BPH in the Elderly: Beyond Alpha – Blockers and 5 – ARIs: Challenging Our Approach

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Mount Sinai Health System
Disclosures

- None
Learning Objectives

- Role of BPH Medical Therapy in the Elderly
- Challenges to Long Term Use
- Alternative Therapies
Most people see what they expect to see, what they want to see, what they have been told to see, what conventional wisdom tells them to see – not what is in front of them in its pristine conditions.

Vincent Bugliosi
Medical Treatment Failure Depends on Definition
Medical Treatment Failure Depends on Definition

We keep the Holy Cow in the barn and the Holy Mackerel in the lake... I guess I don't have to tell you what we keep in there!
Medical Treatment Failure
Traditional Definitions

- Assessed via switch to other therapies
  - Other medications
  - MIST
  - Surgery
  - WAWA
Why Do Patients Fail Medical Therapy?

- Symptoms not relieved
  - Are alpha blockers the same?
  - Differences among 5 ARI’s?
- Intolerable side effects
- Progression of Disease
  - Symptom progression
  - Need for surgery
  - Urinary retention
Why Do Patients Fail Medical Therapy?

- Symptoms not relieved
  - Are alpha blockers the same?
  - Differences among 5 ARI’s?
  - Combination with PDE – 5 may not be effective
  - Antimuscarinics / β3 - agonists target the bladder
BPH = benign prostatic hyperplasia; LUTS = lower urinary tract symptoms.
Treatment Algorithm Male LUTS: Drugs

- Male LUTS
  - Symptom bother, IPSS >7?
    - Nocturnal polyuria only?
      - Storage symptoms predominant/only?
        - Prostate volume >40 ml?
          - Long-term treatment?
            - Residual storage symptoms
              - Edu/Lifestyle with or without α₁-AR antagonist
            - Edu/Lifestyle with or without α₁-AR antagonist
          - Edu/Lifestyle with or without 5-ARI ± α₁-AR antagonist
            - Add muscarinic receptor antagonist + continue with Edu/Lifestyle
              - Watchful waiting with or without Edu/Lifestyle

Conditions or diseases behind symptoms

BPE: benign prostatic enlargement; BOO: bladder outlet obstruction; OAB: overactive bladder; UTI: urinary tract infection

**Pharmacological Options**

**Targeting the bladder**

**Antimuscarinics**

→ Symptom control of OAB (storage) component of LUTS ↓ involuntary bladder contractions

**PDE5 inhibitors** (prostate ± bladder?)

**Targeting the prostate**

**α-blockers**

→ Symptom control by relaxation of prostatic and urethral tissue

**5-ARIs**

→ Long-term symptom control and prevention of disease progression by prostatic tissue shrinkage

5-ARIs: 5α-reductase inhibitors; OAB: overactive bladder

[www.uroweb.org/gls/pdf/12_Male_LUTS_LR%20May%209th%202012.pdf]
Surgical Options

- **Minimally invasive options**
  - Office based
  - Ambulatory based
  - Minimal anesthetic
  - High risk patients
  - Low morbidity

- **Advanced Invasive Options**
  - Improved versions of prostatectomy
Technology Based Treatment of LUTS related to BPH

- ALL surgical approaches based on removing bladder outlet obstruction\(^1\) (\(\_\_\) Tissue)
  - Minimally Invasive Therapies\(^1\)
  - Thermotherapies\(^1\)
  - Novel hybrid therapies\(^2\)
  - Surgical Debulking Procedures\(^1\)
    - Vaporizers and Enucleators\(^1\)
    - Robots Vs. Lasers Vs Electrosurgical Technologies\(^3\)

LUTS: lower urinary tract symptoms
BPH: benign prostatic hypertrophy

Minimally Invasive Therapies: Update

FDA APPROVED
- Prostatic Lifts\(^1\)
  - Transurethral Suture Tacking
- Robotic/Laparoscopic Technology
  - Single Port\(^2\) and Transvesical Approaches\(^3\)
- Vapor Ablation (Steam / CONVECTIVE RADIOFREQUENCY)
- AquaBlation
- Prostatic Arterial Embolization

