

## Benign Prostatic Hyperplasia: An Overview for Pharmacists

Joanna Labrecque, PharmD; Richard Randolph, PharmD; and Roger Davis, PharmD

### AUDIENCE

This activity is designed for community, hospital, and clinical pharmacists.

### GOAL

To review current information on benign prostatic hyperplasia and discuss the management of benign prostatic hyperplasia according to the clinical guidelines released by the US Agency for Health Care Policy and Research.

### OBJECTIVES

1. Define the terminology relating to benign prostatic hyperplasia
2. Describe the anatomy of the prostate in relation to the terminology and pathogenesis of benign prostatic hyperplasia.
3. Explain the clinical presentation and diagnosis of benign prostatic hyperplasia.
4. Describe surgical treatment options for the management of benign prostatic hyperplasia.
5. Review current medical therapy with  $\alpha_1$ -blockers and 5 $\alpha$ -reductase inhibitors.



### CONTINUING EDUCATION CREDIT

This course has been approved for a total of two (2) contact hours of continuing education credit (0.2 CEUs) by the University of Tennessee College of Pharmacy. The University of Tennessee College of Pharmacy is approved by the American Council on Pharmaceutical Education as a provider of continuing pharmaceutical education. ACPE Program Number: 064-000-99-205-H-01. This course expires on May 31, 2002.

From The University of Tennessee, Memphis (J.L., R.D.) and Marcrom's Pharmacy, Manchester, TN (R.R.).

Address correspondence to: Roger Davis, PharmD, College of Pharmacy, The University of Tennessee, Memphis, 226 Capital Blvd., Suite 810, Nashville, TN 37219.

**B**enign prostatic hyperplasia (BPH) is the most common benign neoplastic disease in aging men, primarily affecting men over the age of 50. The risk of developing BPH increases with age.<sup>1</sup> A 1994 telephone survey conducted by the National Center for Health Statistics revealed that the majority of men having disorders of prostate and/or bladder were over the age of 75.<sup>2</sup> The US Agency for Health Care Policy and Research reports that 1 in 4 men will be treated within their lifetime for symptoms occurring from an enlarged prostate.<sup>3,4</sup> In recent years, several new therapies have been developed to provide men with different treatment options for the management of their BPH. It is the intent of this article to provide an overview on current information regarding BPH and to discuss the clinical practice guidelines released by the US Agency for Health Care Policy and Research.<sup>4</sup>

### ... DEFINITION ...

The term BPH has several meanings that are not defined specifically. Most persons associate BPH with any problems involving the prostate. According to Beduschi et al,<sup>5</sup> the term BPH has 3 connotations. (1) Microscopic BPH refers to specific histological findings of hyperplasia due to the proliferation of the stromal and epithelial elements.<sup>5,6</sup> (2) Macroscopic BPH can be a result of microscopic BPH causing substantial enlargement of the prostate.<sup>5,6</sup> Macroscopic BPH may also be referred to as benign prostate enlargement (BPE).<sup>5,6</sup> (3) Clinical BPH represents the distinct signs and symptoms of bladder outlet obstruction (BOO).<sup>5,6</sup> Another common term in discussing BPH is prostatism, which is being replaced by the term lower urinary tract symptoms (LUTS) to help prevent confusion. It has been suggested that BPH be used to describe pathologic findings and LUTS be used to describe voiding difficulties that may develop due to an enlarged prostate.<sup>7</sup>

... ANATOMY AND PATHOPHYSIOLOGY ...

The anatomy of the prostate is divided into 4 distinct zones: central (70% of surface area), peripheral (25%), transitional (4%), and the anterior fibromuscular stroma (1%).<sup>1</sup> The transitional zone surrounds the urethra and it is suggested that BPH arises here, while adenocarcinoma is believed to originate in the peripheral zone.<sup>1</sup> The presence of stromal (smooth muscle and connective tissue) and epithelial (gland) elements as a nodule, in any zone, defines histological BPH.<sup>1</sup> There are many  $\alpha_1$ -receptors located in the smooth muscle of the prostate and the neck of the bladder.<sup>4,8</sup>

The causes of BPH are still not completely understood. They are, however, very complex and are thought to be age-related and androgen-dependent. BPH may be due to the stimulation of cell growth, the inhibition of apoptosis (active cell death), or both. Although the actual role of estrogen is unclear, it is thought that in the presence of androgens, estrogens inhibit the rate of growth thru apoptosis.<sup>1</sup> The overgrowth of stromal and epithelial cells provide significant pressure to the lumen of the urethra resulting in BOO.<sup>1,9</sup> However, not all men with BPH experience BOO.

