Management of benign prostatic hyperplasia by the primary care physician in the 21st century: the new paradigm

Jack Barkin, MD
Humber River Regional Hospital, University of Toronto, Toronto, Ontario, Canada

BARKIN J. Management of benign prostatic hyperplasia by the primary care physician in the 21st century: the new paradigm. The Canadian Journal of Urology. 2008;15(Supplement 1):21-30.

Benign prostatic hyperplasia (BPH) is one of the commonest causes of lower urinary tract symptoms (LUTS) in men over age 50. Fifty percent of men over age 50 will require some type of management for BPH/LUTS symptoms. Until about 15 years ago, the most common management for BPH was a transurethral resection of the prostate (TURP) operation. Initially, once a diagnosis of BPH has been made, most men are treated medically. One must first rule out other serious causes of these symptoms, such as prostate cancer, bladder cancer, and other obstructions. For men with an enlarged prostate, there is a good chance that therapy with a 5-alpha-reductase inhibitor (5-ARI) can prevent disease progression and the need for surgery. There has been a lot of recent work on different combination therapies for the treatment of BPH/LUTS. If a patient's serum prostate-specific antigen (PSA) level is greater than 1.5 ng/ml and his prostate volume is greater than 30 cc and he has significant LUTS, then combination medical therapy of an alpha blocker with a 5-ARI is the most effective therapy. After a careful workup, it is quite reasonable and appropriate for the primary care physician to initiate this therapy for a patient with BPH/LUTS.

Key Words: BPH, LUTS, PSA, combination medical therapy, 5-ARI, alpha blocker, prostate cancer

Introduction

It is estimated that by 2020, approximately 4 million Canadian men will have benign prostatic hyperplasia (BPH) with lower urinary tract symptoms (LUTS) that require treatment. Most of these men will receive either prophylactic therapy (to prevent BPH progression or to prevent possible development of prostate cancer),[1] or therapy for BPH, which is initiated by their primary care physicians.

This raises many questions, such as "Who should receive treatment? What treatment should they get? When should they receive treatment? How long should they be treated for?" and "What are the risks and benefits of medical versus interventional therapy for BPH?"

This article is written to provide guidance for the primary care physician who is faced with a patient who has symptoms associated with BPH. It also aims to serve as a reference for providing therapy for patients who are at high risk of developing prostate cancer.

Address correspondence to Dr. Jack Barkin, Chief of Staff, Humber River Regional Hospital, 960 Lawrence Avenue West, Suite 404, Toronto, Ontario M6A 3B5 Canada

Diagnosis

Not all men who present with LUTS have BPH. The primary care physician must try to differentiate LUTS from true BPH. The symptoms of many conditions such as urethral strictures, bladder stones, recurrent urinary tract infections, bladder cancer, and even prostate cancer can mimic those of LUTS. BPH is, however, by far the most common cause of LUTS in middle-aged to older men.[2]

Why should we try to treat BPH? We know that the natural course of BPH is one of progression,[3-5] which can lead to any number of potential side effects and complications. The patient can start to have recurrent urinary tract infections, hematuria, early signs of renal failure, and finally, can progress to acute urinary retention and even the need for surgery. He may also have concomitant and significant interference with his lifestyle. Men with prostates that have the largest volumes and who have significant symptoms at the time of presentation to a physician have the highest risk for progression of BPH.[6] Patients who are asked to identify their most worrisome and significant concerns about their symptoms of BPH would most likely identify their fear of needing a catheter for acute urinary retention or of ultimately requiring surgery.

How then should we diagnose BPH? We need to first obtain a complete patient history and then do a physical examination that is targeted for BPH/LUTS, Table 1.

Patient history

In taking a patient's history, we are always interested in how the patient's symptoms started. Although fluid balance is often overlooked in primary care, it is critical to document this in the patient who presents with BPH/LUTS. It is often amazing to find out how much fluid a patient is imbibing. Patients are very often surprised when they discover that a reason for their frequent nocturnal bathroom visits could be because they are ingesting 3 to 4 liters of fluid on a daily basis.

In taking the history of a patient with BPH, it is also important to note the medications that the patient is receiving, whether or not he smokes, and the types of possible bladder or prostate irritants (most commonly tea, coffee, alcohol, or spicy foods) that he is ingesting. Activities such as frequent and lengthy bike, car, or airplane rides can also sometimes aggravate the bladder or prostate.

We try to separate the patient's symptoms into two categories: obstructive versus irritative symptoms. Obstructive (voiding) symptoms include weak stream, hesitancy, sensation of incomplete emptying, intermittent stream, and prolonged urination. Irritative (filling) symptoms include frequency, urgency, nocturia, and urge incontinence.

These symptoms can be quantified by using the American Urological Association-Symptom Index (AUA-SI) for BPH.[7] This questionnaire has become the gold standard for assessing BPH symptoms, as part of a medical check-up or as part of a clinical trial. The responses to the questionnaire give the physician (or investigator) an objective means of assessing how the patient might respond to therapy. The patient is asked to fill in the questionnaire on repeated occasions. The maximum possible total score is 35, where a score of 0 to 8 indicates mild BPH symptoms; a score of 8 to 20 indicates moderate BPH symptoms; and a score of 20 to 35 indicates severe BPH symptoms. Changes in scores over time reflect improvement or deterioration in the patient's BPH symptoms.

