

Annual meeting
Belgian Urological Association
 Session 4: BPH + OAB
Metabolic syndrome, erectile dysfunction and BPH
M. Gacci
 University of Florence,
 AOUC Careggi Hospital, Florence

LUTS and ED

US and six European countries

34,800 surveys were mailed out, 14,254 were completed and returned, and 12,815 analyzed

Sexual dysfunction is strongly related to both age and severity of BPH symptoms

50% of men 50-59 years with moderate LUTS have erectile dysfunction

Adapted from Rosen R, Eur Urol. 2003

LUTS and ED

Collaborative Review - Sexual Medicine - LUTS

Critical Analysis of the Relationship Between Sexual Dysfunctions and Lower Urinary Tract Symptoms Due to Benign Prostatic Hyperplasia

Maurio Gacci¹, Jan Erdelyi², Francesco Giuliano³, Dimitris Hatzichristou⁴, Steven A. Kaplan⁵, Murto Magg⁶, Kevin T. McVary⁷, Vincenzo Mirone⁸, Hartmut Pons⁹, Claus G. Roehrborn¹⁰

GENERAL population based studies **BPH /ED population based studies**

Study	ED (%)	LUTS (%)
20-70% of men have ED	44-90% of men have LUTS	
58-82% of men with LUTS have ED	8-26% of men with ED have LUTS	

Gacci M, Eur Urol 2011

LUTS and ED

Critical Analysis of the Relationship Between Sexual Dysfunctions and Lower Urinary Tract Symptoms Due to Benign Prostatic Hyperplasia

Maurio Gacci¹, Jan Erdelyi², Francesco Giuliano³, Dimitris Hatzichristou⁴, Steven A. Kaplan⁵, Murto Magg⁶, Kevin T. McVary⁷, Vincenzo Mirone⁸, Hartmut Pons⁹, Claus G. Roehrborn¹⁰

COMMON PATHOGENETIC MECHANISMS

- Reduced inhibitory signaling
- Increased smooth muscle signaling
- Autonomic hyperactivity
- Public atherosclerosis

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

- Reduced function of nerves and endothelium
- Altered smooth muscle relaxation/contractility
- Arterial insufficiency, reduced blood flow and hypoxia-related tissue damage

Chronic inflammation leads to **Steroid hormone substance** and **Comorbidity: Hypertension, Metabolic syndrome, Diabetes, etc.**

BPH /LUTS ED and **CVD** are interconnected.

Adapted from Gacci et al. Eur Urol 2011

ED and CVD

Erectile Dysfunction and Risk of Cardiovascular Disease

Meta-Analysis of Prospective Cohort Studies

Jin-Yi Dong, BSc,¹ Yong-Hong Zhang, MD, PhD,¹ Li-Qiang Qin, MD, PhD²

Suzhou, China

Dong JY, J Am Coll Cardiol 2011

LUTS and CVD

Are lower urinary tract symptoms in men associated with cardiovascular diseases in a primary care population: a registry study

Inge I. Bouwman^{1,2,3}, Bouwke J. Kruit^{1,2}, Klaas van der Meer¹, Hans de Hartog¹ and Wolter E. van der Horst^{1,2}

RESEARCH ABSTRACT

Characteristics	All men (n=6614) (%)	Men without LUTS (n=2449) (37.0%)	Men with LUTS (n=4165) (63.0%)	p-value
Age, mean (SD), y	56 (12)	56 (12)	56 (12)	
Report of cardiovascular disease (%)	1539(23.2)	1060(19.5)	4794(31.1)	0.000*
Report of hypertension (H05 + K07)	1751(26.5)	1283(23.5)	4684(30.2)	0.000*
Report of erectile dysfunction (%)	89(1.3)	56(1.0)	33(0.8)	0.000*
Report of diabetes mellitus (I09)	368(5.7)	286(5.2)	927(9.9)	0.000*
Report of obesity	360(5.9)	204(3.7)	564(8.0)	0.000*
Report of current smoking	894(13.4)	751(13.8)	1311(11.4)	0.031*
Report of alcohol abuse	254(3.8)	230(4.2)	242(1.1)	0.000*
Report of dyslipidemia	1350(20.4)	1040(19.2)	1940(16.1)	0.000*
Use of LUTS medication (%)	724(10.9)	50(1.1)	717(6.5)	0.000*

men aged 50 years and older from 1998 to 2008

Bouwman I, BMC Family Practice 2014

Review/Commentary/ADA Statement

Low Testosterone Associated With Obesity and the Metabolic Syndrome Contributes to Sexual Dysfunction and Cardiovascular Disease Risk in Men With Type 2 Diabetes

