Benign prostatic hyperplasia (BPH) is one of the most common diseases of aging men. It is estimated that by age 60 years, greater than 50% of men will have histologically documented evidence of the disease. Therapy for this disease has evolved considerably from its inception. Recent data from long-term population-based studies have shed new light on the treatment of this common problem in aging men. The authors review the current state of diagnosis of BPH and medical therapy for this condition in the primary care setting.

During the past decade, numerous changes have occurred in the treatment of patients with benign prostatic hyperplasia (BPH) and in the approach to the management of the disease. The advent of new medications, changes in the dosing regimen, the evolution of combined-drug therapy, and less-invasive surgical approaches have made BPH one of the rapidly changing fields in urology. The flux of new information and the recent results of long-term population-based studies make BPH an ideal topic for review.

Benign prostatic hyperplasia is one of the most common diseases of aging men. By the age of 60 years, more than 50% of men will have microscopic evidence of the disease; by age 85 years, as many as 90% of men will be affected. Benign prostatic hyperplasia is a diagnosis based on histologic findings that may be present without causing significant bladder outlet obstruction (BOO) or voiding symptoms. Therefore, the term benign prostatic obstruction (BPO) has evolved to describe the symptom complex associated with prostatic enlargement resulting in lower urinary tract obstruction. The combination of prostatic hyperplasia with benign prostatic enlargement, BOO, and lower urinary tract symptoms (LUTS) is the basis for the clinical diagnosis of BPO.

This review focuses on the diagnosis and treatment of BPO and LUTS in the primary care setting. It also looks at the medical therapy and its side effects commonly encountered when treating patients with BPO in the primary care office and when referral to specialists may be indicated.

Pathophysiology and Diagnosis of Benign Prostatic Obstruction

The healthy lower urinary tract has two functions. The first function deals with the storage of urine at low pressures while maintaining continence. The other function results in a coordinated relaxation of the external sphincter and bladder neck in conjunction with a detrusor contraction, resulting in bladder emptying.

Prostatic enlargement has an impact on both the storage and voiding phases of bladder function. The voiding (obstructive) symptoms have been attributed to two factors: the physical mass of the enlarged prostate gland (static component), and the tone of the smooth muscle of the prostatic stroma (dynamic component). The storage (irritative) symptoms are secondary to the physiologic bladder changes, which occur as a result of BOO.

The chief complaint of patients with BPO is usually bothersome LUTS typified by urinary frequency, urgency, nocturia, decreased and intermittent force of stream, and the sensation of incomplete bladder emptying. It is estimated that 50% of patients with microscopic evidence of disease are reported to have bothersome LUTS, which affect their quality of life by interfering with normal daily activities and sleep patterns. The severity of LUTS and their impact on patients’ quality of life are highly variable. Patients’ perception of bothersome LUTS and the degree to which the symptoms have an impact on their lives should be a primary consideration in choosing an appropriate disease-specific intervention. However, LUTS are not always associated with BPO but may be due to more serious conditions of the lower urinary tract.

The relationship between LUTS and BPO is complex, and not all men with LUTS will have histologic evidence of BPH. In addition, LUTS are neither specific nor diagnostic of BPO. One should consider that other disorders of the lower urinary tract could produce symptoms similar to BPO in the absence of histologically documented disease. In the initial office assessment of patients who have bothersome LUTS, it is imperative to identify those in whom symptoms may be attributed to other genitourinary pathologic conditions.

Bladder cancer, locally advanced prostate cancer, infection of the lower urinary tract, urethral stricture disease, and bladder calculi can all reproduce LUTS-like symptoms. Certain neurologic dis-
orders can also give rise to LUTS. The classic disorders described in this setting include multiple sclerosis, Parkinson’s disease, and cerebrovascular accident. Therefore, although the occurrence of lower urinary tract symptomatology is consistent and reproducible among men with BPO, it is important to do several basic office screening examinations to ensure that a diagnosis of a more serious disease is not overlooked.¹ The American Urological Association (AUA) recommends the following during the course of the initial office evaluation patients with LUTS:¹

- obtaining a thorough medical history to identify possible alternate causes for voiding dysfunction and comorbidities such as diabetes and congestive heart failure that may complicate treatment;
- doing a thorough physical examination including both a focused neurologic examination and digital rectal examination (DRE);
- ordering urinalysis to screen for hematuria or urinary tract infection;
- ordering measurement of serum prostate-specific antigen (PSA) in men with a life expectancy greater than 10 years;
- ordering cytologic examination of urine in men with predominately irritative symptoms and a history of smoking; and
- obtaining an AUA symptom index (AUA-SI) score on all patients.