Investigational
- Stents / balloons
- Histotripsy (focused ultrasound)
- Intraprostatic Injections\(^5\)
  - Botox, NX 1207, ethanol and other compounds

α-Blockers for Treatment of BPH

- Most commonly used and effective medical therapy for treating LUTS secondary to BPH$^1$
- Prevents clinical symptomatic progression of BPH$^1$
- Efficacious$^2$
- Well tolerated
- Reduce the cost of medical therapy$^3$

1. IMS HEALTH NPA 2008.
Efficacy of α<sub>1</sub>-blocker

<table>
<thead>
<tr>
<th></th>
<th>α&lt;sub&gt;1&lt;/sub&gt;-AR antagonist</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total IPSS</td>
<td>↓ 35 - 40%</td>
</tr>
<tr>
<td>(Q_{\text{max}})</td>
<td>↑ 20 - 25%</td>
</tr>
<tr>
<td>Onset of action</td>
<td>Rapid (days)</td>
</tr>
<tr>
<td>Prostate volume</td>
<td>-</td>
</tr>
<tr>
<td>Long-term risk of AUR or BPH-related surgery</td>
<td>-</td>
</tr>
</tbody>
</table>

AUR: acute urinary retention;
BPH: benign prostatic hyperplasia;
IPSS: International Prostate Symptom Score;
\(Q_{\text{max}}\): maximum urinary flow rate
Alpha-blocker Competitive Efficacy Review
Doxazosin, Terazosin, and Tamsulosin improve in symptoms and Qmax

- About a 3 point improvement in IPSS symptom score
- About a 2-3 ml/sec improvement in Qmax

Data from prescribing product insert information
Alfuzosin and Silodosin Improvement in Symptoms and Qmax

About a 3 point improvement in IPSS
About a 1-2 ml/sec improvement in Qmax

Data from prescribing product insert information
Why Do Patients Fail Medical Therapy

- Symptoms not relieved
  - Are alpha blockers the same?
  - Differences among 5 ARI’s?
  - Combination with PDE – 5 may not be effective
  - Antimuscarinics / β3 - agonists target the bladder

- Intolerable side effects
# ALPHA ADRENERGIC BLOCKERS

## Adverse Effects

<table>
<thead>
<tr>
<th>Drug</th>
<th>Asthenia</th>
<th>Headache</th>
<th>Syncope</th>
<th>↓ BP</th>
<th>↓ Libido</th>
<th>EjD</th>
<th>ED</th>
</tr>
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<tbody>
<tr>
<td>Uroxatral (alfusozin ER)</td>
<td>2.7</td>
<td>3.0</td>
<td>5.7</td>
<td>0.4</td>
<td>nr</td>
<td>nr</td>
<td>1-2</td>
</tr>
<tr>
<td>Cardura (doxazosin IR)</td>
<td>8</td>
<td>9.9</td>
<td>15.6</td>
<td>1.7</td>
<td>0.8</td>
<td>≤ 1</td>
<td>1.1</td>
</tr>
<tr>
<td>Cardura XL (doxazosin XL)</td>
<td>3.9</td>
<td>6</td>
<td>5.3</td>
<td>1.7</td>
<td>nr</td>
<td>nr</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>Rapaflo (silodosin)</td>
<td>1-2</td>
<td>2-4</td>
<td>3.2</td>
<td>2.6</td>
<td>nr</td>
<td>28.1</td>
<td>nr</td>
</tr>
<tr>
<td>Flomax 0.4 mg 0.8 mg</td>
<td>7.8</td>
<td>8.5</td>
<td>19.3</td>
<td>14.9</td>
<td>0.2</td>
<td>1</td>
<td>8.4</td>
</tr>
<tr>
<td></td>
<td>21.1</td>
<td>17.1</td>
<td></td>
<td>0.4</td>
<td></td>
<td>2</td>
<td>18.1</td>
</tr>
<tr>
<td>Hytrin (terazosin)</td>
<td>7.4</td>
<td>4.9</td>
<td>9.1</td>
<td>≤5.5</td>
<td>nr</td>
<td>nr</td>
<td>1.6-2</td>
</tr>
</tbody>
</table>
**5α-reductase inhibitors (5ARIs)**

