Increasing the Flow Treating Benign Prostatic Hyperplasia (BPH)

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Patient Case

- IP is a 64 year old man w/ complaints of urinary frequency, nocturia x 2, & slow stream
  - BP 120/80 mmHg, pulse 72, PSA 1.0 nl/mL
- Diagnosis: BPH

How would you manage this patient?

- Alpha blocker
- 5-alpha reductase inhibitor
- Saw palmetto
- Combination therapy with alpha blocker and 5-alpha reductase inhibitor
Learning Objectives

- REVIEW the likelihood of prostate disorders and identify the urinary symptoms of BPH.
- PROVIDE an update on the appropriate pharmacological treatments for BPH.
- DESCRIBE the impact that pharmacists can have on the management of BPH.
- REVIEW the pharmacist's role in counseling patients on behavioral modifications and drug therapies available to treat BPH.
Overview

- Epidemiology of BPH
- Pathophysiology of BPH
- Review current treatment options
  - Alpha blockers
  - 5-alpha reductase inhibitors
  - Combination therapy
- Considerations in choosing and monitoring pharmacotherapy
Characteristics of BPH

- Benign non-cancerous enlargement of the prostate caused by growth of new cells resulting in varying degrees of bladder outlet obstruction

- LUTS (lower urinary tract symptoms)
  - Urinary frequency, urgency, nighttime urination
  - Hesitancy, intermittency, decreased size and force of urinary stream
  - Incomplete emptying, incontinence

- Not everyone with LUTS has BPH

Anatomy of BPH

Normal

BPH

Hypertrophied detrusor muscle
Obstructed urinary flow

Symptoms of BPH

Obstructive Symptoms (voiding)
- Hesitancy
- Weak stream
- Straining to pass urine
- Prolonged micturition
- Feeling of incomplete bladder emptying
- Urinary retention

Irritative Symptoms (storage)
- Urgency
- Frequency
- Nocturia
- Urge incontinence

Prevalence of BPH Increases With Age

(N = 1,075)

Treatment Options for BPH

- Watchful waiting
- Medical therapy
- Surgical therapy
Watchful Waiting

- Mild symptoms or asymptomatic
- Lifestyle modifications
  - No intake of fluids after 7 pm
  - Cut down on bladder irritants such as caffeine and chocolate
  - Limit use of salt and spices
  - Limit alcohol
  - Limit use of OTC decongestants
Medical Therapy

- Alpha blockers
- 5α-reductase inhibitors
- Combination therapy
Alpha Blockers

Dynamic Component
Increased smooth muscle tone
α-Blockers for BPH

Not FDA-approved for BPH
- Nonselective/no longer recommended for use in BPH
  - Phenoxybenzamine
- Selective $\alpha_1$-antagonist
  - Prazosin

FDA-approved for BPH
- Long-acting $\alpha_1$-antagonist
  - Terazosin
  - Doxazosin
  - Alfuzosin (uroselective)
- Long-acting subtype $\alpha_{1A}$-antagonist (uroselective)
  - Tamsulosin (70% of all $\alpha_1$-receptors are $\alpha_{1A}$)

A Meta-analysis on the Efficacy and Tolerability of 1-Adrenoceptor Antagonists in Patients With Lower Urinary Tract Symptoms Suggestive of Benign Prostatic Obstruction

Clinical placebo-controlled or direct comparative studies derived from a MEDLINE search in October 1998

- Alfuzosin SR and tamsulosin (modified release formulation 0.4 mg) are better tolerated than terazosin and doxazosin
- Patient dropout rate due to side effects with alfuzosin and tamsulosin 0.4 mg was comparable to that with placebo (about 4-10%)
- Terazosin and doxazosin studies had 4-10% increase in dropout rate due to side effects
- Tamsulosin had less effect on blood pressure than alfuzosin (especially in elderly patients) and caused less symptomatic orthostatic hypotension during orthostatic stress testing than terazosin

BPH Treatment: $\alpha_1$-Blockers

Benefits

- Rapid onset
- Long-term maintenance of improved $Q_{\text{max}}$ and AUA symptom score
- Improve lipids, higher HDL, lower LDL, lower triglycerides
- Improve insulin sensitivity and slightly decrease platelet aggregation

$\alpha_1$-Blockers Safety Considerations

- Asthenia$^1$
- Postural hypotension$^1$
- Dizziness$^1$
- Somnolence$^1$
- Nasal congestion$^1$
- Risk of increased falls or accidents due to hypotensive side effects$^2$

Intraoperative Floppy Iris Syndrome (IFIS)

- Risk with tamsulosin or other alpha-blockers
- Small pupil syndrome characterized by flaccid iris during cataract surgery
- May require use of iris hooks or dilator rings during cataract surgery
- Benefit of stopping alpha-blockers prior to surgery has not been established

Doxazosin and Hypertension

- ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial)\(^1\)
  - NHLBI-sponsored study to compare outcomes of four different antihypertensive strategies
    - Diuretics (chlorthalidone)
    - Calcium-channel blockers (amlodipine)
    - Angiotensin-converting enzyme inhibitors (lisinopril)
    - \(\alpha\)-Blockers (doxazosin)
  - \(N = 24,335\) median follow-up 3.3 years

NHLBI = National Heart, Lung, and Blood Institute
Static Component
Increased prostate tissue mass
In some men, BPH is a progressive condition:

- Increase in prostate volume
- Worsening of symptoms
- Deterioration in urinary flow rate
- Increased risk of acute urinary retention (AUR)
- Increased risk of needing surgery for BPH
PSA as a Predictor of Future Prostate Growth

