

Continuing Education for Pharmacists

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New Drugs of 2004 for Treatment of Benign Prostatic Hyperplasia: Avodart and Uroxatral

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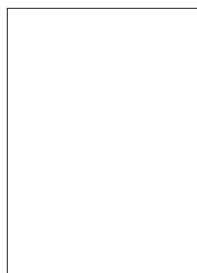
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Goals. The goals of this lesson are to provide background information on benign prostatic hyperplasia and review the newest drugs approved for its treatment (Table 1).

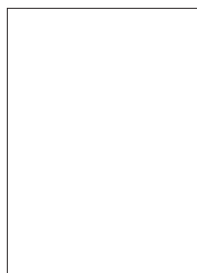
Objectives. At the conclusion of this lesson, successful participants should be able to:

1. explain the etiology and incidence of benign prostatic hyperplasia;
2. identify factors associated with its onset;
3. exhibit knowledge of the pharmacologic classification and therapeutic considerations for the drugs discussed; and
4. select from a list, the indications, mechanisms of action, adverse effects and toxicities, drug interactions, and benefits and limitations of the drugs presented.

Benign prostatic hyperplasia (BPH) is a complex, multifactorial disease with symptoms that can contribute



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significantly to decreased quality of life by interfering with normal daily activities and sleep patterns. It is natural for the prostate gland to enlarge with aging; however, the reason some men develop BPH to greater extent than others is unknown. The number of affected males will undoubtedly increase in the future as life expectancy lengthens. Benign prostatic hyperplasia is the most common noncancerous form of abnormal prostate cell growth. However, BPH is not a precancerous condition.

The Prostate Gland

The prostate gland surrounds the proximal urethra at its point of attachment to the bladder. It secretes seminal fluid, which

contributes about 15 percent of the ejaculate volume. The gland consists of distinct anatomical zones which have different disease susceptibilities. The peripheral zone is the site of development of prostate cancer. The transition zone, which separates the peripheral zone from the central zone, is the site of hyperplastic (i.e., increased cell number) growth that characterizes BPH. As new cells form, adding to an increasingly larger gland, the surrounding capsule permits expansion while at the same time pushes inward upon the urethra. This obstructs the bladder outlet to make urination progressively more difficult. The term *hypertrophy* (increased cell size) is inaccurate when describing BPH.

Beginning with puberty, the previously static prostate gland begins to enlarge rapidly under the influence of increased androgen production. By age 20, it weighs about 20 g (i.e., about the size of a walnut). The size remains constant until the individual's mid-40s when the gland again begins to enlarge, but at a slower rate.

Table 1
New Drugs for Treatment of Benign Prostatic Hyperplasia

Trade/Generic Name (Sponsor/Manufacturer)	Dosage Form	Indication	Date Approved
Avodart/dutasteride (GlaxoSmithKline)	0.5mg soft gelatin capsule	Treatment of symptomatic benign prostatic hyperplasia	10/02*
Uroxatral/alfuzosin (Sanofi-Synthelabo)	10mg extended- release tablet	Treatment of the signs & symptoms of benign prostatic hyperplasia	6/03

* approved in 2002; released to market in 2003

Prostate-specific Antigen.

Prostate-specific antigen (PSA) is produced by epithelial cells within the prostate gland and functions to liquefy the seminal coagulum (i.e., the ejaculate). With a baseline serum concentration of 0.07 ± 0.4 ng/mL, serum PSA levels of ≤ 4.0 ng/mL are normal, 5 to 10 ng/mL are slightly elevated, and ≥ 10 ng/mL are considered moderately to highly elevated. Elevated levels can serve as a marker for the presence of either BPH or prostate cancer.

Influence of Testosterone.