TABLE 1. **Clinical assessment of a patient with benign prostatic hyperplasia**

History and physical examination
Digital rectal examination (DRE)
Urinalysis
Prostate-specific antigen (PSA) determination
To rule out prostate cancer
To assess prostate size (PSA 1.5 ng/ml = 30 cc prostate)
Symptom assessment
Patient interview
Symptom score on patient questionnaire (AUA-SI for BPH; IPSS)
Quality-of-life assessment

AUA-SI = American Urological Association-Symptom Index; BPH = benign prostatic hyperplasia; IPSS = International Prostate Symptom Score

The final question on the AUA-SI for BPH questionnaire is what I call the "motivation" or "quality-of-life" question. This asks: "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?" The possible responses range from "0" (delighted) to "6" (terrible). This question can also be described as a "bothersome index." It provides an idea as to how much the symptoms are bothering the patient as well as his motivation to obtain and accept treatment to lessen his symptoms.

Studies have shown that patients will make significant lifestyle changes in response to their BPH/LUTS.[8] They might avoid going to sporting activities, the theater, or church, or avoid long car rides, which can have a dramatic negative impact on their quality of life. Usually they will decrease fluid intake, which could lead to the development of kidney stones!

Prevalence of BPH increases with age. Approximately 50% of men who are 50 years old have clinical evidence of BPH, but by age 80, more than 80% of men have clinical evidence of this condition.[2,9] BPH symptoms progress over time. As they progress, a man's chance of developing acute urinary retention or the need for surgery increases. Age is the greatest risk factor for the sequelae of BPH.

Physical examination and other tests

After taking a patient's history, the physician should do a focused urological examination of the patient. This involves palpating the flanks to determine if there is kidney enlargement. Next, he or she should palpate and percuss the supra-pubic area to determine if there is an enlarged bladder that contains a significant amount of residual urine. The physician should examine the external genitalia to look for any congenital abnormalities, a tight phimosis, or possibly a meatal stenosis. In addition, he or she needs to assess the testicles to ensure that they are a good size and quality and that there is no obvious evidence of a large hydrocele that could also cause some degree of obstruction by deviation or sheer compression of the urethra.

The final and most important aspect of the physical examination is the digital rectal examination (DRE). It is this critical assessment of the prostate that will provide an estimate of the size, shape, quality, nodularity, and consistency of the prostate. This interpretation will help the investigator to conclude whether the patient has benign enlargement of the prostate or possibly prostate cancer. Ultimately, it is the size of the prostate, when the prostate is benign, that will help us to predict the likelihood that the patient's symptoms or disease will progress.

Many studies have determined that an "enlarged prostate" is a prostate volume that is 30 cc or larger.[6,10] In cases where it is difficult for the physician to determine the prostate volume of a patient, a transrectal ultrasound can be performed. Many studies have shown, however, that a serum prostate-specific antigen (PSA) value of at least 1.5 ng/ml indicates that the prostate volume is at least 30 cc.[4] This makes it easy to identify patients with BPH and enlarged prostates who are at high risk of BPH progression. It is critical to request a serum PSA test for any patient who presents with symptoms of BPH or for whom one is considering medical or interventional therapy for BPH.

Physicians should also request a urinalysis and a creatinine test for patients who present with BPH/LUTS. Other tests that could be included in a patient's baseline assessment include determination of his uroflow rate, post-void residual volume, and sexual functioning.

Treatment

Based on the results of a baseline assessment, the physician can determine if a man needs treatment for BPH. The Canadian Urological Association (CUA) has established algorithms for patient management, which is based on a combination of the degree of symptoms, the amount of bother, and the size of the prostate. Figure 1 and 2.[11] Several studies have shown that that patients who seek treatment for BPH are those with moderate to severe symptoms and enlarged prostates.

If a patient has recurrent urinary tract infections, hematuria, significant residual volume, or any sign of renal failure, aggressive therapy is warranted. These patients should be referred early to a urologist. Any patient with an age-related elevated serum PSA level or a rapidly changing PSA level (a change of > 20% per year or > 0.75 ng/ml per year), or an abnormal DRE should also be referred to a urologist.

Oesterling and colleagues randomly selected men from Olmstead County, Minnesota, who were asymptomatic for prostate cancer. Of the original 537 subjects, 471 completed a DRE, a transrectal ultrasound (TRUS), and PSA testing and had no evidence of prostate cancer. These individuals were the basis for the study population from which the following PSA cut-offs for upper normal limits were derived: < 2.5 ng/ml at age 40 to 49 years; < 3.5 ng/ml at age 50 to 59 years; < 4.5 ng/ml at age 60 to 69 years; or < 6.5 ng/ml at age 70 to 79 years).[12]

