

CME ARTICLE

Benign Prostatic Hyperplasia: New Concepts for the Millennium

Burkhardt Zorn, MD; John J. Bauer, MD; and Judd W. Moul, MD

AUDIENCE

This article is designed for primary care physicians who may be responsible for patients with benign prostatic hyperplasia (BPH).

GOAL

To provide the reader with a basic understanding of the pathophysiology of BPH, its evaluation, and its treatment.

OBJECTIVES

1. To describe the prevalence, definitions, and symptoms of BPH.
2. To describe how BPH is evaluated in patients presenting with lower urinary tract symptoms.
3. To describe available treatment options and the expected results.

CONTINUING MEDICAL EDUCATION ACCREDITATION

Johns Hopkins University School of Medicine designates this continuing medical education activity for 1 credit hour in Category 1 of the Physician's Recognition Award of the American Medical Association.

Johns Hopkins University School of Medicine is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to sponsor continuing medical education for physicians.

This CME activity was planned and produced in accordance with the ACCME Essentials.

From Walter Reed Army Medical Center, Washington, DC (B.Z., J.J.B., and J.W.M.), and the Center for Prostate Disease Research, Uniformed Services University of the Health Sciences Bethesda, MD (J.J.B. and J.W.M.).

The opinions and assertions contained herein are the private views of the authors and are not to be construed as reflecting the views of the US Army and the Department of Defense.

Address correspondence to: Judd W. Moul, MD, Center for Prostate Disease Research, 1530 East Jefferson St, Rockville, MD 20852. E-mail: Judd.Moul@na.amedd.army.mil.

Benign prostatic hyperplasia (BPH) is the most common benign neoplasm in men. Before the advent of medical therapy for BPH in the early 1990s, the estimated number of surgical procedures for BPH was more than 400,000 per year at an estimated annual cost of \$4.5 billion.¹ Transurethral surgery of the prostate (TURP) accounted for the majority of these procedures, but there has been a 52% decrease in its performance since 1990.² This decrease in the performance of TURP is not only a reflection of medical therapy but also of the emergence of minimally invasive techniques to treat BPH. Previous estimates in the early 1990s were that 1 in 4 men is treated in his lifetime for symptoms resulting from BPH and that this treatment accounts for more than 1.7 million office visits per year. The aging population, public awareness of the condition, and the availability of nonsurgical options have increased the percentage of men seeking and receiving treatment.³ The high prevalence of symptomatic BPH has a substantial impact on the quality of life for elderly men and represents an increasing significant financial burden.

The large number of men with BPH and the lack of objective indications for intervention have resulted in the formulation of the clinical practice guidelines for BPH, which was released in February 1994.⁴ These guidelines represent recommendations not only to the urologist but also to the primary care physician, who will be playing an increasingly major role in the treatment of this disease process. This brief review of BPH and the related diagnostic and treatment modalities is intended to provide the primary care physician with an overview of this rapidly changing field.

... DEFINITIONS AND PATHOPHYSIOLOGY OF
BENIGN PROSTATIC HYPERPLASIA ...

In the past, a causal relationship between the presence of BPH and the development of lower urinary tract symptoms was accepted. We now realize that the lower urinary tract symptoms previously attributed to the histologic changes in the prostate consistent with BPH are multifactorial in nature. It is estimated that more than 50% of men at age 60 years and nearly 90% at age 85 years will have histologic evidence of BPH. Of these men, however, only 50% will have clinical enlargement of the prostate and only 50% of these will become symptomatic.^{3,4} This demonstrates that BPH does not always result in benign prostatic enlargement or benign prostatic obstruction. In addition, lower urinary tract symptoms are very common in men in the absence of BPH and are as common and severe in age-matched women.⁵⁻⁷ The preferred term to describe the development of lower urinary tract complaints previously attributable to BPH in the male is now "lower urinary tract symptoms." Most studies still refer to these symptoms of BPH as the focus of study; therefore, BPH will continue to be used throughout this paper.

The pathophysiology of the overactive bladder and its contribution to lower urinary tract symptoms are beyond the scope of this paper. Therefore, only changes in the prostate associated with aging will be discussed, thereby elucidating the rationale for current medical therapy. Once again we must emphasize that not all patients presenting with lower urinary tract symptoms will have BPH, benign prostatic enlargement, or benign prostatic obstruction.

Determinants of prostate growth include aging, circulating androgens, 5 α -reductase, and androgen receptors. The prostate requires adequate levels of testosterone and the ability to convert testosterone to dihydrotestosterone to develop and grow.⁸ For this conversion of testosterone to dihydrotestosterone, an enzyme called 5 α -reductase is required. Genetic lack of this enzyme results in male pseudohermaphroditism and absence of prostatic development. Blockade of the testosterone to dihydrotestosterone conversion has been shown to decrease prostatic epithelial growth, eventually causing shrinkage of the gland. Beyond this androgenic control of growth, the exact mechanism whereby BPH develops is unknown. Intense research is under way to determine the molecular events underlying BPH. Undoubtedly this knowl-

edge will improve our understanding of the mechanism involved and will direct future prevention.

BPH is primarily a stromal process. Early research has demonstrated that the stromal to epithelial ratio is increased as hypertrophy develops (normal = 2:1; BPH = 5:1).⁹ This stromal enlargement is implicated in the mechanical obstruction (static component) of BPH. A significant component of the prostatic adenoma is smooth muscle. The smooth muscle in the adenoma, prostatic urethra, and the bladder neck is innervated by α -adrenergic nerve fibers.¹⁰ Smooth muscle tone in these tissues is responsible for the dynamic component of obstruction seen in patients with BPH.

... SYMPTOMS OF BPH ...

