Evaluating and Treating LUTS in the Primary Care Setting

Faculty

<table>
<thead>
<tr>
<th>Faculty</th>
<th>Institution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pamela Ellsworth, MD</td>
<td>Professor of Urology, Department of Urology, UMass Memorial Medical Center/University of Massachusetts Medical School, Worcester, MA</td>
</tr>
<tr>
<td>Louis Kuritzky, MD</td>
<td>Clinical Assistant Professor, Department of Community Health &amp; Family Medicine, University of Florida, Gainesville, FL</td>
</tr>
<tr>
<td>Matt T. Rosenberg, MD</td>
<td>Medical Director of Mid-Michigan Health Centers, Jackson, MI Section Editor of Urology, International Journal of Clinical Practice</td>
</tr>
</tbody>
</table>

FACULTY DISCLOSURES

- Pamela Ellsworth, MD
  - Speaker/Advisory Board – Pfizer, Allergan
  - Advisory Board – Astellas
- Louis Kuritzky, MD
  - No relevant relationships to disclose
- Matt T. Rosenberg, MD
  - Speaker/Consultant – Astellas, Horizon, Pfizer
  - Speaker – Forest, Ortho-McNeil
  - Consultant – Easai, Ferring, Lilly, Bayer
LEARNING OBJECTIVES

After participating in this educational activity, clinicians should be better able to:

1. Understand that lower urinary tract symptoms in a male could be caused by medical issues, the bladder or the prostate and that a simple history and physical can help delineate the problem.
2. Recognize that erectile dysfunction (ED) and BPH share many of the same co-morbidities.
3. Discuss the different classes of medications available for OAB and BPH.
4. Recognize the risk factors for progression of BPH.

PRE-TEST QUESTION 1

On a scale of 1 to 5, please rate how confident you would be with diagnosing and treating lower urinary tract symptoms in men.

1. Not at all confident
2. Slightly confident
3. Moderately confident
4. Pretty much confident
5. Very confident
Fred presents to the clinic complaining of urgency, frequency and decreased stream. Which of the following is true regarding his symptom complex?

1. The cause is always the prostate or bladder
2. Such symptoms are a normal part of aging
3. The source of the symptoms can be prostate, bladder or other
4. The best way to determine the cause is performing urodynamics

In addition to his urinary symptoms, Fred mentions some problems with his “love life”. Which of the following is true regarding the relationship between Erectile Dysfunction(ED) and Benign Prostatic Hyperplasia (BPH)?

1. There is no relationship as they occur independent of each other
2. They are only seen in the elderly male
3. The severity of one is inversely related to the severity of the other
4. They share many of the same co-morbidities
5. BPH predicts cardiac risk, whereas ED does not
With an appropriate evaluation you diagnose Fred with BPH. He is worried that his problem could get worse. Which of the following is NOT a risk factor for progression of BPH?

1. Age
2. Urine flow rate (Qmax)
3. Prostate volume
4. Diabetes
5. Post void residual

Instead of Fred having urinary obstruction you recognize that he has overactive bladder (OAB). Which of the following is/are considered appropriate therapy for OAB?

1. Alpha blockers
2. Phosphodiesterase 5 inhibitors
3. 5 alpha reductase inhibitors
4. Beta 3 agonists or antimuscarinics
DAVID – 65 Y/O MALE WITH DM

✧ 65 yr old obese male with type 2 DM
✧ At the encouragement of his wife he admits that he has some issues “down there”
  - Urinary urgency, a poor stream, frequency and nocturia
  - Poor erections (“not hard enough”)
  - Symptoms for many years that he thought was a natural part of aging
✧ Meds – metformin, lisinopril and atorvastatin
✧ Physical exam – contributory only for obesity
✧ Labs
  - HgA1C – 6.7%
  - PSA – 2.8 ng/dl
  - Urinalysis - normal

WHAT ARE THE CLUES?

