Management of benign prostatic hyperplasia by family physicians

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The past decade has profoundly changed how physicians manage patients with benign prostatic hyperplasia (BPH). The concepts of symptom indices, symptom complexes, flow rates, prostate-specific antigen (PSA), prostate size and new medical approaches supported by new clinical studies, have provided family practitioners as well as specialists with evidence-based management algorithms to treat BPH. Men with BPH most often visit a physician due to their partner's urging because of the many symptoms, with the most bothersome being nocturia. Today, primary care physicians are the gatekeepers for diagnosing and managing lower urinary tract symptoms (LUTS) in men. They need to be aware of long term negative consequences if these major symptoms are not treated early.

Key Words: symptom complex, BPH, PSA, LUTS, symptom index, flow rate

Introduction

This article is an update of an earlier article concerning diagnosis and management of patients with benign prostatic hyperplasia (BPH) by primary care physicians.[1] It aims to reinforce the importance of early identification of patients with BPH and lower urinary tract symptoms (LUTS) and to provide recent study data that support treatment algorithms.

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LUTS are a constellation of symptoms related to voiding problems, which can be experienced by men or women. These symptoms may be caused by urinary tract infections (UTIs), bladder stones, bladder cancer, prostate cancer, urethral strictures, BPH, or overactive bladder (OAB). The International Continence Society (ICS) defines OAB as a condition characterized by urgency with or without urge incontinence, generally in the presence of frequency and nocturia.[2] It is important to note that a man who has been medically treated for BPH and is voiding better and stronger but still has symptoms of frequency and urgency may require additional pharmacotherapy to manage OAB.[3]

Approximately 60% of men have LUTS. In 50% of men over age 50 who have LUTS, the cause is clinically significant BPH, but it is important for the primary care physician to be able to rule out other causes. Prevalence of LUTS and BPH increases with age.[4]

Diagnosis

The diagnostic algorithm from the Canadian guidelines for the diagnosis and management of clinically significant BPH provides a useful approach, Figure 1.[1,5]

Patient history

BPH symptom score questionnaires

The American Urological Association (AUA) symptom index for BPH[6] -- or the very similar International Prostate Symptom Score (IPSS) sheet for BPH--- consist of a score sheet with seven questions about BPH symptoms plus an eighth question about quality of life (QOL). These questions have been validated and used for over a decade to provide quantified information about symptom severity in BPH and LUTS before and after any treatment.

The symptom indices were designed to detect and quantify the most common symptoms of patients presenting with LUTS. Each of seven questions about symptom frequency in the past month can have a score from 0 (not at all) to 5 (almost always). Based on the total score, LUTS is classed as mild (total score 1 to 7), moderate (8 to 19), or severe (20 to 35). The question about quality of life is scored from 0-6, with 6 being "terrible." The questionnaire is later repeated to determine if symptoms have improved (lower score) or worsened (higher score). The patient becomes his own "control".

The eighth question, about quality of life, probes how "bothered" the patient is by his symptoms. For patients with "moderate symptoms" (greater than equal to 3 out of 6), it can give an indication about whether a patient should be observed or given treatment. This question can be seen as a "motivational index," because a high score for this question can mean that the patient will be more motivated to accept treatment suggestions.

By filling out a BPH symptom score sheet, patients increase their awareness of which voiding symptoms they have and how severe the symptoms are. The symptom score can also serve as an objective parameter for comparing symptoms before and after treatment.