The symptoms associated with BPH have been classified as obstructive or irritative. Obstructive voiding symptoms include hesitancy, intermittency, weak forceless stream, straining to void, and urinary dribbling. Irritative voiding symptoms include frequency, urgency, nocturia, and sensation of incomplete voiding. To better quantify these symptoms, the American Urological Association (AUA) formed a Measurement Committee, which developed a symptom and quality-of-life questionnaire. It is called the International Prostate Symptom Score and has been translated into a number of languages (Table 1). Although the AUA score is validated to determine symptom severity and response to treatment, a lack of specificity is apparent, as there are similar scores between elderly women and men and a general increase with age. Factors such as bladder aging, changes in physiologic production of urine, and other factors associated with aging are not taken into consideration with this measurement tool. An additional tool to assess the degree to which symptoms affect activities of daily living is the BPH Impact Index.¹¹ Health-seeking behavior correlates better with bother than symptom scores. Therefore, patients seek treatment not necessarily for BPH symptoms but for the bother associated with those symptoms.

... EVALUATION ...

In this era of cost containment, careful analysis of diagnostic testing methods to determine the presence or severity of a disease is necessary. In 1994, the Agency for Health Care Policy and Research

recommended medical history, physical exam (to include digital rectal exam), urinalysis, serum creatinine, and the AUA symptom score as a baseline workup for BPH. Optional tests include urodynamic studies, voiding pressure flow studies, uroflow rates, postvoid residual determinations, and prostate-specific antigen (PSA). Tests not recommended include routine intravenous pyelogram, renal ultrasonography, or cystoscopy unless otherwise clinically indicated. The savings that result from not performing an intravenous pyelogram and cystoscopy are at least \$300 dollars per patient evaluated.² Although the majority of patients can be started on medical therapy without further testing, additional testing

can provide direction for therapy in patients with more complex presentations.

Urinalysis and urine cultures are useful for determining whether urinary tract infection or asymptomatic bacteriuria is present. In addition, urinalysis can determine whether microscopic hematuria is present. If hematuria is present, a full urologic evaluation of the urinary tract is indicated regardless of the symptoms of BPH. Elevated creatinine levels may indicate renal deterioration from obstruction and mandate further testing and possibly more aggressive treatment (ie, surgical relief of obstruction). A full discussion of the PSA blood test is beyond the scope of this article; however, PSA has

Table 1. Table1. American Urologic Association Symptom Score and International Prostate Symptom Score

	Not at All	Less than One Time in Five	Less than Half the Time	About Half the Time	More than Half the Time	Almost Always	
Over the past month, how often have you had a sensation of not emptying your bladder completely after you have finished urinating?	0	1	2	3	4	5	
Over the past month, how often have you had to urinate again less than 2 hours after you finished urinating?	0	1	2	3	4	5	
Over the past month, how often have you found you stopped and started again several times when you urinated?	0	1	2	3	4	5	
Over the past month, how often have you found it difficult to postpone urination?	0	1	2	3	4	5	
Over the past month, how often have you had a weak urinary stream?	0	1	2	3	4	5	
Over the past month, how often have you had to push or strain to begin urination?	0	1	2	3	4	5	
Over the past month, how many times did you most typically get up to urinate from the time you went to bed at night until the time you got up in the morning?	0	1	2	3	4	5	
Total I-PSS Score: _____							
	Delighted	Pleased	Satisfied	Mostly mixed	Disatisfied	Mostly unhappy	Terrible
If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about it?	0	1	2	3	4	5	6

IPSS = International Prostate Symptom Score.

become very useful as a potential screening test for the presence of prostate carcinoma.¹² Interested readers are referred to a prior article on prostate cancer screening and the use of the PSA test that appeared in this journal.¹³ Occult prostate cancer may be present in up to 20% of patients who present with symptoms of BPH. Clearly for most patients, it will be beneficial to know whether prostate cancer exists, especially if surgical intervention is planned.

Uroflowmetry has been used frequently to determine the presence of obstruction. The flow rate is defined as fluid expelled via the urethra in milliliters per second. Peak flow rates of less than 12-15 mL/s are suggestive of obstruction. Patients with low urinary flow rates respond better to surgical therapy, but this may not be true of medical therapy.^{14,15} Uroflow is limited by its ability to distinguish obstruction from impaired detrusor contractility.¹⁶ Although almost all urologists have mechanical flowmeters, home urinary flow testing also can be performed by the patient at home and recorded for physician evaluation. Basically, the patient is issued a specimen cup with cubic centimeter measurements and at midstream voids into the cup for 5 seconds. Patients can record these flow rates at various times. This simple test can be used to monitor BPH or measure the response to therapy without expensive equipment.

Postvoid residual determinations have been simplified with office-based ultrasound units, eliminating the need for catheterization. Many primary care offices now have this technology available to them. Data from a Veterans Administration (VA) trial demonstrated that a postvoid residual volume of more than 100 mL increased the risk of urinary retention in BPH patients receiving watchful waiting.¹⁷

Pressure flow studies are the most accurate tool to define obstruction, but they are hindered by lack of consensus about the values that indicate obstruction, as well as by the invasiveness of the procedure. Indications for pressure flow urodynamic studies are shown below:

- Young age (<50 years) or lifelong symptoms
- High residual urine volume
- Known or suspected neurologic disease
- Persistent symptoms after invasive procedure
- New or investigative treatment

In summary, the majority of patients can be started on medical therapy after the evaluation suggested by the Agency for Health Care Policy and

Research. It is also our opinion that a PSA test should be performed to screen for prostate cancer before the start of BPH treatments. In the following sections we attempt to familiarize the primary care provider with the myriad of treatment options present.

... TREATMENT OPTIONS ...

Watchful Waiting

Watchful waiting usually is recommended for men with mild symptom severity, as reflected by an AUA score of 8 or less and little bother. Patients with moderate to severe symptoms are also candidates for watchful waiting, but will often choose alternative therapies to include medical, minimally invasive, or surgical options. In a study comparing TURP with watchful waiting in patients with moderate symptoms, TURP was found to be more effective in reducing treatment failure and improving genitourinary symptoms.¹⁷ In patients with low symptom scores and little bother, the patient and doctor must weigh the risks and benefits of treatment versus watchful waiting.