Christopher Wilson, MD¹, Michael A. Perle, MD², Robert A. Phillips, MD³, T. Bruce Anders, MD⁴, Anna T. Levin, MD⁵, Aron D. Michaloveanu, MD⁶, Alex Serna, MD⁷, Michael E. Jensen, MD⁸, Glenn C. Chrousos, MD⁹

Wang C, Diabetes Care. 2011

MetS definition: at least 3/5 parameters

	WHO (1998)	EGIR (1999)	AACE (2003)	IDF (2005)	NCEP ATP III (2005 Revision)
Required component	IR, BGL, BGL, TGDM, or additional evidence of IR	Hypertension ^a (plasma insulin > 75th percentile)	IR, BGL or IFG (WCF)	CG (WCF)	None
Criteria	Required component and ≥ 2/5 below	Required component and ≥ 2/4 below	Required component and any below based on clinical judgment	Required component and ≥ 2/4 below	≥ 3/5 below
Obesity	Waist > 0.9 (M), > 0.85 (F) or BMI > 30 kg/m ²	WC ≥ 94 cm (M), ≥ 80 cm (F)	BMI ≥ 25 kg/m ²	–	WC > 102 cm (M) > 88 cm (F)
Hyperglycemia (mg/dL)	+	+	+	+	Fasting glucose ≥ 100 or 2
Dyslipidemia (mg/dL)	TG ≥ 150 or HDL-C < 35 (M), < 39 (F)	TG ≥ 150 or HDL-C < 39	TG ≥ 150 and HDL-C < 40 (M), < 50 (F), or Rx	TG ≥ 150 or Rx 3	Fasting glucose ≥ 100 or Rx 2
Hypertension (mm Hg)	> 140/90	> 140/90 or Rx	> 130/85	> (S), > 85 (D) or Rx	TG ≥ 150 or Rx 3
Other criteria	Microalbuminuria ^b	–	–	–	4 HDL < 40 (M), 50 (F), or Rx 4
			Other features of IR ^c		5 > 130 (S), > 85 (D) or Rx 5

MetS and CVD

The Metabolic Syndrome and Cardiovascular Risk

A Systematic Review and Meta-Analysis

Salvatore Mottillo, BSc,[†] Kristian B. Filion, PhD,^{††} Jacques Genest, MD,[‡] Lawrence Joseph, PhD,^{§§} Louise Pilote, MD, MPH, PhD,^{§§§} Paul Poirier, MD, PhD,^{††} Stéphane Rinfret, MD, MSc,^{##} Ernesto L. Schiffrin, MD, PhD,^{**} Mark J. Eisenberg, MD, MPH^{†††}

Mottillo S, J Am Coll Cardiol 2010

MetS and CVD

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CVD: RR → 2,35

Mottillo S, J Am Coll Cardiol 2010

EUROPEAN UROLOGY 76 (2016) 784-794

available at www.elsevier.com/locate/eurol

Journal homepage: www.elsevier.com/locate/eurol

EAU European Association of Urology

Platinum Priority – Collaborative Review – Benign Prostatic Enlargement

Male Lower Urinary Tract Symptoms and Cardiovascular Events: A Systematic Review and Meta-analysis

Mauro Gacci^{*,†}, Giovanni Corona^{*,†}, Arcangelo Sebastianelli^{*,†}, Sergio Senni^{*,†}, Costino De Nunzio^{*,†}, Mario Maggi^{*,†}, Linda Vignozzi^{*,†}, Giacomo Novara^{*,†}, Kevin T. McVary^{*,†}, Steven A. Kaplan^{*,†}, Steven Crouse^{*,†}, Christopher Chapple^{*,†}

