Benign Prostatic Hyperplasia and Lower Urinary Tract Symptoms: Individualized Management in Primary Care

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Education Partner: Integritas Communications
Session 2: Benign Prostatic Hyperplasia and Lower Urinary Tract Symptoms: Individualized Management in Primary Care

Learning Objectives

1. Describe pathophysiologic mechanisms in benign prostatic hyperplasia and lower urinary tract symptoms (BPH-LUTS) and relationships to comorbid conditions and therapeutic approaches.
2. Conduct comprehensive assessments of patients with suspected BPH and associated LUTS.
3. Evaluate the mechanisms of action and clinical profiles of α-blockers, 5-α reductase inhibitors (5-ARIs), and phosphodiesterase type 5 (PDE-5) inhibitors in the treatment of BPH-LUTS with and without ED.
4. Combine pharmacologic and nonpharmacologic interventions for BPH-LUTS based on symptom severity, common comorbidities, risk of disease progression, and patient goals.
5. Monitor treatment efficacy and adherence in patients with BPH-LUTS to guide therapeutic restructuring and optimize patient outcomes.

Faculty

Steven A. Kaplan, MD—Virtual Presenter
E. Darracott Vaughan Jr. Professor of Urology
Chief, Institute for Bladder and Prostate Health
Weill Cornell Medical College
Director, Iris Cantor Men’s Health Center
New York Presbyterian Hospital
Weill Cornell Medical Center
New York, New York

Dr Steven A. Kaplan received a BS in biochemistry from The City University of New York—Brooklyn College in 1978, graduated from Mount Sinai School of Medicine in 1982, and was elected to the Alpha Omega Alpha Medical Honor Society. Dr Kaplan’s postgraduate training included an internship and residency in the department of surgery at Mount Sinai Hospital as well as a residency in urology at the Squier Urological Clinic, Columbia University. From 1988 to 1990 he was an American Urological Association (AUA) Scholar focused on identifying molecular markers and urodynamic parameters that herald bladder and prostate dysfunction.

Dr Kaplan was the Given Foundation Professor of Urology and administrator, as well as vice chairman of the department of urology, at Columbia University from 1998 to 2005. Fellowship director for female urology and voiding dysfunction from 1995 to 2005 at Columbia and at Weill Cornell Medical College since 2005, Dr Kaplan is also the E. Darracott Vaughan Jr. Professor of Urology and chief, Institute for Bladder and Prostate Health at Weill Cornell Medical College, and director, Iris Cantor Men’s Health Center at New York Presbyterian Hospital. He is a serial entrepreneur and founder of Medidata Solutions Inc., a publicly held corporation and one of the premier electronic data capture companies in the world; Medivizor, Inc., a medical informatics platform; and Blabbelon, a novel voice over internet protocol platform.

Dr Kaplan is a diplomate of the American Board of Urology and a fellow of the American College of Surgeons. He is a recognized authority on the study of benign diseases of the prostate and on the association of metabolic factors and voiding dysfunction and female urology. He has published more than 780 articles and 170 abstracts, and has made over 335 presentations in more than 35 countries. The coauthor of 5 books, he is on the editorial boards of Urology, Journal of Urology, and Urology Times.

Dr Kaplan is a member of more than 30 professional organizations, has been awarded 5 National Institutes of Health grants, and has received over 13 million dollars in research funding. He was awarded the John K. Lattimer Award for Lifetime Achievement in Urology by the National Kidney Foundation. Most recently, he chaired the National Institute of Diabetes and Digestive and Kidney Diseases’ Prostate Strategic Planning Committee and the BPH/Prostatitis section of the AUA Core Curriculum.

Session 2
Matt T. Rosenberg, MD
Medical Director
Mid-Michigan Health Centers
Chief, Department of Family Medicine
Foote Health System
Jackson, Michigan

Dr Matt T. Rosenberg earned his medical degree at the University of California, Irvine, School of Medicine, where he trained in general surgery. He also trained in urologic surgery at Brigham and Women’s Hospital in Boston, Massachusetts, before changing fields to general practice.

Dr Rosenberg has a special interest in the medical management of urologic diseases and has authored or coauthored articles published in Urology, Journal of Urology, BJU International, International Journal of Clinical Practice, and other peer-reviewed journals.

He practices in Jackson, Michigan, as medical director of Mid-Michigan Health Centers and on staff at Allegiance Health, where he served as chief of the department of family medicine from 2003 to 2006. Dr Rosenberg is section editor of urology for the International Journal of Clinical Practice and is founder and chairman of the Urologic Health Foundation, a nonprofit group dedicated to the education of primary care physicians in the field of genitourinary disease. In 2011, he was appointed by the American Urological Association’s office of education to be the coordinator of primary care education.

