CME Information

CME Released: 09/30/2002; Valid for credit through 09/30/2003

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Target Audience

This activity is intended for cardiologists, urologists, internists, and primary care physicians.

Goal

The goal of this activity is to educate cardiologists, urologists, internists, and primary care physicians about the use of alpha blockade in two very common diseases in the older male: hypertension and benign prostatic hypertrophy.

Learning Objectives

Upon completion of this activity, participants should be able to:

1. Describe the basic physiology of alpha-adrenergic neural transmission
2. Report the basic principles of the use of alpha-adrenergic blockade in the treatment of BPH
3. Debate the presentation of mild to severe BPH for diagnosis
4. Detail the appropriate treatments for the various presentations of BPH

Credits Available

Physicians - maximum of 1.0 *AMA PRA Category 1 Credit(s)™*

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For Physicians

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Introduction

Benign prostatic hyperplasia (BPH) is the most common benign neoplasm affecting middle-aged and elderly men.[1,2] As many as 1 in 3 men over the age of 50 experience the moderate to severe lower urinary tract symptoms (LUTS) that are consistent with a BPH diagnosis.[3] With the aging of the baby boom generation and the concomitant doubling of the senior citizen population, the number of older men suffering from LUTS consistent with BPH will increase from 5 million to 9 million by the year 2025.[3]

The symptoms of BPH are brought on by the following interrelated conditions:

- Hyperplastic changes in the prostate,
- *Leading to* prostatic enlargement mediated by the epithelial and smooth muscle cells,
- *Leading to* urinary obstruction and increases in outflow resistance,
- *Leading to* detrusor muscle response to obstruction.

Although hyperplastic changes in the prostate begin as early as the third decade of life, symptoms generally appear after the age of 60.[1,4] Nearly half of men aged 70 and older have an American Urological Association (AUA) symptom score indicative of moderate to severe LUTS, and the likelihood of having a peak urinary flow rate suggestive of benign prostatic obstruction (< 15 mL/sec) increases dramatically in men 50 years and older (Figure 3).[3] Furthermore, it has been found that by the ninth decade (81- 90 years of age), nearly 90% of men demonstrate some degree of histologic BPH.[5,6] (See Figures 1-3.)

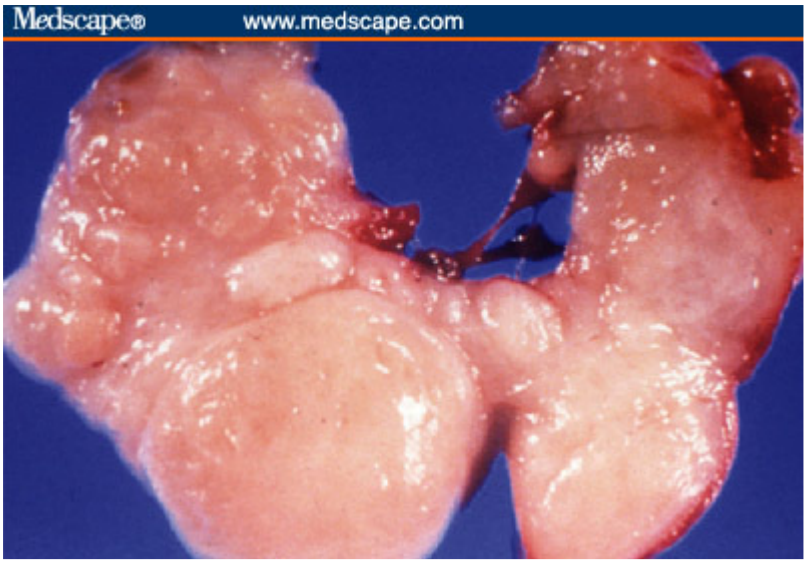

Figure 1. Gross specimen of prostate gland.
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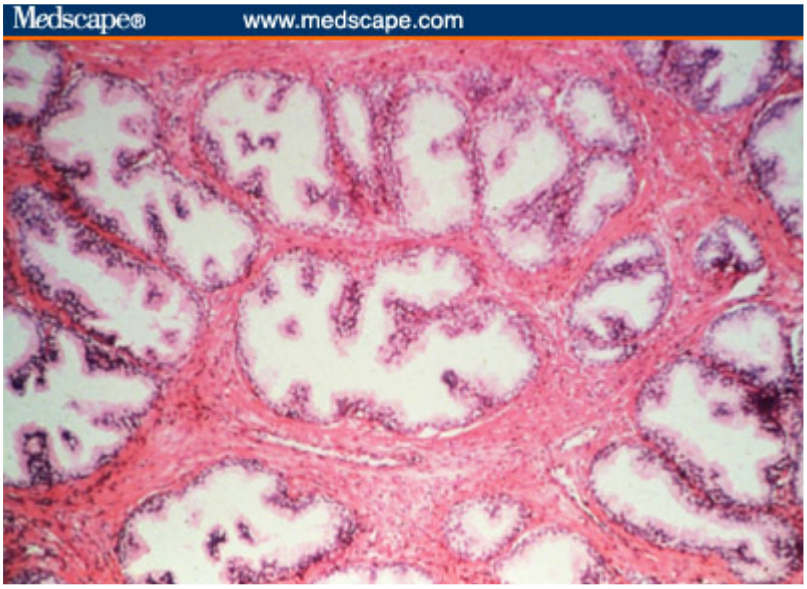

