Perspectives in Men’s Health

April 10-11, 2010 • Caesar’s Palace • Las Vegas, Nevada
BPH Treatment and Future Directions
Neal Shore, MD, FACS
Director, Carolina Urologic Research Center
What is Enlarged Prostate (EP)?

As the prostate grows it constricts the urethra, resulting in varying levels of obstructive and/or irritative urinary symptoms. In severe cases, urine flow is entirely obstructed.

Symptoms of Enlarged Prostate: Obstructive

- Weak urinary stream
- Prolonged voiding
- Straining
- Hesitancy
- Intermittency
- Incomplete bladder emptying
- Post-void dribbling
Symptoms of Enlarged Prostate: Irritative

- Frequency
- Nocturia
- Urgency
- Incontinence
A Modern View of BPH: Clinical, Anatomic, and Pathophysiologic Changes

- **BPH** = Benign prostatic hyperplasia
  - Histologic: stromoglandular hyperplasia
- May be associated with
  - Clinical: presence of bothersome LUTS
  - Anatomic: enlargement of the gland (BPE = benign prostatic enlargement)
  - Pathophysiologic: compression of urethra and compromise of urinary flow (BOO = bladder outlet obstruction)

Symptom Assessments for EP

- **American Urological Association Symptom Index (AUA-SI)**
  - 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)**
  - Same 7 questions as the AUA-SI, with the addition of a disease-specific quality of life question

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Prevalence of EP

- Histologic EP affects 50% of men over age 50 and 90% of men over the age of 80\(^1,2\)

- In a recent survey of men over age 50 in the United States\(^3\)
  - 25% reported moderate to severe symptoms of EP
  - 55% of those consulting a doctor were diagnosed with EP

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Impact of EP on Health Status and Quality of Life (QoL)

The proportion of men who report their health status as “fair” or “poor” was greater in men with worsened symptoms.

The proportion of men who report limited daily activities due to health grows as EP-related symptoms worsen.

EP with Mild Symptoms (AUA-SI ≤7; n = 216)
EP with Moderate-to-severe Symptoms (AUA-SI = 8-35; n = 203)
(AUA-SI = American Urological Association-Symptom Index)

Lack of Diagnosis and Treatment in EP

Approximately half of men with EP have been diagnosed\(^1,2\)

Approximately 20\% of men with moderate-to-severe urinary symptoms never consulted their doctor\(^2\)

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BPH Disease Prevalence and Treatment

U.S. BPH Patient Waterfall, 2004

- **Prevalence**: 17.2 MM
- **Diagnosed**: 8.8 MM
- **Untreated**: 8.4 MM
- **Watchful Waiting**: 6.5 MM
- **Treated for BPH**: 2.3 MM

Treatment Choice, 2004

- **Drug Therapy**: 2.3M (88%)
- **MIT**: 100K (4%)
- **Surgery**: 175K (7%)

Source: BSC BPH Market Forecast, 2/27/04; Urologist quantitative study; IMS data, December 2003
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
  - Emergency departments and physician office visits

- In a 2-year period, outpatient drugs for EP were cost $194 million

*from 1996-1998

## Current Practice and Growing Need for Care in the Aging Population

<table>
<thead>
<tr>
<th></th>
<th>Family Practice/General Medicine¹</th>
<th>Urology¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of active physicians</td>
<td>100,152</td>
<td>9,864</td>
</tr>
<tr>
<td>Number of people per physician</td>
<td>3,000</td>
<td>30,200</td>
</tr>
<tr>
<td>Increase in aging population per practice, 1995-2004</td>
<td>~21%</td>
<td>~8%</td>
</tr>
</tbody>
</table>

From 2005 to 2007, the population of persons 65 years and older is estimated to be ~37 million.² This is expected to grow to ~55 million by 2020.³

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## Baby Boom Generation: Increasing Life Expectancy

Table 11. Life expectancy by age, race, and sex: Death-registration States, 1900–1902 to 1919–21, and United States, 1929–31 to 2002

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National Vital Statistic Reports, Vol. 53, No. 6, November 10, 2004
Pharmacologic Therapy *(Today)*

- 3 million patients are on drug therapy for BPH
  - Driven by increased pharmaceutical advertising
- Average cost **per year** for combined medical therapy is approximately $2,000

  This assumes monthly costs:
  - Alpha Blocker = $70
  - 5-ARI = $100

- Prescription drug plan variability will impacts patient costs
- Medication side effects:
  - **Alpha Blockers**: retrograde ejaculation, dizziness, rhinitis, asthenia, cataract surgery complications
  - **5 Alpha Reductase Inhibitors**: decrease libido, decrease ejaculate, gynecomastia

