Benign prostatic hyperplasia and lower urinary tract symptoms: evidence and approaches for best case management

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Significant lower urinary tract symptoms (LUTS) are very common in men over age 50. It is appropriate for the primary care physician to perform the work up to confirm that benign prostatic hyperplasia (BPH) is causing the LUTS. If the physician determines that the patient has moderate symptoms (an International Prostate Symptom Score [IPSS] ≥ 8), moderate "bother" (≥ 3 on the IPSS "bothersome index" question), and an enlarged (> 30 cc) prostate, then the most effective treatment is combination therapy with an alpha blocker and 5-alpha reductase inhibitor (5-ARI) at the time of confirmed BPH diagnosis. This combination will provide the most dramatic, early symptom response, the most sustained symptom response, and the most durable, reliable prevention of long term sequelae (acute urinary retention or the need for surgery), if the patient is compliant with taking the combination therapy.

Key Words: benign prostatic hyperplasia, BPH, LUTS

Background

As men age, they have a significant risk of having symptoms associated with an enlarged prostate. Age is the greatest risk factor for the presentation of lower urinary tract symptoms (LUTS), and benign prostatic hyperplasia (BPH) is one of the most common causes of LUTS. It is estimated that 50% percent of men over age 60 and almost 90% of men in their 90s have symptoms from an enlarged prostate and require therapy for this.[1] However, BPH and LUTS are also found in younger men. Bushman reported that 18% of men in their 40s report significant bother from enlarged prostate for which they may request medical relief.[2]

Almost 20 years ago, Michael J. Barry, MD, suggested that by using a simple questionnaire, which was later validated, physicians could quantify urine storage and voiding symptoms reported by patients with BPH or LUTS.[3] The questionnaire also included a question about quality of life, which can also be called the "bothersome index" or "motivational index" question. That question asked, "*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?*"

From this was born the International Prostate Symptom Score (IPSS), which became the gold standard outcome measurement for most clinical trials that assessed responses to interventions for the management of BPH.[4] IPSS symptom scores range from 0 to 8 for "mild" symptoms, 9 to 20 for "moderate" symptoms, and 21 to 35 for "severe" symptoms. Responses to the quality-of-life question range from 0 (delighted) to 6 (terrible).

Clinical trials for the treatment of BPH and LUTS look for "symptom response" that is the change in IPSS scores from baseline after measured at a specified time after beginning of treatment. Patients act as their own controls. The trials showed that to perceive a clinical benefit from a therapy, patients needed a minimum 3-point improvement in IPSS. In addition, if a patient's score on the quality-of-life question was 3 or higher, the patient was "bothered enough" by the symptoms

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to be motivated to seek treatment and would be more likely to accept/comply with treatment.[3]

Many reviews have shown that if BPH is untreated, it often progresses, leading to worsening symptoms, complications, the need for surgical intervention, and a poorer quality of life.[5-7]

The greatest predictable risk factors for progression of BPH are: age older than 50, moderate prostate symptoms (IPSS ≥ 8), and prostate volume greater than 30 cc (or PSA ≥ 1.5 ng/mL, where PSA is a surrogate marker for prostate volume) at the time of diagnosis.[8-12]

The following parameters are signs of BPH progression: change in symptom score (IPSS), increase in postvoid residual (PVR) urine volume, recurrent urinary tract infections, hematuria, renal failure, onset of urinary retention, and the need for surgery.[13]

In my experience, in patients with BPH, the most worrisome potential complications and the complications that are most desirable to prevent are urinary retention or the need for surgery. If these complications can be avoided with medical management, most men will accept that treatment option.

The question that needs to be answered is: W*hich medication or combination of medications will provide the most reliable, improved, and prolonged symptom response and the greatest reduction in the risk of progression of BPH*?

Management of BPH

Lifestyle modification

After a patient has presented to a primary care physician and has been determined to have significant LUTS, the first step in patient management is to determine whether LUTS is caused by BPH causing bladder outlet obstruction (BOO) or there is some other cause.

