Benign Prostatic Hyperplasia: A Case-Based Approach
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Release Date: December 15, 2003
Expiration Date: December 14, 2006

Target Audience:
Physicians, pharmacists, nurse practitioners, physician assistants, and certified case managers.

Program Goal:
This program is aimed at the primary care practitioner and is intended to enhance understanding of diagnosis and treatment strategies related to benign prostatic hyperplasia (BPH).

Program Overview:
This program utilizes a case study format to address recommended diagnostic and treatment strategies for BPH that can be appropriately utilized in the primary care setting. This program is aimed at the primary care clinical practitioner and is intended to enhance understanding of the diagnosis and treatment strategies related to benign prostatic hyperplasia (BPH).

One of the typical sequelae of aging in men involves the enlargement of the prostate gland, called benign prostatic hyperplasia or BPH. This online activity will utilize several case studies to illustrate common symptoms, review diagnostic considerations, and explore management options.

Statement of Need:
Benign prostatic hyperplasia is the most common benign tumor in men, yet it is currently under-detected in general medical practice. BPH is responsible for several urinary symptoms in most men over the age of 50, and heightened awareness of BPH can improve both diagnosis and treatment.

Intended Outcome:
This program is aimed at the primary care clinical practitioner and is intended to enhance understanding of the diagnosis and treatment strategies related to benign prostatic hyperplasia (BPH).

Educational Objectives:
Upon completion of this activity, participants should be able to:

1. Identify common symptoms associated with BPH
2. Describe important considerations that will impact the clinician's evaluation of symptoms
3. List the advantages and disadvantages of varied treatment options for BPH

Principal Faculty:
Perinchery Narayan, M.D.
Dr. Narayan is a practicing urologist in Gainesville, Florida. He completed his residency at the University of Minnesota, a fellowship at the University of Minnesota in oncology, and second fellowship in oncology at Harvard Medical School. After the second fellowship was completed, he was Professor of Urology at the University of California in San Francisco for ten years and subsequently Chairman of the Division of Urology at the University of Florida. In addition to his urology practice, he currently serves as Director of the North Florida Research Institute.
Disclosure:
Dr. Narayan discloses that he has received clinical research grants from Boehringer Ingelheim. Dr. Narayan further discloses that he has been a consultant for Boehringer Ingelheim and is currently on their speakers bureau.

Commercial Support:
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Windows 98 SE or above
Internet Explorer 5.5 or above
Netscape 7.02 or above
Flash Player Plugin
*Sound Card & Speakers
800 x 600 Minimum Monitor Resolution
(1024 x 768 Recommended)
Adobe Acrobat Reader (Printable Version Only)

MAC
Mac OS 10.2
Netscape 7.02 only
Flash Player Plugin
*Sound Card & Speakers
800 x 600 Minimum Monitor Resolution
(1024 x 768 Recommended)
Adobe Acrobat Reader (Printable Version Only)
Internet Explorer Not Supported

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Fee: This program is provided free of charge.

Editorial Review Board:
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Dr. Perinchery Narayan is a practicing urologist. He completed his residency at the University of Minnesota, a fellowship at the University of Minnesota in oncology, and second fellowship in oncology at Harvard Medical School. After the second fellowship was completed, he was Professor of Urology at the University of California in San Francisco for ten years and subsequently Chairman of the Division of Urology at the University of Florida. Currently, he is the Director of the North Florida Research Institute with a urology practice in Gainesville, Florida.

Dr. Narayan’s research interest has been in the field of BPH and enlarged prostate and prostate cancer. He has been involved in many clinical trials and for the last ten years, he has been involved in several studies using alpha-blockers for BPH.

