Chapter 104: Benign Prostatic Hyperplasia

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CHAPTER SUMMARY FROM THE PHARMACOTHERAPY HANDBOOK

For the Chapter in the Schwinghammer Handbook, please go to Chapter 81, Benign Prostatic Hyperplasia.

KEY CONCEPTS

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1. Although symptomatic benign prostatic hyperplasia (BPH) is rare in men younger than 50 years, it is common in men aged 60 years and older. Prostate growth is androgen-dependent. Symptoms commonly result from both static and dynamic factors.

2. BPH symptoms may be exacerbated by medications, including antihistamines, phenothiazines, tricyclic antidepressants, and anticholinergic agents. In these cases, discontinuing the causative agent can relieve symptoms.

3. For patients with mild disease who are asymptomatic or have mildly bothersome symptoms and no complications of BPH disease, watchful waiting is indicated. Watchful waiting includes behavior modification, lifestyle modification, discontinuation of medications that contribute to voiding symptoms, and return visits to the physician at 6- or 12-month intervals for assessment of worsening symptoms or signs of bladder outlet obstruction.

4. If symptoms progress to a moderate or severe level, drug therapy or surgery is indicated. α_1-Adrenergic antagonists quickly relieve voiding symptoms, but do not prevent disease progression. 5α-Reductase inhibitors delay symptom progression and reduce the incidence of BPH-related complications in patients with prostates of at least 30 to 40 g, but may not reduce voiding symptoms for 3 to 6 months.

5. All α_1-adrenergic antagonists are equally effective in relieving BPH symptoms. Older second-generation immediate-release formulations of α_1-adrenergic antagonists (eg, terazosin, doxazosin) can cause adverse cardiovascular effects, mainly first-dose syncope, orthostatic hypotension, and dizziness. For patients who cannot tolerate these hypotensive adverse effects, a third-generation, pharmacologically uroselective α_{1A}-adrenergic antagonist (eg, tamsulosin, silodosin) or an extended-release formulation of alfuzosin, a second-generation, functionally uroselective agent, is a good alternative.

6. 5α-Reductase inhibitors are useful primarily for patients with large prostates greater than 40 g who wish to avoid surgery and cannot tolerate the side effects of α_1-adrenergic antagonists. 5α-Reductase inhibitors have a slow onset of action, taking up to 6 months to exert maximal clinical effects, which is a disadvantage of their use, especially as single-drug therapy for BPH. In addition, decreased libido, erectile dysfunction, and ejaculation disorders are common adverse effects, which may be troublesome in sexually active patients.

7. Phosphodiesterase type 5 inhibitors can be used in patients with moderate-to-severe BPH and erectile dysfunction. They improve obstructive and irritative voiding symptoms, but do not significantly increase urinary flow rate or reduce postvoid residual (PVR) urine volume. Hence, a phosphodiesterase type 5 inhibitor is considered less effective than an α-adrenergic antagonist for BPH. A phosphodiesterase type 5 inhibitor may be used alone; however, symptom improvement and an increase in peak urinary flow rate have been demonstrated when it is used along with an α-adrenergic antagonist or a 5α-reductase inhibitor.

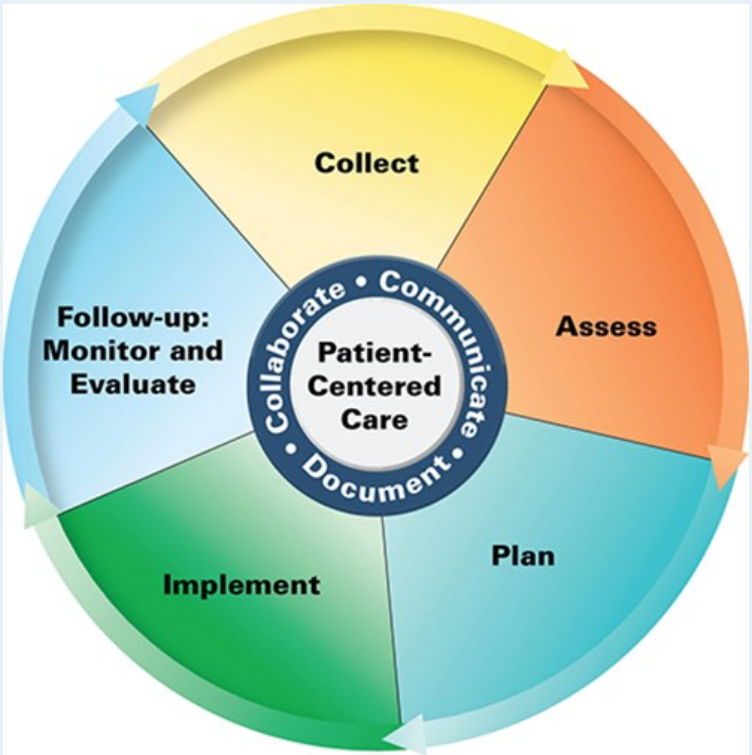
8 Anticholinergic agents are indicated in patients with moderate-to-severe lower urinary tract symptoms (LUTS) with a predominance of irritative voiding symptoms. In this case, the drugs are commonly added to an existing regimen of an α_1-adrenergic antagonist or a 5α-reductase inhibitor. Because older patients are at high risk of systemic and central nervous system anticholinergic adverse effects, uroselective anticholinergic agents or those with a low potential to cross the blood brain barrier are preferred over nonuroselective agents. To minimize the risk of acute urinary retention, anticholinergics should be used cautiously in patients when baseline PVR urine volume is greater than 100 to 150 mL. In addition, the anticholinergic medication burden should be assessed by examining the patient's medication profile before starting an anticholinergic agent.

9 β_3-Adrenergic agonists relax the detrusor muscle to increase the bladder's storage capacity and prolong the interval between voidings. These medications are indicated for treatment of overactive bladder symptoms, including urgency and nocturia, which mimic irritative lower urinary tract voiding symptoms. Thus, a β_3-adrenergic agonist is an alternative to an anticholinergic agent in patients with irritative voiding symptoms that do not respond to α_1-adrenergic antagonists or in patients who cannot tolerate anticholinergic adverse effects.

10 Surgery is indicated for severe symptoms of BPH for patients who do not respond to or do not tolerate drug therapy, or for patients with complications of BPH. It is the most effective mode of treatment because it relieves symptoms and increases peak urinary flow rate in the greatest number of men with BPH. However, the two conventional techniques, transurethral resection of the prostate (TURP) and open prostatectomy, are associated with the highest rates of complications, including retrograde ejaculation and erectile dysfunction. Moreover, because medications are first-line treatment for patients with moderate-to-severe symptoms of BPH, patients who are surgical candidates are often older and more frail. Therefore, minimally invasive surgical procedures are often sought by patients and urologists. Such procedures relieve symptoms and are associated with a lower rate of adverse effects and do not require hospitalization, but they have higher reoperation rates than the standard procedures.

PATIENT CARE PROCESS

Patient Care Process for Benign Prostatic Hyperplasia



Collect

- Patient characteristics (eg, age, race)
- Patient history (past medical history, family history, social—tobacco, recreational drug, or alcohol use)
- Presence of bladder symptoms that are obstructive (slow urinary stream, intermittency, hesitancy, straining to urinate, incomplete emptying, dribbling) and/or irritative (urgency, frequency, nocturia) (see Clinical Presentation box)
- Patient's perception of bothersomeness of voiding symptoms using American Urological Association (AUA) Symptom Score (see Diagnostic Evaluation section)
- Current and past medications, including prescription and nonprescription medications or nonpharmacologic interventions for BPH and medications perceived as causing BPH (see Medication-Related Symptoms section)
- Objective data (see Diagnostic Evaluation section and Clinical Presentation box)
    - BP, heart rate (HR), height, weight, and body mass index (BMI)
    - Digital rectal examination
    - Labs (eg, urinalysis, blood urea nitrogen, serum creatinine, prostate-specific antigen)
    - Urinary flow rates and postvoid residual volume

Assess

- Disease severity (see Table 104-1); patient's views on watchful waiting (in mild cases), medical treatment (in moderate-to-severe cases), and surgery (in severe cases)
- Need for further evaluation based on laboratory and examination findings
- Size of prostate by digital rectal exam or transrectal ultrasound of the prostate
- Presence of BPH, prostate cancer, prostatitis, all of which can cause lower urinary-tract symptoms (LUTS)

Plan*

- Dietary and lifestyle modifications to avoid problematic symptoms and situations (see Medication-Related Symptoms section and Clinical Presentation box)
- Interventions as indicated to encourage heart-healthy lifestyle, smoking cessation, weight loss if needed, management of other chronic diseases
- Drug therapy regimen including specific agent(s), dose, route, frequency, and duration; specify the continuation and discontinuation of existing therapies (see Fig. 104-2 and Tables 104-2, 104-3, and 104-4), advantages or disadvantages of single drug versus combination therapy
- Monitoring parameters including efficacy (symptom relief) and safety (medication-specific adverse effects) (see Table 104-5)
- Patient education (eg, purpose of treatment, dietary and lifestyle modification, drug therapy)
- Comparison of during treatment responses by repeating AUA Symptom Score or using a voiding diary (see Diagnostic Evaluation section)
- Referrals to other providers when appropriate (eg, physician, urologist)

Implement*

- Provide patient education regarding all elements of treatment plan
- Use motivational interviewing and coaching strategies to maximize adherence
- Schedule follow-up

Follow-up: Monitor and Evaluate

- Determine BPH goal attainment
- Presence of adverse effects
- Patient adherence to treatment plan using multiple sources of information

**Collaborate with patient, caregivers, and other healthcare professionals.*

BEYOND THE BOOK

BEYOND THE BOOK

Go to a reference text on anatomy and physiology and review the section on the biological male genitourinary tract. Draw a diagram of these organs that shows the anatomical relationship of the kidneys, ureters, urinary bladder, prostate, urethra, and testicles. Then explain how an enlarged prostate could cause obstruction of urinary outflow from the bladder and lead to overflow incontinence, recurrent urinary tract infection, and renal failure.

INTRODUCTION

Benign prostatic hyperplasia (BPH) is the most common benign neoplasm of American men. A nearly ubiquitous condition among elderly men, BPH is of major societal concern, given the large number of men affected, the progressive nature of the condition, and the healthcare costs associated with it. This chapter discusses BPH and its available treatments: watchful waiting, α_1-adrenergic antagonists, 5α-reductase inhibitors, phosphodiesterase inhibitors, anticholinergic agents, β_3-adrenergic agonist, and surgery. The limitations of phytotherapy are described.

Editors' note: In this and other chapters in Pharmacotherapy*, references to biologic gender (as assigned at birth) are used based on prior literature being discussed or anatomical or physiologic differences. We recognize that not all individuals identify with their gender at birth, and to the degree possible when discussing therapeutics, we avoid use of references to gender. In this chapter, gender is used in discussing prior studies, published guidelines, and other recommendations for diagnosis and treatment based on biological gender and does not necessarily reflect an individual's gender identity.*

EPIDEMIOLOGY

According to the results of autopsy studies, approximately 80% of older men develop histologic evidence of BPH. About half of the patients with microscopic changes develop an enlarged prostate gland, and as a result, they may develop symptoms including difficulty emptying urine from the urinary bladder. Approximately half of symptomatic patients eventually require treatment. Thus, the disease can be characterized by three stages: Benign prostatic hyperplasia (BPH), benign prostatic enlargement (BPE), and benign prostatic obstruction (BPO). While BPH itself may not require treatment, some patients with BPE, depending on the size of the prostate, will be at risk of developing complications of BPH. In these patients, 5α-reductase inhibitors can reduce disease complications and delay the need for prostate surgery. In patients with moderate-to-severe BPO, bothersome voiding symptoms require medical or surgical treatment.

1 The peak incidence of clinical BPH occurs between ages 63 and 65 years. Symptomatic disease is uncommon in men younger than 50 years, but

some urinary voiding symptoms are present by the time men reach 60 years of age. The Boston Area Normative Aging Study estimated that the cumulative incidence of clinical BPH was 78% for patients at age 80 years.[1] Similarly, the Baltimore Longitudinal Study of Aging projected that approximately 60% of men at least 60 years old develop clinical BPO.[2]

NORMAL PROSTATE PHYSIOLOGY

Located anterior to the rectum, the prostate is a small heart-shaped, chestnut-sized gland located below the urinary bladder. It surrounds the proximal urethra like a doughnut.

Soft, symmetric, and mobile on palpation, a normal prostate gland in an adult man weighs 15 to 20 g. Physical examination of the prostate must be done by digital rectal examination during which the prostate is manually palpated by inserting a finger into the rectum. Thus, the prostate is examined through the rectal wall.

The prostate gland comprises three layers: an innermost transition zone, a middle central zone, and an outermost peripheral zone.

The prostate has two major functions: (a) to secrete fluids that make up a portion (20%-40%) of the ejaculate volume and (b) to provide secretions with antibacterial effect possibly related to its high concentration of zinc.

ETIOLOGY

The etiologies of BPH include: (a) patient age of 40 years or more; (b) the stimulatory effect of androgens; (c) increased α-adrenergic tone in smooth muscle of the prostate and prostatic urethra; and (d) chronic inflammation of the prostate.