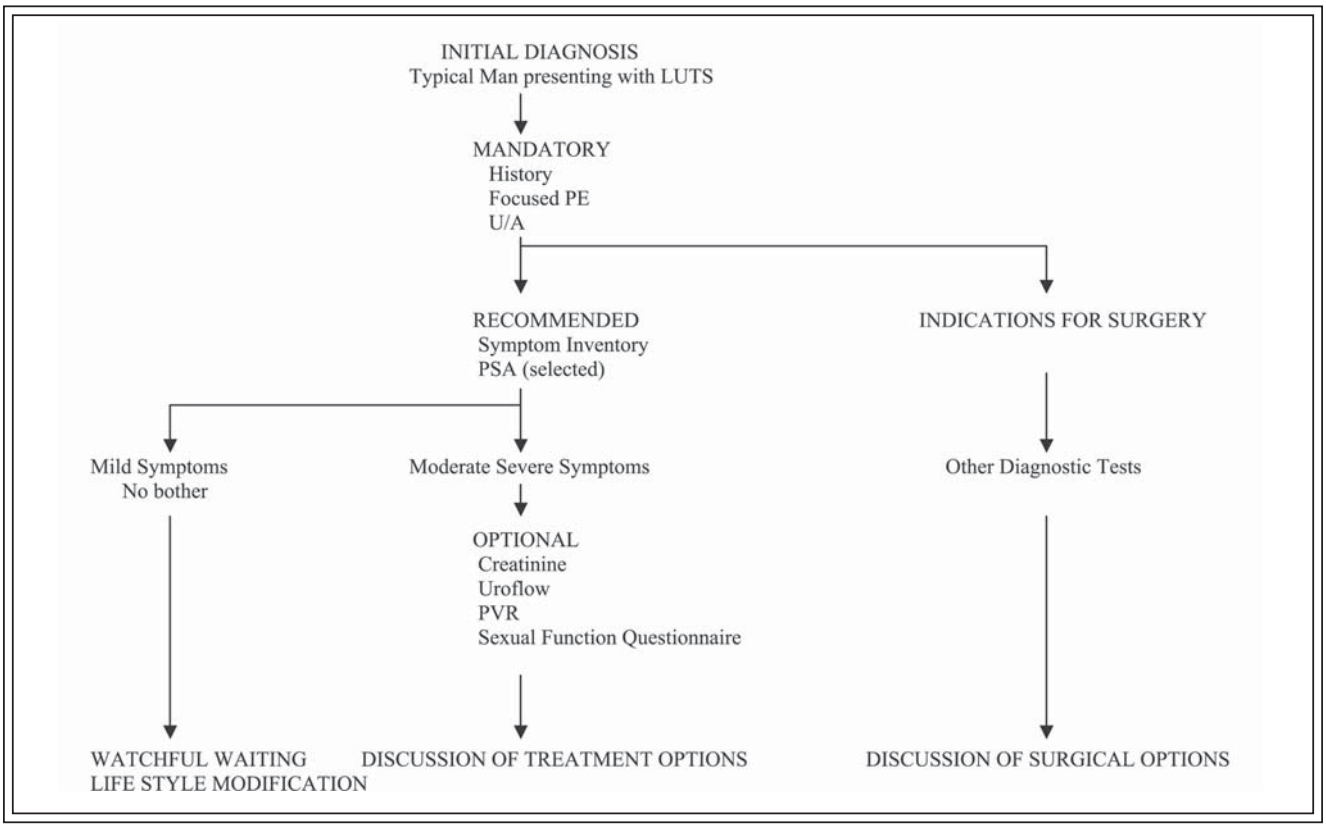

Figure 1. Diagnostic algorithm.[1,5]

These symptoms can be matched to the voiding cycle –storage, voiding, and post micturition, as per the International Continence Society's analysis of symptoms.[7]

The development of symptom score questionnaires for BPH has helped patients and physicians focus on the nature and severity of obstructive and irritating voiding symptoms. These symptoms scores have been used in all recent clinical trials of drugs and interventional therapies for the management of BPH, to demonstrate treatment efficacy.

A key aspect of these questionnaires is that the patient fills them out and then acts as his own control to assess the impact of the treatment. Over time, the symptom score will either improve or deteriorate. A study by Barry and colleagues published in 2000 determined the required change in symptom score for a patient to perceive a clinical difference in his condition.[8]

Having a patient fill out this symptom sheet as part of his clinical history can help the physician define and quantify the patient's symptoms, which can then guide the physical examination. Replies to the seven questions can direct attention to specific voiding symptoms.

PSA test

The prostate-specific antigen (PSA) blood test is another useful parameter to evaluate prostatism or LUTS. Roehrborn et al demonstrated that there is a direct relationship between of a patient's age, prostate size, and serum PSA levels.[9]

As Roehrborn and others have suggested, PSA level is an excellent and reliable surrogate marker for prostate volume.

All prostate cells make PSA. As the benign prostate increases in volume, serum PSA levels will increase. PSA is specific to the prostate, but it is not necessarily specific for prostate cancer. Serum PSA levels increase with inflammation of the prostate--which could be due to prostatitis or a UTI-- obstruction, cancer, sexual intercourse, and trauma--which could be caused by riding a bicycle or a motorcycle to the doctor's office, or by a vigorous digital rectal examination (DRE).