Testosterone is converted within prostatic cells by the enzyme 5 alpha-reductase to its active form dihydrotestosterone (DHT), which is the growth stimulant for glandular epithelium. Following puberty, androgen receptors within the gland are down-regulated so that they are less sensitive to hormonal challenge. This limits additional androgen-stimulated enlargement. Glandular mechanisms responsible for this down-regulation lessen in the aging prostate and androgen-dependent growth resumes. Once the gland enlarges with aging, androgen withdrawal alone will not return the gland to its previous size.

Benign Prostatic Hyperplasia

The precise etiology of BPH is unknown, although medical opinion associates it to a hormonal hypothesis: at least one normally functioning testis is required; and castrated men and men with hypogonadism do not develop BPH. Symptoms include urgency during the day, difficulty initiating urination, weak and/or interrupted urine stream, and excessive nighttime urination (nocturia), the latter being the most bothersome symptom. Untreated BPH can progress to worsening of lower urinary tract symptoms, urinary retention, increased risk of urinary tract infection, bladder calculi, and urinary incontinence. Of great fear to many older males is an association of BPH with declining sexual function. While sexual function is important to most men throughout life, men with BPH are

at increased risk for sexually-related problems including erectile and ejaculation dysfunction and decreased libido.

Glandular size alone does not necessarily correlate with symptom severity. BPH is not a cause of death, although symptoms can significantly alter the patient's quality of life. At present, the estimated lifetime odds of a 50-year-old man in the U.S. developing BPH of sufficient intensity to necessitate treatment is 40 percent.

As stated earlier, increasing age is the strongest risk factor for BPH; a functioning testis is necessary. Other positive risk factors include obesity, alcoholism and hepatic cirrhosis, and hypertension. Men with a first-degree male relative with BPH face a 30 percent increased risk for the condition, with onset at an earlier than average age. American and European men are more likely to develop BPH than Asian and African men. Smoking is the most intensely studied factor and, interestingly, is believed to protect against BPH.

Management of BPH

Management of BPH has changed dramatically over the past decade. Surgical intervention (i.e., transurethral resection of the prostate [TURP]) was the mainstay of treatment in the recent past for men with bothersome symptoms. The 1990s ushered in a fresh variety of medical interventions. The minimally invasive surgical treatments became even less invasive with introduction of laser-inflicted destruction of prostatic tissue, transurethral incision of the prostate (TUIP), transurethral needle ablation (TUNA) and others. Pharmacologic therapy is the preferred treatment today; 85 to 90 percent of cases are treated with medication. Pharmacologic management has positive outcomes since the complications of BPH, including acute urinary retention and symptom progression necessitating eventual surgery, can often be reduced or eliminated. The goal of

therapy is to eliminate symptoms that interfere with daily activities, thus enhancing quality of life.

Pharmacologic Intervention.

Pharmacologic intervention controls symptoms in a majority of patients and involves two approaches: (1) reducing the size of the prostate gland by blocking conversion of testosterone to DHT by 5-alpha reductase, and (2) antagonizing alpha-adrenergic receptors within the gland to dilate smooth muscle surrounding the urethra.

5 Alpha-Reductase Inhibitors.

Two drugs are classified as 5 alpha-reductase inhibitors: Proscar (finasteride), introduced in 1992, and Avodart (dutasteride), approved in 2002 but not marketed until 2003. Proscar inhibits type 2 5 alpha-reductase; Avodart inhibits both types 1 and 2 isoforms. 5 Alpha-reductase inhibitors are most useful in men with BPH whose prostates are >40 g and who have reduced urinary flow rates due primarily to DHT-stimulated overgrowth of glandular tissue.

Alpha-adrenergic Receptor

Antagonists. Smooth muscle comprises a significant portion of the prostate gland. The α_{1a} -receptor subtype is found primarily in the bladder, urethra, and prostate smooth muscle. Prostatic smooth muscle contraction results from norepinephrine stimulation of α_1 -adrenergic receptors. Serum norepinephrine concentration increases naturally with advancing age and correlates with age-related enhancement of symptom severity. α_1 -adrenergic receptor antagonists relax the constricted muscle to improve urinary flow. The new drug, Uroxatral (alfuzosin), joins three other α_1 -receptor antagonists approved for relief of symptoms of BPH: Cardura (doxazosin), Flomax (tamsulosin), and Hytrin (terazosin).

