The American Journal of Medicine (2005) 118, 1331-1339

ELSEVIER

THE AMERICAN JOURNAL *of* MEDICINE®

REVIEW

Managing patients with lower urinary tract symptoms suggestive of benign prostatic hyperplasia

Mary McNaughton-Collins, MD, MPH, Michael J. Barry, MD

General Medicine Division, Massachusetts General Hospital, Boston, Mass.

KEYWORDS:
Benign prostatic hyperplasia;
Diagnosis;
Treatment

ABSTRACT: Many men with lower urinary tract symptoms suggestive of benign prostatic hyperplasia can be managed safely and effectively by primary care providers. After a basic evaluation to exclude other diseases that may cause lower urinary tract symptoms, quantifying the degree of symptoms and bother, and perhaps making an assessment of prostate size, the primary care provider can determine which men require immediate evaluation by a urologist and which men may choose among various treatment options, including watchful waiting and various single agent or combination medication strategies. Recent information about risk factors for disease progression has also helped to inform patient decisions on which treatment option is best for the individual patient. The purpose of this review is to provide primary care providers with an approach to the management of men with lower urinary tract symptoms suggestive of benign prostatic hyperplasia.

Benign prostatic hyperplasia is a common, bothersome problem in aging men, characterized by lower urinary tract symptoms and sometimes associated with urinary incontinence and sexual dysfunction. Men with lower urinary tract symptoms suggestive of benign prostatic hyperplasia have impaired health-related quality of life. The economic impact of benign prostatic hyperplasia and its treatments is substantial. Primary care providers frequently diagnose and treat men with this condition, especially because of the advent of effective medical therapy, in addition to minimally invasive and surgical therapies. The purpose of this review is to provide an approach to the management of men with lower urinary tract symptoms suggestive of benign prostatic hyperplasia.

Requests for reprints should be addressed to Michael J. Barry, MD, Chief, General Medicine Division, Massachusetts General Hospital, 50 Staniford Street, 9th Floor, Boston, MA 02114.

E-mail address: mbarry@partners.org

0002-9343/$ -see front matter © 2005 Elsevier Inc. All rights reserved.
doi:10.1016/j.amjmed.2004.12.033

Epidemiology and risk factors

The absence of a uniform, internationally accepted epidemiologic definition of benign prostatic hyperplasia has hindered understanding its true prevalence. Autopsy studies have shown that the prevalence of histologic benign prostatic hyperplasia increases with age from approximately 8% for men aged 30 to 39 years to 40% to 50% for men aged 50 to 59 years to more than 80% for men aged more than 80 years (Figure 1).[1] Population-based studies have shown that prostate volume increases with age,[2,3] whereas peak uroflow decreases with age.[4] However, from the patient perspective, it is the prevalence of clinical manifestations of benign prostatic hyperplasia that is most important. In a community-based study of Dutch men aged 50 to 74 years, the prevalence of benign prostatic hyperplasia ranged from 4% to 19%, depending on which of 8 case definitions of clinically important disease was used.[5]

The natural history of untreated benign prostatic hyperplasia is becoming clearer as long-term outcomes are being

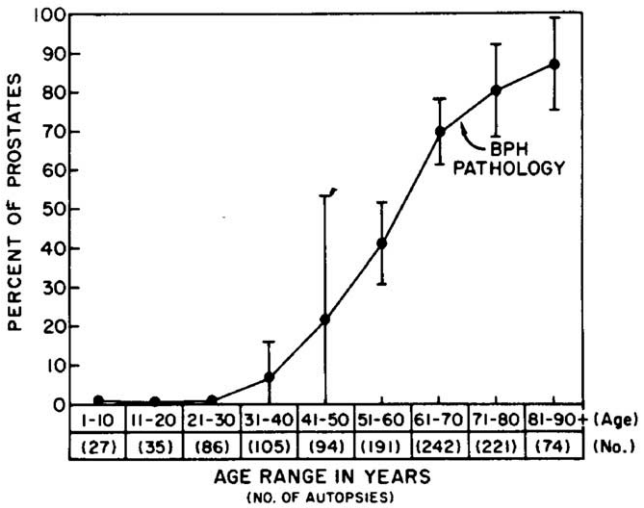

Figure 1 Prevalence of benign prostatic hyperplasia (BPH) histology with age in 1075 human autopsies. (From: Berry SJ, Coffey DS, Walsh PC, et al. The development of human benign prostatic hyperplasia with age. *J Urol.* 1984;132:474, with permission.)

defined in population-based studies[6-8] and placebo groups of large randomized trials.[9-11] Benign prostatic hyperplasia seems to be a progressive condition with certain baseline parameters, such as age, prostate volume, and serum prostate-specific antigen (PSA) level, allowing for risk stratification.[12,13] The risk of progression to benign prostatic hyperplasia-related surgery is approximately 1% to 2.5% per year,[9,10] and the risk of developing acute urinary retention, a painful condition warranting urgent treatment, is approximately 1% to 2% per year,[7-10,14-16] depending on the study population; other complications, such as chronic renal failure secondary to obstructive uropathy or severe urinary tract infection, seem to be rare.