Furthermore, androgens and estrogens aid in a stromal-epithelial interaction that regulates prostate cell growth and proliferation. The stromal-epithelial interactions are caused by an increase in circulating levels of androgens and estrogens, thus affecting the stimulatory and inhibitory peptide growth factors.<sup>9</sup> In a normal prostate, the stromal-epithelial ratio is 2:1, whereas the ratio in BPH is 5:1.<sup>10</sup> This smooth muscle ratio explains the efficacy of drug therapies in BPH treatment that relax the smooth muscle.<sup>1,10</sup>

Finally, dihydrotestosterone (DHT) is the predominant androgen for prostate tissue growth. DHT is produced by  $5\alpha$ -reduction of testosterone within the prostate. By using  $5\alpha$ -reductase inhibitors to block this DHT production, the epithelial overgrowth of the prostate may be stopped in men with BPH.

... CLINICAL PRESENTATION AND DIAGNOSIS ...

The clinical presentation of BPH may vary among men and symptoms do not always correlate with the prostate size. The most common presentation is the development of urinary symptoms including urgency, frequency, hesitancy, postvoid dribble, and weak stream. Urinary symptoms can be broken down into 2 categories: obstructive and irritative (Table 1). Obstructive symptoms (eg, hesitancy, weak stream, overflow incontinence, urinary retention, double voiding, and inability to empty the bladder) result from mechanical obstruction of the urethra. Irritative symptoms are similar to the effects of a urinary tract infection and include urinary frequency, urgency, urge incontinence, and nocturia. The irritative symptoms may be a result of an increased prostate gland that is causing a frequent voiding response and is compromising the bladder volume. These symptoms are common at night due to the natural relaxation of the muscle tone. Hematuria can occur in some instances, but is usually not present. In the event that hematuria is present, further evaluation is recommended due to a more likely explanation of the current urinary symptoms such as cancer or cystitis. It is most often urinary discomfort, rather than a physically enlarged prostate, that causes men to see a physician. Age, immobilization, exposure to cold, alcohol, or anticholinergic and sympathomimetic medications can actually cause these same voiding symptoms. It is for this reason that the presence of voiding difficulties does not automatically indicate benign prostatic disease.

**Table 1.** Signs and Symptoms of BPH

Obstructive symptoms
Hesitancy
Weak stream
Inability to empty bladder
Postvoid dribbling
Urinary retention
Overflow incontinence
Irritative symptoms
Urinary frequency
Urinary urgency
Nocturia
Urge incontinence
Other signs
Hematuria
Enlarged prostate (> 20 grams)
American Urological Association Symptom Index > 7
Renal failure (due to obstructive uropathy)

Adapted from reference 27.

Several factors play a distinct role in diagnosing BPH. A good medical history, physical examination, and laboratory testing are imperative in accurately diagnosing this condition. Obtaining a good medical history is important in determining whether the causes of the voiding symptoms are due to BPH or another process, such as medications (Table 2). The American Urological Association (AUA) has developed a symptom score sheet composed of 7 questions that objectively assess urinary symptom severity.<sup>11</sup> Also known as the International Prostate Symptom Score (I-PSS), the numerical results of the questionnaire indicate the following level of disease severity: 0-7 = mild; 8-20 = moderate; and >20 = severe. I-PSS is also used as a tool in determining the effectiveness of therapy in treating BPH.