The primary care physician can follow a relatively simple diagnostic work up, to assess and stratify the patient who presents with LUTS.[14] This work up includes a complete patient history, a focused physical examination, the IPSS questionnaire, and a urinalysis and serum prostate-specific antigen (PSA) test. The most important stratification assessment is determining that a patient has an "enlarged prostate" which can be accomplished by using serum PSA level as a surrogate marker for prostate size. Today, a prostate is considered to be "enlarged" if has a minimum volume of 30 cc. It has been shown that a PSA of 1.5 ng/mL or higher correlates with a prostate volume of at least 30 cc.[15]

To determine the treatment for men presenting with LUTS that is secondary to BPH, and for which there are no indications for immediate surgery,

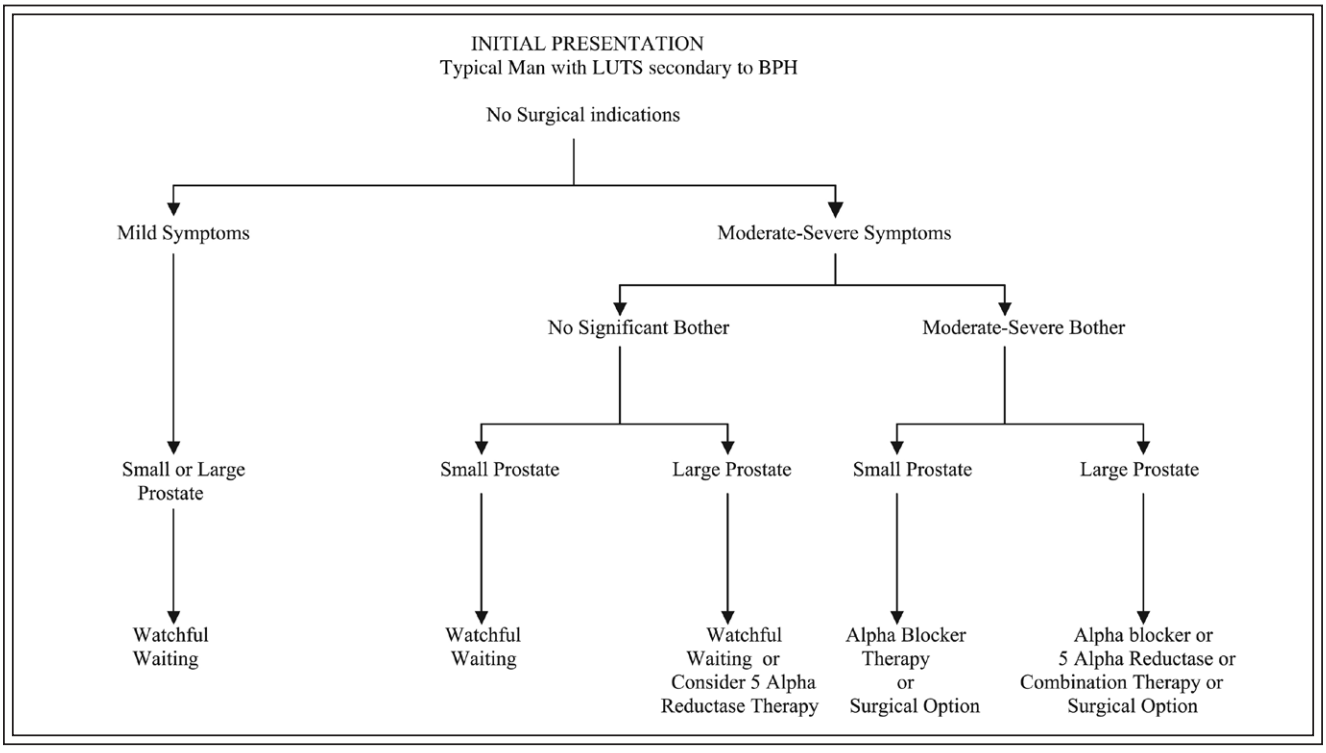

Figure 1. Treatment algorithm.[16]

the primary care physician can follow a treatment algorithm developed by the Canadian Urological Association, Figure 1.[16] The treatment algorithm is based on prostate size, BPH symptoms, and "bother."

For a patient with a small prostate and minimal bother from symptoms, the recommended treatment consists of "watchful waiting" and patient education about lifestyle modification. Examples of lifestyle modification include managing fluid intake during the day and after dinner (decreasing consumption of tea, coffee and alcohol), stopping smoking, decreasing consumption of spicy foods, decreasing use of drugs that affect the bladder (eg, decongestants and antihistamines), avoiding or treating constipation, and performing "bladder training" or pelvic-floor exercises. These suggested lifestyle modifications may decrease symptoms, but they do not reduce the size of the prostate or prevent prostate growth or the progression of BPH.

Medical management of BPH

If conservative treatment such as watchful waiting and lifestyle management of BPH is unsuccessful, then two main classes of drugs may be used to treat patients with symptomatic BPH: alpha blockers and 5-alpha reductase inhibitors (5-ARIs).