The absence of a uniform epidemiologic definition of benign prostatic hyperplasia has also hindered the study of risk factors for benign prostatic hyperplasia. Race seems to influence the risk of having benign prostatic hyperplasia severe enough to warrant surgery, with Asian men less likely to undergo surgical treatment for benign prostatic hyperplasia than white and black men, who have similar risks.[17] Family history also seems to be a risk factor for benign prostatic hyperplasia, especially if the affected individual was younger than 60 years at diagnosis; twin studies indicate a greater than 3-fold higher risk in monozygotic twins with affected siblings.[18] Despite the apparent influence of family history on risk of benign prostatic hyperplasia, the exact role of genetic factors remains unclear.[19,20] Hepatic cirrhosis is negatively associated with benign prostatic hyperplasia, possibly because of the circulating levels of estrogens relative to androgens.[21] Physical activity decreases the frequency of lower urinary tract symptoms.[22,23] The relationship between cigarette smoking and benign prostatic hyperplasia is equivocal, because studies differ on whether there is a positive or negative association,[24] and similarly, the relationship between obesity and benign prostatic hyperplasia is ambiguous.[24]

Pathophysiology

Benign prostatic hyperplasia is characterized histopathologically by both stromal and epithelial cell hyperplasia, which develops primarily in the periurethral or transitional zones of the prostate, in contrast with prostate cancer, which generally arises in the peripheral zones (Figure 2).[25] As multiple small nodules grow and coalesce to form discrete adenomas, varying degrees of bladder outlet obstruction can result ("static" component of benign prostatic hyperplasia). In addition, smooth muscle in the bladder neck, prostate, and prostate capsule is richly innervated with alpha2-adrenergic receptors and also plays a role in bladder outlet obstruction ("dynamic" component of benign prostatic hyperplasia). The lower urinary tract symptoms characteristic of benign prostatic hyperplasia is thought to develop from a combination of static and dynamic

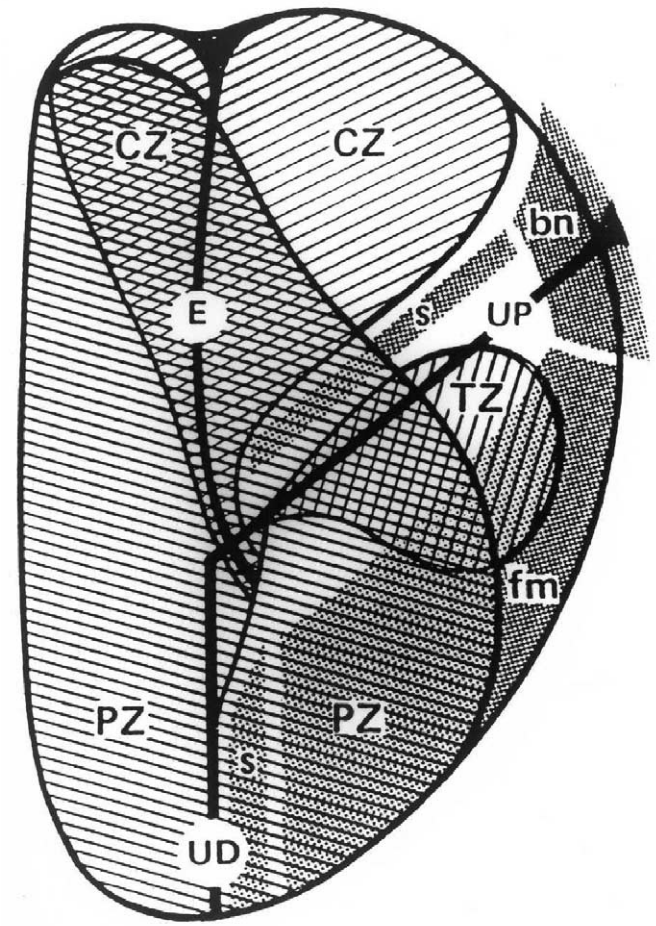

Figure 2 Sagittal diagram of distal prostatic urethral segment (UD), proximal urethral segment (UP), and ejaculatory ducts (E) showing their relationships to a sagittal section of the anteromedial nonglandular tissues (bladder neck [bn], anterior fibromuscular stroma [fm], preprostatic sphincter [s], distal striated sphincter [s]). These structures are shown in relation to a three-dimensional representation of the glandular prostate: central zone (CZ), peripheral zone (PZ), transitional zone (TZ). (From: McNeal J. Normal histology of the prostate. *Am J Surg Pathol.* 12:619;1988, with permission.)

factors, as well as the bladder's response to outflow obstruction.

Traditionally, symptoms have been grouped into two categories: bladder voiding (obstructive) symptoms, which presumably result primarily from bladder outlet obstruction, and bladder filling (irritative) symptoms, which presumably result primarily from detrusor instability.[26] However, this framework for explaining the symptoms associated with benign prostatic hyperplasia is overly simplistic, especially given that studies have shown the severity of lower urinary tract symptoms correlates poorly with the measurements of prostate size, the degree of bladder outlet obstruction, and the severity of uninhibited detrusor contractions. Moreover, improvement in symptoms with treatment does not correlate well with improvement in these objective parameters.

Although the cause of the development and progression of benign prostatic hyperplasia remains obscure, two factors seem to play an important role, namely, aging and the presence of functioning testes. Testosterone is converted by the 5-alpha-reductase enzyme into dihydrotestosterone, the major intraprostatic androgen. Men who were castrated before puberty or with congenital 5-alpha-reductase deficiency do not develop benign prostatic hyperplasia, and men who undergo medical or surgical castration later in life experience apoptosis of the prostatic epithelial cells. The factors postulated to control benign prostatic growth are frequently classified into extrinsic and intrinsic groups. The etiologic factors extrinsic to the prostate gland include androgens, estrogens, nonandrogenic endocrine factors, diet, and genetics, whereas intrinsic factors include various peptide growth factors.[27]

American Urological Association guideline for the diagnosis and treatment of benign prostatic hyperplasia

The Agency for Healthcare Policy and Research has developed[28] and the American Urological Association (AUA) has updated[29] a widely accepted guideline for the diagnosis and treatment of benign prostatic hyperplasia. The following recommendations are based on the consensus of a multidisciplinary panel of experts. For diagnostic tests, the panel used the terms "recommended," "optional," and "not recommended." The details of the grading for diagnostic and treatment recommendations can be found on the website www.auanet.org.