Physical examination is another important tool in determining the cause of urinary complications. Digital rectal examination (DRE) is performed to examine the size and consistency of the prostate gland, as well as to reveal irregularities or growths on the gland. Although some believe that DRE is unreliable, it can help to rule out prostatic carcinoma.<sup>4</sup> The presence of irregularities, masses, or nodules may indicate prostate cancer. It is also believed that a neurological examination should be conducted to detect peripheral and/or autonomic neuropathy associated with abnormalities in urinary function.<sup>12</sup>

Finally, laboratory testing is needed to rule out other potential causes of urinary problems. First, a urinalysis should be obtained to rule out hematuria and/or urinary tract infection. Second, serum creatinine should be evaluated to exclude the possibility of renal insufficiency. Optional tests may be performed in some individuals, such as persons with diabetes, a severe inability to empty the bladder, suspected overflow incontinence, or those who have had a stroke.<sup>5</sup> Uroflowmetry, postvoid residual volume, pressure-flow studies, cystometry, urethrocytometry, and imaging studies are available to evaluate urinary obstructions; however, they are not routinely used in the initial evaluation of patients. A serum prostate specific antigen (PSA) test is needed primarily to differentiate patients with BPH from patients with prostate cancer, but its use remains somewhat controversial for routine testing.<sup>13</sup>

... TREATMENT ...

BPH is largely a quality of life issue. Treatment is required only when it interferes with a patient's

lifestyle and prohibits daily activities.<sup>6</sup> Some men may actually have an enlarged prostate but never experience symptoms and therefore require no treatment. In an algorithm for management of BPH prepared by Beduschi et al<sup>6</sup>, treatment is based upon the patient's AUA symptom score. A score in the mild range suggests watchful waiting and annual evaluation of the prostate via DRE and PSA testing. Moderate to severe scores, however, warrant treatment with 1 or more of the following options: medical therapy, surgical therapy, and minimally invasive procedures. As with all healthcare matters, the patient must ultimately choose which treatment to initiate, and in most cases pharmacological therapy is initiated before surgical therapy due to the potential risk of permanent impotence and incontinence with the latter.<sup>4,8</sup>

**Watchful Waiting**

Watchful waiting can be used for patients with mild to moderate symptoms. The physician merely monitors the patient at this stage with no active therapy initiated.<sup>4</sup> In mild to moderate symptoms, placebo has been shown to be as effective as active therapy.<sup>8</sup> All of these patients should be evaluated yearly by DRE, serum PSA testing, and AUA symptom scale and should be educated regarding over-the-counter medications (sympathomimetic and anticholinergic) that can affect their symptoms and simple lifestyle changes (Table 2). These lifestyle changes consist of avoiding alcohol and caffeine-containing beverages, decreasing fluid intake late in the evenings, and bladder retraining. Bladder training consists of setting a voiding schedule. The

**Table 2.** Medications That Cause Lower Urinary Tract Symptoms\*

Anticholinergic
Antiemetic/Antivertigo
Antihistamines
Tricyclic antidepressants
Any drug having anticholinergic side effects
Sympathomimetic
Bronchodilators
Glaucoma agents
Vasopressors

\*Please note that this table is not an all-inclusive list of drug-related urinary difficulties. Adapted from reference 6.

patient is taught to delay voiding when the urge to void occurs. Also, pelvic muscle exercises, such as kegel exercises, may be performed to strengthen muscle contraction and aid in relaxation. These exercises may help with urinary incontinence caused by BPH. Watchful waiting offers some men an alternative to surgical and medical therapies, while others still require additional treatment due to worsening symptoms.<sup>14</sup> It is important to keep in mind that the major therapeutic goal in BPH is the reduction of symptoms.

### Surgical Therapy

In patients experiencing severe symptoms of BPH such as recurrent urinary tract infections, hematuria, overflow incontinence, uremia, refractory urinary retention, and/or bladder stones, surgery is recommended and produces the best overall improvement of symptoms.<sup>4</sup> Not all patients are good candidates for surgery, therefore, other alternatives need to be discussed with the patient before a treatment plan is put into place.

