Benign Prostatic Hyperplasia
A Management Update for Pharmacists

Tom Smiley, PharmD

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Lesson description

Benign prostatic hyperplasia (also known as *benign prostatic hypertrophy* or *BPH*) refers to a condition associated with benign (i.e., non-cancerous) proliferation of the cellular elements of the prostate. Although prostate cancer is a much more feared diagnosis, BPH is a much more commonly diagnosed condition. Men diagnosed with BPH should be reassured that there is no scientific evidence indicating that BPH increases risk for prostate cancer. This continuing education lesson will help pharmacists with strategies to identify and refer men with symptoms suggestive of BPH for further medical assessment. Pharmacological management, which consists primarily of 5-α reductase inhibitors (finasteride, dutasteride), alpha-blockers (terazosin, doxazosin, alfuzosin, tamsulosin), or combinations of the two classes of drugs, will be discussed in terms of evidence-based benefits and risks of therapy. A discussion of investigational drugs will inform the participant of how these agents may improve BPH management in the future. Finally, the role of surgery in BPH management will also be reviewed.

Learning objectives

After successful completion of this continuing education lesson, pharmacists will be better able to:

1. discuss the epidemiology and pathophysiology of benign prostatic hyperplasia (BPH)
2. assess symptoms of BPH utilizing the International Prostate Symptoms Score
3. identify medications that may cause or exacerbate symptoms of BPH
4. recommend appropriate treatment for BPH and associated lower urinary tract symptoms
5. discuss investigational treatment options for BPH

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Author

Tom Smiley, BScPhm, PharmD
Tom Smiley is a pharmacist consultant with Pharmavision Health Consulting Inc. He also remains active in community practice in Brantford, Ontario. In addition to his clinical experience with patient management over the past 30 years, Tom has developed and presented many continuing education lessons and workshops for pharmacists on the topic of men's health, including benign prostatic hyperplasia.

Expert reviewers

Zubin Austin, BScPhm, MBA, MISc, MEd, PhD
Zubin Austin is Associate Professor at the Leslie Dan Faculty of Pharmacy University of Toronto and practices at Mount Sinai Hospital. He has specific interests in the area of primary care and patient education and has developed and taught patient education programs related to aging and the life course, with a focus on men's and women's health.

He has designed and delivered workshops for patients, patient groups, and health care professionals addressing issues related to healthy aging, medications used in treatment of age-related conditions such as BPH, and lifestyle counselling. His research work has focused on patient education in the primary care context, with a focus on communication of medical information to diverse audiences.

Alan Low, BSc(Pharm), PharmD
After completing his BSc(Pharm) degree, Dr. Alan Low completed a accredited Hospital Pharmacy Residency in BC and practiced as a clinical pharmacist in General Medicine before completing the post-baccalaureate PharmD program at UBC. Alan has held hospital positions in the including Clinical Specialist in General Medicine, Pharmacotherapeutic Specialist (Ambulatory Care/Neurology), and Manager of the Ambulatory Care Pharmacy. He is currently the Chief Operating Officer at Network Healthcare, a Clinical Associate Professor in the Faculty of Pharmaceutical Sciences at UBC, and an independent clinical consultant performing patient consultations. In addition to being invited to numerous presentations at both local and international conferences to speak on general medicine topics, Alan has authored several papers and CPE programs, including ones on benign prostatic hyperplasia and men's health. He is also currently involved with pharmacy practice change initiatives aimed at improving patient-focused care and developing medication management services that are delivered as part of pharmaceutical care practice.

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1. Introduction

Case:

George J. is a 63-year-old man who has been coming to your pharmacy regularly for a number of years to refill prescriptions for antihypertensive medications. He is in today looking a little flustered as he tells you that the doctor just informed him that he has an "enlarged prostate." He is worried about the implications even though the doctor told him that there was no cancer in the prostate.

Benign prostatic hyperplasia (also known as *benign prostatic hypertrophy* or *BPH*) refers to a condition associated with benign (i.e., non-cancerous) proliferation of the cellular elements of the prostate.[1] Although prostate cancer is a much more feared diagnosis, BPH is a much more commonly diagnosed condition. Approximately 50% of men demonstrate histopathologic BPH by age 60, and 90% by age 85.[1] Therefore, BPH can be considered a normal part of aging in men, with treatment considerations largely based on level of bothersome symptoms. In contrast, about 16% of men will be diagnosed with prostate cancer in their lifetime and less than 3% of Canadian men will die from the condition.[2] Men diagnosed with BPH should be reassured that there is no scientific evidence indicating that BPH increases risk for prostate cancer. However, the two conditions may co-exist, and routine screening for prostate cancer should be conducted as for the general population. The Canadian Cancer Society suggests that men over 50 discuss the potential benefits and risks of early detection testing using prostate specific antigen (PSA) and digital rectal examination (DRE) with their doctor.[3]

The prostate is often referred to as the "prostate gland," but it actually consists of branching tubuloalveolar glands arranged in lobules and surrounded by a stroma. Prostate enlargement occurs as a result of cellular accumulation and gland enlargement from epithelial and stromal proliferation and/or impaired preprogrammed cell death.[1] BPH is dependent on dihydrotestosterone (DHT) for progression.[4] The prostate increases in size during puberty and reaches normal adult size (about the size of a walnut) at about 20 years of age. Within the prostate, testosterone is converted by the enzyme 5-α reductase to DHT, which is much more potent than the parent hormone. DHT initiates RNA synthesis, protein synthesis, and cell replication within the prostate. It has been recommended that men be routinely asked about urinary function by their primary care physicians after age 50.[5]

2. Symptoms of BPH

Case (continued):

The following discussion ensues between you and George:

George: *I have a friend who went to the doctor and only had mild symptoms of his urine stream slowing down, and he turned out to have cancer!*

Pharmacist: *I understand your concern, George, but I can help you with perspective on this. Your friend was one of the unlucky ones. Most men with urinary symptoms after the age of 50 or so have an enlarged prostate that does not increase the risk for prostate cancer. You will still need to have regular check-ups, but your chances of having prostate cancer are the same as for any other man your age.*

George: *That does make me feel better about the situation. I have an appointment with the urologist in two weeks to see what we are going to do about my symptoms.*

Pharmacist: *That's great, George. There are many good medications that will help to relieve your symptoms. I'll be happy to answer any questions you might have about your medications or your condition.*

Symptoms associated with BPH are commonly called *lower urinary tract symptoms*, or *LUTS*.[5] Growth of prostate tissue around the urethra and resulting extrinsic compression of the prostatic urethra lead to impaired voiding and weak urine stream associated with BPH.[6] These are often referred to as *obstructive symptoms* of BPH. In addition, men may experience *irritative symptoms* of BPH, which may include increased frequency caused by changes in the bladder wall and incomplete emptying of the bladder, nocturia, and urgency secondary to a hypersensitive bladder.[6] The symptoms, however, do not always correlate with the size of the prostate.[5] Many men seeking medical attention for urinary symptoms fear that they have prostate cancer. Health professionals can reassure patients that BPH is not cancer, and does not increase risk for cancer.[5]

Many physicians use the urinary symptom scoring system developed by the American Urological Association (The American Urological Association Symptom Score or AUASS) to grade urinary symptoms (see Figure 1). This scoring system, also known as the International Prostate Symptoms Score (IPSS), is recommended by the Canadian Urological Association.[7] The scores for symptoms are added to rate BPH as mild, moderate, or severe (see Figure 1).[8] An electronic version of the IPSS may be found online at www.usrf.org/questionnaires/AUA_SymptomScore.html.

Case (continued):

George comes to see you after his visit to the urologist and tells you that he was told he has "moderate" BPH. He also mentions that the urologist confirmed that he did not have prostate cancer. George tells you his IPSS score was 13. The urologist tested his PSA and it was 2.2 ng/mL. He informed George that his prostate was large enough that he should consider treatment with a medication (PSA and associated prostate volumes discussed below). George tells you he is happy that he mentioned a weaker stream to his family doctor at his annual check-up. Otherwise this condition would not have been detected!

Any patient with urinary symptoms should be referred to their physician. However, this may

Figure 1. The International Prostate Symptom Score[5]

For each question, circle the answer that best describes your situation. Add the circled numbers together to get your total score. See the key at the bottom of this form to determine the overall rating of your symptoms.