Diagnosis

Medical history (recommended)

Establishing a working clinical diagnosis of symptomatic benign prostatic hyperplasia requires a careful history because not all lower urinary tract symptoms are caused by benign prostatic hyperplasia, and not all men with benign prostatic hyperplasia have lower urinary tract symptoms. The clinician should elicit a medical history sufficiently detailed to cover all of the patient's symptomatic concerns, including fear of prostate cancer, and then focus on quantifying the lower urinary tract symptoms. Because symptom scores alone do not define the morbidity of a prostate problem as perceived by an individual patient (ie, the amount of bother may differ greatly among individuals with the same degree of symptom severity),[30] determining the amount of bother associated with the lower urinary tract symptoms is important and should be a major factor in deciding whether treatment is necessary. The American Urological Association Symptom Index (AUASI)[31] is a validated, seven-item questionnaire used for assessing the frequency of seven lower urinary tract symptoms (Figure 3). The International Prostate Symptom Score[32] contains the same symptom question set as the AUASI, and it also includes a separately scored quality of life question addressing the degree of bother associated with the symptoms.

Men with lower urinary tract symptoms related to benign prostatic hyperplasia generally have a balance of voiding and filling symptoms that slowly progress with age. Rapid onset, presentation before age 50 years, filling symptoms without voiding symptoms, and a single dominant symptom such as nocturia are "red flags" suggesting a diagnosis other than benign prostatic hyperplasia. Although prostate cancer is frequently a concern among men with lower urinary tract symptoms, men with lower urinary tract symptoms suggesting benign prostatic hyperplasia should be advised that there are no data to suggest that they have an increased risk of prostate cancer.[33-35] The differential diagnosis of lower urinary tract symptoms includes systemic diseases causing urinary frequency and nocturia, such as diabetes, heart failure, and hypercalcemia; bladder outlet obstruction caused by urethral strictures (clues to a stricture include prior genitourinary instrumentation, trauma, or sexually transmitted disease); prostatitis or male chronic pelvic pain syndrome (pain is not characteristic of benign prostatic hyperplasia); and neurologic disease affecting the bladder (relevant neurologic diseases include prior stroke, Parkinson's disease, or diabetic neuropathy). A complete list of medications should be obtained because many medications, especially over-the-counter cold and allergy remedies, can affect the urinary tract. Also, the clinician should inquire about any previous genitourinary malignancies, gross hematuria, and prior acute urinary retention or urinary tract infection. Voiding diaries[36] may be helpful in some patients, especially those with nocturia as the predominant symptom.

Physical examination (recommended)

A physical examination, including a digital rectal examination, focused abdominal examination, and focused neurologic examination, should be performed. The clinician should examine

	Not at all	Less than 1 time in 5	Less than half the time	About half the time	More than half the time	Almost always
1. Over the past month or so, how often have you had a sensation of not emptying your bladder completely after you finished urinating?	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
2. Over the past month or so, how often have you had to urinate again less than two hours after you finished urinating?	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
3. Over the past month or so, how often have you found you stopped and started again several times when you urinated?	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
4. Over the past month or so, how often have you found it difficult to postpone urination?	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
5. Over the past month or so, how often have you had a weak urinary stream?	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
6. Over the past month or so, how often have you had to push or strain to begin urination?	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐

7. Over the last 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 ☐ none	1 ☐ 1 time	2 ☐ 2 times	3 ☐ 3 times	4 ☐ 4 times	5 ☐ 5 or more times

Total AUA Score = sum of questions 1-7 = ___ ___

Figure 3 American Urological Association Symptom Index (with permission).[31]

the size, symmetry, and texture of the prostate. Benign prostatic hyperplasia characteristically produces a symmetrically enlarged, relatively firm prostate on examination. Asymmetry in texture or hard nodules suggest prostate cancer, but these findings are nonspecific. Studies have shown great interexaminer variability of digital rectal examination findings related to prostate cancer.[37] Because the digital rectal examination usually results in an underestimation of prostate size,[38] when a clinician thinks the prostate is enlarged, it usually is; however, it may be enlarged even if the clinician did not think it was. This discrepancy is important because for some benign prostatic hyperplasia medical therapies, efficacy is related to prostate size. The lower abdomen should be palpated for evidence of a grossly enlarged bladder. A focused neurologic examination should assess the lower extremities for peripheral neuropathy, and the perineal area and inner thighs for saddle anesthesia, because a patient with neuropathy or saddle anesthesia is more likely to have a neurologic disorder affecting the bladder than benign prostatic hyperplasia. In addition, patients considering alpha-blocker therapy for benign prostatic hyperplasia should have their baseline supine and standing blood pressure levels checked.

Urinalysis (recommended)

A urinalysis should be performed for evidence of pyuria or hematuria. Although benign prostatic hyperplasia can sometimes cause microscopic hematuria, this finding should prompt further evaluation to exclude a genitourinary malignancy.

Prostate-specific antigen (in select patients) (recommended)

The role of PSA testing in men with lower urinary tract symptoms has been controversial. Men with lower urinary tract symptoms suggestive of benign prostatic hyperplasia are not more likely to harbor prostate cancer,[33-35,39] and the diagnostic yield of PSA measurement as a screening test for prostate cancer deteriorates in the setting of benign prostatic hyperplasia because of the lower specificity. On the basis of these concerns, the initial 1994 Agency for Health Care Policy and Research guideline[28] determined that PSA testing was optional and advised making a shared decision about whether to pursue this diagnostic test in the evaluation of benign prostatic hyperplasia with each individual patient. However, more recent data show that serum PSA is a predictor of the natural history of benign prostatic hyperplasia; men with higher serum PSA levels have a higher risk of future growth of the prostate, symptom and flow-rate deterioration, acute urinary retention, and benign prostatic hyperplasia-related surgery.[13,40-42] Therefore, the revised 2003 AUA guideline[29] actually recommends PSA testing, at least in select men, that is, men likely to have at least a 10-year life expectancy (~75 years with average comorbidity) and in whom the known presence of prostate cancer would change management or the PSA measurement would change the management of the patient's lower urinary tract symptoms. In the absence of strong evidence that PSA testing improves patient outcomes, the panel made this recommendation on the basis of their expert opinion and consensus.

