUTS
Reggio et al, 2007 [29] (Brazil)	2a	PCa screening programme in Joinville (Brazil)	1267 men screened for PCa (mean: 58 yr of age)	IPSS, IIEF-5	LUTS: 40.6% ED: 59.9%	LUTS is an age-independent predictor of ED
Antunes et al, 2008 [30] (Brazil)	2a	PCa screening programme in San Paulo (Brazil)	1008 men screened for PCa (mean: 61 yr of age)	IPSS, IIEF	LUTS: Mild 52%, moderate 30%, severe 17% ED: 81.4%	LUTS: 5.4% of men with no ED and in 27.1% of men with severe ED
Frankel et al, 1998 [31] (UK)	2a	12 countries: Community population and urology clinic*	423 (40 yr of age) community 1271 (>55 yr of age) LUTS/BPH	ICS-male and ICS-sex questionnaires	In-clinic men: ED 60% EJD: 62%	ED-LUTS: in 8% of community population and in 46% of urology clinic
Vallancien et al, 2003 [32] (France)	2b	Alf-One Study Group* (France, Denmark, UK, The Netherlands, Switzerland)	927 men (36–92 yr of age) with LUTS/BPH	IPSS, DAN-PSS, DAN-PSS-Sex	ED 62% EJD: 63%	ED: Age, LUTS, BMI EJD: Age, LUTS, BPH surgery
Li et al, 2008 [33] (Singapore)	2b	Asian multinational registry* (Hong Kong, Malaysia, Philippines, Singapore, Thailand)	994 men (40–88 yr of age) with BPH	IPSS, DAN-PSS, IIEF-5	LUTS: 90% ED: 82%	ED: Age, LUTS

BPH & ED: Physiopathology & Risk Factors

COMMON PATHOGENETIC MECHANISMS

Reduced NO–cGMP signalling · Increased RhoA–ROCK signalling · Autonomic hyperactivity · Pelvic atherosclerosis

FUNCTIONAL CONSEQUENCES AT TISSUE LEVEL (corpora cavernosa, prostate, urethra, and bladder functional alterations)

Reduced function of nerves and endothelium

Altered smooth muscle relaxation or contractility

Arterial insufficiency, reduced blood flow, and hypoxia-related tissue damage

BPH / LUTS ED

Chronic inflammation · Steroid hormone unbalance

Comorbidities: hypertension, metabolic syndrome, diabetes, etc.

Table 4 Common risk factors for erectile dysfunction and benign prostatic hyperplasia/low lower urinary tract symptoms

Smoking
Obesity
Alcohol consumption
Hypertension
Depression
Diabetes
Stress
Anxiety
Sleep disorders
Metabolic syndrome

TABLE I. Selected Risk Factors for LUTS and/or ED Identified in Epidemiological Studies (48–50) and Possible Pathological Mechanisms

Risk factor/comorbid conditions	Mechanism
Age	Vascular dysfunction
	Reduced eNOS signaling
	Increased ROCK signaling
Diabetes, metabolic syndrome, obesity, sedentary lifestyle	ANS overactivity
	Insulin/IGF growth stimulation
	Vascular dysfunction
Atherosclerotic cardiovascular disease, hypertension	Vascular dysfunction
	Reduced eNOS signaling
	ANS overactivity
Inflammatory conditions	Epithelial/stromal cell secretion of IL-8 and other cytokines

Evidence linking disorders of the prostate and bladder with LUTS and SD is irrefutable, but **the contribution of metabolic, cardiovascular, and endocrine factors cannot be discounted.**

Studies supporting alterations in mechanisms associated with metabolic syndrome and cardiovascular disease are critical to our understanding of the pathways underlying the links between LUTS and sexual dysfunction.