Response choices for questions 1–6 →	Not at all	Less than 1 in 5 times	Less than half the time	About half the time	More than half the time	Almost always
1. Incomplete emptying In the past month, how often have you had a sensation of not emptying your bladder completely after you finished voiding?	0	1	2	3	4	5
2. Frequency In the past month, how often have you had to urinate again less than 2 hours after you finished urinating before?	0	1	2	3	4	5
3. Intermittency In the past month, how often have you found you stopped and started again several times when you urinated?	0	1	2	3	4	5
4. Urgency In the past month, how often have you found it difficult to postpone urination?	0	1	2	3	4	5
5. Weak stream In the past month, how often have you had a weak urinary stream?	0	1	2	3	4	5
6. Straining In the past month, how often have you had to push or strain to begin urination?	0	1	2	3	4	5
7. Nocturia In the past month, how many times did you typically get up to urinate from the time you went to bed until you arose in the morning?	0 (none)	1 (one time)	2 (two times)	3 (three times)	4 (four times)	5 (five times)

8. Quality of life due to symptoms If you were to spend the rest of your life with your urinary condition the way it is now, how would you feel about that?	0 (delighted)	1 (pleased)	2 (mostly satisfied)	3 (mixed – about equally satisfied and dissatisfied	4 (mostly dissatisfied)	5 (unhappy)	6 (terrible)

Total score _____

Scoring key: 0–7 = mild; 8–19 = moderate; 20 or more = severe

be more easily said than done if the patient is not forthcoming about their lower urinary tract symptoms (LUTS). Studies which have investigated why men with LUTS attend their physician have found that men with moderate–to-severe symptoms were significantly more likely to seek medical care than men with mild symptoms.[9] Increased visits to the family physician were associated with older age and with a greater interference of symptoms with everyday life. Having said this, there are many men with moderate-to-severe complaints who do not seek medical attention. Reasons for men not reporting LUTS may be related to the following:

- Men may accept their symptoms as a normal part of aging.
- Men may be embarrassed about their condition and a perceived social stigma attached to symptoms such as dribbling and urgency.
- Fear of cancer or surgery may prompt a man to try to ignore his symptoms.

A study that involved a survey of 3,544 men with an IPSS > 7 found that those who consulted their general practitioner (GP) in the previous 2 years more often thought their doctor could improve their condition than those who had not visited their GP.[9] They had also received more advice from others and more information from the media, both of which positively affected their attendance. These were actually stronger predictors of seeking care than IPSS score or effect of symptoms on daily life.[9]

This message has strong implications for the role of the pharmacist. Many men may confide in their pharmacist about an issue they are having or may be seeking advice on non-prescription treatments to control symptoms. This presents an excellent opportunity for pharmacists to explain to patients that over-the-counter remedies such as saw palmetto have not been found useful in treatment of urinary symptoms (see "Phytotherapy," below). Reassuring the patient that their complaint is a common one and that excellent treatments are available by prescription to control the problem will encourage the patient to visit their family physician. In addition, patients should be told that frequency of urinary symptoms increases with age and is usually associated with an enlarged prostate. The importance of visiting a doctor to receive appropriate treatment and rule out other unlikely causes should be underscored. Men who describe symptoms such as hematuria (blood in the urine) that may require more prompt attention or may be associated with a more serious condition should be urgently recommended to see their physician.

Disease symptoms that may mimic BPH include those associated with uncontrolled diabetes, urinary tract infections, neurogenic bladder, urethral strictures, bladder cancer, and congestive heart failure.[8] Medications that can cause or exacerbate symptoms include:[10, 11]

- drugs that cause diuresis (i.e., diuretics)
- drugs with anticholinergic effects (e.g., tricyclic antidepressants, antispasmodics, antihistamines). These agents may reduce bladder emptying.
- decongestants (e.g., pseudoephedrine)
- smooth muscle relaxants (e.g., anti-parkinsonian drugs and calcium channel blockers). These drugs may also reduce bladder emptying.
- opiates (e.g., morphine). These agents may impair autonomic function.

When recommending or dispensing these medications for the first time, pharmacists should mention the potential for associated LUTS and should follow up with patients who are already taking these drugs to determine if they are experiencing any symptoms.

3. Diagnosis and assessment of BPH

The diagnosis and assessment of a patient presenting with LUTS starts with a medical history. The IPSS is an excellent tool for evaluation and quantification of a patient's symptom severity.[5] The final question in the IPSS assessment tool is especially important: "If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that?" This gives the clinician a sense of the effect of the patient's condition on his quality of life and how willing he might be to accept treatment to address his symptoms.[5] The IPSS therefore serves as a good starting point for discussion and further clarification of the patient's symptoms.

The historical gold standard for assessment of prostate size is the digital rectal examination (DRE). The DRE can help to assess the size, shape, symmetry, quality, nodularity, and consistency of the prostate. An important function of this test is to determine the likelihood that prostate cancer exists. Detection of a palpable node suggests prostate cancer and the need for referral by the family physician to the urologist for further assessment. Urinalysis is utilized in order to detect urinary tract infections, bladder cancer, and stones.[5] Additional laboratory studies are considered as appropriate to patient circumstances.

3.1 Prostate specific antigen as a marker of prostate volume and diagnostic tool of BPH

Prostate specific antigen (PSA) is a protein that is synthesized by the epithelial cells of the prostate. Its main function is to liquefy the seminal fluid after ejaculation so that sperm can travel more easily. If damage to the basement membrane surrounding the prostatic ductal system resulting in inflammation occurs, PSA leaks into the serum, causing elevated blood levels of the protein.[12] Although PSA is best known as a biomarker for prostate cancer, it is also used for the diagnosis of BPH and for monitoring of treatment.[5] PSA has been shown to be a more accurate indicator of prostate volume than DRE. In fact, prostate volume as estimated by DRE has been shown to underestimate measured volume by up to 55%.[13, 14] Additional causes of increased PSA values include those circumstances where inflammation of the prostate is an issue. These include prostatitis, urinary tract infection, sexual intercourse, and trauma (e.g., riding a bike or motorcycle often).[15]

Men with a prostate volume of 30 mL or more are at greater risk for suffering moderate-to-severe symptoms of BPH, which include decreased flow rates (2.5 times increase) and acute urine retention (3–4 times increase), compared with men with prostate volume of less than 30 mL.[16] The PLESS trial results suggest that PSA thresholds for detecting a prostate volume of 30 mL vary with age as follows:[16]

- 50–59 years: ≥ 1.3 ng/mL
- 60–69 years: ≥ 1.5 ng/mL
- 70–79 years: ≥ 1.7 ng/mL

Additional studies have confirmed that PSA is an independent predictor of prostate volume increase and BPH progression.[12] Current consensus recommends that a PSA threshold of ≥ 1.5 ng/mL be used to identify those symptomatic men who should be assessed for medical therapy aimed at minimizing disease progression and symptoms. Men with a PSA less than 1.5 ng/mL with symptoms should be treated with a goal of minimizing symptoms only.[12]

4. Management of BPH

The goals of BPH treatment include the following:

- Reduce the symptoms of BPH.
- Prevent progression of BPH in order to reduce risk of acute urinary retention and need for surgery.

The Canadian Urology Association developed the first Canadian guidelines for the management of lower urinary tract symptoms in men with BPH.[7] Figure 2 (next page) overviews the management of a typical man with lower urinary tract symptoms (LUTS) secondary to benign prostatic obstruction (BPO). [7]

Case (continued):

George presents you with a prescription for finasteride 5 mg once daily written by his urologist. He mentions that the urologist told him this drug would help keep the size of his prostate in check and that he should notice an improvement in any BPH symptoms in about 6 months. His doctor told him that because it was available in a generic form that it was less expensive than the other option he was considering. He also mentioned some ways to help relieve symptoms without drugs that may help in the meantime.