Figure 2. Microscopic effects of BPII.
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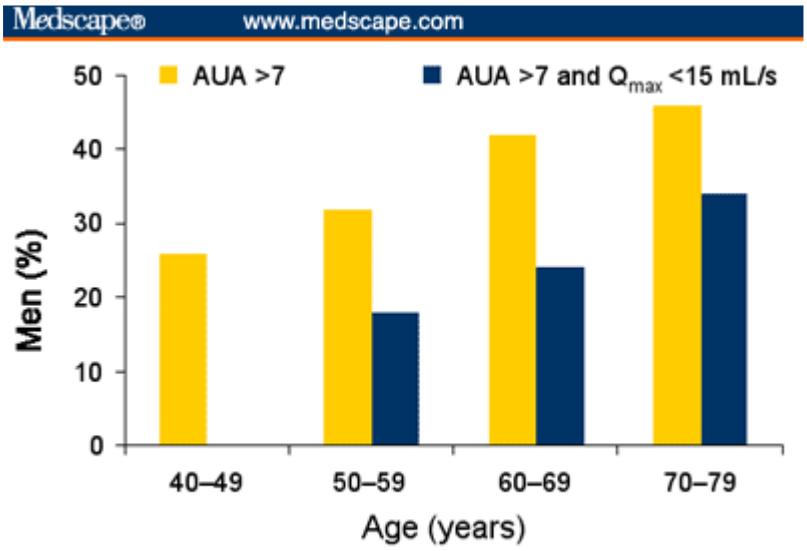

Q_{max}=peak urinary flow rate.

Figure 3. Prevalence by Age of Moderate to Severe LUTS and LUTS Combined with Q_{max}<15 Ml/s. Reprinted with permission from Ahmed Fawzy, MD.

Most men with BPH experience only mild or moderate symptoms of obstruction; however, severe BPH, which is more probable in men over 60 years of age, can lead to urinary retention, renal insufficiency, urinary tract infections, hematuria, and bladder stones.[7,8] Although serious complications such as uremia and irreversible bladder dysfunction are uncommon, the typical symptoms of BPH can be extremely bothersome for patients.[1,8] Early diagnosis of BPH and implementation of effective therapy can help relieve symptoms, improve patients' quality of life, and prevent the complications and morbidity associated with untreated BPH. (See Figure 4.[7])

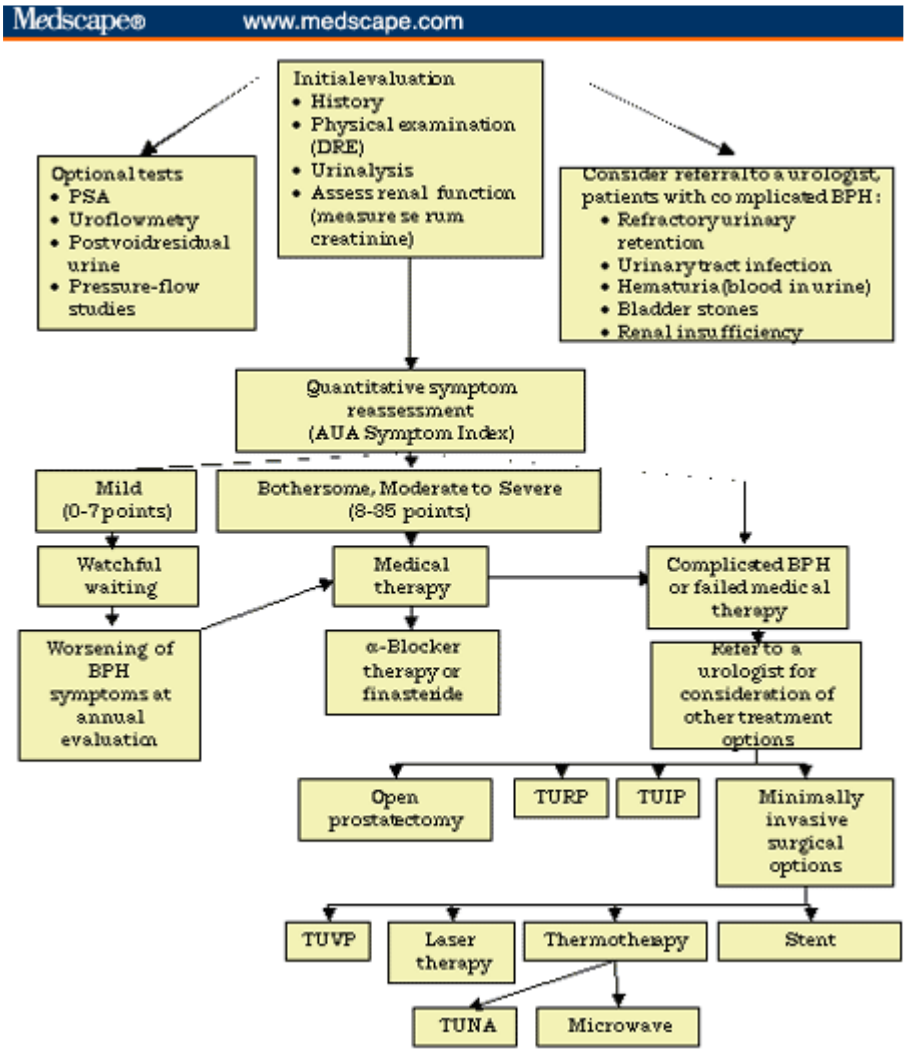

Figure 4. Decision making algorithm for the diagnosis and treatment of BPH. Reprinted with permission from Ahmed Fawzy, MD.