Costabile RA, et al. J Sex Med 2006

Andersson KE, et al. NeuroUrol Urodyn 2011

BPH & ED: Dose-Response Effect

If **ED** and **BPH** are correlated, treating one condition should improve the other

Costabile RA, et al., J Sex Med 2006

Localizzazione degli isoenzimi PDE5 nel tratto urinario inferiore

- **Cellule muscolari lisce**
  - Vascolatura
  - Vescica
  - Uretra
  - Prostata
  - Corpo cavernoso
- **Cellule muscolari striate**
  - Sfintere uretrale esterno

Andersson et al. Neurourol Urodyn 2011;30(3):292-301.
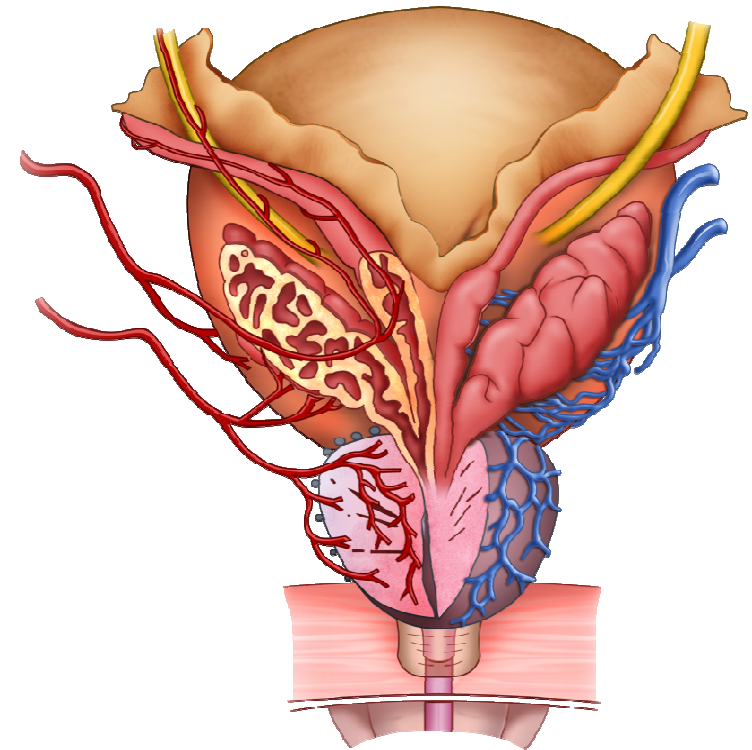
Meccanismi mediante i quali gli i5PDE potrebbero ridurre i BPH-LUTS

Inibizione della PDE5

Modulazione dell'iperattività del SNA e dell'attività nervosa afferente

downregulating dell'attività della rho chinasi

upregulating attività NO/cGMP

Aumento della perfusione pelvica e riduzione dell'ischemia del tratto urinario inferiore