**Medical Therapy for Symptomatic Benign Prostatic Obstruction**

Medical therapy is now the first-line treatment for most men with BPO, despite the advent of newer, minimally invasive surgical techniques. Currently available medical modes of therapy act to inhibit the physiologic mechanisms associated with the development of BPO-associated LUTS. The two classes of medications widely used for the treatment of patients with BPO are the ß-adrenergic receptor antagonists (ß-blockers) and the 5-α-reductase inhibitors (5-ARIs). These medications act to decrease the tone within the prostatic stroma and to decrease the overall gland size.

The ß-blockers reduce prostatic stromal and bladder neck tone through inhibition of ß-adrenergic receptors residing within these locations. ß-Adrenergic blocking agents have been used for more than a decade in the treatment of men with BPO and include terazosin hydrochloride, doxazosin mesylate, tamulosin hydrochloride, and most recently, alfuzosin hydrochloride. ß-Blockade improves the symptoms associated with BPO but does not affect the natural history of the disease. Currently available ß-blockers are similar in clinical efficacy but differ in their treatment-related side effects.

Prostatic growth is an androgen-dependent mechanism mediated by the 5-α-reductase family of enzymes, which convert intraprostatic testosterone to dihydrotestosterone. Because of the progressive nature of the disease, men with enlarged prostates are at an increased risk of the development of complications from progression of their disease. The use of a 5-ARI in this subset of patients modifies the natural history of the disease and reduces the overall risk for acute urinary retention and BPO-related surgery. The 5-ARIs reduce the size of the prostate by reducing the amount of metabolically active intraprostatic androgens. The 5-ARIs currently available include finasteride and dutasteride.

These two classes of drugs have been used as monotherapy or, most recently, in combination with one another with favorable results, as evidenced by a reduction in the AUA-SI score, increased peak urinary flow rates, and a delay in the natural progression of the disease. The choice of combination therapy is often dependent on prostate size and the presence or absence of irritative voiding symptoms.

**Treatment Recommendations**

A continuum of treatment options exists for patients with BPO, including watchful waiting, medical therapy, and surgical intervention. The appropriate therapy for a given patient who has LUTS associated with BPO depends on several factors, including severity of symptoms, degree of bother (impact on patient’s quality of life), prostate size, age, comorbid medical conditions, concurrent medications, and presence or absence of side effects from progression of the disease process.

In the primary care office setting, a thorough medical history and physical examination are required to determine which patients can be offered therapy initially and which should be referred to a specialist (Figure). A subset of patients in whom complications develop from BPO, such as recurrent urinary tract infections, renal insufficiency, bladder calculi, or urinary retention after therapy, require referral to a urologist for further evaluation.

Patients should be stratified in the primary care office setting based on their AUA-SI scores and degree of bother. Patients who have a significant reduction in overall quality of life or those in whom a high degree of bother can be attributed to the development of LUTS will benefit most from disease-specific intervention to improve their quality of life. Conversely, patients with significant LUTS symptoms, in the absence of bother or an impact on overall quality of life, will likely not benefit from therapy as the risk of treatment side effects outweighs the benefit from therapy in this subset of patients.¹

**ß-Blocker Therapy**

ß-Blocker therapy for BPO is based on the theory that the clinical symptoms of BPO are due in large part to increased prostatic smooth muscle tone mediated by ß-adrenergic receptors.⁶ ß-Blockers reduce the tone within the prostatic smooth muscle causing an increase in the diameter of the prostatic urethra and a decrease in outlet resistance.⁷ A family of ß-receptors have been located within the body and identified as ß₁ and ß₂, respectively. ß₁ Receptors are located in the urinary tract as well as within the cardiovascular system where they regulate blood pressure, vasodilation, and venous capacitance.

Selectivity of ß-blockade is important in reducing treatment-related cardiovascular side effects often associated with the use of this class of medications. Targeting of ß₁-receptor subtypes that reside primarily within the genitourinary tract, so called uroselectivity, has led to a reduction in side effects with similar clinical efficacy.⁷
Uroselectivity of α-Blocking Agents—Three generations of α-blockers with varying receptor selectivity and side effect profiles have been used in the treatment of patients with BPO. Currently, only second- and third-generation α-blocking drugs are widely used in clinical practice because the first-generation α-blocking agents have a broad side effect profile.