Different laboratories measure serum PSA levels in different ways. To best compare PSA test results from different times for the same patient, the test should ideally be done in the same laboratory using the same technique.

In addition to total PSA, other measures of PSA can include free-to-total PSA ratio, PSA density, PSA doubling time, age-specific PSA, and PSA velocity (change in the level of PSA over a specific period of time). Sometimes, changes in PSA levels can be used as a measure of the effectiveness of pharmacotherapy.

If a patient's baseline total PSA is in the "grey zone," (higher than expected for age or prostate volume), the physician can request another (repeat) total PSA test or a different type of PSA test, to determine what patient management is warranted: observation or referral for a biopsy.

The total PSA value and all its variations help in diagnosis and treatment decisions, as explained in more detail in the article by Kell, in this supplement.[10]

Physical examination

The assessment of a patient's flanks and abdomen will provide clues about possible hydronephrosis (dilation of the kidney due to obstructed urine flow), bladder obstruction as indicated by a supra-pubic mass, epididymo-orchitis (inflammation of the epididymis and testes caused by a bacterial infection, recurrent UTIs, or bladder stones), or the detection of a meatal stenosis.

A DRE will provide a measure of the prostate's size (for example, the number of finger widths), detect tenderness, induration, irregularities, or nodules, and detect differences between the two sides of the prostate. It is rare to find the classical, discrete, hard, pea-sized nodule that suggests prostate cancer. Rather, subtle differences comparing one side to the other or changes over time are more likely to suggest cancer.

Some anaplastic (poorly differentiated) prostate cancers will NOT produce PSA and thereby not cause an increase in serum PSA levels, so a DRE must be done every time to rule out the "silent PSA " prostate cancer as well as any other DRE abnormalities. Often today, the patient may have a disproportionately high serum PSA value that does not correspond to the size of the prostate found by DRE. This higher-than-expected PSA level suggests the need to look for underlying prostate cancer.

If the prostate feels benign, the patient's PSA levels will accurately predict prostate volume, without the need for doing a transrectal ultrasound. Unfortunately, not all the benign feeling prostates are benign - that is another reason to do the PSA. A PSA value greater than 1.4 ng/mL guarantees a prostate volume of greater than 30 cc, which is the critical cut-off volume that defines an "enlarged" prostate.[1] As we will see, it is this 30 cc volume that is the "watershed" for the different types of medical therapy for BPH.

Patient management

Treatment options for BPH, depending on the patient's symptoms, signs and bother, include watchful waiting, surgery, or pharmacotherapy, as explained in the treatment algorithm from the Canadian guidelines, Figure 2.[1,5]