Patient Age of 40 Years or More

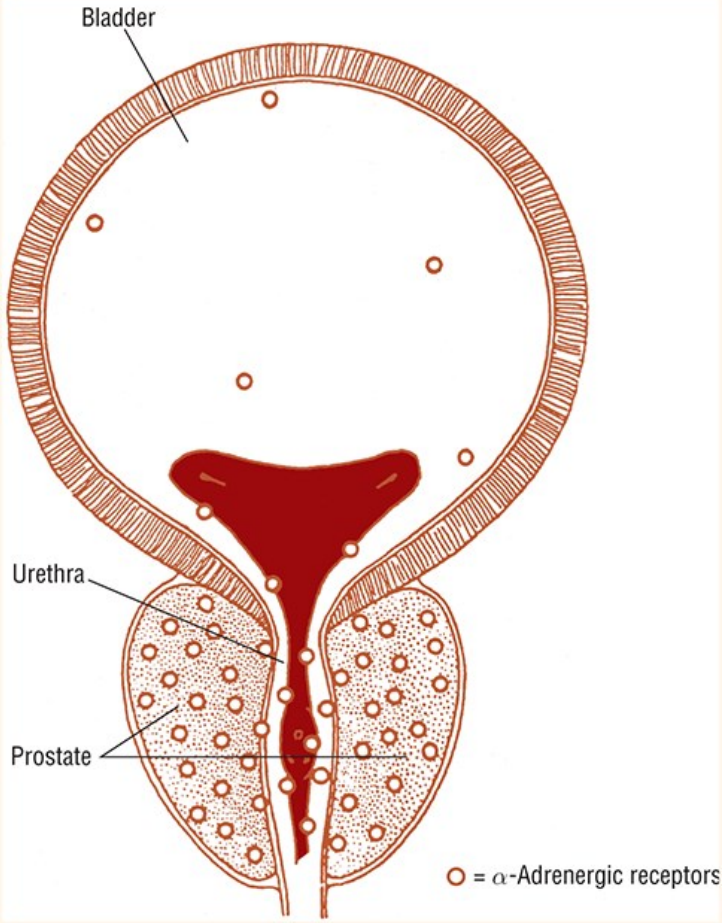
At birth, the prostate is the size of a pea and weighs approximately 1 g. The prostate remains that size until the boy reaches puberty. At that time, the prostate undergoes its first growth spurt, growing to its normal adult size of 15 to 20 g by the time the man is 25 to 30 years old. The prostate remains this size until the patient reaches the age of 40 years, when a second growth spurt begins and continues for the rest of his lifetime. During this second growth spurt, BPE develops.[3]

Stimulatory Effect of Androgens and Increased α-Adrenergic Tone

The prostate gland comprises three types of tissue: epithelial tissue, stromal tissue, and the capsule. Epithelial tissue, also known as *glandular tissue*, produces prostatic secretions. These secretions are delivered into the urethra during ejaculation and contribute to the total ejaculate volume. Androgens stimulate epithelial tissue growth. Stromal tissue, also known as *smooth muscle tissue*, is embedded predominantly with α_1-adrenergic receptors, predominately of the α_{1A} subtype. Stimulation of these receptors by norepinephrine causes smooth muscle contraction, which results in an extrinsic compression of the urethra, reduction of the urethral lumen, and decreased urinary bladder emptying. The normal prostate is composed of a higher amount of stromal tissue than epithelial tissue, as reflected by a stromal-to-epithelial tissue ratio of 2:1. This ratio is exaggerated to 5:1 for patients with BPH, which explains why α_1-adrenergic antagonists are quickly effective for symptomatic management and why 5α-reductase inhibitors reduce an enlarged prostate gland by only 25%.[3] The capsule, or outer shell of the prostate, is composed of fibrous connective tissue and smooth muscle, which also is embedded with α_1-adrenergic receptors. When stimulated with norepinephrine, the capsule contracts around the prostatic urethra (Fig. 104-1).

FIGURE 104-1

Representation of the anatomy of α-adrenergic receptor distribution in the prostate, urethra, and bladder. *(Reproduced from Narayan P, Indudhara R. Pharmacotherapy for benign prostatic hyperplasia. Western Journal of Medicine. 1994;161(5):495-506. Copyright © 1994 with permission from BMJ Publishing Group Ltd.)*



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

Testosterone is the principal testicular androgen in males, whereas androstenedione is the principal adrenal androgen. These two hormones are responsible for penile and scrotal enlargement, increased muscle mass, and maintenance of the normal male libido. These androgens are converted by 5α-reductase in target cells to dihydrotestosterone (DHT), an active metabolite. Two types of 5α-reductase exist. Type I enzyme is localized to sebaceous glands in the frontal scalp, liver, and skin, although a small amount is in the prostate. DHT produced at these target tissues causes acne and increased body and facial hair. Type II enzyme is localized to the prostatic stroma, genital tissue, and hair follicles of the scalp. In the prostate, DHT induces growth and enlargement of the gland.[3]

In prostate cells, DHT has greater affinity for intraprostatic androgen receptors than testosterone, and DHT forms a more stable complex with the androgen receptor. Thus, DHT is considered a more potent androgen than testosterone in the prostate. Of note, despite the decrease in testicular androgen production in the aging male, intracellular DHT levels in the prostate remain normal, probably due to increased activity of intraprostatic 5α-reductase.[4]

Estrogen, a product of peripheral metabolism of androgens, is believed to stimulate the growth of the stromal portion of the prostate gland. Estrogens are produced when testosterone and androstenedione are converted by aromatase enzymes in peripheral adipose tissues.[4] In addition, estrogens may induce the androgen receptor.[2] As men age, the ratio of serum levels of testosterone to estrogen decreases as a result of a decline in testosterone production by the testes and increased adipose tissue conversion of androgen to estrogen.

Chronic Inflammation of the Prostate

Chronic inflammation stimulates stromal cell growth in the prostate. In addition, inflammation causes cytokine release, which stimulates glandular epithelial tissue proliferation and transition zone enlargement. Proposed triggers for chronic inflammation include dyslipidemia, low serum

testosterone, and hyperestrogenism, which have all been associated with metabolic syndrome, a common disorder of aging men and those with BPH.[5-7]

PATHOPHYSIOLOGY

Although the precise pathophysiologic mechanisms causing BPH remain unclear, the role of intraprostatic DHT and type II 5α-reductase in the development of BPH is evidenced by several observations:

1. BPH does not develop in men who are castrated before puberty.
2. Patients with type II 5α-reductase enzyme deficiency do not develop BPH.
3. Castration causes an enlarged prostate to shrink.
4. Administration of testosterone to orchiectomized dogs of advanced age produces BPH.

The pathogenesis of BPH is often described as resulting from both static and dynamic factors. Static factors relate to anatomic enlargement of the prostate gland, which produces a physical block at the bladder neck and thereby obstructs urinary outflow. Enlargement of the gland depends on androgen stimulation of epithelial tissue and estrogen stimulation of stromal tissue in the prostate. Dynamic factors relate to excessive α-adrenergic tone of the stromal component of the prostate gland, bladder neck, and posterior urethra, which results in contraction of the prostate gland around the urethra and narrowing of the urethral lumen.[5,7]

Obstructive voiding symptoms of BPH disease, which include decreased force of the urinary stream and incomplete bladder emptying, may result from static and/or dynamic factors, and this must be recognized when drug therapy is considered. For instance, some patients may present with obstructive voiding symptoms, but have prostates of normal size. In these patients, dynamic factors likely are responsible for the symptoms. However, for patients with enlarged prostate glands, static and dynamic factors likely are working in concert to produce the observed symptoms. Moreover, the likelihood of developing moderate-to-severe obstructive voiding symptoms is directly related to the increasing size of the prostate gland.[5,7]

Dynamic factors may be accentuated if the patient becomes stressed or is in pain. In these situations, increased α-adrenergic tone may precipitate excessive contraction of prostatic stromal tissue. When the stressful event resolves, voiding symptoms often improve.[2]

Irritative voiding symptoms of BPH disease, which include urinary frequency and urgency, result from long-standing bladder outlet obstruction. As BPH progresses, the bladder muscle undergoes hypertrophy so that it can generate a greater contractile force to empty urine past the anatomic obstruction at the bladder neck. Decompensation eventually occurs and the hypertrophied bladder muscle is no longer able to generate adequate contractile force; the bladder becomes ineffective in emptying urine. Acute urinary retention, recurrent urinary tract infections, and renal failure complicate progressive, untreated disease.[8]

MEDICATION-RELATED SYMPTOMS

Medications in several pharmacologic categories should be avoided for patients with BPH because they may exacerbate symptoms. Testosterone replacement regimens, used to treat primary or secondary hypogonadism, deliver additional substrate that can be metabolized to DHT by the prostate. Although no cases of BPH have been reported because of exogenous testosterone administration, cautious use is advised for older patients with prostatic enlargement. α-Adrenergic agonists, used as oral or intranasal decongestants (eg, pseudoephedrine, ephedrine, or phenylephrine), can stimulate α-adrenergic receptors in the prostate, resulting in muscle contraction. By decreasing the caliber of the urethral lumen, bladder emptying may be compromised. β-Adrenergic agonists (eg, terbutaline) may cause relaxation of the bladder detrusor muscle, which prevents bladder emptying.[6] Drugs with significant anticholinergic adverse effects (eg, antihistamines, phenothiazines, tricyclic antidepressants, or anticholinergic drugs used as antispasmodics or to treat Parkinson's disease) may decrease contractility of the urinary bladder detrusor muscle. For patients with BPH who have a narrowed urethral lumen, loss of effective detrusor contraction could result in acute urinary retention, particularly for patients with significantly enlarged prostate glands and a PVR urine volume greater than 150 mL. Diuretics, particularly in large doses, can produce polyuria, which may present as urinary frequency, similar to that experienced by patients with BPH.[8]

CLINICAL PRESENTATION

Patients with BPH can present with a variety of symptoms and signs of disease. All symptoms of BPH can be divided into two categories: obstructive and irritative.

Obstructive symptoms, also known as *prostatism* or *bladder outlet obstruction*, result when dynamic and/or static factors reduce bladder emptying. The force of the urinary stream becomes diminished, urinary flow rate decreases, and bladder emptying is incomplete and slow. Patients report urinary hesitancy and straining and a weak urine stream. Urine dribbles out of the penis, and the urinary bladder always feels full, even after patients have voided. Some patients state that they need to press on their bladder to force out the urine. In severe cases, patients may go into urinary retention when bladder emptying is not possible. In these cases, suprapubic pain can result from bladder overdistension.

Approximately 50% to 80% of patients have irritative voiding symptoms, which typically occur late in the disease course. Irritative voiding symptoms include urinary frequency and urgency. Patients may report waking up every 1 to 2 hours at night to void (nocturia), which significantly reduces quality of life.

Symptoms of BPH vary over time. Symptoms may improve, remain stable, or worsen spontaneously. Thus, BPH is not necessarily a progressive disease; approximately 85% of patients with BPH have stable symptoms when evaluated 4 years after initial diagnosis.[8] Between one-third and two-thirds of men with mild disease stabilize or improve without treatment over 2.5 to 5 years.[2,9] However, worsening symptoms and complications of BPH develop in patients, particularly those with a prostate gland volume greater than 30 to 40 mL or PSAs of 1.4 ng/mL (mcg/L) or greater.[2,9] A patient with a prostate volume of 30 mL or more is three times more likely to develop acute urinary retention.

Collectively, obstructive and irritative voiding symptoms and their negative impact on a patient's quality of life are referred to as *lower urinary tract symptoms* (LUTS). However, LUTS is not pathognomonic for BPH and may be caused by other diseases, such as neurogenic bladder or urinary tract infection.[2]

Another presentation of BPH is silent prostatism. Patients have LUTS but adapt to the symptoms and do not voluntarily complain about them. Such patients do not present for medical treatment until complications of BPH disease arise or a spouse brings in the symptomatic patient for medical care.

When BPH progresses, it can produce complications that include the following:

1. Acute, painful urinary retention, which can lead to acute renal failure.
2. Persistent or intermittent gross hematuria when tissue growth exceeds its blood supply.
3. Overflow urinary incontinence or unstable bladder.
4. Recurrent urinary tract infection that results from urinary stasis.
5. Bladder diverticula.
6. Bladder stones.
7. Chronic renal failure from long-standing bladder outlet obstruction.

Approximately 17% to 20% of patients with symptomatic BPH require treatment because of disease complications.[7] Men older than 70 years with large prostates of more than 40 g and a PVR urine volume greater than 100 mL are three times more likely to have severe symptoms or suffer from acute urinary retention and to require prostatectomy than patients with smaller prostates. Thus, a serum PSA level of 1.4 ng/mL (mcg/L) or greater has been used as a surrogate marker for an enlarged prostate gland to identify patients at risk for developing complications of BPH disease and has been used to guide selection of the most appropriate treatment modality in some patients.[9]

DIAGNOSTIC EVALUATION

Because the obstructive and irritative voiding symptoms associated with BPH are not unique to the disease and can be presenting symptoms of other

genitourinary tract disorders, including prostate or bladder cancer, neurogenic bladder, prostatic calculi, or urinary tract infection, the patient presenting with signs and symptoms of BPH must be thoroughly evaluated.

A careful medical history should be taken to ensure that a complete listing of symptoms is collected to identify concomitant disorders that may be contributing to voiding symptoms. The medical history should be followed by a thorough medication history, including all prescription and nonprescription medications and dietary supplements that the patient is taking. Any drugs that could be causing or exacerbating the patient's symptoms should be identified. If possible, the suspected drugs should be discontinued or the dosing regimen modified to ameliorate the voiding symptoms.

The patient should undergo a physical examination, including a digital rectal examination, although the size of the prostate gland may not correspond to symptoms. Some patients have only a slightly enlarged gland and yet have bothersome or even serious voiding difficulties. Other patients have intravesical enlargement of the prostate gland (ie, the gland grows into the urinary bladder and produces a ball-valve blockage of the bladder neck). This type of prostate enlargement is not palpable on digital examination.

The patient's perception of the severity of BPH symptoms guides selection of a particular treatment modality in a patient. To evaluate the patient's perceptions objectively, validated instruments, such as the AUA Symptom Score (Table 104-1), are commonly used. Using this tool, the patient rates the "bothersomeness" of seven obstructive and irritative voiding symptoms.[9] A patient's perception of bothersomeness is often based on how much these symptoms interfere with daily activities or cause worry or embarrassment in social settings. Each item is rated for severity on a scale from 0 to 5, such that 35 is the maximum score and is consistent with the most severe symptoms. Patients usually are stratified into the three groups shown in the table based on disease severity for the purposes of deciding a treatment approach.

TABLE 104-1

Categories of BPH Disease Severity Based on Symptoms and Signs

Disease Severity	AUA Symptom Score[a]	Typical Symptoms and Signs
Mild	≤7	• Asymptomatic • Peak urinary flow <10 mL/s • PVR urine volume >25-50 mL
Moderate	8-19	• Peak urinary flow rate <10 mL/s • PVR urine volume >25-50 mL • Plus obstructive voiding symptoms and irritative voiding symptoms (signs of detrusor instability)
Severe	≥20	All of the above plus 1 or more complications of BPH[a]

[a]Score range, 0-35.