4.1 Non-pharmacological management of BPH

4.1.1 Watchful waiting

If a man with BPH believes symptoms such as more frequent trips to the washroom and nocturia are not inconvenient enough to warrant medication therapy or surgery, a strategy of "watchful waiting" can be employed. As the name implies, this strategy involves watching for changes in symptoms or in laboratory and physical examinations before taking more aggressive action to control the condition. In general, symptoms in about 15% of men with BPH will improve over time, about 30% will remain stable, and 55% will worsen.[17] If symptoms do progress to a point where optimal health is threatened or symptoms are intolerable or bothersome, then medication or invasive procedures may be considered.

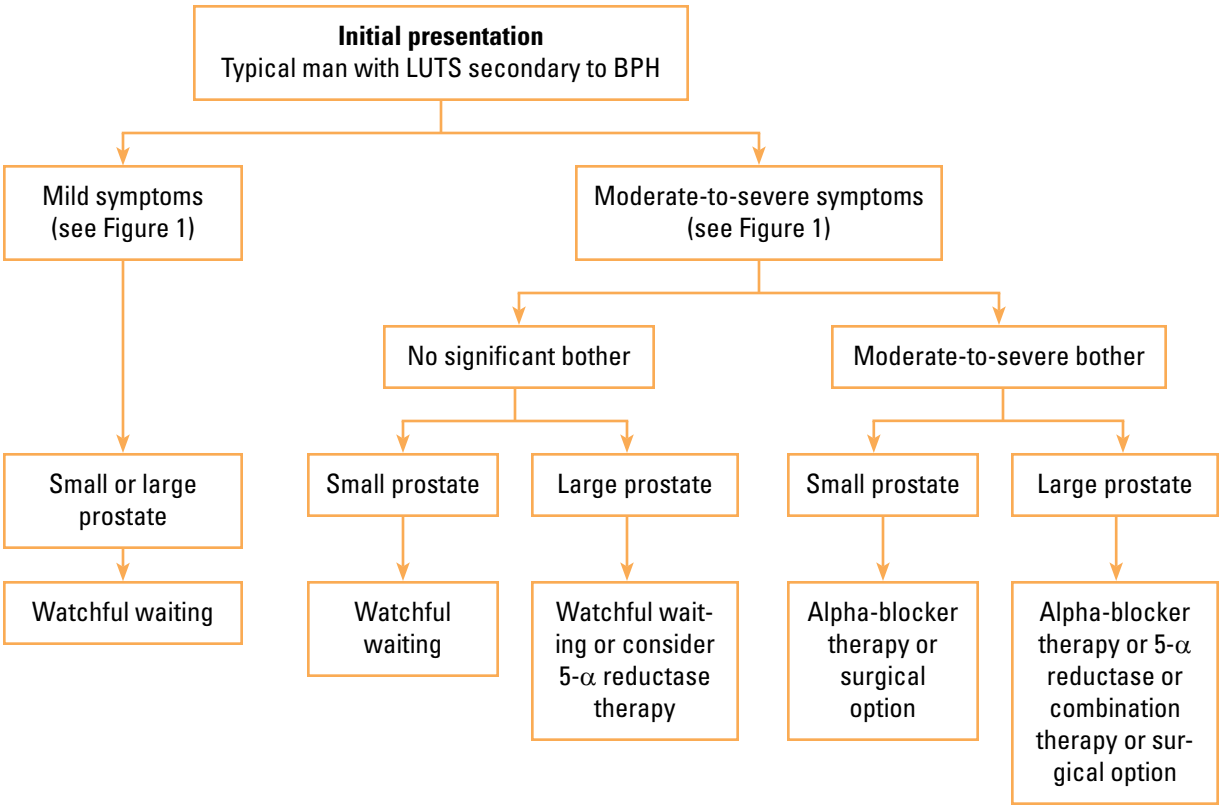
4.1.2 Helping patients self-manage lower urinary tract symptoms

Self-management principles in disease management simply mean that the patient takes responsibility for day-to-day management of their condition by implementing specific care plans and problem-solving skills.[10] The five core self-management skills are:[10]

- problem solving
- decision making
- resource utilization
- forming a patient/health care provider relationship
- taking action

Following are some steps that you can take to help patients self-manage symptoms associated with LUTS:[10]

Figure 2. Treatment algorithm for typical man with benign prostatic obstruction causes of lower urinary tract symptoms – Canadian Urological Association[7]



1. You have already dispelled George's misconception that BPH increases risk for prostate cancer. Further inquiries should be made to determine George's understanding of his condition and clarify and further misconceptions or worries he may have.
2. Supplementing your discussion with literature that clearly outlines the patient's condition and strategies for treatment can help to relieve anxiety and decisional conflict, and can increase patient participation in decision-making.[10] This strategy may also prevent the patient from going to the internet and finding information which may be less than evidence-based. Helpful patient handouts can be found at:
   - Medbroadcast.com at www.medbroadcast.com/channel_condition_info_details.asp?disease_id=20&channel_id=2055&relation_id=42622&rot=4
   - National Kidney and Urologic Diseases Information Clearinghouse at kidney.niddk.nih.gov/kudiseases/pubs/prostateenlargement/
   - MedlinePlus at www.nlm.nih.gov/medlineplus/ency/article/000381.htm
3. Patients such as George will benefit from understating how their fluid intake is related to voiding frequency. Frequency volume charts can help with this. If the patient consumes excessive or inadequate fluid intake or excessive alcohol or caffeine, he can be counselled to modify their actions and determine if symptoms improve. The effect of fluid reduction on symptoms of LUTS has not been tested in an evidence-based fashion.
4. Caffeine has diuretic and bladder irritant effects and increases early detrusor contraction during bladder filling in patients who have overactive bladders. Studies have not been conducted to demonstrate the effects of caffeine reduction in men. However, studies have shown that patients consuming larger quantities of caffeine on a daily basis are more likely to be diagnosed with BPH and undergo surgery. Patients need to understand that caffeine is contained not only in coffee, but also in tea, chocolate, energy drinks, and over-the-counter cold and headache remedies. It seems reasonable to suggest a trial of caffeine intake reduction in individuals who consume large amounts.
5. Like caffeine, alcohol intake is associated with urgency and higher IPSS scores in epidemiological studies. Those who drink large quantities of alcohol should be urged to moderate their

drinking in order to facilitate management of LUTS in addition to other obvious benefits.

6. Discussion needs to take place about any other medications he might be taking. Drugs that may exacerbate LUTS include:
   - drugs that cause diuresis (i.e., diuretics)
   - drugs with anticholinergic effects (e.g., tricyclic antidepressants, antispasmodics, antihistamines). These agents may reduce bladder emptying.
   - decongestants (e.g., pseudoephedrine)
   - smooth muscle relaxants (e.g., anti-parkinsonian drugs and calcium channel blockers). These drugs may also reduce bladder emptying.
   - opiates (e.g., morphine). These agents may impair autonomic function.[11]

   Suitable therapeutic substitutions should be recommended where appropriate. For example, if the patient is using hydrochlorothiazide for blood pressure control, an ACE inhibitor or angiotensin receptor blocker could be recommended. If he is taking a loop diuretic such as furosemide for treatment of heart failure, the drug can be taken in the early evening instead of early morning, since most loop diuretics are short-acting.
   - Patients should be urged to consult their pharmacist any time they are choosing a non-prescription product. Make sure that patients understand that "natural" remedies fall under this category, as many could have an effect on their symptoms.
7. Bladder retraining helps patients overcome the sensation of urinary urgency. The technique involves resisting the sensation of urinary urgency by using distraction and pelvic floor squeezes to postpone voiding. The period of time that voiding is postponed should initially be only about one minute, with time increased as patients can handle the initial time delay easily. A goal for interval time might be 3 to 4 hours. This technique should be used in consultation with a health care professional and with utilization of frequency volume charts. Studies have shown that bladder retraining improves urgency, frequency, and nocturia when used as a primary treatment strategy.

Case (continued):

George thanks you for the time you have spent with him and for the literature about BPH you recommended. You ask him what he thinks he might try with respect to self-managing LUTS; he says he will drink less in the evening, avoid caffeinated drinks, have only one glass of wine with dinner instead of two, and void twice within a short period before going to bed. You tell him that all of those ideas are excellent and that you will contact his doctor to see about the possibility of changing his diuretic to another medication.