Medical Therapies

Although the most widely used medical therapy for BPH includes 2 classes of medications, α -adrenergic blocking agents and 5 α -reductase inhibitors, the use of alternative agents has increased recently. The term alternative implies that the drug is not currently approved for product labeling by the US Food and Drug Administration (FDA). These agents account for 90% of prescriptions for BPH in Germany and almost 50% of prescriptions in Italy.¹⁸ The class of compounds, phytoestrogens, have been touted to have estrogen-like activity and thereby the ability to inhibit luteinizing hormone, causing shrinkage of the prostate with a resultant decrease in symptoms. The following are alternative agents for treatment of BPH:

- Alfalfa: estrogen-like compound
- Forage crops: estrogen-like compound
- Stinging nettle: neurotoxin
- *Serenoa repens* (saw palmetto): 5 α -reductase inhibitor (?)
- Pumpkin seed
- Rye pollen: 5 α -reductase inhibitor (?)

The most frequently used alternative agent is saw palmetto. Differing extraction methods account for its variable ability to inhibit 5 α -reductase and its differing effects in various clinical trials. Of 8 studies

evaluating saw palmetto, 7 reported a decrease in symptoms, 6 reported an increase in flow rates, and 4 reported a decrease in postvoid residual volume.¹⁹ All of these studies were short term, and in the largest trial patients did not have a change in PSA values at 6 months, bringing into question the 5 α -reductase activity of this agent. Many patients are trying alternative therapies or adding these agents to more conventional therapy; however, well-designed, controlled studies are lacking, thereby clouding the issue of these agents effectiveness or utility.

The rationale for α -blocker use in patients with BPH is relaxation of prostate smooth muscle. However, there is increasing evidence that symptom improvement is not directly related to relaxation and relief of obstruction. Numerous studies demonstrate a lack of correlation between improvements in flow rates and symptom changes.²⁰ Therefore, α -blockers also may affect sensory afferents or central nervous system pathways in addition to their action on the prostate. There are currently 3 FDA-approved α -blockers to treat BPH: tamsulosin, terazosin, and doxazosin.

Molecular cloning has allowed the identification of three subtypes of α_1 -receptors; α_{1a} , α_{1b} , and α_{1d} . Tamsulosin has partial selectivity for α_{1a} and α_{1d} , thereby avoiding the vascular effects attributable to α_{1b} .²¹ Highly selective α_{1a} -blockers are being developed by the pharmaceutical industry and are currently in clinical trials. In addition, nonselective and short-acting α -blockers are occasionally used (Table 2).

Terazosin, the first α -blocker approved for BPH, has been the one most extensively investigated. Doxazosin has been similarly studied, and the results of the clinical trials of these two long-acting α_1 -blockers are similar. In a multicenter, randomized, double-blind study comparing once-daily dosing of placebo with once-daily dosing of terazosin 2 mg, 5 mg, or 10 mg, the greatest symptom improvement was found with terazosin 10 mg.²¹ Seventy percent of patients realized a 30% improvement in symptom scores on the 10-mg dose. Peak flow rates increased 2.3 mL/s and the AUA score decreased 7.6 points with terazosin. Table 3 shows the most frequently reported side effects. Fawzy and colleagues reported on a 16-week, multicenter, randomized trial in which doxazosin doses were titrated according to response; 88% of the patients went to the maximal dose of 8 mg.²² Peak flow rates and changes in flow rate were similar to those seen with terazosin, but adverse events were slightly more frequent (Table 3). The Hytrin Community Assessment Trial randomized 2804 patients to

receive placebo or terazosin and allowed the physician to titrate the terazosin dose according to patient response.²³ Of those in the terazosin arm, 70% had their doses titrated to 10 mg, demonstrating that terazosin 10 mg is well tolerated. In an open label extension trial of terazosin with 494 patients, symptom improvements were maintained from 3 to 42 months.²⁴ Of the 213 patients (43.1%) who withdrew prematurely, 55 had therapeutic failure, 96 had adverse effects, and 62 were lost for administrative reasons. It must be recognized that extension trials overestimate improvements by reporting on responders. In an open label extension study of doxazosin, symptom and flow rate improvements also were maintained up to 42 months. Until data are available from the Medical Therapy of Prostatic Symptoms (MTOPS) trial sponsored by the National Institutes of Health, which is comparing placebo, doxazosin, finasteride, and both active medications over a 5-year period, the long-term efficacy of α -blockers will not be known.

Although the longer half-life of doxazosin (22 hours) compared with that of terazosin (12 hours) makes doxazosin more appropriate for once-daily dosing, this difference did not affect clinical outcomes. Both terazosin and doxazosin cause minimal changes in blood pressure in normotensive patients. The addition of these α -blockers in patients already receiving other antihypertensive agents is well tolerated. In an attempt to assess the cost effectiveness of pill-splitting an 8-mg tablet to provide two 4-mg doses, McDairmid and colleagues studied the effect

Table 2. α -Blocker Class and Dosage

Class	Dosage
Nonselective	
■ Phenoxybenzamine	10 mg twice daily
α_1-Blocker Short Acting	
■ Prazosin	2 mg twice daily
α_1-Blocker Long Acting	
■ Terazosin	5–10 mg every day
■ Doxazosin	4–8 mg every day
Partially Selective α_{1a}-Blocker Long Acting	
■ Tamsulosin	0.4–0.8 mg every day

of 4 mg versus 8 mg of doxazosin. He found a significant difference in symptom improvement with the 8-mg dose.²⁵ The difference in symptom scores between 4 mg and 8 mg of doxazosin is greater than the difference in symptom scores between 5 mg and 10 mg of terazosin, thereby bringing into question the cost-effectiveness of pill-splitting. Although both terazosin and doxazosin are recommended as evening medications, recent studies of doxazosin have shown morning dosages are as well tolerated.²⁶

Tamsulosin, a partially selective α_{1a} -blocker, has been investigated in 3 multicenter, randomized, double-blind studies. This agent was formulated to avoid the vascular effects of α_{1b} blockade. Lepor studied 756 American men with BPH and found changes in AUA symptom score and peak flow rates (Table 4).²⁷ Symptom score differences between the 0.4-mg and 0.8-mg doses did reach statistical significance. Changes in blood pressure were not significantly different between hypertensive and normotensive patients. As with the nonselective α_1 -blockers, symptom score and flow rate improvements were maintained in a 40-week extension trial with 418 patients (55%) participating. A lower incidence of asthenia was noted with tamsulosin compared with other long-acting α_1 blockers, but an unexplained increase in retrograde ejaculation also was noted.