David R. Staskin, MD
Associate Professor of Urology
Tufts University School of Medicine
Director, Center for Male and Female Pelvic Health
Steward-St. Elizabeth’s Medical Center
Boston, Massachusetts

Dr David R. Staskin graduated from Hahnemann Medical College in Philadelphia, Pennsylvania, in 1979. He interned at the University of California, San Diego, and then served as a fellow at the National Kidney Foundation, University of Pennsylvania, and the University of California, Los Angeles. He joined the faculty of Boston University Medical Center in 1985, then the faculty of Harvard University-Beth Israel Medical Center in 1989. From 2002 to 2008, Dr Staskin was a member of the faculty of Weill Cornell Medical College at New York Presbyterian Hospital. He recently joined the department of urology at Tufts Medical Center in Boston, Massachusetts, as an associate professor.

Dr Staskin belongs to many leading urological associations and committees, including the Health and Human Services Incontinence Guidelines (member); the World Health Organization’s International Consultation on Incontinence Guidelines for Incontinence (chairperson); the American Urological Association committee “Surgical Management of Female Stress Urinary Incontinence”; the Society of Urodynamics and Female Urology (board of directors); the American Urogynecological Society (former board of directors); and the American Association of Clinical Urologists (board of directors).

He also serves on the following journals as a reviewer: International Urogynecology Journal (editorial board); Current Urology (editorial board); Journal of Urology; Urology; Neurology and Urodynamics; British Journal of Urology International; and The New England Journal of Medicine.

Dr Staskin has published extensively in the areas of female urology, neurourology, and urodynamics. He is the co-editor of the Textbook of Female Urology and Urogynecology (Cardozo and Staskin, eds.), which was awarded the British Medical Society’s first prize for the best second edition medical textbook of 2006.

Dr Staskin is the inventor of SPARC Sling System (American Medical Systems) and has contributed significantly to the development of the Monarc and BioArc slings and Apogee and Perigee for pelvic prolapse repair systems.
**Faculty Financial Disclosure Statements**
The presenting faculty reports the following:

Steven A. Kaplan, MD, has no financial relationships to disclose.


David R. Staskin, MD, is a consultant for Allergan, Inc., AltheRx Pharmaceuticals, Endo Pharmaceuticals Inc./American Systems., Takeda Pharmaceuticals U.S.A., Inc., and Theravida, Inc. He is also a member of the speakers bureau for Allergan, Inc., and Endo Pharmaceuticals Inc./American Medical Systems.

**Education Partner Financial Disclosure Statement**
The content collaborators at Integritas Communications have reported the following:

Jim Kappler, PhD, has no financial relationships to disclose.

**Suggested Reading List**


**Scientific and Clinical Insights into Benign Prostatic Hyperplasia and Lower Urinary Tract Symptoms**

**Steven A. Kaplan, MD**  
E. Darracott Vaughan Jr. Professor of Urology  
Chief, Institute for Bladder and Prostate Health  
Weill Cornell Medical College  
Director, Iris Cantor Men’s Health Center  
New York Presbyterian Hospital  
New York, New York

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**Presenter Disclosure Information**

**Off-Label/Investigational Discussion**

► In accordance with pmiCME policy, faculty have been asked to disclose discussion of unlabeled or unapproved use(s) of drugs or devices during the course of their presentations.

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**Learning Objectives**

1. Describe pathophysiologic mechanisms in BPH-LUTS and relationships to comorbid conditions and therapeutic approaches

2. Conduct comprehensive assessments of patients with suspected BPH and associated LUTS

3. Evaluate the mechanisms of action and clinical profiles of α-blockers, 5-ARIs, and PDE5 inhibitors in the treatment of BPH-LUTS with and without ED

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5. Monitor treatment efficacy and adherence in patients with BPH-LUTS to guide therapeutic restructuring and optimize patient outcomes

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**Scientific Primer in BPH-LUTS**

**Key Points**

- BPH-related bladder outlet obstruction is mediated by compression of the urethra by an enlarged prostate and increased smooth muscle tone around the prostatic urethra
- Medications used to treat BPH-LUTS target these factors
  - α-blockers: block norepinephrine binding to α-1-adrenergic receptors, promoting smooth muscle relaxation
  - 5-ARIs: disrupt DHT production, decreasing prostate cell proliferation, increasing apoptosis, and reducing prostate volume
  - PDE-5 inhibitors: increase NO/cGMP activity and inhibit Rho kinase activity to reduce smooth muscle tone
  - Also may reduce ANS overactivity, local inflammation/ischemia, and prostatic and smooth muscle cell proliferation
- BPH-LUTS is associated with metabolic syndrome
  - Central obesity, insulin resistance, dyslipidemia, and hypertension
**Bladder Function**

*Filling, Storage, and Voiding*

- **Normal function**
  - Storage capacity (300-500 mL)
  - Adequate low pressure urinary storage (bladder)
  - Adequate outlet resistance (sphincter)
  - Empty to completion (minimal residual)
  - Adequate bladder contraction
  - No outlet obstruction

- **Abnormal function**
  - Failure to store or empty
  - Voiding frequently in small amounts
  - Uncontrollable urge (urgency) to empty with frequency
  - Incomplete emptying
  - Hesitancy, poor stream, feeling of incomplete emptying


**Prostate Function**

- **Normal function**
  - Contributes to continence
  - Produces fluid for seminal emission
  - Does not obstruct urinary flow through the urethra