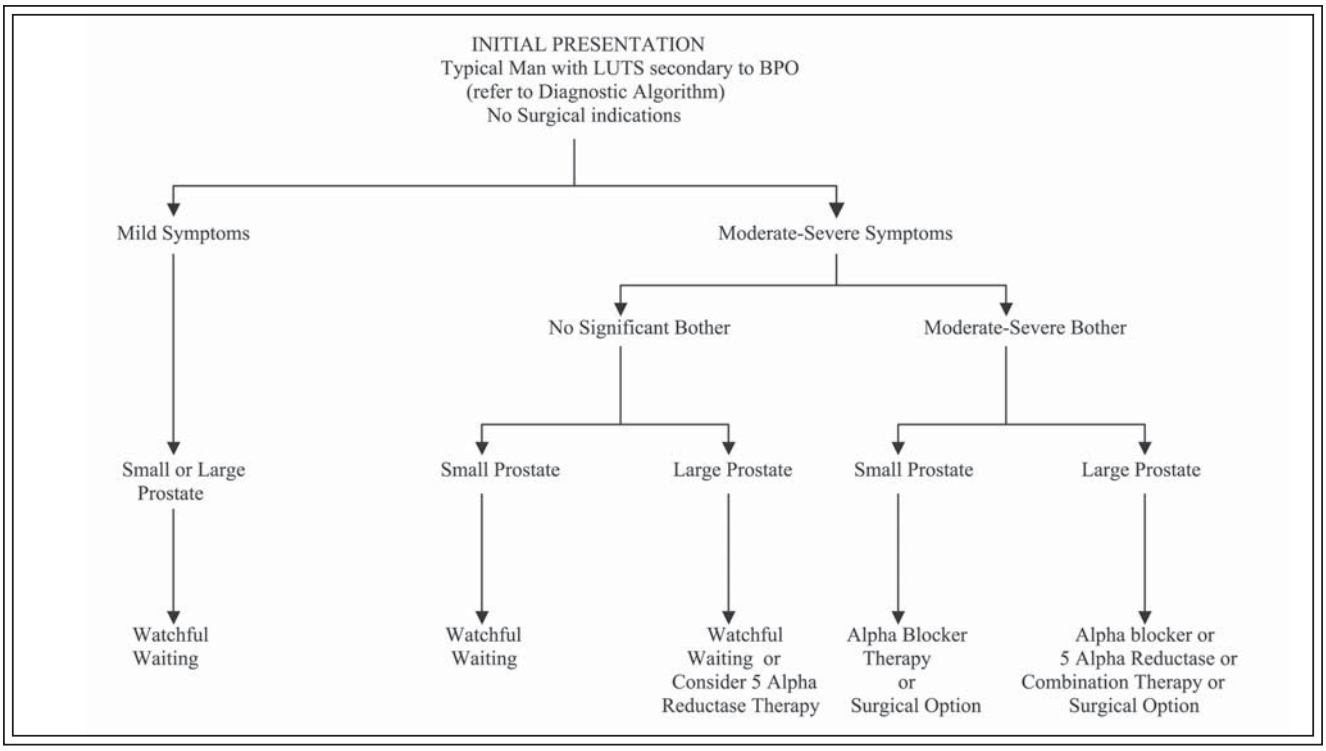

Figure 2. Treatment algorithm.[1,5]

Whereas previously the only option for treating BPH was surgery, drugs from two different classes are now available to treat BPH, and pharmacotherapy can be either monotherapy or combination therapy.

Therapeutic choices

Alpha blockers

The four long-acting alpha blockers that are commonly used to treat BPH are terazosin and doxazosin (older agents) and alfuzosin and tamsulosin (newer agents). With respect to efficacy, the different alpha blockers appear similar. They act by blocking alpha-1a receptors in the smooth muscle of the bladder neck and prostate, which causes the smooth muscle in the bladder neck and prostate to relax or "open." This allows for fuller, stronger, and more complete urination resulting in diminished frequency and nocturia (dynamic obstruction).

Since non-selective alpha blockers can also block alpha 1 receptors found in places other than the prostate -- such as alpha-1d receptors found primarily in the spinal cord, or alpha-1b receptors found primarily in the smooth muscle of peripheral vasculature -- this leads to different potential side effects.[11]

Side effects from alpha blockers include postural hypotension and dizziness (5%-10%), nasal congestion (5%), headache (5%-10%), asthenia (5%-10%), and retrograde ejaculation (3%-10%).[12]

Alfuzosin and tamsulosin are more "uroselective" and have fewer cardiovascular side effects than terazosin and doxazosin.[12,13]

With time, most patients taking alpha blockers for BPH will experience tachyphylaxis, and lose their "BPH symptom control" that was previously produced by the alpha blocker. One reason is that the prostate will continue to grow while the patient takes the alpha blocker. Patients taking alpha blockers should be closely followed to determine if the doses or agents should be altered, as needed.

Alpha blockers "rapidly" (usually within 1 week) improve urine flow and symptoms initially, but they do not reduce prostate size, prevent prostate growth, reduce the long-term risk of symptom progression, or urinary retention, or the need for surgery.[14,15]

Alpha blockers may not be effective due to hypotonic bladder, an irreversible outlet obstruction secondary to scarring, or due to continued bulky growth of the prostate (static obstruction).

