MEDICAL TREATMENT OF LUTS/BPH
--- IDEAL AND REALITY ---

馬偕紀念醫院　泌尿科
林文榮　　醫師

Benign prostatic hyperplasia (BPH)

- BPH = Histological Presence of cellular proliferation of the prostate gland; evident in 50% of men by age 60, in 80% by age 80
- Hyperplasia of the prostate narrows the urethral lumen (static component)
- Prostatic smooth muscle tone, mediated by alpha-adrenergic receptors, can further obstruct the bladder outlet (dynamic component)

Symptoms of BPH (Lower Urinary Tract Symptoms)

- Symptoms of bladder outlet obstruction caused by BPH include:
  - Hesitancy
  - Weakness of urinary stream
  - Intermittent urinary stream
  - A feeling of incomplete bladder emptying and need for repeat voiding
  - Bladder 'irritability,' as manifested by urinary frequency, nocturia, and urinary urgency

storage or obstructive symtptoms and voiding or irritative symptoms

LUTS Are a Constellation of Storage and Voiding Symptoms

Symptoms Often Relate to the Bladder and the Prostate

Storage	Voiding	Post-micturition
Urgency	Hesitancy	Post-void dribble
Frequency	Poor flow	Sense of incomplete emptying
Nocturia	Intermittency	
Urgency incontinence	Straining	
Other incontinence	Terminal dribble	

LUTS = lower urinary tract symptoms.

Abrams P et al. *Neurol Urodyn.* 2002;21:167-178.

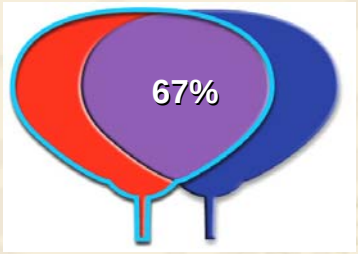
Men With LUTS: Storage and Voiding/Post-micturition Symptoms

Storage

OAB
- *Urgency*
- *Frequency*
- *Nocturia*
- *UUI*

Other Incontinence

Storage + Voiding/Post-Micturition



Voiding/Post-micturition

- *Slow Stream*
- *Intermittency*
- *Straining*
- *Terminal Dribble*
- *Post-micturition Dribble*
- *Incomplete Emptying*

UUI = urgency urinary incontinence.

Irwin DE et al. *Eur Urol*. 2006;50:1306-1315.
Abrams P et al. *Urology*. 2003;61:37-49.

Male LUTS Can Be Associated with the Bladder, the Prostate, or Both

Other conditions associated with LUTS include psychogenic disorders, congestive heart failure, and polypharmacy.

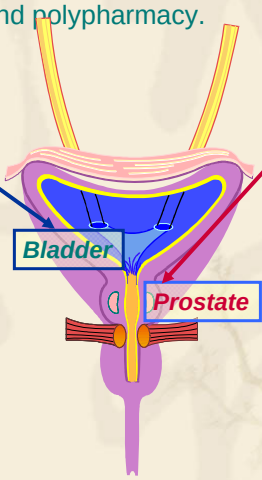
Bladder Condition

OAB

Urgency, with or without urgency incontinence, usually with frequency and nocturia

Pharmacological Therapy for OAB

Antimuscarinics



Prostate Condition

'BPH'

Term used (and reserved for) the typical histological pattern which defines the disease

Pharmacological Therapies for BPH

Alpha-blockers

5-alpha-reductase inhibitors

OAB = overactive bladder; 'BPH' = benign prostatic hyperplasia.

Abrams P et al. *Urology*. 2003;61:37-49.

Treatments for LUTS, BPH, BOO

- Watchful waiting
- Medical therapy
  - Phytotherapy
  - 5α-reductase inhibitors
  - α-blockers
  - Combination therapy
- Office-based treatment
  - TUMT
  - TUNA
  - WIT
- Surgicenter/ hospital-based treatment
  - TURP (gold standard)
  - TUIP
  - Open surgery
  - TUVP
  - ILC
  - VLAP
  - Prostatic stents
  - PVP

Chatelain C et al. In: Chatelain C et al, eds. *Benign Prostatic Hyperplasia*. Plymouth, UK: Health Publication Ltd; 2001;519-534.
DeBruyne FMJ et al. In: Chatelain C et al, eds. *Benign Prostatic Hyperplasia*. Plymouth, UK: Health Publication Ltd; 2001;397-421.
McConnell J. Presented at American Urological Association 2002 Annual Meeting (Abstract 1042, updated).

Treatment options for BPH

LUTS	Treatment options
Mild symptoms	**Reassurance** **Observation**
Moderate symptoms	**Medical therapy** **Minimally invasive therapy (MIT)** **TURP** **Observation**
Severe symptoms	**Medical therapy** **MIT** **TURP** **Open surgery**

Medical Treatment for LUTS/BPH

- Alpha blockers
- 5 alpha reductase inhibitors
- Anticholinergic Agents
- Antidiuretics
- Phytotherapy

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Comparison of α-Blockers

Agent	Dosing	Titration	Uroselective
Terazosin	1 mg, 2 mg, **5 mg, 10 mg**	+	NO
Doxazosin	1 mg, 2 mg, **4 mg, 8 mg**	+	NO
Tamsulosin	**0.4 mg, 0.8 mg**	+/-	YES (High relative affinity for alpha 1a)
Alfuzosin	**10 mg**	-	YES (Highly diffused in prostatic tissue vs. serum)

Product Information, © Abbott Laboratories, © Pfizer Inc., © Boehringer Ingelheim Pharmaceuticals, Inc.
Data on file, Sanofi-Synthelabo Inc.

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BAckup only for urologists
Drop the half life column
goeckra, 2002/10/19

Efficacy of α-blockers in treating BPH

clinical efficacy

15-30% (5-15%) increase in flow rates

Quality of Life

30-45% (10-15%) Improvement in symptom score

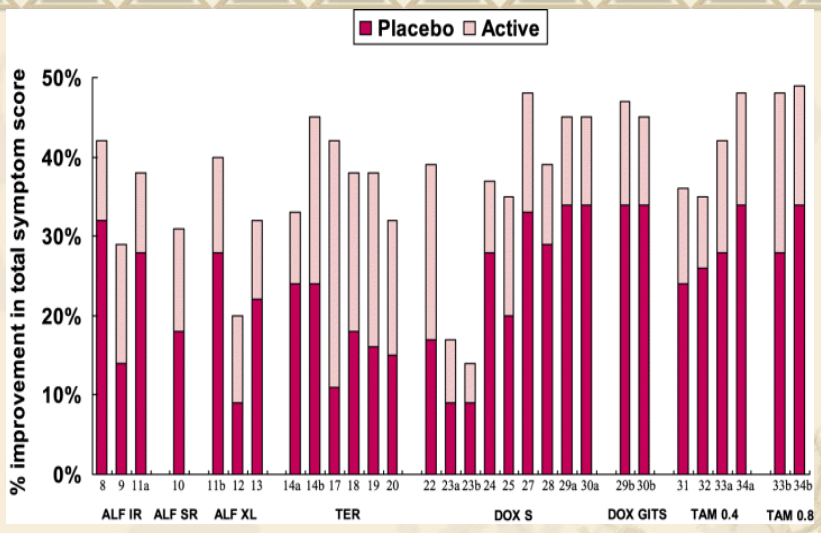

FIGURE 1. *Effect of α_1-AR antagonists on total symptom score in placebo-controlled studies. Total number of patients in all studies: alfuzosin (ALF), n = 2208; terazosin (TER), n = 3229; doxazosin (DOX), n = 3947; and tamsulosin (TAM), n = 1331. IR = immediate release; SR = sustained release; S = standard.*

Djavan, B et al. Urology 64: 1081-1088, 2004.