- **Abnormal function**
  - Obstruction of urinary flow
  - Sphincteric damage (usually surgical)


**Overlapping Clinical Constructs**

**Definitions**

- BPH: Histologic stromoglandular hyperplasia
- BPE: Anatomic increase in prostate gland size
- BOO: All pathophysiologic compressions of urethra and bladder outlet that compromise urinary flow
- BPO: Obstruction confirmed by pressure-flow studies or highly suspected based on flow rates and prostate size
- LUTS: Potential clinical manifestation of these conditions

**Prostate Volume**

*Progressive Hyperplasia*

- A 55-year-old man with a prostate volume of 35 mL and BPH-LUTS can expect a doubling of prostate size in the next 15 years.

**Case Study**

**Robert**

- 65-year-old African American man
  - Retired mechanic
  - Married with 4 children, several grandchildren
  - Visits PCP for follow-up about hypertension
  - Controlled with lisinopril 20 mg daily

- Mentions need to urinate more frequently, although it is often difficult to start and his urine flow has decreased
  - States that he expects to have problems with urination as he ages

Are bothersome urinary issues a normal part of aging?

LUTS Evaluations in Men
An Overview

Clinical Interview
- Symptom profile
  - Categorization
  - Severity
  - Biochemical function
- Other risk factors (eg, smoking, excessive alcohol intake)

Patient History
- Comorbidities
- Medications
- Temporal relationship
- Other risk factors (eg, smoking, excessive alcohol intake)

Physical Exam
- DRE
- General urinary exam
- Neurologic exam
- Abdominal exam

Lab Tests
- PSA level
- Urinalysis
- Blood sugar

Progression Risks
- Factors that suggest symptoms will worsen or patients may develop serious medical complications (eg, AUR)

IPSS, International Prostate Symptom Score; QoL, quality of life.


Clinical Interview for Male LUTS
Symptom Categorization

<table>
<thead>
<tr>
<th>Storage</th>
<th>Voiding</th>
<th>Postmicturition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency</td>
<td>Hesitancy</td>
<td>Dribbling</td>
</tr>
<tr>
<td>Nocturia</td>
<td>Poor flow</td>
<td>Incomplete emptying</td>
</tr>
<tr>
<td>Urgency</td>
<td>Intermittency</td>
<td></td>
</tr>
<tr>
<td>Urge Incontinence</td>
<td>Straining to Start/Continue</td>
<td></td>
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</tbody>
</table>


Consider Co-occurring Issues
Common Comorbidities in BPH-LUTS

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>Registry Patients, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>50</td>
</tr>
<tr>
<td>High cholesterol</td>
<td></td>
</tr>
<tr>
<td>Erectile or other sexual dysfunction</td>
<td></td>
</tr>
<tr>
<td>Digestive tract disorder</td>
<td></td>
</tr>
<tr>
<td>Arthritis</td>
<td>21</td>
</tr>
<tr>
<td>Heart disease/heart failure</td>
<td>11</td>
</tr>
<tr>
<td>Depression/insomnia/sleep disorder</td>
<td></td>
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<tr>
<td>Allergies/asthma/congestion</td>
<td></td>
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<tr>
<td>General pain/fatigue</td>
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</table>


Voids Diary
evaluation of Frequency and Volume

- Differentiate among LUTS pathologies
- Alert patients to modifiable habits and opportunities for change
- Monitor treatment progress and efficacy
- Typically record for 3-7 days
- Voids frequency and timing
- Number and characteristics of incontinence episodes
- Fluid intake
- Other urinary symptoms


BPH-LUTS, Erectile Dysfunction, and Metabolic Abnormalities

<table>
<thead>
<tr>
<th>Pathological Mechanisms: BPH-LUTS and Erectile Dysfunction</th>
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<tbody>
<tr>
<td>Reduced NO–cGMP Signaling</td>
</tr>
<tr>
<td>Increased RhoA–ROCK Signaling</td>
</tr>
<tr>
<td>Autonomic Hyperactivity</td>
</tr>
<tr>
<td>Pelvic Atherosclerosis</td>
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</tbody>
</table>

Common Pathogenic Mechanisms: BPH-LUTS and Erectile Dysfunction

- Reduced function of nerves and endothelium
- Altered smooth muscle relaxation or contractility
- Arterial insufficiency, reduced blood flow, and hypoxia-related tissue damage
- Hypertension, Metabolic Syndrome, Diabetes, etc.

Erectile Function and LUTS Severity
Examine Sexual Function

N=10,636 men who had been sexually active within the last 4 weeks.

IIEF, International Index of Erectile Function.

McVary KT, et al.