This current presentation is about benign prostatic hyperplasia, discussing the diagnosis, evaluation and management of BPH through a case-based presentation.
Benign prostatic hyperplasia is a chronic condition that clinically manifests with lower urinary tract symptoms. These symptoms include urinary hesitancy, weak stream, and incomplete emptying. Enlargement of the prostate and pathologic evidence of obstruction that can be measured by pressure flow studies are also features of this disease. BPH causes bladder outlet obstruction by spasm of the urethral muscles and mechanical compression of the urethra due to the enlarged prostate. Current management of BPH is focused on relieving symptoms in an effort to improve one’s quality of life.
This is an example of a significantly enlarged prostate with epithelial and stroma hyperplasia. The presence of a prostatic nodule close to the urethra illustrates how the mass effect of BPH causes mechanical obstruction. Prostate cancer typically occurs in the peripheral zone. In the digital rectal examination, the peripheral zone can be palpated whereas the transition zone cannot be examined by this method.
Urinary symptoms are very common in men over 40. In a study by Garraway and others (1991), they found that the incidence of urinary symptoms in men over 40 were very common. The most common symptoms were solitary nocturia, urgency, post-void dribbling, and weak urinary stream.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Occasionally</th>
<th>Often</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solitary nocturia</td>
<td>51%</td>
<td>27%</td>
<td>78%</td>
</tr>
<tr>
<td>Nocturia twice or more</td>
<td>23%</td>
<td>7%</td>
<td>30%</td>
</tr>
<tr>
<td>Hesitancy</td>
<td>13%</td>
<td>1%</td>
<td>14%</td>
</tr>
<tr>
<td>Straining</td>
<td>11%</td>
<td>0.4%</td>
<td>11%</td>
</tr>
<tr>
<td>Urgency</td>
<td>43%</td>
<td>7%</td>
<td>50%</td>
</tr>
<tr>
<td>Dribbling</td>
<td>35%</td>
<td>10%</td>
<td>45%</td>
</tr>
<tr>
<td>Stopping-restarting</td>
<td>24%</td>
<td>5%</td>
<td>29%</td>
</tr>
<tr>
<td>Incomplete bladder emptying</td>
<td>20%</td>
<td>3%</td>
<td>23%</td>
</tr>
<tr>
<td>Weak stream force</td>
<td>27%</td>
<td>6%</td>
<td>33%</td>
</tr>
</tbody>
</table>

What Causes BPH?

- The exact cause of BPH is unclear.
- BPH requires an intact male hormonal axis, i.e. normal serum testosterone production.
- Prostate growth requires dihydrotestosterone (DHT). DHT results from intra-prostatic conversion of testosterone. This conversion is mediated by an enzyme 5 alpha reductase.
- Apart from testosterone, other mechanisms for BPH occurrence include stromal-epithelial interaction, growth factors, age related change in estrogen-testosterone ratios and genetic/hereditary factors.


The exact cause of BPH is unclear. What is known is that for BPH to occur, normal levels of testosterone are needed. Men who have low levels of testosterone prior to puberty do not develop BPH. Once established, however, removal of the testicles may not cause complete regression of BPH. This is because there are several other mechanisms that are responsible for BPH maintenance and these include stromal epithelial reactions, growth factors, age-related changes and estrogen to testosterone ratios as well as genetic and hereditary factors.
This slide illustrates hormonal regulation of the prostate. Hormone regulation of the prostate involves hypothalamic pituitary access as well as adrenal and gonadal interactions. The hypothalamus and pituitary hormones together constitute a negative feedback loop that maintains optimal levels of adrenal and testicular androgens. With aging, there is a decrease in the testosterone to estrogen ratios mostly due to increased conversion of the peripheral testosterone to estrogen. In animal studies, estrogens have been shown to stimulate prostatic hyperplasia.
This slide shows that the newer concepts of prostatic cell growth and maintenance have defined a number of mediation participants. These include hormonal influences, including regulation by growth factors from three sources: autocrine factors produced within the cell, paracrine factors produced by cells surrounding the prostate such as fibroblasts and factors produced in the extracellular matrix, and endocrine factors which include the neuroendocrine cells. Within the prostate cell, testosterone is converted to dihydrotestosterone and this conversion is facilitated by the enzyme 5 alpha reductase type 2. The DHT binds to an androgen receptor in the prostate cell and initiates the growth factors and other sequences that maintain prostate cell growth and division.
What is the frequency of BPH and how common is it?

This is a commonly asked question, and researchers predict that the incidence of prostatic disease will dramatically increase given the aging of the U.S. male population and a decrease in death from other causes. Data on disease prevalence suggest that if a man lives long enough, he will most certainly have either BPH or prostate cancer.

Despite the staggering numbers, BPH is under-detected in the general medical practices because people don’t often bring up these problems with their physician. A study by Berry et al (1984) explored the development of BPH with age. He reported that more than 60% of men over age 50 have histologic evidence of BPH, and more than half of these reported clinical symptoms.
The number of aging people is steadily increasing. It is expected that by 2010 there will be twice as many people over age 65 as there were in 1970, and this population is expected to double again by 2040. This means that there will be a lot more people with BPH seeking medical care.
This phenomenon has already been manifested in the increasing number of office visits that have been seen by physicians, both primary care as well as urologists.
Understanding the diagnostic tools needed to assess BPH accurately along with the benefits, risks, and adverse events associated with available therapies will help primary care physicians diagnose and treat cases of BPH.

In a recent study, it has been shown that 89% of primary care physicians reported that up to 30% of their practices have patients who have symptomatic BPH.
BPH Case Studies: Case A

• Patient A is a 65-year-old with symptoms of frequency, straining to void, post-void dribble, and nocturia X3. These symptoms are bothersome to the patient. The rest of his history is unremarkable.

• His physical examination reveals a mildly enlarged prostate. The rest of his exam is normal.