Urine cytology (in select men) (optional)

Urine cytology may be considered in men with a predominance of irritative symptoms, especially with a history of smoking or other risk factors, to aid in the diagnosis of bladder cancer as the cause of the lower urinary tract symptoms, rather than benign prostatic hyperplasia.

Urinary flow rate (optional)

After the initial evaluation of men with lower urinary tract symptoms suggestive of benign prostatic hyperplasia, urinary flow rate recording (uroflowmetry), which can be done in the urologist's office, may be helpful in men with a complex medical history and in men who prefer aggressive treatment for their bothersome lower urinary tract symptoms. Uroflowmetry is generally not necessary before watchful waiting or medical therapy.

Postvoid residual (optional)

After the initial evaluation of the patient, estimation of postvoid residual urine by ultrasound may be appropriate. As with uroflowmetry, postvoid residual measurements are not necessary before embarking on a treatment course of either watchful waiting or medical therapy. However, as with uroflowmetry, postvoid residual measurements may be helpful in sorting out patients with complicated medical histories and for patients desiring invasive therapy for their bothersome benign prostatic hyperplasia symptoms.

Pressure-flow urodynamic study (optional for men considering invasive benign prostatic hyperplasia therapies)

The simultaneous measurement of bladder pressure and urine flow, the pressure-flow urodynamic study, is considered the gold standard for the diagnosis of bladder outlet obstruction.[43] This invasive study is not indicated to predict the response to medical therapy but is considered optional in men before surgical therapy. There is not universal agreement regarding the use of this test, however, because many men with lower urinary tract symptoms who have equivocal or even no evidence of bladder outlet obstruction according to pressure-flow results go on to have good symptomatic results with surgical treatment.[44] The pressure-flow study may be particularly helpful in sorting out symptoms in men with concomitant neurologic diseases known to affect bladder function or in men with persistent symptoms after surgical therapy.

Urethrocystoscopy (optional for men considering invasive benign prostatic hyperplasia therapies)

The endoscopic appearance of the prostatic urethra and bladder does not predict the response to therapy but may guide the choice of therapy in men who have already decided to proceed with an invasive treatment approach. Urethrocystoscopy may be appropriate for men with a history of microscopic or gross hematuria or risk factors for a urethral stricture.

Transrectal or transabdominal prostate ultrasound (optional for men considering invasive benign prostatic hyperplasia therapies)

Although transrectal or transabdominal prostate ultrasound is not necessary before watchful waiting or medical therapy, they may be considered when minimally invasive or surgical treatments are chosen, because the size and shape of the prostate gland may help surgeons and patients select among the various minimally invasive and surgical therapies available.

Serum creatinine (not recommended)

Because of the rarity of obstructive uropathy, the revised Agency for Health Care Policy and Research guideline[29] recommends against routine measurements of serum creatinine in the initial evaluation of men with lower urinary tract symptoms suggestive of benign prostatic hyperplasia.

Filling cystometrography and imaging of the upper urinary tract by ultrasonography or excretory urography (not recommended)

These diagnostic tests are not recommended for the evaluation of a typical patient with lower urinary tract symptoms suggestive of benign prostatic hyperplasia; they may be helpful in evaluating certain patients with hematuria, urinary tract infection, renal insufficiency, or a history of urolithiasis or urinary tract surgery.

Treatment

Until recently, the main goal of the treatment of benign prostatic hyperplasia was the reduction in bothersome lower urinary tract symptoms; newer data have suggested that another legitimate goal of benign prostatic hyperplasia therapy is the reduction in the risk of future complications, such as acute urinary retention and progression to benign prostatic hyperplasia-related surgery. For the goal of reduction in bothersome symptoms, it is important for clinicians to quantify the frequency and severity of a patient's lower urinary tract symptoms, as well as the degree of bother associated with the symptoms to help the patient make the right treatment decision. For the goal of reduction in risks of future complications, it is important to assess the size of the prostate gland, because prostate size predicts these future risks.

Watchful waiting

Watchful waiting, the treatment strategy whereby men are monitored by their clinicians but do not receive an active

therapeutic intervention, is generally the preferred approach for men with mild benign prostatic hyperplasia symptoms (mild symptoms, AUA scores 0-7, are rarely bothersome) or moderate (AUA scores 8-19) to severe (AUA scores 20-35) symptoms without much associated bother. Watchful waiting includes the periodic reassessment of symptoms and bother, and counseling about simple measures to relieve symptoms such as avoiding certain medications (eg, over-the-counter cold and allergy preparations that may exacerbate symptoms), decreasing caffeine and alcohol, and decreasing fluid intake before bedtime. Counseling might also include advice to some men about their risk of future benign prostatic hyperplasia complications and the option of medical intervention if a man has a large prostate gland producing symptoms (even if the man has little associated symptom bother), because men with larger prostate glands may be at increased risk of clinical progression.

Alpha blockers

Alpha-blocker therapy is based on the theory that lower urinary tract symptoms attributed to benign prostatic hyperplasia are caused, in part, by alpha1-adrenergic mediated contraction of smooth muscle in the prostate and bladder neck, leading to bladder outlet obstruction.[45] A variety of alpha-adrenergic receptor blockers such as alfuzosin, doxazosin, tamsulosin, and terazosin are available.[46] The onset of action of alpha-blocker therapy is generally rapid, but some alpha blockers require titration, with higher doses achieving greater symptom improvement (Table 1). In addition, alpha-blocker therapy does not decrease the prostate size or PSA level; the effect of alpha-blocker therapy is independent of prostate size.[46] Although the various alpha blockers seem to have similar clinical effectiveness, the side effect profiles may vary to some degree, depending on the selectivity of the agent. The side effects of alpha-blocker therapy primarily include orthostatic hypotension, dizziness, asthenia, ejaculatory problems, and nasal congestion. Of note, caution is warranted in combining alpha-blocker therapy with the phosphodiesterase type 5 inhibitors used to treat erectile dysfunction (which commonly coexists with benign prostatic hyperplasia), because of the concern of inducing hypotension. Sildenafil at doses higher than 25 mg should not be taken within 4 hours of an alpha blocker, vardenafil should not be taken at all by men receiving alpha blockers, and tadalafil should be taken with tamsulosin only at the lower dose of 0.4 mg daily.