Erectile Function
Better Function
Worse Function
Age Group
50-59 Years
22.3
21.1
19.2
12.4
15.0
11.2
7.5
60-69 Years
18.5
16.9
15.8
12.3
13.5
10.3
7.0
70-79 Years
14.9
13.2
12.0
9.5
10.7
8.1
6.5

Medication Effects in BPH-LUTS
Medication LUTS-Related Effect
Sedatives1
Confusion, secondary incontinence
Alcohol, caffeine, diuretics2
Diuresis
Anticholinergics3
Impaired contractility, voiding difficulty, overflow incontinence
α-Agonists4
Increased outlet resistance, voiding difficulty
ß-Blockers5
Decreased urethral closure, stress incontinence
Calcium-channel blockers1
Reduce bladder smooth muscle contractility
Angiotensin-converting enzyme inhibitors1
Induce cough, stress urinary incontinence
First-generation antihistamines4
Increase outlet resistance
Cholinesterase inhibitors2
Precipitate urge incontinence


LUTS Evaluation
Focused Physical Exam

Evaluation
Abdominal palpation
Genitalia exam
Neurologic exam
DRE

Targets
Tenderness, masses, bladder distension
Meatus, testes, foreskin
General mental status, ambulatory status, motor function
Rectal tone, nodules, pain, prostate size, shape, consistency


Lab Testing
PSA and Prostate Size

• DRE tends to underestimate size of larger prostates
  – Full length and anterior portion of the gland often not examined
• PSA is more accurate than DRE
  – PSA ≥1.5 ng/mL suggests a prostate volume >30 mL


Other risk factors: older age, higher baseline IPSS, and history of AUR, metabolic syndrome, chronic prostatitis, depressive symptoms, or excessive alcohol use2,3

BPH progression was defined as an increase in AUA-SI score, AUR, incontinence, renal insufficiency, or worsened LUTS. BPH-LUTS was defined as a grade 3 or greater on the BPI-LUTS.

TPV, total prostate volume; TPV, total prostate volume; LTS, lower tract symptoms.

TPV
P<0.0001
TPV
P=0.0002
TPV
P=0.0011
TPV
P=0.0028

TPV
<25 mL
21 mL
31 mL
P=0.0001
P=0.0002
P=0.0011
P=0.0028

Incidence of Overall BPH Progression

Other risk factors: physical exam, family history, and other medical history.

Incidence per 100 Patient-Years

40
35
30
25
20
15
10
5
0

LUTS Workup
Robert

• Physical exam
  – BMI, 29.8 kg/m²
  – BP, 125/88 mm Hg
• Medical history
  – Hypertension
    • Lisinopril 20 mg daily
• Family history
  – Brother died of prostate cancer
  – Worried that his symptoms suggest prostate cancer

BMP, body mass index; BP, blood pressure.

What should the PCP tell Robert about the relationship between BPH-LUTS and prostate cancer?
Men With LUTS
Risks of Prostate Biopsy or Cancer Diagnosis

Prostate cancer diagnosis was not more likely based on the presence of LUTS alone, when life expectancy is >10 years and diagnosis of prostate cancer may modify management; aWhen significant nocturia is predominant symptom; bAssess and start treatment before referral.

Robert
Clinical Workup

- Physical exam
  - BMI, 29.8 kg/m²
  - BP, 125/88 mm Hg
- Medical history
  - Hypertension
  - Lisinopril 20 mg daily
- Family history
  - Brother died of prostate cancer

How would you initiate treatment for Robert?

Management Recommendations
LUTS In Men

Recommended Tests
- Relevant medical history
- Assessment of LUTS
- Severity and bother (e.g., AUA-SI)
- Physical exam, including DRE
- Urinalysis
- Serum PSA\textsuperscript{a}
- Frequency/volume chart\textsuperscript{b}

LUTS Cause Little or No Bother

- Complicated LUTS
  - Suspicious DRE
  - Hematuria
  - Abnormal PSA
  - Pain
  - Infection\textsuperscript{c}
  - Palpable bladder
  - Neurologic disease

Bothersome LUTS

- Predominant Significant Nocturia
- Polyuria

Recommended Tests

- Informed Surveillance
  - Monitor symptoms and screen for complications
  - Most appropriate for patients without bothersome symptoms or AUA-SI score ≤7
  - Patient voiding diary
  - Annual reevaluation

I informed Surveillance for Mild BPH-LUTS

87% of men with mild symptoms had symptom worsening, whereas 13% had reduced or stabilized symptoms.

Management Recommendations
Bothersome LUTS In Men

Predominant Significant Nocturia

Recommended Tests

- Standard Treatment
  - Drug Therapy
  - Lifestyle advice
- Drug Treatment

Failure

Detailed Management
BPH-LUTS Management

Behavioral Therapies

- Education and Reassurance
  - Discuss causes of LUTS, including normal prostate and bladder function
  - Discuss natural history of BPH/LUTS (risk of link to prostate cancer)
- Fluid Management
  - Suggest daily fluid intake of 1500-2000 mL
  - Avoid midday or excessive intake based on frequency/volume chart
  - Restrict fluids when symptoms are inconvenient (long journeys, prior to bedtime)
- Caffeine and Alcohol
  - Avoid caffeine (eg, substutue decaffeinated or noncaffeinated drinks)
  - Avoid alcohol in the evening if nocturia is bothersome