Study	Study design	n	Follow-up (years)	Prevalence of LUTS (%)	Prevalence of CVD (%)	OR (95% CI)	p-value
Waldman et al. (2000)	Cohort study	2862	4.7	19.4	17.8	0.94	0.8
Smith et al. (2001)	Cohort study	11,736	4.7	30.1	17.9	1.71	0.001
Wong et al. (2006)	Cohort study	1068	4.8	30.0	23.7	1.42	0.001
El-Sakka et al. (2006)	Cohort study	1044	3.6	13.0	11.5	1.41	0.001
Kaplan et al. (2009)	Cohort study	3794	3.0	28.0	24.9	1.44	0.001
Barbosa et al. (2013)	Cohort study	106	3.0	11.0	11.0	1.00	0.99
Overall						1.35	0.001

Gacci M, Eur Urol, 2016

EUROPEAN UROLOGY 76 (2016) 784-794

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Study name	OR	Lower	Upper	p-value
Waldman et al. 2000	3.50	1.10	13.72	0.03
Smith et al. 2001	2.72	1.75	4.22	0.001
Smith et al. 2005	3.18	2.58	3.91	0.001
Wong et al. 2006	1.63	1.25	2.12	0.001
El-Sakka et al. 2006	0.91	0.34	2.59	0.001
Chapple et al. 2009	3.58	3.56	4.25	0.001
Kaplan et al. 2009	3.48	2.82	4.57	0.001
Wong et al. 2009	1.88	1.61	2.21	0.001
Barbosa et al. 2013	2.52	1.72	3.73	0.001
Scoppelloni et al. 2014	2.25	1.61	2.83	0.001
Overall	2.80	2.56	3.07	0.001

Gacci M, Eur Urol, 2016

EUROPEAN UROLOGY 76 (2014) 744–754
 available at www.sciencedirect.com
 journal homepage: www.elsevier.com/locate/eurow

Male Lower Urinary Tract Symptoms and Cardiovascular Events: A Systematic Review and Meta-analysis

Platinum Priority – Collaborative Review – Best Practice Evidence
 Edited by Mikkel Foss, Christian Gratzke and Jens Sorensen on pp. 737–758 of this issue

Maura Gacci^{1,*}, Giovanni Corona², Arcangelo Sebastianelli³, Sergio Sordi⁴, Costino De Nunzio⁵, Mauro Abbagli⁶, Linda Vignozzi⁷, Giacomo Novara⁸, Kevin F. McVary⁹, Steven A. Kaplan¹⁰, Stavros Grouvas¹¹, Christopher Chapple¹²

Gacci M, Eur Urol, 2016

EUROPEAN UROLOGY 76 (2014) 744–754
 available at www.sciencedirect.com
 journal homepage: www.elsevier.com/locate/eurow

Inflammatory Score

The correlation of extent and grade of inflammation with serum PSA levels in patients with LV prostatitis

L.J. Calkins¹, Y.-L. Liou², H.-J. Chung³, W.-S. Jang⁴

Feature	Details
Anatomical location	Historical pattern
1 glandular	Inflammatory infiltrates lie within duct/gland epithelium and/or lumen
2 periglandular	Inflammatory infiltrates lie within stroma, are centered around duct/glands, and approach duct/glands to within 50 μm
3 stromal	Inflammatory cells lie within prostatic stroma but not centered on prostatic glands/ducts and lie > 50 μm from them
Extent	Tissue area involved by inflammatory cell infiltrates
1 focal	<10%
2 multifocal	10–50%
3 diffuse	>50%
Grade	Morphological description (typical inflammatory cell density, cellularity)
1 mild	Individual inflammatory cells, most of which are separated by distinct intervening spaces (<100)
2 moderate	Coherent sheets of inflammatory cells with no tissue destruction or lymphoid nodules/follicle formation (100–500)
3 severe	Coherent sheets of inflammatory cells with tissue destruction or nodule/follicle formation (>500)

Int Urol Nephrol (2011) 43:295–301

Glandular disruption

A: Severe acute and chronic inflammatory cell infiltrate with glandular and periglandular distribution (H&E stain, original magnification 5X)
 B: Epithelium disruption at higher magnification (H&E stain, original magnification 20X)

Gacci M, Vignozzi L: Pros Can Pro Dis 2014

ORIGINAL ARTICLE
 Metabolic syndrome and lower urinary tract symptoms: the role of inflammation

M. Gacci¹, L. Vignozzi², A. Sebastianelli³, M. Sisti⁴, C. Giannessi⁵, C. De Nunzio⁶, A. Tubaro⁷, G. Corona⁸, G. Rastrelli⁹, B. Sordi¹⁰, S. Sordi¹¹, M. Abbagli¹², K.F. McVary¹³, S.A. Kaplan¹⁴, S. Grouvas¹⁵, and C. Chapple¹⁶

