



ACOFP 46th Annual Convention & Exhibition

March 4-8, 2009

Gaylord National Resort & Convention Center
Washington, D.C.

Men's Health: Medical Management of BPH with Consideration of Sexual Function and Prostate Cancer

Ronnie B. Martin, DO, FACOFP *dist.*

**Saturday, March 7, 2009
9:00-10:00 am**

CME/CEU Information

The American College of Osteopathic Family Physicians is accredited by the American Osteopathic Association Council to sponsor continuing medical education for osteopathic physicians.

The American College of Osteopathic Family Physicians has requested that the AOA Council on Continuing Medical Education approve this program for 1 hour of AOA Category 1A CME credit. Approval is currently pending.

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Please check where applicable and sign below. Provide additional pages as necessary. Date: 02/10/09

Name of CME Activity: ACOFP 46th Annual Convention & Exhibition

Dates and Location of CME Activity: March 4-8, 2009, Gaylord National Resort and Convention Center, National Harbor, MD

Topic: Caring For Patients Who Have Benign Prostatic Hyperplasia

Name of Faculty/Planner/Author/Editor/Reviewer: Ronnie B. Martin, DO, FACOFP *dist.*

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Signature *Ronnie B. Martin* Date: 02/10/09

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**Men's Health: Medical
Management of BPH with
Consideration of Sexual Function
and Prostate Cancer**
Ronnie B. Martin, DO, FACOFP
Professor of Family Medicine
Rocky Vista University
College of Osteopathic Medicine

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BPH Overview

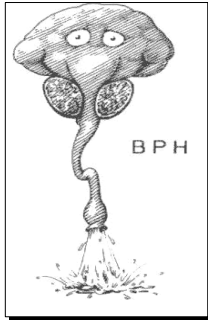
- **Epidemiology**
- **Definition of BPH**
 - **LUTS and BPH**
- **Differential diagnosis**

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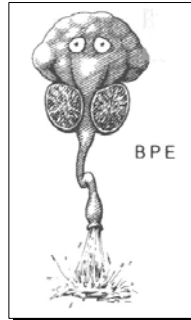
Definitions

LUTS = Lower Urinary Tract Symptoms

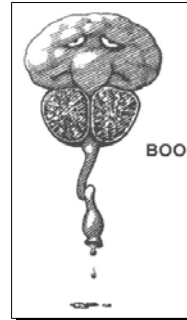
**BPH =
Benign Prostatic
Hyperplasia**



**BPE =
Benign Prostatic
Enlargement**



**BOO =
Bladder Outlet
Obstruction**

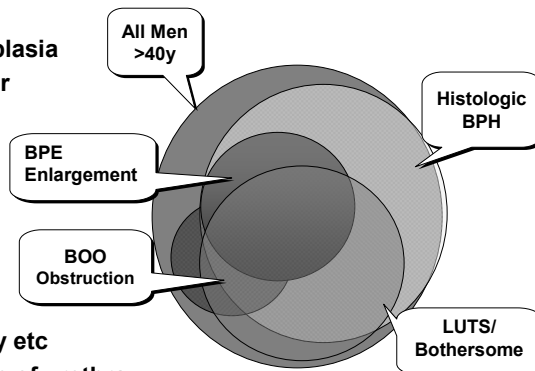


Graphic adapted from Abrams P et al. In: Chatelain C et al, eds. *Benign Prostatic Hyperplasia*. Plymouth, UK: Health Publications Ltd; 2001:227-281.

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A Modern View of BPH: Clinical, Anatomical and Pathophysiological Changes

- **BPH = Benign Prostatic Hyperplasia**
 - Histologic: stromoglandular hyperplasia
- **May be associated with**
 - Anatomical: enlargement of the gland (BPE = benign prostatic enlargement)
 - Clinical Symptoms: Lower Urinary Tract Symptoms such as urgency, frequency etc
 - Physiological: compression of urethra and compromise of urinary flow (BOO = bladder outlet obstruction)



Roehrborn C (reviewer). *Rev Urol*. 2002;3:139-145. Nordling J et al. In: Chatelain C et al, eds. *Benign Prostatic Hyperplasia*. Plymouth, UK: Health Publication Ltd; 2001:107-166.

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Risk Factors for BPH

Increases Risk	Indeterminate Effect	Protective Effect
Male gender and aging (hormonal or dihydrotestosterone hypothesis) ^{1,2}	Smoking ²	High physical activity ¹
Positive family history ²	Obesity ²	Alcohol in moderation ²
Heart disease ¹	Sexual activity ^{1,2}	

1. Meigs JB et al. *J Clin Epidemiol.* 2001;54:935-944. 2. Boyle P et al. In: Chatelain C et al, eds. *Benign Prostatic Hyperplasia.* Plymouth, UK: Health Publication Ltd; 2001:17-68.