Concurrent Medication

- Adjust dose timing to improve LUTS at times of greatest inconvenience
- Substitute antihypertensive diuretics with alternatives with fewer urinary effects (discuss with PCP)
- Adjust dose timing to improve LUTS at times of greatest inconvenience

Toileting and Bladder Retraining

- Use distraction techniques to increase the minimum between-void time to 3 hours
  (daytime) and/or the minimum voided volume to 200-400 mL (daytime)
  - Premeditated renal exercise, pelvic pressure, or pelvic floor exercises
  - Urges to void should be separated by 1 min, then 5 min, then 10 min, etc.
- Use frequency/volume charts to monitor progress

Miscellaneous

- Avoid constipation to man with LUTS


BPH-LUTS Management

Pharmacologic Therapy

<table>
<thead>
<tr>
<th>Medication Class</th>
<th>Minimum Duration for Clinical Effect</th>
<th>Common Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>α-Blockers Selective (eg, tamsulosin, silodosin)</td>
<td>2-4 weeks</td>
<td>Erectile dysfunction, abnormal ejaculation, dizziness/ syncope, hypotension, fatigue, nasal congestion, headache, dry mouth, dry eye</td>
</tr>
<tr>
<td>5-ARIs (eg, flutamide, dutasteride)</td>
<td>2-6 months</td>
<td>Erectile dysfunction, abnormal ejaculation, gynecomastia, decreased PSA level</td>
</tr>
<tr>
<td>PDE-5 Inhibitors (eg, sildenafil)</td>
<td>4 weeks</td>
<td>Headache, indigestion, back pain, flushing, nasal congestion</td>
</tr>
<tr>
<td>Antimuscarinic agents Selective (eg, darifenacin, solifenacin)</td>
<td>12 weeks</td>
<td>Constipation, dyspepsia, dry mouth, dry eyes, headache</td>
</tr>
<tr>
<td>Dual-drug products (eg, tolterodine, trospium)</td>
<td>2-6 months</td>
<td>Erectile dysfunction, abnormal ejaculation, gynecomastia, dizziness, hypotension, headache, decreased PSA level</td>
</tr>
</tbody>
</table>

Source: Meigs et al, 2001; Platz et al, 1998; Gann et al, 1995; Del Maso et al, 2006; Rohrmann et al, 2006. Combined: P=0.005, 95% CI, 0.60-0.92; P<0.006, 95% CI, 0.59-0.92.

Robert

Treatment and Follow-up

- Advised on fluid intake, increased physical activity, and bladder training
- Alfuzosin 10 mg daily
- 1-month follow-up
  - IPSS, 15 (moderate)
  - Previous score, 18 (moderate)
  - Reports little change in fluid intake and occasionally forgetting to take his medication

What can be done to improve Robert’s adherence to the PCP’s treatment recommendations?

Robert

Treatment Tailoring

- Physical exam
  - BMI, 29.8 kg/m²
  - BP, 125/88 mm Hg
- Medical history
  - Hypertension
  - Lisinopril 20 mg daily
- Family history
  - Brother died of prostate cancer
- LUTS workup
  - IPSS, 15 (moderate)
  - Frequency
  - Poor flow and intermittency
  - Strains to urinate
  - PSA level, 1.7 ng/mL
  - DRE, firm and symmetrically enlarged with no nodules
  - Urinalysis, no abnormalities
- Sexual function
  - Some trouble over last year attaining an erection

Is Robert a candidate for combination therapy? Which combinations?

Improving Patient Adherence

- Patient adherence and satisfaction reflect perceived treatment efficacy and side effects
  - Choose agents with fewer side effects
- Consider online patient education about BPH symptoms, treatments, and complications
- Optimize the provider-patient relationship
  - Understand effects of social and demographic parameters
  - For watchful waiting, discuss monitoring parameters and behavioral changes in detail
  - For pharmacotherapy, discuss side effect profiles
  - For more invasive therapy, discuss recovery times, risks, and complications

Detailed Management
Persistent, bothersome BPH-LUTS

**OAB (Storage Symptoms)**
- No Evidence of BOO
- Lifestyle Intervention
- Behavioral Therapy
- Antimuscarinics

- Evidence of BOO
- Discuss Treatment Options
- Shared Decision

- Select Monotherapy or Combination Therapy
- Symptom profile
- Severity
- Predominant BOO vs Mixed OAB/BOO
- Prostate size
- PSA level
- Comorbidities

**Recommended Tests**
- Validated Questionnaires
- Frequency/Volume Chart

**Optional Tests**
- Flow Rate Recording
- PVR
- MIST or Surgery Options

Failure

Reassess and Consider Invasive Therapy for OAB

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Combination Therapy
**ComAT Study**

<table>
<thead>
<tr>
<th>Incidence, %</th>
<th>0.0</th>
<th>5.0</th>
<th>10.0</th>
<th>15.0</th>
<th>20.0</th>
<th>25.0</th>
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<tbody>
<tr>
<td>AR or BPH-Related Surgery</td>
<td>5.2</td>
<td>6.0</td>
<td>6.8</td>
<td>7.6</td>
<td>8.4</td>
<td>9.2</td>
</tr>
<tr>
<td>AR or BPH-Related Surgery</td>
<td>2.2</td>
<td>2.7</td>
<td>3.3</td>
<td>3.9</td>
<td>4.5</td>
<td>5.1</td>
</tr>
<tr>
<td>BPH Clinical Progression</td>
<td>7.8</td>
<td>8.6</td>
<td>9.4</td>
<td>10.2</td>
<td>11.0</td>
<td>11.8</td>
</tr>
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Combination therapy reduced the relative risk of AR or BPH-related surgery by 65.5% compared with tamsulosin (α-blocker) monotherapy and 19.6% compared with doxazosin (5-ARI) monotherapy.