Alpha blockers: Adverse events

- Fatigue
- Orthostatic hypotension leading to dizziness, vertigo, or syncope upon standing
- Decreased libido
- Edema
- Retrograde ejaculation
- Rhinitis
- Dyspnea or wheezing
- Headache
- Angina
- Arrhythmia

There are slight differences in the adverse events profiles of the four agents. (discontinuation due to adverse events: 4-10% for tamsulosin and alfuzosin; additional 4-10% for terazosin and doxazosin.)

AUA guideline on management of BPH, 2003
Marberger, M Eur Urol 2004

Tamsulosin: Adverse Events

	0.4 mg (N=502)	0.8 mg (N=492)	Placebo (N=493)
Headache	19.3%	21.1%	20.1%
Dizziness	14.9%	17.1%	10.1%
Rhinitis	13.1%	17.9%	8.3%
Infection	9.0%	10.8%	7.5%
Abnormal ejaculation	8.4%	18.1%	0.2%
Asthenia/fatigue	7.8%	8.5%	5.5%
Back pain	7.0%	8.3%	5.5%
Diarrhea	6.2%	4.3%	4.5%
Pharyngitis	5.8%	5.1%	4.7%
Chest pain	4.0%	4.1%	3.7%
Orthostatic hypotension	16%	19%	11%
Somnolence	3.0%	4.3%	1.6%

*Occurring in ≥3% of patients.

Product Information, © Boehringer Ingelheim Pharmaceuticals, Inc.

Uroselective > Non-uroselective

- *treating old or very old* BPH patients who are susceptible to orthostatic hypotension
- *treating BPH patients with hypertension demanding multiple antihypertensive agents, exempting α blockers treatment*
- *treating BPH patients with ED requiring the use of PDE 5 inhibitors*

Non-uroselective > Uroselective

- *treating BPH patients with hypertension demanding multiple antihypertensive agents including α blockers*
- *taking BPH patients' sexual function into consideration*
- *concerning the cost*
- *regarding other factors*

Alpha blockers for BPH
--- unsettled issues ---

- *BPH ≠ LUTS*
- *Non-responders/poor responders*
- *Duration*
- *Dosage*
- *Follow up strategy*

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Comparison of α-Blockers

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goeckra, 2002/10/19

Dosage of α-blockers

- The right way to use alpha-blockers to treat LUTS/BPH: dose titration, efficacy, adverse effect
- Asian Urologists seem to be reluctant to use larger doses of α 1-blockers in treating BPH

Chung BH et al (Korea, 2005)[1]	doxazosin 4mg/day
Suzuki H et al (Japan, 2006)[2]	Tamsulosin 0.2mg/day
Rahardjo D et al (Indonesia, 2006)[3]	Tamsulosin 0.2mg/day doxazosin 2mg/day
Xue Z (China, 2007) [4]	Tamsulosin 0.2mg/day doxazosin 4mg/day

1. IJU 2005; 12:159 2. IJU 2006; 13: 1202 3. IJU 2006; 13: 1405 4. IJU 2006; 14: 118

SOME MEN WITH LUT/BPH MAY NEED 8MG OF DOXAZOSIN TO GET A BETTER THERAPEUTIC EFFECT

Study Design - I

- BPH patients taking doxazosin 4mg/day for at least 3 months, yet still having significant LUTS manifested as having an International Prostate Symptom Score (I-PSS) ≥13, a peak flow rate <15 ml/sec and an I-PSS QoL index ≥3
- Doxazosin was increased to 8mg/day for 3 months and **efficacy and safety were accessed**
- Excluding patients taking anti-cholinergics, 5-α reductase inhibitors, or hormonal therapeutic agents

Study Design - II

- Excluding subjects who had been treated with pelvis irradiation or pelvic surgery (including prostate or bladder surgery, but prostate needle biopsy is allowed)
- Excluding subjects who had a suspicion of prostate cancer as shown by an abnormal digital rectal examination or a high PSA velocity (> 0.76 ng/ml/year)
- Excluding subjects who had active infection, inflammation of any organ systems or urinary stones

Study Objectives

- To find out the percentage of subjects who achieved I-PSS reduction by 4 or more points and Q_{max} increase by 20% or more from the baseline at 12 weeks
- To evaluate the general safety and tolerability of doxazosin 8 mg/day
- To determine effects of dose increase on change of I-PSS, QoL, urinary peak flow rate, and postvoid residual urine amount

Results - I

- Initially, 51 patients were enrolled
- Two patients dropped out due to moderate dizziness and headache respectively
- Six patients lost of follow-up
- Totally, 43 patients were eligible for analysis

Results - II

Patient characteristics (N=43)

Age (years)	67.35 (52-84)
Prostate size (c.c.)	35.21 (19.5-70)
PSA (ng/ml)	3.88 (0.671-18.30)
BMI (%)	24.58 (20.45-30.47)
Hypertension	N=9
Taking antihyertensive(s)	N=4
IPSS at baseline	16.30 (13-29)
QoL at baseline	4.19 (3-6)
Qmax (ml/s) at baseline	10.16 (2.7-14.2)

Results – III

	Baseline	At 12 weeks	P value
IPSS	16.30 (13-29)	11.95 (7-20)	<0.001
QoL	4.19 (3-6)	3.05 (1-5)	<0.001
Qmax (ml/s)	10.16 (2.7-14.2)	12.09 (3.2-19)	<0.001
PVR (ml)	76.27 (2.4-234.66)	51.74 (4.61-365.5)	0.004
BP (mmHg), sys	132.09 (106-170)	133.11 (109-185)	0.545
BP (mmHg), dias	78.09 (62-98)	79.53 (66-107)	0.377
BP, standing, sys		129.30 (106-176)	<0.001
BP, standing, dias		76.51 (62-100)	<0.001
PR	71.07 (66-84)	70.88 (58-84)	0.710
PR, standing		73.35 (67-86)	<0.001

Results - IV

- 22/43 having Q_{max} increase by 20% or more from the baseline
- 14/43 having I-PSS reduction by 4 or more points from the baseline
- 11/43 achieving both (not affected by age, BMI, prostate size or serum PSA level)
- Positive global effect: 20/43
- Outcome: 4 mg/day 22
  8 mg/day 18
  TURP 3

Results – V

		P value
IPSS reduction (%)	46.32 (27.78-61.54)	0.622
Qmax increase (%)	42.91 (20.65-82.61)	
IPSS reduction (%)		
Storage symptoms	30.94 (-14.28-66.67)	0.004
Voiding symptoms	83.33 (41.67-60.43)	

Results - VI

Adverse Effect	No. (Totally 10)
Dizziness	4
Palpitation	3
Constipation	1
Back pain	1
Muscle pain	1

- No patient developed postural hypotension.
- Occurrence of AE's was not significantly correlated with age, presence of hypertension and antihypertensive usage.

