10:30 – 11:15am

The Prostate: BPH and Beyond

SPEAKERS
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Presenter Disclosure Information

The following relationships exist related to this presentation:

Mohit Khera, MD, MBA, MPH, serves as consultant to AMS, Auxilium, and Coloplast.

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.

Men’s Health: BPH, ED and Beyond

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Scott Department of Urology
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Learning Objectives

• Diagnose and treat men with BPH
• Discuss the AUA 2014 updated BPH guidelines
• Diagnose and treat men with ED
• Discuss the relationship between ED and cardiovascular disease

Case #1

• David is 64 y/o male with a 6 month history of hesitancy, urgency, frequency and nocturia x 3
• AUA symptom score 27
• PMH: DM, HTN
• Sx: cholecystectomy
• Social: no tob, occ ETOH
• PE: DRE 60 grams
• Labs: PSA 3.2
• Next step?

Prevalence of BPH

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Prevalence</th>
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<tbody>
<tr>
<td>31-40</td>
<td>8%</td>
</tr>
<tr>
<td>51-60</td>
<td>40-50%</td>
</tr>
<tr>
<td>80+</td>
<td>80%</td>
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</table>
**Natural History of BPH: Relationship Between Symptoms and Prostate Volume**


- 631 white men ages 40 to 79 from Olmsted County, MN
- Estimated prostate growth rates increased by 1.6% per year across all ages
- Higher baseline prostate volume associated with higher rates of prostate growth

**Pathophysiology of Clinical BPH: Predictive Risk Factors**

- Increasing age
- Prostatic enlargement
- Lower-urinary-tract symptoms (LUTS)
- Decreased urinary flow rate
- Elevated prostate-specific antigen (PSA)

**Serum PSA ≥ 1.5 ng/mL Can Predict Prostate Enlargement and Risk of Progression**

**Health-Related Quality of Life: LUTS/BPH Compared with Another Chronic Disease (COPD)**

Complaints of Untreated Clinical BPH

- Acute urinary retention
- Urinary tract infection
- Bladder calculi
- Bladder damage
- Renal impairment
- Hematuria

(Each of these are indications for TURP)

Updated 2014 AUA BPH Guidelines

- The updated guideline includes 2 detailed algorithms to facilitate diagnosis and treatment of LUTS secondary to BPH: one on basic management of LUTS in men, and the other on detailed management for persistent, bothersome LUTS
- For facilitation of diagnosis and treatment of younger men with LUTS, the index patient age has been lowered to 45 years (from age 50 years)
- Laboratory tests should include prostate-specific antigen testing and urinalysis to exclude infection or other causes for LUTS
- The routine measurement of serum creatinine levels is not indicated in the initial evaluation of men with LUTS secondary to BPH
- Diagnosis may be facilitated by frequency and volume charts
- If storage symptoms predominate, an overactive bladder from idiopathic detrusor overactivity is the most likely cause if flow study result shows no indication of BOO

Diagnosis of BPH

Initial Evaluation

- Detailed medical history
- DRE and focused physical exam
- Urinalysis
- PSA in selected patients*
- Symptom assessment
  - AUA/IPSS Symptom Index
  - Assessment of patient bother

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

- Oral intake
  - Timing
  - Caffeine
  - Alcohol
- Medications affecting volume
  - Diuretics

Optional Diagnostic Tests

- Uroflow
  - Urinary flow-rate recording (Qmax)
- PVR
- If patient chooses invasive therapy
  - Pressure flow urodynamics
  - Urethrocystoscopy
  - Prostate ultrasound

AUA Symptom Score Index

- Seven-item questionnaire related to BPH symptoms
- Validated and reproducible
- Determines disease severity
- Documents response to therapy
- Allows standardized comparisons of symptom relief when evaluating treatments

AUA Symptom Index Scoring

<table>
<thead>
<tr>
<th>SCORE</th>
<th>INTERPRETATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-7</td>
<td>Mild</td>
</tr>
<tr>
<td>8-19</td>
<td>Moderate</td>
</tr>
<tr>
<td>20-35</td>
<td>Severe</td>
</tr>
</tbody>
</table>

AUA Symptom Index Scoring

Updated 2014 AUA BPH Guidelines

- Patients with mild LUTS secondary to BPH (AUA Symptom Index score < 8) and patients with moderate or severe symptoms (AUA Symptom Index score ≥ 8) who are not (active surveillance)
- If the patient bothered by LUTS should be treated with watchful waiting; if persistent, bothersome LUTS after basic management, then a urologist should be consulted
- For coexisting BOO and overactive bladder symptoms, the patient can be treated with combination alpha-blocker and anticholinergic therapy
- For LUTS resulting from BPH with predominant BOO symptoms, alpha-blockers are the first treatment of choice
- The decision for choice of therapy should consider the patient’s wishes and concerns
Evolution of Medical Therapy
for LUTS/BPH/BOO/BPE