	Type	N [#]	SCORE
ANATOMICAL LOCATION	STROMAL	70 (26%)	1
	PERIGLANDULAR	200 (74%)	2
	GLANDULAR	1 (0%)	3
EXTENT	FOCAL (10%)	206 (76%)	1
	MULTIFOCAL(10-50%)	62 (23%)	2
	DIFFUSE (>50%)	3 (1%)	3
GRADE	MILD	108 (40%)	1
	MODERATE	132 (49%)	2
	SEVERE	31 (11%)	3
GLANDULAR DISRUPTION	ABSENT	179 (66%)	-
	PRESENT	92 (34%)	-

Gacci M, Vignozzi L: Pros Can Pro Dis 2014

MetS and LUTS: the inflammation

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 Metabolic syndrome and lower urinary tract symptoms: the role of inflammation

M. Gacci¹, L. Vignozzi², A. Sebastianelli³, M. Sisti⁴, C. Giannessi⁵, C. De Nunzio⁶, A. Tubaro⁷, G. Corona⁸, G. Rastrelli⁹, B. Sordi¹⁰, S. Sordi¹¹, M. Abbagli¹², K.F. McVary¹³, S.A. Kaplan¹⁴, S. Grouvas¹⁵, and C. Chapple¹⁶

271 consecutive men treated with OP in two tertiary referral centers for LUTS/BPH.

Gacci & Vignozzi, Prostate Can Pro Dis 2013

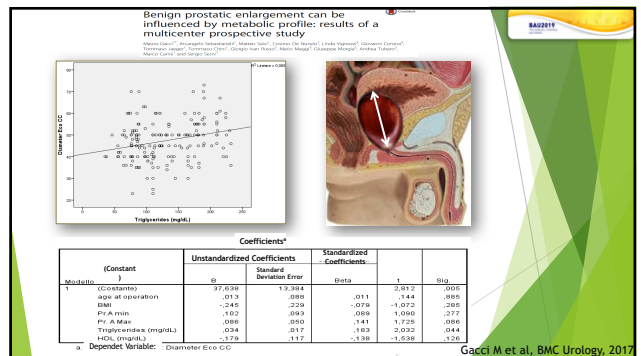
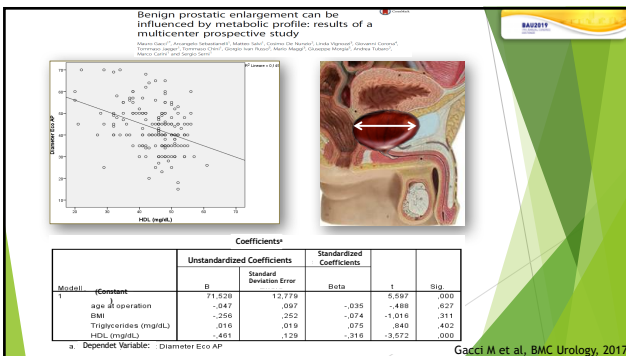
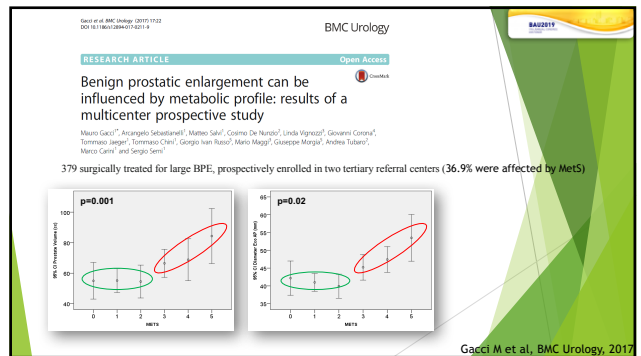
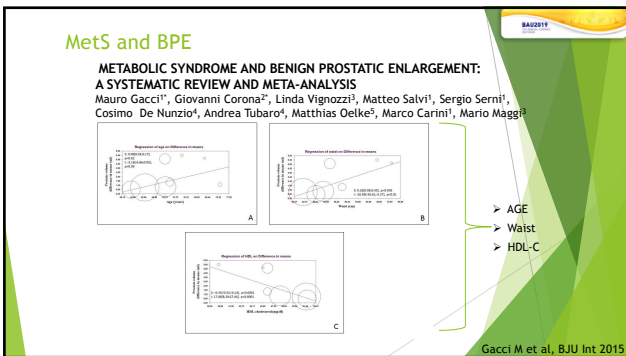
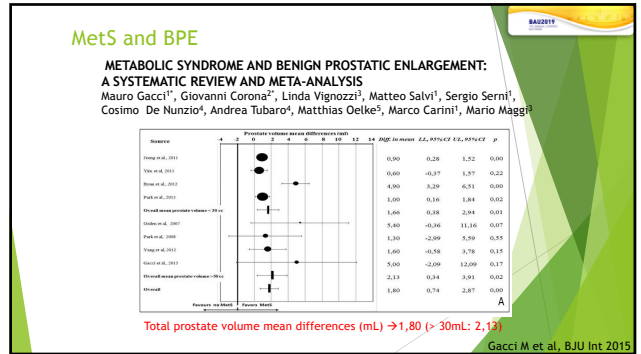
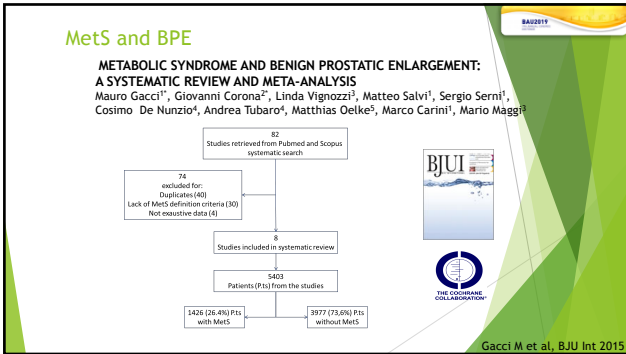
MetS and LUTS: the inflammation