AUA, American Urological Association; BPH, benign prostatic hyperplasia; BUN, blood urea nitrogen; PVR, postvoid residual urine volume.

In addition, the patient can complete a voiding diary in which he records the number of voids, the volume of each void, and voiding symptoms each day for several days. This information is used to evaluate symptom severity and tailor recommendations for lifestyle modifications that may ameliorate symptoms.

The only clinical laboratory test that must be performed is a urinalysis. Because many of the voiding symptoms of BPH could be caused by other urologic disorders, a urinalysis can help screen for hematuria, urolithiasis, and infection. To screen for prostate cancer, another common cause of glandular enlargement, a PSA test may be performed for patients aged 40 years or more, with at least a 10-year life expectancy, in whom the potential benefit of diagnosing the disorder will be outweighed by the cost of the test.[9]

Objective measures of bladder emptying include peak and average urinary flow rate (normal is at least 10 mL/s). These measures are determined using an uroflowmeter, which checks the rate of urine flow out of the bladder. This is a quick noninvasive outpatient procedure in which the patient is instructed to drink water until his bladder feels full and then the patient's urinary flow is clocked during voiding. A low urinary flow rate (<10-12 mL/s) implies failure of bladder emptying due to obstruction or a functional disorder of the detrusor muscle. A patient with such a low urinary flow rate has a fourfold greater risk of acute urinary retention than patients with higher urinary flow rates.[5,7]

Another objective measure is PVR urine volume (normal is 0 mL), which is assessed using abdominal ultrasonography. A PVR urine volume of 25 to 50 mL or more implies failure of bladder emptying and a predisposition for urinary tract infections, whereas a PVR of 100 mL or more has been associated with progressive worsening of BPH symptoms if no specific treatment is initiated.[10]

Because of a weak correlation among voiding symptoms, prostate size, and urinary flow rate, most physicians use a combination of measures, including the patient's assessment of symptoms along with objective evaluation of urinary outflow, PVR, and presence of complications of BPH to determine the need for treatment.

Many other tests can be performed if additional information is needed to assess the severity of BPH disease and its complications, to assist in the preoperative assessment of the patient, or to distinguish prostate enlargement due to BPH from that caused by prostate cancer. Tests include a serum BUN and creatinine, voiding cystometrogram, transrectal ultrasound of the prostate, IV pyelogram, renal ultrasound, and prostate biopsy.

CLINICAL PRESENTATION

CLINICAL PRESENTATION: Benign Prostatic Hyperplasia

General

- A patient is in no acute distress unless he has moderate-to-severe symptoms or complications of BPH.

Symptoms

- Obstructive symptoms: Slow urinary stream, intermittency, hesitancy, straining to urinate, incomplete emptying, dribbling
- Irritative symptoms: Urgency, frequency, nocturia

Signs

- Digital rectal examination reveals an enlarged prostate (>20 g) with no nodules or indurations; prostate is soft, symmetric, and mobile.

Laboratory Tests

- Increased blood urea nitrogen (BUN) and serum creatinine with long-standing, untreated bladder outlet obstruction, elevated prostate-specific antigen (PSA) level

Other Diagnostic Tests

- Increased American Urological Association (AUA) Symptom Score, decreased urinary flow rate (<10 mL/s), and increased PVR urine volume

TREATMENT

The goals of treatment are to control symptoms, as evidenced by a minimum of a three-point decrease in the AUA symptom index, prevent progression of BPH disease by reducing the risk of developing complications, and delay the need for surgical intervention.

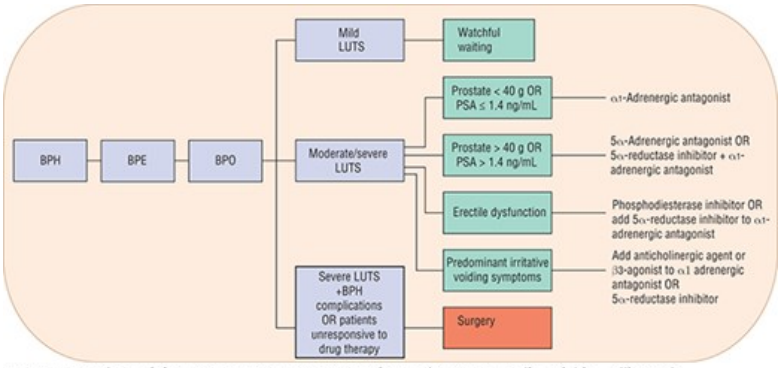
As a disease of symptoms, BPH is treated by relieving bothersome symptoms. However, selection of a single best treatment for a patient must consider the variable costs and adverse effects of treatment options, the inability to predict the course of the disease in an individual patient, and the potential

benefit that may occur in a comparatively small number of treated patients.

The 2021 AUA Guidelines on Management of Benign Prostatic Hyperplasia[9] is the principal tool used in the United States and is similar to the 2021 European Guidelines[11] (Fig. 104-2). In a patient with BPH, BPE, or BPO, if symptoms are mild, watchful waiting is recommended. If symptoms are moderate-to-severe with erectile dysfunction, an α-adrenergic antagonist, a phosphodiesterase inhibitor, or both are recommended. If symptoms are moderate-to-severe with a small prostate and low PSA, an α-adrenergic antagonist is recommended. If symptoms are moderate-to-severe with a large prostate and increased PSA, consider a 5α-reductase inhibitor plus an α-adrenergic antagonist. If symptoms are moderate-to-severe with predominant irritative voiding symptoms, consider an α-adrenergic antagonist plus an anticholinergic agent, or an α-adrenergic antagonist plus mirabegron. If symptoms are severe and the patient has complications of BPH or is not responding to medication therapy, surgical intervention is indicated.[9,11]

FIGURE 104-2

Management algorithm for benign prostatic hyperplasia (BPH).



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

Although phytotherapy is used by some patients alone or along with conventional medications for BPH, head-to-head comparisons with FDA-approved treatments are lacking; consequently, such herbals cannot be recommended at this time.[9,11]

3 Patients with mild disease are asymptomatic or have mildly bothersome symptoms and have no complications of BPH disease. These patients can be managed with watchful waiting, which entails having the patient return for reassessment at intervals of 6 to 12 months. At each return visit, the patient should complete a standardized, validated survey tool to assess severity of symptoms, and objective signs of disease should be assessed using measurements of urinary flow rate and PVR urine volume. Watchful waiting should be accompanied by patient education about the disease and behavior modification to avoid practices that exacerbate voiding symptoms. Behavior modification includes restricting fluids close to bedtime, minimizing caffeine and alcohol intake, frequent emptying of the bladder during waking hours or before long trips (to avoid overflow incontinence and urgency), smoking cessation, and avoiding drugs that could exacerbate voiding symptoms.[3,8,12,13] At each visit, physicians should assess the patient's risk of developing acute urinary retention by evaluating the patient's prostate size or using PSA as a surrogate marker of prostate enlargement.[14]

4 If symptoms progress to the moderate or severe level, or the patient perceives his symptoms to be bothersome, the patient should be offered specific treatment. In these patients, watchful waiting delays—but does not decrease—the need for prostatectomy. In symptomatic patients, watchful waiting can lead to intractable urinary retention, increased PVR urine volumes, and significant voiding symptoms.[9,11] Recommended treatment options include drug therapy with an α_1-adrenergic antagonist or 5α-reductase inhibitor, a combination of an α_1-adrenergic antagonist and a 5α-reductase inhibitor, a phosphodiesterase inhibitor alone or combined with an α_1-adrenergic antagonist or 5α-reductase inhibitor, or the addition of an anticholinergic agent or a β_3-agonist to an α_1-adrenergic antagonist or 5α-reductase inhibitor particularly if the patient has significant irritative voiding symptoms that are not responsive to an α_1-adrenergic antagonist alone or 5α-reductase inhibitor alone, or surgery.

Patients with serious complications of BPH or patients who do not respond to drug therapy should be offered surgical intervention. Drug therapy is considered an interim measure for such patients because it delays worsening of complications and the need for surgical intervention.[9]

Desired Outcomes

The desired outcomes of treatment include reducing LUTS as evidenced by an improvement of AUA Symptom Score by at least three points, an increase in the peak urinary flow rate, and a normalization of PVR to less than 50 mL. In addition, treatment should prevent the development of disease complications and reduce the need for surgical intervention. Treatment should be well tolerated and be cost-effective.

General Approach to Treatment

In selecting the most appropriate treatment for an individual patient, consideration should be given to the severity and quality of the patient's LUTS, the likelihood of developing complications of BPH (based on size of the prostate gland or the PSA level), the patient's preference for medical versus surgical intervention, the patient's risk for adverse effects of treatment, and the cost of treatment.

Concurrent medical illnesses of the patient should also be considered. For example, if the patient has erectile dysfunction and moderate LUTS, then a phosphodiesterase inhibitor might be preferred over an α_1-adrenergic antagonist. If the patient has overactive bladder syndrome and BPH, irritative voiding symptoms may require the addition of an anticholinergic agent or a β_3-adrenergic agonist. If medical treatment is initiated, the patient's level of renal function should be assessed, as the daily dose of some α-adrenergic antagonists and some anticholinergics require modification to avoid accumulation.

Nonpharmacologic Therapy

BPH is a chronic, nonfatal medical illness. All patients should be encouraged to initiate and maintain a heart-healthy lifestyle, including a low-fat diet, high intake of plenty of fresh fruits and vegetables, regular physical exercise, and no smoking.[15] Patients who have overweight or obesity should be encouraged to lose weight. Those with diabetes mellitus, dyslipidemia, or hypertension should be advised to optimize management of those disorders.[5,8] The patient should avoid excess consumption of caffeine-containing beverages (which may induce diuresis). Patients should void before retiring to bed at night and before long car rides.

Pharmacologic Therapy

Drug therapy for BPH can be categorized into three types: agents that relax prostatic smooth muscle (reducing the dynamic factor), agents that interfere with testosterone's stimulatory effect on prostate gland enlargement (reducing the static factor), and agents that relax bladder detrusor muscle (improving the urine storage capacity of the bladder) (Tables 104-2 and 104-3). Of the agents that relax prostatic smooth muscle, second- and third-generation α_1-adrenergic antagonists have been most widely used. These agents relax the intrinsic urethral sphincter and prostatic smooth muscle, thereby enhancing urinary outflow from the bladder. Phosphodiesterase inhibitors also relax bladder neck and prostatic smooth muscle. α_1-Adrenergic antagonists and phosphodiesterase inhibitors do not reduce prostate size. Of the agents that interfere with testosterone's stimulatory effect on prostate gland size, the only agents approved by the FDA are 5α-reductase inhibitors (eg, finasteride, dutasteride). Other agents that interfere with androgen stimulation of the prostate have not been popular in the United States because of the many adverse effects associated with their use. The luteinizing hormone-releasing hormone superagonists leuprolide and goserelin decrease libido and can cause erectile dysfunction, gynecomastia, and hot flashes. Antiandrogens (eg, bicalutamide, flutamide) produce nausea, diarrhea, gynecomastia, and hepatotoxicity. Finally, antimuscarinic agents and β_3-adrenergic agonists relax the detrusor muscle, which reduces irritable voiding symptoms, improves urine storage capacity of the bladder, and increases the interval between voidings.[9,11–13]

TABLE 104-2

Medical Treatment Options for Benign Prostatic Hyperplasia

Category	Mechanism	Drug (Brand Name)
Reduces dynamic factor	Blocks α_1-adrenergic receptors in prostatic stromal tissue	• Prazosin (Minipress)[a] • Alfuzosin (Uroxatral) • Terazosin (Hytrin) • Doxazosin (Cardura)
	Blocks α_{1A}-adrenergic receptors in prostatic stromal tissue	• Tamsulosin (Flomax) • Silodosin (Rapaflo)
	Inhibits phosphodiesterase type 5 in prostate, urethra, bladder, and pelvic blood vessels	• Tadalafil (Cialis)
Reduces static factor	Blocks 5α-reductase enzyme	• Finasteride (Proscar) • Dutasteride (Avodart)
	Blocks DHT at its intracellular receptor	• Bicalutamide (Casodex)[a] • Flutamide (Eulexin)[a]
	Blocks pituitary release of luteinizing hormone	• Leuprolide (Lupron)[a] • Goserelin (Zoladex)[a]
	Blocks pituitary release of luteinizing hormone and blocks androgen receptor	• Megestrol acetate (Megace)[a]
Relaxes detrusor muscle	Blocks muscarinic receptors in detrusor muscle of bladder	• Tolterodine (Detrol)[a] • Oxybutynin (Ditropan)[a] • Trospium (Sanctura)[a] • Solifenacin (Vesicare)[a] • Darifenacin (Enablex)[a] • Fesoterodine (Toviaz)[a]
	Stimulates β_3-adrenergic receptors in detrusor muscle of bladder	• Mirabegron (Myrbetriq)[a] • Vibegron (Gemtesa)[a]

[a]Not FDA approved for treatment of benign prostatic hyperplasia.

TABLE 104-3

Comparison of α_1-Adrenergic Antagonists, 5α-Reductase Inhibitors, Phosphodiesterase Inhibitors, and Anticholinergic Agents and β_3-Adrenergic Agonists for Benign Prostatic Hyperplasia

	α_1-Adrenergic Antagonists	5α-Reductase Inhibitors
Relaxes prostatic smooth muscle	Yes	No
Decreases prostate size	No	Yes
Halts disease progression	No	Yes
Peak onset	1-6 weeks	3-6 months
Efficacy in relieving BOO	++	++ (for patients with enlarged prostates)
Frequency of dosing	One to two times per day, depending on the agent and dosage formulation	Once per day
Decreases PSA	No	Yes
Sexual dysfunction adverse effects	EJD	Decreased libido, ED, EJD
Cardiovascular adverse effects	Yes	No
	Phosphodiesterase Inhibitors	**Anticholinergic Agents**
Relaxes prostatic smooth muscle	Yes	No
Decreases prostate size	No	No
Halts disease progression	No	No
Peak onset	4 weeks	1-2 weeks
Efficacy in relieving BOO	+	+ (irritative symptoms only)
Frequency of dosing	Once per day	Once per day
Decreases prostate-specific antigen	No	No
Sexual dysfunction adverse effects	No	ED
Cardiovascular adverse effects	Yes (mild hypotension)	Yes (tachycardia)
	β_3-Adrenergic Agonists	
Relaxes prostatic smooth muscle	No	
Decreases prostate size	No	
Halts disease progression	No	

Peak onset	2 weeks, but may take up to 8 weeks	
Efficacy in relieving BOO	+ (irritative symptoms only)	
Frequency of dosing	Once per day	
Decreases prostate-specific antigen	No	
Sexual dysfunction adverse effects	No	
Cardiovascular adverse effects	Yes (hypertension)	

BOO, bladder outlet obstruction; BPH, benign prostatic hyperplasia; ED, erectile dysfunction; EJD, ejaculation disorder; PSA, prostate-specific antigen.