Diagnosis of BPH

Initial evaluation. The patient with BPH often presents with irritative or obstructive urinary tract symptoms (Table 1).[8,9] Patients with undiagnosed BPH may also report hernias or hemorrhoids, symptoms that potentially relate to BPH because they involve increased abdominal pressure and straining during voiding.[10]

Table 1. Symptoms of BPH[8,9]

Obstructive	Irritative
Difficulty initiating urination or passing urine	Urinary frequency
Weak stream	Nocturia

Involuntary postvoid dripping of urine	Urgency
Sensation of incomplete bladder emptying	Urge incontinence

Evaluation to confirm a diagnosis of BPH follows a stepwise process to rule out other conditions and to determine the severity of LUTS.[1] The guidelines developed by the US National Institutes of Health's Center for Practice and Technical Assessment (formerly the Agency for Health Care Policy and Research [AHCPR]) for the initial evaluation for BPH include:

- History taking;
- Physical examination, including digital rectal examination (DRE);
- Laboratory testing to rule out urinary tract infection, hematuria, and renal impairment
- Patient completion of the AUA symptom score questionnaire;[1] and
- Additional diagnostic tests such as uroflowmetry.

Patient History

A detailed medical history, including voiding history, should be obtained from the patient who has symptoms of BPH.[1] Other disorders can produce the symptoms of BPH and should be considered in the differential diagnosis (Table 2).

Table 2. Differential Diagnosis of BPH[9]

- Urinary tract infection/bladder stones
- Urethral stricture
- Bladder cancer
- Prostate cancer
- Neurologic diseases
- Medication side effects (anticholinergic or antidepressant drugs)
- Polyuria from diabetes

Urinary tract infections also produce irritative voiding symptoms. However, urinary tract infections are generally associated with pain or discomfort during urination, increased white blood cell count on urine analysis, and a positive urine culture.[8,11] Painful urination can be associated with urethral stricture or bladder neck contracture, and prostate or bladder cancer also produces bladder outlet obstruction with many of the same symptoms as BPH.[8,9,12,13] A history of surgery of the urinary tract may indicate an anatomic cause for symptoms other than BPH, such as urethral stricture or bladder neck contracture.

Furthermore, a patient's report of blood in the urine or a finding of microscopic hematuria may suggest the possibility of bladder cancer.[12] Neurologic diseases, such as multiple sclerosis or Parkinson's disease, may also produce symptoms resembling BPH. The effects of anticholinergic medications (impaired bladder contractility) and sympathomimetics (increased outflow resistance) should be considered as well.[1,9]

The nature of the symptoms, as well as their onset (ie, gradual or acute), can provide diagnostic clues as well.[1,7] Physicians should be aware of the demonstrated association between severe LUTS in BPH patients and concurrent diabetes (either diagnosed or undiagnosed).[14]

It is often helpful to have the patient complete a voiding diary, preferably before the initial evaluation.[1,7] When a patient calls to make an appointment, he can be asked to record when he voids over a 3-day period, noting characteristics such as postvoid dribbling or hesitant stream. Such a record is generally more reliable than patient recall at the time of the visit. The patient's history will also provide information that can help to determine treatment strategies if a diagnosis of BPH is confirmed.

Information relevant to making decisions about treatment includes the patient's perception of his symptoms and the extent to which they interfere with his daily life, concurrent diseases or conditions (eg, hypertension or diabetes mellitus), medications the patient is currently taking, and comorbidities that might make him a poor candidate for surgery.

Physical Examination

The physical examination includes a review to determine the presence of any comorbid conditions and to assess the patient's current health status. The primary focus of the examination is the urinary tract. As such, a DRE and neurologic assessment, evaluating anal sphincter tone in particular, should be conducted to rule out neurologic causes of urinary symptoms.[1,7]

The DRE is a minimally invasive, time- and cost-efficient evaluation of the prostate (Figure 5) Estimation of prostate size is helpful in deciding the treatment plan in patients with large prostates who may benefit from combined treatment of an alpha-blocker plus finasteride. It is useful to recall that the severity of BPH symptoms and degree of obstruction do not necessarily correlate with the size of the prostate.[7,15] The DRE is most useful for assessing the likelihood of other conditions, such as a hard or nodular prostate; if such conditions are present, they should be evaluated further to rule out cancer.[10]

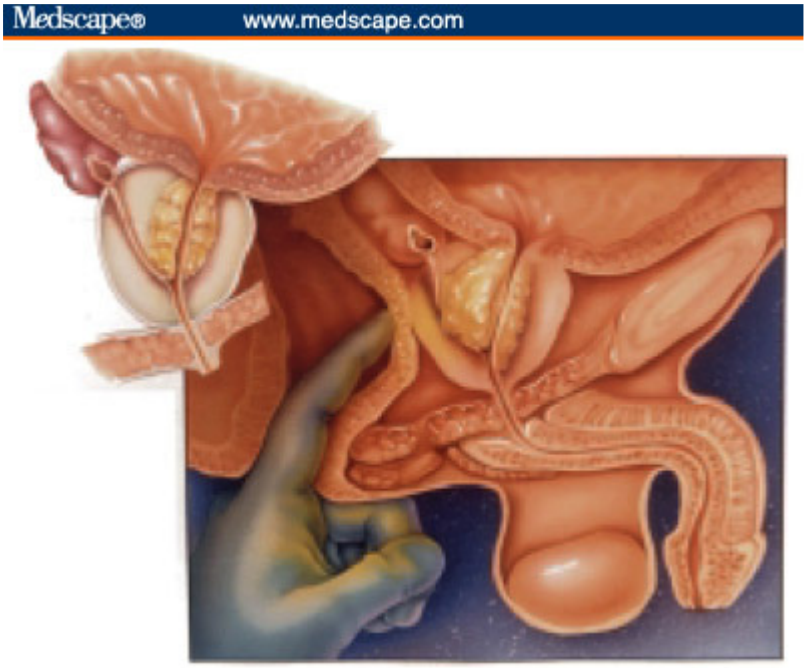

Figure 5. Digital rectal examination.
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Laboratory Analysis

Several routine lab tests are recommended for patients presenting with symptoms suggestive of BPH. Urinalysis or microscopic examination of urinary sediment can rule out urinary tract infection. If dipstick testing is used, the test should include leukocyte esterase and nitrite evaluation for the presence of pyuria and bacteriuria, respectively.[16] The presence of hematuria (> 5 red blood cells/high-power field) or proteinuria requires further investigation to rule out bladder cancer.[16] A referral to a urologist is warranted in these cases.