✧ 65 yr old obese male with type 2 DM
✧ At the encouragement of his wife he admits that he has some issues “down there”
  - Urinary urgency, a poor stream, frequency and nocturia
  - Poor erections (“not firm enough”)
  - Symptoms for many years that he thought was a natural part of aging
✧ Meds – metformin, lisinopril and atorvastatin
✧ Physical exam – contributory only for obesity
✧ Labs
  - HgA1C – 6.7%
  - PSA – 2.8 ng/ml
  - Urinalysis - normal
### FUNCTION OF THE PROSTATE

<table>
<thead>
<tr>
<th>NORMAL FUNCTION</th>
<th>ABNORMAL FUNCTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>✷ Produces fluid for seminal emission</td>
<td>✷ Obstruction of urinary flow</td>
</tr>
<tr>
<td>✷ Does not grow into the urethra thereby allowing unobstructed flow</td>
<td>✷ Poor function seen as <strong>failure to void</strong></td>
</tr>
</tbody>
</table>


---

### NATURAL HISTORY OF PROSTATE GROWTH

<table>
<thead>
<tr>
<th>A common condition as men age</th>
</tr>
</thead>
<tbody>
<tr>
<td>✷ By sixth decade: &gt; 50% have some degree of hyperplasia</td>
</tr>
<tr>
<td>✷ By eighth decade: &gt; 90% will have hyperplasia</td>
</tr>
<tr>
<td>✷ ±10% will require surgical or medical intervention</td>
</tr>
<tr>
<td>✷ A 55-year-old man who is experiencing symptoms, has a PSA of 1.5 ng/ml and a 30 mL prostate volume can expect his prostate to approximately double in size over the next 15 years.</td>
</tr>
</tbody>
</table>

**RISK EVALUATION OF BPH-LUTS PROGRESSION**

**Baseline Factors as Predictors**

Five risk factors

1. Total prostate volume \( \geq 31 \text{ mL} \)
2. PSA \( \geq 1.6 \text{ ng/mL} \)
3. Age \( \geq 62 \)

**Not usually evaluated by the PCP**

4. \( Q_{\text{max}} < 10.6 \text{ mL/s} \)
5. PVR \( \geq 39 \text{ mL} \)

PVR, post-void residual; \( Q_{\text{max}} \), maximum flow rate.


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**ASSESSMENT: DRE VS. PSA**

- There is a strong and clinically useful relationship between serum PSA and prostate volume.

- Digital rectal examination (DRE) is quite inaccurate in estimating the correct prostate size when compared to either transrectal ultrasound (TRUS) or other imaging modalities.

FUNCTION OF THE BLADDER

<table>
<thead>
<tr>
<th>NORMAL FUNCTION</th>
<th>ABNORMAL FUNCTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>✤ Storage capacity of 300 – 500 ml of fluid</td>
<td>✤ Voiding frequently of small amounts (less than capacity)</td>
</tr>
<tr>
<td>✤ Empty to completion after a gentle urge</td>
<td>✤ Uncontrollable urge (urgency) to empty</td>
</tr>
<tr>
<td></td>
<td>✤ Incomplete emptying</td>
</tr>
<tr>
<td></td>
<td>✤ Poor function seen as failure to store or empty</td>
</tr>
</tbody>
</table>


DEFINITION OF OAB

OAB is syndrome or symptom complex defined as: “Urgency, with or without urgency incontinence, usually with frequency and nocturia”

Urgency is the key symptom of OAB

Urgency is defined as “a sudden compelling desire to void, which is difficult to defer”

USING SYMPTOMS TO DISTINGUISH
THE ORIGIN OF THE PROBLEM

DIFFERENTIATING THE ETIOLOGY
OF LUTS?

- Weak flow – think prostate
- Voiding small amounts – think bladder
- Leakage of urine – think bladder or sphincter
- Good flow, normal volume – think too much
  fluid production and evaluate accordingly

It is all about volume and flow


OAB AND BPH CAN COEXIST

BACK TO DAVID

Upon questioning David’s symptoms are consistent with BPH-LUTS. Which would you consider to be the three most prevalent co-morbid conditions associated with BPH-LUTS?