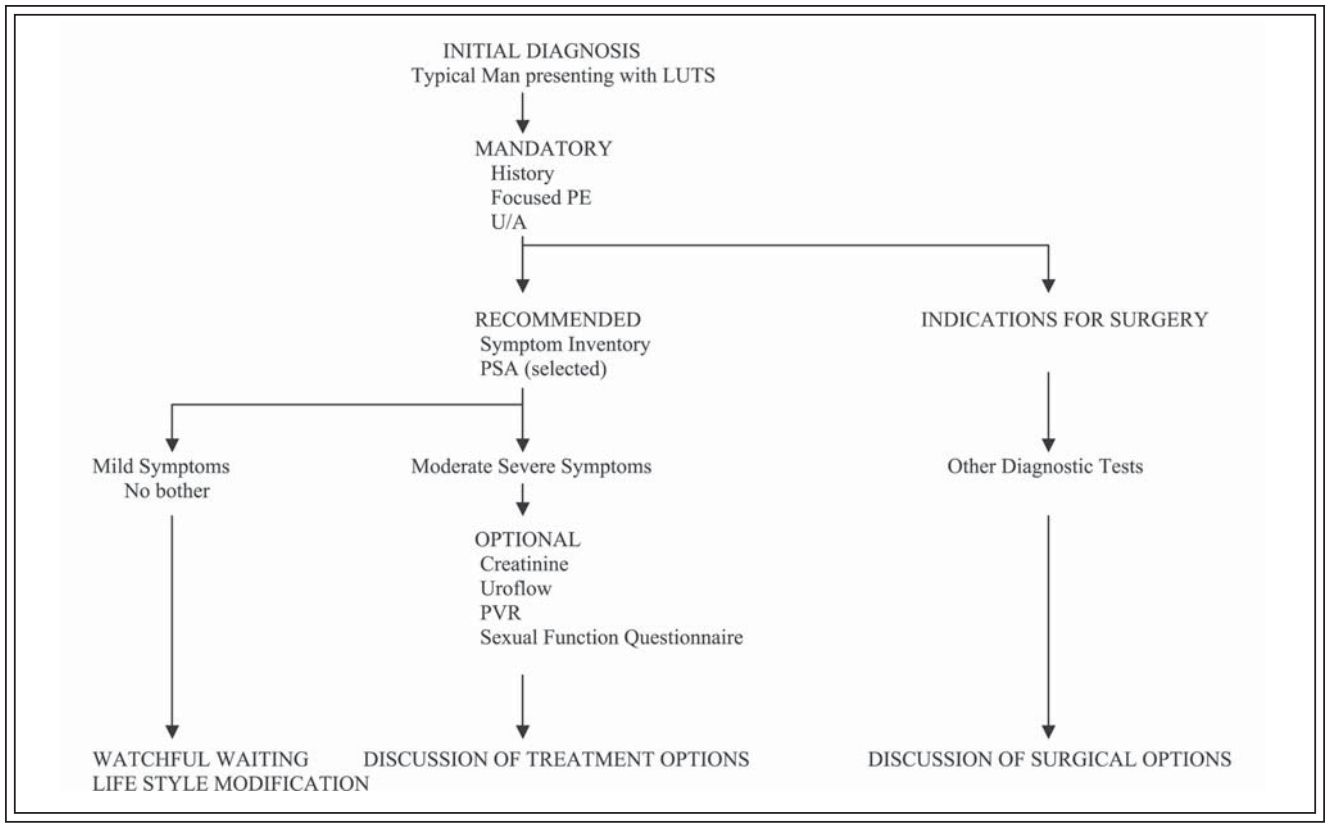

Figure 1. Diagnostic algorithm.[11]

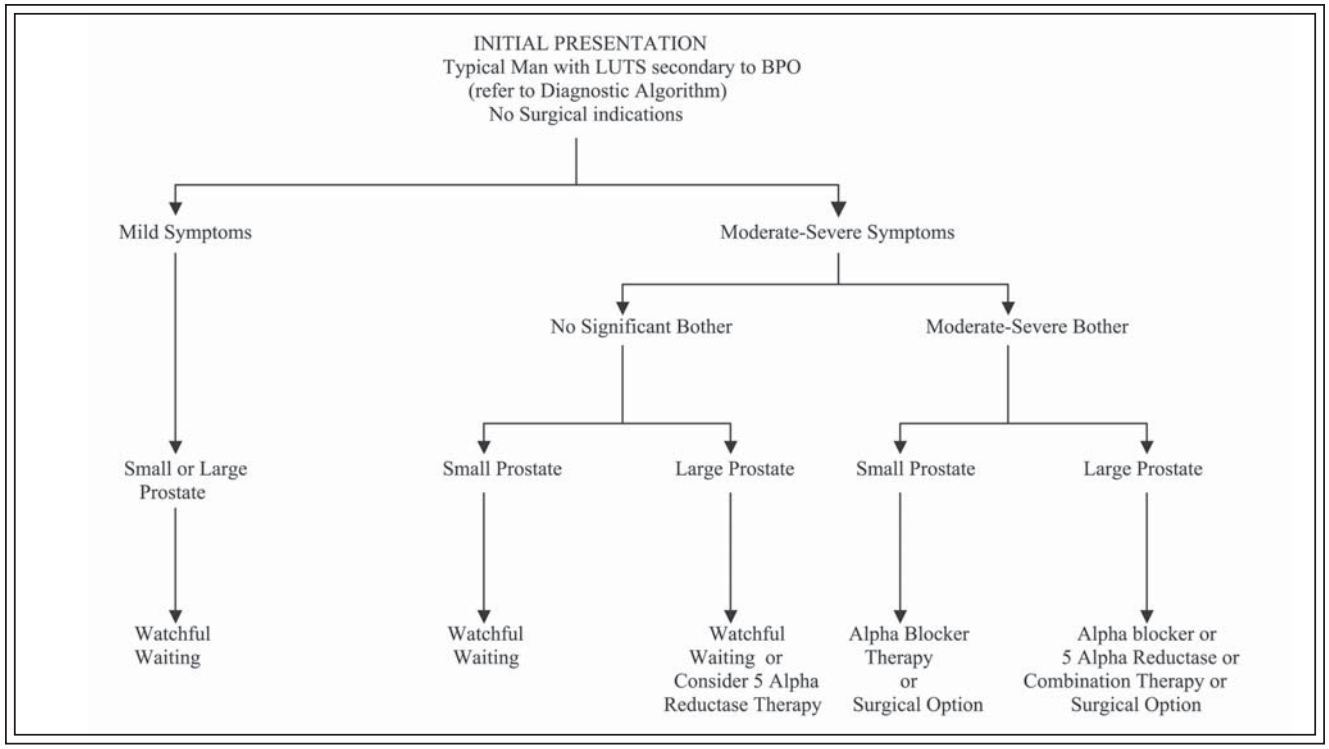

Figure 2. Treatment algorithm.[11]