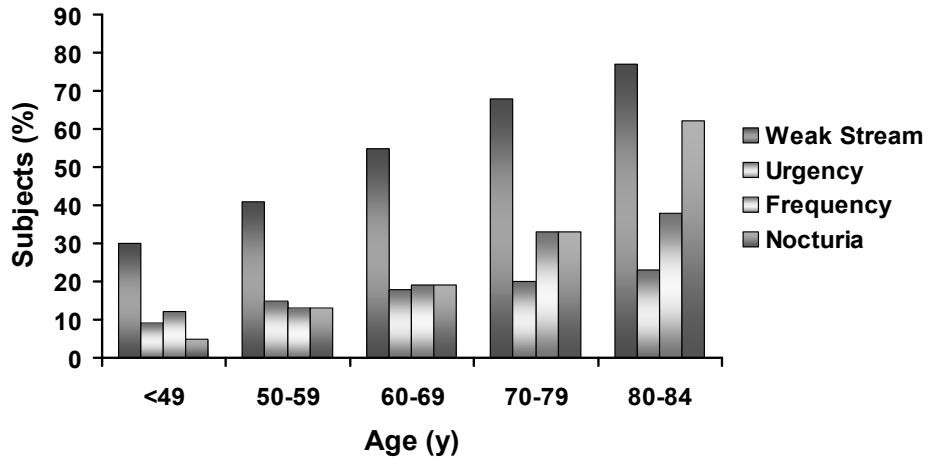
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Problems and Consequences of BPH and LUTS

Histological BPH (Stromoglandular)	By itself may not cause any problems
LUTS	<p>Bothersome Interference with daily living; Nocturia, frequency, urgency, dribbling et al.</p> <p>Diminished quality of life (QoL)</p> <p>Affects sexual function</p>
BPE (=Benign Prostatic Enlargement)	Acute urinary retention,
BOO (=Bladder Outlet Obstruction)	<p>Secondary changes of bladder anatomy and function,</p> <p>Other outcomes (UTI, stones, renal failure, incontinence etc)</p> <p>May require medical or Surgical intervention,</p>

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Prevalence of LUTS in Normal Males Increases With Age



Homma Y et al. *Scand J Urol Nephrol Suppl.* 1994;157:27-30.

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LUTS Symptom Complex: Obstructive and Irritative Symptoms

Voiding (obstructive)

- Hesitancy
- Straining
- Weak flow
- Terminal dribbling
- Prolonged voiding
- Retention
- Overflow incontinence

Storage (irritative)

- Frequency
- Urgency
- Nocturia
- Urge incontinence
- Small voided volume
- Pain

Nordling J et al. In: Chatelain C et al, eds. *Benign Prostatic Hyperplasia*. Plymouth, UK: Health Publication Ltd; 2001:107-166.

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Challenges Facing PCPs in Managing BPH

- **Access problems and increased awareness is making BPH shift from a primarily urologist treated disease to a primary care disease**
- **All Physicians who treat men need to be more aware of the condition at it earlier stages.**
- **Patients may avoid or deny symptoms with physicians and delay treatment**
 - **Concerns about “growing older” or feelings it is “normal for my age”**
 - **Gender issues, cultural and social issues with men and women physicians, health care system etc.**

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Challenges Facing PCPs in Managing BPH

- **Specificity of evaluations and ease of diagnostic tests**
 - **“Just do the blood test, I don’t need the rectal, the ultrasound or the biopsy.”**
- **Concerns about prostate cancer treatment and prognosis.**
- **Addressing patient concerns about medical treatments:**
 - **Efficacy of treatment**
 - **Side effects of treatment**
 - **Cost of medications and other treatment**
- **Sexual dysfunction concerns, depression, and psychosocial issues must also be addressed to treat the disease**
- **Addressing other physical conditions including Somatic Dysfunction and structural abnormalities must be addressed as part of comprehensive treatment.**

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LUTS/BPH Initial Evaluation

- Medical history
 - Oral intake, medications, diet, exercise history, sexual activity, family history, concomitant disease
- Physical exam
 - Including DRE and neurologic exam
 - Uroflowmetry
 - Measurement of residual volume
 - *Ultrasound is not part of initial assessment!!!*
- Urinalysis-(first 1/3 of urine reflects urethra, last 1/3 reflects prostate)
- Serum creatinine, BUN and creatinine clearance
- PSA*
- Symptom assessment—degree of interference with ADL

DRE = digital rectal exam; PSA = prostate-specific antigen
*Per physician's clinical judgment.

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Differential Diagnosis of LUTS

- Prostatic Etiology
 - Obstruction (BPH, BPE, BOO)
- Bladder Dysfunction
 - Detrusor over activity
 - Impaired detrusor contractility
 - Sensory urgency
 - Sphincteric incontinence
 - Polyuria/nocturnal polyuria

1. Chaikin DC, Blaivas JG. *Curr Opin Urol.* 2001;11:395-398. 2. Su L et al. *J Clin Epidemiol.* 1996;49:483-487.

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Differential Diagnosis of LUTS

- **Secondary to Medications or Other Drugs:**
 - Antihistamine
 - Antidepressants
 - Anticholinergics
 - Diuretics
 - Narcotics and Neuroleptics
 - Alcohol
 - Stimulant Medications and Drugs
 - Et al.