- For long-term use in men with enlarged prostates
- Exert an androgen effect on the prostate:
  - Finasteride: inhibits 5α-reductase type 2 only
  - Dutasteride: inhibits 5α-reductase types 1 and 2
- Act to reduce serum DHT concentrations
- Long half-life for dutasteride:
  - Finasteride: 6-8 hours
  - Dutasteride: 3-5 weeks

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5AR1: 5α-reductase receptor 1; 5AR2: 5α-reductase receptor 2; DHT: dihydrotestosterone

Dutasteride 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

Studies done only in men with prostates 30 grams or greater

Mean AUA-SI score change from baseline

Time (months)

Double-blind Phase (n=1180)

Open-label Phase

6.5-point symptom improvement over 4 years (n = 860)

*P < 0.001 between treatment groups
†P < 0.001 vs month 24

Efficacy 5ARIs

- Clinical effects are observed after a minimum treatment period of 6–12 months; therefore, long-term treatment necessary
- After 2–4 years of treatment, IPSS is reduced by ~15–30% and prostate size ↓by 20-30%
- Symptom reduction (IPSS) is dependent on prostate size at treatment initiation
- In men with prostate sizes <30-40 ml efficacy is comparable with placebo

IPSS: International Prostate Symptom Score

[www.uroweb.org/gls/pdf/12_Male_LUTS_LR%20May%209th%202012.pdf]
Efficacy 5ARIs

- Symptom (IPSS) reduction with 5-ARIs depends on:
  - Baseline PSA values >4.4 µg/l → fastest symptom relief
  - Prostate volume >58 ml significant ↓ IPSS compared with smaller prostate volumes
- Reduce the risk of urinary retention or need-for-surgery

IPSS: International Prostate Symptom Score
## Adverse Events of 5α-Reductase Inhibitors are Comparable

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Dutasteride(^1)</th>
<th>Finasteride(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dut</td>
<td>Placebo</td>
</tr>
<tr>
<td>Erectile dysfunction</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Altered libido</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Altered Ejaculation</td>
<td>2</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Gynecomastia</td>
<td>2</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

\(^1\)24 mo study; \(^2\)48 mo study.
Sexual AEs associated with 5ARIs occur early in therapy & decrease after the first year

Graphs adapted from Duodart European Summary of Product Characteristics Dec 2014;
A 5 Year Study Of 5 – Alpha Reductase Inhibitors In Men With Benign Prostatic Hyperplasia: Finasteride Has Equal Efficacy And Prostate Volume Reduction But Has Less Sexual Side Effects And Breast Enlargement Than Dutasteride

Steven A. Kaplan, Doreen E. Chung, Richard K. Lee, Scott Melamed, Alexis E. Te

Weill Cornell Medical College
Cornell University
# Finasteride Versus Dutasteride Results

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Finasteride (817)</th>
<th>Dutasteride (813)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate Volume Reduction % at 12M</td>
<td>-26.7</td>
<td>-26.3</td>
</tr>
<tr>
<td>AUA SI @ 3M</td>
<td>-3.8</td>
<td>-3.6</td>
</tr>
<tr>
<td>AUA SI @ 12M</td>
<td>-5.5</td>
<td>-5.8</td>
</tr>
<tr>
<td>Qmax @ 12M</td>
<td>1.7 ml/sec</td>
<td>2.0 ml/sec</td>
</tr>
</tbody>
</table>

No difference between the two groups.
Sexual Adverse Events

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Finasteride</th>
<th>Dutasteride</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in IIEF</td>
<td>-2.4</td>
<td>-3.5</td>
</tr>
<tr>
<td>Withdrawals</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erectile dysfunction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ejaculatory dysfunction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased libido</td>
<td>1.4%</td>
<td>2.7%</td>
</tr>
<tr>
<td>Breast tenderness / enlargement</td>
<td>1.2%</td>
<td>3.5%</td>
</tr>
</tbody>
</table>

Significantly higher in dutasteride group (p < 0.01)
Five muscarinic receptors have been described ($M_1$-$M_5$). They are expressed in the bladder, salivary glands, and synapses in the CNS. $M_2$ and $M_3$ are most predominant in the bladder. Only $M_3$ is involved in bladder contractility. Inhibition of muscarinic receptors reduces smooth cell contractions of the bladder.