Interventions other than pharmacotherapy

There are a number of aggressive interventional therapy approaches. The ultimate goal is to diminish the bulk of the prostate. This can be done by either resecting the prostate using electrocautery, or vaporizing or enucleating the prostate using a laser approach. One could also "incise" the prostate in certain individuals with small prostates and tighter bladder necks. This will prevent the most common side effect of prostate surgery, which is "retrograde ejaculation." Some centers still try to heat the prostate using microwave therapy. These invasive approaches are often used for patients who have symptoms or signs of significant BPH (i.e., urinary retention, recurrent infections, or renal failure) and have disease that has advanced to the point where medical therapy (which can be much slower) would be ineffective and allow disease progression and patient harm.

Interventional therapy, regardless of the energy source, can lead to ongoing side effects. The patient has a moderate risk of erectile dysfunction, an almost 5% chance of needing a second surgery within 10 years of the primary treatment, and a 1% to 3% chance of some incontinence.[13]

Because of these risks from interventional therapy and the discovery of novel pharmaceutical agents, pharmacotherapy has become very popular to for the management of patients with BPH.

Pharmacotherapy

The types of obstructions that patients can experience with BPH can be classified as either "dynamic" (changing) or "bulky" (fixed).[14] The dynamic component of obstruction is related to the preponderance of alpha receptors that are found in the bladder neck and prostate area. The increased tone of these smooth muscle fibers causes a tightening or "spasming" at the bladder neck and within the prostate. This leads to a functional obstruction. This stimulation of alpha receptors can be blocked with alpha-blocker medications. Over the years, we have moved from what were considered non-selective alpha blockers (which could cause orthostatic hypotension and other vascular side effects) to more uro-selective alpha blockers (which should not affect blood pressure).[15-17] There are two concerns about alpha blockers: they might not prevent progression of prostate disease, and they might cause significant sexual side effects. The major side effect is that it affects ability to ejaculate. Usually, there is no ejaculation, which is due to the decreased propulsion from the seminal vesicles that have lost their alpha stimulus.[18] This can be very disconcerting for men of all ages.

Studies show that from an efficacy standpoint, there is not a huge difference in the performance of different alpha blockers.[19] The most significant characteristic of alpha blockers compared to 5-alpha-reductase inhibitors (5-ARIs) is the speed of symptom response with alpha blockers. Patients can expect symptom relief from as early as 24 hours to a maximum of about 7 to 10 days after taking an alpha blocker.[19] This can be very gratifying for the patient and physician. The caveat to this is that if we prescribe an alpha blocker for a younger man, we can expect that he will become less responsive to treatment after a few years.[4] The prostate will continue to grow, the patient's response to the treatment will diminish, and the disease will continue to progress, since with time, alpha receptors develop resistance to alpha-blocker effects.[20] As well the prostate continues to grow.

Dihydrotestosterone (DHT) is the active metabolite of testosterone, which leads to the growth of the prostate cells and glands. DHT is created by the conversion of testosterone to dihydrotestosterone and estrogen, which is stimulated by the enzyme 5-alpha-reductase.[21] Many years ago, investigators discovered that a number of related men in the Dominican Republic had ambiguous external genitalia as well as very small prostates. Researchers discovered that these men lacked the 5-alpha-reductase enzyme. The scientists hypothesized that if one could reduce the level of DHT after a man had reached puberty, his prostate would not grow, or could potentially shrink. That led to the discovery and development of the 5-ARI family of drugs. Finasteride (Proscar, Merck, Inc.) was the first ARI to be launched in the marketplace. Dutasteride (Avodart, GlaxoSmithKline) was the second 5-ARI to be marketed. Differences between the two drugs are likely related to their different actions on the two 5-alpha-reductase iso-enzymes (type 1 and type 2). Finasteride inhibits type 2, 5-alpha-reductase, whereas dutasteride inhibits both type 1 and type 2, 5-alpha-reductase.[22]

Treatment with finasteride results in an approximately 70% reduction of DHT levels within the prostate, whereas treatment with dutasteride results in a more than 90% reduction of DHT levels within the prostate. The only head-to-head study that compared the two 5-ARIs was the Enlarged Prostate International Comparator Study (EPICS), which concluded that clinically, there were no significant differences between the two 5-ARIs in efficacy, safety, or side-effect profiles for the treatment of BPH.[23] This was a 1-year study.

Preliminary findings from other studies suggest that type 1, 5-alpha-reductase is more prominent in cancer tissue within the prostate, which suggests

that there may be a more profound effect in using dutasteride to help prevent prostate cancer. Studies that may confirm this are not yet completed.

A few years ago, a significant study was published on the ability of a 5-ARI to prevent the development of prostate cancer. This study, the Prostate Cancer Prevention Trial (PCPT), enrolled only American subjects and compared finasteride versus placebo, in men thought not to have prostate cancer. At randomization, the men had a normal PSA and a normal DRE. The study was terminated early, because there was a profound, 25% lower incidence of prostate cancer in men in the treatment arm versus the placebo arm.