1. Heart disease, diabetes, arthritis
2. Hypertension, high cholesterol, ED
3. Diabetes, pain, depression
4. Digestive tract disorders, allergies, arthritis
COMMON COMORBIDITIES IN BPH-LUTS

<table>
<thead>
<tr>
<th>Comorbidity with BPH-LUTS (N = 6,909)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>53</td>
</tr>
<tr>
<td>High cholesterol</td>
<td>45</td>
</tr>
<tr>
<td>Erectile or other sexual dysfunction</td>
<td>36</td>
</tr>
<tr>
<td>Digestive tract disorder</td>
<td>21</td>
</tr>
<tr>
<td>Arthritis</td>
<td>20</td>
</tr>
<tr>
<td>Heart disease/Heart failure</td>
<td>18</td>
</tr>
<tr>
<td>Diabetes</td>
<td>17</td>
</tr>
<tr>
<td>Depression/Anxiety/Sleep disorder</td>
<td>16</td>
</tr>
<tr>
<td>Allergies/cold/flu/congestion</td>
<td>15</td>
</tr>
<tr>
<td>General pain/inflammation</td>
<td>11</td>
</tr>
</tbody>
</table>


LINKING LUTS-BPH AND ED

<table>
<thead>
<tr>
<th>LUTS-BPH</th>
<th>Comorbidities</th>
<th>ED</th>
<th>Comorbidities</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Risk Factors</td>
<td></td>
<td>Risk Factors</td>
</tr>
<tr>
<td></td>
<td>Increasing LUTS severity or symptom worsening</td>
<td>Increasing age</td>
<td>Cardiovascular disease</td>
</tr>
<tr>
<td></td>
<td>Increasing serum dihydrotestosterone</td>
<td>Smoking</td>
<td>Diabetes/Disrupted glucose homeostasis</td>
</tr>
<tr>
<td></td>
<td>Enlarged prostate; &gt;30 mL</td>
<td>High waist circumference</td>
<td>Erectile dysfunction</td>
</tr>
<tr>
<td></td>
<td>Inflammation</td>
<td></td>
<td>Metabolic syndrome</td>
</tr>
<tr>
<td></td>
<td>Elevated IPSS</td>
<td></td>
<td>Obesity</td>
</tr>
<tr>
<td></td>
<td>Refractory to treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Poor flow</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Genetics</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>History of AUR</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>High waist circumference</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Increasing age</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>PSA &gt;1.5 ng/dL</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>PVR &gt;50 mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Increasing bother</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Reduced physical activity</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Evaluating and Treating LUTS in the Primary Care Setting

LUTS-BPH AND ED AND DIRECTLY RELATED

<table>
<thead>
<tr>
<th>Age Group</th>
<th>LUTS Effect</th>
<th>LUTS Effect</th>
<th>LUTS Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>50-59 Years</td>
<td>22.3</td>
<td>19.2</td>
<td>15.3</td>
</tr>
<tr>
<td>60-69 Years</td>
<td>21.1</td>
<td>18.3</td>
<td>13.2</td>
</tr>
<tr>
<td>70-79 Years</td>
<td>18.9</td>
<td>15.8</td>
<td>10.3</td>
</tr>
</tbody>
</table>

BPH-LUTS AND ED

COMMON PATHOPHYSIOLOGIC MECHANISMS

- Reduced NO–cGMP signaling
- Increased RhoA–ROCK signaling
- Autonomic hyperactivity
- Pelvic atherosclerosis

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

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

Chronic inflammationSteroid hormone unbalance

Comorbidities
Hypertension, Metabolic Syndrome, Diabetes, etc.

N=10,636 men who had been sexually active within the last 4 weeks.
IIEF, International Index of Erectile Function.