Alpha blockers

The use of alpha blockers to manage BPH symptoms began in the 80s with the use of the nonselective antihypertensive agent phenoxybenzamine, which was discovered to have a side effect of increasing urine flow. It also caused significant orthostatic hypotension.

The rationale for using an alpha blocker to treat BPH is based on the knowledge that stimulation of alpha receptors in the smooth muscle fibers in the bladder neck, prostatic urethra, and the prostate can increase the smooth muscle tone (tightness) and thereby cause functional obstruction of the bladder with symptoms of decreased urine flow, increased frequency, nocturia, and urgency (due to decreased bladder emptying).

The three main alpha receptor subtypes are alpha 1A, alpha 1B, and alpha 1D. Alpha 1A receptors are found in the smooth muscle of the bladder neck and prostate, alpha 1B receptors are found mainly in the smooth muscle of the peripheral vasculature, and alpha 1D receptors are found mainly in the spinal cord.[17]

Nonselective alpha blockers can block receptors found in places in the body other than the prostate. Recently, "uroselective alpha blockers" that act specifically on alpha-1 receptors became available. These drugs relieve LUTS through three proposed mechanisms: relaxation of the smooth muscle tone in prostate stroma and the bladder neck, relaxation of bladder smooth muscle, and action on the central nervous system.[18-21]

In most men, treatment with alpha blockers provides a fairly fast (within 48 hours to 1 week), 30% to 50% improvement in symptoms compared to placebo. However, patients who receive alpha blockers are only likely to maintain this response for up to 4 years, and alpha blockers do not prevent BPH progression, shrink the prostate, or affect PSA levels.[13,22]

Alpha blockers, including more uroselective preparations, have very similar efficacies.[23] They also have similar rates of potential side effects, including postural hypotension (5%), dizziness (15%), nasal congestion (5%), headache (5%-10%), and asthenia (5%-10%). Tamsulosin is associated with a 3%-10% rate of abnormal ejaculation, and the alpha blockers may cause or improve erectile dysfunction (ED).[19,20,24]

5-alpha reductase inhibitors

Testosterone is broken down to its metabolite dihydrotestosterone (DHT) by the action of the enzyme 5-alpha reductase. DHT is the active chemical that is absorbed into the prostate cells and stimulates prostate cellular and glandular (stromal) growth. The 5-alpha reductase enzyme has two isoenzymes: type 1 and type 2, which are present in different concentrations within the different types of prostate tissue (eg, cancer versus benign disease).[25,26]

If the breakdown of testosterone to DHT is inhibited by a 5-ARI, DHT absorption into the prostate is reduced, and as a result, the prostate shrinks and symptoms caused by the BPH will decrease.[27]

Two 5-ARIs -- finasteride (Proscar) and dutasteride (Avodart) -- are currently available. Dutasteride inhibits both types of 5-alpha reductase isoenzymes, whereas finasteride only inhibits the type 2 isoenzyme. As a result, finasteride reduces DHT production by about 70%, whereas dutasteride reduces it by more than 92%.[28]

In recent monotherapy trials comparing the 5-ARIs to placebo, both finasteride and dutasteride demonstrated significant positive effects.[27,29] The trials enrolled men with symptomatic BPH. In these monotherapy trials, men who received finasteride or dutasteride had greater improvements in clinical symptoms after 6 to 12 months and their IPSS scores were 15% to 30% lower after 2 to 4 years, compared

with men who received placebo.[23] In another trial, finasteride was less effective than alpha blockers in reducing LUTS and achieved virtually the same response as the placebo arm.[30] A long term trial with dutasteride in symptomatic men with prostate volumes of at least 30 cc showed that it reduced symptoms in these patients at least as much or even more effectively than tamsulosin.[31]

Combination therapy

Based on the fact that alpha blockers and 5-ARIs have different mechanisms of action, long term effects, and efficacies (reduction of progression of BPH), two large recent clinical trials were designed to compare long term outcomes achieved by using combination therapy (an alpha blocker and a 5-ARI) compared to monotherapy (an alpha blocker a 5-ARI or placebo).