1. Based on national list price – WalMart Company
BMI, Symptoms, and Prostate Size in the Baltimore Longitudinal Study of Aging

- 479 men from the BLSA followed by MRI
- Relationship between BMI, symptoms, and prostate size assessed
- Increasing BMI is associated with increasing symptom severity and larger glands ($P < .01$)

<table>
<thead>
<tr>
<th>Odds ratio (OR) for moderate/severe IPSS</th>
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<tbody>
<tr>
<td>BMI (kg/m²)</td>
</tr>
<tr>
<td>&lt; 25</td>
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<td>25–30</td>
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<td>&gt; 30</td>
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<td>OR</td>
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<td>Waist circumference (cm)</td>
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<tr>
<td>&lt; 102</td>
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<tr>
<td>&gt; 102</td>
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<tr>
<td>OR</td>
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<tr>
<td>Waist to hip ratio</td>
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<tr>
<td>&lt; 0.9</td>
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<tr>
<td>&gt; 0.9</td>
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<td>OR</td>
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</table>

OR for MRI volume > 40 mL

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<tr>
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<tbody>
<tr>
<td>OR</td>
<td>1.0</td>
<td>1.41</td>
<td>1.27</td>
<td>3.52</td>
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</tbody>
</table>
Central Obesity and BPH

- Relationships between PV and age, obesity index, testosterone, and lifestyle factors tested (N = 146)
  - Waist circumference > 90 cm was associated with BPH (OR = 3.37; P = .037)
  - Men with BMIs ≥ 25 kg/m² and central obesity had significantly increased risk of BPH (OR = 4.88; P = .008), relative to men with low BMIs and normal waist circumference
- High BMI without central obesity did not show an increased risk of BPH

Baby Boomers and The Obesity Epidemic

GETTING BIGGER
The percentage of adults, by state, who were obese in 2005.

- Obesity rates below 20%
- Obesity rates between 20% and 25%
- Obesity rates between 25% and 30%
- Obesity rates over 30%

SOURCE: "F AS IN FAT: HOW OBESITY POLICIES ARE FAILING IN AMERICA," TRUST FOR AMERICA'S HEALTH, AUGUST; CENTERS FOR DISEASE CONTROL AND PREVENTION'S BEHAVIORAL RISK FACTOR SURVEILLANCE SYSTEM
Male patient, age 55 years:
symptomatic EP, PSA = 1.5 ng/mL, negative for prostate cancer

<table>
<thead>
<tr>
<th>Age</th>
<th>PV</th>
<th>PSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>55 yrs</td>
<td>30 mL</td>
<td>1.5 ng/mL</td>
</tr>
<tr>
<td>60 yrs</td>
<td>&gt;40 mL</td>
<td></td>
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<tr>
<td>65 yrs</td>
<td>&gt;50 mL</td>
<td></td>
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<tr>
<td>70 yrs</td>
<td>&gt;61 mL</td>
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</table>

PV= prostate volume

Figure based on Roehrborn C, et al. / Urol. 2000;163:13–20.
### 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>
</table>
| Olmsted County Study¹,²  
(n=2,115)             | >50 years       | Moderate-to-severe symptoms       | >30 mL          | ≥1.4 ng/mL       |
|                     |                 | (AUA-SI >7)                       |                 |                  |
| Baltimore Longitudinal Study of Aging³,⁴  
(n=1,057)             | ≥50 years       | Obstructive symptoms              | Clinical EP diagnosed by DRE | >1.4 ng/mL for 50-59 years*, >1.7 ng/mL for 60-69 years* |
|                     |                 |                                   |                 |                  |
| Medical Therapy of Prostatic Symptoms⁵  
(n=737)                | ≥62 years       | 4-point increase in AUA-SI        | ≥31 mL          | ≥1.6 ng/mL       |

*PSA level associated with prostate enlargement

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Overview of DHT in the Development of EP

- The development and growth of the prostate gland depends on androgen stimulation\(^1\)

- In men, testosterone is converted to dihydrotestosterone (DHT),\(^1\) a more potent androgen,\(^2\) by 5-alpha-reductase (5AR) enzymes\(^1\)

- In the prostate, two types of 5ARs exist: Type I and Type II\(^1\)

- It is known that DHT levels in the prostate remain high with aging, despite a decrease in the production of testosterone\(^3\)

DHT is primarily responsible for the development of EP\(^1\)

Treatment Options: 5AR Inhibitors

- 5ARIs are appropriate treatments for patients with LUTS associated with demonstrable prostatic enlargement