### WHAT TO KEEP IN MIND IN THE EVALUATION OF LUTS

- Lower Urinary Tract Symptoms (LUTS) can be of urologic origin, which includes the prostate and bladder, or can be medical in nature
- A comprehensive history, physical and lab evaluation will generally provide the needed clues

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### EXAMPLES IN THE MEDICAL OR SURGICAL HISTORY THAT CAN CAUSE OR CONFOUND LUTS

- Poorly controlled diabetes causing polyuria/polydipsia
- Antihypertensive diuretics can frequency and urgency whereas some cold medications (e.g., α-agonists) can cause urinary retention or hesitancy
- Nocturia associated with CHF
- Recent surgery causing immobilization or constipation
- Poor urinary hygiene

**The temporal relationship may offer a clue**

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A FOCUSED PHYSICAL EXAMINATION

✧ Abdominal
  – Tenderness, masses, distension
✧ Neurological
  – Mental and ambulatory status, neuromuscular function
✧ Genitourinary
  – Meatus and testes
✧ Rectal
  – Tone
  – Prostate size, shape, nodules and consistency


LABORATORY TESTS

✧ Urinalysis
  – Infection, blood, crystals
  – The urine is not an adequate screener for diabetes since the blood sugar must be above 180 mg/dl before it spills into the urine
✧ A random or fasting blood sugar
  – Diabetes
✧ Prostate specific antigen
  – Prostate specific not cancer specific but can be used in screening
  – Excellent as a surrogate marker for prostate size
    ▪ PSA is more accurate than a DRE when estimating prostate size
    ▪ A PSA of 1.5 ng/ml equates to a prostate volume of at least 30 grams/ml

OPTIONAL TESTS

- International Prostate Symptom Score (IPSS)
- Voiding Diary
- Post Void Residual (PVR)
- Urine Flow Rate (Qmax)

INTERNATIONAL PROSTATE SYMPTOM SCORE (IPSS)

<table>
<thead>
<tr>
<th>Question</th>
<th>Not at all</th>
<th>Less than half time</th>
<th>Less than half the time</th>
<th>More than half the time</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Incomplete emptying; Over the past month, how often have you had a</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>sensation of not emptying your bladder completely after you finished</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>urination?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Frequency; Over the past month, how often have you had to urinate</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>again less than two hours after you finished urination?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Intermittnce; Over the past month, how often have you stopped</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>and started again several times when you urinated?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Urgency; Over the past month, how often have you found it difficult</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>to postpone urination?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Weak Stream; Over the past month, how often have you had a weak</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>urinary stream?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Nocturia; Over the past month, how many times did you need to get</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>out of bed more than 5 times or more times in last month?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total IPSS Score: 7

Modest BPH (1 to 7), moderate BPH (8 to 19), or severe BPH (20 to 35)


NACE - Emerging Challenges in Primary Care: 2014
LUTS - 15
THE PURPOSE OF THE VOIDING DIARY

✧ Identifies voiding frequency and voided volume
✧ Differentiates behavioral vs LUTS pathology
  - Voiding frequently
    - excessive volume (behavioral)
    - small amounts as a result of always being in a rush (behavioral)
    - small amounts (OAB)
✧ Alerts patients to habits/opportunities to modify
✧ Can monitor effect of treatment


POST-VOID RESIDUAL

✧ FACTS
  - 50 ml or less represents adequate emptying
  - 200 ml or more is consistent with clinically significant inadequate emptying
✧ WHEN TO CHECK
  - Clinical suspicion
  - Refractory to therapy for BPH
  - Prior to pharmacologic treatment of OAB

**URINE FLOW RATE**

*It is all about the “arc” of the void*


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**LUTS AND INDICATIONS FOR REFERRAL**

- Suspicion of neurologic cause of symptoms
- History of recurrent UTI or other infection
- Findings or suspicion of urinary retention
- Abnormal prostate exam (nodules)
- Microscopic or gross hematuria
- History of genitourinary trauma
- Prior genitourinary surgery
- Uncertain diagnosis
- Meatal stenosis
- Elevated PSA
- Pelvic pain

**STEP 1: INFORMED SURVEILLANCE**

*If the patient has symptoms but no bother and no complications*

Patients who opt for this may benefit from:

- Education and reassurance
- Lifestyle changes (exercise, weight management)
- Fluid management
- Bladder training: timed and complete voiding
- Medication modification
- Validation: LUTS:BPH significant QoL impact


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**THE NEXT STEP: STEP 2**

Rationale for Alpha-Blocker or PDE5I Therapy

Alpha-blockers
PDE5is
Dynamic component
Rapidly relieve symptoms by inhibiting contraction of prostate smooth muscle


Step 2: Alpha Blockers (AB)

Single medication therapy with an AB is appropriate for the symptomatic patient who has identified bother and has a PSA of < 1.5 ng/ml

- Generally fast acting, relieving symptoms within hours
- Does not affect progression of prostate growth

STEP 2: ALPHA – BLOCKERS

<table>
<thead>
<tr>
<th>Non-Uroselective</th>
<th>Uroselective</th>
</tr>
</thead>
<tbody>
<tr>
<td>Terazosin 1, 2, 5, 10 mg daily</td>
<td>Tamsulosin 0.4 mg daily</td>
</tr>
<tr>
<td>Doxazosin 1, 2, 4, 8 mg daily</td>
<td>Alfuzosin 10 mg daily</td>
</tr>
<tr>
<td>Silodosin 8 mg daily</td>
<td></td>
</tr>
</tbody>
</table>

Potential side effects (decreased incidence with uroselective agents)
- Asthenia, fatigue, dizziness
- Postural hypotension
- Congestion, rhinitis, cough
- Abnormal ejaculation
- Edema
- Headache


STEP 2: PHOSPHODIESTERASE 5 INHIBITORS (PDE5I)

Monotherapy with a PDE5-I is appropriate for the symptomatic patient who has identified bother and has a PSA of < 1.5 ng/ml. The potential favorable impact of this therapy on male sexual function should be considered

- It is believed that the PDE5i increase the signaling of the NO/cGMP pathway, which reduces smooth muscle tone in the lower urinary tract
- It is not believed that use of a PDE5i will reduce progression of prostate growth

STEP 2: PHOSPHODIESTERASE TYPE 5 INHIBITORS

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tadalafil</td>
<td>2.5 mg per day</td>
<td>ED</td>
</tr>
<tr>
<td>Tadalafil</td>
<td>5.0 mg per day</td>
<td>BPH and ED</td>
</tr>
</tbody>
</table>

Common side effects: headache, back pain, myalgia, dizziness, flushing and dyspepsia.

Contraindicated in patients who use nitrates.

Patients should not use tadalafil if sex is inadvisable due to cardiovascular status.


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>Sildenafil1</td>
<td>25, 50, 100</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Vardenafil2</td>
<td>5, 10, 20</td>
<td>1</td>
<td>4-5</td>
</tr>
<tr>
<td>Tadalafil3</td>
<td>2.5, 5, 10, 20</td>
<td>2</td>
<td>17.5</td>
</tr>
<tr>
<td>Avanafil4</td>
<td>50, 100, 200</td>
<td>0.5-0.75</td>
<td>5</td>
</tr>
</tbody>
</table>

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);
Evaluating and Treating LUTS in the Primary Care Setting

**TADALAFIL IN BPH-LUTS**

**ONCE-DAILY DOSING**

N=427 men who completed a 12-week, placebo-controlled, dose-finding study assessing once-daily tadalafil for BPH-LUTS.

HRQoL, health-related quality of life.


**ADVERSE EVENTS WITH TADALAFIL**

**ONCE-DAILY VS ON-DEMAND DOSING**

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>5 mg Once Daily&lt;br&gt;N=238</th>
<th>5/10/20 mg On Demand&lt;br&gt;N=1173</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>

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

*b* Pooled 24-month extension trial data from five 8- or 12-week studies examining on-demand tadalafil for erectile dysfunction.

WHAT ABOUT PDE5IS AND ABS?