+ Notation is a quantitative assessment.

Selection of a medical treatment for a patient with moderate-to-severe symptoms should be determined on a case-by-case basis after the patient and provider discuss the risks, benefits, and costs of various treatments. With drug therapy for BPH, patients must understand that the benefits continue only as long as the medication is taken.

If possible, drug therapy should be initiated with a single agent, usually an α_1-adrenergic antagonist, which is faster acting and more effective than a 5α-reductase inhibitor. In addition, α_1-adrenergic antagonists are effective in reducing LUTS independent of prostate size and have no effect on PSA. Some are also available as less-expensive generic formulations. A 5α-reductase inhibitor is a good first-choice agent for symptomatic patients with a significantly enlarged prostate (>40 g) and an elevated PSA greater than or equal to 1.4 ng/mL (mcg/L). Such patients are at risk for developing complications of BPH, and typically combination drug therapy with an α_1-adrenergic antagonist and a 5α-reductase inhibitor is prescribed. The pharmacologic rationale for such a combination is that using two drugs with different mechanisms of action can be more effective than either drug alone. Also combination drug therapy quickly relieves symptoms, delays disease progression, and reduces the need for surgical intervention. Since it is more expensive and associated with more adverse effects than single-drug therapy, combination drug therapy should be reserved for those patients who will benefit the most from it.

For patients with both erectile dysfunction and BPH, a phosphodiesterase inhibitor alone or in combination with an α-adrenergic antagonist may be used. However, it should be noted that a phosphodiesterase inhibitor alone will only relieve LUTS, and will not produce a clinically significant increase in urinary flow rate or a decrease in PVR. Therefore, a phosphodiesterase inhibitor is generally considered less effective than an α-adrenergic antagonist.

For patients with a predominance of irritative voiding symptoms, an anticholinergic agent could be added to an existing drug regimen for BPH. To reduce the risk of developing systemic anticholinergic adverse effects, a uroselective anticholinergic agent may be prescribed. To avoid the risk of developing acute urinary retention, an anticholinergic agent should be used cautiously when the patient's PVR is greater than 250 to 300 mL. Mirabegron and vibegron are more expensive than many anticholinergic agents. Therefore, they should be reserved as an add-on treatment for patients with irritative voiding symptoms who cannot tolerate anticholinergic adverse effects.

α_1-Adrenergic Antagonists

Three generations of α-adrenergic antagonists have been used to treat BPH. They all relax smooth muscle in the prostate and bladder neck. Because antagonism of presynaptic α_2-adrenergic receptors produces tachycardia and arrhythmias, first-generation α-adrenergic agents, such as phenoxybenzamine, have been replaced by the second-generation postsynaptic α_1-adrenergic antagonists and third-generation uroselective postsynaptic α_{1A}-adrenergic antagonists.

5 The second- and third-generation α_1-adrenergic antagonists are considered equally effective for treatment of BPH.[9,16] These agents generally

improve the AUA Symptom Score by 30% to 40%, decreasing the AUA Symptom Index by three to six points, within 1 to 6 weeks, depending on the need for dose titration; increase urinary flow rate by 2 to 3 mL/s in 60% to 70% of treated patients; and reduce PVR urine volume.[3,12,16] With continued use, durable clinical benefit has been demonstrated for years.[9] Their effectiveness in reducing BPH symptoms and the severity of adverse effects are dose-dependent.[9] They have no effect on prostate volume. α_1-Adrenergic antagonists do not reduce PSA levels, preserving the utility of this prostate cancer marker in this high-risk population.[9]

Older, immediate-release, second-generation α_1-adrenergic antagonists, and tamsulosin are available as inexpensive generic formulations, which may be desirable in selected patients.

Second-Generation α_1-Adrenergic Antagonists

Second-generation agents include prazosin, terazosin, doxazosin, and alfuzosin. These are all nonselective α_1-adrenergic antagonists. At the usual doses used to treat BPH, immediate-release formulations of prazosin, terazosin, and doxazosin antagonize peripheral vascular α_1-adrenergic receptors. As a result, first-dose syncope, orthostatic hypotension, and dizziness are characteristic adverse effects. In older adults, such adverse effects could lead to falls and bone fractures.[3,15,17] To improve tolerance to these adverse effects, therapy should start with a low dose of 1 mg daily and then should be slowly titrated up to a full therapeutic dose over several weeks. Additive blood-pressure-lowering effects commonly occur when these agents are used with antihypertensive agents, which limit the use of these agents for some patients. These agents differ in terms of duration of action and dosage formulation. Prazosin requires twice- to thrice-daily dosing and has significant cardiovascular adverse effects. For these reasons, it is not recommended in the current AUA guidelines for treatment of BPH.[9] Extended-release dosage formulations of doxazosin and alfuzosin offer the convenience of once-daily dosing, treatment initiation with a full therapeutic dose, and decreased dose-related hypotension because they produce lower peak serum concentrations than immediate-release products.

An α_1-adrenergic antagonist is not preferred as single-drug therapy for treatment of both BPH and hypertension in a patient. In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) of 24,000 patients with hypertension, doxazosin produced more congestive heart failure than amlodipine, lisinopril, or chlorthalidone.[18] Thus, both the AUA and the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure[9,19] recommend that patients with BPH and hypertension be treated with separate and appropriate drug treatment for each medical condition.

When using immediate-release formulations of the second-generation α_1-adrenergic antagonists terazosin and doxazosin, slow titration up to a therapeutic maintenance dose is necessary to minimize orthostatic hypotension and first-dose syncope. Conservatively, dosages should be increased in an orderly stepwise process, at 2- to 7-day intervals, depending on the patient's response to the medication. A faster titration schedule can be used as long as the patient does not develop orthostatic hypotension or dizziness. Two sample titration schedules for terazosin are as follows:

Schedule 1: Slow titration

- Days 4 to 14: 2 mg at bedtime
- Weeks 2 to 6: 5 mg at bedtime
- Weeks 7 and on: 10 mg at bedtime

Schedule 2: Quicker titration

- Days 1 to 3: 1 mg at bedtime
- Days 4 to 14: 2 mg at bedtime
- Weeks 2 to 3: 5 mg at bedtime
- Weeks 4 and on: 10 mg at bedtime

In addition, patients should take their dose at bedtime so that they can sleep through hypotensive side effects that are most likely to occur when peak blood levels are achieved. Patients should continue taking the drug as long as they continue to respond to it. Durable responses for 10 years have been reported for doxazosin.[9]

Alfuzosin is considered functionally and clinically uroselective in that usual doses used to treat BPH are less likely than other second-generation agents to cause cardiovascular adverse effects in animal or human models.[9] This clinical effect has been observed more often with the once-daily, extended-release formulation of alfuzosin, which is the only commercially available formulation in the United States. Its clinical uroselectivity has been postulated to be due to higher concentrations of alfuzosin achieved in the prostate versus serum after usual doses,[20,21] absence of high peak serum levels with the extended-release formulation, and the fixed dosing schedule of the extended-release formulation. Extended-release alfuzosin dosing is FDA approved for 10 mg daily, with no dose titration increase. This formulation is particularly convenient for patients who have difficulty remembering varying doses needed for up-titration dosing schedules.

Third-Generation α_1-Adrenergic Antagonists

Three subtypes of α_1-adrenergic receptors exist: (a) α_{1A}, which comprise 70% to 75% of the α-adrenergic receptors in the prostate, bladder neck, prostatic urethra, seminal vesicles, spermatic duct, and vas deferens (when stimulated, smooth muscle contraction and the emission phase of ejaculation occurs)[20,21]; (b) α_{1B}, which cause peripheral arterial smooth muscle contraction when stimulated; and (c) α_{1D}, which are found in the detrusor muscle of the bladder, prostate, urethra, and brain, but their function remains to be defined.[22]

Third-generation α_1-adrenergic antagonists preferentially inhibit α_{1A}-adrenergic receptors. Tamsulosin and silodosin are the only third-generation α_{1A}-adrenergic antagonists available in the United States. Blockade of these receptors relaxes smooth muscle of the prostate and bladder neck and improves bladder emptying in patients with BPH, but blockade is likely to cause ejaculatory disorders. In addition, both of these agents have low affinity for vascular α_{1B}-adrenergic receptors, which explains why hypotension is not as frequent with usual daily doses as compared with second-generation agents.[9]

Silodosin has 50-fold greater selectivity for the α_{1A}-adrenergic receptor than the α_{1D}-adrenergic receptor and has 100-fold greater selectivity for the α_{1A}-adrenergic receptor than the α_{1B}-adrenergic receptor.[9,23] Silodosin demonstrates greater pharmacologic uroselectivity than tamsulosin, which has a 10-fold greater selectivity for the α_{1A}-adrenergic receptor than the α_{1D}-adrenergic receptor and has 2.5-fold greater selectivity for the α_{1A}-adrenergic receptor than the α_{1B}-adrenergic receptor.[24] These pharmacologic differences are not associated with a significant difference in efficacy, but there is a higher incidence of ejaculatory disorders as an adverse effect in silodosin-treated patients as opposed to tamsulosin-treated patients.[23–25]

The uroselectivity of α_{1A}-adrenergic receptors has multiple implications. Dose titration is minimal; therefore, patients can start treatment with a therapeutic dose of tamsulosin 0.4 mg daily or silodosin 8 mg daily. Patients can be instructed to take the dose anytime during the day. It should be noted that the product labeling of tamsulosin and silodosin state that they should be taken 30 minutes after the same meal every day. Food decreases their oral bioavailability, reduces the peak serum concentration of the drug, and lowers the risk of hypotensive adverse effects. The onset of peak action is quick, in the range of 1 week. Increasing the daily dose of tamsulosin to 0.8 mg daily produces inconsistent improvements in effectiveness but does increase adverse effects.[26] These agents are well tolerated in patients with well-controlled hypertension; and the addition of tamsulosin to furosemide, enalapril, nifedipine, and atenolol does not result in hypotension.[27]

As compared with tamsulosin, silodosin requires dosage reduction in patients with a creatinine clearance of 30 to 50 mL/min (0.5-0.83 mL/s), is contraindicated in patients with severe hepatic insufficiency or a creatinine clearance less than 30 mL/min (0.5 mL/s), and has the potential to produce more adverse effects because of elevated plasma concentrations if used concurrently with potent CYP 3A4 inhibitors (eg, clarithromycin, itraconazole, ketoconazole, ritonavir) or P-glycoprotein inhibitors (eg, cyclosporine). Silodosin also causes more ejaculatory dysfunction than tamsulosin.[25,28] Finally, silodosin is commercially available from only one source, whereas tamsulosin is available as a generic formulation.

The usual doses of α_1-adrenergic antagonists are summarized in Table 104-4.

TABLE 104-4

Dosing of Drugs Used in Treatment of Benign Prostatic Hyperplasia

Drug	Brand Name	Initial Dose	Usual Dose	Special Population Dose
α-Adrenergic Antagonists				
Prazosin	Minipress	0.5 mg twice a day orally	1-5 mg twice a day orally	To uptitrate the dose, double the dose every 2 weeks.
Terazosin	Hytrin	1 mg at bedtime orally	10-20 mg daily orally	Take extra care if the patient is taking other drugs that lower blood pressure. No dosage adjustment is required for patients with renal or hepatic impairment.
Doxazosin	Cardura	1 mg daily orally	8 mg daily orally	When switching from the immediate- to the extended-release formulation, start with 4 mg of the extended-release formulation no matter what maintenance dose of immediate-release doxazosin the patient is taking. No dosage adjustment is required for patients with renal or hepatic impairment.
	Cardura XL	4 mg daily orally	4-8 mg daily	
Alfuzosin	Uroxatral	10 mg daily orally	10 mg daily orally (no dose titration)	This is an extended-release formulation, and it should not be chewed or crushed. The drug should be taken after meals and used cautiously in patients with creatinine clearance less than 30 mL/min (0.5 mL/s). No dosage adjustment is required for patients with mild hepatic impairment. It is contraindicated in patients with moderate-to-severe hepatic impairment.
Tamsulosin	Flomax	0.4 mg daily orally	0.4-0.8 mg daily orally	This is an extended-release formulation, and it should not be chewed or crushed. The drug should be taken after meals. No dosage adjustment is needed in patients with renal or liver impairment.
Silodosin	Rapaflo	8 mg daily orally	8 mg daily orally (no dose titration)	This drug is contraindicated when creatinine clearance is less than 30 mL/min (0.5 mL/s). If creatinine clearance is 30-50 mL/min (0.5-0.83 mL/s), use 4 mg daily orally, preferably after the same meal each day. No dosage adjustment is required for patients with mild-to-moderate hepatic impairment. Should not be given to patients on potent CYP 3A4 inhibitors or with severe hepatic impairment.
5α-Reductase Inhibitors				
Finasteride	Proscar	5 mg daily orally	5 mg daily orally	No dosage adjustment in patients with renal impairment. Use cautiously in patients with hepatic impairment.
Dutasteride	Avodart	0.5 mg daily orally	0.5 mg daily orally	No dosage adjustment in patients with renal impairment. Use cautiously in patients with hepatic impairment.
Dutasteride + tamsulosin	Jalyn	1 tablet (equivalent to 0.5-mg	1 tablet daily orally	No dosage adjustment needed in patients with renal or moderate hepatic impairment.