- 5ARIs indicated for EP include:
  - Finasteride
  - Dutasteride

Treatment Options: Alpha Blockers

- **Alpha blockers**
  - Appropriate treatment options for patients with LUTS secondary to BPH\(^1\)

- **Mechanism\(^2,3\):**
  - Relax smooth muscle
  - Ease pressure on urethra and bladder
  - Improve urinary flow (\(Q_{\text{max}}\)) and bothersome symptoms

- **Agents indicated for symptomatic BPH include\(^1\):**
  - Alfuzosin
  - Doxazosin
  - Silodosin
  - Tamsulosin
  - Terazosin

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The Role of Chronic Inflammatory Infiltrates

• **Medical Therapy of Prostatic Symptoms (MTOPS) trial:**
  ~ 40% of biopsy specimens had chronic inflammatory infiltrates
  – Older patients, with larger glands and higher PSA levels

• **Average follow-up of 4.5 years**
  – 21% of patients with infiltrates had overall progression, while 13.2% of patients *without* infiltrates had overall progression
  – Similar ↑ in rates for symptom progression, invasive therapy

• **Cytokine-rich milieu caused by chronic inflammation may cause alterations in microenvironment and chronic repetitive wound healing leading to BPH nodules**
  – Further research needed to identify putative antigen, immune response, and new classification of BPH

Data Supporting the Role of Apoptosis in BPH

- In vitro studies suggest a reduction of apoptosis (programmed cell death) in BPH
  - Inhibition of apoptosis thought to be due to the activation of the Bcl-2 pathway
  - Enhanced expression of Bcl-2 may be involved in deregulation of cell death, resulting in growth imbalance favoring proliferation
  - Prostate outgrowth compartmentalized in stroma, where cell death is absent
  - Survivin, an inhibitor of apoptosis, overexpressed in stromal compartment
    - Levels of survivin related to IPSS, quality-of-life score, and postvoid residual volume in one study
- Studies of both finasteride and dutasteride have shown proapoptotic effects

• A Prospective Randomized Two Dose Level Comparison of Single-Injection Transrectal Intraprostatic NX-1207 and Finasteride in Men With Lower Urinary Tract Symptoms Due to Benign Prostatic Hyperplasia

• Neal Shore, Barton Wachs, Rafael Wurzel, James Bailen, Sheldon Freedman, Kevin Cline, Chris Threatt,

• William Fitch III, Barrett Cowan, Pat Hezmall
NX-1207

- therapeutic protein with prostate selective pro-apoptotic properties
- dissolved in PBS (saline) pH 7.2
- stored at -20°C, thawed within 1 hour prior to injection
NX-1207 Pre-Clinical Studies

Animal histopathology: glandular atrophy

Rat prostate
Control
H & E, original magnification x 50

Rat prostate
1 year post injection NX-1207
H & E, original magnification x 50
NX-1207  Phase 2 Studies

NX02-0014*  N=175
3 dose range (2.5, 5, 10 mg)
Placebo controlled (saline solution)
Double blind, prospective, randomized

Efficacy: AUASI  9.35 points (all dose) (p=.017)
11.03 points (2.5 mg)

Qmax  2.19 mL/sec (all dose)
2.58 mL/sec (2.5 mg)

PGV  -6.84 cc (all dose) (p=.027)
-6.79 cc (2.5 mg)

NX02-0016  Present Study

*Presented at South Central Section AUA, Colorado Springs, September 8, 2007
      New England Section AUA, Boston, September 28, 2007
A Prospective Randomized Two Dose Level Comparison of Single-Injection Transrectal Intraprostatic NX-1207 and Finasteride in Men With Lower Urinary Tract Symptoms Due to Benign Prostatic Hyperplasia

Primary endpoint: AUASI Improvement, 90 days.

Secondary endpoints: PGV Change, 90 days.
AUASI Improvement, 30 days.
Qmax Change, 90 days.
<table>
<thead>
<tr>
<th>Cohort</th>
<th>N</th>
<th>AUA Score Baseline/90 days</th>
<th>Mean Improvement</th>
<th>p</th>
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<tbody>
<tr>
<td>NX-1207 2.5 mg</td>
<td>48</td>
<td>23.15/13.44</td>
<td>9.71</td>
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<tr>
<td>NX-1207 0.125 mg</td>
<td>7</td>
<td>22.29/18.0</td>
<td>4.29</td>
<td>(p=.034)*</td>
</tr>
<tr>
<td>Finasteride 5 mg p.o.</td>
<td>24</td>
<td>20.17/16.04</td>
<td>4.13</td>
<td>(p=.001)*</td>
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* vs. NX-1207 2.5 mg.
## NX-1207 Results