Combination therapy reduced the incidence of AR or BPH-related surgery by 65.5% compared with tamsulosin (α-blocker) monotherapy and 19.6% compared with doxazosin (5-ARI) monotherapy

**PDE-5 Inhibitors and α-Blockers**

**Effects on BPH-LUTS, Erectile Dysfunction, and Flow Rate**

<table>
<thead>
<tr>
<th>Source</th>
<th>IPSS Mean Differences</th>
<th>IIEF Score Mean Differences</th>
<th>Qmax Mean Differences</th>
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<tbody>
<tr>
<td>Kaplan et al, 2007</td>
<td>-2</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>Bechters et al, 2006</td>
<td>-2</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>Liguori et al, 2009</td>
<td>-2</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>Tuncel et al, 2009</td>
<td>-2</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>Gacci et al, 2012</td>
<td>-2</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>Overall</td>
<td>-2</td>
<td>5</td>
<td>8</td>
</tr>
</tbody>
</table>

- α-blocker alone
- + PDE-5 inhibitor
- α-blocker alone
- + PDE-5 inhibitor
- α-blocker alone
- + PDE-5 inhibitor

Comparing α-blockers alone, the combination regimens significantly improved IPSS (P<0.001), IIEF scores (P<0.0001), and Qmax (P<0.0001)

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PDE-5 inhibitors include tadalafil, vardlenafil, sildenafil, and vardenafil, and the side effects are headache and vision.

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**Combination Therapy MTOPS Study**

Compared with placebo, doxazosin (α-blocker) or finasteride (5-ARI) reduced the risk of clinical progression by 39% or 34%, respectively. Compared with placebo, combination therapy reduced the risk of clinical progression by 66%.

**Early vs Delayed Combinations**

**5-ARI and α-Blocker**

- All Patients with PSA values
  - Patients with 1.5< PSA value <10
  - Patients with 1.5< PSA value <10

**AUR**

- All Patients with PSA values
  - Patients with 1.5< PSA value <10

**Surgery**

- All Patients with PSA values
  - Patients with 1.5< PSA value <10

**Total Costs**

- All Patients with PSA values
  - Patients with 1.5< PSA value <10

Better Outcomes With Delayed Combination Therapy

**Combination Therapy**

**Early vs Delayed Combinations**

**5-ARI and α-Blocker**

**Clinical Progression**

- Patients with PSA values
  - Patients with 1.5< PSA value <10

**AUR**

- Patients with PSA values
  - Patients with 1.5< PSA value <10

**Surgery**

- Patients with PSA values
  - Patients with 1.5< PSA value <10

**Total Costs**

- Patients with PSA values
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Better Outcomes With Delayed Combination Therapy

**Combination Therapy**

- Clinical progression defined as the occurrence of an AUR or prostate surgery during the 12 months after the prescription of the initial treatment
- Delayed combination therapy initiation of an α-blocker and a 5-ARI on the same day, or a 5-ARI within 45 days of initial α-blocker treatment

**Treatment Tailoring**

- If a PDE-5 inhibitor is prescribed, how should it be dosed?

- LUTS workup
  - IPSS, 15 (moderate)
    - Frequency
    - Poor flow and intermittency
    - Strains to urinate
  - PSA level, 1.7 ng/mL
  - DRE, firm and symmetrically enlarged with no nodules
  - Afluzosin 10 mg daily
  - Self-report of some erectile dysfunction

- The PCP considers adding a 5-ARI or PDE-5 inhibitor to the treatment regimen

**Clinical Progression**

- Defined as an increase of 0.4 points on the AUA-SI score, AUR, urinary incontinence, and/or the occurrence of a recurrent UTI.

