Review Article

Noninvasive treatment of benign prostatic hyperplasia

Where do we stand in 2005

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ABSTRACT

Noninvasive treatment of lower urinary tract symptoms (LUTS) due to benign prostatic hyperplasia (BPH) includes self-management and medical treatment. Self-management should be encouraged as an initial step for all men with uncomplicated LUTS/BPH. It consists of 3 elements, namely: education and reassurance, lifestyle modification of fluid intake and concurrent medical therapy and finally behavioral interventions including management of post-void dribbling and bladder retraining. If self-management fails, medical or surgical interventions are required. Further, research is required to define and test the effectiveness of self-management either as a primary intervention or to augment existing medical therapies. Benign prostatic hyperplasia patients in need of rapid onset of symptom relief and those with small prostates benefit from the use of alpha-blockers. Although 5-alpha-reductase inhibitors (5 ARIs) provide symptomatic benefits, the onsets of these are slower than those observed with the alpha-blockers. Amongst available therapies, only 5 ARIs have been shown to reduce the risk of acute urine retention (AUR) and BPH-related surgery compared to placebo. The Medical Therapy of Prostatic Symptoms (MTOPS) Study provides rational basis for combined alpha-blockers plus 5 ARIs in patients with a high index of disease progression (prostate volume >30 g and prostate-specific antigen >1.6 ng/ml). Preliminary studies suggest that anticholinergics could be safe in LUTS/BPH and can help to alleviate irritative bladder symptoms due to overactive bladders commonly associated with BPH.

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The natural history of benign prostatic hyperplasia (BPH) is variable. Most men experience progression of the disease by reduction of the flow rate by 2% every year and increase of the international prostate symptom score (IPSS) by 0.18 points every year. Nevertheless, some men may remain stable and others may even improve without treatment. Predictors of disease progression are prostatic specific antigen (PSA) >1.5 ng/ml and prostate volume >30 g. In the last decade, the management of lower urinary tract symptoms (LUTS) due to BPH has dramatically changed. The standard therapy for men with uncomplicated LUTS/BPH involves a cascade of noninvasive treatment, minimally invasive procedures and invasive endoscopic or open surgical techniques. The choice depends on balancing symptom severity and bothers with benefits, risks and side effects.[1,2] The aim of the present review is to shed light on the most recent advances in noninvasive treatment of LUTS/BPH including self-management and medical treatment.

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Self-management. Self-management should be the primary strategy for all men with uncomplicated LUTS/BPH. Self-management is also termed watchful waiting or active monitory. It does not mean doing nothing. It varies from the annual review of symptoms with simple investigations (symptom score, flow rate) to an intensive program of education, reassurance and advise delivered in a multidisciplinary setting.[2,3] Self-management consists of 3 elements namely: education and reassurance, lifestyle modification of fluid intake and concurrent medical therapy and finally behavioral interventions including management of post-void dribbling and bladder retraining.

Education and reassurance. Most patients want information about their condition. The patient must be learned about the natural history and the different treatment options of LUTS/BPH. The pros and cons of each treatment option must be discussed with patient. It is also important to know the patients perspectives and his sexual ability. Anxiety regarding prostate cancer can be the principal reason why a man consult his doctor about his LUTS; in this situation reassurance is the only intervention required.

Life style modification. Life style modification useful for self management of LUTS/BPH include: fluid management and concurrent medical therapy.

Fluid management. Recommending changes only possible if detailed information about fluid intake and how this relates to voiding are known. Frequency volume charts (voiding diaries) are the easiest way to achieve this. Patients document the type and volume of fluids consumed, and the time and volumes of urine passed.[4] From these charts, fluid intake, its relationship to voiding patterns, voided volume (bladder capacity), and frequency both day and night can be estimated. This information would be difficult to obtain through questioning alone.[2]

There are number of basic components to fluid management: (i) The overall fluid intake should be approximately 1500-2000 ml/day (with minor modifications made for climate and activity). There is a belief promoted by the mineral water industry, and now held by many, that drinking 3 liters of water every day affords some health benefit. While dehydration should always be avoided, there is no evidence to support that drinking more water is better for you.[5] (ii) A patient should reduce or avoid fluid intake at specific times when urinary frequency is inconvenient (but overall daily fluid intake should not be reduced). (iii) The patient should avoid fluid intake 2 hours prior to sleep if nocturia is a symptom (but, again, overall daily fluid intake should not be reduced). (iv) The patient should avoid or moderate intake of caffeine and alcohol which may have a diuretic and irritant effect on the bladder, thereby increasing fluid output and enhancing frequency, urgency and nocturia.[2]

Concurrent medical therapy. Medication with an effect on the urinary tract can both cause and exacerbate LUTS. Diuretics cause a diuresis. Tricyclic antidepressants, antispasmodics and anti-histaminics have anticholinergic effects that may reduce bladder emptying. Anti-parkinsonian drugs and calcium channel blockers cause smooth muscle relaxation that may also reduce bladder emptying. Where a suitable alternative exists with less effect on the urinary tract, changes can be made such as substituting a thiazide diuretic used for hypertension, for a beta-blocker or ACE inhibitor. Where substitution cannot be made, such as with loop diuretics for heart failure, patients can be advised to alter the time drugs they taken. Taking a loop diuretic early in the evening rather than first thing in the morning will reduce daytime frequency and nocturia.[2]

Behavioral interventions. This includes: management of post-void dribbling and bladder retraining.