### Prostate Volume Reduction

(Intent to Treat)

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<thead>
<tr>
<th>Cohort</th>
<th>N</th>
<th>PGV Baseline/90 days</th>
<th>Mean Improvement</th>
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</thead>
<tbody>
<tr>
<td>NX-1207 2.5 mg</td>
<td>48</td>
<td>45.85/40.95</td>
<td>-4.90 g</td>
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<tr>
<td>NX-1207 0.125 mg</td>
<td>7</td>
<td>48.74/49.87</td>
<td>+1.13 g</td>
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<tr>
<td>Finasteride 5 mg p.o.</td>
<td>24</td>
<td>47.34/42.45</td>
<td>-4.90 g</td>
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* vs. NX-1207 2.5 mg.
# NX-1207 Results

## $Q_{\text{max}}$ Improvement

(Intent to Treat)

<table>
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<tr>
<th>Cohort</th>
<th>N</th>
<th>$Q_{\text{max}}$ Baseline/90 days</th>
<th>Mean Improvement</th>
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<tbody>
<tr>
<td>NX-1207 2.5 mg</td>
<td>47</td>
<td>9.55/11.75</td>
<td>2.18 cc/sec (p=.08)*</td>
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<tr>
<td>NX-1207 0.125 mg</td>
<td>6</td>
<td>8.83/9.13</td>
<td>0.30 cc/sec</td>
</tr>
<tr>
<td>Finasteride 5 mg p.o.</td>
<td>24</td>
<td>9.00/11.35</td>
<td>2.35 cc/sec (N.S.)</td>
</tr>
</tbody>
</table>

* $Q_{\text{max}}$ not powered for statistical comparison.
NX-1207 Summary

- Mean AUASI Improvement (Intent to Treat) of 9.71 points (p= .034)
- Mean PGV Reduction of 4.90 cc (p= .013)
- Mean Qmax Improvement of 2.18 mL/sec (p= .08)
NX-1207
Conclusions

- Primary endpoint: AUASI (9.71 points, p=.034) significantly improved
- Secondary endpoint: PGV (4.90 g, p=.013) significantly reduced
- Office-based
- Analgesic and anesthetic-free
- Injection usually takes 1-2 minutes to perform
- No compliance problem
- No catheterization
12-Week Results of a Phase II Trial of 100 and 300 Units Botulinum Neurotoxin Type A (BoNT-A) for the Management of Benign Prostatic Hyperplasia

E David Crawford, Robert Donnell, Kathryn Hirst, Steven A Kaplan, John W Kusek, Kevin T McVary, Lance Mynderse, Lee Nyberg, Claus G Roehrborn, Christopher P Smith, and Reginald Bruskewitz for the MIST Study Group

Presentation to AUA 2009, Chicago IL
Study Design: Primary Objective

- Primary objective is to determine whether two different doses of BoNT-A injected into the prostate gland demonstrate sufficient improvement in the management of lower urinary symptoms due to BPH to warrant more extensive research.
Study Design: Primary Outcome

- Primary outcome is successful treatment within the first 12 weeks after injection, defined as no evidence of dangerous levels of toxicity related to study therapy and the occurrence of either one or both of the following:
  - Improvement in the AUA symptom score index by 30% from baseline.
  - Qmax improvement of more than 30% from baseline.
Primary outcome: Pass means ≥ 30% change from baseline in AUA SS and/or Qmax

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<th>100 Units</th>
<th>300 Units</th>
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<tr>
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<td>Qmax fail</td>
<td>Qmax pass</td>
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<tr>
<td>AUA SS fail</td>
<td>17 (27%)</td>
<td>10 (16%)</td>
</tr>
<tr>
<td>AUA SS pass</td>
<td>20 (32%)</td>
<td>16 (25%)</td>
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</table>

BOTH ARMS PASS EFFICACY CRITERIA
73% at 100 Units and 81% at 300 Units
Conclusions

- Intraprostatic injection of 100 or 300 units of BoNT-A passed both efficacy and safety criteria for treatment success at 12 weeks in a phase II randomized double-blind trial.
- Examination of longer term effects to 12 months post-treatment is ongoing.
Lower Urinary Tract Symptoms (LUTS) and Sexual Dysfunction

- Large-scale epidemiological studies (largest in US + 6 European countries, with N of 12,815) demonstrated LUTS are an independent risk factor for sexual dysfunction
- Exact nature of cause not established; several theories
  - Autonomic hyperactivity/↑ sympathetic tone
  - Alterations in Rho/Rho kinase pathway
  - Endothelial dysfunction
  - Atherosclerosis-induced pelvic ischemia
  - Age-related hormone imbalances
- Data suggest treatment of sexual dysfunction with alpha-blockers or phosphodiesterase type 5 inhibitors, or combination of agents that improve LUTS/sexual dysfunction