Avodart (Dutasteride)

Dutasteride forms a stable enzyme complex with both type 1 and type 2 isoforms of 5 alpha-reductase. This binding is both competitive and

specific for the enzyme. Dutasteride, therefore, inhibits conversion of testosterone to DHT, the androgen primarily responsible for early development and consequent age-related enlargement of the prostate gland. Drug effect on reduction of DHT is dose-dependent and attained within one to two weeks of daily dosing. After that time, median serum DHT concentration reductions of 85 percent and 90 percent, respectively, are attainable with dutasteride 0.5 mg daily. In patients with BPH, the median decrease in serum DHT concentration at one year and two years is 94 percent and 93 percent, respectively.

Dutasteride (0.5 mg once daily) reduces the risk of both acute urinary retention and BPH-related surgical intervention. The drug decreases prostate volume and increases the maximum urinary flow rate, which in turn improves BPH-related symptoms.

Adverse Effects. In pre-marketing clinical trials, impotence, decreased libido, ejaculation disorder, and gynecomastia (enlarged, tender breast tissue) were present in ≥ 1 percent of men receiving Avodart and at greater incidence than men receiving placebo over a 24-month period. The incidence of impotence, decreased libido and ejaculation disorder decreased with increasing duration of treatment. The incidence of gynecomastia remained constant over the treatment period.

Dutasteride is absorbed through the skin, so women who are pregnant or who may become pregnant should not handle the capsules due to the potential risk of a fetal anomaly to males. Any skin area in contact with leaking capsules should be washed immediately and thoroughly with soap and water.

Both 5 alpha-reductase inhibitor drugs reduce PSA levels; by six months, dutasteride reduces levels by approximately 50 percent. When assessing BPH or screening for prostate cancer, the PSA value should be doubled to obtain an accurate value in patients receiving

the 5 alpha-reductase inhibitor drugs.

Drug Interactions. Dutasteride is metabolized by cytochrome P450 isoenzyme CYP3A4. Blood concentrations of dutasteride may be increased in the presence of inhibitors of CYP3A4 such as ritonavir, ketoconazole, verapamil, diltiazem, cimetidine, and ciprofloxacin. Dutasteride is not metabolized by cytochrome P450 isoenzymes CYP1A2, CYP2C9, CYP2C19, or CYP2D6.

Indications and Uses. Avodart is indicated for the treatment of symptomatic BPH in men with an enlarged prostate to improve symptoms, reduce the risk of acute urinary retention, and reduce the risk of the need for BPH-related surgery. Clinical investigations have shown that Avodart arrests the disease process in men with an enlarged prostate.

Patients should be advised to read the manufacturer's Patient Information leaflet before starting therapy with Avodart and with each prescription refill. They should also understand that their ejaculate volume may be decreased during treatment with Avodart, but that this decrease does not appear to interfere with normal sexual function. Men treated with Avodart should not donate blood until at least six months after stopping therapy to avoid introducing the drug to a pregnant woman. Advice for the patient is summarized in Table 2.

Dosage and Administration. The recommended dose of Avodart is 0.5mg orally once a day. The capsules should be swallowed whole. Doses may be administered with or without food. The product is supplied as soft gelatin capsules containing 0.5mg dutasteride.