- **α-blocker**
- **5-ARI**
- **Antimuscarinic**

Evolution of Medical Therapy
for LUTS/BPH/BOO/BPE

- **PDE 5 inhibitor**
- **Antimuscarinic**
- **α-blocker**

Evolution of Medical Therapy
for LUTS/BPH/BOO/BPE

- **PDE 5 inhibitor**
- **Antimuscarinic**
- **Other drugs**

Finasteride and Prostate Cancer

- The PCPT enrolled 18,882 men and randomized to placebo vs. finasteride 5 mg daily for 7 years
- Reduction of prostate cancer by 24.6% in the treatment arm, with an increased rate of development of Gleason 7–10 prostate cancers (37% treatment vs 22.2% placebo)
- Subsequent reanalysis found multiple counterarguments against the increased risk for HGPC:
  - Lack of reliability of Gleason scoring following SARI treatment
  - Reduction in prostate volume and subsequent increased detection of malignancy
  - Increased sensitivity of PSA as a prostate cancer detection marker in the finasteride group


Minimally Invasive Techniques for BPH

- Transurethral needle ablation (TUNA)
- Transurethral microwave therapy (TUMT)
- Transurethral incision of the prostate (TUIP)
- Urolift

Invasive Treatments for BPH

- Transurethral Resection of the Prostate (TURP)
  - Laser
  - Bipolar
  - Monopolar
- Suprapubic prostatectomy
  - Open
  - Robotic

Erectile Dysfunction: Diagnosis and Treatment

Case #2

- Bill is a 59 y/o male with a 2 year history of worsening ED. He is unable to maintain his erections. He is happily married but ED causing stress in marriage.
- PMH: HTN, gout
- PSx: hernia, TURP
- Social: smokes 2ppd, occ ETOH
- PE: testis- 18cc bilaterally, DRE- 50 grams and benign, B DP pulses 1+
- Labs: PSA 2.5
- Next step?

Treating Erectile Dysfunction in Modern Times

Massachusetts Male Aging Study (MMAS)

Prevalence and Severity of ED by Age Group

- Overall prevalence of ED among men aged 40 to 70 years (N=1290) was 52%

US Epidemiologic Studies of ED

<table>
<thead>
<tr>
<th>Study</th>
<th>Prevalence Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1992 National Health and Social Life Survey</td>
<td>5% among men 18–59 years of age</td>
</tr>
<tr>
<td>(NHSLS)1</td>
<td></td>
</tr>
<tr>
<td>2001–2002 US respondents in Global Study of</td>
<td>22.5% men 40–80 years of age</td>
</tr>
<tr>
<td>Sexual Attitudes and Behaviors (GSSAB) survey2</td>
<td>with “erectile difficulty”</td>
</tr>
<tr>
<td>2001–2002 National Health and Nutrition</td>
<td>18.4% among men ≥20 years of age</td>
</tr>
<tr>
<td>Examination Survey (NHANES)31</td>
<td>or 18 million men</td>
</tr>
<tr>
<td>2002–2005 Boston Area Community Health (BACH)</td>
<td>47% among men 30–79 years of age</td>
</tr>
<tr>
<td>Survey4</td>
<td></td>
</tr>
<tr>
<td>2011 National Health and Wellness Survey (NHWS)5</td>
<td>29.5% among men ≥40 years of age</td>
</tr>
</tbody>
</table>

* The overall prevalence of mild, moderate, and severe ED was 17.2%, 25.2%, and 6.6%, respectively.
Most Men With ED Do Not Receive Treatment

- In a study of 6,228,509 men with ED1
  - 25.4% received treatment (i.e., PDE5 inhibitor, injection or urethral prostaglandins or androgen replacement)
  - 74.6% were untreated
- In a population-based study of men 40 years and older with ED, 77% were not receiving pharmacotherapy with a PDE5 inhibitor2
- Potential reasons for not seeking treatment3
  - Feelings of shame
  - Concern that the physician won’t take the sexual problem seriously