		dutasteride + 0.4-mg tamsulosin) daily orally		
Phosphodiesterase Inhibitor				
Tadalafil	Cialis	5 mg daily orally	5 mg daily orally	If creatinine clearance is 30-50 mL/min (0.5-0.83 mL/s), use 2.5 mg daily orally. Do not use if creatinine clearance is less than 30 mL/min (0.5 mL/s). Use cautiously in patients with mild-moderate hepatic impairment. Avoid in patients with severe hepatic impairment.
Anticholinergic Agents				
Darifenacin	Enablex	7.5 mg daily orally	7.5-15 mg daily orally	This is an extended-release formulation and it should not be chewed or crushed. To up-titrate the dose, double the dose after 2 weeks. If the patient is taking a potent CYP3A4 inhibitor (eg, ketoconazole, itraconazole, ritonavir, nelfinavir, and clarithromycin), do not exceed 7.5 mg daily orally. No dosage adjustment is needed for patients with renal impairment. Use a maximum dose of 7.5 mg daily for patients with moderate hepatic impairment. Do not use in patients with severe hepatic impairment.
Fesoterodine	Toviaz	4 mg daily orally	4-8 mg daily orally	This is an extended-release formulation, and it should not be chewed or crushed. If the patient is taking a potent CYP3A4 inhibitor (eg, ketoconazole, itraconazole, ritonavir, nelfinavir, and clarithromycin), do not exceed 4 mg daily orally. If the creatinine clearance is less than 30 mL/min (0.5 mL/s), do not exceed 4 mg daily orally. Use is not recommended in patients with severe hepatic impairment.
Oxybutynin	Ditropan	5 mg two to three times a day orally	5-10 mg two to three times a day orally	Increase daily dose at 5-mg increments at weekly intervals. No specific dosing modifications available for patients with renal or hepatic impairment; use cautiously in these patients.
	Ditropan XL	5 mg daily orally	5-30 mg daily orally	This is an extended-release formulation, and it should not be crushed or chewed. Increase daily dose at 5-mg increments at weekly intervals. No specific dosing modifications available for patients with renal impairment; use cautiously in these patients.
	Oxytrol TDS	1 patch (3.9-mg oxybutynin) twice weekly	1 patch (3.9 mg) twice weekly	This is a transdermal patch. Apply to abdomen, hip, or buttock. Rotate application site. Do not expose patch to sunlight. No specific dosing modifications available for patients with renal or hepatic impairment; however, use cautiously in these patients.
	Gelnique 10% gel	1-g gel (100-mg oxybutynin) daily	1-g gel (100-mg oxybutynin) daily	This is available as premeasured dose packets. Apply to abdomen, thighs, upper arms, or shoulders. Wash hands after application. Do not bathe, shower, or swim for 1 hour after application. Cover application site with clothing until medication dries on skin. Rotate application site daily. No specific dosing modifications available for patients with renal or hepatic impairment; use cautiously in these patients.
Solifenacin	VESIcare	5 mg daily orally	5-10 mg daily orally	If the creatinine clearance is less than 30 mL/min (0.5 mL/s) or the patient has moderate hepatic impairment, do not exceed 5 mg daily orally. Do not use if the patient has severe hepatic impairment. If the patient is taking a potent CYP3A4 inhibitor (eg, ketoconazole,

				itraconazole, ritonavir, nelfinavir, and clarithromycin), do not exceed 5 mg daily orally
Tolterodine	Detrol	2 mg twice daily orally	1-2 mg twice daily orally	If the patient has significant renal impairment or severe hepatic impairment, limit dose to 1 mg twice a day.
	Detrol LA	4 mg daily orally	2-4 mg daily orally	This is an extended-release formulation, and it should not be chewed or crushed. If the creatinine clearance is 10-30 mL/min (0.17-0.5 mL/s) or the patient has mild-moderate hepatic impairment, do not exceed 2 mg daily orally. If the creatinine clearance is less than 10 mL/min (0.17 mL/s), do not use Detrol LA. If the patient has severe hepatic impairment, use of the extended-release formulation is not recommended.
Trospium	Sanctura	20 mg twice daily orally	20 mg twice daily orally	Avoid alcohol ingestion for 2 hours after a dose. Use cautiously in patients with moderate-severe hepatic impairment. In patients older than 75 years, use the immediate-release formulation and start with 20 mg daily orally. If the creatinine clearance is less than 30 mL/min (0.5 mL/s), use 20-mg immediate-release formulation
	Sanctura XR	60 mg daily orally	60 mg daily orally	This is an extended-release formulation, and it should not be chewed or crushed. This is not recommended in patients with creatinine clearance less than 30 mL/min (0.5 mL/s). This should be used cautiously in patients with severe hepatic impairment.
β_3-Adrenergic Agonist				
Mirabegron	Myrbetriq	25 mg daily orally	25-50 mg daily orally	This is an extended-release formulation. Do not chew, crush, or divide tablet. In patients with a creatinine clearance of 15-29 mL/min (0.25-0.48 mL/s) or those with moderate hepatic impairment, the maximum daily dose should be 25 mg daily. This drug is not recommended in patients with creatinine clearance less than 15 mL/min (0.25 mL/s) or those with severe hepatic impairment.
Vibegron	Gemtesa	75 mg daily orally	75 mg daily orally (no dose titration)	This tablet may be crushed and administered in applesauce or put into a glass of water for ease of administration. No dosage adjustment for patients with a creatinine clearance of 15 mL/min (0.25 mL/s) or more. Do not use in patients with creatinine clearance less than 15 mL/min (0.25 mL/s). No dosage adjustment for patients with mild-to-moderate hepatic impairment. Do not use in patients with severe hepatic impairment.

Adverse Effects

Approximately 10% to 12% of patients discontinue taking second-generation α_1-adrenergic antagonists because of adverse effects, especially those that affect the cardiovascular system (eg, syncope, dizziness, hypotension).[9,11] Patients who tolerate hypotension poorly should avoid immediate-release formulations of second-generation α_1-adrenergic antagonists. This includes patients with poorly controlled angina, serious cardiac arrhythmias, patients with reduced circulating volume, patients with untreated hypertension, and patients taking multiple antihypertensives.[15] Alfuzosin, extended-release doxazosin, or a third-generation α_1-adrenergic antagonist is preferred in these patients.

Tiredness and asthenia, anejaculation and retrograde ejaculation, flu-like symptoms, and nasal congestion are the most common dose-related adverse effects of tamsulosin and silodosin. These adverse effects are extensions of their α_{1A}-adrenergic antagonist activity and are dose-related, but with proper education patients likely will not discontinue treatment. However, if the patient is sexually active and ejaculatory dysfunction is problematic, switching the patient from a third-generation to a second-generation α_1-adrenergic antagonist has been effective.[27,29–32]

Tamsulosin use has been associated with dementia based on analysis of a cohort of patients in the Medicare database from 2006 to 2012.[33] It was hypothesized that dementia was due to blockade of α_{1A}-adrenergic receptors in the brain, as this association was not found with second-generation α_1-adrenergic antagonists.[33] However, conflicting data showing no such association have also been reported.[34]

Floppy iris syndrome has been associated with doxazosin, silodosin, and tamsulosin use, although the number of reported cases is highest with tamsulosin.[35] The mechanism for this adverse reaction is related to blockade of α_{1A}-adrenergic receptors in iris dilator muscles. As a result, during cataract surgery, pupillary constriction occurs despite the use of mydriatic agents and the iris billows out (floppy iris), both of which complicate the procedure or can increase the likelihood of postoperative complications, including posterior capsular rupture, retinal detachment, residual retained lens material, or endophthalmitis. Permanent loss of vision can result.[35,36]

Patients who are taking α_1-adrenergic antagonists and who plan to undergo cataract surgery should inform their ophthalmologist that they are taking this medication so that appropriate measures can be taken during eye surgery, for example, use of iris retractors, pupillary expansion rings, or potent mydriatic agents.[36] No benefit has been demonstrated with holding the α_1-adrenergic antagonist preoperatively.

For patients who are scheduled to have cataract surgery, and who have not yet started an α_1-adrenergic antagonist, they should be advised to delay the start of the α_1-adrenergic antagonist until surgery has been completed.[3,9]

Patients with severe sulfa allergy should avoid tamsulosin.

Drug Interactions

Caution is needed when CYP 3A4 inhibitors—for example, cimetidine and diltiazem—are used with α_1-adrenergic antagonists because a drug-drug interaction could lead to decreased metabolism of the latter agents. In contrast, concurrent use of potent CYP 3A4 stimulators such as carbamazepine and phenytoin may increase hepatic catabolism of α_1-adrenergic antagonists.

Phosphodiesterase inhibitors (eg, sildenafil, vardenafil, tadalafil) may produce hypotension if used in large doses along with α_1-adrenergic antagonists. The mechanisms for this interaction are related to the intrinsic vasodilatory effects of phosphodiesterase inhibitors and the higher susceptibility of elderly patients to venous pooling because of autonomic incompetence.[37] The prevalence of hypotension depends on the specific phosphodiesterase inhibitor and α_1-adrenergic antagonist agent, specifically the combination of tadalafil and a third-generation α_{1A}-adrenergic antagonist is least likely to produce a clinically significant drug interaction, as compared with other combinations.[38] Therefore, a patient's blood pressure should be stabilized on the α_1-adrenergic antagonist before starting a phosphodiesterase inhibitor. In addition, patients who are taking phosphodiesterase inhibitors with α_1-adrenergic antagonists should have their blood pressure monitored closely when initiating combined drug use.

5α-Reductase Inhibitors

6 Finasteride competitively inhibits type II 5α-reductase, the predominant isoform of the enzyme in the prostate, which suppresses intraprostatic DHT by 80% to 90%, and decreases serum DHT levels by 70%.[9] Dutasteride is a nonselective inhibitor of type I and II 5α-reductase. It more quickly and completely suppresses intraprostatic DHT production and decreases serum DHT levels by 90%.[39] However, direct comparison clinical trials show no advantages of these pharmacodynamic differences between these two agents.[39] 5α-Reductase inhibitors are indicated for management of moderate-to-severe BPH disease for patients with enlarged prostate glands of at least 40 g or a PSA greater than 1.4 ng/dL (mcg/L).[9,11,40,41] For such patients, 5α-reductase inhibitors may slow disease progression and decrease the risk of disease complications, thereby decreasing the ultimate need for surgical intervention. When taken continuously for 4 or 6 years, dutasteride or finasteride, respectively, has been shown to decrease the risk of acute urinary retention and prostatectomy.[3,42,43] For patients with severe disease, these agents generally should be used with a 6-month short course of an α_1-adrenergic antagonist; the latter will provide fast symptom relief until the 5α-reductase inhibitor starts to work. 5α-Reductase inhibitors may be preferred for patients with BPH and an enlarged prostate gland who have uncontrolled arrhythmias, have poorly controlled angina, are taking multiple

antihypertensive agents, or are unable to tolerate hypotensive adverse effects of α_1-adrenergic antagonists.[13]

5α-Reductase inhibitors also reduce or stop prostate-related bleeding by inhibiting prostatic vascular endothelial growth factor. Thus, the prevalence of gross hematuria in patients with BPH may be reduced with treatment of 5α-reductase inhibitors.[9]

5α-Reductase inhibitors reduce prostate size by 25%, increase peak urinary flow rate by 1.6 to 2.0 mL/s, improve voiding symptoms in approximately 30% of treated patients, and produce few serious adverse effects.[9,11,12]

Compared with α_1-adrenergic antagonists, 5α-reductase inhibitors have several disadvantages. 5α-Reductase inhibitors have a delayed peak onset of clinical effect, which is undesirable for patients with bothersome symptoms. Long-term treatment is needed; an adequate minimum period for a clinical trial is 6 to 12 months. In addition, patients experience less objective improvement of the AUA Symptom Score and urinary flow rate with 5α-reductase inhibitors than with α_1-adrenergic antagonists.[9] 5α-Reductase inhibitors cause more sexual dysfunction than α_1-adrenergic receptor antagonists; therefore, physicians consider 5α-reductase inhibitors to be the second-line agents for treatment of BPH in sexually active males (Tables 104-3 and 104-5).[9,44]

TABLE 104-5

Monitoring of Drugs Used in Treatment of Benign Prostatic Hyperplasia

Drug	Adverse Reaction	Monitoring Parameter	Comment
α_1-Adrenergic antagonists	• Syncope • Lightheadedness • Orthostatic hypotension • Tachycardia • Nasal congestion • Ejaculatory dysfunction • Priapism • Floppy iris syndrome	• Blood pressure • Heart rate	If prescribing an immediate-release formulation, start the patient on the lowest possible dose and instruct the patient to take the first dose at bedtime. Slowly uptitrate the dose over several weeks. Stabilize the patient's blood pressure on the α_1-adrenergic antagonist before adding any other hypotensive agent. If the patient needs cataract surgery, instruct the patient to inform the ophthalmologist so that appropriate measures can be taken during the procedure to prevent intraoperative complications. If the patient has a painful erection lasting longer than 4 hours, the patient should seek immediate medical attention.
5α-Reductase inhibitors	• ED • Decreased libido • Ejaculatory dysfunction • Gynecomastia	• PSA	The patient's PSA level should decrease by 50% if he is adherent to therapy.
Phosphodiesterase inhibitor	• Headache • Dizziness • Nasal congestion • Dyspepsia • Back pain • Myalgia • Hearing loss • Vision loss	• Blood pressure • Pulse • Hearing loss • Changes in vision	If the patient experiences hearing or vision loss, discontinue tadalafil.

Anticholinergic agents	• Dry mouth • Constipation • Headache • Tachycardia • Blurry vision • Acute urinary retention • Drowsiness • Confusion • Angioedema • Anaphylaxis • ED	• Mental status • Bowel habits • Ability to urinate	Adverse effects are dose-related and generally reversible. Patients with signs of severe allergic reaction need immediate medical attention.
β_3-Adrenergic agonist	• Hypertension • Tachycardia • Dry mouth • Nausea • Constipation • Diarrhea • Headache • Nasopharyngitis • Impaired cognition	• Blood pressure • Bowel habits	Adverse effects are dose-related and generally reversible.