OAB Symptoms Are Prevalent in Both Women and Men

Prevalence, %

Age, years

18-24 25-34 35-44 45-54 55-64 65-74 75+

Men Women

Median Percentage Reductions in Tolterodine ER-Treated vs Placebo-Treated Men

Median percentage change in UUI episodes from baseline to week 12

Placebo (n = 86)  Tolterodine ER 4 mg (n = 77)

-40  -71*

Tolterodine Did Not Increase the Incidence of Urinary Retention

Placebo-Controlled Study of Men

<table>
<thead>
<tr>
<th>Urinary symptom adverse events</th>
<th>Placebo (n = 72)</th>
<th>Tolterodine (n = 149)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>(%)</td>
</tr>
<tr>
<td>Micturition disorder</td>
<td>2</td>
<td>2.8</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>3</td>
<td>4.2</td>
</tr>
<tr>
<td>Dysuria</td>
<td>1</td>
<td>1.4</td>
</tr>
<tr>
<td>Micturition frequency</td>
<td>2</td>
<td>2.8</td>
</tr>
<tr>
<td>Micturition urgency</td>
<td>1</td>
<td>1.4</td>
</tr>
<tr>
<td>Strangury</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td><strong>Acute urinary retention</strong></td>
<td><strong>1</strong></td>
<td><strong>1.4</strong></td>
</tr>
<tr>
<td>Bladder discomfort</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>Urethral disorder</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>Urinary incontinence</td>
<td>2</td>
<td>2.8</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td><strong>9</strong></td>
<td><strong>12.5</strong></td>
</tr>
</tbody>
</table>

Doxazosin With or Without Tolterodine for Men With BOO and DO

LUTS (n = 144)
  Urodynamic evaluation
  BOO + DO (n = 68)
  Doxazosin × 3 mo
  Improved
    Yes
    Doxazosin × 3 mo (n = 24)
    No
    Doxazosin + tolterodine × 3 mo (n = 44)

Doxazosin
  65%
  35%

Doxazosin + Tolterodine
  73%
  27%

BOO = bladder outlet obstruction; DO = detrusor overactivity
Patients with DO had involuntary detrusor contractions 10 cm H₂O
Results are presented for DO arm; additional results in publication
Please see full prescribing information
A Practical Algorithm for the Diagnosis and Management of EP

Man >50 years old presents with urinary symptoms

Determine if patient has Enlarged Prostate (≥30 mL):
Digital rectal exam (DRE)
PSA ≥1.5 ng/mL

- No
  - Treat symptoms

- Yes
  - Treat symptoms and reduce prostate size

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):8.”
GnRH Antagonists
Rationale for Treatment of LUTS/BPH

Bela S. Denes, MD, FACS
Sr. Director – Clinical Research and Development
Effect of castration on endothelin receptors

Robert J. PADLEY*, Douglas B. DIXON* and J. Ruth WU-WONG†

* These results indicate that surgical castration in dogs produces a change in the ET receptor density in the prostate and brain, and may have implications for the effect of hormone ablation therapy on ET receptor expression in prostate cancer patients.

Clinical Science (2002) 103 (Suppl. 48), 442S–445S
LHRH Antagonists

Oxarelix-mode of action

- Competitive receptor binding
- Immediate suppression of LH & FSH
- Initial Stimulation
- Desensitisation
- Receptor down regulation

Advantages of antagonists

- No flare
- Fast onset of action
- Intermittent therapy may be possible
- Diminished risk of side-effects in benign indications (osteoporosis, metabolic syndrome, loss of libido, hot flashes etc.)

LHRH-antagonists are a novel therapeutic class overcoming the side-effects associated with agonists.
Ozarelix (Phase 2b) BPH

4th generation LHRH antagonist

- Positive Phase 2 Study Data in Patients with BPH
  - Primary Endpoint – Improvement in IPSS
  - Improved Secondary End Points including Urine Flow, Residual Urinary Volume, and Quality of Life
  - Convenient Dosing (Injection Day 1 & Day 15)
  - Effects seem to last for six months
  - Well Tolerated
Herbal Therapies Used for EP

- *Pygeum africanum*: known as *Prunus africana*, African plum tree, African prune
  - Open-label, noncomparative studies showed overall improvement in signs/symptoms of BPH
  - Double-blind studies yielded more variable results
- *Serenoa repens*: known as saw palmetto, American dwarf palm tree, cabbage palm, ju-zhong, palmier nain, sabal, sabal fructus, saw palmetto berry
  - Some studies have shown alleviation of symptoms, as well as improvements in IPSS, QOL scores, flow rates, residual volumes, dysuria, and nocturia
  - Limited published data: many studies of short duration and varied in study design; many occurred before validated symptom scale scores available