Uroxatral (Alfuzosin)

Uroxatral is a selective antagonist of post-synaptic alpha₁-adrenoreceptors, which are located in the prostate, bladder base, bladder neck, prostatic capsule, and prostatic urethra. Blocking these receptors

Table 2
Patient Information for
Avodart

- Take this medicine exactly as your doctor directed. The dose is one capsule each day, swallowed whole. Do not break or chew the capsules. You may take the capsules with or without food, but you should take each dose at approximately the same time each day.
- Tell your doctor if you have ever had an allergic reaction to dutasteride or finasteride.
- Be sure to tell your doctor if you have liver disease before starting to take this medicine.
- Be sure to tell your doctor about all other prescription, nonprescription (OTC) and herbal or natural medicines you are taking.
- Some OTC medicines (antihistamines, decongestants, cough/cold remedies, hay fever remedies, sleep aids) have a warning on their label advising persons with an enlarged prostate not to take them unless directed by a doctor. If you see such a warning on the label of an OTC product, ask your doctor or pharmacist if it is okay for you to take the OTC product.
- Do not donate blood until at least six months after your final dose to prevent pregnant women from receiving it in the transfusion.
- Do not take this medicine if you are a woman or child. If you are a woman who is pregnant or capable of becoming pregnant, do not handle the capsules.
- If you miss a dose, take it as soon as you think about it later that day. Do not make up the missed dose by taking two doses the next day.
- Store these capsules at room temperature (77° F) or lower.
- If the capsules are cracked or leaking, do not take them and contact your pharmacist.

Consult the Product Information supplied by the manufacturer for complete patient instructions.

causes the smooth muscle in the bladder neck and prostate to relax, which results in increased urine outflow with reduced symptoms of BPH.

Table 3
Patient Information for
Uroxatral

- Take this medicine exactly as your doctor directed. The dose is one tablet each day swallowed whole. Do not crush or chew the tablets. Take them with food and with the same meal each day.
- Tell your doctor if you have ever had an allergic reaction to alfuzosin or any other alpha-blocker.
- Be sure to tell your doctor if you have liver or kidney disease, or high or low blood pressure before starting to take this medicine.
- The manufacturer warns that this medicine should not be used in women or children under 18, or for hypertension.
- This medicine may cause symptoms related to low blood pressure (hypotension), such as dizziness or fainting, especially when you first begin taking it. Use extreme caution when driving, operating machinery, or performing hazardous tasks during this period.
- Be sure to tell your doctor about all other prescription, nonprescription (OTC) and herbal or natural medicines you are taking.
- Some OTC medicines (antihistamines, decongestants, cough/cold remedies, hay fever remedies, sleep aids) have a warning on their label advising persons with enlarged prostate not to take them unless directed by a doctor. If you see such a warning on the label of an OTC product, ask your doctor or pharmacist if it is okay for you to take the OTC product.
- The manufacturer warns that this medicine should not be taken with other medicines such as itraconazole, ketoconazole and ritonavir that affect a certain enzyme in your body. If you want more information, ask your doctor or pharmacist.

Consult the Product Information supplied by the manufacturer for complete patient instructions.

The currently available alpha₁-adrenergic receptor antagonists listed earlier are similar in that they produce an approximately 20 to 30 percent increase in the maximum urine flow rate, with improvement of up to 50 percent in patients' urinary symptoms. A claimed

advantage of these drugs over 5 alpha-reductase inhibitor therapy is their rapid onset of action. For example, alfuzosin can increase maximum flow rate by 34 percent following a single dose. Some symptom relief with improved quality of life is noted after one week of treatment, with full benefit usually achieved after two to three months. However, these drugs do not reduce the size of the prostate gland.

Adverse Effects. Pre-market clinical trials involved 473 men who received daily doses of 10mg of alfuzosin. Ages ranged from 49 to 92 years (average age 64.2 years). In these studies, 4 percent of men taking alfuzosin withdrew from the study due to adverse events, compared with 3 percent of men in the placebo group. Adverse events reported by ≥ 2 percent of patients receiving alfuzosin, and at a greater incidence than those within the placebo group, included dizziness, upper respiratory tract infection, headache, and fatigue. Additional responses reported in postmarketing investigations included rash, tachycardia, chest pain, and priapism.