We will now initiate a case-based discussion on the diagnosis, evaluation and management of BPH. Several common types of patients with BPH will be presented to indicate how urologists, using national guidelines, manage BPH. This discussion will focus mostly on the medical management and not dwell too much on surgical management because of time limitations.

Patient A is a 65-year-old with symptoms of frequency, straining to void, post-void dribble, and nocturia times three. These symptoms are bothersome to the patient; the rest of his history is unremarkable. His physical examination reveals a mildly enlarged prostate and the rest of his examination is normal.
Case A (cont.)

How would you further evaluate this patient?

A. Obtain a AUA/IPSS score
B. Perform urine analysis and serum PSA
C. Perform renal function studies and imaging studies of the upper tract
D. All of the above
E. Both A and B

The questions are – how would you further evaluate this patient?

A) Obtain an AUA/IPSS score
B) Perform urinalysis and serum PSA
C) Perform renal function studies and imaging studies of the upper tract
D) All of the above
E) Both A and B

After you have indicated the correct answers, the next few slides will show you what most urologists would do with the supporting rationale.
Case A (cont.)

* The correct answer is E.

* Patients with symptoms of lower urinary tract (LUTS) should be evaluated using the American Urology Association (AUA) International Prostate Symptom Score (IPSS) system. This is a validated scoring system that is reproducible, accepted internationally and useful both to diagnose and evaluate results of therapy. It can be administered to patients while in the waiting room, and avoids the doctor having to remember all important questions regarding symptoms.

* The questionnaire consists of seven questions that can be scored from 0-5 to give a total maximum score of 35. Patients with scores 0-7 have mild symptoms and don't need treatment, 8-19 are moderate and 20-35 are severe. Patients with moderate and severe symptoms are recommended treatment if symptoms are bothersome.

* To determine if symptoms are bothersome, there is one additional question on quality of life that can be scored from 1-6. Patients who have a score 3 or above are considered to have bothersome symptoms.

The correct answer is E.

Patients with symptoms of lower urinary tract should be evaluated using the AUA symptom score. The AUA is a validated scoring system that is reproducible, accepted internationally and used to both diagnose and evaluate the results of therapy. It can be administered to patients while in the waiting room, and avoids the doctor having to remember all the important questions regarding symptoms. While some patients and physicians feel that this questionnaire need not be used and they could save time by just conducting a one-on-one discussion, it has been found that this questionnaire is reproducible and has been useful serially in evaluating patient therapies as well as response to therapy.
The AUA/IPSS is shown in this slide. The questionnaire consists of seven questions that can be scored by assigning zero to five points to give a total maximum score of thirty-five. Patients with scores ranging from zero to seven have mild symptoms and generally don’t need treatment. Patients with scores ranging from eight to nineteen have moderate symptoms, and those with scores ranging from twenty to thirty-five have severe symptoms. Treatment is recommended for those patients who report moderate and severe symptoms when their symptoms are bothersome.

The AUA/IPSS is reproducible and is a valuable gauge of symptom severity. It is a cornerstone tool for understanding the extent of symptomatology and response during clinical trials. This evaluation instrument is easily administered by the medical staff in the setting of primary care centers, and should be a part of the initial evaluation of BPH that can be used to effectively monitor ongoing treatment.
Quality of life. The big question.

To determine if the symptoms are bothersome, there is one additional question focusing on quality of life. This question can be scored from one through six, and patients who have a score of three or above are considered to have bothersome symptoms. The original BPH impact index actually included four questions; however, they can all be summarized into this one question. If you were to spend the rest of your life with your prostate symptoms just as they are now, how would you feel about that? Patients who score a three or above, have either a mixed or unsatisfied quality of life and therefore need treatment.
What is the laboratory evaluation in patients with BPH?

The AUA guidelines recommend that, apart from a history and physical and a focused physical examination, patients with uncomplicated BPH should have a urinalysis and serum PSA. A serum creatinine is not recommended in uncomplicated BPH although it may be done for unrelated reasons. Urinalysis is important to document the presence of infection, hematuria, and renal disease – all of which may be in the differential diagnosis of patients with BPH. Serum PSA is indicated in all patients with BPH because patients may have concomitant prostate cancer. Prostate cancer in early stages has no symptoms and only an elevated PSA. In later stages, prostate cancer patients may present with symptoms similar to BPH.
This slide shows the American Cancer Society Guidelines for prostate specific antigen (PSA) screening. Routine screening with PSA is recommended by the American Cancer Society and the American Urology Association. PSA screening has resulted in the incidence of prostate cancer in the United States peaking in 1992 and now declining. It is recommended that all men aged 50 to 69 have screening after telling them the risks and benefits. After age 70, it is recommended that screening not be done routinely but on a case-by-case basis. It is also recommended that one start screening at age 40 if the person is of African-American descent or if the patient has a positive family history of prostate cancer – since these patients are at higher risk for prostate cancer.
The prostate specific antigen (PSA) is an important measure and is critical in ruling out prostate cancer. The baseline can be obtained at an initial consultation and for purposes of general practitioners, if the PSA levels are less than four and there are no nodules on digital rectal examination, one can initiate treatment for BPH. If the PSA levels are under four, yearly testing is indicated. If the PSA levels are over four, it is recommended that the patient be referred to a urologist for work up and possible prostate biopsy.
What is the role of imaging studies in BPH?