Second-generation α-blocking agents (terazosin, doxazosin, alfuzosin) selectively block the α1 receptor and not the α2 receptor at typical therapeutic doses, leading to a decrease in the occurrence of side effects compared with the first-generation agents. They improve urinary flow rates with less frequency of observed tachycardia and cardiac arrhythmias than observed with first-generation α-blocking agents. However, all second-generation α-blockers may cause dose-related hypotension to varying degrees.

Alfuzosin—Alfuzosin, which is pharmacologically classified as a second-generation α-blocking agent, acts clinically as a uroselective third-generation agent, resulting in a reduction of cardiovascular and ejaculatory side effects when compared with those of terazosin and doxa-
Tamsulosin is currently the only third-generation uroselective \( \alpha_{1a} \)-receptor antagonist. The pharmacoselectivity of tamsulosin has multiple implications for its use clinically. Overall, cardiovascular side effects are reduced with tamsulosin. Also, administration of this medication does not require dose titration. When compared with alfuzosin, however, tamsulosin is associated with a higher incidence of retrograde ejaculation.9

**Effectiveness of \( \alpha \)-Blockade—\( \alpha \)-Blockers are currently recommended for the treatment of moderate to severe BPO. The \( \alpha \)-adrenergic receptor antagonists such as doxazosin, terazosin, tamsulosin, and alfuzosin are all equally effective in the treatment of BPO and LUTS, but they vary slightly in their side effect profiles and dose titration, based primarily on their degree of uroselectivity.9

Dose titration at the initiation of therapy is required for terazosin and doxazosin. The uroselectivity of alfuzosin and tamsulosin makes dose titration at the initiation of therapy unnecessary. The known sexual and cardiovascular side effects of medical therapy should be considered along with the patient’s age and prostate size when choosing a first-line mode of medical therapy. Younger patients may desire drugs that cause less erectile dysfunction and ejaculatory-associated side effects, whereas the older male population may benefit from medications that are more uroselective and reduce the cardiovascular events associated with their administration.

In a meta-analysis of placebo-controlled studies and direct comparison studies of 6333 patients, terazosin, doxazosin, alfuzosin, and tamsulosin were equally effective in improving voiding symptoms and increasing urinary flow rate.9,10 These agents tend to be effective independent of the size of the prostate gland, leading to improvement in 30% to 40% of patients. Approximately 30% of patients have at least a 30% improvement in peak urinary flow rate, which tends to be a 16% to 25% improvement above pretreatment values.4 When compared directly with placebo, \( \alpha \)-blocking agents significantly increase peak and mean urinary flow rates by 15% to 30%, variably decrease postvoid residual bladder volume, and improve obstructive and irritative voiding symptoms by 30% to 50% when measured by AUA-SI scoring.9

As expected, patients with more severe symptoms have a greater degree of improvement after therapy. The onset of action of these medications is within hours; however, the peak effects do not occur for 2 to 4 weeks, and durable treatment responses have occurred for up to 4 years.9 \( \alpha \)-Blocker-mediated relaxation of the prostate gland, prostatic capsule, and bladder neck most commonly improves the obstructive symptoms associated with BPO and affect the irritative symptoms to varying degrees.9 However, not all patients respond to \( \alpha \)-blocker therapy. This failure to respond may be reflective of a subset of patients in whom the cause of their symptoms is a critical mechanical obstruction of the bladder neck as opposed to increased \( \alpha \)-adrenergic tone at the bladder neck and prostate.9

**Terazosin and Doxazosin—**Terazosin and doxazosin are the first two \( \alpha \)-blockers to have been approved by the US Food and Drug Administration (FDA) for the treatment of patients with BPO. Both are highly selective \( \alpha_{1a} \)-receptor antagonists. The Hytrin Community Assessment Trial (HYCAT) noted that terazosin is superior to placebo.11,12 Administration of terazosin resulted in a reduction of AUA-SI scores by 37.8% and an increase in peak urinary flow rates of 2.2 mL/s greater than baseline values.12

Roehrborn et al13 conducted a pooled analysis of three double-blind, placebo-controlled trials of doxazosin therapy. Their data indicate that administration of doxazosin was associated with a reduction of symptom scores by 34.7% and an increase in peak urinary flow rate by 2.2 mL/s.13 Most patients treated with either terazosin or doxazosin showed improvement after 4 weeks of therapy, and some showed improvement as early as 2 weeks after initiation of treatment. However, the lack of uroselectivity of these medications may contribute to the occurrence of cardiovascular side effects associated with their use.

Common side effects of both medications include first-dose syncope, orthostatic hypotension, dizziness, asthenia, nasal congestion, ejaculatory problems, and headaches.9,11-13 Most of these side effects are deemed to be mild, and they can be reduced by dose titration of the medication at the initiation of therapy and bedtime dosing.