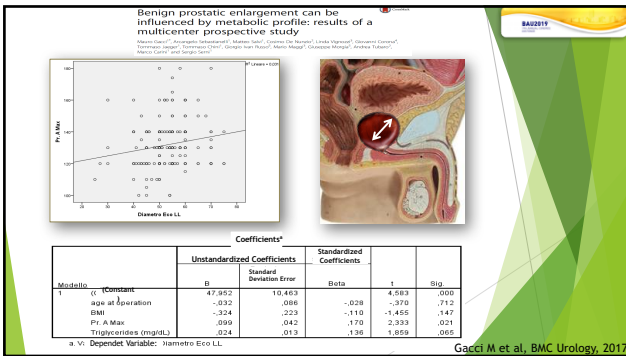
Fat Boosts, While Androgen Receptor Activation Counteracts, BPH-Associated Prostate Inflammation

Linda Vignozzi^{1,2}, Mauro Gacci³, Ilaria Cellai^{1,2}, Raffaella Santi⁴, Giovanni Corona^{1,2,5}, Annamaria Morelli⁶, Giulia Rastrelli^{7,8}, Paolo Coniglion⁹, Arcangelo Sebastianelli³, Elena Mareschi¹⁰, Gabriella Nepi¹¹, Cosimo De Nunzio¹², Andrea Tubaro¹³, Roberto Mattiacci¹⁴, Marco Carini¹⁵, and Mario Abbagli¹⁶

A multi-center cohort of BPH patients (n = 244) + effects of MetS insults on (hBPH)

Vignozzi & Gacci, Prostate 2013





RCTs have used mostly spontaneously-reported AEs to assess the effect of BPH medical treatments on sexual function

Treatment	Erectile Dysfunction % (Active / placebo arm)	Ejaculation Disorders % (Active / placebo arm)	Altered libido % (Active / placebo arm)
Tamsulosin (0.4 mg)	6.1	8.4 / 0.2*	1 / 1.2
Sildenafil	---	28.1 / 0.9***	---
Doxazosin (4 or 8 mg)	14.4 / 12.2	4.5 / 2.3*	7 / 5.7
Finasteride	13.2 / 8.8	6.2 / 1.5****	9.8 / 5.2
Dutasteride	18.5 / 12.2	7.2 / 2.3*	10 / 5.7
Finasteride + doxazosin	7.9 / 4.6	2.5 / 0.9**	4.3 / 2.3
Dutasteride + tamsulosin	22.6 / 12.2	11.6*	11.6 / 5.7
Dutasteride + tamsulosin	9.6	10.9**	6.4