Etiologies of ED1-3

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasculogenic</td>
<td>Cardiovascular disease, hypertension, diabetes mellitus, hyperlipidemia, smoking, major surgery (radical prostatectomy) or radiotherapy (pelvis or retroperitoneum)</td>
</tr>
<tr>
<td>Neurogenic</td>
<td>Spinal cord and brain injuries, Parkinson’s disease, Alzheimer’s disease, multiple sclerosis, stroke</td>
</tr>
<tr>
<td>Local penile/cavernous</td>
<td>Peyronia’s disease, cavernous fibrosis, penile fracture</td>
</tr>
<tr>
<td>Hormonal</td>
<td>Hypogonadism, hyperprolactinemia, hyper- and hypothyroidism, hyper- and hypocortisolism</td>
</tr>
<tr>
<td>Drug-induced</td>
<td>Antihypertensives, antidepressants, antipsychotics, antidiabetics, recreational drugs</td>
</tr>
<tr>
<td>Psychogenic</td>
<td>Performance-related issues, traumatic past experiences, relationship problems, anxiety, depression, stress</td>
</tr>
</tbody>
</table>

Efficacy Measures: IIEF-EF

International Index of Erectile Function (IIEF) Erectile Function (EF) Domain Measured on a 30-point scale

- No ED
- Mild ED
- Moderate ED
- Severe ED

- How often were you able to get an erection during sexual activity?
- When you had erections with sexual stimulation, how often were your erections hard enough for penetration?
- When you attempted sexual intercourse, how often were you able to penetrate (penetrate) your partner?
- During sexual intercourse, how often were you able to maintain your erection after you had penetrated (penetrated) your partner?
- During sexual intercourse, how often did you feel that you had control over your penis?
- How do you rate your confidence that you can get and keep your erection?


Efficacy Measures: Sexual Encounter Profile

SEP2 “Were you able to insert your penis into your partner’s vagina?” Y N

SEP3 “Did your erection last long enough to have successful intercourse?” Y N

Diagnostic Evaluation of Men with ED

- Patient with ED (self-reported)
- Medical and psychosexual history (use of validated instruments, eg, IIEF)
- Identify other sexual problems
- Identify common causes of ED
- Identify reversible risk factors for ED
- Assess psychological status
- Laboratory tests
  - Glucose-lipid profile (if not assessed in the last 12 months)
  - Total testosterone (morning sample)

Correlation Between ED and CVD

- The prevalence of silent coronary artery disease in patients with ED ranges from 8 to 56%1
- Mulhall et al. demonstrated that 20% of patients diagnosed with vasculogenic ED have an abnormal cardiac stress test.2

Correlation Between ED and CVD

- Thompson et al. 2005¹
  - 4,247 men without ED followed prospectively
  - 57% with ED at 5 years
  - Men with ED had a significantly higher incidence of developing CVD

- Montorsi et al. 2005 ² ³
  - Prevalence of ED was 49% in men with symptomatic CAD.
  - Patients noticed ED on average 39 months before the onset of angina.

¹ Thompson et al JAMA 2005; 294:2996
² Montorsi et al Eur Urol 2003; 44:360
³ Montorsi et al AJC 2005; 96(12): 19M

Cardiac Risk Stratification

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<th>Low-risk category</th>
<th>Intermediate-risk category</th>
<th>High-risk category</th>
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<td>Asymptomatic, &lt;2 risk factors for CAD (excluding sex)</td>
<td>2 risk factors for CAD (excluding sex)</td>
<td>High-risk amythias</td>
</tr>
<tr>
<td>LV/CHF (NYHA class I or II)</td>
<td>Mild or moderate, stable angina</td>
<td>Unstable or refractory angina</td>
</tr>
<tr>
<td>Post-successful coronary revascularization</td>
<td>Previous (&lt;6-8) or recent MI (≤ 6 weeks)</td>
<td>Recent MI (&lt;2 weeks)</td>
</tr>
<tr>
<td>Controlled hypertension</td>
<td>LV/CHF (NYHA class III)</td>
<td>LV/CHF (NYHA class IV)</td>
</tr>
<tr>
<td>NIDDM or moderate or severe atherosclerotic disease (eg, stroke, peripheral vascular disease)</td>
<td>Noncardiac sequelae of athereosclerotic disease (eg, stroke, peripheral vascular disease)</td>
<td>Uncontrolled hypertension</td>
</tr>
<tr>
<td>Moderate-to-severe valvular disease</td>
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Treatment Algorithm for ED


Cardiac Risk Impacts ED Management:
Princeton III Consensus Recommendations

Cardiac Risk Stratification

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Current ED Treatment Approaches