✧ Recent studies show benefit of PDE5i/AB combination therapy over AB monotherapy
  - Improvement in IPSS
  - No added benefit in urodynamic parameters
✧ Concerns over hemodynamics effects of combination therapy not demonstrated


PDE-5 INHIBITORS AND A-BLOCKERS
Effects on IPSS, 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>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td>Kaplan et al, 2007</td>
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<td>Bechara et al, 2008</td>
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<td>Liguori et al, 2009</td>
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<td>Tuncel et al, 2009</td>
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<tr>
<td>Gacci et al, 2012</td>
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<td></td>
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<tr>
<td>Overall</td>
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</table>

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

Compared with α-blockers alone, the combination regimens significantly improved IPSS (P=0.05), IIEF scores (P<0.0001), and Qmax (P<0.0001)

These studies examined the PDE-5 inhibitors tadalafil, sildenafil, and vardenafil, and the α-blockers alfuzosin and tamsulosin.

Evaluating and Treating LUTS in the Primary Care Setting

**THE NEXT STEP: STEP 3A**


**RATIONALE FOR COMBINING AB/PDE5I WITH ANTIMUSCARINIC/BETA - 3**

STEP 3A: ADDITION OF AN ANTIMUSCARINIC OR BETA-3 AGONIST

*If the patient has symptoms of both obstruction and irritation as well as bother*

✧ In multiple studies the addition of an antimuscarinic to an α-blocker was more efficacious in reducing voiding frequency, nocturia, or IPSS compared to α-blockers or placebo alone.

✧ Not yet studied
- β3 agonists + α-blocker
- β3 agonist + PDE5i
- Antimuscarinic + PDE5i


<table>
<thead>
<tr>
<th>Drug</th>
<th>Brand Name</th>
<th>Dose</th>
<th>Dosing</th>
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</thead>
<tbody>
<tr>
<td>Oxybutynin IR</td>
<td>Ditropan</td>
<td>5 mg</td>
<td>1 – 3 times per day</td>
</tr>
<tr>
<td>Tolterodine IR</td>
<td>Detrol</td>
<td>1-2 mg</td>
<td>Twice per day</td>
</tr>
<tr>
<td>Trospium Chloride</td>
<td>Sanctura</td>
<td>20 mg</td>
<td>Twice per day</td>
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ANTIMUSCARINICS – EXTENDED RELEASE

Extended release medications have a better tolerability than their immediate release counterparts.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Brand Name</th>
<th>Dose</th>
<th>Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Darifenacin</td>
<td>Enablex</td>
<td>7.5 mg, 15 mg</td>
<td>Daily</td>
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<tr>
<td>Fesoterodine</td>
<td>Toviaz</td>
<td>4 mg, 8 mg</td>
<td>Daily</td>
</tr>
<tr>
<td>Oxybutynin ER</td>
<td>Ditropan XL</td>
<td>5 – 30 mg</td>
<td>Daily</td>
</tr>
<tr>
<td>Oxybutynin TDS</td>
<td>Oxytrol</td>
<td>3.9 mg</td>
<td>Twice per week</td>
</tr>
<tr>
<td>Oxybutynin 10% gel</td>
<td>Gelnique</td>
<td>100 mg</td>
<td>Daily</td>
</tr>
<tr>
<td>Solifenacin</td>
<td>Vesicare</td>
<td>5 mg, 10 mg</td>
<td>Daily</td>
</tr>
<tr>
<td>Tolterodine ER</td>
<td>Detrol LA</td>
<td>2, 4 mg</td>
<td>Daily</td>
</tr>
<tr>
<td>Trospium Chloride</td>
<td>Sanctura XR</td>
<td>60 mg</td>
<td>Daily</td>
</tr>
</tbody>
</table>


COMMON SIDE EFFECTS OF ANTIMUSCARINICS

- Dry Mouth
- Constipation
- Headaches
- Blurred vision

Clinicians should manage constipation and dry mouth before abandoning effective antimuscarinic therapy.

Balance of efficacy and tolerability should be considered and discussed with each patient.

CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS FOR ANTIMUSCARINICS

✧ Contraindications-
  - Urinary or gastric retention
  - Uncontrolled narrow-angle glaucoma

✧ Warnings & Precautions –
  - Angioedema of face, lips, tongue and/or larynx
  - Clinically significant bladder outlet obstruction
  - Decreased gastrointestinal motility
  - Treated narrow angle glaucoma
  - May have CNS effects i.e., somnolence
  - Use with caution in patients with myasthenia gravis


BETA-3 ADRENERGIC AGONISTS

<table>
<thead>
<tr>
<th>Drug</th>
<th>Brand Name</th>
<th>Dose</th>
<th>Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mirabegron</td>
<td>Myrbetriq</td>
<td>25 mg, 50 mg</td>
<td>Daily</td>
</tr>
</tbody>
</table>

Myrbetriq™ (mirabegron) prescribing information, Astellas Pharma US, Inc. June 2012. 56
COMMON SIDE EFFECTS OF MIRABEGRON

- Hypertension
- Nasopharyngitis
- Urinary Tract Infections
- Headaches

Balance of efficacy and tolerability should be considered and discussed with each patient.

CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS FOR MIRABEGRON

- Contraindications – NONE
- Precautions & Warnings –
  - Not recommended for use in severe uncontrolled hypertensive patients
  - Use with caution in patients with urinary retention or bladder outlet obstruction
  - Use with caution in patients taking antimuscarinic drugs for overactive bladder
  - Caution with use in patients taking drugs metabolized by CYP2D6 (i.e., metoprolol or desipramine) as mirabegron is a moderate inhibitor of CYP2D6
**THE NEXT STEP: STEP 3B**


**RATIONALE FOR COMBINING AB/PDE5I WITH 5ARI**

STEP 3B: ADDING A 5 ALPHA REDUCTASE INHIBITOR (5ARI)

The addition of a 5ARI is appropriate for the symptomatic patient with BPH-LUTS who has identified bother and has a PSA of 1.5 ng/ml or greater

- Prostate growth may result in symptom progression, AUR and surgery
- Prostate growth is stimulated by dihydrotestosterone (DHT) with is converted from testosterone by the 5-alpha reductase enzyme
- Decreasing DHT may induce prostatic epithelial apoptosis and atrophy which can lead to approximately 18% – 28% reduction in prostate size and approximately a 50% reduction in PSA levels after 6 - 12 months


5 ARIS

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Finasteride</td>
<td>5 mg daily</td>
</tr>
<tr>
<td>Dutasteride</td>
<td>0.5 mg daily</td>
</tr>
</tbody>
</table>

Potential side effects

- Diminished ejaculatory volume
- Erectile dysfunction
- Decreased libido
- Gynecomastia
- Increase risk of high-grade prostate cancer *

* Conflicting data in the literature

COMBINATION THERAPY

- Starting with combination therapy may allow immediate symptom relief from the AB or a PDE5 while facilitating prostate reduction from the 5ARI
- Two prolonged studies (MTOPS and CombaT) using a AB and a 5ARI have shown that combination therapy is better than either monotherapy alone
- One 26 week study showed that use of tadalafil with finasteride was better than finasteride alone


α-BLOCKER PLUS 5 ARI OUTPERFORMS MONOTHERAPY

IPSS - Adjusted Mean Change From Baseline (LOCF)

- Tamsulosin (n = 1582)
- Dutasteride (n = 1592)
- Combination (n = 1575)

P<0.001 Combination vs Tamsulosin
P<0.001 Combination vs Dutasteride

IPSS = International Prostate Symptom Score
LOCF = last observation carried forward

**PDE5I PLUS 5 ARI OUTPERFORMS MONOTHERAPY**

*IPSS Total Score— LS Mean Changes at 4, 12, and 26 Weeks*

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**EARLY VS DELAYED COMBINATIONS**

5-ARI and α-Blocker

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1. **Clinical Progression**
   - All Patients
   - Patients with PSA values
   - Patients with 1.5< PSA value <10

2. **AUR**
   - All Patients
   - Patients with PSA values
   - Patients with 1.5< PSA value <10

3. **Surgery**
   - All Patients
   - Patients with PSA values
   - Patients with 1.5< PSA value <10

4. **Total Costs**
   - All Patients
   - Patients with PSA values
   - Patients with 1.5< PSA value <10

---

**Clinical progression** defined as the occurrence of AUR or prostate surgery during the 12 months after first prescription fill.