Conclusions

- About one fourth of patients can benefit from dose increase of doxazosin up to 8 mg/day in treating BPH
- Voiding symptoms improve more than storage symptoms from dose increase
- Dose increase is safe regarding drop-out rate, AE occurrence and BP change

5α-Reductase Inhibitors

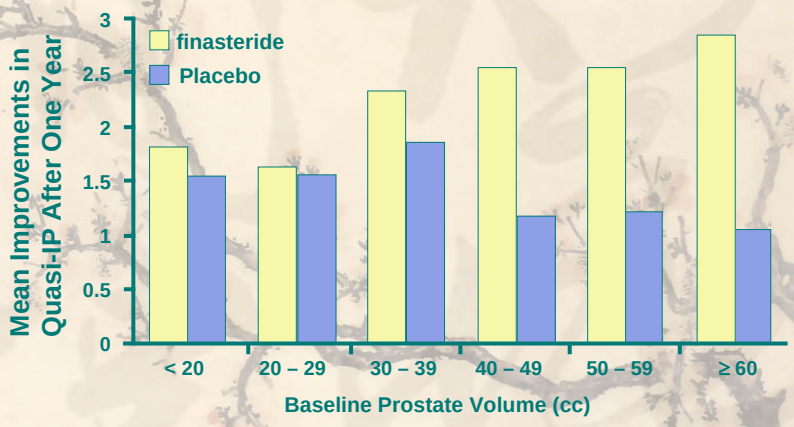
- 5α-reductase (5AR) isoenzymes convert testosterone (T) to the more potent dihydrotestosterone (DHT)
- Agents that inhibit 5AR enzymes (5ARIs) reduce DHT in serum and prostate
- Decreased androgenic activity induces epithelial atrophy and shrinkage of the prostate, improving LUTS and flow rate

Bartsch G et al. In: Chatelain C et al, eds. *Benign Prostatic Hyperplasia*. Plymouth, UK: Health Publication Ltd; 2001:423-457.

Finasteride

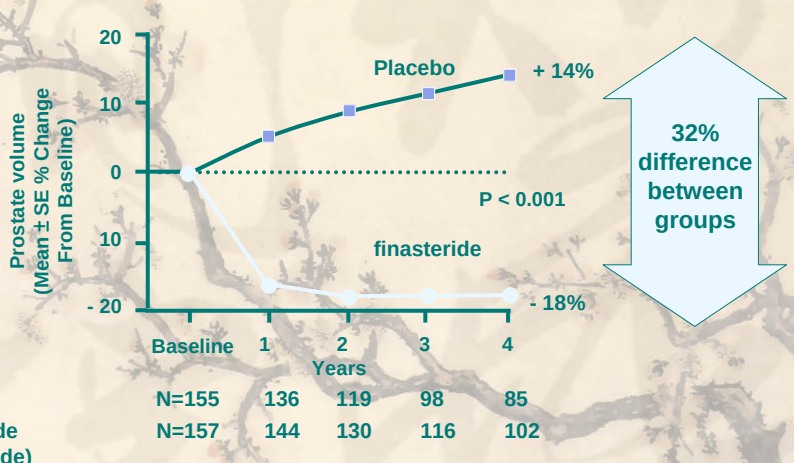
- Mechanism of action: Inhibits conversion of testosterone to dihydrotestosterone
- Shrinks overall gland size, reduces obstruction
- Must be taken for at least 3 months before efficacy can be determined

Symptom Response by Prostate Volume



Adapted from Boyle P, et al. Prostate volume Predicts outcome of treatment of benign prostatic hyperplasia with finasteride: analysis of randomized clinical trials. Urology. 1996; 48:398 - 405

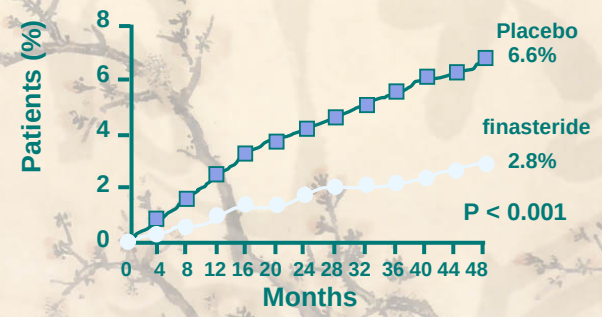
Effect of Finasteride Prostate Volume



Placebo	N=155	136	119	98	85
finasteride (finasteride)	N=157	144	130	116	102

McConnell JD, et al. The effect of finasteride on the risk of acute urinary retention and the need for surgical treatment among men with benign prostatic hyperplasia. Finasteride Long- Term Efficacy and Safety Study group. N Engl J Med. 1998; 338:557 - 563

Effect of Finasteride on Development of AUR

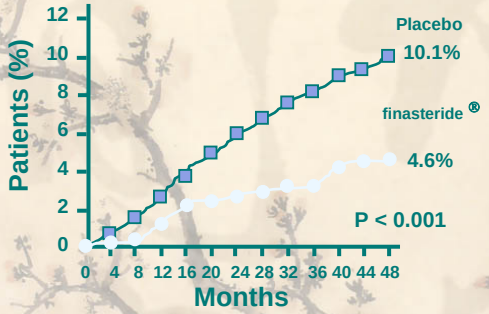


57% overall risk reduction

Placebo				
No. of events, cumulative	36	61	81	99
No. at risk per year	1503	1454	1398	1347
finasteride				
No. of events, cumulative	14	25	32	42
No. at risk per year	1513	1487	1449	1421

Adapted from McConnel JD, et. al. The effect of finasteride on the risk of acute urinary retention and the need for surgical treatment among men with benign prostatic hyperplasia. Finasteride Long- Term Efficacy and Safety Study Group. N Engl J Med. 1998; 338:557-563. Data on file, Merck & Co., Inc. DA-PRO19(2)

Effect of Finasteride on Need for BPH Surgery



55% overall risk reduction

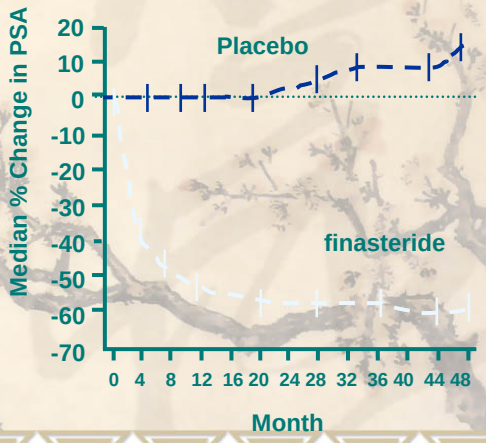
Placebo				
No. of events, cumulative	37	89	121	152
No. at risk per year	1503	1454	1398	1347
finasteride				
No. of events, cumulative	18	40	49	69
No. at risk per year	1513	1487	1449	1421

Adapted from McConnel JD, et. al. The effect of finasteride on the risk of acute urinary retention and the need for surgical treatment among men with benign prostatic hyperplasia. Finasteride Long- Term Efficacy and Safety Study Group. N Engl J Med. 1998; 338: 557-563. Data on file, Merck & Co., Inc. DA-PRO19(2)

PSA and Finasteride

- Approximate 50% decrease in PSA (may vary in individual patients)
- Double value in patentees treated 6 months or more for comparison with normal ranges
- Percent-free PSA unaffected
- Any sustained increase in PSA levels for patients on finasteride should be carefully evaluated

Median Percent Change +/- 95% CI in Prostate Specific Antigen



Data on file, Merck & Co., Inc DA-PRO26(1)

Finasteride: Adverse Reactions

	Year 1 (%)		Years 2 – 4* (%)	
	Finasteride	Placebo	Finasteride	Placebo
Impotence	8.1	3.7	5.1	5.1
Decreased libido	6.4	3.4	2.6	2.6
Decreased ejaculate	3.7	0.8	1.5	0.5
Ejaculation disorder	0.8	0.1	0.2	0.1
Breast enlargement	0.5	0.1	1.8	1.1
Breast tenderness	0.4	0.1	0.7	0.3
Rash	0.5	0.2	0.5	0.1

* Combined Years 2-4: N + 1524 and 1516, finasteride and placebo, respectively. reported postmarketing adverse effects include: hypersensitivity reactions, including puritus, urticaria, and swelling of the lips and face; testicular pain.