Riduzione dell' infiammazione

Andersson et al. *Neurourol Urodyn* 2011;30(3):292-301.
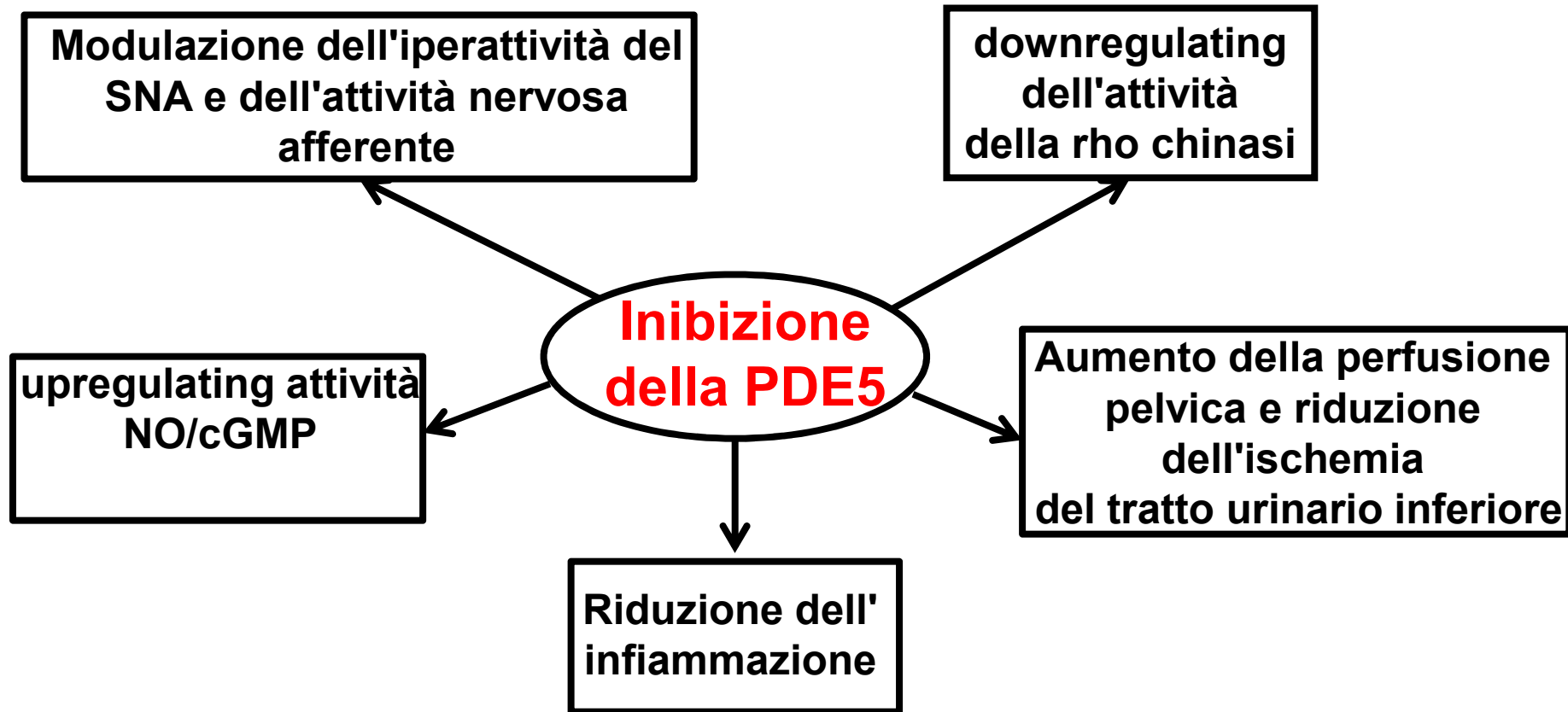
Aumento della perfusione pelvica e riduzione dell'ischemia del tratto urinario superiore

- Si ritiene che l'aumento della perfusione vascolare del tratto urinario inferiore abbia un effetto terapeutico sui LUTS[1-4]

- L'attività della PDE5, espressa principalmente nelle arterie deferenziali-vescicali umane (che originano dalle arterie vescicali inferiori), viene inibita in vitro da tadalafil[5]

- In ratti spontaneamente ipertesi, tadalafil aumenta l'ossigenazione dei tessuti della prostata indicando un possibile meccanismo che spieghi i benefici dei PDE5 inibitori sui sintomi del tratto urinario inferiore[5]

- L'aumento della perfusione ematica prostatica a seguito della somministrazione di tadalafil è stata dimostrata con ecografia con mezzo di contrasto[6]

1. Berger et al. BJU Int 2005;96(7):1073-8.
2. Pinggera et al. BJU Int 2008;101(3);319-24.
3. Azadzoi. Adv Exp Med Biol 2003;539(Pt A):271-80.
4. Waldkirch et al. *World J Urol* 2005;23(6):405-10.
5. Morelli et al. *J Sex Med* 2011;doi: 10.1111/j.1743-6109.2011.02416.x.
6. Bertolotto et al. *Radiol Med* 2009;114(7):1106-14.

Riduzione dell'infiammazione

- La guanilato ciclasi solubile, e quindi il cGMP, svolge un ruolo chiave nell'inibizione mediata dall'ossido nitrico del rolling e dell'adesione dei leucociti[1]

- L'inibizione della PDE5 può ridurre il danno aterosclerotico e l'infiammazione complessiva riducendo il reclutamento dei leucociti

- Tadalafil ha attenuato l'espressione di diversi marker infiammatori (TNF-α, IL-1β e IL-8)[2,3]

cGMP: guanosina monofosfato ciclica, NO: ossido nitrico, PDE5: fosfodiesterasi di tipo 5, TNF-α: fattore di necrosi tumorale α, IL-1β: interleuchina 1β, IL-8: interleuchina 8

1. Ahluwalia et al. Proc Natl Acad Sci USA 2004;101(5):1386-91.
2. Roumeguère et al. Eur Urol 2010;57(3):522-8.
3. Tsai et al. Ann Thorac Surg 2006;81(1):272-8.