Comparing 2 nonconcurrent, randomized, multicenter trials shows that terazosin produces greater improvements in symptom scores and flow rates than tamsulosin. These findings must be confirmed with a double-blind, randomized, placebo-controlled trial comparing terazosin with tamsulosin. The advantages of uroselectivity with tamsulosin may be

at the cost of beneficial effects on sensory afferents or central nervous system pathways. Furthermore, the lack of titration and the quicker effects on symptom scores and flow rates may be at the cost of overall efficacy.

Medications also can be used to shrink the size of the prostate gland and ultimately improve symptoms related to the static component of BPH. In the first large placebo-controlled multicenter trial with men treated with 5 mg of finasteride per day, a significant decrease in AUA scores, increase in maximum urinary flow rate, and decrease in prostate volume were seen (Table 5).²⁸ Adverse events and dropout rates were related to changes noted in sexual function such as decreased ejaculate and impotence. The open label extension trial demonstrated durable response to 48 months.²⁹ The Proscar Long-term Efficacy and Safety Study trial is a randomized, double-blind study with 1503 patients randomized to receive placebo and 1513 randomized to receive finasteride. This study demonstrated reduced symptoms and prostate volume, increases in urinary flow rates, reduced need for surgery, and a lower incidence of acute urinary retention in the finasteride arm.³⁰

One of the concerns with finasteride is the lowering of serum PSA levels. Patients should have a 50% reduction of the PSA level over a 6-month period while they are on finasteride. If this reduction does not occur, a urologic consultation is indicated to rule out the possibility of occult prostate cancer. On the other hand, some feel that finasteride could actually be a chemopreventive agent for prostate cancer; an ongoing NIH study, the Prostate Cancer Prevention Trial is evaluating this possibility.

Table 3. Comparison of the Efficacy and Side Effects of Doxazosin and Terazosin

Agent	Change in AUA Score	Change in Flow Rate (cc/s)	Dizziness (%)	Headache (%)	Asthenia (%)	Hypotension (Postural) (%)	Tachycardia (%)	Impotence (%)
Doxazosin	-5.7	+2.9	15.6	9.8	8.0	2.0	1.2	0.9
Terazosin	-7.6	+2.3	9.1	7.0	7.4	3.9	1.1	1.6

AUA = American Urologic Association.

Comparison of α -blocker therapy with 5 α -reductase inhibitor therapy was first reported in a 12-month VA cooperative trial. Terazosin was compared with placebo, finasteride, or a combination of finasteride and terazosin in 1200 men.³¹ In this study, finasteride was found to be no more effective than placebo. On further analysis, patients in this study had smaller prostates on average than those described in other published studies. A meta-analysis of finasteride studies found a statistical improvement over placebo in symptom scores and flow rates if the prostate volume was 40 g or greater at baseline.³² The MTOPS trial has enrolled more than 3200 patients in the same 4 treatment arms as the VA study, beginning in December 1995. This study is controlling for prostate size and may give additional evidence of efficacy and duration of response over a 5-year period. Slight improvement in symptoms and flow rates was seen in the combination arm of the VA study, and this finding also will be addressed with the MTOPS trial.

Summary of Medical Therapy. The use of α -blockers is usually recommended as first-line therapy for mild to moderate BPH symptoms because of the relative efficacy, rapid onset of action, and low cost. The value of a more selective α -blocker such as tamsulosin must be weighed against cost and efficacy. The Proscar Long-term Efficacy and Safety Study trial has demonstrated the long-term value of finasteride to decrease the need for surgery and progression to urinary retention. The effect of α -blockers on the natural history of BPH will not be known until the completion of the MTOPS trial. The value of combination

therapy (α -blockers and 5 α -reductase inhibitors) also must be determined. Research to predict which patients are destined to fail to respond to medical therapy may result in cost savings, because more appropriate therapies can be instituted earlier in the course of this disease process.

Surgical Therapy for BPH

Transurethral surgery of the prostate is still considered the gold standard by which other treatment modalities are measured. Patients with very large prostate glands (greater than 80-100 g) may be best served by open prostatectomy. Over the last few years, newer procedures that are less invasive and cause less morbidity have been developed (Table 6).

Table 4. Efficacy and Side Effects of Tamsulosin

Dosage	Change in AUA Score	Change in Flow Rate (cc/s)	Asthenia (%)	Dizziness (%)	Rhinitis (%)	Ejaculation (%)
0.4 mg	-8.3	+1.75	5	10	12	6
0.8 mg	-9.6	+1.78	5	11	15	18

AUA = American Urologic Association.
Adapted from reference 27.

Table 5. Efficacy and Side Effects of Finasteride

Time of Evaluation	Decrease in Prostate Volume (%)	Change in Peak Urinary Flow (cc/s)	Change in AUA Score	Decreased Libido (%)	Decreased Ejaculate Volume	Impotence Rate (%)
12 m	-19.2	+1.6	-2.6	3.3	2.6	3.7
36 m	-26.6	+2.4	-3.6	1.6	0.9	2.1
48 m	-23.8	+2.2	-3.6	1.5	0.3	2.1

AUA = American Urologic Association.

The use of these newer procedures results in outcomes somewhere between those of traditional surgical and medical therapy. However, absolute and relative indications for surgery remain (Table 7).

The more traditional therapies of open prostatectomy and TURP are the most effective treatments, yet cause the most morbidity. These operations are the best studied and have the greatest proven urodynamic improvements. TURP is associated with an 18% perioperative morbidity rate. These complications include transfusions in 5% to 15%, electrolyte disturbances in 2%, and stress incontinence in 1.5%

to 2.0%, as seen in combined series of Medicare patients in the late 1980s.¹ The impotence rate reported by the Agency for Health Care Policy and Research is 13%, but newer randomized trials with specific investigations of erectile function show a 1% to 8% incidence.³³ In general, TURP and open prostatectomy are still the procedures that create the greatest improvement in objective and subjective improvement and currently have acceptable morbidity.