Differential Diagnosis of LUTS

- **Neurological Etiology-CNS Abnormality**
 - Somatic Dysfunction producing rediculopathy
 - ANS Dysfunction
 - Peripheral Demyelination Disorder
 - Spinal Cord abnormality

Quantitative Symptom Assessment

- American Urological Association Symptom Index (AUASI) recommended for initial assessment;
- 7 questions are used to;
 - Determine disease severity
 - Document response to therapy
 - Allow standardized comparisons of symptom relief when evaluating treatments
- International Prostate Symptom Score (IPSS) = AUASI with one additional question (question 8) on QOL as a function of urinary symptoms (Bother Score)

“If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that?”

Barry MJ et al. *J Urol.* 1992;148:1549-1557. Clinical Practice Guideline, Number 8. AHCPR Publication No. 94-0582. O’Leary MP. *Urology.* 2000;56(suppl 5A):7-11.

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AUA Symptom Index (AUA-SI) International Prostate Symptom Score (IPSS)

Urinary Symptoms	Not at all	Less than one time in five	Less than half the time	About half the time	More than half the time	Almost always
1. Over the past month, how often have you had a sensation of not emptying your bladder completely after you finished urinating?	0	1	2	3	4	5
2. Over the past month, how often have you had to urinate again less than 2 hours after you finished urinating?	0	1	2	3	4	5
3. Over the past month, how often have you found you stopped and started again several times while urinating?	0	1	2	3	4	5
4. Over the past month, how often have you found it difficult to postpone urination?	0	1	2	3	4	5
5. Over the past month, how often have you had a weak urinary stream?	0	1	2	3	4	5
6. Over the past month, how often have you had to push or strain to begin urination?	0	1	2	3	4	5
7. Over the past month, how many times did you typically get up to urinate from the time you went to bed until the time you got up in the morning?	Never	1 time	2 times	3 times	4 times	5 or more Times
	0	1	2	3	4	5
Total for Urinary Symptoms:						

Adapted from Barry M et al. *J Urol.* 1992;48:1549-1557. 2. O’Leary MP. *Urology.* 2000;56(suppl 5A):7-11.

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7. Over the past month, how many times did you typically get up to urinate from the time you went to bed until the time you got up in the morning?	Never 0	1 time 1	2 times 2	3 times 3	4 times 4	5 or more Times 5
Total for Urinary Symptoms:						

Adapted from Barry M et al. *J Urol.* 1992;48:1549-1557. 2. O'Leary MP. *Urology.* 2000;56(suppl 5A):7-11.

Classification of Symptom Scores

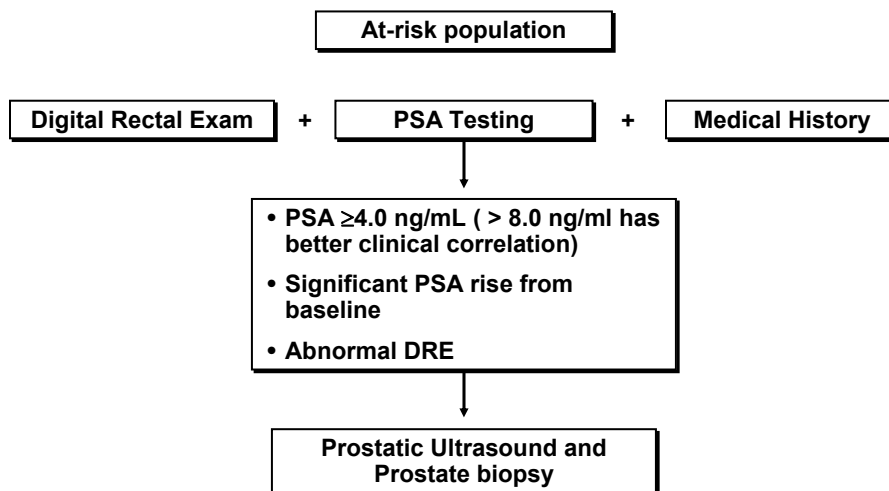
Symptom Score: AUA-SI and IPSS	
Mild (0-7)	Moderate (8-19) to Severe (20-35)
<ul style="list-style-type: none"> • Offer watchful waiting • Reassure patient • Reassess periodically 	<ol style="list-style-type: none"> 1. Provide patient education materials and do physical examination to determine cause 2. Modify life style, fluid intake, evaluate medications, 3. Discuss treatment options, including benefits and risks

- IPSS bother score: delighted to terrible (0-6)
"If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that?"
- Successful treatment of BPH is measured by
 - Decrease of symptom score
 - Increase in peak flow rate and Q_{max}
 - Decrease of bother score

Clinical Practice Guideline, Number 8. AHCPR Publication No. 94-0582.
 O'Leary MP. *Urology*. 2000;56(suppl 5A):7-11.