4.2 Pharmacological treatment options for BPH

There are two classes of drugs approved for treatment of BPH in Canada. Long-term 5-α reductase inhibitors, alpha-blockers, and combinations of the two classes are effective for symptom control, while only 5-α reductase inhibitors as monotherapy or in combination therapy are able to prevent progression of BPH.[18]

4.2.1 5-α reductase Inhibitors

Case (continued):

After you discuss George's prescription for finasteride with him, he tells you that he has a friend who is taking something different for his BPH and he wonders why the doctor has chosen this particular therapy for him.

Finasteride and dutasteride selectively inhibit the activity of the enzyme 5-α reductase, which is responsible for converting testosterone to DHT. DHT is the active androgen in the prostate gland, and appears to promote both cell proliferation and differentiation.[19] The 5-α reductase inhibitors effectively reduce prostate volume, arrest the disease process, and improve symptoms over time.[19] As illustrated in Figure 2, these agents are indicated when BPH is associated with a large prostate regardless of patient symptoms (alone if no significant symptoms, or in combination with an alpha-blocker for moderate-to-severe bother).[7] If BPH patients who require treatment for symptoms alone cannot tolerate alpha-blockers, a 5-α reductase inhibitor may be used with close to the same benefits but slower onset of action. [18]

Efficacy of finasteride

- In the Proscar Long-Term Efficacy and Safety Study (PLESS), 3040 men with moderate-to-severe BPH symptoms were randomized to receive finasteride 5 mg or placebo for 4 years.[20] The outcome results were as follows:[20]
  - surgery for BPH – 5% finasteride group, 10% placebo group (relative risk reduction 55%)
  - acute urinary retention – 3% finasteride group, 7% placebo group (relative risk reduction 57%). The benefit of finasteride with respect to reduced need for surgery and improved acute urinary retention was evident at 4 months and continued throughout the trial.
  - decreases in American Urological Association Symptom Score (AUASS) – 2.6 finasteride group, 1.0 placebo group ($p<0.001$)

  - significant improvement in urinary flow rates and reduced prostate volume in finasteride group vs. placebo group (0<0.001)
- A long-term trial that included 156 men taking finasteride for 7 to 8 years found that long-term treatment with the drug was well tolerated and resulted in long-term symptom relief and improvement in prostate volume and urinary flow.[21]
- A subgroup analysis of data from the PLESS study showed that men using finasteride experienced significantly less bother, activity interference, and worry due to urinary symptoms than the placebo group.[22] The differences were greatest in men with prostate-specific-antigen (PSA) levels above 1.4 ng/mL and enlarged prostates. These factors (i.e, elevated PSA and large prostate size) were found to predict long-term changes in symptoms and flow rate.[23]
- A study of pressure-flow parameters in men with enlarged prostates using finasteride for 2 years revealed that decreases in detrusor pressure continued to decline over the entire 2 years of the study.[24]

Efficacy of dutasteride

- The efficacy of dutasteride has been studied in three parallel, multicenter, randomized placebo-controlled trials of 24 months duration. Men aged 50 years or with a clinical diagnosis of BPH, a transrectal ultrasonography prostate volume of more than 30 mL, and an AUASS of 12 or more and Q_{max} (urine flow) of 15 mL/sec or less. Following are outcome results:[25]
  - surgery for BPH – 2.2% dutasteride group, 4.1% placebo group (relative risk reduction 48%)
  - acute urinary retention – 1.8% dutasteride group, 4.2% placebo group (relative risk reduction 57%).
  - decreases in AUASS – 4.5 dutasteride group, 2.3 placebo group (p<0.001)
  - significant improvement in urinary flow rates and reduced prostate volume in dutasteride group vs. placebo group (p<0.001)

Note the similar efficacy results in terms of relative risk reduction of need for BPH surgery and incidence of acute urine retention between the PLESS trial (finasteride) and the three parallel multicenter, randomized placebo-controlled trials conducted with dutasteride.[25, 26] Although dutasteride blocks both isoenzymes of 5-α reductase (type I and type II), while finasteride blocks only type II, there appears to be no benefit clinically in the added suppression of serum DHT afforded by dutasteride.[27]

Safety profiles of finasteride and dutasteride

Dutasteride and finasteride are well tolerated, with the most commonly reported side effects being erectile dysfunction (7–8% vs. 4% placebo), decreased libido (4–5% vs. 3% placebo), ejaculatory disorders (2–4% vs. 1% placebo), and gynecomastia (1–2% vs. 2% placebo).[25, 26] The PLESS study reported nasal congestion in 9% of patients taking finasteride vs. 6% taking placebo and hypotension in 4% taking finasteride vs. 2% taking placebo.[26] All differences from placebo mentioned were statistically significant except gynecomastia incidence. These events occurred most often in the first year of treatment, with up to 10% of patients reporting sex-related adverse events in this time frame.[19] Dutasteride and finasteride cause reduction of PSA levels from baseline by about 50% after one year of therapy. In men taking these agents it is reasonable to use a PSA level of 2.0 ng/mL (instead of 4.0 ng/mL) as a point where further diagnostic workup for prostate cancer is undertaken.

4.2.2 Alpha-blockers

Approximately 40% of the total urethral pressure in patients with BPH results from the influence of alpha-adrenergic activity of the autonomic nervous system, or the alpha-adrenergic "tone" of the prostate smooth muscle. By blocking the α_1 receptors in the prostatic smooth muscle, symptoms of bladder outlet obstruction can be reduced.[28] There are three different α1 receptor subtypes. In the human prostate stroma the α_{1A} receptor predominates (70–100%).[29] This knowledge has led to the development of a number of drugs marketed for symptomatic control of LUTS associated with BPH.

The 4 long-acting alpha blockers commonly used to treat BPH are terazosin, doxazosin, alfuzosin, and tamsulosin. The Canadian Urology Association has deemed all 4 available α_1-blockers as appropriate treatment options for patients with LUTS secondary to BPH.[7] Terazosin, doxazosin, and alfuzosin are non-sub-type-selective alpha blockers, while tamsulosin blocks α_{1A} and α_{1D} receptors with 10-fold greater affinity than α_{1B} receptors.[29] Alfuzosin is shorter acting than tamsulosin. The specificity for prostate receptors exhibited by tamsulosin and alfuzosin reduces the propensity for dizziness and postural hypotension that is more commonly associated with initiation of terazosin and doxazosin. For this reason, the doses of alfuzosin and tamsulosin do not need to be titrated upwards as is normally the protocol for terazosin and doxazosin.

Efficacy of alpha-blockers

Many reviews suggest that the efficacy of terazosin, doxazosin, alfuzosin, and tamsulosin is compar-

able. Randomized placebo-controlled trials suggest the following with respect to efficacy:[29]

- The IPSS score improves by 4–6 points.
- The single disease-specific quality-of-life question score of IPSS improves by 1–1.5 points.
- The maximum urinary flow rate changes by 2–3 mL/sec.
- Onset of action usually occurs within one week with respect to symptoms and flow rate improvement. The full benefit of α-adrenergic blockers is often not realized until about 2 to 4 weeks after initiation of therapy, with about 60% to 70% of patients realizing improvement in bladder obstruction and urine output symptoms after this period of time.[30] Tamsulosin and alfuzosin may have a faster onset of action than the other 2 currently available agents because there is no delay associated with titrating the dose upwards to avoid adverse effects.[29]
- Of note, these agents do not prevent progression to acute urine retention or need for surgery, since these factors are driven by prostate volume increases and the natural history of BPH, which is not affected by alpha-blockers.
- Lower costs of terazosin and doxazosin should be weighed against potential for better safety profile with alfuzosin and tamsulosin (see below) when deciding on the particular alpha-blocker to utilize.

Safety profiles of alpha-blockers

Terazosin and doxazosin lower blood pressure through action on vascular smooth muscles.[11] Tamsulosin and alfuzosin have no effect on blood pressure and therefore pose less risk of adverse events when used with antihypertensive agents.[11] Blood pressure changes associated with α_1-adrenergic blockers are usually less pronounced in normotensive individuals. Pharmacists must caution patients about the potential for orthostatic hypotension with first doses of terazosin and doxazosin (see Table 2). Table 1 outlines adverse event profiles with currently available alpha-blockers used for treatment of BPH symptoms.