Imaging studies of the upper tract such as renal ultrasound, intravenous pyelography, and CT scan are not recommended in patients with uncomplicated BPH. These studies add to unnecessary cost and do not provide additional information useful in management. Imaging studies are most useful in patients with complications or findings such as hematuria or when the diagnosis is in doubt.
### Case A (cont.)

When would you treat a patient with BPH/LUTS?

A. When he has moderate or severe symptoms (AUA/IPSS>8) that are bothersome and normal prostate on rectal exam
B. When he has bothersome symptoms (AUA/IPSS>8) and an enlarged prostate on rectal exam
C. When he has mild symptoms (AUA/IPSS<7), and an enlarged prostate
D. All of the above
E. Either A or B

When you would treat a patient with BPH and LUTS such as the case that was just presented?

A) When he has moderate or severe symptoms. That is, an AUA score over eight with symptoms that are bothersome and a normal prostate and rectal examination
B) When he has these bothersome symptoms and an enlarged prostate on rectal examination
C) When he has mild symptoms
D) All of the above
E) Either A or B
Case A (cont.)

• The correct answer is E.
• Current recommendations for treatment is based on moderate or higher patient symptoms that are bothersome. Mild symptoms need not be treated. The size of the prostate matters only to decide type of treatment. Patients with large prostates may need more than one type of medication to relieve symptoms. Patients with normal prostates still need treatment if they have bothersome symptoms.

The correct answer is E.

Current recommendations for treatment is based on moderate or higher patient symptoms that are bothersome. Mild symptoms need not be treated. This is because many of the patients in that age group will have mild symptoms that are not bothering them. The size of the prostate, however, matters only to decide the type of treatment. Patients with large prostates may need one or more types of medications to relieve symptoms. Patients with normal prostates however still need treatment if they have bothersome symptoms because as mentioned initially patients can have spasm of the urethra and even those with normal prostates can have symptoms that need relief.
Case A (cont.)

How would you treat this patient?

A. Give him a trial of alpha-blockers
B. Treat him with combination of alpha-blockers and 5 alpha reductase inhibitors
C. Treat him with 5 alpha reductase inhibitors only
D. Refer him to a urologist for surgery

The next question is – How would you treat this patient?

A) Give him a trial of alpha-blockers
B) Treat him with a combination of alpha-blockers and 5 alpha reductase inhibitors
C) Treat him with 5 alpha reductase inhibitors only
D) Refer him to a urologist for surgery
The correct answer is A.

Currently, the first line management with patients with symptomatic lower urinary tract symptoms is to begin alpha-blocker therapy.
What is the rationale for alpha-blocker therapy in BPH?

A. The prostate, urethra and bladder neck predominantly contain alpha adrenergic receptors
B. Alpha-blockers relax urethral bladder neck and prostatic muscle tone by blocking alpha-receptors
C. In clinical trials, alpha-blockers relieve symptoms and improve urinary flow that has been impaired due to BPH/LUTS
D. All of the above
The correct answer is D.

Studies have shown that smooth muscles of the prostate, urethra and bladder neck are mediated predominantly by alpha adrenergic receptors. Alpha-receptors are subdivided into primarily three types: Alpha 1A, Alpha 1B, and Alpha 1D. Approximately seventy to eighty percent of prostatic receptors are Alpha 1A. The 1B subtype is present mainly in blood vessels, and the 1D is present in the bladder and spinal cord.
This slide shows the alpha-receptor's selectivity in a diagrammatic form. As mentioned, the predominant receptors in the prostate and bladder neck are the 1A-receptors. The vascular receptors are mostly 1B. The newer receptor that has been researched recently is the alpha 1D which has been found both in the bladder and spinal cord. It is thought that these receptors mediate the urgency and frequency type of irritable bladder, and certain agents such as tamsulosin which selectively block the alpha 1D can improve not only the urine flow but also the bladder contractility in these patients.

The only alpha-blocker that is selective for both alpha 1A and alpha 1D is tamsulosin hydrochloride.

Patient B is a 55-year-old with symptoms of frequency, mild straining to void, and nocturia X2 (AUA/IPSS = 5). These symptoms are not bothersome to the patient. The rest of his history is unremarkable.