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Ruling Out Prostate Cancer



U.S. preventive services task force. *Am Fam Physician*. 2003; 15;67(4):787-92; Canto EI, *Annu Rev Med*. 2002;53:355-368.

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Conclusions

- Histologic BPH is highly prevalent in men over the age of 50
- LUTS resulting from BPH require treatment if they interfere with ADL, sexual function or QoL
- LUTS/BPH can be evaluated using the AUA-SI or IPSS questionnaire coupled with physical examination
- Screen for prostate cancer with DRE and PSA tests should be a part of the examination of all men > 50yrs/age.
- Patient should be referred to a urologist in case of complications and/or inconclusive findings, failure to respond to therapy, worsening condition.

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Patients With LUTS/BPH Should Be Evaluated for Sexual Dysfunction

- Men with LUTS/BPH are at increased risk for sexual problems^{1,2}
- Sexual problems include²
 - Erectile dysfunction (ED)
 - Ejaculation disorders (EjD)
 - Desire disorder (ie, decreased libido)
 - Combination of the above
- Many currently available LUTS/BPH treatments affect sexual function³

1. Girman CJ et al. *Urology*. 1998;51:428-436. 2. Rosen R et al. Program Abstracts of the American Urological Association 2002 Annual Meeting (Abstract 500161). 3. Liefeld HHJ et al. *BJU Int*. 2002;89:208-213.

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A Look at the Domains of Sexual Function Keeping a Finger on the Prostate's Function

- Desire (Libido)
- Erection (Arousal)
- *Ejaculation*
 - Force
 - Volume
- Orgasm/Satisfaction (Sensation)

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Many Treatments Affect Sexual Function

Treatment	Libido	Ejaculation	Erection
Watchful waiting	Age-related	Age-related	Age-related
α -Adrenergic blockers	—	↓*	±?
5 α -Reductase inhibitors	↓	↓↓	↓
Phytotherapy	—	—	—
MIT	—	↓	—
Laser	—	↓	±?
TUIP	—	↓↓	—
TURP	—	↓↓↓	±?
Open prostatectomy	—	↓↓↓	(↓)

*Effects vary by agent.
Council for Urogenital Health, faculty opinion.

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Multinational Survey of the Aging Male (MSAM-7)

Objectives

- **Evaluate sexual function and prevalence of LUTS in a representative population of men aged 50-80 years**
- **Demonstrate the relationship between sexual disorders and severity of LUTS**

Patients

- **14,254 men aged 50-80 years in 7 countries: United States, United Kingdom, France, Germany, Italy, Spain, the Netherlands**

Rosen R. Multinational Survey of the Aging Male (MSAM-7). Presented at the Annual Meeting of the American Urological Association; May 26, 2002; Orlando, Fla.

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MSAM-7: Conclusions

- **Older men still have active sex lives q.s. 65% of men 70-79 in survey.**
- **Independent of other risk factors or age, patients with more severe LUTS have a greater decrease in sexual function, including EjD, ED and frequency of intercourse.**
- **Sexual function should be considered in the initial evaluation of patients with BPH and in the choice of treatment**

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Summary: Overall Approach to Management

- Men with LUTS/BPH are at increased risk for sexual problems¹⁻³
- Sexual problems include
 - Erectile dysfunction (ED)
 - Ejaculation disorders (EjD)
 - Desire disorder (ie, decreased libido)
 - Combination of the above
- Many treatments currently available for LUTS/BPH affect sexual function^{4,5}
- Health-care provider should screen for sexual problems in patients suspected of BPH and continue monitoring once therapy is initiated

1. Meigs JB et al. *J Clin Epidemiol.* 2001;54:935-944. 2. Girman CJ et al. *Urology.* 1998;51:428-436. 3. Rosen R. Multinational Survey of the Aging Male (MSAM-7). Presented at the Annual Meeting of the American Urological Association; May 26, 2002; Orlando, Fla. 4. Leliefeld HHJ et al. *BJU Int.* 2002;89:208-213. 5. Clifford GM et al. *Eur Urol.* 2000;38:2-19.

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Treatment Principles for LUTS/BPH

- Objective of treatment is to improve symptoms and bother, eliminate interference with daily activities, and restore QoL
- Joint treatment decision-making with the patient after reviewing risks and benefits of each therapeutic option
- Initial evaluation and initiation of treatment, usually by primary care provider (PCP)

Council for Urogenital Health, faculty opinion.