Differences from placebo
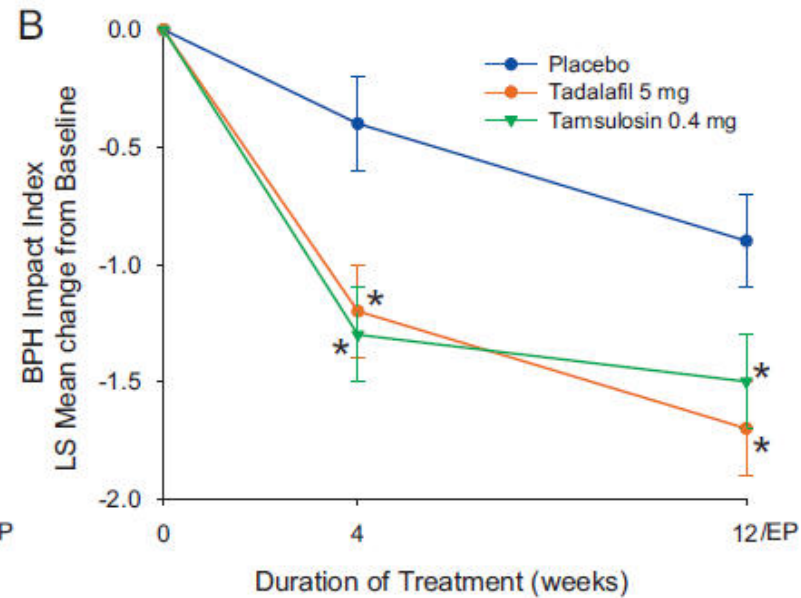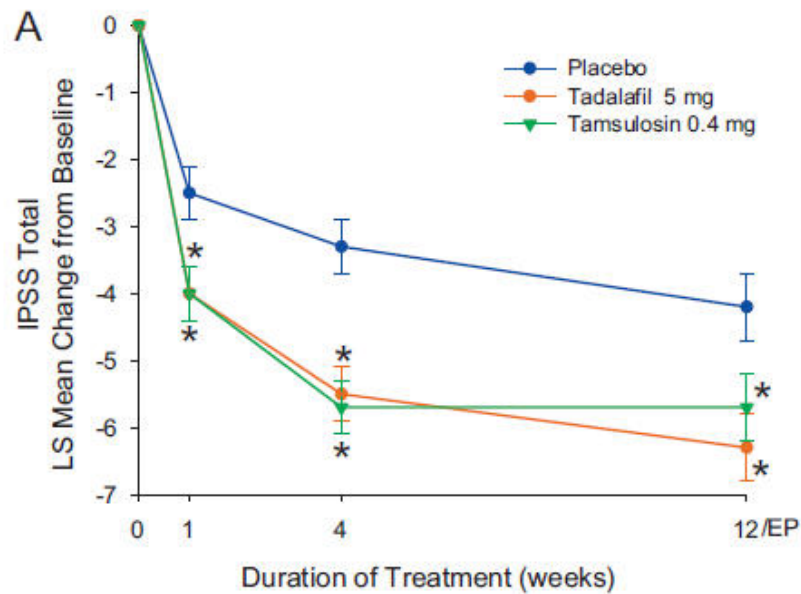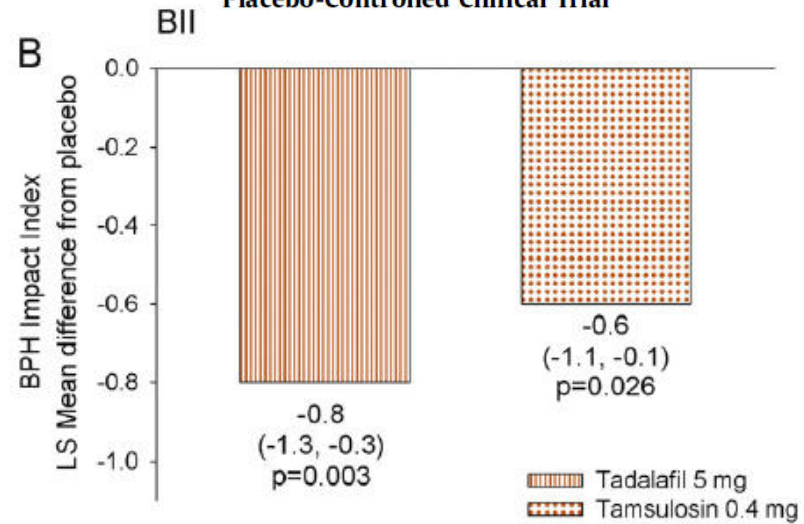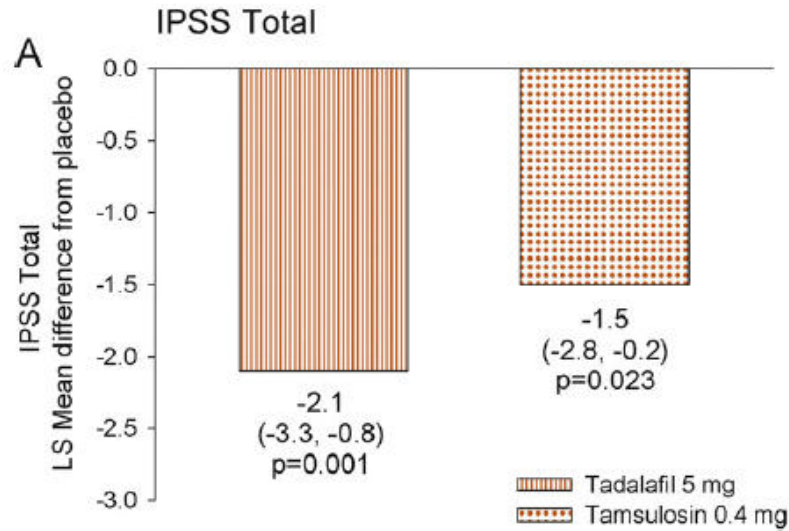
* $p < 0.05$ versus placebo based on ANCOVA.