Initially, there was some concern about the findings from this trial, because it appeared that men in the treatment arm who did develop cancer, had a higher-grade cancer (Gleason score 8-10) that was more virulent (aggressive). The presently accepted explanation for this finding is that this was a result of a "volume artifact." The higher-grade cancer was there from the outset, but was missed because the prostate was bigger in the placebo group. After the prostate shrank under the influence of the 5-ARI, the investigator had an increased chance of hitting the focal area of high-grade cancer with the biopsy needle.

A similar study is currently underway in patients at higher risk of prostate cancer. This study, the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial compares dutasteride versus placebo in patients who have already had a biopsy that was negative for prostate cancer, where the biopsy was performed because the men were deemed to be at high risk of prostate cancer since they had an elevated serum PSA level, an abnormal DRE, or a significant family history of prostate cancer. All patients in the REDUCE trial will receive a routine biopsy at 2 and 4 years.

Several monotherapy studies (such as the Prospective European Doxazosin and Combination Therapy [PREDICT] and the Proscar Long-term Efficacy and Safety Study [PLESS] studies) using either finasteride or dutasteride for the treatment of enlarged prostates (greater than 30 cc) have shown that monotherapy can provide a durable and prolonged prevention of disease progression in BPH. The studies have also demonstrated that one can achieve a significant volume reduction of the prostate with 5-ARI therapy.

BPH combination therapy

The question then arose as to whether the combination of an alpha blocker and a 5-ARI would be more effective than either agent alone in preventing disease progression, acute urinary retention, or the need for surgery in the long run. This question was addressed in a large study with published results, the "Medical Therapy Of Prostate Symptoms" (MTOPS) trial, and is being investigated in a second large study, "Combination of Avodart and Tamsulosin" (CombAT), which has completed 2 of the 4 years of its planned duration.

In MTOPS, patients were randomized to receive 1 of 4 types of treatment: monotherapy with the alpha blocker doxazosin (Cardura), monotherapy with the 5-ARI finasteride (Proscar), combination therapy with both agents, or placebo. The patients were followed for 5 years. At the end of 5 years, compared to patients treated with placebo, those who received combination therapy had a 67% lower risk for clinical progression of BPH. There was no significant difference in disease progression among patients treated with either monotherapy, although there was a trend to better outcomes with finasteride. Treatment efficacy was similar with either monotherapy and was superior to placebo but was not as good as combination therapy.[4]

Other studies such as the Veterans Administration Cooperative (VA-Coop) Study and PREDICT that looked at monotherapy and combination therapy that included finasteride also did not show a huge difference between monotherapy treatment arms, but showed a benefit from combination therapy. In the VA-Coop study, there appeared to be no difference in the short-term response to 5-ARI versus placebo.

These studies led to the belief that it was the "small volume" prostates (less than 30 cc) that prevented the differentiation of the efficacy of the alpha blocker (doxazosin) compared to the 5-ARI (finasteride). The patients with small volume prostates did not seem to get any significant symptom response over that achieved by the placebo in these one-year trials. That belief stimulated the development of the MTOPS and the later CombAT study.

To be included in MTOPS, patients had to have symptoms of benign enlargement of the prostate, no evidence of prostate cancer, a serum PSA value of less than 4 ng/ml, and only at least mild symptoms on the International Prostate Symptom Score (IPSS) scale.

In the CombAT trial, the investigators recruited patients who were at "higher risk" for disease progression.[4,24] They had to have a prostate volume greater than 30 cc (as determined by transrectal ultrasound), a serum PSA value of 1.5 ng/ml to 10 ng/ml, and an IPSS score of at least 12, which meant that these patients all had at least moderate IPSS symptoms of BPH. As previously stated, this would suggest that these patients were at a higher risk for disease progression. The actual baseline average prostate

volume was 54 cc. Compared to MTOPS, CombAT used different drugs: the alpha blocker tamsulosin (Flomax) and the 5-ARI dutasteride. The 2-year data of this 4-year trial demonstrated a significant reduction in IPSS scores in the combination arm compared to either monotherapy arm. For the first time, even with symptom management, as early as 15 months, the 5-ARI showed greater efficacy than the alpha blocker. This was unexpected and significant.[25]

MTOPS did not use questionnaires to assess quality of life in the same way that CombAT did. At the recent European Urological Association Congress (EUA) meeting in Milan, Italy, I reported the responses to the quality of life question in the CombAT trial (question number 8 on the AUA-SI BPH questionnaire) after 2 years of treatment. The responses to this question showed that patients in the combination arm had a greater improvement in their response to the "Quality of Life" question than patients in either monotherapy arm. By about 18 months, patients who received the 5-ARI dutasteride monotherapy had a better response than patients who received the alpha blocker tamsulosin alone.[26]

In MTOPS also, the incidence of acute urinary retention (AUR) decreased and there was a significant decrease in the need for surgery in patients in the combination arm compared to those in either monotherapy arm. We are awaiting the 4-year results of the CombAT trial to see if the same pattern will be reported.

The next question that needs to be asked is: "If a man is prescribed combination therapy, does he have to continue taking this therapy for the rest of his life?" This question has been addressed previously, using finasteride and either a non-selective alpha blocker (Hytrin or Cardura) or a uro-selective alpha blocker (tamsulosin). More recently, results were reported from a trial that looked at dutasteride and the uro-selective alpha blocker, tamsulosin, the "Symptom Management After Reducing Therapy-1 (SMART-1), trial. Patients received combination therapy for 6 months, in a blinded manner. At the end of 6 months, some patients in the combination arm continued treatment and some patients in the alpha-blocker arm discontinued treatment. Three months later, when some patients were receiving monotherapy with dutasteride and some were still receiving combination therapy, they were asked "Do you feel the same, better, or worse compared to the way you felt 3 months ago?". This same question was asked again 3 months later. The results demonstrated that at 6 months, approximately 77% of men receiving monotherapy felt as well as men who were receiving combination therapy.