The AHCPR guidelines recommend obtaining serum creatinine levels to evaluate renal function in men with LUTS.[1] As many as 10% of men with BPH may have renal insufficiency, which can mean an increased risk -- 25% vs 17% for those without insufficiency -- of complications after surgical treatment for BPH.[1,17]

The American Cancer Society recommends annual DRE of the prostate starting at age 40 years and prostate-specific antigen (PSA) testing beginning at age 50 years for the early detection of cancer. High-risk individuals, such as African Americans or those with a family history of prostate cancer, should undergo annual PSA testing

starting at an earlier age.[18] Although African Americans are known to be at increased risk for prostate cancer, screening is widely underutilized in this patient population.[19]

A test to measure free PSA levels has become available. The test, which measures the percentage of free PSA in total serum PSA, was developed primarily as a more effective tool for detection of prostate cancer (Table 3).[20] Measurement of free PSA is most useful for patients with an elevated PSA value between 4 ng/mL and 10 ng/mL.[20] Recent studies also indicate that comparing the ratio of free or complexed PSA to total PSA enables the practitioner to differentiate between prostate cancer and BPH.[21] The relationship of total/free PSA has also been demonstrated to be a useful estimate of prostate size.[15]

Table 3. Free Serum PSA: Relevance of Values in Assessing Risk for Prostate Cancer[20]

Finding	Indication
Free PSA ≤ 25% in a patient with a standard PSA value between 4 ng/mL and 10 ng/mL	High risk for prostate cancer
Free PSA > 25% in a patient with a standard PSA value between 4 ng/mL and 10 ng/mL and normal prostate consistency on DRE	Consistent with BPH and low risk for prostate cancer

DRE = digital rectal examination; PSA = prostate-specific antigen

Treatment Options for BPH

The goals of treatment for BPH are outlined in Table 4. Treatment options include watchful waiting, medical therapy, and surgical intervention. Newer, minimally invasive therapies are emerging as viable alternatives to standard surgical treatment.

Table 4. Goals of Therapy for BPH

- Decrease symptoms
- Improve quality of life
- Reduce bladder outlet obstruction
- Decrease postvoid residual urine volume
- Reverse urinary retention/renal insufficiency when present
- Prevent disease progression

Watchful waiting. Decision making regarding the best treatment approach is based on the degree of symptomatology and comorbid conditions.[1] Generally, patients who are asymptomatic, or who have only mild symptoms of BPH that are not bothersome and not affecting their quality of life, are treated with watchful waiting and annual reassessment.[7,8] Because the progression of BPH is generally slow and unpredictable, not all patients experience worsening of symptoms, even if objective measurements such as peak flow rates continue to decline.[9] Certain lifestyle changes may be beneficial adjuncts to watchful waiting (Table 5).

Table 5. Lifestyle Modifications Implemented in Combination With Watchful Waiting[22]

- No intake of fluids after 7:00 PM
- Cut down on bladder irritants such as caffeinated drinks and chocolate
- Limit use of salt and spices
- Limit intake of alcoholic beverages
- Limit use of over-the-counter decongestants (which cause tightening of the urethral sphincter)

Surgery. At the opposite extreme from asymptomatic patients, or patients with only mild symptoms, are patients who present with urinary retention, recurrent urinary tract infections, gross hematuria, bladder stones, or renal insufficiency secondary to BPH, or who fail medical treatment (ie, complicated BPH). These patients should be considered for the surgical treatment option.[9]

The development and refinement of surgical procedures in recent years has increased the range of surgical options. Within this range, it is now possible for patient and physician to determine the ideal procedure, taking age, health status, and prostate size into account, and in a context where a patient's desired outcomes are weighed against a procedure's potential complications.

The most invasive surgical technique is open prostatectomy, which involves general surgery to remove the transitional zone of the prostate, without removing the peripheral zone. However, this has been replaced by transurethral resection of the prostate (TURP), a procedure introduced more than 50 years ago that remains the "gold standard" for the definitive treatment of BPH. Two more-recent evolutions of this technique include transurethral incision of the prostate (TUIP) and transurethral vaporization of the prostate (TUVP), which has demonstrated efficacy comparable to that of TURP in relieving symptoms and increasing peak urinary flow rates. Finally, stent placement -- a technique borrowed from interventional cardiology -- has emerged as a viable, minimally invasive treatment for both temporary management and ongoing treatment of BPH in specific patients.

A description of all of these surgical interventions is beyond the scope of this discussion. In each case, it is important that patients understand the various treatment options, the probable outcomes, and the risks and benefits of each as reflected by a "balance sheet" (see Table 6[7,23-28]). Throughout the therapeutic regimen, the patient should undergo reassessment to determine response to therapy and the possible need for alternative treatment.