Prescribing Information for finasteride

5α-Reductase Inhibitors: Comparison of Physiologic Effects

Add half life?	Finasteride	Dutasteride
5AR inhibition	Type II	Type I and II
Serum DHT	⇓ ~70%	⇓ >90%
Serum T	⇑ 14%-20%	
Serum PSA	Total PSA ⇓ ~50%; Free PSA ⇓ ~50% F/T ratio unchanged	
Prostate volume	⇓ 20%-30%	⇓ 15%(?)-26%
Dosage	5 mg qd	0.5 mg qd

Bartsch G et al. In: Chatelain C et al, eds. *Benign Prostatic Hyperplasia*. Plymouth, UK: Health Publication Ltd; 2001:423-457. Roehrborn CG et al. *Urology*. 2002;60:434-441.

5α-Reductase Inhibitors: Comparison of Clinical Effects

	Finasteride 48 M controlled trial (3040) men		Dutasteride 24 M controlled trial (4325 men)	
	Finasteride	Placebo	Dutasteride	Placebo
Volume changes	-18%	+14%	-26%	-2%
IPSS reduction	-3.3	-1.3	-4.5	-2.3
Qmax improvement	+1.9	+0.2	+2.2	+0.6
AUR risk reduction	57%		57%	
Surgery risk reduction	55%		48%	

PLESS NEJM 1998 for finasteride and Roehrborn et al Urology. 2002 Sep; 60(3)434-41 for dutasteride

5α reductase inhibitors for BPH
--- unsettled issues ---

- *BPH ≒ LUTS*
- *To whom and when to start*
- *Side effects (dosage, duration)*
- *Cost*

Combination therapy

- Dual mechanism of action
- Reduce clinical progression of BPH
- Improve LUTS symptoms
- Improve maximum urinary flow rates

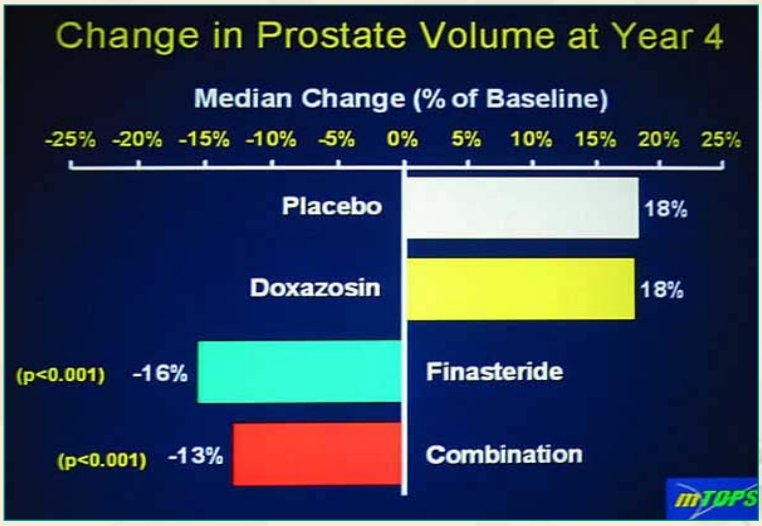
MTOPS study design

- N = 3,047 men aged ≥50 yrs
- Criteria for enrollment/baseline characteristics
  - AUA symptom score 8 to 30 (mean: 17)
  - Maximum urine flow: 4 mL/sec (mean: 10.6)
  - Voided volume ≥125 mL/sec
  - Mean prostate volume: 31 cc
  - Post void residual volume (avg.): 39 mL

MTOPS study design (continued)

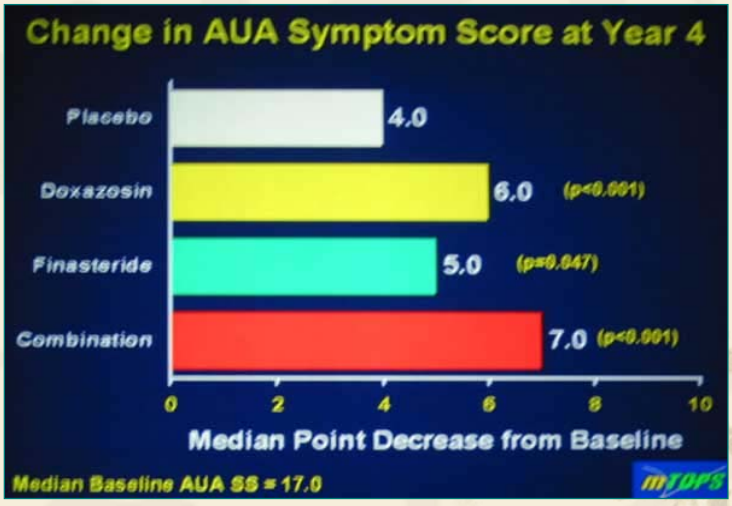
- Treatment groups
  - Placebo
  - Finasteride, 5 mg
  - Doxazosin, 4 or 8 mg
  - Combination therapy (finasteride + doxazosin)

MTOPS: Prostate volume



McConnell, JD, et al. N Engl J Med 2003; 349:2287-2398.

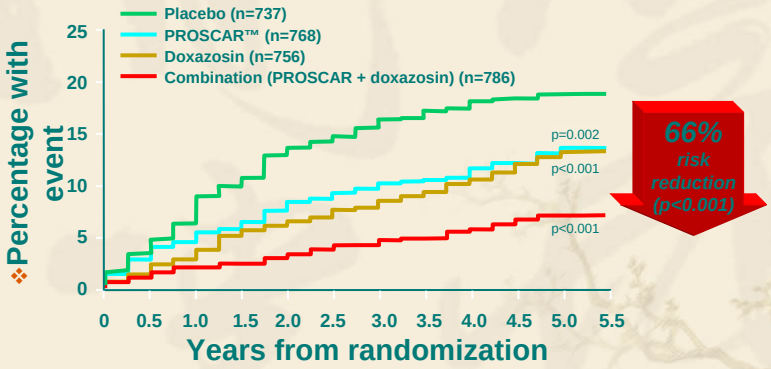
MTOPS: AUA symptom scores



McConnell, JD, et al. N Engl J Med 2003; 349:2287-2398.

MTOPS: 5-yr progression of BPH

Cumulative incidence of BPH progression

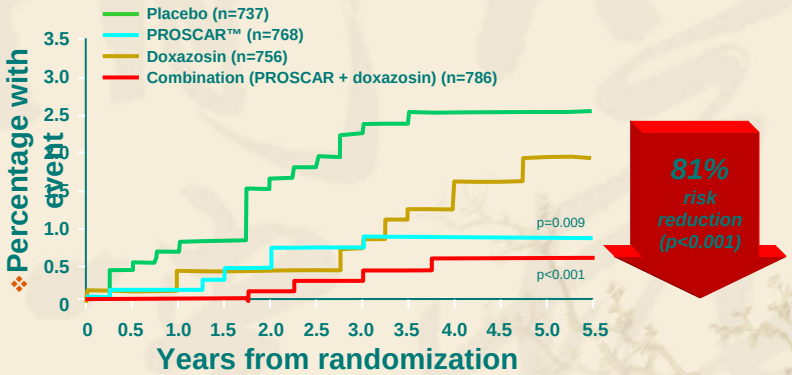


P values are for the comparison with placebo.