His physical examination reveals a mildly enlarged prostate. The rest of his exam is normal.

Now we come to Case B.

Patient B is a 55-year-old with symptoms of frequency, mild straining to void and nocturia times two. This patient has an AUA/IPSS score of five. These symptoms are not bothersome to the patient. The rest of his history is unremarkable. His physical examination reveals a mildly enlarged prostate and the rest of his examination is normal.
BPH Case Studies: Case B

How would you treat this patient?

A. Trial of alpha-blockers
B. Trial of saw palmetto
C. Watchful waiting
D. Refer to urologist

How would you treat this patient?

A) Trial of alpha-blockers
B) Trial of saw palmetto or other herbal agent
C) Watchful waiting
D) Refer to a urologist
The correct answer is C.

Watchful waiting is indicated in patients with BPH with mild symptoms and an IPSS score under seven. Studies have shown that many patients over the age of fifty, as previously mentioned, have mild symptoms of BPH that are not bothersome. Watchful waiting involves the following: monitoring symptoms and careful observation for complications; keeping a patient voiding diary. Many of these patients may be benefited with certain fluid restrictions that prevent them from getting up at night. Periodic evaluation for symptom progression or complications without surgical or medical intervention. Re-evaluation should occur annually. One must also recognize that there is considerable practice variation among primary care physicians in their thresholds for urologic referrals and adjust for these variations.
Patient C is a 60-year-old with severe symptoms of BPH (AUA/IPSS = 30). Symptoms predominantly consist of decreased force of stream, straining to void, feeling of incomplete emptying, and nocturia X3. He is bothered by the symptoms. His quality of life (QOL) score is poor and 4 using a 1-6 scale. The rest of his history is unremarkable.

His genital examination is normal. Rectal examination reveals his prostate to be very large. The rest of his physical exam is NL.

Now let's go to Case C.

Patient C is a 60-year-old with severe symptoms of BPH and an AUA/IPSS score of 30. Symptoms predominantly consist of decreased force of stream, straining to void, feeling of incomplete emptying, and nocturia times three. He is extremely bothered by these symptoms. His quality of life score is poor and 4 on a 1 to 6 scale. The rest of his history is unremarkable. His genital examination is normal. Rectal examination reveals his prostate to be very large. The rest of his physical examination is normal.
The patient had a normal urine analysis and his PSA was 3.5. What is the next step in management?

A. Start alpha-blockers  
B. Start alpha-blockers and 5 alpha reductase inhibitors in combination right away  
C. Get ultra sound (US) of prostate before treatment  
D. Refer to a urologist

The patient had a normal urinalysis and his PSA was 3.5.

What is the next step in management:
A) Start alpha-blockers  
B) Start alpha-blockers and 5 alpha reductase inhibitors in combination right away  
C) Get an ultrasound of the prostate before treatment  
D) Refer to a urologist
The correct answer is A.

Initial management of all symptomatic patients should be with alpha-blockers. Combination therapy should be used in large prostates only when alpha-blockers fail to satisfactorily relieve symptoms. An ultrasound of the prostate may be performed if alpha-blockers fail to relieve symptoms adequately and prior to initiating 5 alpha reductase inhibitor therapy.
This patient need not be referred to urology. Uncomplicated BPH may be treated by family practitioners and internists provided they are aware of potential complications that need referral to urology.

Complications include: hematuria (gross or microscopic); pain; infection; progression of symptoms; development of PSA elevation; acute urinary retention and renal failure.
Case C (cont.) Moderate Symptoms vs. Severe Symptoms: Role of Alpha-Blockers

- It has been shown in several studies that patients with severe symptoms will respond to alpha-blockers just as well as patients with moderate symptoms. Regardless of symptom severity or prostate size, initial management of BPH patients should be with alpha-blocker therapy. Alpha-blockers will improve symptoms rapidly.

- Alpha-blockers may be used long term without tolerance development (no deterioration of efficacy with time.) Overall, 60-80 percent of patients with symptoms will improve on alpha-blocker therapy.

The question often arises - moderate symptoms versus severe symptoms and the role of alpha-blockers. It has been shown in several studies that patients with severe symptoms will respond to alpha-blockers just as well as patients with moderate symptoms regardless of symptom severity or prostate size, initial management of BPH should be with alpha-blocker therapy. Alpha-blockers will improve symptoms rapidly. Alpha-blockers may also be used long-term without tolerance development. That is, no deterioration with efficacy over time. Overall, sixty to eighty percent of patients with symptoms will improve on alpha-blocker therapy.
This slide shows the efficacy of tamsulosin, which was evaluated in a two-part, multi-center placebo-controlled clinical trial, enrolling approximately 1,500 patients.