Oelke M et al. Eur Urol 2012

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
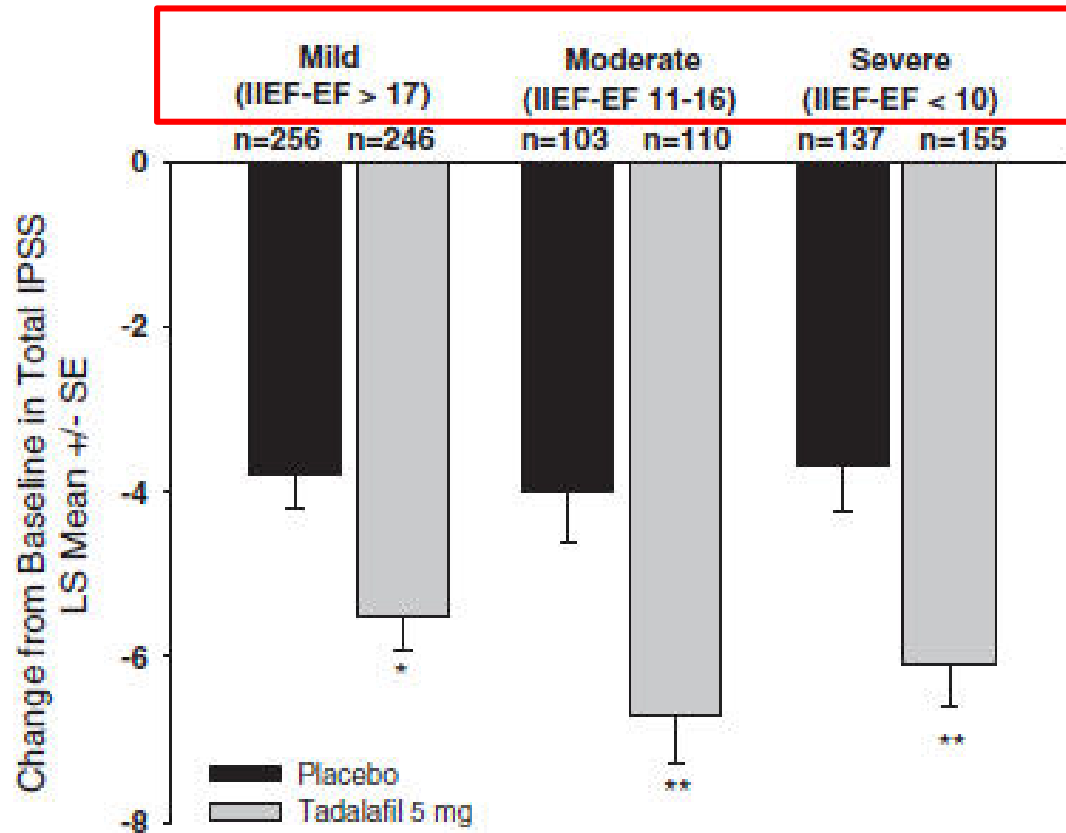
Figure 1 Change in total IPSS by baseline IIEF-EF Domain category. Data labels represent LS Mean change from baseline values; $^{*}P < 0.05$ vs. placebo, $^{**}P < 0.001$ vs. placebo. IIEF-EF, International Index of Erectile Function-Erectile Function; IPSS, International Prostate Symptom Score; LS = least-squares