Adapted from McConnell JD et al *N Engl J Med* 2003;349(25):2385-2396; Bautista OM et al *Control Clin Trials* 2003;24:224-243.

MTOPS: AUR incidenced

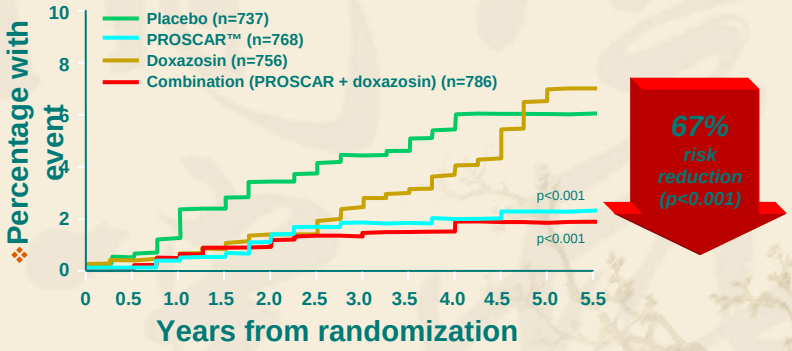
Cumulative incidence of AUR



Adapted from McConnell JD et al *N Engl J Med* 2003;349(25):2385-2396; Bautista OM et al *Control Clin Trials* 2003;24:224-243.

MTOPS: need for invasive tx

Cumulative incidence of BPH-related surgery



*Endoscopic (e.g., transurethral prostatectomy) or open surgeries primarily; other therapies were minimally invasive (e.g., transurethral microwave therapy)

Adapted from McConnell JD et al *N Engl J Med* 2003;349(25):2385-2396; Bautista OM et al *Control Clin Trials* 2003;24:224-243.

Combination therapy for BPH
--- unsettled issues ---

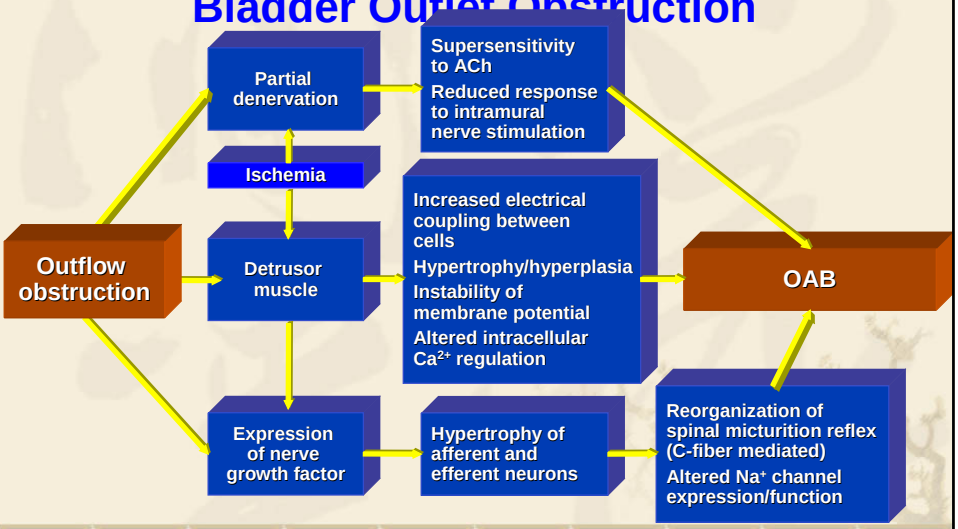
- ***Cost***
- ***Dosage, Duration***
- ***Discontinuation of alpha blockers***
- ***Side effects***

Prevalence of OAB in Men With BOO

- OAB occurs in 52% to 80% of men with BOO.
- Up to 28% of men with BOO continue to have OAB after surgical relief of the obstruction.
- Anti-muscarinics may be of help.

Abrams PH et al. *J Urol*. 1979;121:640-642.
Chapple CR et al. *BJU Int*. 1994;73:117-123.

Potential Etiology of OAB in Men With Bladder Outlet Obstruction

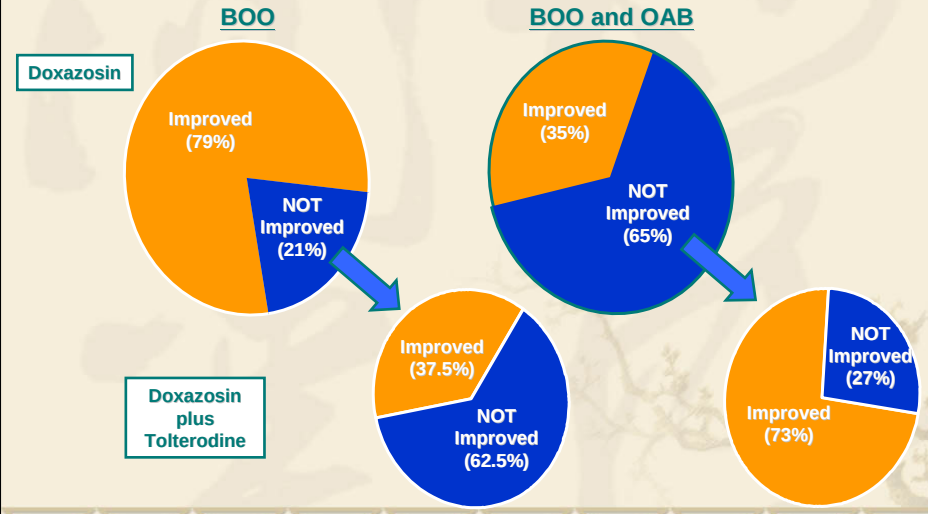


Ach = acetylcholine.

Steers WD. *Rev Urol*. 2002;4(suppl 4):S7-S18.

Evidences Supporting Efficacy and Safety of Anti-muscarinic Treatment of Male LUTS

Comparison of Doxazosin With or Without Tolterodine in Men With Symptomatic BOO and OAB



Please see full prescribing information.

Lee JL et al. *BJU Int.* 2004;94:817-820

Most Common Adverse Effects

Doxazosin only

- Dizziness (3/144, 2%)
- Postural hypotension (2/144, 1.3%)
- Abnormal ejaculation (2/144, 1.3%)

Combined therapy

- Dry mouth (16/60, 27%)
  - 14 or 16 patients reporting (87%) classified it as mild or moderate
- Temporary acute urinary retention (2/60, 3.3%)
  - Resolved after drug discontinuation and overnight catheter

Lee JL et al. *BJU Int.* 2004;94:817-820.

Safety of Detrol® in Men With OAB and Coexisting BOO

Study Design

- Multinational, double-blind study (n = 222) comparing 12 weeks of Detrol® 2 mg bid and placebo
  - Urodynamically obstructed
  - IBCs on UDS
  - No prior therapy for BPH
- Primary objective was safety
  - The effects of Detrol® on urinary flow and detrusor pressure at maximum flow
  - PVR and adverse effects

IBC = involuntary bladder contraction; UDS = ultra-Doppler sonography; PVR = postvoid residual.

Abrams P et al. *Neurourol Urodyn.* 2001;20:547-548.

Detrol® Did Not Decrease Maximum Flow Rate in Men With OAB and BOO

Q_{max} (mL/s)	Placebo (n = 72)	Detrol® (n = 149)
Baseline, median (range)	8.0 (2.4-15.0)	8.5 (2.0-20.0)
Week 12, median (range)	8.8 (2.5-17.0)	8.5 (2.0-32.0)
Estimated difference (95% CI) in median change (Detrol® vs placebo)	–0.7 (–1.6 to 0.4)	

Abrams P et al. *Neurourol Urodyn*. 2001;20:547-548.