*referred as abnormal ejaculation; **includes anorgasmia, retrograde ejaculation, semen volume decreased, orgasmic sensation decreased, orgasm abnormal, ejaculation delayed, ejaculation disorder, ejaculation failure, and premature ejaculation; ***retrograde ejaculation; ****includes decrease volume of ejaculate

Adapted from FDA Prescribing Information documents for: 1. Finasteride (last update 21-12-14); 2. Dutasteride (last update 22-04-13); 3. Sildenafil (last update 21-07-13); 4. Proscar (last update 11-02-14); 5. Avodart (last update 01-04-13). Access to documents in February 2017 through www.accessdata.fda.gov

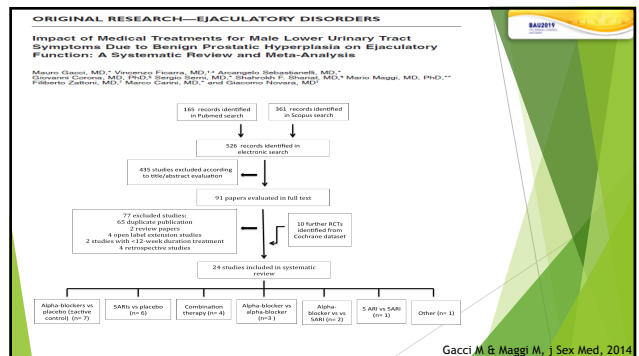
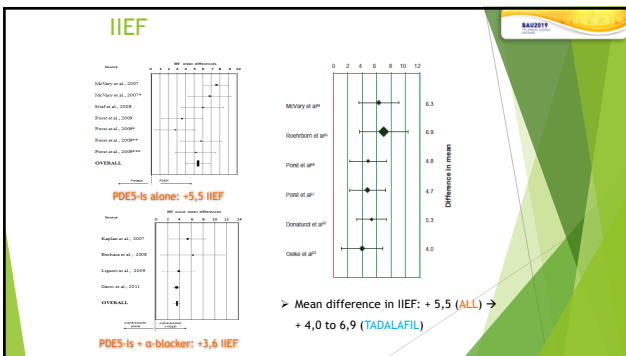
A Systematic Review and Meta-analysis on the Use of Phosphodiesterase 5 Inhibitors Alone or in Combination with α -Blockers for Lower Urinary Tract Symptoms Due to Benign Prostatic Hyperplasia

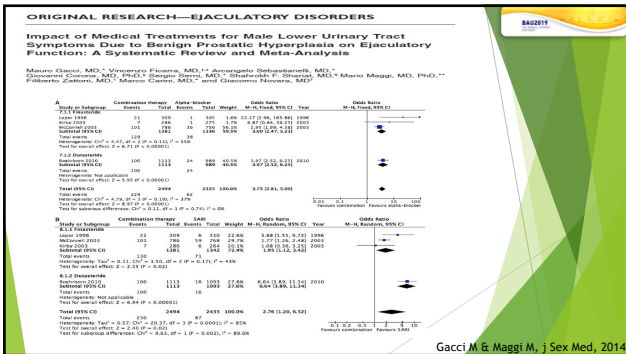
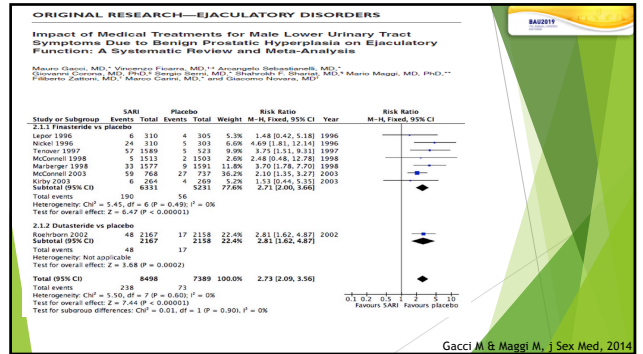
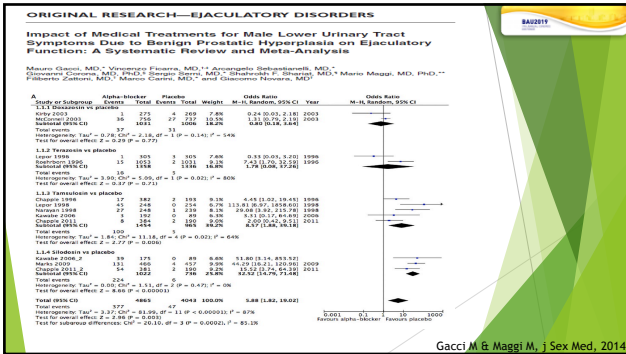
Gacci M et al, Eur Urol 2012