ED, erectile dysfunction; PSA, prostate-specific antigen.

Prostate Cancer and 5α-Reductase Inhibitors

In the Prostate Cancer Prevention Trial, patients with BPH who had large prostate glands and a PSA level less than 3 ng/mL (mcg/L) were prescribed finasteride 5 mg daily for up to 7 years. Finasteride reduced the 7-year prevalence of prostate cancer by 25%.[45] However, finasteride was associated with a 27% increase in the number of patients who developed high-grade prostate cancer, which usually is invasive. Although originally thought to be a disadvantage of finasteride use, it is now thought that the higher incidence of prostate cancer was due to biopsy sampling bias. That is, since finasteride reduces the size of the prostate gland, this results in increased sensitivity of sampling biopsies to detect prostate cancer.[46]

Another clinical trial produced similar results. The Reduction by Dutasteride in Prostate Cancer Events (REDUCE) study compared the effect of 4 years of continuous use of dutasteride versus placebo on reducing the incidence of prostate cancer in more than 6,700 men at high risk for developing prostate cancer. At the end of the study, dutasteride-treated patients had a 22.8% decreased relative risk of prostate cancer. Of the patients with biopsy-positive prostate cancer, a similar number of patients in each treatment group developed high-grade tumors (Gleason grade 7-10) with no statistical difference between the groups.[47]

Thus, when finasteride is administered long-term to patients with BPH, it could be useful as chemoprophylaxis in patients with a family history of prostate cancer or in men of African descent who have an increased risk of developing prostate cancer. Although a cause-effect relationship has not been established, the possibility of developing a high-grade prostate cancer should be discussed with the patient before initiating a 5α-reductase inhibitor for prevention of prostate cancer.[45,48]

Dosing

Table 104-6 compares the pharmacokinetic properties of finasteride and dutasteride. They both exhibit good oral bioavailability, are extensively metabolized by the liver, and are highly protein bound. The principal difference is in the drugs' half-life: 5 to 6 hours for finasteride and 5 weeks for dutasteride. Although dutasteride's long half-life may allow for intermittent dosing as opposed to daily dosing, insufficient clinical data are available to recommend such a dosing schedule.

TABLE 104-6

Comparison of Pharmacokinetic Properties of Finasteride and Dutasteride

	Finasteride	Dutasteride
Daily oral dose (mg)	5	0.5
Dosage formulation	Tablet	Capsule
Effect of food on absorption	No effect	No effect
% Oral bioavailability	63	60
Time to peak absorption (hours)	1-2	2-3
Elimination half-life	5-6 hours	5 weeks
% Protein binding	90	99

Maximal reductions in prostate volume or symptom improvement may not be evident for 12 months, but noticeable changes from baseline should occur after 6 months of continuous treatment.

Patients must continue to take 5α-reductase inhibitors as long as they respond. Durable responses to finasteride and dutasteride have been reported with continued treatment for 6 years[43] and 4 years,[40] respectively. Upon discontinuation of the drug, prostate size and voiding symptoms generally return to baseline.

No clinically relevant drug interactions have been reported with 5α-reductase inhibitors.

Adverse Effects

5α-Reductase inhibitors can produce sexual dysfunction, and this has led to discontinuation of therapy in up to 12% of treated patients in one-pooled analysis.[40] Decreased libido has been reported in 2% to 10% of treated patients.[44] Erectile dysfunction has been reported in 3% to 16% of patients.[40,44] This could be secondary to ejaculation disorders or a drug-induced decrease in DHT and subsequent inhibition of nitric oxide synthase (which is needed to produce nitric oxide, a vasodilatory substance) in cavernosal tissue.[32] Although sexual dysfunction often improves with time as the patient continues to take the medication, decreased libido and erectile dysfunction may persist after discontinuation of the 5α-reductase inhibitors.[49–51] The role of 5α-reductase inhibitors in causing erectile dysfunction is not clear, as older adult men with BPH commonly develop erectile dysfunction as they age or have concurrent medical illnesses or concomitant drug therapies that may predispose to the development of sexual dysfunction.

Ejaculation disorders (dry sex or delayed ejaculation) have been reported in 3% to 8% of treated patients.[49,50] These disorders, which are possible results of decreased prostatic secretion, are reversible with drug discontinuation. In one analysis, dutasteride was associated with a higher frequency of sexual dysfunction than finasteride.[52]

Other minor adverse effects include nausea, abdominal pain, asthenia, dizziness, flatulence, headache, rash, muscle weakness, and gynecomastia.[9,53] Mental depression and an increased risk of self-harm have been associated with the first 1.5 years of treatment with a 5α-reductase inhibitor; however,

a cause-effect relationship has not been established.[54,55]

5α-Reductase inhibitors are in FDA pregnancy category X, which means that they are contraindicated in pregnant females. Exposure of the male fetus to finasteride may produce pseudohermaphroditic offspring with ambiguous genitalia, similar to those of patients with a rare genetic deficiency of type II 5α-reductase. Because of this teratogenic effect, women who are pregnant or seeking to become pregnant should not handle 5α-reductase inhibitor tablets and should not have contact with semen from men being treated with 5α-reductase inhibitors. Women health professionals of childbearing age should handle this product with protective gloves if they might be pregnant.

Effects of 5α-Reductase Inhibitors on PSA

DHT stimulates prostate epithelial cells to produce PSA. Since 5α-reductase inhibitors inhibit intracellular conversion of testosterone to DHT, these medications can decrease PSA production.

Usual doses of 5α-reductase inhibitors produce a median reduction of serum PSA levels of 50% at months 6 to 12 after the start of treatment. To interpret a PSA level in a patient being treated with a 5α-reductase inhibitor, it is generally recommended that the actual measured level be doubled to get an estimate of the true level.[9] This formula applies particularly when the baseline PSA value is 4 ng/mL (mcg/L) or more.[56] PSA levels must be measured and a digital rectal examination should be performed before treatment begins. After 6 months of therapy, the patient should have a repeat PSA. This PSA level can be used as the new baseline for the patient. Alternatively, when compared to the pretreatment PSA, if the during-treatment level does not decline by 50% but the patient has been adherent to the 5α-reductase inhibitor regimen, he should be evaluated for prostate cancer. Annually thereafter, the patient should have a PSA assay and digital rectal examination if the patient has a 10-year life expectancy. Patients with an increase in PSA level of 0.3 ng/mL (mcg/L) or more above the baseline nadir level should be evaluated for prostate cancer[9] or noncompliance to the prescribed regimen.

Phosphodiesterase Type 5 Inhibitors

Several observations led to the use of phosphodiesterase type 5 inhibitors for management of BPH. (1) BPH and erectile dysfunction are often present concurrently in the same patient. (2) The pathophysiology of BPH and erectile dysfunction may be common in so far as both disorders may be associated with increased smooth muscle contraction and pelvic atherosclerosis. (3) Improvement of BPH symptoms has been reported to ameliorate erectile dysfunction; and vice versa. (4) Using a phosphodiesterase type 5 inhibitor with a 5α-reductase inhibitor is reasonable as the former will effectively treat erectile dysfunction, a side effect of the latter.[9,57]

Phosphodiesterase type 5 inhibitors relax smooth muscle in the prostate, urethra, bladder neck, and pelvic blood vessels, probably by increasing cGMP. By so doing, phosphodiesterase type 5 inhibitors interrupt the Rho-protein kinase pathway (which regulates smooth muscle contraction mediated by endothelin and α-adrenergic stimulation), improve perfusion of pelvic organs and oxygenation to tissue[57], and possibly decrease inflammation.[58]

In multiple clinical trials of patients with moderate LUTS, tadalafil caused a mean two-point improvement in both obstructive and irritative voiding symptoms using the AUA Symptom Index Score or International Prostate Symptom Score (IPSS), with the level of improvement similar to that observed with α_1-adrenergic antagonists.[58,59] However, no or minimal increase in urinary flow rate or reduction in PVR occurred with tadalafil alone. Tadalafil 2.5 mg was inferior to 5 mg, and doses of 10 or 20 mg were not superior to 5 mg.[60] This is the basis of the current product labeling dose of tadalafil 5 mg daily for BPH. The onset of clinical symptom improvement is within 4 weeks.[60] Tadalafil is more effective for BPH in younger men with symptomatic LUTS. It may be that these patients are more likely to be sexually active. Therefore, when treating both BPH and erectile dysfunction, tadalafil improves a patient's perception of the medication's effectiveness.[37]

A few other BPH studies have employed sildenafil 50 or 100 mg daily, vardenafil 10 mg twice a day, or tadalafil 10 or 20 mg daily.[60] Based on a recent meta-analysis, all phosphodiesterase type 5 inhibitors produce comparable improvements of LUTS, but tadalafil is the only one that has been FDA approved for the treatment of BPH.[60] Tadalafil has the longest plasma half-life and longest duration of action among the phosphodiesterase type 5 inhibitors. This pharmacokinetic characteristic is conducive for the treatment of BPH, which is a chronic illness.

Dosing Recommendations

The recommended tadalafil dose is 5 mg daily. Based on the limited clinical benefit, cost, and potential adverse effects of tadalafil, its use should be reserved for patients with both BPH and erectile dysfunction. Patients with known cardiovascular disease should be assessed and stratified according to the Princeton Consensus Panel guidelines[61] to identify those patients who can safely use tadalafil. If used in combination with an α-adrenergic antagonist, precautions should be taken to minimize hypotension, specifically, the patient's blood pressure should be stabilized on the α_1-adrenergic antagonist before adding tadalafil.[37] If used in combination with a 5α-reductase inhibitor, tadalafil may be used instead of an α-adrenergic antagonist, and the combination may be associated with less sexual dysfunction, particularly in younger, sexually active patients.

Adverse Effects

The most common adverse effects with tadalafil are headache, flushing, gastroesophageal reflux, sinusitis, visual disturbances, and back pain, which are generally mild and reversible and do not require discontinuation of therapy. Headache and dizziness are related to the vasodilatory effect of tadalfil. If tadalafil is an add-on to an existing α_1-adrenergic antagonist and the patient is at risk of hypotensive adverse effects, it is recommended that: (a) the patient's blood pressure be stabilized on the α_1-adrenergic antagonist before tadalafil is started; (b) once tadalafil is started, separate its administration from the α_1-adrenergic antagonist by 4 hours; and (c) preferentially prescribe tamsulosin, silodosin, or alfuzosin as opposed to other α_1-adrenergic antagonists. Back pain has been linked to tadalafil's inhibition of phosphodiesterase type 11. This usually responds to acetaminophen or a nonsteroidal anti-inflammatory agent.

Drug Interactions

Nitrates by any route of administration are contraindicated in patients taking tadalafil.

Anticholinergic Agents

Five types of muscarinic receptors have been identified: (1) M_1 that concentrate in the brain, stomach, and salivary glands; (2) M_2 that comprise 71% to 75% of the muscarinic receptors in the urinary bladder and also are found in the gastrointestinal tract and the atrioventricular node of the heart; (3) M_3 comprise 25% to 29% of the muscarinic receptors in the urinary bladder, and are also distributed in salivary glands, gastrointestinal tract, airways, and eyes; (4) M_4 that are found in the urinary bladder and central nervous system; and (5) M_5 that are found in the brain and eyes. Although M_2 receptors predominate in the urinary bladder, increased M_3 receptor stimulation has been linked with irritative bladder symptoms and overactive bladder syndrome. For this reason, M_3 selective anticholinergic agents eg, (eg, solifenacin and tolterodine) are considered uroselective. However, since M_3 receptors are widely distributed in other organ systems, this explains why darifenacin, a uroselective anticholinergic agent, causes dry mouth, constipation, and mydriasis.[8,9]

8 Treatment with an α_1-adrenergic antagonist, 5α-reductase inhibitor, or surgery may improve urinary flow rate and bladder emptying; however, the patient may still complain of irritative voiding symptoms, which mimic those of overactive bladder syndrome. A variety of anticholinergic agents have been added to an α-adrenergic antagonist regimen to relieve these symptoms.[9,11]

By blocking muscarinic receptors in the detrusor muscle, anticholinergic agents can reduce uninhibited detrusor contractions, a sequela of prolonged bladder outlet obstruction. Thus, irritative voiding symptoms are reduced. The peak clinical effect is observable in several weeks. It is recommended that a patient should be reevaluated 4 to 6 weeks after starting an anticholinergic agent for BPH. These agents do not improve urinary flow rate or consistently improve AUA symptom scores. Because older patients are sensitive to the central nervous system adverse effects and dry mouth, such patients should be started on the lowest effective dose and then slowly titrated up.[9,11] Anticholinergic agents are contraindicated in patients with narrow angle glaucoma, urinary or gastric retention, or severely decreased intestinal motility. The total anticholinergic burden should be considered prior to making the decision to initiate an anticholinergic agent if the patient is already taking other anticholinergic agents (eg, antipsychotic, antidepressant, antihistamine, antiparkinsonian agents). When multiple anticholinergic agents are taken concurrently, anticholinergic adverse effects, including dry mouth, nausea, constipation, blurred vision, and confusion, will more likely occur and be more severe.

For patients who poorly tolerate systemic anticholinergic adverse effects, options include darifenacin, which is a uroselective M_3 receptor antagonist; anticholinergics, which preferentially inhibit M_3 receptors more than other receptors (eg, solifenacin)[62]; transdermal oxybutynin, which bypasses first-pass hepatic metabolism to an active metabolite with anticholinergic adverse effects; or extended-release formulations of anticholinergic agents (eg, tolterodine), which produce lower peak plasma concentrations as compared to immediate-release formulations. For older adults at risk of sedation and confusion from anticholinergic agents, trospium or fesoterodine has a lower propensity to cross the blood brain barrier and may be a good choice.[63]

In the presence of BPH, anticholinergic agents can cause acute urinary retention in patients with poor detrusor contractility. Therefore, before prescribing an anticholinergic agent, a PVR urine volume should be measured; it should be 100 to 150 mL or less.[9] By so doing, patients at high risk of acute urinary retention would be excluded from treatment.