Porst H et al. J Sex Med 2013

Study or Subgroup	PDE5-Is and a-blockers			PDE5-Is			Weight	Mean Difference IV, Random, 95% CI	Year	Mean Difference IV, Random, 95% CI
	Mean	SD	Total	Mean	SD	Total				
PDE5-Is plus a-blocker versus PDE5-Is alone for IIEF										
Rose AD 2002	20.86	3.23	14	13.5	4.13	14	16.4%	7.36 [4.61, 10.11]	2002	
Kaplan SA 2007	25.7	4.9	21	21.4	5.7	21	15.0%	4.30 [1.09, 7.51]	2007	
Liguori G 2009	19.9	4.8	23	18.8	4.8	21	16.1%	1.10 [-1.74, 3.94]	2009	
Jin Z 2011	18.4	4.4	168	16.8	5.6	82	20.4%	1.60 [0.22, 2.98]	2011	
Jin LC 2013	12.6	3.2	12	13	4.2	11	15.4%	-0.40 [-3.47, 2.67]	2013	
Singh DV 2013	17	5.705	44	17.27	6.826	44	16.8%	-0.27 [-2.90, 2.36]	2013	
Total (95% CI)			282			193	100.0%	2.25 [0.07, 4.43]		

Heterogeneity: Tau² = 5.57; Chi² = 22.51, df = 5 (P = 0.0004); I² = 78%
Test for overall effect: Z = 2.02 (P = 0.04)

PDE5-Is and a-blockers PDE5-Is

Figure 3 The improvement of erectile dysfunction (ED) in combination therapy compared with PDE5 inhibitor

Study or Subgroup	PDE5-Is plus a-blockers			PDE5-Is			Weight	Mean Difference IV, Random, 95% CI	Mean Difference IV, Random, 95% CI
	Mean	SD	Total	Mean	SD	Total			
PDE5-Is plus a-blocker versus PDE5-Is alone for IPSS									
Jin LC 2013	6.5	1.2	12	15.5	1.9	11	21.2%	-9.00 [-10.31, -7.69]	
Jin Z 2011	13.6	5.8	168	16.8	5.3	82	21.0%	-3.20 [-4.64, -1.76]	
Kaplan SA 2007	13.5	4.2	21	14.9	4.2	21	18.9%	-1.40 [-3.94, 1.14]	
Liguori G 2009	9	4	21	12.5	5.6	19	17.8%	-3.50 [-6.54, -0.46]	
Singh DV 2013	10	2.898	44	13.5	3.85	44	21.1%	-3.50 [-4.92, -2.08]	
Total (95% CI)			266			177	100.0%	-4.21 [-7.09, -1.32]	

Heterogeneity: Tau² = 9.75; Chi² = 54.58, df = 4 (P < 0.00001); I² = 93%
Test for overall effect: Z = 2.86 (P = 0.004)