4.2.3 Combination therapy with alpha-blocker plus 5-α reductase inhibitor

Alpha-blockers and 5-α reductase inhibitors have complementary effects in relieving BPH symptoms. The following are some study outcomes which speak to the value of using these agents in combination:

- The Medical Therapy of Prostate Symptoms (MTOPS) study randomized over 3000 men, 50 years of age or older, with an American Urological Association symptoms score of 8–30 (moderate-to-severe symptoms), to receive doxazosin titrated up to 8 mg/day, finasteride 5 mg/day, the combination of drugs, or placebo once daily.[35] In each group the following were measured: BPH-related events (four-point rise in AUASS, creatinine rise attributed to BPH, acute urinary retention, recurrent urinary tract infection or urosepsis, and incontinence), incidence of BPH invasive therapy, change in urine flow (Q_{max}), and change in AUASS. Significant results were as follows:
  - At five years, rate of acute urinary retention and invasive surgery was significantly higher in the doxazosin and placebo groups compared to the finasteride and combination groups. Overall, the risk of BPH progression was reduced by 66% with combined therapy vs. placebo and vs. either monotherapy (34% for finasteride and 39% for doxazosin).
  - Changes in AUASS and Q_{max} were highest in the combination group at year 4 (3.0 and 2.3 mL/sec difference between combination and placebo).
  - Doxazosin group had slightly higher changes in AUASS and Q_{max} than finasteride group, but both groups were not significantly better than placebo.
  - A PSA greater than 1.6 ng/mL predicted

Table 1. Adverse events with alpha-adrenergic blockers[31-34]

	Terazosin vs. PLB	Doxazosin vs. PLB	Alfuzosin vs. PLB	Tamsulosin vs. PLB
Dizziness	3–26% vs. 3-7%	17–24% vs. 4–6%	2.1–7.4% vs. 1.3–2.9%	3–11% vs. 0–5%
Hypotension	2–9% vs. 0.5–1%	2.5–8.0% vs. 0.0%	0.7–3.4% vs. 0–3.4%	0% vs. 0.5–1.0%
Ejaculatory disorders	0–1.4% vs. 0–1.0%	0.0 vs. 0.0%	0–0.6% vs. 0–1.3%	1.0–26.0% vs. 0–1%
Discontinuations	16–38% vs. 8–17%	11–22% vs. 4–23%	11% vs. 6%	7–13% vs. 9–11%

**PLB = placebo*

symptom and overall BPH progression in the doxazosin group, acute urinary retention in all groups, and BPH-related therapy in the doxazosin and combination groups but not in the finasteride group.

Results of the MTOPS trial show that it is reasonable to use combination therapy for most men with BPH and to use a 5-α reductase inhibitor alone in patients who cannot tolerate alpha-blocker therapy.[18]

- The Effects of Combination Therapy with Dutasteride and Tamsulosin on Clinical Outcomes in Men with Symptomatic Benign Prostatic Hyperplasia (CombAT) study included 4844 men with BPH, 50 years of age or older, with an IPSS score of 12 or greater, a prostate volume of 30 cm^3 or greater, PSA of 1.5–10 ng/mL, and maximum urinary flow rate of more than 5 mL/sec and less than or equal to 15 mL/sec with minimum voided volume of at least 125 mL.[36] Participants were randomized to receive tamsulosin, dutasteride, or both for 4 years. Following are significant results:[36]
  - Combination therapy was significantly better than tamsulosin monotherapy but not dutasteride monotherapy in reducing relative risk of acute urinary retention of BPH-related surgery.
  - Combination therapy was significantly better than tamsulosin monotherapy and dutasteride monotherapy for reducing the relative risk of BPH clinical progression.
  - Combination therapy was significantly better with respect to symptom benefit than either monotherapy at 4 years.

Men in the CombAT study all had prostatic enlargement in addition to moderate-to-severe LUTS due to BPH and therefore were at high risk of disease progression.[36] The MTOPS study required only that men have moderate-to-severe symptoms, but not necessarily enlarged prostate. Therefore, the results of the CombAT study support the long-term use of dutasteride and tamsulosin in men with moderate-to-severe LUTS due to BPH and prostatic enlargement at increased risk of progression, as opposed to the conclusions drawn from the MTOPS trial outlined earlier supporting combination therapy in "most" men with BPH.[18, 36]

If a patient is benefiting from combination therapy after 6–9 months, a trial of alpha-blocker discontinuation may be considered.[5] This recommendation is based on outcomes of the Symptom Management after Reducing Therapy (SMART) study and the Proscar and Alpha-Blocker Combination Followed by Discontinuation Trial (PROACT) trial.[37, 38] Results of both trials revealed that most patients can safely discontinue their alpha-blocker therapy after 6 to 9 months of combination therapy with no efficacy reduction. Advantages include lower cost, lower potential for side effects, and increased potential for medication adherence.

The adverse effect profile of combination therapy is consistent with the contributions of the adverse effect profiles of each therapy.

4.3 Investigational therapies for treatment of BPH

Anticholinergics

Symptoms due to overactive bladder (e.g., frequency, urgency) in BPH are initially addressed by alpha-blockers due to their fast onset of action and effectiveness. A number of studies have assessed the efficacy of anticholinergics such as tolterodine for the treatment of LUTS associated with BPH:

- In an open-label study, tolterodine extended release (ER) 4 mg daily for 6 months was given to 43 men who had not tolerated alpha-blocker therapy.[41] The AUASS scores dropped by 6.1; peak urinary flow rate increased by 1.9 mL/second. Nocturia decreased from 4.1 to 2.9 episodes nightly.[41]
- A randomized trial compared tolterodine ER, tamsulosin, placebo, and the combination of tolterodine ER and tamsulosin.[42] Results showed that tamsulosin alone and the combination resulted in significant improvement in IPSS compared to the other two groups. Tamsulosin and tolterodine combination were significantly better than either drug alone or placebo with respect to IPSS QOL score. The most prevalent adverse effect was dry mouth (27% in the combination group). Other adverse events were low in all groups.[42]

Phosphodiesterase-5 inhibitors

A study that randomized men with BPH to sildenafil plus alfuzosin or alfuzosin alone found that patients receiving the combination had significant improvement in their LUTS. This effect has been shown to be shared among the 3 current phosphodiesterase inhibitors available (sildenafil, vardenafil, and tadalafil). The phosphodiesterase-5 inhibitors need to be dosed separately from alpha-blockers due to the potential for hypotensive effects.[18]

Botulinum toxin A

A trial of 30 men with BPH randomized men to trans-perineal injection of 100 units of botulinum toxin or saline into each lobe of the prostate.[43]