**Delayed combination therapy** initiation of a 5-ARI >30 days and <180 days after initial α-blocker treatment.

**Early combination therapy** initiation of an α-blocker and a 5-ARI on the same day, or a 5-ARI within 30 days of initial α-blocker treatment

OR, odds ratio.

N=13,551 men ≥50 years of age and treated for BPH-LUTS with a 5-ARI and an α-blocker.


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Roehrborn CG, et al. *28TH Annual EAU Congress; Milan, Italy; 15-19 March 2013*
THE NEXT STEP: STEP 4

STEP 4: REFERRAL

For the patient with symptoms and bother who is refractory to therapy

- “Alarm symptoms” or “red flags”
- Failure to respond in a reasonable amount of time
  - Alpha blockers, PDE5is, antimuscarinics and β3 agonists should work quickly
  - 5 ARIs work slowly

SUMMARY

- The cause of LUTS-BPH can be medical, the prostate or the bladder
- A simple evaluation in the office of the PCP can elicit the cause in most cases
- There appears to be a shared pathophysiology that underlies benign prostatic hyperplasia (BPH) and erectile dysfunction (ED)
- The treatment of LUTS-BPH should occur in a step-wise fashion that depends on symptom severity, sexual function and risk factors

POST-TEST QUESTIONS
Fred presents to the clinic complaining of urgency, frequency and decreased stream. Which of the following is true regarding his symptom complex?

1. The cause is always the prostate or bladder
2. Such symptoms are a normal part of aging
3. The source of the symptoms can be prostate, bladder or other
4. The best way to determine the cause is performing urodynamics

In addition to his urinary symptoms, Fred mentions some problems with his “love life”. Which of the following is true regarding the relationship between Erectile Dysfunction(ED) and Benign Prostatic Hyperplasia (BPH)?

1. There is no relationship as they occur independent of each other
2. They are only seen in the elderly male
3. The severity of one is inversely related to the severity of the other
4. They share many of the same co-morbidities
5. BPH predicts cardiac risk, whereas ED does not
POST-TEST QUESTION 3

With an appropriate evaluation you diagnose Fred with BPH. He is worried that his problem could get worse. Which of the following is NOT a risk factor for progression of BPH?

1. Age
2. Urine flow rate (Qmax)
3. Prostate volume
4. Diabetes
5. Post void residual

POST-TEST QUESTION 4

Instead of Fred having urinary obstruction you recognize that he has overactive bladder (OAB). Which of the following is/are considered appropriate therapy for OAB?

1. Alpha blockers
2. Phosphodiesterase 5 inhibitors
3. 5 alpha reductase inhibitors
4. Beta 3 agonists or antimuscarinics
POST-TEST QUESTION 5

On a scale of 1 to 5, please rate how confident you would be with diagnosing and treating lower urinary tract symptoms in men.

1. Not at all confident
2. Slightly confident
3. Moderately confident
4. Pretty much confident
5. Very confident

POST-TEST QUESTION 6

Which of the statements below describes your approach to participating in diagnosing and treating lower urinary tract symptoms in men?

1. I do not participate in the diagnosis and treatment of lower urinary tract symptoms in male patients, nor do I plan to this year.
2. I did not participate in the diagnosis and treatment of lower urinary tract symptoms in male patients before this course, but as a result of attending this course I’m thinking of doing this now.
3. I do participate in the diagnosis and treatment of lower urinary tract symptoms in male patients and I now plan to change my treatment methods based on completing this course.
4. I do participate in the diagnosis and treatment of lower urinary tract symptoms in male patients and this course confirmed that I don’t need to change my methods.