Research and Reports in Urology

The use of a single daily dose of tadalafil to treat signs and symptoms of benign prostatic hyperplasia and erectile dysfunction

Research & Rep 2013





Pharmacological Treatments

	Serenoa Repens	α-blockers	5-ARI	PDE5-Is
Hyperplasia reduction	YES	NO	YES	NO
Anti-inflammatory effect	YES	NO	NO	YES
Smooth cells relaxation	NO	YES	NO	YES
Side Effects	Mild gastrointestinal	Hypotension Retrograde Ejaculation	Sexual Dysfunction (Libido, Erection etc.) Gynecomastia	Hypotension Cefalea Dyspepsia
PSA	Unchanged	Unchanged	Diminished	Unchanged
Cautions	None	Antihypertensive drugs interactions	No sexual intercourse with pregnant or fertile women	Concomitant administration of Nitric Oxide

PROSTATE CANCER AND PROSTATIC DISEASES (2018) 2:161-167
<https://doi.org/10.1088/1473-1208-2018-2-161>

REVIEW ARTICLE

Prostatic inflammation: a potential treatment target for male LUTS due to benign prostatic obstruction

M. Samarinas¹, M. Gacci², A. de la Taille³, S. Gravas⁴

Study	Treatment intervention	Type of study	Number of patients	Follow-up (months)	IPSS (PMD) (95% CI)	p-value	Kaplan-Meier (PMD) (95% CI)	p-value
Coxix et al [10]	PDE5-Inhibitor	Meta-analysis	3676/7	4-24	-1.01 [-1.19, -0.74]	<0.001	-0.01 [-0.03, 0.01]	Not significant
Kalish et al [17]	5-ARI vs tamsulosin/finasteride	Meta-analysis	21/25	4-44	-2.09	<0.001	0.05	0.007
	Colonyrhinibic		4/0					
	Tamoxifen plus finasteride		2/0		[-1.38, -1.95]		[0.26, 1.63]	
Naves et al [16]	HE5-Inhibitor	Meta-analysis	122/13	4-15	3%	0%	1.37	<0.001
	HE5-Inhibitor		40/46	15-56	1.05	0.02	-0.16	0.8
	HE5-Inhibitor				[-1.11, 3.46]		[-4.80, 0.20]	

Samarinas M, Gacci M, et al: Prostate Cancer Dis 2018



LUTS and ED: Guidelines

CLINICAL PRACTICE

CONSENSUS
Erectile dysfunction and lower urinary tract symptoms: a consensus on the importance of co-diagnosis

Author: M. Kirby, C. Chapple, G. Jackson, J. Cassidy, D. Edwards, G. Heald, D. Rahn, A. Kava, M. Santoro, T. S. Gupta, M. Gupta

Risk factor

Risk factor	ED	LUTS
Age	✓ (3)	✓ (11)
Sedentary lifestyle and lack of exercise	✓ (38)	✓ (10)*
Smoking and excessive alcohol intake	✓ (38)	✓ (10)*
Depression	✓ (59)	✓ (45)
Insomnia	✓ (40)	✓ (45)
Hypertension	✓ (39)	✓ (88)
Cardiovascular disease	✓ (36)	✓ (10)*
Hyperlipidaemia	✓ (30)	✓ (30)
Type 2 diabetes mellitus	✓ (39)	✓ (10)*
Osteoporosis/osteopenia	✓ (45)	✓ (45)
Hypogonadism	✓ (89)	✓ (43)
Prostate disorder	✓ (40)	✓ (10)*
Inflammation	✓ (10)*	✓ (10)*

Patient presents with LUTS

Follow diagnostic guidelines as appropriate. For example:
NICE guidelines for BPH patients/
Consider co-diagnosis of ED

Patient presents with ED

Follow diagnostic guidelines as appropriate. For example:
NICE guidelines for ED patients/
Consider co-diagnosis of LUTS

All about co-diagnosis?