Although randomized clinical trials have shown that alpha-blocker therapy reduces symptoms and clinical progression, as defined primarily by worsening symptoms,[10,47] these agents do not reduce the risk of progression to surgery or acute urinary retention.[10] In addition, alpha-blocker monotherapy can no longer be considered an optimal strategy to manage concomitant hypertension;[48] in general, hypertension should be managed separately from benign prostatic hyperplasia.

Table 1 Medications commonly used in the treatment of men with lower urinary tract symptoms attributed to benign prostatic hyperplasia

Drug	Tablet/capsule sizes (mg)	Recommended dose steps
Alpha blockers		
Alfuzosin*	2.5	2.5 mg TID
Alfuzosin extended release*	10	10 mg QD
Doxazosin	1, 2, 4, 8	1, 2, 4, 8 mg QD
Doxazosin GITS*	4, 8	4, 8 mg QD
Tamsulosin	0.4	0.4, 0.8 mg QD
Terazosin	1, 2, 5, 10	1, 2, 5, 10 mg QD
5-alpha-reductase inhibitors		
Finasteride	5	5 mg QD
Dutasteride	0.5	0.5 mg QD

QD = every day; TID = three times per day; GITS = Gastrointestinal Therapeutic System.
*Not available in the United States as of this writing.

5-alpha-reductase inhibitors

Finasteride and dutasteride are the 5-alpha-reductase inhibitors available to date. These agents block conversion of testosterone to dihydrotestosterone. For symptom reduction, these agents work less quickly and less effectively than alpha blockers. They are not first-line therapy for patients with bothersome symptoms and no evidence of prostate enlargement. A 5-alpha-reductase inhibitor can be considered for men who have symptoms and an enlarged prostate as determined by digital rectal examination. If a PSA is available, a cutoff of more than 2.5 ng/mL has an approximate 0.70 positive predictive value for a prostate larger than 40 g, and an approximate 0.70 negative predictive value.[49] However, 5-alpha-reductase inhibitors do reduce prostate size,[9,50] and they address the treatment goal of prevention of disease progression, by reducing the rate of progression to surgery (from 8.3% to 4.2% over 4 years in one trial) or acute urinary retention (from 6.6% to 2.8% in the same trial) for men with larger prostates.[9] Data from the same trial indicate that approximately 15 patients with larger prostates would have to take finasteride for 4 years to prevent the development of acute retention or progression to surgery in one of those patients. These agents can also decrease gross hematuria because of benign prostatic hyperplasia in men in whom other causes, such as bladder or prostate cancer, have been ruled out. The main side effects include ejaculatory dysfunction, erectile dysfunction, and decreased libido; however, in a long-term study of 5-alpha-reductase inhibitor versus placebo, any adverse effects were noted in the first year.[50] The 5-alpha-reductase inhibitors also decrease the PSA level by approximately 50%.[50,51] Although these agents do not seem to interfere with the detection of prostate cancer, the PSA levels must be interpreted differently. The simplest strategy is to double the measured PSA and then interpret it as usual.[52]

Of note, finasteride has been studied as chemoprevention for prostate cancer; although finasteride reduced the 7-year

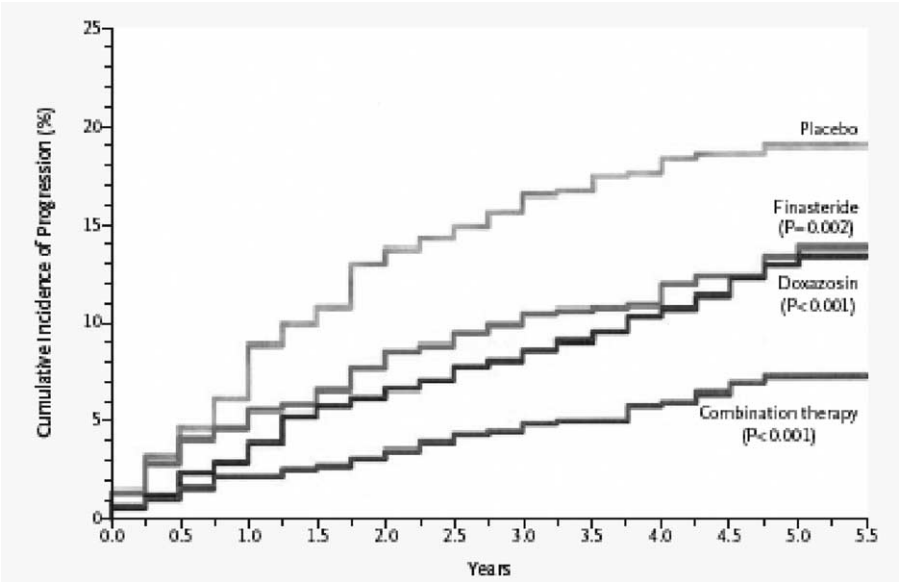

Figure 4 Combination therapy for benign prostatic hyperplasia. The cumulative incidence of progression of benign prostatic hyperplasia on placebo, finasteride, doxazosin, and combination therapy with finasteride and doxazosin. Progression was defined by an increase of at least 4 points over baseline in the American Urological Association symptom score, acute urinary retention, urinary incontinence, renal insufficiency, or recurrent urinary tract infection. *P* values are for the comparison with placebo. (From: McConnell, JD, Roehrborn, CG, Bautista, OM, et al. The long-term effect of doxazosin, finasteride and combination therapy on the clinical progression of benign prostatic hyperplasia. *New Engl J Med.* 2003;349:2392, with permission, Copyright © 2003, Massachusetts Medical Society, All rights reserved.)

cumulative risk of a prostate cancer diagnosis from 24.4% with placebo to 18.4%, the risk of a high-grade prostate cancer increased from 5.1% with placebo to 6.4% with finasteride.[52] The apparent increase in high-grade cancers may simply represent a grading artifact attributable to finasteride.[53] These controversial findings should be covered in a discussion on whether to prescribe finasteride or dutasteride for men with benign prostatic hyperplasia.