A similar study that was even closer to real life was completed recently: the PRoscar and alpha-blOcker combinAtion followed by disContinuation Trial (PROACT). In this study, if a patient was already taking an alpha blocker, he continued taking the same alpha blocker in combination with Proscar for 9 months. If he was not already taking an alpha blocker, he was prescribed tamsulosin. At the end of 9 months, the alpha blocker was dropped in some patients. Patients were asked a similar question about their satisfaction with their present therapy, and the patient "satisfaction level" of responses were similar to those in the SMART-1 trial.

Both studies (SMART-1 and PROACT) support the belief that one could consider prescribing combination therapy for 6 to 9 months followed by discontinuation of the alpha blocker. The physician could expect that a significant number of patients would continue to be very comfortable remaining on 5-ARI monotherapy.

The main side effects that one might see with the 5-ARIs include gynecomastia, decreased libido, and some degree of erectile dysfunction, which occur in less than 5% of patients.

Over the last 25 years that we have been actively treating BPH with medical therapy, there has been a significant evolution in the specificity and efficacy of both alpha blocker and 5-ARIs. Today, most men — if they do not have absolute indications for intervention (as discussed earlier) — should at least be offered a trial of medical therapy to try to treat BPH symptoms and prevent disease progression, acute urinary retention, and the need for surgery. Table 2.

It seems that the "golden number" for the prostate volume that will respond to 5-ARI treatment is 30 cc. If a man has a prostate volume of at least 30 cc, or has a serum PSA level of at least 1.5 ng/ml (which is used as a surrogate marker for a prostate volume of 30 cc), then he can expect a significant response from treatment with a 5-ARI, which will shrink the prostate and alleviate his symptoms. The monotherapy of the 5ARI will cause symptom relief much more slowly than the combination therapy of an alpha blocker and a 5ARI. If a patient's symptoms are more significant, then the combination of an alpha blocker plus a 5-ARI is the most effective initial form of medical management. The patient and physician can decide together the duration of combination therapy and whether the patient can switch to monotherapy with a 5-ARI. If the patient's prostate volume is small, and if his symptoms are significant enough to require treatment, then an alpha blocker alone will help to provide a very rapid and significant symptom response.

TABLE 2. **Drugs commonly used to treat benign prostatic hyperplasia**

Monotherapy	**Combination therapy**
Phytotherapeutic agents	-
Saw palmetto	
Alpha blockers	Alpha blocker + 5-ARI combination rationale:
Quick onset of action (weeks)	Prostate greater than 30 cc or serum PSA level
Do not shrink prostate size	greater than 1.5 ng/ml
No effect on serum PSA	Based on MTOPS and CombAT trials
Non-selective agents (doxazosin, terazosin)	Better than alpha blocker or 5-ARI monotherapy
May need dose titration	Reduced risk of symptom progression
Cardiovascular side effects	Reduced risk of acute urinary retention
Selective agents (tamsulosin, alfuzosin)	
No titration	
Minimal cardiovascular side effects	
Sexual dysfuction (tamsulosin, silodosin, alfuzosin)	
5-alpha-reductase inhibitors (5-ARIs)	Potential future combinations
Slow onset of action (3-6 months)	Alpha blocker + anti-cholinergic
Reduce prostate size by approximately 25%	(anti-muscarinic) drug
Reduce serum PSA by 50% after 6 months	5-ARI + anti-cholinergic drug
No dose titration	Alpha blocker + PDE5 inhibitor
Sexual side effects	5-ARI + PDE5 inhibitor
Prostate cancer chemoprevention	
In development	
PDE 5 inhibitors (tadalafil, sildenafil, etc.)	-

5-ARI = 5-alpha-reductase inhibitor; CombAT = Combination of Avodart and Tamsulosin;
MTOPS = Medical Therapy Of Prostate Symptoms;
PDE5 = phosphodiesterase-type 5; PSA = prostate-specific antigen

The other benefit from medical therapy is that any side effect is usually easily reversed by stopping the medication.

Even when a patient with BPH is treated with combination therapy (a 5-ARI and an alpha blocker), he might sometimes still have the same voiding symptoms seen in patients with primary overactive bladder (OAB).[27]

The patient may report that he is voiding with a greater stream and less hesitancy, but still has voiding frequency and urgency, and possibly urgency incontinence. In this case, treating him with an added anticholinergic agent,[28] an antimuscarinic agent,[29] or a bladder relaxant might be very helpful[a] in providing relief and control of symptoms. Concern that this treatment will precipitate acute urinary retention is usually unfounded.

Recently, it has been shown that phosphodiesterase-5 (PDE5) inhibitors such as sildenafil (Viagra, Pfizer) can affect the treatment of LUTS associated with BPH. The addition of a PDE5 inhibitor appears to increase oxygenation (because of the decrease in the nitric oxide metabolism) and stabilize the prostate and bladder. Voiding frequency and urgency may improve. It is interesting to note that there is no increase in the uroflow rates in these patients.

Conclusions

Compared to 25 years ago, the management of BPH today has undergone a paradigm shift. Years ago, TURP was the most common operation performed by a urologist to treat symptoms associated with BPH, and many men with BPH presented with acute, or chronic urinary retention. In the 21st century, most men are initially treated medically for their BPH/LUTS, and if they receive proper care, only a very small percentage of patients will develop urinary retention or will require surgical intervention to manage their BPH.