% Change in PV at 48 Months

- Low PSA tertile (0.2 to 1.3 ng/mL): 0.7 mL/year
- Middle PSA tertile (1.4 to 3.2 ng/mL): 2.1 mL/year
- High PSA tertile (3.3 to 9.9 ng/mL): 3.3 mL/year

Left untreated 1 in 6 patients with a PSA of >1.4 ng/mL will experience AUR or BPH-related surgery over a 4-year time period.
$5-\alpha$ Reductase Inhibitors (5-ARI)

Static Component
Increased prostate tissue mass
<table>
<thead>
<tr>
<th><strong>5-α Reductase Inhibitors</strong></th>
<th><strong>Dutasteride (Avodart)</strong></th>
<th><strong>Finasteride (Proscar)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Selectivity</strong></td>
<td>Type I and II</td>
<td>Type II</td>
</tr>
<tr>
<td><strong>Half-life</strong></td>
<td>5 weeks</td>
<td>6-8 h</td>
</tr>
<tr>
<td><strong>Short/Long-term efficacy</strong></td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td><strong>Titration</strong></td>
<td>Not required</td>
<td>Not required</td>
</tr>
<tr>
<td><strong>Side effects</strong></td>
<td>Impotence, decreased libido, abnormal ejaculation, gynecomastia</td>
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</tr>
<tr>
<td><strong>↑ mean peak urinary flow rate</strong></td>
<td>0.7 – 1.1 mL/s</td>
<td>~ 1.9 mL/s</td>
</tr>
<tr>
<td><strong>GENERIC available</strong></td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Risk of AUR and BPH-Related Surgery

- In a general population, men over the age of 60 have a 23% lifetime (20 years) risk of AUR
  - This risk increased in men with symptomatic BPH and enlarged prostate

- Men over the age of 60 with an enlarged prostate and obstructive symptoms have a 39% lifetime (20 years) risk of BPH-related surgery

5-α Reductase Inhibitors (5-ARI)

- Both Dutasteride & Finasteride:
  - Reduce Risk of Acute Urinary Retention
  - Reduce Risk of BPH-Related Surgery
5α-Reductase Inhibitors Side Effects

- Sexual side effects
  - Impotence
  - Decreased ejaculate volume
  - Libido
  - Gynecomastia
Precautions, Contraindications, and Warnings

- 5-ARIs should not be used in women and children.
- Caution should be used in the administration of dutasteride to patients with liver disease.
- Women who are pregnant or may become pregnant should not handle the capsules or tablets because of the possibility of absorption through the skin and potential risk to a male fetus.
- Men treated with dutasteride should not donate blood until at least 6 months following their final dose to prevent pregnant women from receiving dutasteride through a blood transfusion.

Data on file, GlaxoSmithKline.
Establish a new baseline after 3-6 months of treatment and use this value to assess potentially cancer-related changes in PSA.

To interpret an isolated PSA value in a man treated with a 5-ARI for 6 months or more, double the PSA value for comparison with normal values in untreated men.
Prostate Cancer Prevention Trial

- 18,882 men 55 years of age and older randomized to placebo vs. finasteride; followed for a total of seven years (PSA < 3 with normal DRE)
- 803 of 4,368 evaluable men treated with finasteride, and 1,147 of 4,692 on placebo diagnosed with prostate cancer (18% vs. 24%; 95% CI; P ≤ .001)
- High grade tumors were more prevalent in the finasteride group 37% vs. 22%; P ≤ .001

CI = confidence interval
Prostate Cancer Prevention Trial

- Higher detection rate of prostate cancer than the 16.7 lifetime risk in other studies
- Focus on histology, not survival
- Higher grade tumors with finasteride (95% CI; $P \leq .001$)
  - Competitive advantage of tissue not dependent on androgens
  - Lower PSA delayed threshold for biopsy

Comparing Alpha Blockers and 5-alpha Reductase Inhibitors

- From comparative trials, alpha-1 blockers are more effective than finasteride in improving symptoms and increasing urinary flow (no data for dutasteride)
- Finasteride works best in patients with large prostate volumes (>40 ml)
Comparing Alpha Blockers and 5-alpha Reductase Inhibitors

- Dutasteride appears to work as well in both large and smaller prostates
- 5-alpha reductase inhibitors reduce the risk of AUR and surgery
- Alpha blockers have not been shown to alter progression of the disease
- Both 5-alpha reductase inhibitors and alpha blockers improve symptoms
Combination Therapy

- Pivotal Study

Medical Therapy of Prostatic Symptoms

MTOPS

Medical Therapy of Prostatic Symptoms (MTOPS)

- NIH sponsored study comparing doxazosin, finasteride, or the combination with placebo
  - 3,047 men enrolled in this double-blind, placebo-controlled, prospective randomized trial
  - Mean follow-up 4.5 years
  - Mean AUA 17, PV 37

NIH = National Institutes of Health
MTOPS: Cumulative Incidence of BPH Progression

- Placebo
- Finasteride
- Doxazosin
- Combination

$P < .0001; \text{df} = 3$

BPH: Herbals
Saw Palmetto, Pygeum Africanum

- Lack of evidence
  - Study limitations: vary design, small numbers, various preparations
  - Few and small randomized clinical trials

- 2006 New England Journal of Medicine RCT:
  - 225 men, 49 years or older, moderate-to-severe BPH
  - Saw Palmetto, 160 mg bid vs. placebo (one year)
  - No advantages with saw palmetto at one year
    - AUA score
    - Peak flow
    - Prostate size
    - Bother score/QOL

- Multiple formulations are problematic without FDA regulation

RCTs = randomized controlled trials
Patient Case

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Conclusion

- BPH is prevalent among older men
- Determination of therapy is based on patient
- Treatment choice based on BPH symptoms, prostate size and adverse effect profiles