β_3-Adrenergic Agonists

Approximately 95% of the β-adrenergic receptors in the urinary bladder are of the β_3 subtype. When stimulated, β_3-adrenergic receptors increase production of cyclic adenosine monophosphate (cAMP), which relaxes the detrusor muscle.[9,11]

9 β_3-Adrenergic agonists relax the detrusor muscle during the storage phase of the micturition cycle, thereby reducing irritative voiding symptoms, increasing urinary bladder capacity, and increasing the interval between voidings. They do not inhibit voiding or reduce urinary flow rate, nor do they increase PVR urine volume or cause acute urinary retention.[64] The clinical efficacy of these agents for LUTS is comparable to that of anticholinergic agents, but they are better tolerated. They do not produce anticholinergic adverse effects, nor do they cause acute urinary retention.

β_3-Adrenergenic agonists are indicated for symptomatic management of overactive bladder syndrome, which presents with symptoms that overlap with the irritative component of LUTS. For this reason, they are used as an alternative to anticholinergic agents in patients with LUTS, when irritative symptoms persist despite treatment with an α_1-adrenergic antagonist or 5α-reductase inhibitor.[64] The usual starting dose of mirabegron is 25 mg daily, increasing to 50 mg daily if needed. Increasing the dose to 100 mg is no more effective than 50 mg. A usual daily dose of 25 mg daily is recommended for patients with impaired renal function (creatinine clearance of 15-20 mL/min [0.25-0.33 mL/s]) or moderate hepatic impairment. Mirabegron should not be used in patients with severe hepatic dysfunction or a creatinine clearance less than 15 mL/min (0.25 mL/s).

Vibegron offers several potential advantages over mirabegron. It does not penetrate the blood brain barrier, has no significant blood pressure effects, and may be faster acting than mirabegron. For patients who have difficulty swallowing a tablet, it may be crushed and mixed with applesauce or stirred into a glass of water. Vibegron also does not cause significant interactions with cytochrome 3A4, 2D6, or 2C9.[64]

Adverse effects of mirabegron include mild headache, dry mouth, nausea, diarrhea, constipation, nasopharyngitis, and in rare cases QT-interval prolongation. None of these adverse effects cause discontinuation of treatment. Mirabegron increases systolic blood pressure by 0.5 to 1 mm Hg and heart rate by 1 bpm. Although these increases are generally small, older adults with BPH often have essential hypertension and the concern is that this may be worsened by mirabegron. Therefore, patients with uncontrolled hypertension or a systolic or diastolic blood pressure of 180 mm Hg or 110 mm Hg or higher, respectively, should avoid mirabegron. Regular blood pressure monitoring is advised in patients with poorly controlled blood pressure, significant congestive heart failure, cardiomyopathy, or patients who are 80 years of age or older.[9,11]

Combination Drug Therapy

Many drug combinations have been used for BPH. Typically, patients begin treatment with one medication and additional medications are added when LUTS does not improve or BPH symptoms worsen. To further reduce irritative voiding symptoms in a patient who is already taking an α_1-adrenergic antagonist, an anticholinergic agent, β_3-adrenergic agonist, or a phosphodiesterase type 5 inhibitor may be added.[8] When used alone, a 5α-reductase inhibitor has a slow onset of action. To achieve faster symptom relief, an α_1-adrenergic antagonist, anticholinergic agent,[65] β_3-adrenergic agonist, or a phosphodiesterase inhibitor[63,66] can be added. When any drug combination is used, the benefit of reducing bothersome symptoms must be balanced by the increased risk of adverse effects and drug interactions, higher cost of treatment, lower rates of adherence to treatment, and modest

improvement in objective measures of BPH improvement.[63,65] Table 104-7 summarizes commonly prescribed combination regimens.

TABLE 104-7

Commonly Prescribed Combination BPH Regimens, Indications, and Precautions

Combination Regimen	Rationale	Comments
α_1-Adrenergic antagonist + 5α-reductase inhibitor	Moderate/severe LUTS with enlarged prostate gland of 40 g or more (or PSA >1.4 ng/mL [mcg/L])	These patients are at risk of developing complications of long-standing BPH.
α_1-Adrenergic antagonist + anticholinergic agent OR 5α-reductase inhibitor + anticholinergic agent	Moderate/severe LUTS with irritative symptoms not responding to an α_1-adrenergic antagonist alone[12] OR Moderate/severe LUTS with enlarged prostate gland of 40 g or more, and irritative symptoms	Use these combinations cautiously in patients already taking medications with anticholinergic effects/side effects. Avoid in patients with postvoid residual urine volume that is greater than 100 to 150 mL. Preferentially choose an anticholinergic agent with less likelihood to cross the blood brain barrier and cause confusion (eg, solifenacin).[14]
α_1-Adrenergic antagonist + β_3-adrenergic agonist OR 5α-reductase inhibitor + β_3-adrenergic agonist	Moderate/severe LUTS with irritative symptoms not responding to an α_1-adrenergic antagonist alone OR Moderate/severe LUTS with enlarged prostate gland of 40 g or more and irritative symptoms	Preferred regimen for patients with poor tolerance to side effects of anticholinergic agents. Do not use this combination in patients with unstable hypertension.
α_1-Adrenergic antagonist + phosphodiesterase inhibitor	Moderate/severe LUTS with irritative or obstructive symptoms not responding to an α_1-adrenergic antagonist alone[66] OR Moderate/severe LUTS with concomitant erectile dysfunction	This combination may cause hypotension. To minimize, preferentially use alfuzosin, tamsulosin, or silodosin when also prescribing tadalafil.[55]
5α-Reductase inhibitor+ phosphodiesterase inhibitor	Moderate/severe LUTS with enlarged prostate gland of 40 g or more and with irritative or obstructive symptoms not responding to a 5α-reductase inhibitor alone	The phosphodiesterase inhibitor can offset erectile dysfunction of 5α-reductase inhibitor.[9]

BPH, benign prostatic hypertrophy; LUTS, lower urinary tract symptoms.

Of all the combination medication regimens, an α_1-adrenergic antagonist plus a 5α-reductase inhibitor has been extensively studied and is

recommended to use at the outset for patients with both moderate-to-severe symptoms, an enlarged prostate gland of at least 40 g and PSA of at least 1.4 ng/mL (mcg/L). Such patients are at high risk for disease progression, as evidenced by symptom worsening and development of disease complications, including acute urinary retention, recurrent urinary tract infection, or the need for surgical intervention.[67]

In the landmark Multiple Treatment of Prostate Symptoms Study (MTOPS), a combination regimen of finasteride and doxazosin for 5 years was shown to prevent symptom progression by 66%, decrease the risk of developing acute urinary retention by 81%, and decrease the need for prostate surgery by 67%. Moreover, urinary symptom improvement and higher urinary flow rates at 15 to 18 months were observed in patients treated with combination therapy, as compared with monotherapy with finasteride alone or doxazosin alone.[67] In another key clinical trial, the Combination of Avodart and Tamsulosin (COMBAT) study, dutasteride versus tamsulosin versus a combination of dutasteride and tamsulosin were evaluated in patients with prostate glands of 40 mL or greater and PSA of 1.5 ng/mL (mcg/L) or higher. The combination regimen was more effective in reducing symptoms 9 months after the start of treatment than dutasteride alone or tamsulosin alone. In addition, after a long-term follow-up of 4 years, the combination of dutasteride and tamsulosin prevented disease progression and reduced the need for prostate surgery.[68]

Although not proven by direct comparison trials, any combination of 5α-reductase inhibitor and α_1-adrenergic antagonist probably is similarly effective for patients with the aforementioned characteristics. The disadvantages of a combination regimen include increased medication cost, decreased adherence to multidrug treatment regimens, and an increased incidence of adverse drug effects (eg, sexual dysfunction).[62]

When this combination is used to prevent BPH progression, patients must continue both medications. Studies have shown if the 5α-reductase inhibitor is discontinued, LUTS recurs, and the prostate size may increase.[62] However, when the combination is used for LUTS in patients who are not at risk of BPH complications, the α_1-adrenergic antagonist may be discontinued after 6 or 9 months of continuous treatment with the 5α-reductase inhibitor.[9,11]

Surgical Interventions

10 The gold standard for treatment of patients with complications of BPH is prostatectomy.[9,11] Surgical intervention is indicated for patients with moderate-to-severe symptoms, who are not responsive to or cannot tolerate adverse effects of drug therapy, who are noncompliant with drug therapy, or who prefer surgical intervention. Surgical intervention is always indicated for patients with complications of BPH, including acute urinary retention not responsive to drug treatment, chronic urinary retention associated with decreased renal function or overflow urinary incontinence, urolithiasis, recurrent urinary tract infection, or recurrent hematuria.[9,11] Surgical removal of the prostatic adenoma offers the highest rate of symptom improvement, but it also has the highest complication rate.

With the availability of 5 medical treatment options for the treatment of BPH, most symptomatic patients are first managed medically. As a result, the number of surgeries for BPH has decreased significantly and the patients who are treated surgically for BPH tend to be older and more likely to have sarcopenia and/or frailty.[69–71] This has stimulated the technology development of a plethora of lasers and miniaturization of tools to expand the number and type of minimally invasive surgical procedures, which can be performed on an outpatient basis with local anesthesia, result in less blood loss, are less expensive than chronic medical treatment for BPH, and are associated with fewer adverse events than conventional prostatectomy procedures, which include transurethral resection of the prostate (TURP) or open prostatectomy.[11,70] However, all minimally invasive surgical procedures are also associated with a smaller improvement in voiding symptoms and a higher reoperation rate and shorter time to recurrence of LUTS than TURP or open prostatectomy.[11,70]

With TURP, an endoscopic resectoscope with a loop electrocautery inserted through the urethra is used to remove the inside core of the prostatic adenoma. This enlarges the opening at the bladder neck and prostatic urethra. Often performed as outpatient surgery, this procedure produces on average a peak urinary flow rate increase by 10 mL/s and improves the AUA Symptom Score by 10 to 18 points in approximately 90% of patients.[9,11] A common complication of TURP is retrograde ejaculation, occurring in up to 75% of patients. Bleeding, urinary incontinence, and erectile dysfunction occur in smaller, but significant numbers of patients (2%–15%).[70] Approximately 2% to 10% and 12% to 15% of patients require second surgeries within 5 and 8 years, respectively.[70]

A conventional open prostatectomy requires a suprapubic or perineal incision to allow the surgeon to remove the entire prostate gland. This procedure is reserved for large prostate glands of 80 to 100 g or more, and is a good choice when the patient has concurrent bladder stones or bladder

diverticuli that can be corrected at the same time. Open prostatectomy is being performed laparoscopically or robotically. This procedure requires that the patient to be hospitalized. Once the entire prostate gland is excised along with the internal urethral sphincter, the urinary bladder and remaining urethra must be reconnected. The incision is stabilized by leaving an indwelling urethral catheter in place for 1 or 2 weeks. Adverse effects including bleeding, urinary and soft tissue infection, retrograde ejaculation in 77% of patients, erectile dysfunction in 16% to 33% of patients, and urinary incontinence in 2% of patients. The reoperation rate is 3% to 5% at 10 years.[9,70]

Table 104-8 lists common minimally invasive surgical procedures for BPH. Although the AUA guidelines include recommended indications for each procedure largely based on prostate gland size, additional key considerations include the availability of technology at the facility, skill and expertise of the surgeon, patient preference for one type of procedure over another, whether the patient's health insurance covers the cost of the procedure, and associated adverse effects of the procedure.

TABLE 104-8

Common Minimally Invasive Surgical Procedures for BPH

Procedure	Methodology	Indication	Comment
Transurethral incision of the prostate (TUIP)	Multiple incisions of the bladder neck widen the bladder neck to increase bladder emptying. Prostate tissue is not removed.	Best in men with small prostates 30 mL or less. Has outcomes similar to TURP.	The reoperation rate for TUIP is slightly higher than with TURP.
Prostatic urethral lift (Urolift)	Adjustable nitinol and stainless steel implants are inserted transurethrally. These implants tack open the obstructing prostate lobes and enhance bladder emptying. Prostate tissue is not removed.[71–73]	• Indicated for prostate glands that are 30 to 80 mL. • This procedure may be a good option for sexually active men as it appears to preserve erectile and ejaculatory function.[72–74]	Unsuitable for men with obstructing median lobes, prostates greater than 80 mL, or men with urinary retention.
Potassium titanyl phosphate (KTP or Green Light) Laser vaporization of the prostate	The laser is inserted transurethrally. The laser fiber vaporizes and coagulates prostate tissue. No tissue is available for pathologic analysis.	• Indicated for prostate glands that are less than 80 mL. Some prostate tissue is removed. • Laser vaporization may be preferred over TURP in patients with frailty, those taking anticoagulants, or those at risk of bleeding.[75]	
Robotic waterjet treatment (Aquablation)	• Using image guidance and robotics, a cystoscope with ablation probe is inserted transurethrally. A targeted saline jet stream resects the prostate.[75–77] • Resection time is less than 10 minutes. • The saline is not heated, which reduces thermal injury to tissue.	Indicated for prostate glands that are 30 to 80 mL. May be a good option for sexually active patients, as sexual function appears to be unaffected by the procedure.	
Water vapor thermal therapy (Rezum)	• Water vapor is heated using a bedside radiofrequency device. Vapor energy is delivered to and injected into the prostate	• Indicated for prostate glands that are 30 to 80 mL, or in patients with an enlarged median lobe.[70,71,78]	• It may take up to 3 months for peak clinical effects to be evident. This

	transurethrally, and it causes cell necrosis. The procedure includes 4 or 5 injections.[78] • This modality produces localized necrosis of the prostate without damaging the urethra since the prostatic pseudocapsule is resistant to heated water vapor.[78]	• May be a good option for sexually active patients, as sexual function appears to be unaffected by the procedure.	is because necrosed prostate tissue must be resorbed. • Avoid this procedure in patients with implanted urethral sphincters or penile prosthesis.[78]
Thulium (ThuLEP) or Holmium (HoLEP) Laser Enucleation of the Prostate	Transurethrally, a resectoscope peels the prostate away from its capsule. The prostate is morcellated in the bladder and then extracted. The laser is then used for hemostasis.	• Indicated for large prostate glands that are greater than 80 mL. Excised prostate tissue is removed and available for pathologic review. • Laser prostatectomy is preferred over conventional therapy in patients who are taking anticoagulants or have a risk of bleeding.[79,80]	

Data from Reference 70.