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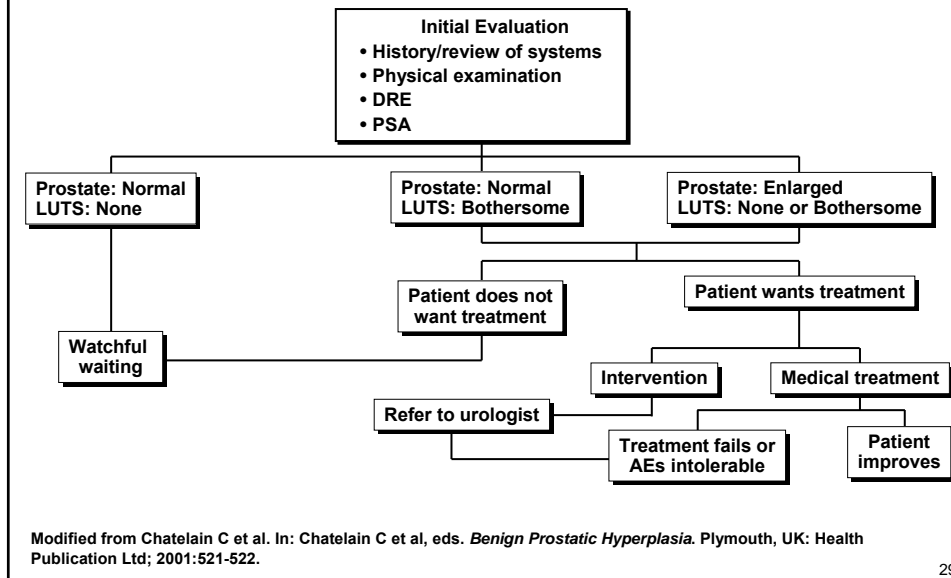
Treatment Principles for LUTS/BPH (cont)

- Referral to urologist for complex differential diagnosis, cases refractory to treatment, and patients presenting with complications such as
 - Gross hematuria
 - Bladder stones
 - Recurrent UTI
 - Upper tract damage
- Back-referral to PCP for continued management

Symptom Assessment for PCPs

- Three simple questions¹
 - Urinary function (“Can you pee?”)
 - Erectile function (“Can you get it up?” or “Can you get and maintain an erection satisfactory for sex?”)
 - Ejaculatory function (“Can you climax?”)
- Quantification of problems as needed
 - AUA Symptom Index^{2,3}
 - Quality of Life Question⁴
 - BPH Impact Index⁴
 - Sexual Function Questionnaire⁴

Initial Evaluation and Management of Patients Presenting With LUTS/BPH



Treatments for LUTS, BPH, BOO

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

Phytotherapy: Overview

- Described as dietary supplements and marketed for specific ailments, such as prostate health and ED¹⁻³
- Available as single-plant or combination extracts^{1,2,4}
- Used extensively in Europe¹; increased use in the US in recent years¹
- Often obtained over the Internet¹⁻⁴
- More than \$1.5 billion in US sales tracked per year for prostate health¹

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

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Phytotherapeutics Presumed Mechanisms of Action

Origin/Name	Components	Suggested Effects
<i>Serenoa repens</i> = <i>Sabal serrulatum</i> American dwarf palm tree/ Saw palmetto fruit ^{1,2}	Free fatty acids, phytosterols (β -sitosterol and others), aliphatic alcohols ¹	Antiandrogenic ^{1,2} ↓ 5 α Reductase isoenzymes ¹ ↓ Growth factor (GF)-induced proliferation ¹ ↓ Inflammation ^{1,2}
<i>Hypoxis rooperi</i> South African star grass ^{1,2}	β -sitosterol and other phytosterols ¹	↑ TGF β , which enhances apoptosis ^{1,2} ↓ Inflammation ²
<i>Pygeum Africanum</i> African plum ^{1,2}	Phytosterols, unsaturated long-chain fatty acids ²	↓ β -FGF- and EGF-induced fibroblast proliferation ¹ ↓ Inflammation ² /edema
<i>Urtica dioica</i> Stinging nettle ^{1,2}	Lectins, phenol, sterols, lignans ²	↓ GFs, ↓ ATPase, ↓ Cell growth ¹ Modulates SHBG ¹
<i>Secale cereale</i> Rye pollen ^{1,2}	Alpha amino acids, phytosterols, carbohydrates	↓ Urethral resistance ² Inhibits α receptor ² ↓ 5 α Reductase ²
<i>Cucurbitae peponis semen</i> Pumpkin seeds ^{1,2}	Sterols, carotinoids, minerals (Se, Mg) ²	Antiandrogenic Anti-inflammatory

1. Fagelman E, Lowe FC. *Urol Clin N Am*. 2002;29:23-29. 2. Dreikorn K et al. In: Chatelain C et al, eds. *Benign Prostatic Hyperplasia*. Plymouth, UK: Health Publication Ltd; 2001;479-515.