After a four-week single blind placebo evaluation period, 735 patients were randomized for double-blind therapy with tamsulosin 0.4 mg, 0.8 mg or placebo once daily for 13 weeks. What this slide shows is that there is rapid improvement in symptoms according to the AUA symptom score of both tamsulosin groups compared with placebo in the second part of the study. The AUA symptom score was a precursor to the IPSS and is interchangeable. It is shown that there is a significant difference when patients use tamsulosin compared to placebo. And this was maintained up to the 13 weeks of the trial period.
The next slide shows the improvement in urine flow rate when tamsulosin was used in the 13-week trial. In this slide, significant improvement in peak urinary flow was observed by first evaluation at week one and was maintained relatively constant throughout the study. The improvement was statistically significant over placebo but there was not that much difference in urinary flow rate between the two groups that were given 0.4 mg versus 0.8 mg. This was one of the reasons why the FDA recommended 0.4 mg as the recommended dose for treatment of BPH.
The next slide shows that tamsulosin can be used with good efficacy long term. Recently, in the *Journal of Urology*, we published a long-term trial with six years use of tamsulosin. In this long-term, multi-center extension trial, all of the patients who met the original eligibility criteria were given open labeled medications and what was shown was that the AUA symptoms scored improvements observed in the earlier studies were maintained throughout the six-year period. There was no tolerance effect and the symptom improvements did not decrease over time. Additionally tamsulosin’s long-term efficacy was maintained without additional associated cardiovascular events such as postural hypertension.
BPH Case Studies: Case D

- Patient D is a 75-year-old with moderate symptoms of BPH (IPSS = 19). His quality of life is poor with a score of 5/6. Symptoms are moderately bothersome. His medical history is significant for hypertension, heart disease, and diabetes.
- He is on multiple medications including diuretics, ace inhibitors, and lipid lowering agents.
- His urine analysis is normal, his PSA is within normal and he has no complications of BPH.
- His residual urine measured by ultrasound is 60 cc. His prostate size is 30 grams.

Now we go on to Case D.

Patient D is a 75-year-old with moderate symptoms of BPH and IPSS of nineteen. His quality of life is poor with a symptom score of five out of six. His symptoms are markedly bothersome. His medical history is also significant for hypertension, heart disease, and diabetes. He is on multiple medications, including diuretics, ACE inhibitors, and lipid-lowering agents. His urinalysis is normal. His PSA is within normal limits and he has no complications of BPH. His residual urine as measured by ultrasound is sixty cc and his prostate size is thirty grams.
**BPH Case Studies: Case D**

How would you treat this patient?

A. Alpha-blockers
B. Alpha-blockers with 5 alpha reductase inhibitors
C. Refer to a urologist

How would you treat this patient?

A) Alpha-blockers
B) Alpha-blockers with 5 alpha reductase inhibitors
C) Refer to a urologist
BPH Case Studies: Case D

- The correct answer is A.
- Since the patient has no complication of BPH, he does not need to be referred to a urologist prior to initial management.
- Since his prostate size is under 40 grams, he need not be treated with combination therapy.

The correct answer is A.

Since the patient has no complications of BPH, he need not be referred to a urologist prior to initial management. Since his prostate size is under 40 grams, he will not need to be treated with combination therapy.
Combination therapy for patients with BPH has been shown to be beneficial only in patients with prostate size over 40 grams. The VA co-operative trial showed that alpha-blockers provided the same benefits as combination of alpha-blockers with finasteride (Proscar®) in patients up to one year of treatment with mean prostate size of 36.5 cc.


Combination therapy for patients with BPH has been shown to be beneficial only in patients with prostate size over 40 grams. The VA Cooperative Trial showed that alpha-blockers provided the same benefits as combination of alpha-blockers with finasteride (Proscar®) in patients up to one year of treatment when the mean prostate size was 36.5 cc.
Pharmacologic Treatment of BPH:
VA Cooperative Studies BPH Study Group

- 1,229 Men with BPH randomized to 4 arms in a 52-week trial
- 305 Men treated with terazosin
- 310 Men treated with finasteride
- 309 Men treated with terazosin plus finasteride
- 305 Men on placebo

Results: Men who were treated with finasteride had no better improvements in symptoms than those on placebo. Terazosin treatment improved symptoms compared to placebo. The median baseline prostatic volume in this study was 37.5 cc for the terazosin group, 36.2 cc for the finasteride group, 37.2 cc for the terazosin plus finasteride group, and 38.4 cc for the placebo group.


This next slide shows the pharmacologic therapy of BPH studied by the VA Cooperative Studies Benign Prostatic Hyperplasia Study Group. In this trial 1,229 men with BPH were randomized to one of four arms in a one-year clinical trial. Approximately three hundred men were treated with terazosin, another three hundred with finasteride, another three hundred with terazosin plus finasteride and three hundred were on placebo.