Transurethral incision of the prostate is a procedure that was popularized by Orandi in the 1970s as a less invasive alternative to TURP.³⁴ Rather than resecting the tissue, one or two incisions are made in the prostate from the bladder neck to just proximal to the external sphincter, allowing the prostate to spring open. In properly selected patients (patients with smaller prostates with less than 20 g of adenoma), the results of transurethral incision of the prostate are similar to those of TURP with less morbidity. Transurethral incision of the prostate is one of the most underused but effective treatments for BPH.

Originally described by Bush in the 1960s to decrease the morbidity associated with TURP, transurethral electrovaporization of the prostate was not widely accepted until recently.³⁵ Rather than being resected, the tissue is vaporized with a broad-surfaced electrode that has a high cutting current. Early results are similar to those with TURP for smaller glands, with less need for transfusion. The combination of TURP and transurethral electrovaporization of the prostate is being studied and used for patients with larger prostate glands.

Laser prostatectomy was introduced in the early 1990s, but its use has diminished recently with the emergence of competing technologies. Types of laser prostatectomy include visual laser ablation of the prostate, contact laser ablation of the prostate, and interstitial laser therapy. Visual laser ablation of the prostate uses a specialized laser fiber that reflects the laser energy at 90-degree angles; it is applied under direct vision through a cystoscope, causing coagulative necrosis of the prostate tissue over time.³⁶ The most extensively studied laser energy is Nd:YAG (neodymium: yttrium-aluminum-garnet), which in controlled studies showed efficacy comparable to that of TURP (Table 8). The biggest drawback of visual laser ablation of the prostate is prolonged postoperative catheterization and a delay of weeks to months before recognizing an improvement in symptoms. Contact laser ablation of the prostate uses a quartz or silicon tip heated by laser

Table 6. Surgical and Minimally Invasive Therapies for Benign Prostatic Hyperplasia

<p>Minimally Invasive Devices</p> <ul style="list-style-type: none"> ■ Transurethral Microwave Thermotherapy ■ Transurethral Balloon Dilation ■ Transurethral Needle Ablation ■ Prostatic Stents ■ Interstitial Laser Coagulation <p>Surgical Therapies</p> <ul style="list-style-type: none"> ■ Transurethral Resection of the Prostate <ul style="list-style-type: none"> • By electrocautery • By laser coagulation ■ Transurethral Vaporization of the Prostate <ul style="list-style-type: none"> • By electrocautery • By laser ■ Transurethral Incision of the Prostate ■ Open Surgical Enucleation

Table 7. Indications for Surgery for Benign Prostatic Hyperplasia

<p>Absolute</p> <ul style="list-style-type: none"> ■ Urinary retention unresponsive to medical therapy ■ Detrusor decompensation <p>Relative</p> <ul style="list-style-type: none"> ■ Repeat episodes of hematuria ■ Repeat or persistent urinary tract infection ■ Severe symptoms ■ Bladder stones
--

energy to vaporize prostatic tissue. Vaporization of the prostatic tissue is a slow process, and contact laser ablation of the prostate has proven best suited for small prostates. It has been used sparingly. Interstitial laser therapy could be included in the discussion of minimally invasive techniques, but will be mentioned here. Laser energy can be applied directly into the substance of the prostate with a specially designed fiber that emits laser energy at 360 degrees. This fiber is placed into the adenoma transurethrally with a cystoscope. Because the fiber is placed into the adenoma, damage to the urethral lining and the subsequent irritative symptoms are avoided. Catheterization for 5 or more days is still required because of prostatic swelling. This technique can be performed with local or regional anesthesia and has favorable short-term results.³⁷

Summary of Surgical Procedures. Only TURP, transurethral incision of the prostate, and open prostatectomy have long-term results. TURP remains the gold standard with which to compare other treatment modalities. Use of visual laser ablation of the prostate and contact laser ablation of the prostate has declined with the evolution of transurethral electrovaporization of the prostate and resurgence of transurethral incision of the prostate. Interstitial laser therapy is a minimally invasive technique performed under local anesthesia with good short-term results, but it requires further evaluation before its role in the treatment of BPH is defined.

Minimally Invasive Therapies for BPH

In an attempt to achieve less morbidity than that associated with TURP but to achieve better outcomes than those associated with medical therapy, minimally invasive techniques have been developed. These include transurethral microwave thermotherapy, transurethral balloon dilation, transurethral needle ablation, and prostatic stents.

Transurethral balloon dilation is a procedure whereby a deflated balloon is placed through the urethra into the prostate gland under direct vision or ultrasound guidance. The balloon is then inflated to stretch the prostatic urethra until the prostatic capsule is fractured. Results suggest that more than 50% of patients have recurrence of original symptoms and durable results were few.³⁸ Few urologists currently use this technique because of these sub-optimal results.

In transurethral microwave thermotherapy, microwave heating of the prostate is performed through a transurethral microwave probe with a

rectal temperature-sensing probe. The urethral probe also contains a cooling mechanism so the urethral lining is not damaged. The thermotherapy causes coagulative necrosis over time with an average 12% to 18% loss of prostate volume, which corresponds with symptomatic and objective improvement. Recent studies have shown the amount of energy delivered correlates with shrinkage and symptom improvement.³⁹ The addition of an α -blocker perioperatively decreases the number of patients requiring catheterization past 1 week from 12% to 2%.⁴⁰ No difference was noted in symptom scores at 12 weeks in these studies. The α -blocker was stopped at 6 weeks. A comparison of transurethral microwave thermotherapy and α -blocker therapy showed transurethral microwave thermotherapy to be superior with respect to symptomatic and objective improvement at 6 months (Table 9).⁴¹ Refine-ments in the physics and amount of thermal energy to be delivered are currently being investigated.