Saw Palmetto: Recent Data

• 225 men > 49 years of age, with moderate to severe symptoms of BPH, were enrolled
• 1-year double-blind treatment with saw palmetto or placebo
• No significant changes noted in primary or secondary outcome measures (subjective and objective)
  – AUA-SI scores
  – Maximal urinary flow rate
  – Prostate size
  – Residual urinary volume
  – Quality of life
  – Serum PSA levels
• Incidence of side effects comparable for saw palmetto/placebo

Considerations With Herbal Therapies for EP

- Many European studies examining herbal therapies
- Numerous questions remain unanswered
  - Beneficial and adverse effects
  - Standardization of extracts
  - Concomitant use with mainstream medications
  - Prevention of complications

Patient Expectations?

- Do they want to take a pill for the rest of their life?
- What are their co-morbidities – how many drugs are they currently taking?
- Can they afford medical therapy?
- Are they comfortable with possibility of post treatment catheterization?
- What is their lifestyle (“on the go” or sedentary)?
- Are they willing/able to undergo anesthesia?
- Do they want the problem resolved now and forever?
Treatment Options: Watchful Waiting

- An appropriate option for patients with mild symptoms
- No active intervention is initiated, although patients are generally reexamined yearly by their physician
- The choice of a watchful waiting strategy may depend on the patient’s tolerability of symptoms

Treatment Options: Alpha Blockers

- Alpha blockers
  - Appropriate treatment options for patients with LUTS secondary to BPH

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

- Agents indicated for symptomatic BPH include:
  - Alfuzosin
  - Doxazosin
  - Silodosin
  - Tamsulosin
  - Terazosin

BPH = Benign Prostatic Hyperplasia

Treatment Options: 5AR Inhibitors

- 5ARIs are appropriate treatments for patients with LUTS associated with demonstrable prostatic enlargement

- 5ARIs indicated for EP include:
  - Finasteride
  - Dutasteride

EP-Related Surgery Options

- Transurethral resection of the prostate (TURP) and minimally invasive procedures may be an appropriate option for patients

- Minimally invasive options include
  - Transurethral Microwave Thermotherapy (TUMT)
  - Transurethral Needle Ablation of the Prostate (TUNA)
  - Transurethral Incision of the Prostate (TUIP)
  - Transurethral Laser Coagulation (TLC)
  - Water-induced Thermal Therapy (WIT)

MIT Treatments

- Transurethral Microwave Thermotherapy
  - Prolieve Thermodilatation® System
  - Targis® System
  - TherMatrix® System
  - Prostalund® (Coretherm) System
- Transurethral Needle Ablation
  - Prostiva®
Action of Treatment

Temperature \rightarrow \text{Prostate} \rightarrow =\text{Necrosis} \rightarrow \text{Time}
Temperature and Time

Temperature and time for coagulation necrosis

- Glandular
- Stroma

Treatment must end above the curve

Not below the curve

Potential Mechanisms of Action

• **Prostate gland volume reduction**
  • Microwave heat may reduce the prostate volume by coagulating the tissue, relieving outlet obstruction
    • Extent of necrosis is governed by intraprostatic temperature achieved and the time heat is delivered

• **Denervation of alpha-receptors**
  • Microwave heat may ablate alpha receptors having a similar effect as alpha blockers for BPH
H2H Randomized Comparison of 2 TUMT Devices

- Post-approval study comparing the Prolieve vs Targis Systems
  - Understand patient periprocedural experience and outcomes
- Patients were treated according to FDA approved DFU and followed for 6 months
Study Design

- Controlled, Randomized
  - 3 sites: Modesto, CA; Denver, CO; Myrtle Beach, SC
  - 30 patients (16 Prolieve / 14 Targis)
  - AUA $\geq 10$; peak flow $\leq 12$

- Primary Endpoint
  - Catheterization Rates

- Secondary Endpoints
  - VAS, AUA Symptom Relief, Peak Flow, QOL, Sexual Function

- Well Matched Population
  - Mean Age: 66 Prolieve / 65.9 Targis
  - Prostate Volume: 41 Prolieve / 40.8 Targis
  - BPH Medication: 50% Prolieve / 50% Targis
Study Conclusion

- Prolieve System treated patients required significantly fewer catheterizations than Targis System patients ($P<0.001$).