Take-home messages

To diagnose and treat patients with BPH/LUTS:

- The primary care physician can determine if BPH is the cause of LUTS.
- If the patient has hematuria, recurrent urinary tract infections, signs of renal function deterioration, signs of urinary retention, an abnormal serum PSA value, or an abnormal DRE, or if the patient is refractory to or rejects medical therapy, he should be referred to a urologist.
- A serum PSA cutoff of 1.5 ng/ml can be used as a surrogate for a prostate volume of at least 30 cc (which is the smallest prostate volume that has the best chance of responding to therapy with a 5-ARI).
- If a man has an enlarged prostate and is significantly bothered by LUTS, combination therapy with a 5-ARI and an alpha blocker is likely the most effective therapy.
- After many months of combination treatment with a 5-ARI and an alpha blocker, discontinuing the alpha blocker might need to be considered.
- 5-ARI medications may help prevent prostate cancer developement without increasing the risk of causing a high-grade cancer.
- When a patient who is receiving combination therapy with a 5-ARI and an alpha blocker still experiences LUTS, adding an antimuscarinic agent can be considered.

Disclosure:

Dr. Jack Barkin is an active urologist and Chief of Staff at the Humber River Regional Hospital in Toronto. He sits on the medical advisory board for Abbott, GlaxoSmithKline, Merck Frosst, sanofi-aventis and Boeringer-Ingelheim. He has done the clinical research on Avodart, Flomax, Hytrin, Xatral and Proscar, both in monotherapy and combination. He has spoken all over the world for all of the companies outlined. □

References

1. Thompson IM, Goodman PJ, Tangen CM et al. The influence of finasteride on the development of prostate cancer. *New Engl J Med* 2003;349:215-224.
2. Arrighi HM, Metter EJ, Guess HA, Fozzard JL. Natural history of benign prostatic hyperplasia and risk of prostatectomy: The Baltimore Longitudinal Study of Aging. *Urology* 1991;38(1 suppl):4-8.
3. Burke JP, Jacobson DJ et al. Diabetes and benign prostatic hyperplasia progression in Olmsted County, Minnesota. *Urology* 2005;67(1):22-25.
4. McConnell JD, Roehrborn CG, Bautista OM, Andriole JR GL et al. The long-term effect of doxazosin, finasteride, and combination therapy on the clinical progression of benign prostatic hyperplasia. *New Engl J Med* 2003;349:2387-2398.
5. Araujo AB, Johannes CB et al. Relation between psychosocial risk factors and incident erectile dysfunction: prospective results from the Massachusetts Male Aging Study. Am J Epidemiol 2000;152(6):533-541.
6. Crawford E, Wilson S, McConnell J et al. Baseline factors as predictors of clinical progression of benign prostatic hyperplasia in men treated with placebo. *J Urol* 2006;75:1422–1427.
7. Barry MJ, Fowler FJ Jr, O''Leary MP, Bruskewitz RC, Holtgrewe LH et al. The American Urological Association Symptom Index for Benign Prostatic Hyperplasia. *J Urol* 1992;148:1549-1557.
8. Garraway WM, Russell EB, Lee RJ, Collins GN et al. Impact of previously unrecognized benign prostatic hyperplasia on the daily activities of middle-aged and elderly men. *Br J Gen Pract* 1993;43(373):318-321.
9. Guess HA, Arrighi HM, Metter EJ, Fozard JL. Cumulative prevalence of prostatism matches the autopsy prevalence of benign prostatic hyperplasia. *Prostate* 1990;17(3):241-246.
10. McConnell JD, Bruskewitz R, Walsh P, Andriole G, Lieber M, Holtgrewe HL 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. *N Engl J Med* 1998;338:557-563.
11. Curtis JC, Herschorn S, Corcos J, Donnelly B, Elhilali et al. Canadian guidelines for the management of benign prostatic hyperplasia. Can J Urol 2005;12(3):2677-2683.
12. Vogelzang NJ, Scardino PT, Shipley WU, Frans MJ. Comprehensive Textbook of Genitourinary Oncology. pp 91-92.
13. Holtgrewe HL. Current trends in management of men with lower urinary tract symptoms and benign prostatic hyperplasia. *Urology* 1998;51(4A Suppl):1-7.
14. McNeal J. Pathology of benign prostatic hyperplasia. Insight into etiology. *Urol Clin North Am* 1990;17(3):477-486.
15. Hofner K et al. Alfuzosin: a clinically uroselective a1-blocker. *World J Urol* 2002;19:405-412.
16. Roehborn CG. Alfuzosin: overview of pharmacokinetics, safety, and efficacy of a clinically uroselective alpha-blocker. *Urology* 2001;58(Suppl 6A):55-64.
17. Morgan TO, Jacobsen SJ, McCarthy WF, Jacobson DJ, McLeod DG, Moul JW. Age-specific reference ranges for serum prostate-specific antigen in black men. New Engl J Med 1996;335(5):304-310.
18. Altwein J. XVIIth EAU Congress, Birmingham UK, Feb 2002, Sanofi-Synthelabo satellite.
19. Chapple CR. Pharmacotherapy for benign prostatic hyperplasia--the potential for alpha 1-adrenoceptor subtype-specific blockade. *Br J Urol* 1998;81(Suppl 1):34-47.
20. Mochtar CA, Kiemeney LA, Laguna MP, van Riemsdijk MM et al. Prognostic role of prostate-specific antigen and prostate volume for the risk of invasive therapy in patients with benign prostatic hyperplasia initially managed with alpha1-blockers and watchful waiting. *Urology* 2005;65(2):300-305.
21. Gormley GJ, Stoner E, Bruskewitz RC et al. The effect of finasteride in men with benign prostatic hyperplasia. *N Engl J Med* 1992;327:1185-1191.