Efficacy Antimuscarinics in Male LUTS

Meta-analysis: subgroup analysis of 582 men from 4 RCTs (phase III) evaluating the efficacy and safety of solifenacin (12 weeks) in male OAB patients (n=2,848)

- Placebo (n=219)
- Solifenacin 5 mg (n=121)
- Solifenacin 10 mg (n=242)

*P<0.05; **P <0.001 vs. placebo

RCT: randomised controlled trial; OAB: overactive bladder
## Antimuscarinics ONLY in Male LUTS

<table>
<thead>
<tr>
<th>Trials</th>
<th>Duration (weeks)</th>
<th>Treatment</th>
<th>Patients [N]</th>
<th>Voiding frequency [%]</th>
<th>Nocturia [%]</th>
<th>Urgency Incontinence [%]</th>
<th>IPSS [%]</th>
<th>LE</th>
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</thead>
<tbody>
<tr>
<td>Kaplan et al. (2005)</td>
<td>25</td>
<td>Tolterodine 1 x 4mg/d (after α-blocker failure)</td>
<td>43</td>
<td>-35.7 (^a)</td>
<td>-29.3 (^a)</td>
<td>-</td>
<td>-35.5 (^a)</td>
<td>2b</td>
</tr>
<tr>
<td>Roehrborn et al. (2006)</td>
<td>12</td>
<td>Placebo</td>
<td>86</td>
<td>-4</td>
<td>-</td>
<td>-40</td>
<td>-</td>
<td>1b</td>
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<tr>
<td></td>
<td></td>
<td>Tolterodine 1 x 4mg/d</td>
<td>77</td>
<td>-12</td>
<td>-</td>
<td>-71 (*)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Kaplan et al. (2006)</td>
<td>12</td>
<td>Placebo</td>
<td>374</td>
<td>-7.9</td>
<td>-17.6</td>
<td>-</td>
<td>-</td>
<td>1b</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tolterodine 1 x 4mg/d</td>
<td>371</td>
<td>-10.8 (^*)</td>
<td>-18.8</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Kaplan et al. (2006)</td>
<td>12</td>
<td>Placebo</td>
<td>215</td>
<td>-13.5</td>
<td>-23.9</td>
<td>-13</td>
<td>-44.9</td>
<td>1b</td>
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<tr>
<td></td>
<td></td>
<td>Tolterodine 1 x 4mg/d</td>
<td>210</td>
<td>-16.5</td>
<td>-20.1</td>
<td>-85 (*)</td>
<td>-54</td>
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<tr>
<td>Dmochowski et al. (2007)</td>
<td>12</td>
<td>Placebo</td>
<td>374</td>
<td>-5.6</td>
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<td>-</td>
<td>1b</td>
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<tr>
<td></td>
<td></td>
<td>Tolterodine 1 x 4mg/d</td>
<td>371</td>
<td>-8.7</td>
<td>-18.8</td>
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<td>-</td>
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<tr>
<td>Höfner et al. (2007)</td>
<td>12</td>
<td>Tolterodine 1 x 4mg/d</td>
<td>741</td>
<td>-20 (^a)</td>
<td>-42.9 (^a)</td>
<td>-100</td>
<td>-37.9 (^a)</td>
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<td>Herschorn et al. (2009)</td>
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<td>Placebo</td>
<td>124</td>
<td>-10.2</td>
<td>-</td>
<td>59.3</td>
<td>-</td>
<td>1b</td>
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<tr>
<td></td>
<td></td>
<td>Fesoterodine 1 x 4mg/d</td>
<td>111</td>
<td>-13.2 (^*)</td>
<td>-</td>
<td>-84.5 (^*)</td>
<td>-</td>
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<tr>
<td></td>
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<td>Fesoterodine 1 x 8mg/d</td>
<td>109</td>
<td>-15.9 (^*)</td>
<td>-</td>
<td>-100 (^*)</td>
<td>-</td>
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</table>