Men who were treated finasteride had no better improvement in symptoms than those on placebo. Terazosin alone improved symptoms compared to placebo. The median baseline prostatic volume in this study was 37.5 cc for the terazosin group and 36.2 for the finasteride group and 37 for terazosin plus finasteride.

What this study showed was that in patients with average prostate sizes, finasteride does not seem to improve symptoms over alpha-blocker terazosin when used in combination, therefore the current recommendation is that patients with average prostate sizes (sizes less than 40 grams) should not be treated with combination treatment. Data on this combination therapy is still evolving, and there is a recent NIH trial called the Medical Therapy of Prostatic Symptoms (MTOPS) trial showing that combination therapy may be beneficial when given for a long term (i.e., over two years), but this data has still not been published.
Case D (cont.)

What type of alpha-blocker will be appropriate for this patient?

A. Short-acting alpha-blockers (prazosin)
B. Long-acting alpha-blockers (doxazosin, terazosin)
C. Long-acting selective alpha-blockers (tamsulosin)

What type of alpha-blocker will be appropriate for this patient who is 75-years-old and has multiple medical problems, especially cardiovascular disease?

A) Short-acting alpha-blockers such as prazosin
B) Long-acting alpha-blockers such as doxazosin and terazosin
C) Long-acting selective alpha-blockers such as tamsulosin
Case D (cont.)

• The correct answer is C.

• In this patient with history of HTN, heart disease, and diabetes on diuretics and antihypertensive medications, and age of 75 yrs, non-selective alpha-blockers may cause postural hypotension. Initial treatment by most urologists at present would be with selective alpha-blocker, tamsulosin.

The correct answer is C.

In this patient with a history of hypertension, heart disease, and diabetes, who is on diuretics and antihypertensive medications, and age of 75 years, non-selective alpha-blockers may cause postural hypertension. Initial treatment by most urologists at present would include a selective alpha-blocker such as tamsulosin.
Case D (cont.)

- Short-acting alpha-blockers need to be used three times a day and prazosin especially is associated with significant side effects of first dose hypotensive episodes.
- Long-acting once-a-day alpha-blockers also have significant incidence of postural hypotension. These agents are nonselective and are indicated for the treatment of hypertension. Therefore when used for LUTS, some patients may exhibit side effects due to lower blood pressure.

Short-acting alpha-blockers need to be used three times a day, and prazosin is particularly associated with significant side effects of first dose hypertensive episodes. Long-acting once-a-day alpha-blockers also show a significant incidence of postural hypertension.

These agents are nonselective and are indicated for the treatment of hypertension. Therefore when used for lower urinary tract symptoms, some patients may exhibit side effects due to lower blood pressure, and this has attendant consequences and complications as from falls and hip fractures.
Tamsulosin HCl is a long-acting, once-a-day selective alpha-blocker. In clinical research trials, it has been shown that this drug has 20 times more selectivity for the alpha 1A and alpha 1D subtype receptors. As we discussed previously, the predominant receptor in the bladder neck and prostate is the alpha 1A and the 1D is also important in improving bladder storage although this research is still ongoing. Because of the selectivity of tamsulosin, however, it has less systemic side effects such as postural hypertension. In clinical trials, tamsulosin has been shown to produce hypertension in only 0.2% of patients.
Nonselective Alpha-Blockers and Hypertension

- ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial)
  - 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)
  - Doxazosin arm halted due to significantly higher incidence of secondary endpoints
    - Congestive heart failure
    - Stroke
    - Combined cardiovascular events
  - N=24,335


This next slide shows the effect of non-selective alpha-blockers and hypertension and their relationship.

The ALLHAT Trial was a large, randomized, double-blind, active controlled trial conducted by the National Heart, Lung and Blood Institute that examined the outcomes of hypertension treatment with four commonly prescribed classes of effective agents. In this trial, an interim analysis determined that patients treated with doxazosin had a significantly higher incidence of combined cardiovascular events than patients treated with chlorthalidone. In particular, the risk of congestive heart failure was doubled among those in the doxazosin group and there was a significantly elevated risk for stroke, angina and coronary artery revascularization. Therefore the doxazosin arm of the ALLHAT trial was discontinued.
Nonselective Alpha-Blockers and Hypertension (cont’d)

• “Dual strategy” of using alpha-blockers may not be optimal antihypertensive strategy
• Hypertension in men with BPH should be independently treated with the most effective antihypertensive strategy, and the symptoms of BPH should be treated with the most appropriate alpha-blocker, e.g., tamsulosin HCl, which has minimal impact on the cardiovascular system