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α -Adrenergic Blockers: Rationale

- Prostate smooth muscle tone is mediated via α 1-adrenergic receptor¹
- Increased tone leads to reduction in flow rate (obstruction) and increasing LUTS¹
- Blockage of the receptor leads to improvement of flow rate and LUTS¹
- Central α -receptors and the effect of agents on these receptors likely play an additional role
- Density of adrenergic receptors changes with prostate size and age
- To date, three α 1-adrenergic receptor subtypes have been identified (A, B, D)¹

AUA Guidelines on Alpha-Blockers

- “Alfuzosin, doxazosin, tamsulosin and terazosin are appropriate treatment options for patients with LUTS secondary to BPH.
- Although there are slight differences in the adverse-event profiles of these agents, the Panel believes that all four agents have equal clinical effectiveness.”
- “The primary adverse events reported with alpha-blocker therapy are orthostatic hypotension, dizziness, tiredness (asthenia), ejaculatory problems, headache and nasal congestion.”
- “The adverse event profile appears slightly different between the four alpha-blocking agents.
- The effect on sexual function is slightly different between the four agents.

Comparison of α -Adrenergic Blockers

Agent	Dosing	Titration	Uroselective
Terazosin (Hytrin®)	1 mg, 2 mg, 5 mg, 10 mg, 20 mg	+	NO
Doxazosin (Cardura®)	1 mg, 2 mg, 4 mg, 8 mg, 16 mg	+	NO
Tamsulosin (Flomax®)	0.4 mg, 0.8 mg	+/-	YES (Relative affinity for α_{1A} receptors over α_{1B})
Alfuzosin (Uroxatral®)	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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Terazosin (Hytrin): Adverse Events*

	Terazosin (n=636)	Placebo (n=360)
Dizziness	9.1%†	4.2%
Asthenia/fatigue	7.4%†	3.3%
Postural hypotension	3.9%†	0.8%
Somnolence	3.6%†	1.9%

*Occurring in $\geq 3\%$ of patients.

† $P < .05$ comparison between groups.

Product Information, © Abbott Laboratories.

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Doxazosin (Cardura): Adverse Events*

	Doxazosin (n=665)	Placebo (n=300)
Dizziness (includes vertigo)	15.6%[†]	9.0%
Headache	9.9%	9.0%
Fatigue	8.0%[†]	1.7%
Somnolence	3.0%	1.0%

*Occurring in ≥3% of patients.
[†]P<.05 for treatment differences.
 Product Information, © Pfizer Inc.

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Tamsulosin (Flomax): 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%
Somnolence	3.0%	4.3%	1.6%
Abnormal ejaculation	8.4%	18.1%	0.2%
Asthenia/fatigue	7.8%	8.5%	5.5%
Back pain	7.0%	8.3%	5.5%

*Occurring in ≥3% of patients.
 Product Information, © Boehringer Ingelheim Pharmaceuticals, Inc.

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Alfuzozin (Uroxatral: A New Uroselective α -Adrenergic Blocker

- Originally introduced in Europe in 1987
- Approved by the US FDA June 12, 2003

Data on file, Sanofi-Synthelabo Inc.

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- 1. Alfuzosin Improves BPH Symptoms:
IPSS Total Score and Subscores**
- 2. Alfuzosin 10mg Improves Flow Rate
8 Hours After The First Dose**
- 3. Alfuzosin maintains long-term efficacy
(Peak Flow Rate – Qmax)**

*ITT = all patients completing trial (n=45); **Evaluable = pts with complete data (n=34)
Marks L., Roehrborn C. et. al., Urology, 2003 In Press

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Alfuzosin - Adverse Events*

	Alfuzosin (n=473)	Placebo (n=482)
Dizziness	5.3%	2.9%
Respiratory tract infection	3.0%	0.8%
Headache	3.0%	2.1%
Orthostatic Hypotension	3.0%	3.0%

Low or no incidence of:

- Sexual side-effects including lowest EjD
- Rhinitis
- First dose syncope

*Occurring in $\geq 3\%$ of alfuzosin-treated patients.
Roehrborn C et al. *BJU*. 2003, in press.

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Summary: α -Adrenergic Blockers

- Rapid relief of symptoms¹ and improvement in flow rate^{1,2}
- Efficacy shown in multiple randomized clinical trials comparable among long-acting agents at appropriate therapeutic doses^{1,2}
- Effective regardless of prostate size¹
 - Reduce symptoms equally well in patients with and without BOO³
- Low risk of morbidity⁴
- Differences between agents with regard to
 - Cardiovascular side effects²
 - Sexual side effects²
- No effect on serum PSA – no interference with prostate cancer detection¹

1. Vallancien G. *Urology*. 1999;54:773-775. 2. Narayan P, Tewari A. *Urology*. 1998;51(suppl 4A):38-45. 3. Witjes WP et al. *J Urol*. 1996;155:1317-1323. 4. Council for Urogenital Health, faculty opinion.