IPSS: International Prostate Symptom Score

# PVR and Urinary Retention

## Monotherapy Antimuscarinics

<table>
<thead>
<tr>
<th>TRIAL</th>
<th>Duration [weeks]</th>
<th>Treatment</th>
<th>Patients [N]</th>
<th>PVR [ml]</th>
<th>Retention N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kaplan et al. 2005</td>
<td>25</td>
<td>Tolterodine 1x4 mg/d</td>
<td>43</td>
<td>-22*</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Roehrborn et al. 2006</td>
<td>12</td>
<td>Placebo</td>
<td>86</td>
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<td>0</td>
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<tr>
<td></td>
<td></td>
<td>Tolterodine 1x4 mg/d</td>
<td>77</td>
<td>1</td>
<td>1.3</td>
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</tr>
<tr>
<td>Kaplan et al. 2006</td>
<td>12</td>
<td>Placebo</td>
<td>374</td>
<td>2</td>
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<tr>
<td>Kaplan et al. 2006</td>
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<td>Placebo</td>
<td>215</td>
<td>-3.6</td>
<td>3</td>
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<tr>
<td></td>
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<td>Tolterodine 1x4 mg/d</td>
<td>210</td>
<td>+5.3</td>
<td>2</td>
<td>0.9</td>
</tr>
<tr>
<td>Dmochowski et al. 2007</td>
<td>12</td>
<td>Placebo</td>
<td>374</td>
<td>2</td>
<td>0.5</td>
<td></td>
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<tr>
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<td>Tolterodine 4 mg/d</td>
<td>371</td>
<td>4</td>
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<tr>
<td>Höfner et al. 2007</td>
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<tr>
<td>Chapple et al. 2009</td>
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<td>Placebo</td>
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<td>+1.1</td>
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<td>1.9</td>
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<tr>
<td></td>
<td></td>
<td>Tolterodine 1x4 mg/d</td>
<td>329</td>
<td>+14.3 *</td>
<td>6</td>
<td>1.8</td>
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<tr>
<td>Herschorn et al. 2010</td>
<td>12</td>
<td>Placebo</td>
<td>124</td>
<td>1</td>
<td>0.8</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Fesoterodine 1x4 mg/d</td>
<td>120</td>
<td>+9.6**</td>
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<td>0.8</td>
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<tr>
<td></td>
<td></td>
<td>Fesoterodine 1x8 mg/d</td>
<td>114</td>
<td>+20.2**</td>
<td>6</td>
<td>5.3</td>
</tr>
</tbody>
</table>

* P=0.023

**P=0.035

PVR: post-void residual

Adapted from Oelke M. UniMed Science. Hampel (Ed) 2009 pp84 - 97
Herschorn S et al. Urology 2010: 75; 1149 - 55
The Health Improvement Network (THIN) Database: Focused Safety Study of Acute Urinary Retention (AUR) in Men

Luis Alberto García-Rodríguez, Elisa Martín-Merino, Elvira Luján Massó-González, Claus G. Roehrborn

This study was funded by Pfizer Inc
<table>
<thead>
<tr>
<th>Use</th>
<th>Number (%) of Patients</th>
<th>Controls (n=10,000)</th>
<th>RR†</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-use</td>
<td>1706 (93)</td>
<td>9727 (97)</td>
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<tr>
<td>Timing of use</td>
<td></td>
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<tr>
<td>Current use</td>
<td>94 (5)</td>
<td>154 (2)</td>
<td>2.9</td>
<td>2.2–3.7</td>
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<tr>
<td>Recent use</td>
<td>15 (&lt;1)</td>
<td>39 (&lt;1)</td>
<td>1.7</td>
<td>0.9–3.1</td>
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<tr>
<td>Past use</td>
<td>29 (2)</td>
<td>80 (&lt;1)</td>
<td>1.6</td>
<td>1.0–2.5</td>
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<tr>
<td>Duration: Current use</td>
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<td></td>
<td></td>
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<tr>
<td>≤30 days</td>
<td>38 (40)</td>
<td>22 (14)</td>
<td>8.3</td>
<td>4.8–14.2</td>
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<tr>
<td>31 days-1 year</td>
<td>28 (30)</td>
<td>60 (39)</td>
<td>2.0</td>
<td>1.2–3.1</td>
</tr>
<tr>
<td>&gt;1 year</td>
<td>28 (30)</td>
<td>72 (47)</td>
<td>2.0</td>
<td>1.3–3.1</td>
</tr>
<tr>
<td>Daily dose/indication: Current use</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low/medium dose</td>
<td>84 (89)</td>
<td>138 (90)</td>
<td>2.8</td>
<td>2.1–3.8</td>
</tr>
<tr>
<td>High dose urogenital</td>
<td>10 (11)</td>
<td>16 (10)</td>
<td>3.0</td>
<td>1.3–6.8</td>
</tr>
</tbody>
</table>

