Increasing Awareness, Diagnosis, and Treatment of BPH, LUTS, and EP

~ E. David Crawford, MD

Introduction to Enlarged Prostate

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What is Enlarged Prostate (EP)?

Symptoms of Enlarged Prostate: Obstructive
Symptoms of Enlarged Prostate: Irritative

Overview of DHT in the Development of EP

- The development and growth of the prostate gland depends on androgen stimulation.  
- In men, testosterone is converted to dihydrotestosterone (DHT), a more potent androgen, by 5-alpha-reductase (5AR) enzymes.
- In the prostate, two types of 5ARs exist: Type I and Type II.
- It is known that DHT levels in the prostate remain high with aging, despite a decrease in the production of testosterone.

5ARs' Role in the Conversion of Testosterone to DHT

Characteristics of EP

- Common prostate condition in men over 50.
- Prostate size ≥30 mL.
- Prostate-specific antigen (PSA) ≥1.5 ng/mL.
- Progressive disease.
- Major cause of urinary symptoms in older men.

References:
The Burden of EP in the United States (US)

- **Population Growth of Men At-Risk for EP**
  - Number of Men (in millions)
  - 2000: 44.8
  - 2010: 56.5
  - 2020: 64.7
  - 2030: 72.0
  - 2040: 79.1
  - 2050: 84.5

- **Prevalence of EP**
  - EP affects 50% of men over age 50 and 90% of men over the age of 80.
  - In a recent survey of men over age 50 in the United States:
    - 25% reported moderate to severe symptoms of EP
    - 55% of those consulting a doctor were diagnosed with EP

- **Economic Burden of EP**
  - In 2000, the direct cost of EP reached $1.1 billion in the US alone (not including outpatient pharmaceuticals)
    - Medical services at hospital inpatient and outpatient settings
    - Hospital departments and physician office visits
  - In a 2-year period, outpatient prescription drugs for EP were estimated to cost $194 million a year*
The Personal Impact of EP

Concern for
Need of surgery

Concern for AUR

Concern for cancer

Symptoms

Bother

Interference and QoL


Summary of Disease Burden of EP

• The majority of men over age 50 are affected by BPH, which can include EP
• Considerably underdiagnosed and undertreated
• Economic and societal burden
• Can decrease quality of life
  – Creates strains on personal life
  – Interferes with daily activities
  – Causes concerns about AUR and prostate-related surgery

Enlarged Prostate: A Progressive Disease

Predictors of Clinical Progression of EP

<table>
<thead>
<tr>
<th></th>
<th>Age Progression</th>
<th>Symptoms</th>
<th>Prostate Volume</th>
<th>PSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olmsted County Study</td>
<td>≥50 years</td>
<td>Moderate-to-severe symptoms (AUA-SI &gt;7)</td>
<td>&gt;30 mL</td>
<td>&gt;21.4 ng/mL</td>
</tr>
<tr>
<td>(n = 2,115)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baltimore Longitudinal Study of Aging</td>
<td>≥50 years</td>
<td>Obstructive symptoms</td>
<td>Clinical EP diagnosed by DRE</td>
<td>&gt;1.4 ng/mL, for 50-59 years*, &gt;1.7 ng/mL for 60-66 years*</td>
</tr>
<tr>
<td>(n = 1,087)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical Therapy of Prostatic Symptoms</td>
<td>≤62 years</td>
<td>4-point increase in AUA-SI</td>
<td>&gt;21 mL</td>
<td>&gt;21.6 ng/mL</td>
</tr>
<tr>
<td>(n = 737)</td>
<td></td>
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</tr>
</tbody>
</table>

*PSA level associated with prostate enlargement

Natural History of Untreated EP Progression

Male patient, age 55 years:
symptomatic EP, PSA = 1.5 ng/mL, negative for prostate cancer

55 years old
PV: 30 mL, PSA = 1.5 ng/mL

60 years old
PV: >40 mL

65 years old
PV: >50 mL

70 years old
PV: >61 mL

Disease progression can increase the risk of AUR and prostate-related surgery.


Overview and Outcomes of AUR

- Common urological emergency
  - Greater resistance to urine flow
  - Bladder over-distention
  - Can have neuropathic causes
- Outcomes of AUR
  - Inability to urinate with increasing pain
  - Visits to the emergency room
  - Emergency catheterization
  - Urinary tract infection
  - Continuing failure to spontaneously void
  - Surgery

AUR is a painful, time-consuming, and feared condition that often results in emergency catheterization.