The dual strategy of using alpha-blockers, such as terazosin and doxazosin, for treating two diseases, such as BPH and hypertension, is no longer an optimal treatment strategy. Hypertension in men with BPH should be independently treated with the most effective antihypertensive strategy. According to most cardiologists, optimal treatment for hypertension does not rely on alpha-blockers. The symptoms of BPH should be treated with the most appropriate alpha-blockers, and most urologists choose tamsulosin hydrochloride because of its minimal impact on the cardiovascular system.
## Summary of Pharmacologic Agents for BPH

<table>
<thead>
<tr>
<th>Product</th>
<th>Finasteride (Proscar®)</th>
<th>Terazosin (Hytrin®), Doxazosin mesylate (Cardura®)</th>
<th>Tamsulosin HCl (Flomax®) Capsules</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class</td>
<td>5 alpha reductase inhibitor</td>
<td>alpha₁-antagonist selective alpha-blocker</td>
<td>alpha₁₂-antagonist subtype-selective alpha-blocker</td>
</tr>
<tr>
<td>Dosing</td>
<td>Once daily</td>
<td>Once daily</td>
<td>Once daily</td>
</tr>
<tr>
<td>Symptom improvement</td>
<td>3 to 6 Months</td>
<td>2 to 4 Weeks</td>
<td>1 Week</td>
</tr>
<tr>
<td>Mechanism of action</td>
<td>• Reduction of prostatic volume</td>
<td>• Relaxation of prostatic smooth muscle</td>
<td>• Relaxation of prostatic smooth muscle</td>
</tr>
<tr>
<td>Adverse events</td>
<td>• Sexual dysfunction</td>
<td>• Postural hypotension</td>
<td>• Rhinitis</td>
</tr>
<tr>
<td></td>
<td>• Lowers PSA levels</td>
<td>• Dizziness</td>
<td>• Dizziness</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Headache</td>
<td>• Abnormal ejaculation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Asthenia</td>
<td></td>
</tr>
</tbody>
</table>

This next slide shows you a summary of the various pharmacologic agents for BPH. In it are discussed drugs such as finasteride (Proscar®), terazosin (Hytrin®), doxazosin mesylate (Cardura®) and now the generic variations of these as well as tamsulosin (Flomax®). All four pharmacologic treatments are safe and effective with notably few drug interactions. The major differences, however, are in the convenience and satisfaction especially the timed relief of symptoms and signs of BPH and the ease of dosing which can be achieved with tamsulosin.
Surgical Treatment

- Invasive
  - Transurethral resection of the prostate (TURP): the “gold standard”
  - Open prostatectomy

- Minimally invasive
  - Transurethral incision of the prostate (TUIP)
  - Transurethral needle ablation (TUNA)
  - Laser prostatectomy
  - Microwave therapy

This next slide shows you a summary of surgical treatments.

Although we are not going to discuss too much about this, the standard treatment for BPH, the goal standard is the transurethral resection of the prostate and in very large prostates that are more than 70 to 80 grams, open prostatectomy. Transurethral resection, however, has considerably decreased in the popularity among the patients because of side effects such as retrograde ejaculation and the small but significant incidence of incontinence.

There are a number of minimally invasive therapies, the most popular of which now include the transurethral needle ablation, the microwave therapy and the laser prostatectomy. Now also shown in the next slide a variety of alternative therapies.
It has been shown that up to 25 to 30% of patients who come to your office are taking some kind of phytotherapy or herbal product. Among these, the saw palmetto or the berries of the saw palmetto extracts have been found to be the most popular. There have been some trials that compare them to placebo, and findings show that they do have a beneficial effect although not as much as the alpha-blockers.
**Desirable Attributes of Drug Therapy for BPH**

<table>
<thead>
<tr>
<th>Physician-Friendly</th>
<th>Patient-Friendly</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Effective in the treatment of BPH</td>
<td>• Effective in the treatment of BPH</td>
</tr>
<tr>
<td>• No need for titration</td>
<td>• Rapid onset of action</td>
</tr>
<tr>
<td>• Minimal drug interaction</td>
<td>• No need for titration</td>
</tr>
<tr>
<td>• Minimal side effects</td>
<td>• Once-daily dosing</td>
</tr>
</tbody>
</table>

In summary, there are several equally effective pharmacologic agents currently available in the marketplace for treatment of BPH and its symptoms. These agents differ mostly in their ease of dosing and potential for side effects. I and many of my colleagues prefer tamsulosin because this agent is available as a once-a-day drug, has minimal cardiovascular side effects, and needs no titration. If patients forget to take their pill once in a while as they often do, they can go right back on tamsulosin unlike some other agents where they have to start at a lower dose and work back up to an appropriate dose. Also I’m able to prescribe this drug without too much concern in elderly patients who have multiple other illness or are also on other medications since tamsulosin has fewer drug-to-drug interactions and is reasonably well-tolerated by older patients.
Thank you for your participation in this presentation.

This concludes our program. Thank you for participating in Benign Prostatic Hyperplasia: A Case-Based Approach.