*Percentages for timing of use are based on overall study cohort (1844 cases; 10,000 controls); percentages for duration and daily dose are based on the number of patients currently using antimuscarinics (94 cases, 154 controls).
†Relative risk estimates were adjusted for age, calendar year, general practitioner visits, and oral antimuscarinic use.
Treatment with Tolterodine plus Tamsulosin Resulted in Significant Treatment Benefit at Week 12

- *P < .001 between-group comparisons.
- †P = .001 between-group comparisons.
- ‡P < .05 between-group comparisons.

Why Do Patients Fail Medical Therapy

- Symptoms not relieved
  - Are alpha blockers the same?
  - Differences among 5 ARI’s?
- Intolerable side effects
- BPH progression
  - Symptom progression
  - Need for surgery
  - Urinary retention
Doxazosin superior in terms of symptom progression prevention

p < 0.0001 ; df = 3

McConnel et al MTOPS (Medical Therapy of Prostatic Symptoms)  NEJM Dec 2003
Cumulative Incidence of AUR

Finasteride responsible for the majority of the risk reduction

$p = 0.0034$; $df = 3$

McConnel et al. MTOPS (Medical Therapy of Prostatic Symptoms). NEJM Dec. 2003
CombAT IPSS

Adjusted mean change from baseline (LOCF)

Adjusted mean change from baseline in IPSS ± standard error

0.0
p < 0.001 Combination versus Tamsulosin

p < 0.001 Combination versus Dutasteride

Baseline 3 6 9 12 15 18 21 24 27 30 33 36 39 42 45 48
Study month

Combination (n = 1610)  
Dutasteride (n = 1623)  
Tamsulosin (n = 1611)
Stratification by baseline total prostate volume (mL) for AUR or surgery risk

Patients (%)
## MTOPS: Adverse Events

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Combination N = 786</th>
<th>Finasteride N = 768</th>
<th>Doxazosin n = 756</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erectile Dysfunction</td>
<td>5.11%</td>
<td>4.53%</td>
<td>3.56%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>5.35%</td>
<td>2.33%</td>
<td>4.41%</td>
</tr>
<tr>
<td>Postural Hypotension</td>
<td>4.33%</td>
<td>2.56%</td>
<td>4.03%</td>
</tr>
<tr>
<td>Asthenia</td>
<td>4.20%</td>
<td>1.56%</td>
<td>4.08%</td>
</tr>
<tr>
<td>Decreased libido</td>
<td>2.51%</td>
<td>2.36%</td>
<td>1.56%</td>
</tr>
<tr>
<td>Abnormal Ejac</td>
<td>3.05%</td>
<td>1.78%</td>
<td>1.10%</td>
</tr>
</tbody>
</table>