Source: Adapted from American Urologic Association Treatment of ED Guidelines.
Androgens Enhance PDE5i Efficacy

- Shabsigh et al.¹
  - 75 hypogonadal men (T<400 ng/dl) failed sildenafil 100mg
  - Randomize to testosterone gel or placebo
  - All men received sildenafil 100 mg as needed for 12 weeks
  - IIEF significantly improved in TRT vs placebo (4.4 vs 2.1, p=0.029)

- Rosenthal et al.²
  - 24 hypogonadal men failed 3 trials of sildenafil 100mg within 3 months
  - Started on 4 weeks of testosterone gel and then restarted on sildenafil
  - After 16 weeks, 92% of men who initially failed sildenafil therapy reported improvements in potency

- Khera et al.³
  - Multicenter registry of hypogonadal men (n=849) treated with TRT and followed for 12 months
  - Patients already on PDE5i therapy also had a significant increase in BMSFI scores after starting TRT

²Rosenthal et al. Urology 2006 Mar; 67(3):571-4
³ Khera et al. JSM 2011 Nov;8(11):3204-13

Medical Therapy of ED

- Sildenafil  April 1998
- Vardenafil  August 2003
- Tadalafil: November 2003
- Avanafil: January 2014

PDE5 Inhibitors: Pharmacokinetics

<table>
<thead>
<tr>
<th></th>
<th>Sildenafil¹</th>
<th>Tadalafil²</th>
<th>Vardenafil³</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tmax (min)</td>
<td>60</td>
<td>120</td>
<td>60</td>
</tr>
<tr>
<td>Terminal t1/2 (hrs)</td>
<td>4</td>
<td>17.5</td>
<td>4-5</td>
</tr>
</tbody>
</table>

Impact of a high fat meal

- Mean delay in Tmax of 60 minutes; mean reduction in Cmax of 29%
- Rate and extent of absorption are not influenced by food
- Reduction in Cmax of 18-50%

Recommended administration times

- ~60 minutes before sexual activity
- Use as needed prior to sexual activity

Avanafil

- Tmax (min): 30-45min
- Terminal t1/2 (hrs): 5 hours

Impact of a high fat meal:

- Rate of absorption is reduced, Tmax of 1.12 to 1.25 hours and a mean reduction in Cmax of 39% (200 mg)
- 3.8% decrease in AUC

Recommended administration times: 15 minutes prior to intercourse

IMPORTANT SAFETY INFORMATION

- Administration of PDE5is with any form of organic nitrates, either regularly and/or intermittently, is contraindicated. PDE5is have been shown to potentiate the hypotensive effects of nitrates

- There is a potential for cardiac risk during sexual activity in patients with preexisting cardiovascular disease. Patients should therefore not use PDE5is if sexual activity is inadvisable due to cardiovascular status or any other reason

- Patients with the following characteristics (recent serious cardiovascular events, resting hypotension or unstable hypertension, unstable angina, angina with sexual intercourse, New York Heart Association Class 2 or greater congestive heart failure, or hereditary degenerative retinal disorders, including retinitis pigmentosa) were not included in the clinical safety and efficacy trials. PDE5is are therefore not recommended for those patients

- PDE5is have systemic vasodilatory properties and may augment the blood pressure-lowering effect of other antihypertensive medications. Physicians should carefully consider whether patients with underlying cardiovascular disease could be affected adversely by such vasodilatory effects, especially in combination with sexual activity

- Caution is advised when PDE5 inhibitors are coadministered with alpha-blockers. Patients who demonstrate hemodynamic instability on alpha-blocker therapy alone are at increased risk of symptomatic hypotension with concomitant use of PDE5 inhibitors. Patients should be stable on alpha-blocker therapy prior to initiating treatment with a PDE5 inhibitor. In those patients who are stable on alpha-blocker therapy, PDE5 inhibitors should be initiated at the lowest dose

IMPORTANT SAFETY INFORMATION
Summary

• BPH increases with age with 80% of men having the BPH at the age of 80
• Complications of untreated BPH include acute urinary retention, urinary tract infections, bladder calculi, bladder damage, renal impairment and hematuria
• Combination alpha-blocker and 5 alpha-reductase inhibitor is superior to either drug alone in retarding the clinical progression of BPH in men with large prostate glands
• Numerous minimally invasive and invasive techniques exist for the treatment of BPH
• ED is a progressive disease with the prevalence increasing with age
• Patients with ED should have a cardiovascular assessment as ED and CVD often present simultaneously
• There are now numerous effective treatment options available for men presenting with ED