Transurethral needle ablation uses radiofrequency as a source of energy to heat the prostatic tissue with subsequent coagulative necrosis. A special device with 2 radio antenna are placed into the prostatic adenoma at various locations under cystoscopic guidance to provide the thermal energy for coagulative necrosis to occur. Treatment effect is delayed because of swelling, and the best results are with smaller prostates. A recent trial comparing transurethral needle ablation with TURP shows sim-

Table 8. VLAP vs TURP in a Double-Blind, Randomized Trial

Treatment	Change in AUA Score at 6 Months	Change in Mean Flow Rate at 6 Months (mL/s)
VLAP (n = 19)	-11.4	+2.9
TURP (n =23)	-8.3	+9.9

AUA = American Urologic Association; VLAP = visual laser assisted ablation of the prostate; TURP = transurethral surgery of the prostate.
Adapted from reference 33.

ilar improvement in symptoms but lesser improvements in urodynamic parameters with transurethral needle ablation at 6 months.⁴² Additional studies have demonstrated destruction of adrenergic nerves, which may be contributory to symptom improvement with this and other forms of thermotherapy.⁴³ The improvement realized short term is durable to at least 3 years (Table 10).⁴⁴

Table 9. Terazosin vs Transurethral Microwave Thermotherapy at 2 Weeks and 6 Months

Treatment	AUA Score	Mean Maximum Flow Rate (mL/s)
Terazosin		
2 wk	14.0	10.9
6 mo	11.0	11.6
TUMT		
2 wk	15.8	7.7
6 mo	6.8	13.9

AUA = American Urologic Association; TUMT = transurethral microwave thermotherapy. Adapted from reference 41.

Table 10. Summary of World Literature for Transurethral Needle Ablation

Transurethral Needle Ablation	Change in AUA Score	Change in Maximum Flow Rate (mL/s)
At 12 mo (n = 546)	-13.1	+6.0
At 24 mo (n = 176)	-14.3	+6.3
At 36 mo (n = 88)	-14.7	+7.0

AUA = American Urologic Association Adapted from reference 44.

A therapy recently approved by the FDA that is appropriate for select patients with BPH is the prostatic stent.⁴⁵ These stents are expandable titanium metal mesh cylindrical tubes, which are placed into the prostatic urethra. Once these stents are in place, the prostatic mucosa overgrows the metal stent material, protecting the stent from exposure to urine. These stents can be placed under local anesthesia and could obviate the need for chronic Foley or suprapubic catheterization. The greatest utility for these stents may be in patients with urinary retention who are unable to tolerate other therapies.

Summary of Minimally Invasive Therapies. With refinements in treatment delivery and a better understanding of their effects, minimally invasive therapies are becoming an increasingly used modality in the treatment of BPH. The ultimate role of these therapies will be defined by longer term results and clinical trials comparing them with existing treatment modalities.

... CONCLUSIONS ...

BPH therapies are multiple and diverse. Many newer, yet unproved, techniques to treat BPH are now being proposed. Intense research will lead to a clearer understanding of the molecular biologic events leading to the development of BPH. Although the exact etiology is unknown, BPH growth is under androgenic and neurogenic control. The 5 α -reductase inhibitor finasteride and the α -adrenergic blockers terazosin, doxazosin, and tamsulosin are FDA-approved medical treatments. Alternative medical treatments (eg, saw palmetto) are also widely used. The gold standard of surgical therapy remains TURP or open prostatectomy, but less invasive options including transurethral incision of the prostate and coagulation procedures are available. Minimally invasive treatments based on laser and radio-frequency administration of heat to shrink the gland and the prostatic stent are also available. The next decade will see continued improvements in our understanding of BPH, and outcome research will further clarify the most effective therapies for this condition.

Acknowledgements

The authors thank Joanne De Ausen, Renee Mooneyhan, and Michelle Hohensee from the Center for Prostate Disease Research for making the figure and typing the manuscript.

... REFERENCES ...