Transurethral surgical procedures are needed for patients experiencing severe urinary retention, large residual volume, and/or failure of pharmacologic therapy.<sup>15</sup> Transurethral resection of the prostate (TURP) offers the best rate of symptom improvement and is the most common surgical procedure for BPH.<sup>16</sup> After undergoing TURP, 90% of men have an overall improvement in symptoms.<sup>2,14</sup>

Open prostatectomy is another type of standard therapy. Prostatectomy is generally reserved for large prostates (> 40 grams) due to the risk of complications occurring after surgery, the most common of which are retrograde ejaculation and impotence.<sup>15,17</sup> Other side possible effects include excessive bleeding (requiring transfusion), infection, urinary incontinence, the inability to remove clots (clot retention), bladder neck contracture, and dilutional hyponatremia.<sup>4,15,17</sup>

### Minimally Invasive Procedures

Two new procedures have been developed to decrease costs, lessen use of anesthesia, and reduce postoperative complications.<sup>17</sup> These procedures decrease the length of stay in the hospital and can be performed as outpatient surgery. Transurethral incision of the prostate (TUIP) is indicated for small prostates (< 40 grams). This procedure takes only minutes to perform and there is less blood loss than with TURP or open prostatectomy. TUIP has the added advantage of not producing retrograde ejaculation to the extent observed with TURP.<sup>17</sup> Visual

laser ablation of the prostate (VLAP) is also used in patients with relatively small prostates (<40 grams) and for patients receiving anticoagulants. This procedure, also done on an outpatient basis, results in the least amount of blood loss when compared with other procedures.<sup>17</sup> Most patients go home with a temporary urinary catheter after VLAP because of sloughing of coagulated prostate tissue that occurs over several weeks.<sup>12</sup>

Urethral stents and balloon dilation are 2 types of procedures that offer temporary relief of symptoms to patients who are not candidates for surgery. These procedures are relatively safe and simple to perform; however, their results are inconsistent.<sup>18</sup>

### Medical Therapy

*Nonselective  $\alpha_1$ -Blockers.* Because there are many  $\alpha_1$ -receptors located in the smooth muscle of the prostate and the neck of the bladder,  $\alpha_1$ -blockers are used in the treatment of mild-to-moderate BPH.<sup>4,8</sup> These agents competitively inhibit  $\alpha_1$ -adrenergic receptors causing the veins and arterioles to dilate—thus relaxing the smooth muscles and decreasing bladder resistance—allowing improvement of urinary flow.

Phenoxybenzamine, the first agent studied for treatment of LUTS in BPH, was associated with many unfavorable side effects involving cardiovascular responses, which led to the development of selective  $\alpha_1$ -adrenergic blocking agents.<sup>8</sup> Prazosin, terazosin, doxazosin, and tamsulosin are the only drugs to date in this class, of which the last 3 carry US Food and Drug Administration (FDA) approval for treatment of BPH (Table 3). Terazosin, doxazosin, and tamsulosin are long-acting selective  $\alpha_1$ -blockers, thereby offering easier compliance with a once-daily dose versus 2 to 3 times daily dosing schedule required by prazosin. The most common side effects from each of these agents are postural hypotension, dizziness, fatigue, and lightheadedness.

The “first-dose” phenomenon is the result of postural hypotension occurring after receiving the first dose of an  $\alpha_1$ -blocker. This phenomenon is more likely to occur (1) if therapy is stopped and then started again, (2) if the initial dose is high or the dose is increased too rapidly, and (3) if patients are receiving  $\beta$ -blockers, diuretics, or are on a low-sodium diet. To minimize its occurrence, the initial dose should be low, titrating slowly upward to an effective dose, and should be taken at bedtime. Elderly patients, who may suffer from hypotension-related syncopal episodes at night leading to falls, should be counseled to help minimize this risk.

**PRAZOSIN.** Prazosin is a short acting  $\alpha_1$ -blocker with a 3 hour half-life, necessitating more frequent dosing. Although prazosin is indicated for the management of hypertension, it remains an option for treatment of BPH symptoms despite its lack of FDA approval. Prazosin is associated with urinary frequency and urinary incontinence along with the common side effects of the 1 class antagonist.