Detrol® Did Not Increase the Incidence of AUR in Men With OAB and BOO

Adverse Effects

	Placebo (n = 72)		Detrol® (n = 149)	
	N	%	N	%
Micturition disorder	2	2.8	7	4.7
Urinary tract infection	3	4.2	6	4.0
Dysuria	1	1.4	3	2.0
Micturition frequency	2	2.8	3	2.0
Micturition urgency	1	1.4	2	1.3
Strangury	0	–	2	1.3
Urinary retention	1	1.4	1	0.7
Bladder discomfort	0	–	1	0.7
Urethral disorder	0	–	1	0.7
Urinary incontinence	2	2.8	0	–
Overall	9	12.5	19	12.8

Abrams P et al. *Neurourol Urodyn*. 2001;20:547-548.

Antimuscarinics in LUTS/OAB
Where Are We now?

European Urology 50 (2006) 675–683

Available at www.sciencedirect.com
Journal homepage: www.europeanurology.com

European Association of Urology

Review – Bladder Outlet Obstruction

Anticholinergic Drugs in Patients with Bladder Outlet Obstruction and Lower Urinary Tract Symptoms: A Systematic Review

Giacomo Novara[a,], Antonio Galfano[a], Vincenzo Ficarra[b], Walter Artibani[a]*

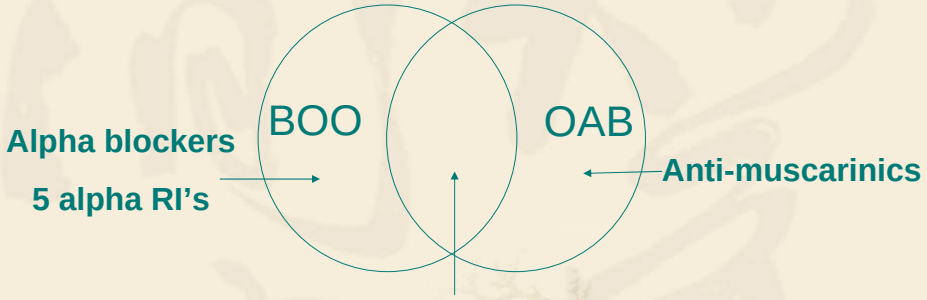
[a]Department of Oncological and Surgical Sciences, Urology Clinic, University of Padua, Padua, Italy
[b]Department of Urology, University of Verona, Verona Italy

Conclusion

- ‘The available data may be considered promising and the use of anticholinergic drug was demonstrated to be quite safe’
- ‘The evidence coming from the limited number of RCTs available, considering their methodologic or clinical weaknesses, are not sufficient to support the clinical use of a therapy with alpha-blocker and anticholinergic drugs’
- ‘Well-designed, large, double-blind, placebo-controlled, long-term RCTs are needed to assess the safety and, above all, efficacy of antimuscarinic drugs, alone or in combination with alpha-blocker’

RCT = randomized controlled trial.

Combination therapy for BPH
--- unsettled issues ---



Alpha blockers

5 alpha RI's

Anti-muscarinics

How to treat?

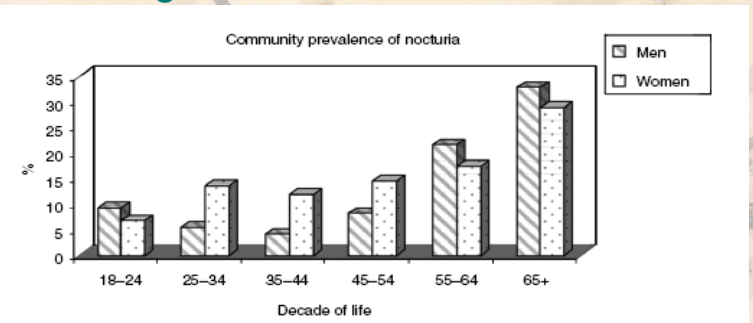
Efficacy? Safety?

Cost?

DESMOPRESSIN IN TREATING NOCTURNAL POLYURIA

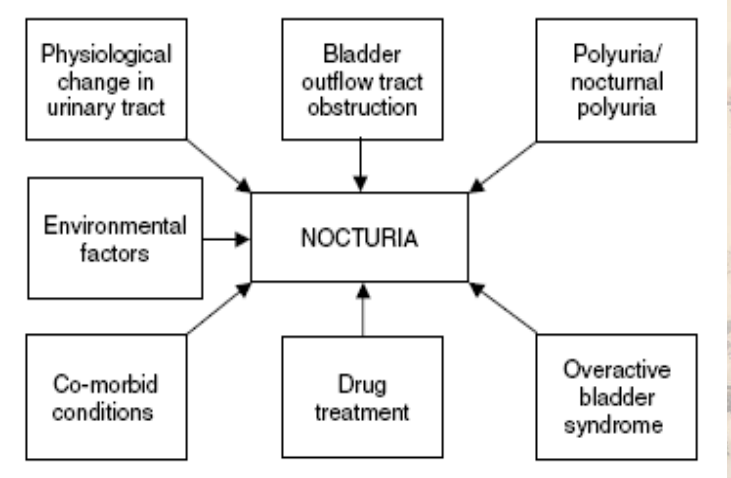
Nocturia (Nycturia)

- One or more times to void urine at night
- One of the most bothersome LUTS
- More frequent with aging
- Affecting both men and women



Br J Urol 1994; 74: 551 Am J Obstet Gynecol 2001; 185: 514 J Urol Nephrol 2004; 38: 112
J Clin Pract 2005; 59: 938

Cause of Nocturia - I



J Clin Pract 2005; 59: 938

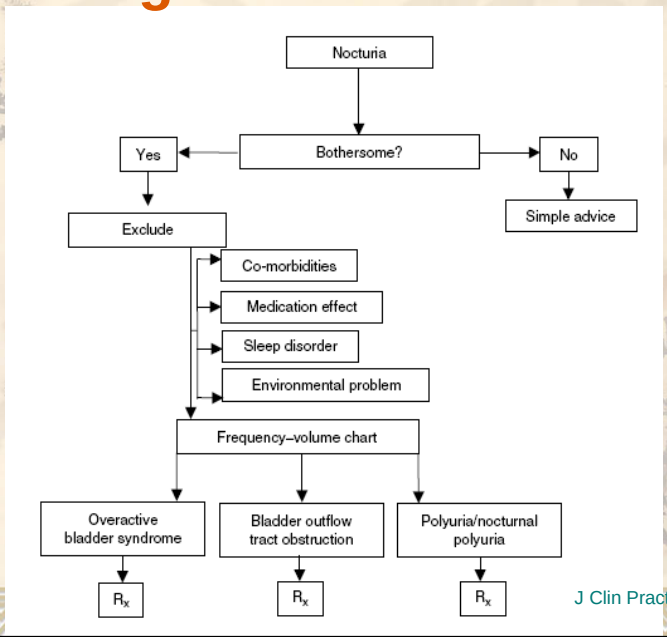
Cause of Nocturia - II

Physiological changes predisposing nocturnal urinary frequency in the elderly

- Increased 24 h urine volume output
- Increased urinary frequency
- Reduction in the ability of the kidney to concentrate urine
- Reduction in functional bladder capacity
- Reduced sensation of bladder filling
- Delayed diuresis in response to a fluid load
- Alteration in the circadian rhythm of anti-diuretic hormone secretion
- Increased level of Na secretion by night