**Progression defined as the occurrence of AUR or prostate surgery during the 12 months after the prescription of the initial treatment**

**Early vs Delayed Combinations**

- Delayed combination therapy initiation of an α-blocker and a 5-ARI on the same day, or a 5-ARI within 45 days of initial α-blocker treatment
- Oral, twice daily
- Dose of 120 mg of tamsulosin twice daily for 2 days before the initial α-blocker treatment

**Better Outcomes With Delayed Combination Therapy**

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**PDE-5 Inhibitors**

**Pharmacokinetics**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Available doses, mg</th>
<th>T_{max}, hours</th>
<th>T_{1/2}, hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sildenafil</td>
<td>25, 50, 100</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Vardenafil</td>
<td>5, 10, 20</td>
<td>1</td>
<td>4-5</td>
</tr>
<tr>
<td>Tadalafil</td>
<td>2.5, 5, 10, 20</td>
<td>2</td>
<td>17.5</td>
</tr>
<tr>
<td>Avanafil</td>
<td>50, 100, 200</td>
<td>0.5-0.75</td>
<td>5</td>
</tr>
<tr>
<td>Lodenafil</td>
<td>NA in US</td>
<td>2</td>
<td>11-13</td>
</tr>
<tr>
<td>Udenafil</td>
<td>NA in US</td>
<td>1-1.5</td>
<td>11-13</td>
</tr>
</tbody>
</table>

Lipids (high fat meals) and alcohol delay absorption but increase bioavailability.

Lodenafil and udenafil are not approved by the US Food and Drug Administration.

NA, not available; T_{1/2}, half-life; Tmax, time required to achieve maximum concentration.

1. See Drugs@FDA (http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020895s036lbl.pdf);
2. See Drugs@FDA (http://www.accessdata.fda.gov/drugsatfda_docs/label/2008/021400s011lbl.pdf);
3. See Drugs@FDA (http://www.accessdata.fda.gov/drugsatfda_docs/label/2007/021368s012lbl.pdf);
4. See Drugs@FDA (http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/202276s001lbl.pdf);

**Adverse Events With Tadalafil**

**Once-Daily vs On-Demand Dosing**

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>5 mg Once Daily</th>
<th>5/10/20 mg On Demand</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>2.1%</td>
<td>15.8%</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>3.8%</td>
<td>11.8%</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>5.9%</td>
<td>11.4%</td>
</tr>
<tr>
<td>Back pain</td>
<td>5.0%</td>
<td>8.2%</td>
</tr>
<tr>
<td>Influenza-like illness</td>
<td>2.5%</td>
<td>3.2%</td>
</tr>
<tr>
<td>Discontinuation due to adverse events possibly related to the study drug</td>
<td>0.8%</td>
<td>3.1%</td>
</tr>
</tbody>
</table>

*24-month extension trial of tadalafil 5 mg once daily for erectile dysfunction.

**Robert**

**Treatment Tailoring**

- **LUTS workup**
  - IPSS, 15 (moderate)
  - Poor flow, intermittency, straining to urinate
  - PSA level, 1.7 ng/mL
  - DRE, firm and symmetrically enlarged with no nodules
  - Alfuzosin 10 mg daily
  - Self-report of some erectile dysfunction
- The PCP decides to adjust the treatment regimen

**What would be your recommended approach to tailoring treatment?**

**Alternative Presentations**

- **Physical exam**
  - BMI, 29.8 kg/m²
  - BP, 125/88 mm Hg
- **Medical history**
  - Hypertension
  - Lisinopril 20 mg daily
- **Family history**
  - Brother died of prostate cancer

**Red Flags: Consider Urologist Referral**

- Presence of LUTS associated with results of DRE suggesting prostate cancer
- Hematuria
- Abnormal PSA levels
- Recurrent UTI
- Palpable bladder
- History/risk of urethral stricture
- Neurologic disease raising likelihood of primary bladder disorder

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Conclusions

• BPH-LUTS is a progressive condition characterized by storage, voiding, and postmicturition symptoms
• Common comorbidities of BPH-LUTS include hypertension, metabolic syndrome, and erectile dysfunction
  – These conditions are pathogenically linked
• Effective medical management of BPH-LUTS often requires behavioral modifications and pharmacotherapy
• In select patients, multidrug therapy can more effectively reduce BPH-LUTS and risks of disease progression compared with monotherapy

Build-a-Case

Joseph: Patient Background

• 65-year-old Caucasian man
  – Retired 10 years ago
  – Lives with wife of 40 years
• Presents to his PCP
• Reports feeling somewhat tired during the day

Joseph: Medical History

• Dyslipidemia
  – Simvastatin 40 mg daily
• Takes longer to urinate

Build-a-Case

How does the fact that Joseph has mild hepatic impairment due to a history of excessive alcohol intake affect your approach to patient assessment or treatment?

Additional Considerations in BPH-LUTS

Alcohol Use, Hepatic Impairment

• Prescribing considerations for patients with mild, moderate, or severe hepatic impairment
  – α-Blockers are not recommended in patients with severe hepatic impairment
  – No dose adjustment required for silodosin or tamsulosin in patients with mild or moderate hepatic impairment
  – Effects of hepatic impairment on finasteride and dutasteride have not been studied
• These agents are metabolized extensively in the liver, and caution is required for individuals with abnormal liver function

1. See Drugs@FDA (http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/019668s021lbl.pdf);
2. See Drugs@FDA (http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020579s027lbl.pdf);
3. See Drugs@FDA (http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/022206s006lbl.pdf);
4. See Drugs@FDA (http://www.accessdata.fda.gov/drugsatfda_docs/label/2008/021287s011lbl.pdf);
5. See Drugs@FDA (http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021319s023s025lbl.pdf);
6. See Drugs@FDA (http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/020180s037lbl.pdf).
How does the fact that Joseph complains of disturbed sleep and daytime fatigue affect your approach to patient assessment or treatment?