Although this drug is extensively metabolized in the liver and careful monitoring is suggested in patients with hepatic failure, there are no set guidelines for monitoring liver enzymes. Routine monitoring is not commonly performed and should be conducted at the discretion of the practitioner. The available dosage strengths are 1mg, 2mg, and 5mg capsules with the maximum dose being 20mg/day. The initial

**Table 3.** Medications for the Treatment of BPH

Class/Drug	MOA	Dose	Side effects	Drug interactions
$\alpha_1$ -blockers	Relaxes prostate smooth muscle, decreasing bladder outlet resistance to urinary flow			
Prazosin		Start dose initial IV low, then increase 3-15mg a day in 2-3 divided doses (max dose 20mg/d)	Dizziness, orthostatic hypotension, syncope, headache, urinary incontinence.	Decreased effect with NSAIDs. Increased effect with diuretics and antihypertensive agents. Also increase effect of clonidine.
Terazosin		Initially 1mg/d, increasing as needed to a max dose of 20mg/day	Dizziness, headache, fatigue, hypotension, edema, palpitations, nasal congestion.	Decreased effect with NSAIDs. Increased effect with diuretics and antihypertensive agents. Also increased effect of clonidine.
Doxazosin		0.5-1mg/day initially increasing as needed to 1-8mg/day	Dizziness, hypotension, headache, fatigue, decreased libido, rhinitis, palpitations.	Decreased effect with NSAIDs. Increased effect with diuretics and antihypertensive agents.
Tamsulosin	$\alpha_{1A}$ antagonist	0.4mg/day, 30 m after a meal	Headache, dizziness, decreased libido, ejaculation disturbances, diarrhea.	Metabolism by CyP-450 enzyme: potential warfarin interaction, Increased effect with cimetidine.
5 $\alpha$ -reductase inhibitor	Impares prostate growth by inhibiting the conversion of testosterone to DHT			
Finasteride		5mg/day	Decreased libido, increased impotence, decreased volume of ejaculate.	No clinically significant interactions reported.

MOA = Mechanism of action; NSAID = nonsteroidal anti-inflammatory drug. Adapted from *Facts and Comparison*.

interest in prazosin for BPH management has led to the development of longer acting  $\alpha_1$ -blockers that have received FDA approval for their use in treatment. Due to the short half-life of prazosin, requiring frequent dosing, and its potential urinary side effects, prazosin is not often prescribed for the management of BPH.

**TERAZOSIN.** Terazosin, a long-acting  $\alpha_1$ -blocker, received FDA approval for its use in hypertension and BPH in 1993.<sup>19</sup> Its half-life is 11-12 hours, thus allowing once-daily dosing. Terazosin produces a rapid response, with approximately 70% of patients experiencing an increase in urinary flow and improvement in BPH symptoms within 2 weeks.<sup>20</sup> The most significant side effects are dizziness, fatigue, postural hypotension, somnolence, and nasal congestion/rhinitis.<sup>20</sup> It has been shown that terazosin has no effect on serum PSA and has approximately a 1.2% chance of affecting sexual function.<sup>20-22</sup> The recommendation for initial dosing for severe hypotensive episodes is 1mg at bedtime, followed by step-by-step titration up until the lowest effective dose has been achieved to relieve symptoms. The most common maintenance dose is 10mg daily. Once this dose has been reached, therapy should be continued for a minimum of 4-6 weeks in order to determine if a beneficial response has been seen. If no positive response is seen, then the dose may be increased to 20mg daily.<sup>20</sup> Terazosin is available as a 1mg, 2mg, 5mg, and 10mg capsule, with 20mg being the maximum daily dose.

**DOXAZOSIN.** Doxazosin is another long-acting, selective  $\alpha_1$ -blocker, with a long half life (22 hrs), allowing once-daily dosing. Dizziness, headache, and fatigue were commonly seen in normotensive and hypertensive patients.<sup>23</sup> The maximum dose for treatment of BPH is 8mg/day, beginning with 1mg/day and titrating upwards as needed for additional therapeutic effect. Syncope and hypotension can also occur in patients with their first dose of doxazosin. Dosage forms include 1mg, 2mg, 4mg, and 8mg tablets.

**$\alpha_{1A}$ -Selective Blockers.** The newest available  $\alpha_1$ -blocker, tamsulosin, received FDA approval in 1997 for the treatment of LUTS with BPH.<sup>8</sup> Tamsulosin has a higher affinity for the 1A subtype of adrenoceptors than any other agent in its class.<sup>24</sup> It is thought that this may be the reason tamsulosin has fewer cardiovascular side effects (eg, syncope or postural hypotension) than the other agents. In patients treated with tamsulosin, however, there is a significant increase in the risk of ejaculatory disturbances (approximately 8.4% with a daily dose of 0.4mg).