Silodosin (Rapaflo) is a new alpha blocker that is available in the United States. This drug predominantly blocks alpha-1a receptors and blocks alpha-1d receptors to a lesser extent. In a double-blind placebo-controlled study of sildosin versus tamsulosin, patients taking

silodosin achieved uroflow response in 4-6 hours and symptom response in 3-4 days, which was better than early-treatment results with tamsulosin. The study also suggested that because of the sildosin's uroselectivity, vascular side effects were minimized.[16]

5-alpha reductase inhibitors

In the prostate, the enzyme 5-alpha reductase reduces testosterone to dihydrotestosterone (DHT), which is the principal androgen responsible for stimulating prostate growth. The 5-alpha reductase inhibitors (5-ARIs) prevent the conversion of testosterone to DHT in the serum and the prostate, which causes the prostate to shrink or to dramatically slow its continued growth.[17,18]

Two 5-ARIs --finasteride (Proscar) and dutasteride (Avodart) -- are currently available.

The 5-alpha reductase enzyme has two isoenzymes: type 1 and type 2. Finasteride acts on type 2 receptors, and dutasteride acts on type 1 and type 2 receptors. Tests have been done to determine if there is an impact of the different types of isoenzyme blockade. Because of the dual blockade, it has been shown that dutasteride lowers DHT production in the prostate by over 90%, whereas finasteride only lowers it by 70%.[19]

Side effects of 5-ARIs are loss of libido (in 3%-8% of patients), ejaculatory dysfunction (1%-5%), reduction in ejaculate volume and some erectile dysfunction (5%-10%), and some breast tenderness (1%).[20,21] The side effects of breast tenderness and decreased libido might appear to be surprising, given that 5-ARIs prevent the breakdown of testosterone, so the effective serum level of testosterone should be higher. However, testosterone is metabolized to DHT and estrogen in the liver. This increased estrogen or change in the estrogen-to-testosterone ratio as a result of 5-ARI therapy may be a cause of the decreased libido and breast tenderness in a small number of men.

The benefits of 5-ARIs are reduced BPH symptoms, reduced prostate size, improved voiding, long-term prevention of disease progression, reduced risk of urinary retention, and reduced risk of the need for surgery.[20,21]

Deciding on optimal therapy

The use of the symptom score sheet will identify and quantify-- for the patient and the physician-- symptoms that are most frequent and bothersome and will indicate the extent to which symptoms are causing a poorer quality of life.

By using objective parameters such as patient age, clinical physical examination findings, DRE findings, serum PSA levels, and urine flow rates, clinicians can identify men who are at risk of progression of LUTS/BPH and who would consequently benefit from medical therapy to prevent complications of BPH. These assessments can also identify men in need of immediate surgery for irreversible, significant, benign disease as well as men who should have further investigation to rule out possible malignant disease.

Several key papers provide evidence that supports the treatment guidelines.

MTOPS study

The Medical Therapy of Prostate Symptoms (MTOPS) was designed to determine if medical therapy (monotherapy or combination) would prevent or delay the progression of BPH, and/or prevent acute urinary retention, the need for surgery, renal insufficiency, recurrent UTI or urosepsis, incontinence, or a deterioration in quality of life.[15]

Patients were randomized into four treatment groups and received an alpha blocker (doxazosin) alone, a 5-ARI (finasteride) alone, combination therapy, or placebo.

Prostate volume decreased most in the patients treated with finasteride alone to the same extent as the patients treated with finasteride plus an alpha blocker. Prostate volume increased in size in patients treated with placebo or the alpha blocker alone. Patients who received combination therapy had the highest maximum flow rate, most improved symptom scores, a 67% reduced risk of BPH progression (compared to patients taking placebo), and a 69% lower risk of needing surgery (compared to patients taking placebo).

TABLE 1. **Patient characteristics at baseline: CombAT versus MTOPS**

Mean +	**CombAT (n = 4844)**	**MTOPS (n = 3047)**
Age (yrs)	66.1 + 7.01	62.6 + 7.3
Caucasian	4259 (88%)	2509 (82%)
Total IPSS	16.4 + 6.16	16.9 + 5.9
Prostate volume (cc)		
Total	55.0 + 23.58	36.3 + 20.1
Transition zone	29.5 + 21.97*	16.4
Serum PSA (ng/mL)	4.0 + 2.08	2.4 + 2.1
Qmax (mL/sec)	10.7 + 3.62	10.5 + 2.6
Post void residual volume (mL)	67.7 + 64.87	68.1 + 82.9

*Subgroup of 656 men
CombAT = Combination of Avodart and Tamsulosin;
MTOPS = Medical Therapy of Prostate Symptoms