1. Holtgrewe HL, Mebust WK, Dowd JB. Transurethral prostatectomy: Practice aspects of the dominant operation in American urology. *J Urol* 1989;141:248-253.
2. Holtgrewe HL, Bay-Nielsen H, Carlsson P. The economics of the management of lower urinary tract symptoms and benign prostatic hyperplasia. In: *Proceedings of the 4th International Consultation on Benign Prostatic Hyperplasia (BPH)*. 1997;4:63-80.
3. Barry MJ. The epidemiology and natural history of benign prostatic hyperplasia. *Curr Opin Urol* 1994;4:3-6.
4. Benign Prostatic Hyperplasia Guideline Panel. *Clinical Practice Guideline: Benign Prostatic Hyperplasia*. Rockville, MD: US Dept of Health and Human Services, Agency for Health Care Policy and Research; 1994. AHCPR publication no. 94-0582
5. Diokno AC, Brock BM, Brown BM. Prevalence of urinary incontinence and other urological symptoms in the noninstitutionalized elderly. *J Urol* 1986;136:1022-1025.
6. Lepor H, Machi G. Comparison of AUA symptom index in unselected males and females between fifty-five and seventy-nine years of age. *Urology* 1993;42:36-40.
7. Chai TC, Belville WD, Mcguire EJ. Specificity of the American Urological Association voiding symptom index: Comparison of unselected and selected samples of both sexes. *J Urol* 1993;150:1710-1713.
8. Thiypen AE, Silver RI, Guileyardo JM. Tissue distribution of steroid 5 alpha-reductase isozyme expression. *J Clin Invest* 1993;92:903-910.
9. Bartsch G, Muller HR, Oberholzer M. Electron microscopic stereological analysis of the human prostate and of benign prostatic hyperplasia. *J Urol* 1979;122:487-491.
10. Lepor H, Tang R, Meretyk S. The alpha-adrenoreceptor subtype mediating tension of the human prostate smooth muscle. *Prostate* 1993;22:640-642.
11. Barry MJ, Fowler FJ, O'Leary MP. Measuring disease-specific health status in men with benign prostatic hyperplasia. *Med Care* 1995;33:145-155.
12. Osterling JE. Prostate-specific antigen: Improving its ability to diagnose early prostate cancer. *JAMA* 1992;267:2236-2238.
13. Moul JW. Epidemiology and screening for prostate cancer. *Am J Manag Care* 1997;8:1200-1205.
14. Jensen KM, Jorgensen JB, Mogensen P. Urodynamics in prostatism, I: Prognostic value of uroflowmetry. *Scand J Urol Nephrol* 1988;22:109-117.
15. Witjes WP, Rosier FW, Wildt MJ. Urodynamic and clinical effects of terazosin therapy in patients with symptomatic benign prostatic hyperplasia. *J Urol* 1996;155:1317-1323.
16. Chancellor MB, Blaivas JG, Kaplan SA. Bladder outlet obstruction versus impaired detrusor contractility: The role of uroflow. *J Urol* 1991;145:810-812.
17. Wasson JH, Reda DJ, Bruskewitz RC. A comparison of transurethral surgery with watchful waiting for moderate symptoms of benign prostatic hyperplasia. The Veterans Affairs Cooperative Study Group on Transurethral Resection of the Prostate. *N Engl J Med* 1995;322:75-79.
18. Buck AC. Phytotherapy for the prostate. *Br J Urol* 1996;78:325-336.
19. Carraro JC, Raynaund JB, Koch G. Comparison of phytotherapy (Permixon) with finasteride in the treatment of benign prostatic hyperplasia: A randomized international study of 1098 patients. *Prostate* 1996;29:231-240.
20. Lepor H, Williford WO, Barry MJ. The impact of medical therapy on bother due to symptoms, quality of life, and global outcome and factors predicting response. Veterans Affairs Cooperative Studies Benign Prostatic Hyperplasia Study Group. *J Urol* 1998;160:1358-1367.
21. Lepor H. Prostate selectivity of alpha blockers: From receptor biology to clinical medicine. *Eur Urol* 1996;29(suppl):S12-S16.
22. Fawzy A, Braun K, Lewis GP. Doxazosin in the treatment of benign prostatic hyperplasia in normotensive patients: A multicenter study. *J Urol* 1995;154:105-109.
23. Roehrborn CG, Oesterling JE, Lloyd K. Hytrin Community Assessment Trial. Evaluation of the clinical effectiveness of terazosin vs placebo in the treatment of patients with symptomatic benign prostatic hyperplasia. *J Urol* 1995;153:272A.
24. Lepor H. Long-term efficacy and safety of terazosin in patients with benign prostatic hyperplasia. *Urology* 1995;45:406-413.
25. McDiarmid SA, Mcguirt R, Emery RT. A randomized double-blind study assessing the optimal dosage of doxazosin in treating patients with benign prostatic hyperplasia. *J Urol* 1998;159(suppl):S330.
26. Kaplan SA, Meade D, Alisera P. Doxazosin in physiologically and pharmacologically normotensive men with benign prostatic hyperplasia. *Urology* 1995;46:512-517.
27. Lepor H. Alpha-adrenergic blockers: A promising medical alternative to prostatectomy? *Rev Urol* 1999;1:45-54.
28. Gormley GJ, Stoner E, Bruskewitz RC. The effect of finasteride in men with benign prostatic hyperplasia. *N Engl J Med* 1992;327:1185-1191.
29. Moore E, Bracken B, Bremner W. Proscar: Five year experience. *Eur Urol* 1995;28:304-309.
30. McConnell JD, Bruskewitz R, Walsh P. The effect of finasteride on the risk of acute urinary retention and the need for surgical treatment among men with benign prostatic hyperplasia. Finasteride Long-Term efficacy and Safety Study group. *N Engl J Med* 1998;338:557-563.
31. Lepor H, Williford WO, Barry MJ. The efficacy of terazosin, finasteride, or both in benign prostatic hyperplasia. *N Engl J Med* 1996;335:533-539.
32. Boyle P, Gould AL, Roehrborn CG. Prostate volume predicts outcome of treatment of benign prostatic hyperplasia with finasteride: Meta-analysis of randomized clinical trials. *Urology* 1996;48:398-405.
33. Kabalin JN. Invasive therapies for benign prostatic hyperplasia, part I. 1997 *Monographs in Urology* 1997;18:19-47
34. Orandi A. Transurethral incision of the prostate compared with transurethral resection of the prostate in 132 matching cases. *J Urol* 1987;138:810-815.
35. Gallucci M. Transurethral electrovaporization of the prostate (TVP) vs TURP. A multicentric randomized comparative study. *Eur Urol* 1996;30:116-119.

- 36.** Cowles RS, Kabalin JN, Childs S. A prospective randomized comparison of transurethral resection to visual laser ablation of the prostate for treatment of benign prostatic hyperplasia. *Urology* 1995;46:155-160.
- 37.** Whitfield HN. Interstitial laser (Indigo) in BPH: A randomized controlled, prospective study. *J Urol* 1996;155:318A.
- 38.** Chiou RK, Lynch B. Randomized comparison of balloon dilation and transurethral incision for symptomatic benign prostatic hyperplasia: Long-term follow-up. *J Urol* 1993;149:464A.
- 39.** D'Ancona B, Van der Bij AK, Francisca EA. High energy TUMT in patients categorized according to the American Society of Anesthesiologists operative risk classification. *Urology* 1999;53:322-328.
- 40.** Djavan B, Shariat S, Fakhari M. Neoadjuvant and adjuvant alpha-blockade improves early results of high-energy TUMT for lower urinary tract symptoms of BPH. *Urology* 1999;53:251-259.
- 41.** Shariat S, Ghadwidel K, Marberger M. High-energy transurethral microwave thermotherapy (TUMT) versus alpha-blockade treatment for benign prostatic hyperplasia (BPH): A prospective randomized clinical trial. *J Urol* 1999;161:139-143.
- 42.** Roehrborn CG, Burkhard FC, Brushewitz RC. The effects of TUNA and TURP on pressure-flow urodynamic parameters: analysis of the US randomized study. *J Urol* 1999;162:92-97.
- 43.** Williams JC. Interstitial laser coagulation of the prostate: Effects on intraprostatic nerve fibers. *Tech Urol* 1996;2(3):130-135.
- 44.** Issa MM, Myrick SE, Symbas NP. The TUNA procedure for BPH: Basic procedure and clinical results. *Infect Urol* 1998;11:148-155.
- 45.** Kletscher BA, Oesterling JE. Prostatic stents. Current perspectives for the management of benign prostatic hyperplasia. *Urol Clin North Am* 1995;22:423-430.