The half-life of tamsulosin ranges from 11 to 15 hours, thereby enabling once-daily dosing. Unlike the other  $\alpha_1$ -blockers, tamsulosin dosing does not need to be titrated because of its lack of cardiovascular side effects.<sup>8</sup> When used in combination with other antihypertensive agents, there were no clinically significant changes in blood pressure.<sup>25</sup> It appears that the clinical efficacy of tamsulosin is similar to that of terazosin and doxazosin with regards to reducing voiding difficulties and increasing improvement of urinary flow.<sup>23,26</sup> Of particular interest is the fact that this agent undergoes hepatic metabolism by the cytochrome p-450 enzymes; caution should therefore be used in patients with hepatic dysfunction. There is also potential for drug-drug interactions with agents that share the same metabolic pathway, although these interactions have not been established (Table 3). Specific studies have been performed with nifedipine, atenolol, enalapril, digoxin, theophylline, and furosemide in concurrent use with tamsulosin. To date, dosage adjustment is not necessary with the above medications.<sup>27</sup> There are currently only 2 documented drug-drug interactions; warfarin and cimetidine.<sup>27</sup> The recommended dose of tamsulosin is 0.4mg once daily, 30 minutes after the same meal without regards to time of day.<sup>28</sup> The maximum dose studied is 0.8mg/day and should only be used if therapeutic goals are not met on 0.4mg/day. The only dosage form currently available is 0.4mg capsules.

The goal for future therapies is to further refine current  $\alpha_{1A}$ -blockers in order to maximize their potential benefit while minimizing their potential side effects. In unpublished reports, 2 agents are being studied for BPH treatment: KMD3213 and JTH601. KMD3213 appears to be similar to tamsulosin, while the latter is demonstrating a stronger affinity for the prostate  $\alpha_{1A}$ -receptors than tamsulosin. It is postulated by Kawabe<sup>26</sup> that JTH601 affects different receptor sites than either prazosin or tamsulosin.

**$5_\alpha$ -reductase inhibitors.** There are 2 isoenzymes of  $5_\alpha$ -reductase: type I is present in the skin whereas type II is located in the prostate. Approved in 1992, finasteride remains the only type II  $5_\alpha$ -reductase inhibitor approved by the US FDA for its use in the treatment of BPH (Table 3). This class was developed to block the conversion of testosterone to dihydrotestosterone (DHT) by the  $5_\alpha$ -reductase enzyme located in the prostate.<sup>5,28</sup> The resulting decrease in DHT, which is responsible for prostate development, causes reduction of the prostate volume and size preventing further symptom development caused by BPH.<sup>15</sup>

Impotence, decreased libido, and decreased ejaculate volume are the main side effects that somewhat limit its role in the clinical management of BPH.<sup>28,29</sup> It appears that finasteride offers its greatest benefit to patients having a prostate volume greater than 30mls.<sup>29,30</sup> A 4-year evaluation of finasteride use in BPH showed improvement of symptoms and reduction in prostate volume, increased urinary flow rate, and reduction of potential surgeries and acute urinary retention.<sup>28</sup> Finasteride is effective and well tolerated in patients with BPH, however, it may take up to 12 months or more to see clinical improvement of prostate size.<sup>8</sup> Shrinkage of the prostate may first be detected after 3 months of initial treatment and continues to evolve for 12 to 24 months.<sup>8</sup> When finasteride 5mg/day is taken for 6 to 12 months, however, it can lead to a 20% to 30% reduction in prostate size.<sup>7</sup> It has also been discovered that this agent decreases serum level of the PSA.<sup>31</sup> Lepor et al<sup>32</sup> suggest the use of finasteride in patients following failure of  $\alpha_1$ -blocker therapy in men having large prostates. Finasteride is available as a 5mg film-coated tablet and with a mean terminal half-life ranging from 4 to 15 hours, also given once daily. The recommended dose of finasteride is 5mg/day with no titration necessary. The dosage form is available as a capsule and is a teratogen, therefore, it is recommended that pregnant females not handle the capsule as well as women of child-bearing age that may come into contact with semen of males taking oral finasteride.