PDE5-Is plus a-blocker versus PDE5-Is alone for Qmax								**(Fixed)**	
Kaplan SA 2007	11.5	2.9	21	10.3	2.4	21	42.0%	1.20 [-0.41, 2.81]	
Liguori G 2009	15	4	21	14.3	5.2	19	13.0%	0.70 [-2.20, 3.60]	
Singh DV 2013	13.54	5.587	44	11.46	3.867	44	27.0%	2.08 [0.07, 4.09]	
Tuncel A 2010	20	3.6	20	18.5	4.3	20	18.0%	1.50 [-0.96, 3.96]	
Total (95% CI)			106			104	100.0%	1.43 [0.38, 2.47]	

Heterogeneity: Chi² = 0.73, df = 3 (P = 0.87); I² = 0%
Test for overall effect: Z = 2.68 (P = 0.007)

PDE5-Is plus a-blockers PDE5-Is

Figure 4 The improvement of lower urinary tract symptoms (LUTS) in combination therapy compared with PDE5 inhibitor

BPH & ED: Dose-Response Effect

If **ED** and **BPH** are correlated, treating one condition should improve the other

IIEF and **IPSS**, measure the effect on QOL due to a medical condition and are sensitive to treatment effects.

These **QOL instruments were not designed** to **assess** physiological **causality or associations**

The danger of looking *only* at these QOL instruments is that a **variety of factors** outside of the measured parameter **may be influencing the condition being studied**

BPH & ED: Dose-Response Effect

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§

Hypotheses

If BPH symptom response is not direct and largely dependent on the tadalafil treatment effect on ED, several observations would be expected. 1) Men without ED would have little to no improvement in LUTS/BPH and would demonstrate a strong subgroup effect of ED comorbidity. 2) A dominant (eg greater than 50%) indirect treatment effect on LUTS/BPH (mediated through improvement in erectile function as measured by IIEF-EF) would be observed. 3) A strong correlation between changes in IIEF-EF and total I-PSS would be observed (ie changes in IIEF-EF would increase as I-PSS decreases). This

BPH & ED: Dose-Response Effect

Table 3. Total, direct and indirect effects of tadalafil on total I-PSS improvement and IIEF-EF increase based on unidirectional and bidirectional path model analysis

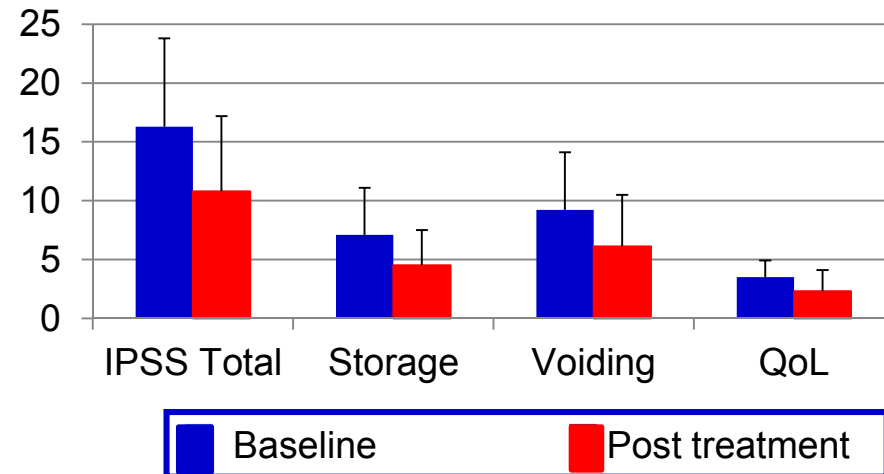| Variable	Total Treatment Effect Estimate	Direct Treatment Effect Estimate (% Total)	Indirect Treatment Effect Estimate (% Total)	p Value
Unidirectional model: I-PSS reduction	2.25	1.57 (70.0)	0.67 (30.0)	<0.001
Bidirectional model:				
I-PSS reduction	2.26	2.09 (92.5)	0.17 (7.5)	0.32
IIEF-EF improvement	4.25	3.76 (88.6)	0.48 (11.4)	0.002