Earlier trials that compared combination therapy with finasteride plus an alpha blocker versus placebo concluded that this combination therapy was no better than placebo in treating symptoms of BPH. However, the reasons postulated for failure were that the trial durations may have been too short (12 months) and the inclusion criteria may have included prostates that were too small to see any benefit from the shrinking effect seen with 5-ARIs.[22,30,32]

Taking the weaknesses of these earlier trials into account, two large, "longer term" (4-or 5-year) trials of combination therapy were performed and the results were recently reported. These trials -- Medical Therapy of Prostate Symptoms (MTOPS) and Combination of Avodart and Tamsulosin (CombAT) -- investigated the effects of delivering long term combination therapy to treat BPH. The goal was to determine if "signs of progression" of BPH -- such as deterioration of IPSS score, development of acute urinary retention, or the need for surgery -- were reduced in the combination-therapy arm versus the monotherapy arms (in CombAT) or versus the monotherapy arms or placebo (in MTOPS).

In MTOPS, patients were randomized to one of the four treatment arms: an alpha blocker (doxazosin) alone or a 5-ARI (finasteride) alone or combination therapy (finasteride plus doxazosin) or placebo. In CombAT), patients were randomized to an alpha blocker (tamsulosin) alone or a 5-ARI (dutasteride) alone or to combination therapy with (dutasteride plus tamsulosin).[13,33]

In MTOPS, to be included in the study, patients had to be at least age 50, have no clinical signs of prostate cancer, and have an IPSS score of at least 8. There was no minimum requirement for prostate size. In CombAT, the inclusion criteria were the same as previously determined and accepted characteristics to predict those men at higher risk for progression of BPH symptoms -- age 50 and older, prostate volume greater than 30 cc, and moderate IPPS (≥ 12). As a result, the members of the ethical review boards excluded the placebo arm in CombAT, since they felt that in this at-risk population, the risk of disease progression after 4 years was too high to justify withholding treatment.

The primary endpoint in MTOPS was a composite endpoint of clinical progression of BPH (ie, renal failure, recurrent urinary tract infections, urinary retention, etc.) at 4 years. At 1 year the rate of clinical progression of BPH was not significantly improved in the combination arm versus the placebo or monotherapy arms. However, at 4 years the rate of clinical progression of their BPH symptoms and signs was significantly lower in the combination therapy arm versus the other arms.

The primary endpoints of CombAT were improvement in IPSS at 2 years and reduction in risk of AUR or surgery at 4 years.[31,33]

In CombAT, up to 3 months, the slopes of the curves of "symptom response" over time were identical for tamsulosin and for combination therapy. As early as 15 months, however, patients treated with the 5-ARI dutasteride achieved a better *symptom response* compared to patients treated with the alpha blocker tamsulosin -- which was the first time that a trial showed that patients with BPH achieved a better symptom response with a 5-ARI than with an alpha blocker. At 4 years, symptom improvement for patients in the combination arm was statistically superior to that of patients in either monotherapy arm. (There was no placebo arm).

Both trials also looked at the incidence of acute urinary retention, which, if not reversible, results in the need for surgery on the prostate. In MTOPS, McConnell et al reported a 67% risk reduction in acute urinary retention or the need for surgery at 4 years in the combination arm *compared to placebo*. The risk reduction for same endpoints in the CombAT trial was virtually identical -- 66%. However, the 66% improvement in this trial was combination therapy compared to the active treatment tamsulosin, not versus placebo as shown in the MTOPS trial.

In CombAT, 6% of participants in the combination arm versus 4% of participants in either monotherapy arm withdrew from the study due to severe adverse effects. The difference in withdrawal rates was not statistically significant.

Another very significant difference between alpha blockers and 5-ARIs is that there is an expectation of a 50% drop in PSA levels after a patient has been taking a

5-ARI for at least 6 months, whereas there is no impact on PSA if a patient is taking an alpha blocker.[29]

Conclusion

Significant LUTS is very common in men over age 50. After ruling out causes of LUTS other than BPH, it is necessary and fairly easy for the primary care physician to perform the patient workup to confirm that BPH is causing the LUTS. The primary care physician can manage the patient by following a patient-assessment algorithm. If the primary care physician determines that the patient has moderate symptoms (IPSS ≥ 8), moderate "bother" (≥ 3 on IPSS on the "bothersome index" question), and an enlarged (> 30 cc) prostate, then the most effective, recommended treatment is combination therapy with an alpha blocker and 5-ARI *from the outset*. This combination therapy will provide the most dramatic, early symptom response (decline in IPSS), the most sustained symptom response, and the most durable prevention of the long term sequelae of BPH progression -- acute urinary retention or the need for surgery. If the patient complies with taking the combination medical therapy, his PSA levels are expected to decline by 50%, and his symptom response is expected to persist. If a patient's PSA levels does not decline by 50%, or if his symptom score does not improve, then he should be referred to a urologist. □

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.

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