*Saw Palmetto.* The widespread use of alternative medicine for treatment of BPH is common in Europe. Seventy percent of German spending on alternative agents is for the management of LUTS. In France, spending patterns for management of prostatism were 45% in herbal remedies.<sup>8</sup> The most common herbal product used in the United States for BPH is saw palmetto (*Serenoa repens*).

Saw palmetto is believed to work by inhibiting the conversion of testosterone to dihydrotestosterone as well as preventing dihydrotestosterone binding to cellular and nuclear receptor sites, thereby increasing the metabolism and excretion of DHT.<sup>33</sup> Most of the studies that have been conducted, however, have been small with very short-term evaluations performed.<sup>33</sup>

Currently no herbal therapies have been approved by the US FDA for symptoms relating to BPH. Few placebo-controlled studies have been published in well known peer-reviewed medical journals on herbal therapies and the role they play in BPH.<sup>8</sup> However, the medical community is

taking a closer look at alternative therapies and studies regarding these products are forthcoming.

...SUMMARY ...

For many men who are symptomatic, sometimes doing nothing may be the best approach to managing mild symptoms of BPH. Watchful waiting has been shown to be as effective as active therapy with the lowest incidence of side effects. Some men who have failed medical therapy will elect to try watchful waiting as compared to surgery rather than accept the risk associated with surgery. Watchful waiting is not for everyone and patients should discuss its benefits and risk with their physician.

Surgical therapy and the use of minimally invasive procedures are recommended for patients with moderate-to-severe symptoms of BPH. Generally, these therapies and procedures result in unwanted side effects and can be more costly than medications. Although newer surgical techniques have been developed and have been found to produce less morbidity than TURP, this treatment alternative remains the most common surgical procedure. Minimally invasive procedures are primarily used as short-term treatments before surgical therapy. Surgery is highly recommended in patients with severe symptoms of BPH.

According to the AHCPR practice guidelines of 1994,  $\alpha_1$ -blockers are recommended as first-line agents in patients who require or choose medical therapy. These agents are very effective at improv-

**Table 4.** Cost Comparison of Drugs Used in Treating BPH

Drug	Dose	Cost/30 days
Prazosin	3 - 15mg/d, in divided doses	\$22.40 - \$54.25
Doxazosin	2 - 4mg/d	\$29.13 - \$30.58
Terazosin	10mg/d	\$43.45
Tamulosin	0.4mg/d	\$39.24
Finasteride	5mg/d	\$63.23

Adapted from reference 34.

ing symptoms of BPH and increasing urinary flow rate regardless of the prostate size.  $\alpha_1$ -blockers, with the exception of tamsulosin, have an ability to reduce blood pressure in hypertensive men with BPH yet provide little or no effect on men with a normal blood pressure. Tamsulosin, an  $\alpha_{1A}$ -adrenoreceptor antagonist, is expected to have minimal cardiovascular side effects because of its selectivity for  $\alpha_{1A}$  adrenoreceptors. Overall, their onset of action is rapid, they have little effect on the PSA, and are relatively low in cost (Table 4). The main disadvantage with these agents, however is their hypotensive side effect, which is especially important relative to its use in the elderly population, who may already be at an increased risk for falls.

The use of finasteride is suggested after failure of an  $\alpha_1$ -blocker or in men with significant enlargement of the prostate (> 40 grams). In comparison with  $\alpha_1$ -blockers, finasteride has fewer cardiac side effects, does not need dosage titration, and decreases prostate size. Not only can finasteride alter the progression of the disease, but it also improves urinary symptoms. The negative aspect of this agent is the duration of therapy required to receive a positive response and its yearly cost. It may take up to 12 months to see significant clinical improvement with finasteride, whereas rapid reduction of symptoms occurs with  $\alpha_1$ -blockers due to their more rapid onset of action. The use of  $\alpha_1$ -blockers has been suggested for the first 3 to 6 months of finasteride therapy to help provide relief of urinary symptoms while awaiting finasteride's onset of action. Although it has been postulated that finasteride and  $\alpha_1$ -blockers be used in combination therapy because of their unique mechanism of actions, the data is lacking in proving their efficacy in combination.<sup>27</sup> Currently, combination therapy is not recommended for initial treatment of BPH.

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