Phytotherapy

Although phytotherapy is widely used in Europe for the management of BPH, the published data on herbal agents are largely inconclusive and conflicting. Studies often lack placebo controls, which are essential for assessing treatments for BPH because spontaneous regression of mild symptoms can occur. Furthermore, because these agents are marketed under the Dietary Supplements Health and Education Act, their efficacy, safety, and quality are not regulated by the FDA. For these reasons, herbal products—including saw palmetto berry (*Serenoa repens*), stinging nettle (*Urtica dioica*), South African star grass (*Hypoxis rooperi*), pumpkin seed (*Cucurbita pepo*), and African plum (*Pygeum africanum*)—are not recommended for treatment of BPH.[14] Excellent reviews on phytotherapy for BPH have been published.[9,81]

EVALUATION OF THERAPEUTIC OUTCOMES

The primary therapeutic outcome of BPH therapy is improvement of voiding symptoms with minimal treatment-related adverse effects. As a disease for which therapy is directed at the voiding symptoms that the patient finds most bothersome, assessment of outcomes depends on the patient's perceptions of the effectiveness of therapy. Use of a validated, standardized instrument, such as the AUA Symptom Score, for assessing patient's voiding symptoms is important in this process.[9,11] A clinically significant improvement is generally associated with a decrease in score of three points or more. The efficacy of any new medication or medication combination for treatment of BPH should be assessed 6 to 12 weeks after its start. Symptomatic improvement of LUTS is expected, although 5α-reductase inhibitors will require at least 6 months to shrink an enlarged prostate.[9,11,16]

For patients being considered for surgical treatment, objective measures of bladder emptying are useful and include the urinary flow rate and PVR urine volume (see Diagnostic Evaluation section).

Because this patient population is at high risk for prostate cancer, PSA should be measured and a digital rectal examination performed annually if a patient has a life expectancy of at least 10 years. For patients taking 5α-reductase inhibitors, a second PSA taken 6 months after the start of treatment should be compared with baseline measurements. If the patient is suspected of having developed renal impairment as a consequence of long-standing bladder outlet obstruction, then BUN and serum creatinine should be evaluated at regular intervals.

CONCLUSION

A ubiquitous disease of aging men, symptomatic BPH requires medical attention to preserve the patient's quality of life and to prevent disease complications, many of which can be life-threatening in this patient population. In men who have no or mildly bothersome symptoms, watchful waiting and behavior modification are the best treatment approach, as BPH remains stable or even regresses in approximately half of these men.

For patients with voiding symptoms that are moderately to severely bothersome, pharmacotherapy is indicated. An α_1-adrenergic antagonist is the agent of first choice. Second-generation agents include terazosin, doxazosin, and alfuzosin, and third-generation agents include tamsulosin and silodosin. Immediate-release formulations of terazosin and doxazosin cause more cardiovascular adverse effects than do extended-release formulations (eg, doxazosin or alfuzosin), or uroselective α_{1A}-adrenergic agents (eg, tamsulosin, silodosin, or alfuzosin). 5α-Reductase inhibitors are preferred drug treatment for patients with enlarged prostates greater than 40 g who poorly tolerate the hypotensive adverse effects of α_1-adrenergic antagonists. However, 5α-reductase inhibitors have a slow onset of action. For patients who do not respond to monotherapy, combination drug therapy could be attempted.

The combination of 5α-reductase inhibitor and α_1-adrenergic antagonist is well established for patients at high risk of developing complications of BPH. In this subset of patients, continuous use of both medications is necessary.

For patients with both moderate-to-severe LUTS and erectile dysfunction, a phosphodiesterase inhibitor alone or combined with an α-adrenergic antagonist may be prescribed. For patients with moderate-to-severe LUTS with a predominance of irritative voiding symptoms, an anticholinergic agent, mirabegron, or a phosphodiesterase inhibitor may be added to an existing drug treatment regimen for BPH. Before starting an anticholinergic agent in a patient with BPH, the patient's PVR should be less than 100 to 150 mL.

For patients who do not respond to or cannot tolerate adverse effects of medical therapy, or who have complications of BPH, surgery is required. Although it has more adverse complications than pharmacotherapy or watchful waiting, TURP is considered the gold standard. Minimally invasive surgical procedures are an attractive alternative for older patients with frailty, as the procedures can be performed on an outpatient basis using local anesthesia. The risk of serious adverse effects are less with a minimally invasive surgical procedure than with TURP.

ABBREVIATIONS

ALLHAT	Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial
AUA	American Urological Association
BPE	benign prostatic enlargement
BPO	benign prostatic obstruction
BPH	benign prostatic hyperplasia
BUN	blood urea nitrogen
cAMP	cyclic adenosine monophosphate
cGMP	cyclic guanosine monophosphate
COMBAT	Combination of Avodart and Tamsulosin (Study)
CYP	cytochrome P-450
DHT	dihydrotestosterone
GI	gastrointestinal
IPSS	International Prostate Symptom Score
LUTS	lower urinary tract symptoms
MTOPS	Multiple Treatment of Prostate Symptoms (Study)
PSA	prostate-specific antigen
PVR	postvoid residual (pertains to urine volume)
REDUCE	Reduction by Dutasteride in Prostate Cancer Events
TURP	transurethral resection of the prostate
TUIP	transurethral incision of the prostate

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SELF-ASSESSMENT QUESTIONS

1. A patient complains of LUTS despite treatment with silodosin 8 mg daily for 1 month. The patient's AUA symptom index was 30 at baseline and is now 29. Which of the following statements is a correct interpretation of the change in the AUA symptom index?

   A. The reduction in the AUA symptom score is considered clinically significant.

   B. The patient probably didn't answer the AUA symptom index questions correctly, which explains why he is still complaining of LUTS.

   C. Based on the patient's current AUA symptom index, the patient requires a prostatectomy.

   D. The patient's current AUA symptom score indicates that the patient has mild symptoms.

   E. Based on the data provided, silodosin is ineffective in this patient.

2. Which of the following statements about α_1-adrenergic antagonists is correct?

   A. The daily dose of silodosin should be increased when the creatinine clearance is less than 30 mL/min (0.5 mL/s).

   B. Extended-release doxazosin is more likely to cause ejaculatory dysfunction than immediate-release terazosin.

   C. Concurrent use of silodosin with antihypertensives is not recommended.

   D. Prazosin is not recommended for BPH because it must be taken two to three times a day.

E. Uptitrating the dose of alfuzosin over 2 to 3 weeks is essential for clinical effectiveness.

3. Which one of the statements about α_1-adrenergic antagonists and floppy iris syndrome is correct?

A. Only tamsulosin has been associated with this adverse effect.

B. Vision loss is typically painful and affects both eyes.

C. A hallmark of this side effect is small pupils that are not responsive to mydriatic agents.

D. α_1-Adrenergic antagonists should be stopped 4 weeks before cataract surgery.

E. Cataract surgery is a contraindication for α_1-adrenergic antagonist use.

4. What is the appropriate minimum length of a clinical trial of a 5α-reductase inhibitor?

A. 3 to 6 hours

B. 3 to 6 days

C. 6 to 12 weeks

D. 6 to 12 months

E. 3 to 6 years

5. Which one of the following statements about combination therapy using a 5α-reductase inhibitor and an α_1-adrenergic antagonist for BPH is correct?

A. The combination produces fewer adverse effects that using either drug alone.

B. The combination is indicated in patients with a prostate gland size of 15 g or less and moderate-to-severe LUTS.

C. LUTS responds quicker to the combination than to either drug used alone.

D. Combination therapy delays disease progression and reduces the need for surgery.

E. Combination therapy, but not either drug alone, increases the risk of high-grade prostate cancer.

6. Which one of the following medications can worsen LUTS?

A. Hydrochlorothiazide

B. Aspirin

C. Prednisone

D. Irbesartan

E. Cephalexin

7. A patient has a urinary flow rate of 8 mL/s, AUA symptom index of 20, a PVR of 0 mL, and a prostate gland size of 20 g. He complains of nocturia three times/night and poor quality sleep. The best management approach is:

A. Watchful waiting

B. An α_1-adrenergic antagonist

C. A 5α-reductase inhibitor

D. A combination of an α_1-adrenergic antagonist and a 5α-reductase inhibitor

E. A combination of tolterodine plus an α_1-adrenergic antagonist

8. A 60-year-old patient has moderate LUTS due to BPH and erectile dysfunction. He is sexually active. The best management approach is

A. Watchful waiting

B. An α_1-adrenergic antagonist

C. A 5α-reductase inhibitor

D. A phosphodiesterase type 5 inhibitor

E. A combination of an α-adrenergic antagonist and a 5α-reductase inhibitor

9. For patients with BPH and essential hypertension, treating both conditions with a single α_1-adrenergic antagonist is not recommended because patients would be at increased risk of

A. Metabolic syndrome

B. Congestive heart failure

C. Diabetes mellitus

D. Renal failure

E. Liver failure

10. When used for BPH, trospium

A. Reduces the size of an enlarged prostate gland

B. Halts disease progression

C. Reduces irritative voiding symptoms

D. Decreases PSA levels

E. May decrease PVR

11. When used for LUTS, vibegron

A. Halts disease progression

B. Reduces irritative voiding symptoms

C. Reduces obstructive voiding symptoms

D. Decreases PSA levels

E. May increase PVR

12. When counseling a patient taking silodosin, which one of the following instructions is correct?

    A. Take each dose after the same meal each day.

    B. Start with 1 mg/day and slowly titrate up over several weeks.

    C. This drug should not be taken with nitrates.

    D. This drug can be taken in divided doses during the day.

    E. This drug works on the bladder to reduce voiding symptoms.

13. A patient with BPH has an AUA symptom score of 30, complains of LUTS, and has a prostate size of 35 g. The best choice treatment is:

    A. Watchful waiting

    B. An α_1-adrenergic antagonist

    C. A 5α-reductase inhibitor

    D. A combination of an α-adrenergic antagonist and a 5α-reductase inhibitor

    E. A prostatectomy

14. Which one of the following statements is true about drug treatment for BPH?

    A. Alfuzosin inhibits 5α-reductase.

    B. Terazosin selectively inhibits α_{1A}-adrenergic receptors.

    C. A medication must shrink the prostate to be effective for BPH.

    D. All of the α_1-adrenergic antagonists are equally effective.

    E. An effective treatment will lower the peak urinary flow rate.

15. For which one of the following conditions in a patient with BPH should an anticholinergic agent be avoided?

    A. Urinary flow rate of 20 mL/s

    B. Essential hypertension

    C. Prostate gland of 30 g

    D. A history of diabetes mellitus

    E. A postvoid residual urine volume of 250 to 300 mL or more

SELF-ASSESSMENT QUESTION-ANSWERS

1. **A.** A three-point decrease in AUA symptom index is considered clinically significant. This patient has only a one point change in AUA symptom index which suggests that silodosin is ineffective. See the Desired Outcomes section.

2. **D.** Prazosin is a second-generation α_1-adrenergic antagonist, like terazosin and doxazosin. It has a short half-life and has to be taken 2 to 3 times a day. For this reason, it is not recommended for BPH by the American Urological Association. See the Second-Generation α1-Adrenergic Antagonists section.

3. **C.** Floppy iris syndrome is characterized by small pupils, a billowing iris, and increased intraoperative complications during cataract surgery. See the Adverse effects (α1-Adrenergic Antagonists) section.

4. **D.** Although LUT and urinary flow rate may show earlier improvement, maximum prostate shrinkage may take 6 months. See the 5α-Reductase Inhibitors section.

5. 5. **D.** Combination therapy may delay BPH progression and reduce the need for prostate surgery, but it causes more adverse effects than treatment with one drug. It should be reserved for symptomatic patients at risk for BPH complications, which includes patients with an enlarged prostate of 40 g or more. See the Combination Drug Therapy section.

6. **A.** Hydrochlorothiazide is a diuretic, which causes polyuria. This can worsen LUTS. See the Medication-Related Symptoms section.

7. **B.** A patient with moderate BPH with minimal enlargement of the prostate should be treated with an α_1-adrenergic antagonist. See the Pharmacologic Therapy section.

8. **D.** An ideal candidate for tadalafil has both moderate BPH and erectile dysfunction. The two conditions can be treated with one medication. See the Pharmacologic Therapy section

9. **B.** Based on the ALLHAT study, use of an α_1-adrenergic antagonist alone for treatment of essential hypertension can produce more congestive heart failure than amlodipine, lisinopril, or chlorthalidone. Therefore, in a patient with BPH and essential hypertension, the use of an α_1-adrenergic antagonist to treat both conditions is not recommended. See the Second-Generation α1-Adrenergic Antagonists section.

10. **C.** Anticholinergics relax the detrusor muscle, thereby inhibiting involuntary detrusor contractions. This decreases irritative voiding symptoms. See the Anticholinergic Agents section.

11. **B.** Vibegron relaxes the detrusor muscle, thereby inhibiting involuntary detrusor contractions. This decreases irritative voiding symptoms. See the β3-Adrenergic Agonists section.

12. **A.** Food decreases the oral bioavailability of silodosin, which is beneficial, in so far as this food-drug interaction helps decrease peak serum concentrations of tamsulosin. This decreases the drug's effect on blood pressure. Therefore, it is recommended that silodosin should be taken after the same meal each day. See the Third-Generation α1-Adrenergic Antagonists section.

13. **D.** The patient with an enlarged prostate and severe symptoms is an ideal candidate for combination therapy. This approach will relieve LUTS quickly and also shrink an enlarged prostate. See the Combination Drug Therapy section.

14. **D.** The α_1-adrenergic antagonists differ only in side effects. They are considered equally effective. See the α1-Adrenergic Antagonists section.

15. **E.** Anticholinergics are contraindicated in patients with a postvoid urine residual volume of 250 to 300 mL. In such patients, an anticholinergic agent may cause acute urinary retention. See the Anticholinergic Agents section.