Risk of EP-Related Surgery in Men with EP

Risk of EP-Related Surgery in Men with EP

Risk of EP-Related Surgery in Men with EP

Summary of Progressive Disease

- Age, severity of urinary symptoms, PSA and prostate volume are predictors of clinical progression of EP
- Disease progression increases the risk of AUR and EP-related surgery
  - Men 70 to 79 years of age are up to 3 times more likely to have AUR
  - Men with a baseline prostate volume >30 mL are at greater risk for AUR, as men with greater PSA and symptom severity at baseline
- AUR is a painful condition that results in emergency catheterization
- As men age, their risk for developing EP, and progressing to AUR and prostate-related surgery increases
Diagnosing EP

A Practical Algorithm for the Diagnosis and Management of EP

- Man >50 years old presents with urinary symptoms
- Determine if patient has Enlarged Prostate (230 mL):
  - Digital rectal exam (DRE)
  - PSA ≥ 1.5 ng/mL
- Treat symptoms only
- Treat symptoms and modify disease

Adapted from Figure 3, entitled “Practical Algorithm for the Treatment of EP in Primary Care” in Kaplan S. Weill Medical College of Cornell University Reports on Men’s Urologic Health. 2006;1(1):1–8.

Symptom Assessments for EP

- American Urological Association Symptom Index (AUA-SI)¹
  - 7 item, patient-rated questionnaire to evaluate symptom severity
  - Scaled 0-5, with a maximum score of 35:
    - ≤ 7 mild symptoms
    - 8-19 moderate symptoms
    - 20-35 severe symptoms
- International Prostate Symptom Score (IPSS)²
  - Same 7 questions as the AUA SI, with the addition of a disease-specific quality of life question


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

PSA = prostate-specific antigen

Arresting Disease Progression

- Symptom worsening
- Decreased urinary flow
- AUR
- Prostate-related surgery

Summary of EP Diagnosis

- Diagnosis involves assessment of symptom severity and determination of prostate volume
- The PSA test is an effective tool to estimate prostate size
- PSA of 1.5 ng/mL suggests a prostate volume ≥30 mL
- The goal of medical therapy should be to arrest disease progression and reduce the risk of long-term disease complications

Pharmacologic Treatment Goals and Options for EP

- Alpha blockers:
  - Relax smooth muscle
  - Ease pressure on urethra and bladder
  - Improve urinary flow ($Q_{\text{max}}$) and bothersome symptoms

Treatment Options: Alpha Blockers

Treatment Options: AVODART® - A 5AR Inhibitor

- Dutasteride (AVODART)
  - Dual Type I and II inhibitor
  - Dual 5ARI blocks the conversion of testosterone to DHT by competitively inhibiting both Type I and Type II pathways

The clinical benefit of more complete DHT suppression has not been established.

AVODART® (dutasteride) - Phase III Data: Reducing Size, Symptoms, and Risk

AVODART Reduces Size

Pooled Results from Three Randomized, Placebo-controlled, 2-year Clinical Studies Followed by 2-year Open-label Extension Phase of AVODART 0.5 mg daily

AVODART Reduces Symptoms

Pooled Results from Three Randomized, Placebo-controlled, 2-year Clinical Studies with 2-year Open-label Extension Phase with AVODART 0.5 mg daily
AVODART Reduces the Risk

AUR

57% risk reduction

Placebo

AVODART

EP-related surgery

48% risk reduction

Placebo

AVODART

*P < 0.001 vs placebo. Results of 3 combined, double-blind, prudential studies of 4295 men with BPH.


A Practical Algorithm for the Treatment of EP in Primary Care

Man >50 years old presents with urinary symptoms

Determine if patient has Enlarged Prostate (≥30 mL):

- DRE
- PSA (≤10 ng/mL)

No

Yes

Reassess periodically


Treat symptoms only

α-blocker

Treat symptoms and modify disease

5ARI

Combination 5ARI plus α-blocker

Two-year Results From the Combination of AVODART and Tamsulosin (CombAT) Study

CombAT Study Design

Screening

4-week placebo run-in

Safety follow-up

Pre-screen

Baseline

Visit every 3 months

Follow-up (4 years)

Combination daily (n = 1610)

Tamsulosin 0.4 mg daily (n = 1611)

AVODART 0.5 mg daily (n = 1623)

Primary measures:

IPSS

AUR, Surgery


CombAT Major Entry Criteria

- **Age**: ≥50 years
- **EP diagnosis**: Diagnosis by history and DRE
- **IPSS**: ≥12 (moderate-to-severe symptoms)
- **Prostate volume**: ≥30 cc by TRUS
- **Serum PSA**: 1.5 – 10.0 ng/mL
- **Qmax**: >5 and ≤15 mL/sec (moderate-to-severe impairment)
- **Minimum voided volume**: ≥125 mL (based on two voids at screening)

DRE = digital rectal exam; TRUS = transrectal ultrasound; Qmax = maximum urinary flow.