J Clin Pract 2005; 59: 938

Management of Nocturia

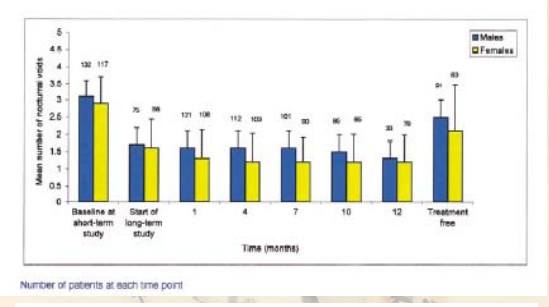


J Clin Pract 2005; 59: 938

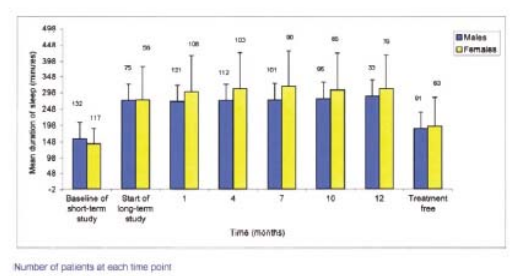
Desmopressin for Nocturia

- Less secretion of vasopressin with aging
- Diminishing renal response to vasopressin with aging
- The only analog of vasopressin --- desmopressin (since 1967)
- Effective in reducing nocturia
- Concern of side effects
- Questions remain regarding its use

Efficacy of Desmopressin in Treating Nocturia



Mean number of nocturnal voids in male and female patients by treatment period.
(from 3 to 1.7 times)



Mean duration of first sleep period in male and female patients by treatment period.
(from 161 to 269 min.)

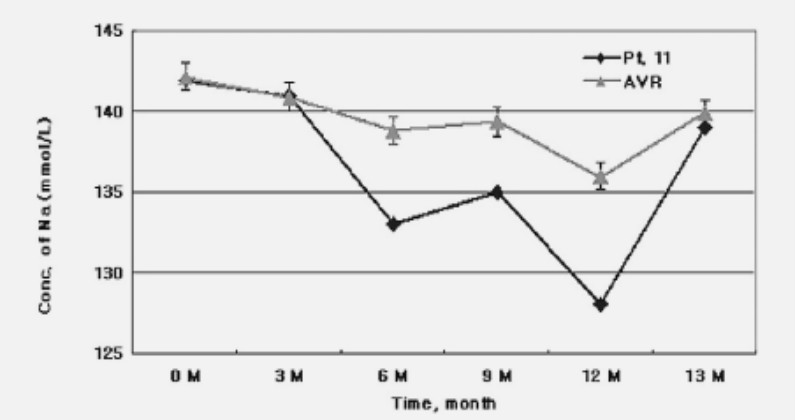
J Urol 2004; 172: 1021

Safety of Desmopressin in Treating Nocturia

Adverse Event	N=132 Men No. (%)	N=132 Men No. Events	N=117 Women No. (%)	N=117 Women No. Events
Most frequent (2% or more) adverse events related to study medication:				
Dizziness	6 (5)	7	2 (2)	2
Headache	6 (5)	7	8 (7)	17
Micturition frequency	2 (2)	2	3 (3)	3
Nausea	3 (2)	3	2 (2)	2
Peripheral edema	3 (2)	3	4 (3)	4
Urinary tract infection	1 (1)	2	3 (3)	3

J Urol 2004; 172: 1021

Serum Sodium Concentration Change from the Use of Desmopressin



J Urol 2007; 178: 200

Risk Factors for Hyponatremia from the Use of Desmopressin - I

Results of Logistic Regression of Risk of Significant Hyponatremia

	Odds ratio	95% Wald confidence limits		*P*-value
Age (years)	1.16	1.09	1.25	<0.0001
Baseline 24-hr urine volume/bodyweight (ml/kg)	1.09	1.04	1.16	0.0016
Baseline serum sodium (mmol/L)	0.76	0.64	0.91	0.0025
Weight gain at time of minimum s-sodium (%)	1.31	1.07	1.61	0.0106

N = 594 as 2 patients with significant hyponatremia and 36 patients without were excluded due to missing values of one or more of the characteristics.

Neurourol Urodyn 2006; 25: 105

Risk Factors for Hyponatremia from the Use of Desmopressin - II

Subgroups Based on Age and Basal Serum Sodium

Age	Basal s-sodium	n	No. of patients with significant hyponatremia	Risk
<65	Normal	336	3	<1%
	Low	5	0	—[a]
≥65	Normal	260	22	8%
	Low	8	6	75%

[a]Risk not assessed due to insufficient data.

Neurourol Urodyn 2006; 25: 105

The Suggested Way of Using Desmopressin In Treating Nocturia

- Titration of Desmopressin from 0.1 to 0.4mg
- Restriction of night-time fluid intake
- Monitoring BW and serum sodium conc.
- Caution when used in men > 65 y/o
- Bewaring of side effects
- Additive use of diuretics?

Drugs 2005; 65: 99

PHYTOTHERAPY FOR MEN WITH LUTS/BPH

Phytotherapy for BPH

Common Name	*Botanical Name*
Saw palmetto (fruit)	***Serenoa repens***
African plum (bark)	***Pygeum africanum***
Purple coneflower	***Echinacea purpurea***
Pumpkin (seeds)	***Cucurbitae peponis***
Rye (pollen)	***Secale cereale***
South African star grass (root)	***Hypoxis rooperi***
Stinging nettle (root)	***Urtica dioica***

Proposed mechanisms of action of herbal therapies in treating BPH

- 5-α Reductase inhibition
- Antiandrogenic effects
- Antiestrogenic effects
- Growth factor inhibition
- α-Receptor blockade
- Anti-inflammatory effects
- Effects of detrusor function and contractility

Phytotherapy: Overview

- Described as dietary supplements[1,2]
- Available as single plant extracts or combinations[2]
- Used extensively in Europe[2]
- Increased US use in recent years[3]
- Often obtained over the Internet[1,4,5]
- $1.5 billion US sales per year[2]
- Saw palmetto extract is most widely used

1. ProstaCare. Available at http://www.earth-heart.com/prosta.html. Accessed 12/3/02. 2. Dreikorn K et al. In: Chatelain C et al, eds. *Benign Prostatic Hyperplasia*. Plymouth, UK: Health Publication Ltd; 2001;479-511. 3. Wilt TJ et al. *JAMA*. 1998;280:1604-1609. 4. MH0001-Saw palmetto berry extract. Available at http://www.synergylabs.net/formulas/mh001.html. Accessed 12/3/02. 5. Lowe FC, Fagelman E. *Urology*. 1999;53:671-678.

Saw Palmetto for BPH - I

- The berry of the American dwarf palm tree
- Several mechanisms (antiandrogenic effects, antiestrogenic effects, androgen receptor blockade, growth factor inhibition, alpha-adrenergic blockade, and so on) proposed, real modes of action unclear
- Although a number of encouraging short-term studies and meta-analyses are available, only few fulfilled the WHO criteria, i.e. RCT, 12-month duration.