Postural hypotension with or without dizziness may develop within a few hours following dosing of alfuzosin. As with other alpha-adrenergic antagonists, syncope is a potential outcome. Patients should be warned and encouraged to avoid potentially dangerous situations where they could be injured. Alfuzosin should also be given with care to patients with symptomatic hypotension or those who have experienced a hypotensive reaction to other medications. The drug should not be used in patients with moderate or severe hepatic insufficiency, since blood levels are increased in these patients. Alpha₁-adrenergic receptor antagonists do not affect PSA levels.

Drug Interactions. CYP3A4 is the principal hepatic enzyme isoform involved in the drug's metabolism. Administration of potent inhibitors of CYP3A4, such

as ketoconazole, itraconazole or ritonavir, can increase alfuzosin serum levels and should not be co-administered with the new drug unless medically necessary. The moderately-potent inhibitor of CYP3A4, diltiazem, also increases serum alfuzosin levels, but in clinical trials, no changes in blood pressure were observed.

Indications and Uses.

Uroxatral is indicated for the treatment of the signs and symptoms of benign prostatic hyperplasia. Uroxatral is not indicated for the treatment of hypertension.

Although BPH is not a precancerous condition, prostate carcinoma and BPH cause many of the same symptoms. And, these two diseases frequently coexist. Patients believed to have BPH should be examined prior to starting therapy with Uroxatral to rule out the presence of prostatic cancer.

Patients should be informed about symptoms related to postural hypotension, such as dizziness, when beginning Uroxatral. They should be cautioned about driving, operating heavy machinery, or performing hazardous tasks during this period. Patient information for Uroxatral is summarized in Table 3.

Dosage and Administration.

The recommended dosage is 10mg daily taken immediately after the same meal each day. The tablets should not be chewed or crushed. Uroxatral is supplied as extended-release tablets containing 10mg alfuzosin.

Continuing Education Quiz

New Drugs of 2004 for Treatment of Benign Prostatic Hyperplasia: Avodart and Uroxatral

1. Which of the following anatomical zones of the prostate gland is the site of hyperplastic growth that characterizes BPH?

- a. Central
- b. Peripheral
- c. Transition
- d. Posterior

2. Which of the following statements is true?

- a. BPH invariably leads to prostate cancer.
- b. The prostate gland secretes seminal fluid.
- c. The capsule surrounding the prostate gland prevents expansion of the gland.
- d. BPH refers to Benign Prostate Hypertrophy.

3. All of the following statements are true EXCEPT:

- a. PSA can serve as a marker for the presence of BPH.
- b. PSA functions to liquefy the seminal coagulum.
- c. PSA can serve as a marker for the presence of prostate cancer.
- d. PSA is produced by epithelial cells in the testes.

4. Which of the following is the strongest risk factor for BPH?

- a. Increasing age
- b. Obesity
- c. Hepatic cirrhosis
- d. Alcoholism

5. Which of the following is currently the preferred treatment for BPH?

- a. Transurethral incision
- b. Transurethral needle ablation
- c. Transurethral resection
- d. Pharmacologic therapy

6. Dutasteride acts by:

- a. inhibiting 5 alpha-reductase.
- b. antagonizing alpha-adrenergic receptors.

7. Alfuzocin acts by:

- a. inhibiting 5 alpha-reductase.
- b. antagonizing alpha-adrenergic receptors.

8. Which of the following drugs has a warning that women who are or who may become pregnant should not handle the capsules due to the potential for development of fetal anomaly to males?

- a. Dutasteride
- b. Alfuzosin

9. Unless directed to do so by a physician, patients taking either of the drugs mentioned above should be advised not to self-medicate with all of the following OTC medicines EXCEPT:

- a. antihistamines.
- b. decongestants.
- c. aspirin.
- d. sleep aids.

10. Patients taking alfuzocin should be given all of the following points of advice EXCEPT:

- a. be careful driving, operating heavy equipment or performing hazardous tasks when beginning therapy with this medicine.
- b. these tablets should not be chewed or crushed.
- c. take this medicine with the same meal each day.
- d. do not donate blood while taking this medicine.