- Prolieve System patients experienced faster initial symptom relief and had better treatment tolerability. Further research is required to demonstrate significance.
The Spanner
Spanner Procedure: Insertion and Removal
Clinical Experience

A Temporary Intraurethral Prostatic Stent Relieves Prostatic Obstruction Following Transurethral Microwave Thermotherapy

Neal D. Shore,⁎,† Martin K. Dineen,‡ Mark J. Saslawsky,§ Jeffrey H. Lumerman and Alberto P. Corica§

Purpose: The Spanner™, a novel prostatic stent, for prostatic obstruction following transurethral microwave thermotherapy.

Materials and Methods: Following transurethral thermotherapy at 1 of 9 clinical sites 186 patients meeting criteria (86). Baseline evaluations included post-voiding urine volumes. International Prostate Symptom Score (IPSS) values were obtained after randomization (Spanner insertion) with the study protocol (11) and adverse events recording. The Spanner was...

Use of a Temporary Prostatic Stent After Transurethral Microwave Thermotherapy Reduced Voiding Symptoms and Bothe Without Exacerbating Irritative Symptoms

Martin K. Dineen, Neal D. Shore, Jeffrey H. Lumerman, Mark J. Saslawsky, and Alberto P. Corica

OBJECTIVES
To evaluate the ability of a temporary prostatic stent (Spanner [Sp]) to manage voiding symptoms, irritative symptoms, and bother after transurethral microwave thermotherapy (TUMT) for prostatic obstruction.

METHODS
Patients were randomized to the Sp (n = 100) or standard of care (SOC, n = 86) after TUMT with 3 to 10 days of routine catheterization. We evaluated International Prostate Symptom Score (IPSS) voiding subscore, IPSS irritative subscore, voiding diary data, and Benign Prostatic Hyperplasia Impact Index (BII) 7 to 10 days before TUMT and repeated them 1, 2, 4 (stent removed), 6, and 12 months after TUMT.

- Reduced Post Void Residuals
- Improved IPSS Scores
- Highly preferred over the Foley
- Did not exacerbate irritative symptoms
Conclusions

• The Spanner had no related SAE’s. Adverse events were comparable to the SOC

• The majority of patients were satisfied and would recommend the Spanner

• Investigators reported insertion and removal of the device as very easy to slightly difficult with mild to no patient discomfort

• Spanner effectively improved PVR, IPSS and QoL during post TUMT recovery
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 ≥1.5 ng/mL

No
- Treat symptoms
  - α-blocker

Yes
- Treat symptoms and reduce prostate size
  - 5ARI
  - Combination 5ARI plus α-blocker

Reassess periodically

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):8."
BPH Treatment Relief*

* As Outlined by American Urologic Association, 2003
BPH Patient Treatment Options

**Non surgical options**

- **Watchful Waiting**
  - ADVANTAGE
    - No Cost
    - Least invasive
  - DISADVANTAGES
    - In effective

- **Prescription Drugs**
  - ADVANTAGE
    - Non-invasive
    - Easy
  - DISADVANTAGES
    - Sexual side effects
    - Retrograde ejaculation
    - Loss of libido
    - Drug interaction
    - Less effective over time
    - Expensive over long term
    - Not effective for everyone

- **TUMT/TUNA**
  - ADVANTAGE
    - Safe and Effective
    - Typically Well Tolerated by Patients
    - General anesthesia not required/recommended
    - Return to Normal Activities Quickly
    - High catheter free rate
    - Little impact on sexual function
    - Covered by Medicare and most Insurances
  - DISADVANTAGES
    - Not suitable for all prostate sizes and types
    - Not as durable as a surgical procedures
    - Impact on peak flow?

**Surgical options**

- **LASER Ablation**
  - ADVANTAGE
    - Safe and Effective
    - Long term durability
    - Faster recovery than traditional surgery (TURP)
      - Bleeding
      - Catheter time
      - Hospital stay
    - Can treat larger glands
  - DISADVANTAGES
    - Requires general anesthesia
    - May require hospital stay and catheter
    - Retrograde ejaculation

- **Traditional Surgery**
  - ADVANTAGE
    - Effective on all size glands
    - Long term durability
    - Treatment with most history
  - DISADVANTAGES
    - Surgical procedure
    - Require hospital stay and catheter
    - General anesthesia required
    - Sexual side effects
    - Longer recovery time than laser ablation
    - Most invasive
Physician Perception of BPH Treatment Options
(Survey of 400 Urologists, 2004)

1 Efficacy defined as short and long-term durability, early symptom relief, and overall efficacy;
2 Non-invasiveness defined as minimal anesthesia required, minimal discomfort, limited hospitalization, limited post-procedure catheterization, and overall non-invasiveness.