Combination therapy

The combination of an alpha blocker and a 5-alpha-reductase inhibitor is an attractive option because of the different mechanisms of action of the agents. The use of combined treatment seems most appropriate for men with bothersome symptoms necessitating quick relief and who also have a substantial risk of progression. Although short-term (<1 year) treatment with combination therapy was shown to be no more effective for symptom relief than alpha-blocker therapy alone,[54] the long-term (5-year) combination of finasteride plus doxazosin (Figure 4)[10] decreased the risk of overall clinical progression of benign prostatic hyperplasia, defined largely by worsening symptoms (an increase of at least 4 points over baseline in the AUA symptom score), more than treatment with either drug alone. In addition, combination therapy or finasteride alone (not doxazosin alone) reduced the risk of acute urinary retention and the need for invasive therapy. The side effects reported with combination therapy reflect the combined side effect profiles of both alpha blockers and 5-alpha-reductase inhibitors.

Complementary and alternative medicines

Although the use of phytotherapy for "prostate health" is widespread nationally and internationally, the guideline panel considers complementary and alternative medicines for benign prostatic hyperplasia as "emerging therapies" and does not recommend them as treatments for benign prostatic hyperplasia at this time. Meta-analyses have demonstrated some improvement in lower urinary tract symptoms with phytotherapies, such as extracts of saw palmetto,[55] rye grass pollen,[56] Pygeum africanum,[57] and beta sitosterols.[58] However, the effects seem to be small, and the trials have generally had methodologic problems, such as short durations of follow-up and incomplete outcome assessments. The mechanisms of action of these preparations are poorly defined and their compositions vary, so standardization has been a concern.

Minimally invasive therapies

Minimally invasive office-based techniques have been developed to relieve lower urinary tract symptoms without hospitalization and with less sedation and fewer side effects. Transurethral microwave thermotherapy heats and coagulates prostate tissue using a microwave antenna, transurethral needle ablation uses radiofrequency needles placed directly into the prostate to generate heat and cause coagulation, and transurethral water-induced thermotherapy uses heated water circulated through a catheter system and pressure from a balloon within the prostatic urethra to cause coagulation necrosis of prostatic tissue. The mechanisms by which these procedures work are poorly understood, and their long-term effectiveness

remains unclear. However, they seem to produce an initial level of symptom relief intermediate between drug therapy and transurethral prostatectomy.

Surgical therapies

The "gold standard" for treating symptomatic benign prostatic hyperplasia is still transurethral prostatectomy. Surgical intervention is an appropriate option for men with very bothersome lower urinary tract symptoms and who have acute urinary retention or other benign prostatic hyperplasia-related complications. Generally, men will have tried medical therapy before proceeding with surgery, but this is not a requirement, because some men may simply prefer the most definitive therapy initially for their bothersome symptoms. As with other benign prostatic hyperplasia decisions, it is ultimately the patient's view of the risks and benefits that drive the choice of treatment. Transurethral prostatectomy generally requires a brief hospital stay and a temporary indwelling catheter. In a randomized clinical trial comparing transurethral prostatectomy and watchful waiting,[59] the patients who underwent transurethral prostatectomy experienced a reduction in both symptoms and benign prostatic hyperplasia complications. In addition, the risks of sexual dysfunction and incontinence, traditionally considered potential side effects of transurethral prostatectomy, were no greater with transurethral prostatectomy. Retrograde ejaculation, however, is a common outcome of transurethral prostatectomy, and men should be warned to expect this result when considering transurethral prostatectomy. The symptom improvement with transurethral prostatectomy is generally durable, with a 5-year risk for reoperation of only 5%.[60] Although the standard transurethral prostatectomy uses a wire electrode to resect obstructing tissue, there are variations on this theme that involve rolling electrodes or laser energy to vaporize the prostate tissue. Although these methods may cause less bleeding in the short term, the longer term outcomes are not yet defined. For men with very large prostates in whom transurethral prostatectomy may be challenging, an open prostatectomy is an option, which also generally results in dramatic and durable symptom improvement. The guideline suggests that the choices of surgical approach (open or endoscopic) and energy source (electroresection vs laser) are technical decisions based on the patient's prostate size, the surgeon's experience and judgment, and the patient's comorbidities.[49]