Table 2. Approved therapies for treatment of BPH

Drug and dose	Indications	Adverse effects	Comments
5-α reductase inhibitors (modify progression of BPH and provide symptom control)			
Finasteride[39] 5 mg daily with or without food	Monotherapy – Treatment and control of BPH and prevention of urologic events to reduce risk of acute urinary retention and surgery. Combination therapy with doxazosin to reduce risk of symptomatic progression of BPH.	• Impotence – 8.1% vs. 3.7% PLB yr 1, 5.1% vs. 5.1% yrs 2–4 • Decreased libido – 6.4% vs. 3.4% yr 1, 2.6% vs. 2.6% yrs 2–4 • ↓ ejaculate volume – 3.7% vs. 0.8% yr 1, 1.5% vs. 0.5% yrs 2–4 • Gynecomastia – 0.5% vs. 0.1% yr 1, 1.8% vs. 1.1% yrs 2–4	• Causes regression of enlarged prostate, improves urinary flow and symptoms associated with BPH. Not indicated for reducing risk of prostate cancer. • Inhibits only type II 5-α reductase, although no benefits have been demonstrated when both type I and type II receptors are inhibited. • 6 mos. until full clinical benefit. • No significant drug interactions identified. • Decreases PSA values by 50% (screening value should be doubled).
Dutasteride[40] 0.5 mg once daily with or without food	Monotherapy – Treatment of symptomatic BPH in men with enlarged prostates. Reduces risk of acute urinary retention and surgery. Combination therapy with tamsulosin to reduce prostate size and improve urinary flow and symptoms of BPH.	• Impotence – 4.7% vs. 1.7% PLB, 0–6 mos., 1.4% vs. 1.5%, 7–12 mos. • Decreased libido – 3.0% vs. 1.4% PLB, 0–6 mos., 0.7% vs. 0.6%, 7–12 mos. • Ejaculatory disorders – 1.4% vs. 0.5% PLB, 0–6 mos., 0.5% vs. 0.3%, 7–12 mos. • Breast Disorders – 0.5% vs. 0.2% PLB, 0–6 mos., 0.2% vs. 0.3%, 7–12 mos.	• Capsules must not be opened or chewed, as contents may cause irritation of oropharyngeal tract. • Inhibits both type I and type II 5-α reductase, although no benefits have been demonstrated when both type I and type II receptors are inhibited compared to type II only. • 6 mos. until full clinical benefit. • Drug concentrations may increase with potent CYP 3A4 inhibitors (e.g., ketoconazole). • Decreases PSA values by 50% (screening value should be doubled).
Alpha-blockers (symptom control – do not modify progression of BPH)			
Terazosin[31] (to max. 10 mg od) 1 mg hs × 1 wk, 2 mg od × 1 wk, 5 mg od × 1 wk, 10 mg od Dosage titrated until to desired symptom improvement or flow rate.	As monotherapy for treatment of symptoms of BPH.	• Headache 14.1% • Asthenia 11.0% • Dizziness 18.9% • Somnolence 4.8% • Nasal congestion 4.6% • Palpitation 4.6% • Nausea 3.9% • Peripheral edema 3.6% • Tachycardia 2.9% • Dyspnea 2.8% • Chest pain 2.2% • Nervousness 2.2%	• Requires titration to dose which may delay time to clinical effect compared to alfuzosin and tamsulosin. • "First-dose" effect may result in hypotension with first dose or first few doses (incidence reduced by titration). • Caution when used with PDE-5 inhibitors, as hypotension risk may be exacerbated. • Significant increase in serum levels when given with verapamil. Increases hypotension and tachycardia risk.

continued next page

Drug and dose	Indications	Adverse effects	Comments
Doxazosin[32] 1 mg od to start, increased to 2 mg od, then 4 mg od, then 8 mg od if necessary based on patient's urodynamics and BPH symptomatology.	As monotherapy for treatment of symptoms of BPH. Has been used in combination therapy with finasteride to reduce risk of symptomatic progression of BPH.	• Headache 16.5% • Fatigue 14.8% • Dizziness 14.6% • Postural dizziness 8.7% • Edema 6.6% • Somnolence 4.9% • Nausea 3.9% • Dyspnea 3.9% • Platelet decrease 3.9% • Palpitation 3.6% • Sexual dysfunction 3.5% • Dry mouth 3.4% • Vertigo 3.0% • Rhinitis 3.0% • Diarrhea 2.9% • Chest pain 2.7% • Asthenia 2.7%	• Requires titration to dose, which may delay time to clinical effect compared to alfuzosin and tamsulosin. • "First-dose" effect may result in hypotension with first dose or first few doses (incidence reduced by titration). • Caution when used with PDE-5 inhibitors as hypotension risk may be exacerbated.
Alfuzosin[33] 10 mg daily after the same meal each day. 10 mg daily after a meal from 1st day of catheterization and continued beyond catheter removal unless relapse of acute urinary retention or disease progression.	As monotherapy for treatment of symptoms of BPH. As adjunctive therapy with urethral catheterization for acute urinary retention related to BPH and management following catheter removal.	• Fatigue – 2.7% vs. 1.8% PLB. • Joint disorders – 2.1% vs. 2.2% PLB • Upper respiratory tract infection – 6.1% vs. 3.4% PLB • Dizziness – 5.7% vs. 2.8% PLB • Headache – 3.0% vs. 1.8%	• Does not require titration as do terazosin and doxazosin. • Time to effect approximately one week. • Should not be given with potent inhibitors of CYP 3A4 (e.g., ketoconazole, ritonavir, itraconazole).
Tamsulosin Capsule (SR) **Tamsulosin CR**[34] 0.4 mg once daily at same time each day after food (capsule)/ with or without food (CR tablet)	As monotherapy for treatment of symptoms of BPH. Has been used in combination therapy with dutasteride to reduce risk of symptomatic progression of BPH.	• Infections and infestations – 5.6% vs. 4.5% PLB • Reproductive system and breast disorders – 3.3% vs. 0.6% PLB • GI system disorders – 3.9% vs. 2.0% PLB • Nervous system disorders – 3.1% vs. 2.5% PLB • Respiratory, thoracic, and mediastinal disorders – 2.8% vs. 0.8% PLB • MSK and connective tissue disorders – 2.5% vs. 2.0% PLB • Cardiac disorders – 2.2% vs. 2.2% PLB	• Does not require titration as do terazosin and doxazosin. • Time to effect approximately one week. • No clinically significant drug interactions identified. Caution with warfarin, as studies have not been conducted.

Results showed a 65% significant improvement in IPSS and a significant 51% reduction in PSA compared to controls. Long-term follow up for up to 30 months in 77 patients revealed similar results.[44] No adverse events have been experienced.

Phytotherapy

The Canadian guidelines for the management of benign prostatic hyperplasia state that patients interested in complementary approaches for symptoms of BPH may be counselled that some plant extracts (particularly saw palmetto berry extract and *Pygeum africanum*) have shown some efficacy in small but "unconvincing" studies.[7] More evidence is required before recommending these agents as standard therapy. However, they do appear to be safe.

- A recent randomized double-blind study conducted by Bent and colleagues randomized 225 men over 49 years of age, with moderate-to-severe symptoms of BPH as defined by the American Urological Association Symptoms Index (AUASS), to saw palmetto 320 mg/day or placebo.[45] After 52 weeks, groups did not differ in changes in AUASS score, maximum urine flow rate, prostate size, residual urine volume after voiding, or levels of PSA, creatinine, and testosterone.[46] A trial assessing the effectiveness and safety of 320–960 mg/day of standardized saw palmetto extracts in men with moderate symptoms (the CAMUS trial) was redesigned after it was found that there were no differences between the treatment and placebo after one year.[47] The trial is now assessing whether or not increasing doses has any effect on symptoms of BPH in the short term. There is currently no evidence to suggest that saw palmetto maintains prostate health or prevents development of urinary symptoms, as reported by a recent Cochrane Database Systematic Review.[48]

4.4 Surgery

The Canadian gGuidelines for the mManagement of BPH benign prostatic hyperplasia state that transurethral resection of the prostate (TURP) should be considered the gold standard treatment for patients with bothersome moderate or severe LUTS who request active treatment of who either fail or do not want medical therapy.[7]

TURP is the most commonly employed surgical procedure for BPH and reduces symptoms in 88% of patients.[8] It involves the scraping away of excess prostate tissue by an instrument (resectoscope) armed with cutting tools. This narrow instrument reaches the prostate through the urethra while the patient is under anesthesia (general or spinal block). The procedure is very effective, and urine flow symptoms are usually improved within a few days. Infrequently, TURP can cause temporary impotence and loss of bladder control. More commonly, retrograde ejaculation may occur (approximately 70% of patients), where semen flows backward into the bladder during orgasm instead of out through the penis.[8] This problem can be remedied by a relatively simple stretching procedure done on an outpatient basis. Complications of hematuria, reoperation, dilutional hyponatremia, and the need for blood transfusion have been decreased significantly with advances in optics and energy generation/delivery systems.[18]

Holmium laser enucleation (HOLEP) is used for larger prostate glands and for patients using anticoagulation. It has been associated with reduced hospitalization, bleeding, and duration of catheterization. Greenlight laser or photoselective vaporization prostatectomy is suitable for most men considering surgical alternatives, especially those using anticoagulation.[18]

Transurethral incision of the prostate (TUIP) was devised as a minimally invasive technique in an effort to obtain the same results as TURP but at lower cost and less risk of sexual dysfunction. It is an endoscopic procedure using only one or two incisions to reduce constriction of the urethra without removing any of the prostate gland. It is generally offered to younger patients where retrograde ejaculation and fertility are important issues. Outcomes are similar to those with TURP, although the procedure takes less time to perform and causes less bleeding.[8]

Open prostatectomy (surgical removal of the inner portion of the prostate using a suprapubic or retropubic approach) is indicated for men whose prostates are too large to be resected comfortably and safely.[7]

Transurethral microwave therapy (TUMT) involves microwave energy delivered via a microwave antenna placed in a urethral catheter. It causes deep, rapid tissue heating, while a cooling system circulates water to protect adjacent tissue. TUMT is a reasonable treatment choice for the patient who has moderate symptoms, small-to-moderate gland size, and a desire to avoid more invasive therapy for potentially less effective results.