CombAT Patient Characteristics at Baseline

<table>
<thead>
<tr>
<th></th>
<th>All Patients N=4844</th>
<th>Combination* n=1610</th>
<th>AVODART n=1623</th>
<th>Tamsulosin n=1611</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>66.1</td>
<td>66.0</td>
<td>66.0</td>
<td>66.2</td>
</tr>
<tr>
<td>Caucasian ethnicity (%)</td>
<td>88</td>
<td>88</td>
<td>88</td>
<td>87</td>
</tr>
<tr>
<td>Mean IPSS score (points)</td>
<td>16.4</td>
<td>16.6</td>
<td>16.4</td>
<td>16.4</td>
</tr>
<tr>
<td>Mean prostate volume (cc)</td>
<td>55.0</td>
<td>54.7</td>
<td>54.6</td>
<td>55.8</td>
</tr>
<tr>
<td>Mean Qmax (mL/sec)</td>
<td>10.7</td>
<td>10.9</td>
<td>10.6</td>
<td>10.7</td>
</tr>
<tr>
<td>Mean serum PSA (ng/mL)</td>
<td>4.0</td>
<td>4.0</td>
<td>3.9</td>
<td>4.0</td>
</tr>
<tr>
<td>Previous 5ARI use (%)</td>
<td>11</td>
<td>11</td>
<td>12</td>
<td>11</td>
</tr>
<tr>
<td>Previous alpha blocker use (%)</td>
<td>50</td>
<td>50</td>
<td>51</td>
<td>51</td>
</tr>
</tbody>
</table>

*AVODART plus tamsulosin


CombAT: Reduction in Urinary Symptoms

- **IPSS - Adjusted Mean Change From Baseline (LOCF)**
  - Tamsulosin (n = 1582)
  - AVODART (n = 1592)
  - Combination (n = 1575)

<table>
<thead>
<tr>
<th></th>
<th>Tamsulosin</th>
<th>AVODART</th>
<th>Combination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjusted Mean Change From Baseline (LOCF)</td>
<td>-4.3</td>
<td>-4.9</td>
<td>-6.2</td>
</tr>
</tbody>
</table>

P < 0.001 Combination vs Tamsulosin

P < 0.001 Combination vs AVODART

2. Data on file, GlaxoSmithKline.

CombAT: Reduction in Total PV

Adjusted Mean Percentage Change from Baseline (LOCF)

- **Month 24**

<table>
<thead>
<tr>
<th></th>
<th>Tamsulosin</th>
<th>AVODART</th>
<th>Combination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjusted Mean Percentage Change from Baseline (LOCF)</td>
<td>-28.0</td>
<td>-26.9</td>
<td>-30.0</td>
</tr>
</tbody>
</table>
## CombAT: Continuous Improvement in Qmax

Adjusted Mean Change From Baseline (LOCF)²

<table>
<thead>
<tr>
<th></th>
<th>Tamsulosin (n = 1519)</th>
<th>AVODART (n = 1502)</th>
<th>Combination (n = 1492)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.4</td>
<td></td>
<td>1.9</td>
<td></td>
</tr>
<tr>
<td>0.9</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

P<0.006 Combination vs. AVODART and tamsulosin


### Most Common Drug-related Adverse Events* - CombAT

<table>
<thead>
<tr>
<th>Drug-related AEs</th>
<th>CombAT</th>
<th>Tamsulosin</th>
<th>AVODART</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erectile dysfunction</td>
<td>7.4%</td>
<td>3.6%</td>
<td>6.0%</td>
</tr>
<tr>
<td>Retrograde ejaculation</td>
<td>4.2%</td>
<td>1.1%</td>
<td>0.6%</td>
</tr>
<tr>
<td>Libido decreased</td>
<td>3.4%</td>
<td>1.7%</td>
<td>2.8%</td>
</tr>
<tr>
<td>Ejaculation failure</td>
<td>2.4%</td>
<td>0.8%</td>
<td>0.5%</td>
</tr>
<tr>
<td>Semen volume decreased</td>
<td>1.8%</td>
<td>0.8%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Loss of libido</td>
<td>1.7%</td>
<td>0.9%</td>
<td>1.3%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1.6%</td>
<td>1.7%</td>
<td>0.7%</td>
</tr>
<tr>
<td>Breast enlargement</td>
<td>1.4%</td>
<td>0.8%</td>
<td>1.8%</td>
</tr>
<tr>
<td>Nipple pain</td>
<td>1.2%</td>
<td>0.3%</td>
<td>0.6%</td>
</tr>
<tr>
<td>Breast tenderness</td>
<td>1.0%</td>
<td>0.3%</td>
<td>1.0%</td>
</tr>
<tr>
<td>Discontinued due to drug-related AEs</td>
<td>5%</td>
<td>3%</td>
<td>3%</td>
</tr>
</tbody>
</table>

*Drug-related AEs occurring in ≥1% of subjects within any treatment group.


### CombAT Summary

- Clinical trial in >4,800 men with moderate to severe lower urinary tract symptoms and enlarged prostate
- The CombAT study demonstrated a benefit for combination therapy over monotherapies in the first 12 months of therapy.
- Significant improvement in urinary symptoms and prostate size with combination therapy at 24 months


### PSA in Relation to the Prostate

- PSA production and use in EP¹
  - DHT stimulates the growth of glandular epithelial cells in the prostate, which produce high levels of PSA¹
  - Predictive of prostate volume in men with EP²
- PSA is prostate-specific, not cancer-specific
- Prostate cancer cells also produce PSA³
- PSA ≥1.5 ng/mL suggests EP⁴

¹ Schalken J. BJU Int. 2004;93 (suppl 1):5-9.