22. Bartsch G, Rittmaster RS, Klocker H. Dihydrotestosterone and the concept of 5a-reductase inhibition in human benign prostatic hyperplasia. *Eur Urol* 2000;37:367-380.
23. Andriole GL, Kirby R. Safety and tolerability of the dual 5alpha-reductase inhibitor dutasteride in the treatment of benign prostatic hyperplasia. *Eur Urol* 2003;44:82-88.
24. Siami P, Roehrborn CG, Barkin J, Damiao R, Wyczolkowski M, Duggan A, Major-Walker K, Morrill BB; CombAT study group. Combination therapy with dutasteride and tamsulosin in men with moderate-to-severe benign prostatic hyperplasia and prostate enlargement: the CombAT trial rationale and study design. *Contemp Clin Trials* 2007;28(6):770-779.
25. Roehrborn CG, Siami P, Barkin J, Damiko R, Major-Walker K, Morrill B, Montorsi F, CombAT study. The effects of dutasteride, tamsulosin and combination therapy on lower urinary tract symptoms in men with benigh prostatic hyperplasia and prostatic enlargement: 2 year results from the CombAT study. *J Urol* 2008;179(2):606-621.
26. Barkin J. Improvements in patient-reported QOL with dutasteride, tamsulosin and the combination: 2-year results from the CombAT trial. 2008 EAU Milan Italy. Abstract 99.
27. Carr L. Overactive bladder. *Can J Urol* 2008;15(Suppl 1):31-36.
28. Roehrborn CG, McVary KT, Kaminetsky JC et al. The efficacy and safety of tadalafil adminstered once a day for lower urinary tract symptoms (LUTS) in men with benign prostatic hyperplasia (BPH). *J Urol* 2006;175(4 suppl):527.
29. Lee JY, Kim DK, Chancellor MB. When to use antimuscarinics in men who have lower urinary tract symptoms. *Urol Clin of North Am* 2006;33(4):531-537.

DISCUSSION

Question: (Dr. Miner)
From the PCP's point of view what is the primary reason for treatment of BPH? How do we share with patients that it is not just a matter of the lifestyle or aging? What is the morbidity and mortality of BPH? Can the severity of the impact on lifestyle be compared to that of COPD?

Answer: (Dr. Barkin)
We know that symptomatic BPH will progress over time if it is not treated in 85% of men. The progression can lead to increased urinary tract infections, hematuria, potentially hydronephrosis, urinary retention and the need for surgery. Most men will compensate early on from the symptoms and signs of BPH by adjusting their lifestyles. For example, no long car trips, no movies, no golf etc. Studies had shown that moderate symptoms of BPH can impact on quality of life as much as severe COPD.

Question: (Dr. Miner)
In a busy PCP's practice, how does one assess urination (i.e. what is a quick and easy screening questions to evaluate urinating)? How reliable is the presence of nocturia, frequency and urgency in differentiating LUTS of BPH from OAB?

Answer: (Dr. Barkin)
In a busy PCP practice the best way to quantify and assess the severity of BPH/LUTS is to ask the patient to answer the 7 question IPSS Questionnaire. The score of less than 8 signifies mild, 8-20 moderate and more than 20 severe disease. A patient with a score of moderate to severe will definitely progress. Question 8-on the quality of life question is the one that will indicate if the patient is motivated to or will accept some type of treatment. That is the question that addresses the patient's desire to tolerate the symptoms for now or the rest of his life. BPH is one of the commonest causes of LUTS symptoms in a man over the age of 50. By doing a urinalysis, focused clinical physical examination including a DRE (digital rectal examination) and creatinine one can rule out most of the other serious causes and offer a "TRIAL of Therapy". If the patient does not respond to the latter, referral to the urologist would be appropriate.

Question: (Dr. Rosenberg)
If a 30-year-old male with no family history of prostate disease comes in to PCP's office with symptoms of LUTS, what are the guidelines on PSA screening?

Answer: (Dr. Barkin)
A 30-year-old male with LUTS, but no family history of prostate cancer should not have a PSA unless the digital rectal examination (DRE) is abnormal. The recommendation is to start PSA testing at the age of 50, unless the family history is significant for prostate cancer (first degree relative) or the patient has an abnormal DRE or belongs to a high risk group, such as African-American/Canadian males.

Question (Dr. Greenberg)
What is the existing evidence on using 5-ARI for prophylaxis in males over 50 years of age with no symptoms or family history of prostate disease?

Answer: (Dr. Barkin)
In the recent 7 year PCPT (Prostate Cancer Prevention Trial) for men over 50 that had no clinical evidence of prostate cancer by PSA or DRE, there was a 25% lower incidence of detecting prostate cancer in those treated with daily finasteride versus placebo. Another study that enrolled only "high risk" patients meaning those that had had a "negative biopsy" that had been done because there was a suspicion of prostate cancer based on an abnormal DRE, elevated PSA or a strong concern because of a positive family history, is now more than half -way finished. This trial compares dutasteride to placebo for 4 years to determine if there is a difference in the incidence of prostate cancer detection. This study is called "REDUCE" The patient that is considering a 5-ARI for "chemo-prevention" of prostate cancer has to weigh the benefit of decreased prostate cancer incidence with the risk of potential drug side effects.