Additional surgical procedures that are use less frequently include transurethral needle ablation (TUNA – placement of radiofrequency needles in the prostate), balloon dilatation, absolute ethanol injection, high-intensity focused ultrasound, water-induced thermotherapy, and plasma kinetic tissue management. These are all minimally invasive surgical therapies (MIST) aimed at reducing hyperplastic tissue in the prostate.[7, 8]

5. Summary: The role of pharmacists in management of BPH

Community pharmacists encounter patients more often than any other health professional does. Studies have shown that men more often respond to advice and media than they do to their own urinary symptoms. Therefore, pharmacists are in an ideal position to inquire about potential urinary symptoms associated with medications and/or medical conditions. Men may disclose or hint at the presence of urinary symptoms during discussion with a pharmacist. Even a remark intended to be humorous such as "I can't go anywhere further than 2 hours from the toilet" should be followed up on. Another opportunity for intervention might occur when a man asks for advice about choice of a non-prescription-requiring product such as saw palmetto. Having a patient complete an IPSS would be an excellent way to open discussion about the topic and motivate a patient to visit their physician.

Recommendation of appropriate medications is another very important role for the pharmacist. Alpha- blockers (i.e., terazosin, doxazosin, alfuzosin, and tamsulosin) are indicated for treatment of BPH symptoms but are not effective for attenuating progression of BPH. They are clinically effective after a week or so and therefore are especially helpful for those with bothersome LUTS. The 5-α reductase inhibitors (i.e., finasteride, dutasteride) are indicated for men with larger prostates, as these agents do reduce progression of BPH. They are also effective for controlling symptoms but require up to 6 months before clinical effectiveness in this regard is realized. Therefore, a combination of alpha-blocker and 5-α reductase inhibitor is often prescribed. If a patient is doing well, the alpha-blocker may be discontinued after 6 to 9 months and symptom control monitored. This recommendation will increase cost-effectiveness of therapy, will reduce potential for side effects, and may help to improve patient adherence.

References

1. Leveillee RJ, Patel VR, Bird VG, Moore CR. Prostate Hyperplasia, Benign. emedicine.medscape.com/article/437359-print . 2010.
2. American Cancer Society. What are the key statistics about prostate cancer? http://www.cancer.org/docroot/cri/content/cri_2_4_1x_what_are_the_key_statistics_for_prostate_cancer_36.asp . 2010.
3. Canadian Cancer Society. Prostate Cancer. http://www.cancer.ca/Canada-wide/Prevention/Get%20screened/Early%20detection%20for%20prostate%20cancer.aspx?sc_lang=en . 2010
4. Thompson JF. Geriatric Urologic Disorders. Applied Therapeutics: The Clinical Use of Drugs , 101.1-101.33. 2010.
5. Tanguay S, Awde M, Brock G et al. Diagnosis and management of benign prostatic hyperplasia in primary care. Can Urol Assoc J 2009;3(3 Suppl 2):S92-S100.
6. Cornell Physicians. BPH: Signs and Symptoms. www.cornellurology.com/BPH/symptom/ . 2010.
7. Nickel JC, Herschorn S, Corcos J et al. Canadian guidelines for the management of benign prostatic hyperplasia. Can J Urol 2005;12(3):2677-2683.
8. Dull P, Reagan RW, Jr., Bahnson RR. Managing benign prostatic hyperplasia. Am Fam Physician 2002;66(1):77-84.
9. Wolters R, Wensing M, van WC, van der Wilt GJ, Grol RP. Lower urinary tract symptoms: social influence is more important than symptoms in seeking medical care. BJU Int 2002;90(7):655-661.
10. Brown CT, Emberton M. Self-management for men with lower urinary tract symptoms. Curr Urol Rep 2009;10(4):261-266.
11. Edwards JL. Diagnosis and management of benign prostatic hyperplasia. Am Fam Physician 2008;77(10):1403-1410.
12. Bartsch G, Fitzpatrick JM, Schalken JA, Isaacs J, Nordling J, Roehrborn CG. Consensus statement: the role of prostate-specific antigen in managing the patient with benign prostatic hyperplasia. BJU Int 2004;93 Suppl 1:27-29.
13. Roehrborn CG, Girman CJ, Rhodes T et al. Correlation between prostate size estimated by digital rectal examination and measured by transrectal ultrasound. Urology 1997;49(4):548-557.
14. Roehrborn CG. Accurate determination of prostate size via digital rectal examination and transrectal ultrasound. Urology 1998;51(4A Suppl):19-22.
15. Toguri A, Barkin J. Management of benign prostatic hyperplasia by family physicians. Can J Urol 2010;17 Suppl 1:26-34.
16. Emberton M, Cornel EB, Bassi PF, Fourcade RO, Gomez JM, Castro R. Benign prostatic hyperplasia as a progressive disease: a guide to the risk factors and options for medical management. Int J Clin Pract 2008;62(7):1076-1086.
17. McSherry J, Weiss R. Managing benign prostatic hyperplasia in primary care. Patient-centred approach. Can Fam Physician 2000;46:383-389.
18. Sandhu JS. Therapeutic options in the treatment of benign prostatic hyperplasia. Patient Prefer Adherence 2009;3:213-223.
19. Harkaway RC, Issa MM. Medical and minimally