Table 6. Balance Sheet for Treatment Modalities for BPH[7,28-33]

Treatment Outcome	Surgical Therapies				Medical Therapies		Watchf Waitin
	TURP	TUVP	TUIP	Open Prostatectomy	Alpha-Blockers	Finasteride	
Chance for symptom improvement (90% CI)	75% to 96%	Estimated similar to TUR	78% to 83%	94% to 99.8%	59% to 86%	54% to 78%	31% to 55
Degree of symptom improvement (% reduction in symptom score)	85%	73% to 77	73%	79%	51%	31%	Unknown
Morbidity/complications associated with surgical or medical treatment; about 20% of all complications assumed to be significant (90% CI)	5.2% to 30.7%	11% to 35	2.2% to 33.3%	6.98% to 42.7%	2.9% to 43.3%	13.6% to 18.8%	1% to 5% (complica from BPH progressi
Chance of dying within 30-90 days of treatment (90% CI)	0.53% to 3.31%	*	0.2% to 1.5%	0.99% to 4.56%	0.8% (chance of death ≤ 90 days 67-year-old man)		

Risk of total urinary incontinence (90% CI)	0.68% to 1.4%	Minimal, but temporary incontinence up to 14	0.06% to 1.1%	0.34% to 0.74%	Incontinence associated with agir		
Need for operative treatment for surgical complications in the future (90% CI)	0.65% to 10.1%	*	1.34% to 2.65%	0.6% to 14.1%	NA		
Risk of impotence (90% CI)	3.3% to 34.8%	~11	3.9% to 24.5%	4.7% to 39.2%	About 2% (1 of 50 men aged 67 years becomes impotent per year)	2.5% to 5.3% (also, decreased volume of ejaculate)	About 2% of 50 mer aged 67 y becomes impotent year)
Risk of retrograde ejaculation (% of patients)	25% to 99%	12.5% to 23	6% to 55%	36% to 95%	4% to 11%†	0	0
Loss of work time (days)	7-21	Estimated similar to TUR	7-21	21-28	3.5	1.5	1
Hospital stay (days)	3-5	1.5-2.5	1-3	5-10	0	0	0

*Not enough information available on procedure.

†Tamsulosin appears to be the only alpha$_1$-blocker with significant rates of associated ejaculatory dysfunction.[4]

CI = confidence interval; NA = not applicable; TUIP=transurethral incision of the prostate; TURP = transurethral resection of the prostate; TUVP = transurethral vaporization of the prostate.

In any case, it should be noted that, given the efficacy of treatments such as alpha$_1$-adrenergic blockade, it is estimated that the percentage of men requiring surgical intervention will decrease in coming years. On the other hand, it is also true that, given the growth among the elderly population in the United States -- 1 in 5 individuals will be elderly by the year 2025 -- the actual numbers of BPH-related surgeries performed will no doubt increase significantly.[3]

Medical treatment. Patients with bothersome, relatively moderate to severe symptoms usually do not require surgery; surgical intervention is reserved for patients with complicated BPH or BPH that fails to respond to medical treatment.[9] This leaves patients with moderate to severe BPH; for these patients, medical therapy with one of the currently approved agents is considered first-line treatment.[8]

Given the following patient:

- 56-year-old male;
- Smoker;
- Excessive nocturia;
- Pain on urination; and
- Prostate enlarged on DRE

Diagnosis: moderate to severe BPH.

Thus, for this fairly typical presentation, the first line of treatment should be medical rather than surgical. The most commonly used pharmacologic agents for treating BPH are:

- Long-acting alpha$_1$-adrenoceptor blockers, which address BPH's dynamic component; and
- 5-alpha-reductase inhibition, eg, with finasteride, which addresses the static aspect of BPH.

For a more complete list, see Table 7.[29-31] Selection of the most appropriate agent for the individual patient increases the probability of successful treatment.

Table 7. Approved Medical Therapies for BPH[35,36]

	Terazosin	Doxazosin Mesylate	Tamsulosin	Finasteride	Dutasteride
Mode of action	Long-acting alpha$_1$-adrenoceptor blocker	Long-acting alpha$_1$-adrenoceptor blocker	Long-acting alpha$_1$-adrenoceptor blocker	5-alpha-reductase inhibitor	5-alpha-reductase inhibitor
Selectivity	alpha$_1$	alpha$_1$	alpha$_{1a}$	NA	NA
Half-life	12 h	22 h	14-15 h	6-8 h	5 weeks
Short-term efficacy	+	+	+	+*	+
Long-term efficacy	+	+	+	+*	+
Side effects	Dizziness, headache, fatigue	Dizziness, headache, fatigue	Headache, abnormal ejaculation, rhinitis, dizziness	Impotence, decreased libido, effects on PSA levels	Decreased libido, abnormal ejaculation, impotence, breast tenderness
Titration	Required	Required	Not required	Not required	Not required
Increase in mean peak urinary flow rate	2.6-3.0 mL/s	2.3-3.3 mL/s	0.5-1.8 mL/s	~1.9 mL/s	0.7-1.1 mL/s
Cost (average wholesale price $US)	$1.78 (5 mg)	$1.08 (4 mg)	$1.55 (0.4 mg)	$2.28 (5 mg)	Unavailable

*Finasteride may have beneficial effects on men with larger prostates

NA = not applicable. PSA = prostate-specific antigen.

Alpha1-Adrenoceptor Antagonist Therapy

The dynamic component of BPH is associated with prostatic smooth muscle tone. Smooth muscle accounts for a significant portion of the prostate adenoma.[32] Prostatic smooth muscle is innervated by a dense network of adrenergic and cholinergic neurons. As seen in **Part I: Physiology**, by James Pool, MD, the sympathetic innervation of the prostate is mediated through adrenergic neurons from a hypogastric ganglion.[33]

Cell and tissue studies have shown that there is a functional predominance of alpha$_1$-adrenoceptors in the prostatic stroma vs the epithelium, with as many as 98% of the long-acting alpha$_1$-adrenoceptor binding sites in the prostate located in the prostatic stroma vs the epithelium.[34] It has been suggested that alpha$_1$-adrenoceptor -mediated smooth muscle tone may account for up to 40% of the total urethral pressure in BPH.[35]

Administration of alpha$_1$-blockers relaxes both the bladder neck and the prostatic smooth muscle, thus decreasing pressure in the bladder and urethra and improving urinary flow.[36]