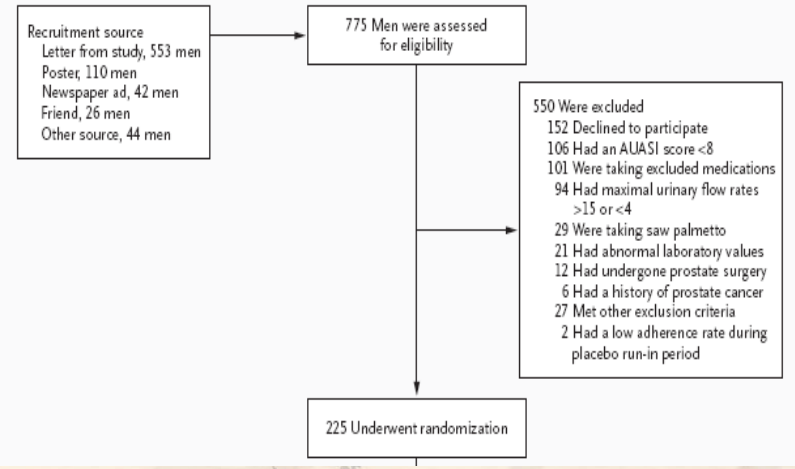
Saw Palmetto for BPH - II

Results of the largest clinical study concerning saw palmetto: 6-month randomized comparison of Permixo (n=533) versus finasteride (n=545)

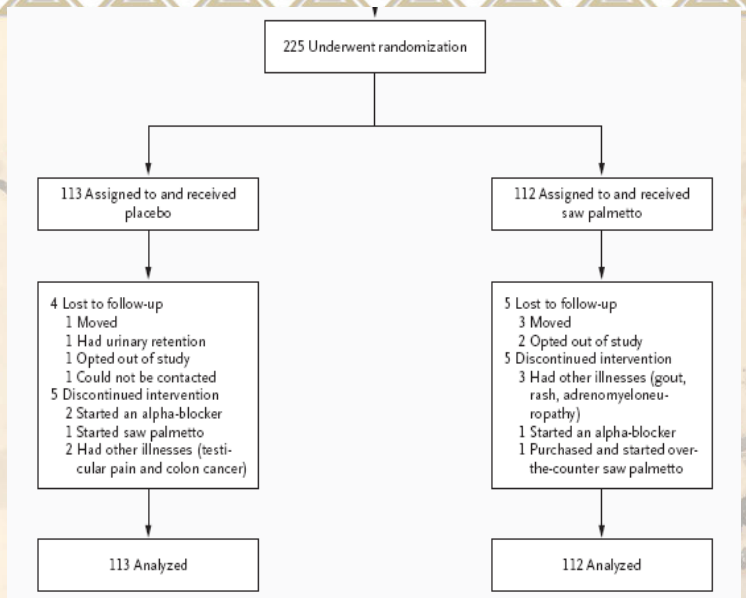
	Baseline	6 months
Symptom score		
Permixon	15.7	9.9
Finasteride	15.7	9.5
Peak urinary flow (mL/second)		
Permixon	10.6	13.3
Finasteride	10.8	14.0
Prostate volume (mL)		
Permixon	43.0	41.5
Finasteride	44.0	36.7
Serum PSA (ng/mL)		
Permixon	3.26	3.22
Finasteride	3.23	1.99

Prostate 1996; 29; 231

Saw Palmetto for BPH - III



N Engl J Med 2006; : 557



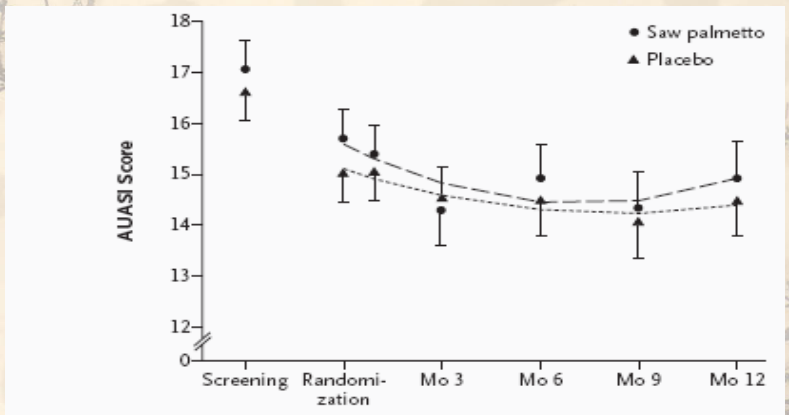
N Engl J Med 2006; : 557

Baseline Characteristics

Characteristic	Saw Palmetto (N = 112)	Placebo (N = 113)
Age — yr	62.9±8.0	63.0±7.4
AUASI score	15.7±5.7	15.0±5.3
BPH Impact Index score	3.4±2.2	2.8±2.1
Prostate volume — ml	34.7±13.9	33.9±15.2
TZ volume — ml	13.2±10.4	12.5±11.0
Maximal flow rate — ml/sec	11.4±3.5	11.6±4.3
PVR — ml	80.0±51.9	84.5±63.8
PSA — ng/dl	1.8±1.4	1.6±1.4

N Engl J Med 2006; : 557

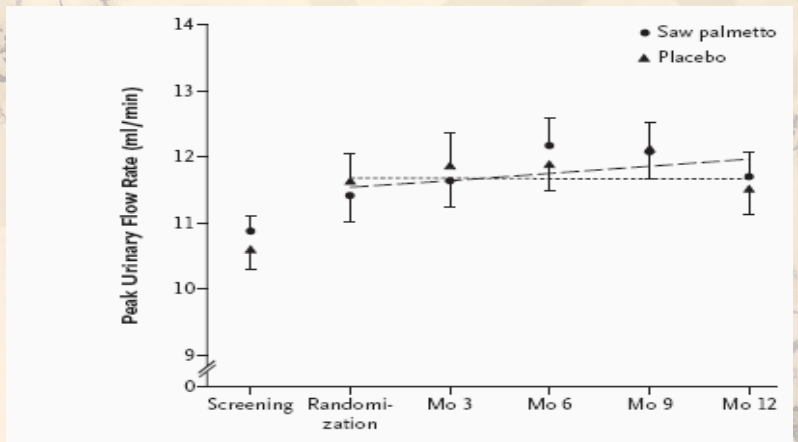
Mean (±SE) Change in American Urological Association Symptom Index Scores in the Two Groups



No. Analyzed						
Saw palmetto	112	112	108	108	108	107
Placebo	113	113	112	111	109	109

N Engl J Med 2006; : 557

Mean (±SE) Change in Peak Urinary Flow Rates in the Saw Palmetto and Placebo Groups



No. Analyzed						
Saw palmetto	112	106	101	101	100	101
Placebo	113	107	102	106	103	105

N Engl J Med 2006; : 557

There was no significant difference between the saw palmetto and placebo groups in the change in AUASI scores, maximal urinary flow rate, prostate size, residual volume after voiding, quality of life, or serum prostate-specific antigen levels during the one-year study. The incidence of side effects was similar in the two groups.

Saw palmetto did not improve symptoms or objective measures of benign prostatic hyperplasia.

N Engl J Med 2006; : 557

Medical Treatment of LUTS/BPH

- Following the guidelines
- Individualized
- Surgery if necessary

Indications of surgical treatment of LUTS/BPH

- Presence of complications of LUTS/BPH
- Failure of medical therapy: BPH progression or persisting bothering symptoms
- The patient's choice

Complications of TURP

Mortality	0.2-0.4%
TUR syndrome	2%
Transfusion	3-7%
Incontinence	0.5-1.2%
Erectile dysfunction	10-30%
Urethral stricture	2-5%
Retrograde ejaculation	60-70%
Others	

Laser treatment of BPH

- Ho:YAG: HoLAP, HoLRP, HoLEP
- KTP: PVP (photoselective vaporization of the prostate)
- Tm:YAG: VP (vaporesection of the prostate)
- Diode: vaporization of the prostate

Thank you for your kind attention