All about co-diagnosis? All about co-diagnosis? All about co-diagnosis?

Consider all risk and comorbidities as appropriate. For example:

- Hypertension
- Diabetes mellitus
- Hyperlipidaemia
- Hypertension
- Low testosterone
- BMI
- Water co-retention

Consider other possible underlying conditions:

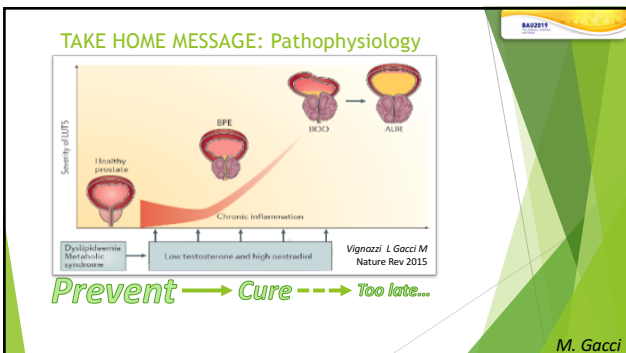
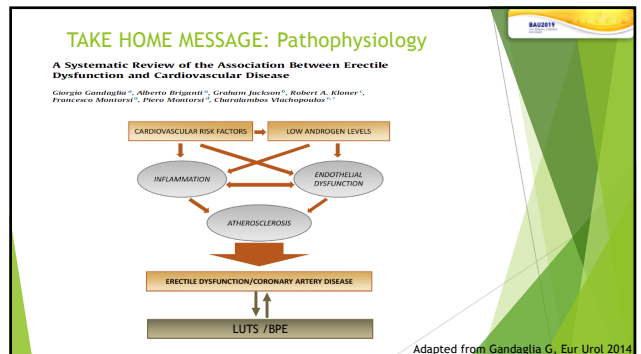
- Cardiovascular disease
- Inflammation
- Hypertension

Kirby M, Int J Clin Pract 2013

LUTS and ED: Guidelines

Guidelines	Assessment	Medical Treatment	Invasive Treatment
AUA	No recommendation	Report of adverse events	Report of adverse events Treatment Algorithm
EAU	Sexual function should be assessed, with validated questionnaires	Report of adverse events PDES-Is	Report of adverse events PUL
Japanese	No recommendation	Report of adverse events Specific question CQ15	Report of adverse events Specific question CQ15
Korean	No recommendation	Report of adverse events	Report of adverse events

Lack of specific recommendations



TAKE HOME MESSAGE: Diagnosis

Follow the clues....

TAKE HOME MESSAGE: Diagnosis

The diagram features an iceberg floating in the ocean. The tip of the iceberg, which is above the water line, is labeled 'Diagnosis'. The much larger, submerged part of the iceberg is labeled 'Disease'. To the left of the iceberg, three golden stick figures are seated at a table, representing a medical team. To the right, another golden stick figure stands, representing a patient. A dashed green arrow points from the 'Diagnosis' label down to the tip of the iceberg, and a solid green arrow points from the submerged 'Disease' part up to the tip, illustrating the relationship between the visible diagnosis and the underlying disease.

TAKE HOME MESSAGE: Treatment

This slide displays two research abstracts from the European Association of Urology (EAU). The top abstract is titled 'Critical Analysis of the Relationship Between Sexual Dysfunction and Lower Urinary Tract Symptoms Due to Benign Prostatic Hyperplasia'. The bottom abstract is titled 'Male Lower Urinary Tract Symptoms and Cardiovascular Events: A Systematic Review and Meta-analysis'. To the right of the abstracts is an image of two hands holding a pink heart and a yellow pill. The name 'M. Gacci' is printed in the bottom right corner.

TAKE HOME MESSAGE: Treatment

The slide uses a billiard ball analogy to discuss treatment. On the left, a pool table with many colorful balls is labeled 'Pool -American- billiard'. The text 'Treatment' and 'Effectiveness' is written over the balls, with 'TAES' written vertically. On the right, a five-pin Italian billiard table with five balls (one red, one yellow, one blue, one white, one red) is labeled 'Five-pin -Italian- billiard'. The text 'Age', 'ED', 'CVD', 'LUTS', and 'Comorbidities' is written over the balls, with 'LUTS' written vertically. The background features a green geometric pattern.