In the United States, the alpha$_1$-blockers doxazosin, terazosin, and tamsulosin have been approved as first-line medical therapy for symptomatic BPH patients. Both the short- and the long-term efficacy data for these 3 alpha-blockers are similar; therefore, the choice of agent should be made based on safety profiles, dosing schedules, and individual patient needs.[3,4]

Doxazosin. Doxazosin (*Cardura*) is one of the most effective and widely used treatments for symptoms associated with uncomplicated BPH. This medication produces long-lasting symptomatic benefit and improvement of urodynamic parameters in most patients. Its main advantage is rapid onset of action (1-2 weeks). In placebo-controlled studies, both hypertensive and normotensive patients who received doxazosin experienced increased peak urinary flow rate and relief of obstructive and irritative symptoms of BPH.[37,38]

The major side effects of doxazosin are dizziness, headache, and fatigue. Sexual dysfunction is not commonly associated with doxazosin use, and the medication has been shown to have no adverse effect on renal function or insulin sensitivity.[39,40]

Doxazosin is initially administered at a dosage of 1 mg once daily, in the morning or at night, followed by uptitration every 1-2 weeks until relief is obtained.[30] Most patients will achieve effective relief of symptoms with a 4-mg dose of doxazosin; however, comparable side-effect profiles and increased benefits have been demonstrated when patients not responding to 4 mg are uptitrated to 8 mg.[41] At steady state, maximal plasma concentrations are achieved within 1-4 hours.[42] Because the pharmacokinetics of doxazosin are not significantly affected by age, no adjustment in dose is required in the elderly.[40]

A time-release formulation of doxazosin (*Cardura XL*) has recently been introduced in Europe, with approval pending in the United States. This allows patients to begin immediately on the 4-mg time-release dosage, avoiding titration; as with the standard formulation, patients may be increased to 8 mg if necessary.

Investigators have evaluated the long-term efficacy and safety of doxazosin. One study enrolled normotensive (n = 272) and hypertensive (n = 178) patients.[43,44] Over a 2-year period, overall peak urinary flow rate and average flow rate improved significantly from baseline (1.9 and 1.0 mL/sec, respectively). Among 28 hypertensive patients who completed 48 months of therapy, the positive effects of doxazosin on BPH and diastolic blood pressure control were sustained. This study demonstrated that doxazosin is well tolerated during long-term therapy.[44]

Terazosin. Terazosin (*Hytrin*) has short- and long-term efficacy profiles similar to those of doxazosin, as well as a similar side-effect profile. The main difference is a shorter half-life (12 hours), which may contribute to an increased incidence of dizziness, headache, and fatigue if the medication is taken in the morning. For this reason, it is recommended that terazosin be given at bedtime. With its longer half-life (22 hours), doxazosin can be taken in the morning or evening, with no difference in the incidence of side effects.[30]

The initial dose of terazosin is 1 mg at bedtime with close monitoring after initial administration to minimize the possibility of a hypotensive response. Subsequently, the dose may be increased stepwise to 2 mg, then 5 mg, up to a maximum dose of 10 mg, which is the usual dose required for a clinical response. The patient may need to be treated with 10 mg for a minimum of 4 to 6 weeks to determine response to dosing.[30]

The Hytrin Community Assessment Trial[45] assessed long-term terazosin therapy in patients with BPH. In this 1-year, double-blind, placebo-controlled, multicenter study, a total of 2084 patients aged 55 years or older with moderate to severe symptoms of BPH and peak urinary flow rate < 15 mL/sec received terazosin or placebo. Results showed relief of BPH symptoms (37.8%) and improved quality of life (33.3%) from baseline in patients receiving terazosin compared with those in the placebo group (18.4% and 15.8%, respectively). Peak urinary flow rate values improved by 2.2 mL/sec on average in the patients who received terazosin, compared with 0.8 mL/sec in the placebo group. In this study, terazosin was given once daily in a dose ranging from 2-10 mg.[45]

Another long-term, open-label, multicenter study found that the benefits of terazosin remained constant over 42 months.[46]

Tamsulosin. Tamsulosin (*Flomax*) is another alpha$_1$-receptor blocker with efficacy and side effect profiles similar to terazosin and doxazosin. Unlike the other alpha$_1$-receptor antagonists, however, tamsulosin was not developed as an antihypertensive agent. As a result, if used to treat BPH in their standard (ie, non-time-release) formulations, these other alpha$_1$-antagonists must be up-titrated to their effective dosages to avoid orthostatic hypotension and potential syncope. Tamsulosin, on the other hand, has the clinical advantage that, in addition to being relatively long-acting with a rapid onset of action, it has been demonstrated not to affect steady blood pressure levels in either normotensive or hypertensive patients.[47] These patients can therefore be started and maintained on the therapeutic dosage.

Tamsulosin has a half-life of 14-15 hours. Follow-up over 3 years has confirmed the long-term efficacy of this drug with significant and sustained improvement in symptom scores and in urinary flow rates.[48] Because the primary adverse events associated with tamsulosin are dizziness and abnormal ejaculation -- tamsulosin appears to be the only alpha$_1$-blocker with significant rates of associated ejaculatory dysfunction -- it is important for physicians to discuss these side effects with patients prior to prescribing this medication.[4,48]

Alfuzosin. The recently introduced alfuzosin (*Xatral XL*) is available in Europe but not in the United States. Large-scale studies[49,50] ranging in duration from 1-3 years have confirmed that the drug displays long-term efficacy in reducing LUTS, decreasing bladder outlet obstruction, and improving quality-of-life measurements. It also has a strong safety and tolerability profile.An application for regulatory approval of alfuzosin was filed with the US Food and Drug Administration in December 2000.[51]