- **Drug Therapy (2.3M patients)**
- **TUMT**
- **TUNA**
- **Laser Ablation**
- **TURP**
AUA Guidelines for Diagnosing and Treating BPH

**Initial evaluation**
- History and physical examination
- Digital rectal examination
- Urinalysis
- Prostate-specific antigen level
- Symptom index

**Mild symptoms** (symptom score ≤ 7)
-**Optional tests**
  - Uroflowmetry
  - Postvoiding residual volume
- Discussion with patient
  - Patient chooses noninvasive therapy
    - Watchful waiting
  - Patient chooses invasive (“definitive”) therapy
    - TUMT/TUNA

**Moderate or severe symptoms** (symptom score ≥ 8)
- Any of the following:
  - Refractory retention
  - Persistent hematuria
  - Renal insufficiency
  - Bladder stones
-**Optional tests**
  - Urodynamic testing
  - Cystourethroscopy
  - Transrectal ultrasonography
- Discussion with patient
  - Patient chooses noninvasive therapy
    - Medical therapy
  - Patient chooses invasive (“definitive”) therapy
    - TUMT/TUNA

**Surgery**
### Benefit of Therapies for BPH

<table>
<thead>
<tr>
<th>THERAPY</th>
<th>AUA Symptom Score</th>
<th>PEAK Flow Rate</th>
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<tbody>
<tr>
<td>Medications:</td>
<td></td>
<td></td>
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<tr>
<td>Alpha Blockers</td>
<td>-6.38</td>
<td>2.26</td>
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<tr>
<td>5-ARIs</td>
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<td>1.66</td>
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<tr>
<td>MIT:</td>
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<tr>
<td>TUMT</td>
<td>-10.21</td>
<td>4.21</td>
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<tr>
<td>TUNA</td>
<td>-9.32</td>
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<td>Surgical Procedures:</td>
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<tr>
<td>Laser Ablation</td>
<td>-20.20</td>
<td>10.97</td>
</tr>
<tr>
<td>TURP</td>
<td>-14.80</td>
<td>10.77</td>
</tr>
</tbody>
</table>

1. BPH: Now we can begin to tailor treatment. Gjertson, Konstantin, Kaplan. Cleveland Clinic Journal of Medicine. 2004
2. After 10-16 months of follow-up. Adapted from pooled data from multiple studies between 1991 and 2000.
Urgent® PC
Office-based Neuromodulation
Treatment with Urgent® PC

- Provides Percutaneous Tibial Nerve Stimulation (PTNS)
- Stimulation delivered via a 34 ga. needle electrode
- Needle electrode inserted above medial malleolus
- The needle electrode is connected to a battery-powered stimulator
Urgent® PC

- Easy to administer in 30 minute sessions
- Effective – Approximately 2/3 of patients report a reduction in their symptoms\(^5\)
- May work even if other treatments have failed
- Low risk – Most common side-effects include transient mild pain or skin inflammation at or near the stimulation site

---

The Need for a Different Option …

- 20% of patients refractory to conservative treatment
- 80% of patients stop drugs before 1 year
- Many patients don’t want surgery
- Physicians want solutions for their patients
- Physicians want treatment they can control


Urgent® PC Therapy

- 30 minute, in-office treatment
- Series of 12 treatments, typically a week apart
- Maintenance therapy tailored to each patient’s response
PTNS compared to Drug⁹

- **Patient perception of cure/improvement:** 80% in PTNS group; 55% in tolterodine LA group
- **Physician perception of cure/improvement:** 80% in PTNS group; 61% of tolterodine LA group
- **Comparable reductions in voiding episodes and urge incontinence**
- **Side-effects:** No serious adverse events were associated with either treatment. Constipation and dry mouth reported more often in tolterodine LA group

Advances in the Management of Prostate Disease: Summary for EP

- Factors affecting progression of EP and related symptoms include chronic inflammation, apoptosis, PV, serum PSA and PSA velocity, DRE results, $Q_{max}$, central obesity, BMI, PVR, and TZV
- Alpha blockers and 5-ARIs have been proven to treat symptoms
  - Alpha blockers useful in increasing sexual function
  - 5-ARIs decrease prostate volume and diminish risk of AUR or surgery
  - Combination therapy beneficial for moderate to enlarged PV
- PDE5 inhibitors emerge as a new therapeutic class in the treatment of LUTS and BPH
- New combinations of alpha blocker and antimuscarinic drugs appear to be safe and increase efficacy in men with predominant irritative symptoms
BPH is a Quality of Life Disease ....

.... As specialists, we must address the problem while understanding any further impact on patient’s quality of life.