CombAT study

The 4-year results from the Combination of Avodart and Tamsulosin (CombAT) study: were recently published.[22] CombAT differed from MTOPS in a number of ways, Table 1. It included only patients with proven, enlarged prostates (over 30 cc), that is, patients who, because of their larger prostate volumes alone, were at "higher risk" of BPH progression. The study was designed to determine whether dutasteride and tamsulosin in combination were more effective than either monotherapy alone for improving BPH symptoms, preventing progression, and improving long-term outcomes compared to untreated BPH.[23]

Combination therapy with an alpha blocker (tamsulosin) and a 5-ARI (dutasteride) resulted in significant improvement in symptoms and long term outcomes and was much better than monotherapy for all measures of BPH progression, Table 2.[23]

This is believed to be the first time that a 5-ARI outperformed an alpha blocker in "symptom control" alone as early as 15 months. Previously, as in MTOPS, the alpha blocker was always shown to be more effective for symptom control when compared to the 5-ARI.

The 4 year study results, like the 2 year results,[24] demonstrated an improvement (in quality of life question). The improvement is demonstrated by a symptom score reduction out of 6 as compared to the baseline score. The scores improved most with combination therapy (2.2-point reduction) versus dutasteride alone (1.8-point reduction) versus tamsulosin alone (1.2-point reduction).

The 4 year primary endpoint of the CombAT trial was different from the 2 year endpoints. The primary endpoint at 4 years was the risk reduction of developing acute urinary retention or the need for surgery. Patients who received combination therapy had a 66 % lower risk. It must be remembered that in MTOPS, the 67% risk reduction in developing urinary retention and the need for surgery was compared to placebo, whereas in CombAT, the 66% risk reduction was compared to a well-accepted active treatment: tamsulosin. This supports the previous statement that alpha blockers in the long term do not prevent progression of BPH.

The incidence of ejaculatory side effects in the combination arm was surprisingly greater than this incidence in the two monotherapy arms combined (10% versus 6%). The side effects experienced by the individuals on combination therapy represented a combination of side effects seen from each of the individual monotherapies.

Concern about the increased incidence of different types of side effects raised the question about the possibility of "withdrawal" of one of the medications after a period of time. Because the alpha blocker usually does not provide a long term effect in all patients, further studies were performed looking at alpha blocker withdrawal. The results of these studies, one using finasteride and the other using dutasteride, were similar.

In most cases, men with improvement on combination therapy may, after 6-9 months, stop taking the alpha blocker and still maintain good symptom response. However, about 20% of men with severe symptoms may require continued use of the alpha blocker.[5,25-27]

TABLE 2. **CombAT: BPH clinical progression at 4 years[23]**

	Combination (n = 1610)		**Dutasteride (n = 1623)**		**Tamsulosin (n = 1611)**	
At year 4	**n**	**%**	**n**	**%**	**n**	**%**
Clinical progression	203	12.6%	289	17.8%*	347	21.5%*
Risk reduction versus combination (95% CI)			31.2% (17.7%-42.5%)		44.1% (33.6%-53.0%)	
IPSS incr. > 4 points	139	8.6%	212	13.1%*	229	14.2%*
AUR	26	1.6%	37	2.3%	82	5.1%*
Incontinence	49	3.0%	60	3.7%	65	4.0%
UTI	3	0.2%	5	0.3%	5	0.3%
Renal insufficiency	1	< 0.1%	2	0.1%	7	0.4%

Crude rate based on ITT population
*$p < 0.001$ versus combination

PSA and medical therapy

The 5-ARIs lead to an "expected" reduction in serum PSA levels of about 50% within 6-9 months of starting therapy.[15,22] Failure to see a reduction in serum PSA levels, or seeing a rise in PSA levels following a drop in PSA to its lowest levels after treatment, might indicate treatment non compliance or the suspicion of prostate cancer.[28]

The prostate should be examined carefully, as it should shrink with 5-ARI therapy, which may allow prostate nodules to become more readily palpable and more easily biopsied.

A pretreatment PSA level is critical for comparison with post-treatment levels. Tracking PSA levels is important, since a rise in PSA levels (or an absence of the expected drop in PSA levels) in a patient receiving 5-ARIs requires referral for a biopsy, to rule out a now-suspected underlying prostate cancer.