The Question of Uroselectivity

In recent years, the concept of uroselectivity has been widely discussed. The theory of uroselectivity emerges from the hypothesis that alpha$_1$-blockers specifically designed to target alpha$_1$-adrenoceptors found in the prostate may yield high efficacy combined with a lower incidence of undesirable side effects such as dizziness, headache, asthenia, nasal congestion, and orthostatic hypotension. For these reasons, efforts have been undertaken to isolate alpha$_1$-adrenoceptor subtypes specific to the prostate, bladder neck, and urethral areas. The alpha$_{1a}$-adrenoceptor subtype has been identified as dominant in the prostate, representing about 60% to 85% of resident adrenoceptors, and recent investigations of alpha$_1$-blocker drugs have attempted to assess their degree of specificity at alpha$_{1a}$-adrenoceptor sites.[52]

However, this theory remains questionable on several points. Despite the dominance of alpha$_1$-adrenoceptors in the prostate, evidence indicates that more than 1 alpha$_1$-adrenoceptor subtype exists in the lower urinary tract. It also appears unlikely that alpha$_1$-adrenoceptors, as well as other adrenoceptors found in the prostate, are unique to the lower urinary tract. Furthermore, most explorations of uroselectivity have used animal models. The results of these clinical trials cannot be extrapolated to human subjects. Last and perhaps most significantly, there is evidence that alpha$_1$-adrenoceptor sites outside the prostatic region might contribute to the symptoms of BPH.[52] For example, Ishizuka and colleagues found that doxazosin may reduce activity in the parasympathetic nerves to the bladder through spinal cord mediation.[53]

The comparative efficacy and adverse-effect profiles of the 3 long-acting alpha-blockers will be ascertained only by conducting controlled comparative clinical trials. According to the 4th International Consultation on BPH:

> None of [the alpha$_1$-adrenoceptor antagonists] has any distinct selectivity for alpha$_1$-adrenoceptor subtypes nor for the prostate that could be used as an indicator of clinical selectivity...The validity and clinical significance of any perceived differences in adverse events will require confirmation in appropriately designed investigations....Such studies will give credibility to claims of quantitative, clinically significant differences between drugs.[54]

5-Alpha-Reductase Inhibitors

The static element of BPH is associated with increased prostatic tissue mass; this mass mechanically blocks the urethra and produces resistance to urinary flow from the bladder, resulting in the symptoms of BPH. Local proliferation of stromal cells eventually results in hyperplastic growth in the periurethral and transition zones of the prostate. Over time, this progressive proliferation may lead to increased prostate size and bladder outlet obstruction.[9] The recommended pharmacologic approach to treating this hyperplastic mass is reduction with 5-alpha-reductase inhibitors.

Finasteride. Testosterone is a key element in the pathophysiology of BPH in that it is converted in the prostate to 5-alpha-dihydrotestosterone, which stimulates growth of glandular and stromal cells.[29,55] By blocking the action of 5-alpha-reductase, the antiandrogen finasteride (*Proscar*) inhibits conversion of testosterone to dihydrotestosterone.[56] In turn, proliferation of prostatic epithelial cells declines, resulting in the shrinkage of the enlarged prostate gland by about 30% in nearly 60% of users.[29]

Clinical trials have documented significant reductions in total prostatic volume, decreased AUA symptom scores, and increased peak urinary flow rates in patients receiving finasteride.[57,58] A recent study demonstrated that use of finasteride led to ongoing improvements in pressure-flow parameters over a 2-year period.[59] As an added benefit, finasteride has been shown to be useful in stopping hair loss associated with male baldness.[60] The potential drawbacks of finasteride therapy are the length of time required for symptomatic relief (up to 6-12 months) and the fact that the drug decreases total serum PSA values.[8,30] The most common adverse events are related to sexual dysfunction, with a large proportion of men reporting decreased libido (10%), ejaculatory dysfunction (8%), and impotence (16%).[4]

In the Veterans Affairs and PREDICT trials, finasteride was compared with the long-acting alpha$_1$-antagonists terazosin and doxazosin, respectively. In both trials, the alpha$_1$-adrenoceptor therapies significantly improved BPH symptoms, while finasteride alone failed to induce significant symptomatic improvement.[61,62]

However, recent studies support the use of finasteride for specific conditions associated with BPH, particularly among men with larger (> 40 cm^3) prostate glands and baseline PSA levels ≥ 1.4 ng/mL.[59,63] Foley and colleagues[64] found that finasteride was effective in suppressing hematuria secondary to BPH and alleviating the need for surgery related to hematuria. In the recent Ploscar Long-term Efficacy and Safety Study (PLESS), patients with large prostates (median, 46 cm^3 in patients receiving active treatment) and at risk for acute urinary retention (AUR) were treated with finasteride over a 4-year period. In the finasteride-treated group, the likelihood of developing AUR was significantly decreased and rates of surgery related to AUR were lower.[65]

Alpha-Blocker Therapy for Concomitant BPH and Hypertension

It has been estimated that as many as 1 in 4 men over the age of 60 has both BPH and hypertension and that the 2 diseases may have a common etiology in the sympathetic nervous system.[40,44] Although the 2 diseases are distinct, the effectiveness and safety of alpha-blockers in the treatment of each led to the logical conclusion that 1 therapy could be used to treat both conditions.[66] The sixth report from the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-VI) recommends that patients with concomitant BPH and hypertension receive alpha$_1$-blocker therapy as their initial line of treatment.[67] This approach is particularly appropriate and beneficial in the patients most likely to experience BPH and hypertension -- elderly males.