MTOPS (Medical Therapy of Prostatic Symptoms), NEJM Dec 2003

Other reported AEs <2%: peripheral edema, dyspnea, allergic reaction, somnolence

*AEs reported above are the rates per 100 person-years of follow up (incidence density). Mean follow up = 4.5 yrs
**CombAT Trial: Adverse Events**

reported over 24 months

<table>
<thead>
<tr>
<th>Event</th>
<th>Combination N = 1,610</th>
<th>Dutasteride N = 1,623</th>
<th>Tamsulosin n = 1,611</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ejaculation disorders</td>
<td>8.4%</td>
<td>1.4%</td>
<td>2.7%</td>
</tr>
<tr>
<td>(RE, ejaculation failure, semen volume decreased)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erectile Dysfunction</td>
<td>7.4%</td>
<td>6.0%</td>
<td>3.8%</td>
</tr>
<tr>
<td>Decreased libido</td>
<td>5.1%</td>
<td>4.1%</td>
<td>2.6%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1.6%</td>
<td>0.7%</td>
<td>1.7%</td>
</tr>
<tr>
<td>Breast disorders</td>
<td>3.6%</td>
<td>3.4%</td>
<td>1.4%</td>
</tr>
<tr>
<td>(enlargement, tenderness, nipple pain)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Journal of Urology, Feb 2008
Other reported AEs <2%; peripheral edema, dyspnea, allergic reaction, somnolence
Long-Term Effects of Doxazosin, Finasteride and Combination Therapy on Quality of Life in Men with Benign Prostatic Hyperplasia

**Figure 1.** Mean change from baseline in quality of life measures over time in MOS-SF-36 Physical Component Summary and MOS-SF-36 Mental Component Summary. Wei-Lachin test of stochastic ordering was used to determine p values for all followup visit measurements.

Change in Sexual Function in Men with Lower Urinary Tract Symptoms/Benign Prostatic Hyperplasia Associated with Long-Term Treatment with Doxazosin, Finasteride and Combined Therapy

Δ C, ejaculatory function. D, sexual problem assessment

Reproducible Results: Rapid & Durable

AUASI

QOL

Qmax (ml/s)

Years

RAPID

DURABLE

0 1 2 3 4 5

LIFT IDE Randomized Study
LOCAL IDE Study
BPH6 Randomized Study
Australian Study
European Multicenter Study

Roehrborn AUA2017; Gratzke BJUI 2017; Gange AUA2017; McNicholas Eur Urol 2013; Chin Urology 2012
IPSS and Qmax were significantly improved from baseline. 

- **IPSS**
  - BL: 22
  - 2 wks: 18.6
  - 1 mon: 14.5
  - 3 mon: 10.6
  - 6 mon: 9.8
  - 1 yr: 10.3
  - 2 yr: 10.2
  - 3 yr: 10.5
  - 4 yr: 11.4

- **Qmax (mL/sec)**
  - BL: 9.9
  - 1 mon: 13.1
  - 3 mon: 16.4
  - 6 mon: 15.7
  - 1 yr: 15.5
  - 2 yr: 14.7
  - 3 yr: 13.3
  - 4 yr: 13.7
Quality of life and BPH II remained significantly improved\textsuperscript{1-3}.
Medical Treatment Failure

- Focus has been on BPH / Bladder issues
  - Bladder failure
  - Delaying MIST / surgery
Sooner Than Later?

BPH Starts

Healthy Bladder

Drugs Can Be Insufficient

Bladder Worsens

Surgery Can Be Too Late

Permanently Damaged

Disease Progression
Prostate Volume Change Over 4 Years in Placebo and α-Blocker Treatment Arms

CombAT, Combination of Avodart and Tamsulosin; MTOPS, Medical Therapy of Prostate Symptoms; REDUCE, REduction by Dutasteride of prostate Cancer Events.

Medical Treatment Failure

• What % stay on medical therapy?
  – 77.1% @ 54 months \(^1\)
  – 56.9% @ 42 months \(^2\) (terazosin)
  – 58.4% @ 48 months \(^3\) (doxazosin)

Medical Treatment Failure

- Emerging data on long term consequences
  - Dementia
  - Depression
  - Suicide risk
Medical Treatment Failure
Cognitive Issues are Real!
Medical Treatment Failure
There Are No Rules!