Prostate cancer and 5-ARIs

The Prostate Cancer Prevention Trial (PCPT) revealed that compared to patients given placebo, patients given finasteride had 24% lower risk of detection of prostate cancer.[29] Patients enrolled in this trial had PSA levels lower than 4 ng/mL and no clinical indications of underlying prostate cancer (normal DRE). All patients had a prostate biopsy at the end of the study (at 5.5 years on average). The pathological biopsy results raised some questions concerning the increased risk of detecting a more aggressive cancer (higher Gleason score) in the treatment arm of the study compared to the placebo arm of the study. Most people do believe that this was a volume reduction artifact.[30]

Results from the Reduction by Dutasteride of Prostate Cancer Events or REDUCE trial were also recently reported. This trial only enrolled patients who had already undergone a prostate biopsy "for cause," which was shown to be negative. Because of that enrollment criterion, some people believe that these patients were at higher risk of subsequently having prostate cancer detected. Study subjects were randomized to dutasteride or placebo for 4 years. They each had a biopsy at 2 years and at 4 years (end of study).

REDUCE also showed a 23% lower risk of detecting prostate cancer in patients who were treated with dutasteride versus patients who received placebo. The recently reported end-of-study biopsy results from the REDUCE trial found that patients receiving dutasteride did not show a statistically significant increased risk of developing high-grade cancer.[28]

Medical management and sexual health

Erectile dysfunction (ED) was a side effect in some men taking tamsulosin (0.8%-2%) and the 5-ARI inhibitors (5%-9%).[12,20,21] This can be assessed and managed with drugs for ED.

Canadian guidelines

The Canadian Urological Association developed guidelines for the management of BPH that are clearly represented in the algorithms mentioned earlier, Figures 1 and 2. The decisions are made based on the size of the prostate in combination with the severity of symptoms and the degree of symptom bother. The importance of taking a patient history and doing a DRE is pivotal in deciding whether to immediately start the symptomatic patient on an alpha blocker alone, a 5-ARI alone, or combination therapy of an alpha blocker with a 5-ARI.[5]

Recently, Nashlund et al reported results from a trial that was designed to determine the consequences from delay in adding a 5-ARI to an alpha blocker at the outset versus initiating combination therapy at the time of the initial diagnosis of the patient with significant BPH symptoms. They found that for every 30 day delay in adding the 5-ARI dutasteride, the patient had a 2%-3% increased chance of developing urinary retention or needing surgery within 1 year of commencmeny of the medical therapy. [31]

Indications for referral to a urologist

Any of the following symptoms or signs reported by the patient or detected by the primary care physician warrant a referral to a urologist for investigation or management:

1. Acute or chronic urinary retention.
2. Significant microscopic or any gross hematuria.
3. Recurrent UTIs.
4. Renal insufficiency.
5. Failure of response to medical therapy.
6. Suspicion of prostatic cancer at baseline (elevated PSA or abnormal DRE).
7. Insufficient expected lowering or unexpected rise in PSA after 5-ARI treatment.
8. Patient concerns.

Summary

For a patient presenting with BPH symptoms, the primary care physician can use the AUA or IPSS symptom score sheets to determine the severity of

prostatic obstruction. Severity of symptoms, degree of bother, size of the prostate, and PSA levels are part of the Canadian guidelines algorithm, and when combined with the patient's age if over 50, these can help the physician identify and diagnose patients with clinically significant BPH and predict which patients are at risk for progression of BPH disease.

The guidelines also suggest which medical management strategy --an alpha blocker alone, a 5-ARI alone, or combination therapy— will provide the most rapid response and is the best treatment choice to prevent long term disease progression, urinary retention, or the need for surgery in a patient with symptomatic BPH.

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, AstraZeneca, Bayer, Boehringer-Ingelheim, Eli Lilly, GlaxoSmithKline, Merck Frosst, Paladin, Pfizer, sanofi-aventis and Solvay. He has done the clinical research on AndroGel, Avodart, Casodex, Cialis, Detrol, Flomax, Hytrin, Levitra, Xatral, Proscar and Viagra. He has spoken all over the world for all of the companies outlined.

Dr. Allan Toguri is an active senior urologist at The Scarborough Hospital. He has participated at the advisory board meetings of Astra Zeneca, Merck Frosst, and GlaxoSmithKline. He has been involved in clinical trials involving the 5-alpha reductase inhibitors and alpha blockers. □

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