Controlled studies have been conducted using doxazosin in normotensive and hypertensive men with BPH; pooled results show that doxazosin increased peak urinary flow rates in both patient populations. Hypertensive patients had a significant and desirable decrease in blood pressure (baseline, 162/99 mm Hg; end point, 143/89 mm Hg), whereas minor, clinically insignificant reductions in blood pressure were observed in normotensive patients (baseline, 139/82 mm Hg; end point, 134/78 mm Hg).[68] Doxazosin has also been shown to produce small, statistically significant improvements in total and low-density lipoprotein cholesterol and triglycerides.[40] Importantly, the alpha$_1$-blockers doxazosin and terazosin have been shown to be safe for patients who are

physiologically normotensive as well as for patients who are pharmacologically normotensive due to their use of concomitant antihypertensive medications.[40,69]

Combination Medical Therapy

To address both the dynamic (smooth muscle tone) and static (tissue mass) components of BPH, investigators have produced combination therapy with alpha$_1$-adrenoceptor antagonists and 5-alpha-reductase inhibitors and tested this combination in several clinical trials.

A Veterans Affairs cooperative placebo-controlled study compared the effectiveness of finasteride plus terazosin therapy with monotherapy. Patients who received either terazosin monotherapy or finasteride plus terazosin therapy experienced the greatest relief of symptoms and the greatest improvement in peak urinary flow rates. Combination therapy was no more effective than terazosin monotherapy.[61]

The Prospective European Doxazosin and Combination Therapy (PREDICT) study utilized 4 arms in which the combination of doxazosin plus finasteride was compared with doxazosin alone, finasteride alone, and placebo in double-blind fashion. The findings reported for doxazosin, and doxazosin in combination with finasteride, were similar to those of the Veterans Affairs study.[62] The apparent lack of finasteride effect over placebo in the Veterans Affairs study may have been due to differences in prostate volume among the subjects enrolled in this trial compared with patients in other trials[58] -- finasteride is more effective in patients with larger prostate glands. The results of a multicenter National Institutes of Health clinical trial were presented at the AUA meeting in Orlando on May 28, 2002.

For the NIH-sponsored Medical Therapy of Prostatic Symptoms (MTOPS) Trial, physicians at 17 medical centers treated about 3000 men, aged 50 and over, for an average of 4.5 years. The men all had BPH and were evenly randomized to 1 of the 4 following groups:

- 5 mg finasteride;
- 4 mg or 8 mg doxazosin;
- Both drugs; or
- Placebo.

The aim of the trial was to prevent BPH progression, defined primarily as a significant worsening of symptoms, recurring urinary tract infection, urinary retention, incontinence, or invasive therapy such as surgery.

MTOPS found that combination therapy with the 5-alpha-reductase inhibitor finasteride (*Proscar*) plus the alpha$_1$-receptor blocker doxazosin (*Cardura*) reduced the risk of BPH progression by 67%. The risk of progression was reduced by 39% with doxazosin alone and by 34% with finasteride alone.

Compared with placebo, the risk of urinary retention was reduced by 79% with combination therapy, by 67% with finasteride, and by 31% with doxazosin (not significantly different from placebo); the risk of invasive therapy was reduced by 69% with the combination, 64% with finasteride, and 8% with doxazosin (not significantly different from placebo).

All treatments produced significant improvements in AUA symptom score [median improvement at 4 years: placebo = 4.0, doxazosin = 6.0, finasteride = 5.0, combination = 7.0] and Q_{max} [median improvement (mL/sec) at 4 years: placebo = 1.4, doxazosin = 2.5, finasteride = 2.2, combination = 3.7]. Improvements in AUA symptom score and Q_{max} scores were significantly greater with combination therapy compared with doxazosin or finasteride therapy alone. Frequently occurring adverse events were similar to those in previously reported trials. Men in the placebo group with higher baseline serum PSAs, prostate volumes, and ages and lower Q_{max} were significantly more likely to progress.

In MTOPS, the rates of urinary tract infection and urinary incontinence were low in all drug treatment groups, and no patient in any group developed kidney problems from BPH. MTOPS thus demonstrates that in selected

patients, combination treatment with the 5-alpha-reductase inhibitor finasteride (*Proscar*) plus the alpha$_1$-receptor blocker doxazosin (*Cardura*) decreases the risk of progression of disease.

Plant Extracts

Plant extracts are widely used for the treatment of BPH in Europe. However, an evaluation of the efficacy of these compounds is limited in that the majority of phytotherapy studies are not well designed and lack placebo-controlled data. The plant extract beta-sitosterol is purported to reduce the symptoms of BPH. A randomized, double-blind, placebo-controlled, multicenter study reported improvements in urine flow parameters and symptoms with beta-sitosterol, but no change in prostate volume in treatment or placebo groups.[70]

A meta-analysis of clinical trials of the plant compound made from saw palmetto (*Serenoa repens*), formulated as the brand *Permixon*, found significant improvements in peak flow rates and nocturia compared with placebo. Further studies to assess *Permixon*'s benefits are under way.[71,72]

Conclusion

For patients presenting with no, or minimal, bothersome symptoms, watchful waiting is an acceptable first-line treatment strategy. However, patients on watchful waiting must be closely monitored, with follow-up at 6-12 months to assess whether symptoms have worsened and whether intervention is needed.

For patients with bothersome symptoms of BPH, medical therapy with long-acting alpha$_1$-blockers is the preferred, logical first-line choice of therapy. The 3 alpha$_1$-blockers currently available in the United States demonstrate comparable levels of efficacy, and physician selection of the most appropriate drug should be made on an individualized basis.

The MTOPS study data presented at the 2002 AUA meeting strongly support the beneficial effects of combined treatment using the long-acting alpha$_1$-antagonist doxazosin plus the 5-alpha-reductase inhibitor finasteride to prevent BPH progression in selected patients.

For patients in whom a reasonable course of medical treatment fails to resolve the symptoms of BPH or who present with complicated BPH, surgical treatment should be considered. In this case, the newer, minimally invasive procedures represent a highly effective treatment and are associated with lower morbidity than the established TURP procedure.

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