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5 α -Reductase Inhibitors: Rationale

- Male hormones have permissive role in BPH¹(testosterone [T] and dihydrotestosterone [DHT])
- 5 α -reductase (5AR) isoenzymes convert T to the more potent DHT¹
- Men deficient in 5AR type II have nonpalpable prostates and do not develop BPH or prostate cancer¹
- Agents that inhibit these isoenzymes (5 α -reductase inhibitors, or 5ARIs) reduce DHT in serum and prostate¹
- Decreased androgenic activity induces epithelial atrophy and shrinkage of the prostate, improving LUTS and flow rate^{1,2}

1. Bartsch G et al. In: Chatelain C et al, eds. *Benign Prostatic Hyperplasia*. Plymouth, UK: Health Publication Ltd; 2001:423-457. 2. Stoner E. *J Urol*. 1992;147:1298-1302.

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5 α -Reductase Inhibitors: Comparison of Physiologic Effects

Physiologic Effect	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%
Serum half-life	6-8 hours	5 weeks
Dosage	5 mg od	0.5 mg od

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.

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Clinical Efficacy of 5 α -Reductase Inhibitors Is Comparable*

	Finasteride ¹ 48-Mo Controlled Trial in 3040 Men		Dutasteride ² 24-Mo Controlled Trial in 4325 Men	
	Finasteride	Placebo	Dutasteride	Placebo
Volume changes	-18%	+14%	-26%	-2%
IPSS reduction	-3.3	-1.3	-4.5	-2.3
Q _{max} improvement	+1.9	+0.2	+2.2	+0.6
AUR risk reduction	57%		57%	
Surgery risk reduction	55%		48%	

*Not from a comparative trial.

1. McConnell JD et al. *NEJM*. 1998;338:557-563. 2. Roehrborn C et al. *Urology*. 2002;60:434-441.

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Adverse Events of 5 α -Reductase Inhibitors Are Comparable*

	Finasteride ¹		Dutasteride ²	
	Finasteride	Placebo	Dutasteride	Placebo
Erectile dysfunction	8	4	7	4
Altered libido	6	3	4	2
Ejaculatory disorder	4	1	2	<1
Gynecomastia and breast tenderness	1	0.2	2	<1

*Not from a comparative trial.

1. McConnell JD et al. *NEJM*. 1998;338:557-563. 2. Roehrborn C et al. *Urology*. 2002;60:434-441.

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Combination Therapy: Rationale

- 5ARIs and α -adrenergic blockers have complementary actions
 - 5ARIs act on the hormonal axis
 - α -adrenergic blockers act on adrenergic receptors in the lower urinary tract and the spinal cord/CNS
- Main reported effects
 - α -adrenergic blockers induce rapid and sustained symptom and flow rate improvement
 - 5ARIs reduce risk of progression to AUR or BPH-related surgery

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MTOPS Trial: Medical Therapy of Prostatic Symptoms: Doxazosin, Finasteride, or Combination

- Double-masked, randomized, placebo-controlled, multicenter study
- 3047 men aged ≥ 50 years with BPH
- Average follow-up: 4.5 years
- Primary outcome: time to clinical progression
 - AUR
 - Renal insufficiency due to BPH
 - $\geq 50\%$ rise in baseline serum creatinine and ≥ 1.5 mg/dL
 - Recurrent UTI or urosepsis
 - Incontinence
 - ≥ 4 -point rise in baseline AUA symptom score confirmed within 2-4 weeks
- Secondary outcomes
 - Changes in symptom and flow rate over time
 - Rate of invasive therapies for LUTS/BPH

MTOPS=Medical Therapy Of Prostatic Symptoms.
McConnell JD et al. *NEJM*, In Press 2003.

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Conclusions From MTOPS for Medical Therapy of LUTS/BPH

- In selected patients, combination therapy with an α -adrenergic blocker and a 5ARI is most effective in
 - Reducing risk of clinical progression
 - Improving AUA symptom score
 - Improving maximum urinary flow rate
- Monotherapy also significantly reduces the risk of clinical progression of BPH
- Finasteride (5ARI) and combination therapy significantly reduce the risk of AUR and invasive therapy
- Doxazosin (α -adrenergic blocker) prolongs time to progression of AUR and invasive therapy, but does not reduce overall risk
- Both long-term monotherapy and combination therapy are safe and effective

McConnell J et al. Program Abstracts of the American Urological Association 2002 Annual Meeting (Abstract 1042, updated).

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MTOPS Trial Most Frequent Adverse Events

	<u>Percent of Patients*</u>			
	<u>COMB</u>	<u>DOX</u>	<u>FIN</u>	<u>PLAC</u>
Erectile dysfunction	5.6 [†]	3.9	4.9 [†]	3.6
Dizziness	5.9 [†]	4.8 [†]	2.5	2.5
Postural hypotension	4.6 [†]	4.4 [†]	2.7	2.5
Asthenia	4.6 [†]	4.5 [†]	1.7	2.2
Decreased libido	2.8 [†]	1.7	2.5 [†]	1.5
Abnormal ejaculation	3.4 [†]	1.2	1.9 [†]	0.9
Peripheral edema	1.4 [†]	1.0	0.8	0.7
Dyspnea	1.3 [†]	1.0	0.6	0.6
Somnolence	0.9 [†]	0.9 [†]	0.4	0.4
Syncope	0.7 [†]	0.5	0.5	0.3

*Calculated as a rate per 100 patient-years follow-up.