Additional Considerations in BPH-LUTS

Disturbed Sleep, Daytime Fatigue

- Nocturia increases risk of falls and hip fractures in older individuals
- CAMUS trial
  - Men with LUTS and smaller prostates and/or lower PVR volumes were at greatest risk for sleep problems
  - Data suggest that systemic and/or nonprostatic factors contribute to poor sleep in these patients
- Lack of studies evaluating effects of BPH-LUTS medications on sleep parameters

CAMUS, Complementary and Alternative Medicine for Urological Symptoms.

How does the fact that Joseph has a large waist circumference affect your approach to patient assessment and treatment?

Additional Considerations in BPH-LUTS

Large Waist Circumference

- Increased waist circumference is associated with worsened voiding
- Mechanistic relationships between obesity, erectile dysfunction, and BPH-LUTS
  - Obese men have relatively low testosterone/high estrogen hormonal profiles
  - May increase risks of BPH-LUTS and erectile dysfunction
  - Hyperinsulinemia may induce prostate growth
- Lifestyle modifications for obesity
  - How long until erectile function improves?
  - How long until BPH-LUTS improve?

CAMUS, Complementary and Alternative Medicine for Urological Symptoms.

Build-a-Case

Joseph: Patient Workup

- Urinary symptoms
  - Terminal dribbling
  - Weak urine stream
  - Urinates 2 or 3 times each night
- Physical exam
  - Abdomen is soft
  - No signs of malignancy

Build-a-Case

Joseph: Patient Workup

- BMI, 29.9 kg/m²
- BP, 135/85 mm Hg
- Does not smoke or drink alcohol
- Urinalysis negative
- Some trouble achieving an erection

BMI, body mass index; BP, blood pressure.
Joseph Potential Evaluation Techniques

- **DRE**\(^1,2\)
  - Rule out induration, mass, or nodularity indicative of neoplasm or inflammatory process
  - Anal sphincter tone assessed to rule out neurologic causes
- **PSA testing**\(^1,2\)
  - Compared with DRE, PSA better estimates prostate volume
  - High PSA levels suggest higher risk of disease progression\(^3\)
  - PSA levels can guide treatment selection and follow-up frequency
- **Serum creatinine measurement**\(^2,4\)
  - Screening test for obstructive uropathy
  - Serum creatinine test can be useful in patients with high PVR volumes
  - Guidelines no longer recommend routine creatinine measurement

---

**Build-a-Case**

**Joseph: Additional Workup**

- **DRE**
  - Nontender, enlarged, normally shaped prostate
  - No nodules
- **PSA level, 1.7 ng/mL**
- **Other lab tests normal**
- **Diagnosis of LUTS secondary to BPH**

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**How does the presence of comorbid type 2 diabetes affect your treatment choices for Joseph?**

- Intensive glycemic control did not reduce the risk or severity of LUTS in men with type 1 diabetes
- Precise mechanisms underlying associations between diabetes and nocturia are unclear

---

**How does the presence of controlled hypertension affect your treatment choices for Joseph?**

- Risk of hypertension increases by 5.3% and 5.0% with each year of age and IPSS point, respectively\(^1\)
- **ALLHAT**\(^1,2\)
  - Compared chlorthalidone (thiazide diuretic) and doxazosin (α-blocker) to prevent new onset of heart failure
  - Doxazosin was associated with a 2-fold higher risk of congestive heart failure among high-risk hypertensive patients
How does the presence of chronic pelvic pain syndrome affect your treatment choices for Joseph?

**Build-a-Case**

**Joseph: Initial Treatment**
- Silodosin 8 mg daily
- Increased physical activity
- Modified fluid intake

**Build-a-Case**

**Joseph: Follow-up**
- More physical activity
- Adherent to silodosin
- Little symptomatic improvement
  - Nocturia
  - Weak urinary stream
  - Voiding up to 10 times daily
- Sexual symptoms worsened

**Concluding Comments**

- α-Blockers and 5-ARIs, alone or in combination, may precipitate a number of adverse effects
  - Dizziness, hypotension, sexual dysfunction
- Compared with more uroselective medications, nonselective α-blockers produce fewer effects on ejaculation
- PDE-5 inhibitors are safe and effective in combination with or instead of α-blockers for patients with BPH-LUTS ± erectile dysfunction
- Data supporting antimuscarinic monotherapy are lacking
  - Combination regimens with α-blockers can reduce storage symptoms
  - Baseline PVR should be checked before initiating therapy

Additional Considerations in BPH-LUTS

**Chronic Pelvic Pain Syndrome**
- Chronic pelvic pain syndrome often precedes BPH-LUTS
  - Chronic pelvic pain syndrome commonly develops in patients between 35 and 50 years of age
  - BPH-LUTS commonly affects men aged ≥60 years
- MTOPS and REDUCE trials revealed associations between histologic prostate inflammation and:
  - Prostate enlargement
  - LUTS severity