invasive therapies for the treatment of benign prostatic hyperplasia. Prostate Cancer Prostatic Dis 2006;9(3):204-214.
20. McConnell JD, Bruskewitz R, Walsh P et al. The effect of finasteride on the risk of acute urinary retention and the need for surgical treatment among men with benign prostatic hyperplasia. Finasteride Long-Term Efficacy and Safety Study Group. N Engl J Med 1998;338(9):557-563.
21. Vaughan D, Imperato-McGinley J, McConnell J et al. Long-term (7 to 8-year) experience with finasteride in men with benign prostatic hyperplasia. Urology 2002;60(6):1040-1044.
22. Bruskewitz R, Girman CJ, Fowler J et al. Effect of finasteride on bother and other health-related quality of life aspects associated with benign prostatic hyperplasia. PLESS Study Group. Proscar Long-term Efficacy and Safety Study. Urology 1999;54(4):670-678.
23. Roehrborn CG, McConnell J, Bonilla J et al. Serum prostate specific antigen is a strong predictor of future prostate growth in men with benign prostatic hyperplasia. PROSCAR long-term efficacy and safety study. J Urol 2000;163(1):13-20.
24. Schafer W, Tammela TL, Barrett DM et al. Continued improvement in pressure-flow parameters in men receiving finasteride for 2 years. Finasteride Urodynamics Study Group. Urology 1999;54(2):278-283.
25. Roehrborn CG, Boyle P, Nickel JC, Hoefner K, Andriole G. Efficacy and safety of a dual inhibitor of 5-alpha-reductase types 1 and 2 (dutasteride) in men with benign prostatic hyperplasia. Urology 2002;60(3):434-441.
26. McConnell JD, Bruskewitz R, Walsh P et al. The effect of finasteride on the risk of acute urinary retention and the need for surgical treatment among men with benign prostatic hyperplasia. Finasteride Long-Term Efficacy and Safety Study Group. N Engl J Med 1998;338(9):557-563.
27. Laborde EE, McVary KT. Medical management of lower urinary tract symptoms. Rev Urol 2009;11(Suppl 1):S19-S25.
28. Beduschi MC, Beduschi R, Oesterling JE. Alpha-blockade therapy for benign prostatic hyperplasia: from a nonselective to a more selective alpha1A-adrenergic antagonist. Urology 1998;51(6):861-872.
29. Roehrborn CG. Efficacy of alpha-Adrenergic Receptor Blockers in the Treatment of Male Lower Urinary Tract Symptoms. Rev Urol 2009;11(Suppl 1):S1-S8.
30. Lee M. Tamsulosin for the treatment of benign prostatic hypertrophy. Ann Pharmacother 2000;34(2):188-199.
31. Hytrin product monograph. 2010.
32. Cardura product monograph. 2010
33. Xatral product monograph. 2010.
34. Flomax CR product monograph. 2010.
35. McConnell JD, Roehrborn CG, Bautista OM et al. The long-term effect of doxazosin, finasteride, and combination therapy on the clinical progression of benign prostatic hyperplasia. N Engl J Med 2003;349(25):2387-2398.
36. Roehrborn CG, Siami P, Barkin J et al. The effects of combination therapy with dutasteride and tamsulosin on clinical outcomes in men with symptomatic benign prostatic hyperplasia: 4-year results from the CombAT study. Eur Urol 2010;57(1):123-131.
37. Barkin J, Guimaraes M, Jacobi G, Pushkar D, Taylor S, van Vierssen Trip OB. Alpha-blocker therapy can be withdrawn in the majority of men following initial combination therapy with the dual 5alpha-reductase inhibitor dutasteride. Eur Urol 2003;44(4):461-466.
38. Nickel JC, Barkin J, Koch C, Dupont C, Elhilali M. Finasteride monotherapy maintains stable lower urinary tract symptoms in men with benign prostatic hyperplasia following cessation of alpha blockers. Can Urol Assoc J 2008;2(1):16-21.
39. Proscar product monograph. 2010
40. Avodart product monograph. 2010
41. Kaplan SA, Walmsley K, Te AE. Tolterodine extended release attenuates lower urinary tract symptoms in men with benign prostatic hyperplasia. J Urol 2008;179(5 Suppl):S82-S85.
42. Kaplan SA, Roehrborn CG, Rovner ES, Carlsson M, Bavendam T, Guan Z. Tolterodine and tamsulosin for treatment of men with lower urinary tract symptoms and overactive bladder: a randomized controlled trial. JAMA 2006;296(19):2319-2328.
43. Brisinda G, Cadeddu F, Vanella S, Mazzeo P, Marniga G, Maria G. Relief by botulinum toxin of lower urinary tract symptoms owing to benign prostatic hyperplasia: early and long-term results. Urology 2009;73(1):90-94.
44. Maria G, Brisinda G, Civello IM, Bentivoglio AR, Sganga G, Albanese A. Relief by botulinum toxin of voiding dysfunction due to benign prostatic hyperplasia: results of a randomized, placebo-controlled study. Urology 2003;62(2):259-264.
45. Bent S, Kane C, Shinohara K et al. Saw palmetto for benign prostatic hyperplasia. N Engl J Med 2006;354(6):557-566.
46. Bent S, Kane C, Shinohara K et al. Saw palmetto for benign prostatic hyperplasia. N Engl J Med 2006;354(6):557-566.
47. Lee J, Andriole G, Avins A et al. Redesigning a large-scale clinical trial in response to negative external trial results: the CAMUS study of phytotherapy for benign prostatic hyperplasia. Clin Trials 2009;6(6):628-636.
48. Tacklind J, MacDonald R, Rutks I, Wilt TJ. Serenoa repens for benign prostatic hyperplasia. Cochrane Database Syst Rev 2009;(2):CD001423.

Questions

Case 1: *Frank Jones is a 67-year-old man who has been coming to your pharmacy for a number of years to pick up his prescriptions for hypertension and dyslipidemia. He is currently taking hydrochlorothiazide 25 mg once daily and atorvastatin 20 mg once daily. Frank confides in you that he has been needing to visit the washroom more frequently lately, to the point where it is embarrassing to go to a social outing that requires him to sit in the same seat for more than an hour. You tell Frank that a visit to his doctor is in order.*

1. Frank tells you that the problem has been getting gradually more noticeable over the past 5 years but he chose to ignore it. He is afraid that he might have prostate cancer. Which of the following statements about BPH and risk of prostate cancer is true?
   a. When BPH is associated with increased levels of DHT, prostate cancer risk is also increased.
   b. About 50% of men demonstrate histopathologic BPH by age 60. The condition is benign and much more common than prostate cancer.
   c. With symptoms of frequency and reduced volume, the chances of being diagnosed with BPH or prostate cancer are about even.
   d. An enlarged prostate indicates that prostate cancer is a more likely diagnosis than BPH.

2. After you try to convince Frank to see his doctor, he agrees to complete an IPSS questionnaire. His score is 15. How would you interpret this?
   a. The score indicates little, if any, prostate symptoms.
   b. The score indicates mild prostate symptoms.
   c. The score indicates moderate prostate symptoms.
   d. The score indicates severe prostate symptoms.

3. Frank is back 3 weeks later and thanks you for convincing him to see his doctor. He has had assessments conducted and found out his PSA is 1.8 ng/mL. He is also very happy that the doctor has ruled out prostate cancer. How should the PSA result be interpreted?
   a. He should be treated with therapy that addresses disease progression ± symptoms.
   b. He should be treated with therapy to address disease progression only.
   c. He does not need to be treated with pharmacotherapy, but watchful waiting is indicated.
   d. He should be treated for symptoms only.

4. Which of the following drugs would be the *least* appropriate to recommend for replacement of Frank's hydrochlorothiazide prescription (which may be contributing to symptoms)?
   a. ramipril
   b. irbesartan
   c. metoprolol
   d. verapamil

Case 2: *John Carpenter is a 58-year-old man who comes into the pharmacy with a prescription for finasteride and tamsulosin. He tells you that these are the first chronic prescriptions he has taken his entire life. He has the occasional back problem and takes ibuprofen 400 mg q4h prn for the pain.*

5. Which of the following statements about these 2 drugs is correct?
   a. Finasteride will help control symptoms within 1–2 weeks.
   b. Tamsulosin needs to be titrated in order to prevent hypotension-related side effects.
   c. Finasteride improves prostate volume but not urine retention issues.
   d. Tamsulosin therapy does not improve prostate volume.

6. After 7 months of treatment John is doing well, but his doctor wants him to stop taking the tamsulosin to see if he continues to do well. What is the rationale behind this?
   a. Tamsulosin toxicity may occur after 6 months due to storage of a drug metabolite in the liver.
   b. Tamsulosin may not be required after 6 months because finasteride also controls symptoms.
   c. Tamsulosin often cures symptoms of BPH after being taken for 6 months.
   d. Tamsulosin requires that the patient take a one-month "drug holiday" due to tolerance issues.

7. John tells you that he has a friend who takes dutasteride instead of finasteride. He would like to know what the differences are. Which of the following statements is true?
   a. Dutasteride is more effective than finasteride due to inhibition of type I and type II 5-α reductase receptor types.
   b. Finasteride has a higher drug interaction risk than dutasteride.
   c. Both drugs decrease PSA screening values by approximately 50%.
   d. Dutasteride should be taken with food, while finasteride can be taken without regard to food.

8. John said he tried taking saw palmetto on his own before going to the doctor. Which of the following statements about saw palmetto is true?

a. Randomized controlled studies have demonstrated benefit for treatment of symptoms but not disease progression.
b. Randomized controlled studies have demonstrated benefit for treatment of disease progression but not symptoms.
c. Randomized controlled studies have demonstrated benefit for both treatment of symptoms and disease progression.
d. Randomized controlled studies have demonstrated benefit for neither treatment of symptoms nor disease progression.

9. John tells you that another friend of his is taking finasteride and alfuzosin instead of finasteride and tamsulosin. Which of the following statements is correct?

a. Alfuzosin is more effective than tamsulosin but is associated with more side effects.
b. Tamsulosin is more effective than alfuzosin but is associated with more side effects.
c. Tamsulosin and alfuzosin are of approximately equal effectiveness.
d. Alfuzosin requires less time to reach clinical effectiveness than tamsulosin.

10. After 3 years, John has been recommended for surgery. Which of the following statements about surgery is true?

a. TUIP is a less expensive procedure than TURP.
b. Transurethral microwave therapy is most appropriate for patients with a large prostate.
c. Greenlight laser therapy is contraindicated in patients using warfarin.
d. TURP is associated with a low incidence of retrograde ejaculation (< 10%).