Table 2. Changes in total I-PSS by ED status

ED Status	Tadalafil 5 mg			Placebo			Treatment Difference LS Mean (SE)
	No.*	Mean	SD	No.*	Mean	SD	
Yes:							
Baseline	579	17.7	5.5	566	17.5	5.8	−2.3 (0.3)†
End point	579	11.8	6.9	566	14.0	7.1	p <0.0001.
Change	579	−5.9	6.5	566	−3.5	6.0	
No:							
Baseline	163	17.1	6.3	167	16.8	6.4	−2.2 (0.6)‡
End point	163	11.7	6.8	167	13.6	7.7	p=0.0007.
Change	163	−5.4	5.9	167	−3.3	6.1	

Tadalafil independently (directly) **improves signs and symptoms** associated withLUTS/ BPH in men **regardless of ED status**

Brock GB et al. J Urol 2014

EFFECTS OF SILODOSIN ON SEXUAL FUNCTION
REALISTIC PICTURE FROM THE EVERYDAY CLINICAL PRACTICE

Salonia et al

Age (years; mean [SD])	63.2 (12.0)
BMI (kg/m^2; mean [SD])	25.8 (3.3)
CCI (No. [% of valid cases])	
= 0	68 (68%)
= 1	11 (11%)
≥ 2	21 (21%)

Reported side effects and their consequence on silodosin drop-off (% of valid cases)

	Adverse Effects (AEs)	AEs-related drop-off
Hypotension	15 (15%)	2 (2%)
Nasal congestion	1 (1%)	1 (1%)
Diarrhoea	3 (3%)	3 (3%)
Anejaculation	48 (48%)	6 (6%)
Hypospermia	23 (23%)	0 (0%)
Reduced orgasmic feeling	11 (11%)	0 (0%)
Absent orgasmic feeling	6 (6%)	0 (0%)
Erectile dysfunction	10 (10%)	0 (0%)
Low sexual desire	7 (7%)	0 (0%)
Reduced virility	5 (5%)	0 (0%)

All the p-values are ≤ 0.001

Baseline   Post treatment

IPSS Total   Storage   Voiding   QoL

IIEF-Q9   IIEF-Q10

Salonia A et al. AUA 2014
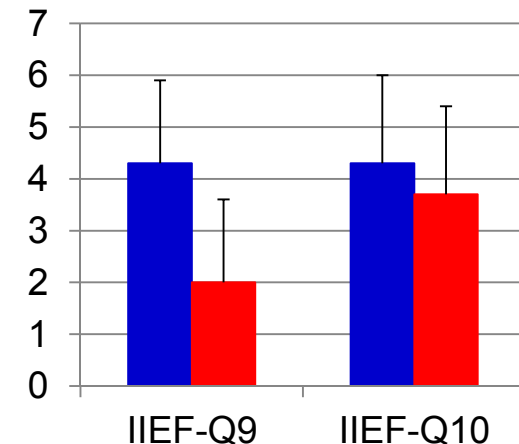
Perché trattare i BPH-LUTS con PDE5i?

- Una considerevole quantità di prove collega i LUTS alla DE nell'invecchiamento maschile[1]

- È stata accertata la presenza di PDE5 nella prostata e nella vescica umana[2,3]

- L'inibizione della PDE5 colpisce diverse vie di segnalazione e quindi può svolgere un ruolo nei LUTS

[1]Ponholzer et al. *Int J Impot. Res.* 2007;19:544-550
[2]Uckert et al. *J Urol.* 2001;166:2484-90.
[3]Filippi et al. *Endocrinology.* 2007;148:1019-29.

BPH & ED

Evidence based medicine: what it is and what it isn't

It's about integrating individual clinical expertise and the best external evidence

Evidence based medicine **is not restricted to randomised trials and meta analyses**

Evidence based medicine is the conscientious, explicit, and judicious **use of current best evidence** in making decisions about the care of individual patients. The practice of evidence based medicine means **integrating individual clinical expertise with the best available external clinical evidence** from systematic research.

While it is tempting to speculate that causality exists between LUTS and ED, further data are required to support this claim

Sackett DL et al. BMJ 1996