References

1. Berry SJ, Coffey DS, Walsh PC, Ewing LL. The development of human benign prostatic hyperplasia with age. *J Urol*. 1984;132:474-479.
2. Masumori N, Tsukamoto T, Kumamoto Y, et al. Japanese men have smaller prostate volumes but comparable urinary flow rates relative to American men: results of community based studies in 2 countries. *J Urol*. 1996;155:1324-1327.
3. Bosch J, Hop W, Niemer A, et al. Parameters of prostate volume and shape in a community based population of men 55 to 74 years old. *J Urol*. 1994;152:1501-1505.
4. Girman C, Panser L, Chute C, et al. Natural history of prostatism: urinary flow rates in a community-based study. *J Urol*. 1993;150:887-892.
5. Bosch J, Hop WC, Kirkels WJ, Schroder FH. Natural history of benign prostatic hyperplasia: appropriate case definition and estimation of its prevalence in the community. *Urology*. 1995;46:34-40.
6. Jacobsen SJ, Girman CJ, Guess HA, et al. Natural history of prostatism: longitudinal changes in voiding symptoms in community dwelling men. *J Urol*. 1996;155:595-600.
7. Jacobsen S, Jacobson D, Girman C, et al. Natural history of prostatism: risk factors for acute urinary retention. *J Urol*. 1997;158:481-487.
8. Meigs J, Barry M, Giovannucci E, et al. Incidence rates and risk factors for acute urinary retention: the health professionals followup study. *J Urol*. 1999;162:376-382.
9. McConnell JD, Bruskewitz R, Walsh P, et al. 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.
10. McConnell JD, Roehrborn CG, Bautista OM, et al. The long-term effect of doxazosin, finasteride, and combination therapy on the clinical progression of benign prostatic hyperplasia. *N Engl J Med*. 2003; 349:2387-2398.
11. Roehrborn CG, Bruskewitz R, Nickel JC, et al. Sustained decrease in incidence of acute urinary retention and surgery with finasteride for 6 years in men with benign prostatic hyperplasia. *J Urol*. 2004;171: 1194-1198.
12. Roehrborn C, Bruskewitz R, Nickel G, et al. Urinary retention in patients with BPH treated with finasteride or placebo over 4 years. Characterization of patients and ultimate outcomes. *Eur Urol*. 2000; 37:528-536.
13. Roehrborn CG, Malice M, Cook TJ, Girman CJ. Clinical predictors of spontaneous acute urinary retention in men with LUTS and clinical BPH: a comprehensive analysis of the pooled placebo groups of several large clinical trials. *Urology*. 2001;58:210-216.
14. Andersen J, Nickel J, Marshall V, et al. Finasteride significantly reduces acute urinary retention and need for surgery in patients with symptomatic benign prostatic hyperplasia. *Urology*. 1997;49:839-845.
15. Wasson J, Reda D, Bruskewitz R, et al. A comparison of transurethral surgery with watchful waiting for moderate symptoms of benign prostatic hyperplasia. *N Engl J Med*. 1995;332:75-79.
16. Barry MJ, Fowler FJ, Bin L, et al. The natural history of patients with benign prostatic hyperplasia as diagnosed by North American urologists. *J Urol*. 1997;157:10-15.
17. Platz EA, Kawachi I, Rimm EB, et al. Race, ethnicity, and benign prostatic hyperplasia in the health professionals follow-up study. *J Urol*. 2000;163:490-495.
18. Partin AW, Page WF, Lee BR, et al. Concordance rates for benign prostatic disease among twins suggest hereditary influence. *Urology*. 1994;44:646-650.
19. Sanda MG, Beaty TH, Stutzman RE, et al. Genetic susceptibility of benign prostatic hyperplasia. *J Urol*. 1994;152:115-119.
20. Sanda MG, Doehring CB, Binkowitz BS, et al. Clinical and biological characteristics of familial benign prostatic hyperplasia. *J Urol*. 1997; 157:876-879.
21. Cetinkaya M, Cetinkaya H, Ulusoy E, et al. Effect of postnecrotic and alcoholic hepatic cirrhosis on development of benign prostatic hyperplasia. *Prostate*. 1998;36:80-84.
22. Platz EA, Kawachi I, Rimm EB, et al. Physical activity and benign prostatic hyperplasia. *Arch Intern Med*. 1998;158:2349-2356.
23. Meigs JB, Mohr B, Barry MJ, et al. Risk factors for clinical benign prostatic hyperplasia in a community-based population of healthy aging men. *J Clin Epidemiol*. 2001;54:935-944.
24. Boyle P, Liu G, Jacobsen S, et al. Epidemiology and natural history. In: Chatelain C, Denis L, Foo K, et al., eds. *Benign Prostatic Hyperplasia (5th International Consultation on BPH)*. Health Publication, Ltd., Jersey, UK. (distributed by: Plymbridge Distributors, Ltd., Plymouth, UK); 2001:19-68.