- No widespread accepted criteria
- Urology focused
Long Term Use of Statins

- **Statin – associated muscle symptoms (SAMS)**
  - ? Nocebo effect
  - Negative expectations about effects of treatment arising from information provided by clinicians / media about possible side effects
  - Leads to higher than expected rates
- **We sometimes over attribute an adverse event rather than examine other possible causes**
Long Term Use of Statins

- **Cognitive function**
  - Pandemic of dyslipidemia and insulin resistance
  - Evolving demographic patterns affecting prevalence of dementia

- **Associated risk between high cholesterol and Alzheimer’s Disease**
  - Conflicting hypotheses if statins help or are a detriment
Long Term Use of Statins

- FDA concluded that there was no direct effect
  - Labeling for statins amended to include cognitive side effects such as memory loss and confusion
Long Term Use of 5 – α Reductase Inhibitors

- Hypothetical link between 5 – ARI and depression
  - Role of 5 – ARI in synthesis of endogenous regulating neuroactive steroids and modulation of neuroendocrine stress response
  - Dysregulation can lead to depression
  - Positive association between cognitive function and androgens
Long Term Use of 5 – α Reductase Inhibitors

- Linkage date between Medicare claims and PCPT (focused on finasteride)
  - 10% higher rate of depression claims

Long Term Use of 5 – α Reductase Inhibitors

- Population – based retrospective matched cohort study > 93,000 Canadian men using either finasteride / dutasteride
  - Medication duration: 1.57 years
  - Mean age 75
  - Suicide attempts significantly elevated until 18 months of follow up and not thereafter
  - Depression and self harm WERE increased

Long Term Use of 5 – α Reductase Inhibitors

- Cross sectional survey of 4035 Polish men with BPH
  - 1.5 fold increased rate of depression
  - ? How many were alopecia use

Pietrzyk, 2015
Long Term Use of 5 – α Reductase Inhibitors

- In former users of finasteride with persistent sexual side affects (post finasteride syndrome)
  - Mean age 31.7 (controls 26.2)
  - Higher rates of depression and suicide

Long Term Use of 5 – α Reductase Inhibitors

- Challenge in analyzing data
  - Assessment of depression (Beck Depression Inventory versus ICD – 9,10)
  - Medication duration (< 1 year to > 7 years)
  - Controls (placebo, control, alpha blocker)
Long Term Use of 5 – α Reductase Inhibitors

- Overall summary suggests a real possibility of 5 – ARI use and decreased cognitive function
  - Should be part of the shared decision making discussion
Medicare data (2006–2012) in men aged ≥65 years and diagnosed with BPH.

- Men taking tamsulosin (n = 253,136) were matched at a 1:1 ratio using propensity-scores to patients who used no BPH-medication (n = 180,926), dutasteride (n = 34,027), and finasteride (n = 38,767).
Long Term Use of Tamsulosin

- The median follow-up period for all cohorts was 19.8 months.
- After propensity-score matching, the tamsulosin cohort had an incidence of dementia of 31.3/1000 person-years compared with only 25.9/1000 person-years in the no-BPH-medication cohort.
Mean follow-up of 7.3 years, N=3434
- 23.2% developed dementia of which 79.9% developed Alzheimer disease.
- 10-year cumulative dose-response relationship observed for dementia and Alzheimer Dz (test for trend, P < .001).
- Results were robust in secondary, sensitivity, and post hoc analyses.

**Conclusions and Relevance** Higher cumulative anticholinergic use is associated with an increased risk for dementia. Efforts to increase awareness among health care professionals and older adults about this potential medication-related risk are important to minimize anticholinergic use over time.
Assess associations between anticholinergics and risk of dementia in persons 55 years or older

- 284,343 cases (63.1% women)
  - 1 – 11 years prior to Dx of dementia
  - OR 1.06 – 1.49 (TSDD > 1095)
  - 10.3% attributable rate.
Medical Treatment Failure
Depends on Definition
Key Points

- Criteria arbitrary and not well defined
  - Is it enough if the patient is happy
- Does medical therapy make sense for a QOL condition?
- In a BPH world where MIST / surgery are improving does medical therapy make sense?

WE NEED TO DEFINE MEDICAL FAILURE
No one has a monopoly on truth, and science continues to advance. Yesterday’s heresies may be tomorrow’s conventional wisdom.

Dean Ornish
I Reject Most Conventional Wisdom

Steven A. Kaplan