Doxazosin monotherapy in hypertensive men with cardiac risk factors has been associated with an increased incidence of congestive heart failure.13-14 Therefore, it should not be assumed that the use of an \( \alpha \)-blocker to treat LUTS adequately controls the patient’s hypertension; the addition of a second antihypertensive medication may be necessary.1

**Alfuzosin—**Alfuzosin is an \( \alpha_{1a} \)-receptor blocker which has recently been approved by the FDA for the treatment of patients with BPO and LUTS. Alfuzosin has been used for more than a decade in Europe with good results. It is considered to be a clinically uroselective agent.9,15,16 Clinical uroselectivity may be due to preferential binding of alfuzosin to prostatic \( \alpha_{1a} \)-receptors as opposed to vascular \( \alpha_{1a} \)-receptors.9,15,16 Alfuzosin is available in both immediate and sustained-release preparations with noted similar clinical efficacy of both. Alfuzosin results in a 32% improvement in symptom scores and an increase of peak urinary flow rate of 2.7 mL/s.9,15,16

Cardiovascular side effects were noted more often with the immediate-release preparation of alfuzosin when compared with the extended formulation but were mild overall. Because of its functional uroselectivity, alfuzosin acts to reduce obstructive voiding symptoms in patients with BPO with less potential for causing significant reductions in systolic or diastolic blood pressure as compared with doxazosin and terazosin.9,15-17 Alfuzosin has also been associated with a
reduction in retrograde ejaculation when compared directly with tamsulosin.9

**Tamsulosin**—Tamsulosin is a uroselective α1a-receptor antagonist with higher affinity for the α1a-receptor subtype located in the prostatic stroma and bladder neck.9,17 In placebo-controlled trials, tamsulosin treatment resulted in similar increases in peak urinary flow rate and reduction of AUA-SI scores, as do doxazosin and terazosin. However, the uroselectivity of tamsulosin results in less postural hypotension and dizziness associated with its use when compared with doxazosin and terazosin.17

When compared with other available agents, tamsulosin has the highest incidence of ejaculatory disturbances in short-term clinical trials.9,17 In a direct comparison with placebo, the frequency of drug-related ejaculation disorders with tamsulosin, 0.4 mg/day, and with placebo were 4.5% and 0.5%, respectively. The receptor affinity of tamsulosin and the minimal occurrence of side effects make dose titration at the initiation of therapy unnecessary.9,17

### 5 α-Reductase Inhibitors

The 5 α-reductase inhibitors (5-ARIs) reduce LUTS associated with BPO by reducing the size of the prostate. Inhibition of the 5 α-reductase isoenzymes types 1 and 2 causes a drop in the metabolically active intraprostatic levels of dihydrotestosterone required for prostate growth. A reduction in gland size decreases the static component of BPO, improving urinary symptoms in men with demonstrated prostatic enlargement. The 5-ARIs are not as effective in reducing LUTS when compared with α-blocking agents and should not be used in men with LUTS without prostatic enlargement.

The side effects associated with use of the 5-ARIs are primarily sexual, and their incidence declines after the first year of therapy.

Decreased libido, ejaculatory dysfunction, and erectile dysfunction have all been reported more commonly with the 5-ARIs when compared with placebo. Currently, medications are available that selectively inhibit one or both of the 5 α-reductase isoenzymes.

**Finasteride**—Finasteride was the first 5-ARI available to treat patients for BPO. Finasteride competitively inhibits 5 α-reductase type 2, but it is only weakly active against type 1. It acts to reduce serum dihydrotestosterone levels by 65% to 70% and prostatic levels by 85% to 90%.18 Serum testosterone levels are unaffected, so effects on libido, fertility, and sexual function are uncommon.18 Finasteride acts to shrink the prostate by inducing prostatic epithelial apoptosis and atrophy, with few stromal changes.18 However, even after treatment with finasteride, the prostate still receives some androgenic stimulus from the 30% of serum dihydrotestosterone, and 10% of intraprostatic dihydrotestosterone converted by the type 1 isoenzyme.

The long-term efficacy and safety of finasteride is well established. Most notably, the Proscar Long-term Efficacy and Safety Study (PLESS) demonstrated significant and durable differences when compared with placebo for long periods.19 Finasteride is generally well tolerated. The side effect profile observed in the PLESS trial was typical, with patients reporting decreased libido (6.4% vs 3.4% in the group receiving placebo); decreased ejaculate (3.7% vs 0.8%); and less than a 1% incidence of ejaculation disorders, rash, and breast enlargement or tenderness.19 In the longer-term study, the side effects improved after the first year, loss of libido decreasing to 2.6% for both groups and impotence rates falling to 5.1% for finasteride and rising to 5.1% for placebo.19 Generally, symptom scores decreased by 2.5 and peak urinary flow rates increased by 1.5 mL/s.