[†]Higher compared to placebo at $P < .05$.

McConnell JD et al. *NEJM*. In Press 2003.

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Open Prostatectomy: Overview

Advantages

- Excellent clinical results: relieves obstruction and irritative symptoms
- Treats large prostates (>80 g)
- Low retreatment rate

Disadvantages

- Most invasive of all treatment modalities
- Catheterization time: 3-7 days postsurgery
- Considerable morbidity/mortality

Debruyne FMJ et al. *Benign Prostatic Hyperplasia. 5th International Consultation on Benign Prostatic Hyperplasia.* Paris, France. June 25-28, 2000:397-421.

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Sexual Side Effects of Surgical Interventions

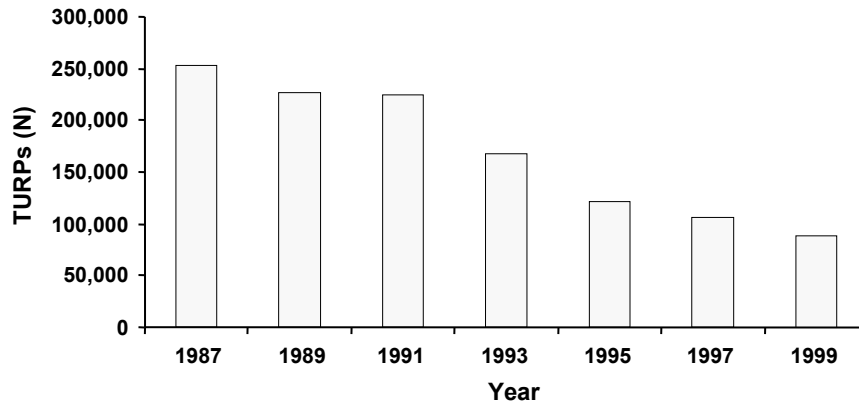
Surgical Intervention	n	Impotent After Surgery	RGE (%)*
TUIP	144	4.6	38.8
TURP	1543	13.6	70.4
Open surgery (OPSR + OPSS)	784	15.6	65.0
OPSS	647	16.4	80.8

RGE = retrograde ejaculation; TUIP = transurethral incision of the prostate; TURP = transurethral resection of the prostate; OPSR = retropubic prostatectomy; OPSS = suprapubic transvesical prostatectomy.
Adapted from Downs TM and O'Leary MP. *Curr Opin Urol.* 1999;9:9-14.

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Changing Treatment Modalities

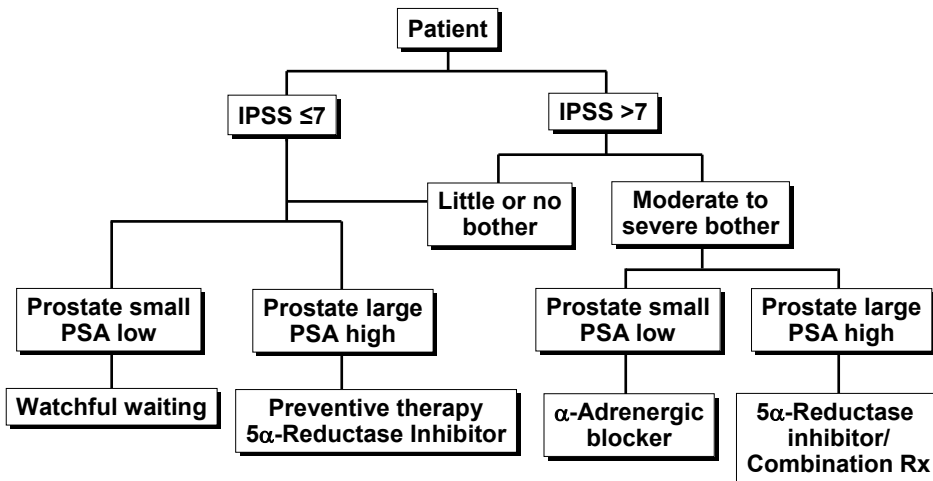
Decline in TURPs in Medicare Patients



Medicare B/Med data. HCFA. Baltimore, MD.

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Medical Therapy Algorithm



Council for Urogenital Health, faculty opinion.

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Overall Conclusions

- **BPH/LUTS represents a significant medical problem for older men**
- **Therapy should be guided to relieve obstructive, irritative, and sexual symptoms, with an eye toward improving quality of life**
- **For appropriate patients, PCPs can initiate medical therapy with either an alpha adrenergic blocker, a 5-alpha reductase inhibitor, or both**