CME QUESTIONS: TEST #059907

Johns Hopkins University School of Medicine is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to sponsor continuing medical education for physicians. Johns Hopkins University School of Medicine designates this continuing medical education activity for 1.0 credit hour in Category 1 of the Physician's Recognition Award of the American Medical Association. This CME activity was planned and produced in accordance with the ACCME Essentials and Standards for Commercial Support.

Instructions

After reading the article "Benign Prostatic Hyperplasia: New Concepts for the Millenium," select the best answer to each of the following questions. In order to receive 1 CME credit, at least 7 of the 10 answers must be correct. Estimated time for this activity is 1 hour. CME credits are distributed on a yearly basis.

1. Regarding benign prostatic hyperplasia (BPH), which of the following is true?

- a) almost 50% of patients over age 80 years will have histologic evidence of BPH
- b) all patients with BPH have urinary symptoms
- c) the amount of enlargement correlates with symptom severity
- d) "lower urinary tract symptoms" is now the term preferred rather than BPH to describe changes in the lower urinary tract in the aging male

2. The American Urologic Association (AUA) symptom index:

- a) is only appropriate in white males
- b) is validated to determine symptom severity and response to therapy
- c) determines the best treatment for an individual patient
- d) determines health-seeking behavior

3. All of the following are recommended in the patient with BPH symptoms except:

- a) history
- b) digital rectal exam
- c) serum creatinine level
- d) prostate-specific antigen (PSA) test
- e) AUA symptom score

4. The most appropriate treatment of patients with mild BPH symptoms (AUA score of <8) is:

- a) watchful waiting
- b) medical therapy
- c) minimally invasive therapy
- d) surgical therapy

5. Which of the following statements are true of medical therapy for BPH?

- a) α -Blockers relax the dynamic component of obstruction
- b) 5 α -Reductase inhibitors decrease the static component of obstruction
- c) alternative medicines have no proven efficacy
- d) Highly selective α c-receptor antagonists have fewer side effects than nonselective α_1 -receptor antagonists.
- e) nonselective α_1 -blockers are normally taken at bedtime to avoid side effects

6. The Veterans Administration Trial comparing terazosin (Hytrin) with finasteride (Proscar) reached all of the following conclusions except:

- a) terazosin therapy resulted in greater symptom improvement than finasteride therapy
- b) finasteride was no more effective than placebo in this trial
- c) the results were skewed because patients in this study on average had larger prostates

(CME QUESTIONS CONTINUED FROM PREVIOUS PAGE)

CME TEST FORM

AJMC Test #059907

Benign Prostatic
Hyperplasia: New
Concepts for the
Millennium

(Test valid through
July 31, 2000.
No credit will be given
after this date.)

Please circle your answers:

- 1. a b c d
- 2. a b c d
- 3. a b c d e
- 4. a b c d
- 5. a b c d e
- 6. a b c
- 7. a b c d
- 8. a b c d
- 9. a b c d
- 10. a b c d

(PLEASE PRINT CLEARLY)

Name _____

Address _____

City _____

State/ZIP _____

Phone # _____

Please enclose a check for \$10, payable to
American Medical Publishing, and mail with this form to:

The AJMC CME Test
American Medical Publishing
Suite 102
241 Forsgate Drive
Jamesburg, NJ 08831

PROGRAM EVALUATION

Johns Hopkins University School of Medicine appreciates your opinion on this article. Please fill out the questionnaire below, tear off along the dotted line, and mail along with your CME test form. We thank you for your evaluation, which is most helpful in planning future programs.

On the whole, how do you rate the information presented in the article?

excellent good fair poor

Is the information presented useful in your practice?

yes no

Do you have recommendations to improve this program?

yes no

Comments:

Were any portions of this program unsatisfactory or inappropriate?

yes no

If so, which?

Do you find the information presented in these articles to be fair, objective, and balanced?

yes no

Is there subject matter you would like included in the future?

yes no

Comments:

In your opinion, were the authors biased in their discussion of any commercial product or service?

yes no

Comments:

Program Title

Physician Name

Address

City, State, ZIP

Specialty

(CME QUESTIONS CONTINUED FROM PREVIOUS PAGE)

7. Which of the following statements are true regarding the rationale for using more selective α_1 -receptor antagonists?

- a) there is less orthostatic hypotension
- b) there is less asthenia
- c) there is no need for titration to the maximal dose
- d) there is decreased retrograde ejaculation

8. Which of the following were findings in The Proscar Long-Term Efficacy and Safety Trial?

- a) reduction in need for surgery with Proscar versus watchful waiting
- b) reduction in the incidence of urinary retention with Proscar versus watchful waiting
- c) confirmed 50% reduction of serum PSA level at 6 months
- d) a decreased chance of prostate cancer

9. Absolute and relative indications for surgery for BPH include:

- a) hematuria
- b) bladder stones
- c) repeat or persistent urinary tract infection
- d) urinary incontinence

10. Comparing open prostatectomy with transurethral surgery of the prostate (TURP) with transurethral incision of the prostate (TUIP), efficacy can be described as:

- a) open prostatectomy > TURP > TUIP
- b) open prostatectomy = TURP > TUIP
- c) open prostatectomy = TURP = TUIP
- d) open prostatectomy > TURP = TUIP

11. Which of the following use thermotherapy to achieve improvements in BPH symptoms?

- a) transurethral microwave therapy
- b) transurethral needle ablation
- c) transurethral balloon dilation
- d) prostatic stents

12. Possible reasons for choosing nonselective α_1 -blockers rather than more selective agents include:

- a) cost
- b) beneficial effects on nonprostate smooth muscle sites to include sensory afferents and central nervous system pathways
- c) lack of correlation between improvement in flow rates and symptom changes
- d) ability of these agents to help in control of hypertension