By reducing prostatic size, finasteride has a direct impact on the progression of BPO, altering the natural history of the disease. Studies have shown that finasteride use reduces the incidence of acute urinary retention or the need for surgical treatment of BPO.19,20

Finasteride has been noted to predictably lower the prostate-specific antigen (PSA) levels by 50%, potentially complicating detection of prostate cancer. However, prostate cancer detection rates did not differ significantly between the group receiving placebo and the group receiving finasteride in the PLESS study.19

Doubling the PSA value and using normal ranges for untreated men preserves the usefulness of PSA as a tumor marker.18 However, men who do not have a predictable halving of their PSA level after the initiation of finasteride therapy should be followed up closely and evaluated for the presence of prostate cancer.

In a landmark meta-analysis study of more than 2600 patients from six randomized clinical trials, Boyle et al21 determined that differences in prostate size accounted for approximately 80% of the variation in outcomes seen between studies, and that prostate size was the key determinant of outcome with finasteride. The benefit was significantly different from placebo for prostate volumes greater than 40 mL, and increased with enlargement of the prostate.21

**Dutasteride**—Dutasteride is a dual inhibitor of 5 α-reductase isoenzymes types 1 and 2 within the prostate gland. Dutasteride has been evaluated in men with prostate gland volumes greater than 30 mL, and it was noted to produce rapid, consistent, and near-complete suppression of dihydrotestosterone. Prostate-specific antigen levels were halved without affecting the ratio of free PSA to total PSA, allowing the doubling of PSA values for use in prostate cancer screening.18,22 Further analysis showed that the net improvement with dutasteride over placebo increased with increasing total prostate volume, transition zone volume, and serum PSA level.

Dutasteride is well tolerated with adverse events reported to be erectile dysfunction, altered libido, ejaculatory disorders, and gynecomastia.18,22

Dutasteride appears to be just as qualified as finasteride for the treatment of patients with BPO and has a more rapid biochemical action. Maximal flow rates became significantly different from those with placebo at 3 months and for symptoms at 6 months. In the PLESS trial, flow rates became significantly different between the two groups at 4 months and symptom scores diverged at 8 months.18,19 Patients with larger prostates and higher PSA values had the greatest improvement.
Role of Combination Therapy
Considering the multiple etiologies of BPO, combination therapy with α-blockade and a 5-ARI would be predicted to have an additive effect on the treatment of patients. However, two large randomized trials evaluating the use of doxazosin alone or in combination with finasteride showed that both were effective as monotherapy but the combination showed no benefit over using either one alone. These results, however, were obtained in men with small to moderate-sized prostate glands.

The Medical Therapy of Prostatic Symptoms Trial (MTOPS), recently published in the New England Journal of Medicine, revisited the question of combination therapy. The investigators aimed to determine whether clinical disease progression could be prevented or delayed by finasteride, doxazosin, or both. The investigators followed up a total of 3047 men for 4.5 years; the study participants had an average baseline prostate volume of 36.5 mL.

The results demonstrate that combination therapy was superior to either drug alone for preventing disease progression. Finasteride and combination therapy significantly reduced the likelihood of overall acute urinary retention or progression to surgery. All treatment arms increased the peak urinary flow rates and symptoms scores over placebo, but combination therapy was significantly better than either drug alone. These results have changed our approach to the treatment of men with BPO based on their symptoms and prostate size.

Men with small to medium prostates with significant symptoms should receive α-blockade as their primary mode of therapy. Patients with large prostates without significant LUTS should receive 5-ARI therapy as an initial therapeutic intervention. Finally, those with large prostates and significant symptoms will benefit most from combination therapy in the treatment of their disease.

Comment
Medical therapy for BPO has evolved along with our understanding of the underlying pathophysiology of the disease process. The basis for the diagnosis remains a thorough and detailed history and physical examination. Primary care physicians should base the choice of medical therapy primarily on the patient’s symptoms and prostate size. In addition, they should also consider the degree of uroselectivity and medication-related side effects when choosing an initial therapeutic regime. High-risk patients who have complications of BPO, or those in whom a predictable response to therapy is not observed, including those who have failed initial medical therapy, should be referred to a urologist for further evaluation.

References