25. McNeal J. Normal histology of the prostate. *Am J Surg Pathol*. 1988; 12:619-633.
26. Abrams P. New words for old: lower urinary tract symptoms for "prostatism." *BMJ*. 1994;308:929-930.
27. Lee C, Cockett A, Cussenot O, et al. Regulation of prostate growth. In: Chatelain C, Denis L, Foo K, et al., eds. *Benign Prostatic Hyperplasia (5th International Consultation on BPH)*. Health Publication, Ltd., Jersey, UK. (distributed by: Plymbridge Distributors, Ltd., Plymouth, UK); 2001:81–106.
28. McConnell JD, Barry MJ, Bruskewitz RC, et al. Benign prostatic hyperplasia: diagnosis and treatment. Clinical Practice Guideline, Number 8. Agency for Health Care Policy and Research, Public Health Service, U.S. Department of Health and Human Services, Rockville, MD; 1994.
29. American Urological Association Practice Guidelines Committee. American Urological Association guideline on management of benign prostatic hyperplasia (2003). Chapter 1: Diagnosis and treatment recommendations. *J Urol.* 2003;170:530-547.
30. Barry MJ, Fowler FJ, O'Leary MP, et al. Measuring disease-specific health status in men with benign prostatic hyperplasia. *Med Care*. 1995;33:AS145-AS155.
31. Barry MJ, Fowler FJ Jr, O'Leary MP, et al. The American Urological Association symptom index for benign prostatic hyperplasia. The Measurement Committee of the American Urological Association. *J Urol*. 1992;148:1549-1557.
32. Barry M, Batista J, Donovan J, et al. Measuring the symptoms and health impact of benign prostatic hyperplasia and its treatments. In: Chatelain C, Denis L, Foo K, et al., eds. *Benign Prostatic Hyperplasia (5th International Consultation on BPH)*. Health Publication, Ltd., Jersey, UK. (distributed by: Plymbridge Distributors, Ltd., Plymouth, UK); 2001:203–225.
33. Porter CR, Kim J. Low AUA symptom score independently predicts positive prostate needle biopsy: results from a racially diverse series of 411 patients. *Urology*. 2004;63:90-94.
34. Blanker MH, Groeneveld FPMJ, Thomas S, et al. Prostate cancer detection in older men with and without lower urinary tract symptoms: a population-based study. *J Am Geriatr Soc*. 2003;51:1041-1042.
35. Young JM, Muscatello DJ, Ward JE. Are men with lower urinary tract symptoms at increased risk of prostate cancer? A systematic review and critique of the available evidence. *BJU Int*. 2000;85:1037-1048.
36. Abrams P, Klevmark B. Frequency volume charts: an indispensable part of lower urinary symptom assessment. *Scand J Urol Nephrol*. 1996;179:47-53.
37. Smith D, Catalona W. Interexaminer variability of digital rectal examination in detecting prostate cancer. *Urology*. 1995;45:70-74.
38. Roehrborn C, Girman C, Rhodes T, et al. Correlation between prostate size estimated by digital rectal examination and measured by transrectal ultrasound. *Urology*. 1997;49:548-557.
39. Catalona W, Richie J, Ahmann F, et al. Comparison of digital rectal examination and serum prostate specific antigen in the early detection of prostate cancer: results of a multicenter clinical trial of 6,630 men. *J Urol.* 1994;151:1283-1290.
40. Roehrborn C, Boyle P, Gould A, Waldstreicher J. Serum prostate-specific antigen as a predictor of prostate volume in men with benign prostatic hyperplasia. *Urology*. 1999;53:581-589.
41. Roehrborn C, McConnell J, Lieber M, et al. Serum prostate-specific antigen concentration is a powerful predictor of acute urinary retention and need for surgery in men with clinical benign prostatic hyperplasia. *Urology*. 1999;53:473-480.
42. Roehrborn CG, McConnell J, Bonilla J, et al. Serum prostate specific antigen is a strong predictor of future prostate growth in men with benign prostatic hyperplasia. PROSCAR long term efficacy and safety study. *J Urol*. 2000;163:13-20.
43. Abrams P. In support of pressure-flow studies for evaluating men with lower urinary tract symptoms. *Urology*. 1994;44:153-155.
44. McConnell J. Why pressure-flow studies should be optional and not mandatory studies for evaluating men with benign prostatic hyperplasia. *Urology*. 1994;44:156-158.
45. Lepor H. The pathophysiology of lower urinary tract symptoms in the ageing male population. *Br J Urol*. 1998;81(Suppl 1):29-33.
46. Lepor H, Williford WO, Barry MJ, et al. 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.
47. Djavan B, Marberger M. A meta-analysis on the efficacy and tolerability of alpha1-adrenoceptor antagonists in patients with lower urinary tract symptoms suggestive of benign prostatic obstruction. *Eur Urol*. 1999;36:1-13.
48. Major cardiovascular events in hypertensive patients randomized to doxazosin vs chlorthalidone: the antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT). ALLHAT Collaborative Research Group. *JAMA*. 2000;283:1967–1975.
49. Roehrborn CG, Boyle P, Gould AL, Waldstreicher J. Serum prostate-specific antigen as a predictor of prostate volume in men with benign prostatic hyperplasia. *Urology*. 1999;53:581-589.
50. Roehrborn CG, Boyle P, Nichol JC, et al. Efficacy and safety of a dual inhibitor of 5-alpha reductase types 1 and 2 (dutasteride) in men with benign prostatic hyperplasia. *Urology*. 2002;60:434-441.
51. Andriole GL, Guess HA, Epstein JI, et al. Treatment with finasteride preserves usefulness of prostate-specific antigen in the detection of prostate cancer: results of a randomized, double-blind, placebo-controlled clinical trial. PLESS Study Group. Proscar Long-term Efficacy and Safety Study. *Urology*. 1998;52:195-201.
52. Thompson I, Goodman P, Tangen C, et al. The influence of finasteride on the development of prostate cancer. *N Engl J Med*. 2003;349:215-224.
53. Roehrborn CG. Prevention of prostate cancer with finasteride. *N Engl J Med*. 2003;349:1569-1572.
54. Lepor H, Williford WO, Barry MJ, et al. The efficacy of terazosin, finasteride, or both in benign prostatic hyperplasia. Veterans Affairs Cooperative Studies Benign Prostatic Hyperplasia Study Group. *N Engl J Med*. 1996;335:533-539.
55. Wilt TJ, Ishani A, Stark G, et al. Saw palmetto extracts for treatment of benign prostatic hyperplasia: a systematic review. *JAMA*. 1998;280: 1604-1609.
56. MacDonald R, Ishani A, Rutks I, Wilt T. A systematic review of Cernilton for the treatment of benign prostatic hyperplasia. *BJU Int*. 1999;85:836-841.
57. Ishani A, MacDonald R, Nelson D, et al. Pygeum africanum for the treatment of patients with benign prostatic hyperplasia: a systematic review and quantitative meta-analysis. *Am J Med*. 2000;109:654-664.
58. Wilt T, MacDonald R, Ishani A. Beta-sitosterol for the treatment of benign prostatic hyperplasia: a systematic review. *BJU Int*. 1999;83: 976-983.
59. Donovan J, Peters T, Neal D, et al. A randomised trial comparing transurethral resection of the prostate, laser therapy and conservative treatment of men with symptoms associated with benign prostatic enlargement: the CLASP study. *J Urol*. 2000;164:65-70.
60. Wasson J, Bubolz T, Lu-Yao G, et al. Transurethral resection of the prostate among Medicare beneficiaries: 1984 to 1997. *J Urol*. 2000; 164:1212-1215.