Management of post-void dribbling. The post-micturition dribble is a very common and bothersome symptom, it is underreported by patients and does not feature in the International Prostate Symptoms Score (IPSS).[6] By milking the urethra with a combination of leaning forwards, perineal pressure and contracting the pelvic floor muscles, urine that collects in the "U-bend" of the urethra after voiding can be expelled.[2] Randomized studies have shown that urethral milking and pelvic floor contractions to be more effective than counseling alone in reducing post-micturition dribble.[7]

Bladder retraining. Bladder retraining involves patients resisting the sensation of urinary urgency with distraction techniques and pelvic floor squeezes to postpone voiding, thereby overcoming abnormal voiding patterns. Initially, voiding should be postponed only for a short period of time, such as a minute. Once this is achieved with ease, patients can progress and postpone voiding for longer and longer aiming to increase their bladder capacity to 300-400 ml and their inter-void time to 3-4 hours. The success rate of self-management is only subjective and is based upon reduction of symptoms. If self-management fails, medical or surgical intervention is required. Many self-management interventions discussed in this review have little or no scientific evidence to support them as effectiveness studies have not been performed. However, approximately one third of men with LUTS/BPH are managed in UK secondary

care setting by self-management.[3] The widespread use of self-management suggests its effectiveness. Further research is, therefore, required to define and test the effectiveness of self-management either as a primary intervention or to augment existing medical therapies.

Medical Treatment. The principles of medical treatment of LUTS/BPH are to fight against the causative factors. The static component of prostatic obstruction can be hit by 5-α-reductase inhibitors (5 ARIs) or phytotherapy. The dynamic component of prostatic obstruction can be treated by α-blockers. Irritative or storage bladder symptoms can be treated by anticholinergics and partially by α-blockers, and finally α-blockers may also have an impact at the spinal cord level.[8]

Medical treatment is indicated in patients of uncomplicated LUTS/BPH with mild to moderate symptoms (IPSS <8-20) and these awaiting, unwilling or unsuitable for surgery. Medical treatment must be stopped in cases of complicated LUTS/BPH including patients with refractory hematuria, repeated attacks of acute urinary retention (AUR), repeated attacks of urinary tract infections (UTIs) and renal insufficiently secondary to BPH.

Alpha-blockers. Short- and long- acting α1-selective antagonists treat the dynamic component of BPH through relaxation of smooth muscle in the prostate, by blockade of α1-receptor-mediated sympathetic stimulation. A number of double-blind, placebo-controlled studies evaluating the efficacy of α1-blockers have been conducted in patients with symptomatic BPH.[9,10] Alpha-blocker studies have recently undergone meta-analysis by the American Urological Association (AUA).[11] The α1-blockers alfuzosin, doxazosin, tamsulosin and terazosin demonstrate statistically significant improvement, compared with placebo, in symptom scores, maximum flow rate (Qmax) and quality of life. In common with meta-analysis of α1-blocker studies conducted in 1999, the AUA guidelines conclude that the 4 α1-blockers examined provided equivalent benefit in improving symptoms and flow.[11,12] Discontinuation due to adverse events ranges between 4 and 10% for alfuzosin and tamsulosin; rates that are comparable with placebo. However, for terazosin and doxazosin, an additional 4-10% of patients withdraw due to adverse events.[12] The most common adverse events, observed with α1-blockers at a significantly higher frequency than placebos are dizziness and postural hypotension, although there may be differences between individual agents within the class.[12] In general, the α1-blockers are associated with a similar incidence of sexual adverse events compared with placebo except for tamsulosin which has an incidence of retrograde or delayed ejaculation of 4.5-10% versus 0-1% for placebo.[13]

5 α–reductase inhibitors (5 ARIs). 5 ARIs inhibit the conversion of testosterone to dihydrotestosterone (DHT); the primary androgen involved in both normal and abnormal prostate development. By reducing the production of DHT, 5 ARIs significantly reduce prostate volume in men with BPH. Two 5 ARIs are currently available for the treatment of BPH: finasteride and dutasteride, which differ in their profile of 5 α –reductase (5 AR) binding and inhibition of the type 1 and type 2 isoenzymes of 5 AR. Finasteride is a mono-inhibitor of 5 AR type 2, whilst dutasteride is a dual inhibitor of both 5 AR type 1 and type 2.[14] Dutasteride treatment results in an increased and more consistent level of serum DHT suppression, namely >90% DHT suppression in >85% of subjects receiving dutasteride, compared with >90% in 2.2% of subjects receiving finasteride.[15] The effects of finasteride on the symptoms and progression of BPH have been evaluated in the Proscar Long-term Efficacy and Safety Study (PLESS); a large-scale, long-term, double-blind, placebo-controlled trial.[16] Finasteride reduced prostate volume by 18%, improved symptom score by 2.6 points, increased Qmax by 1.9 ml/s and reduced the risk of AUR by 57% and surgery by 55%. Although the 7-year Prostate Cancer Prevention Trial (PCPT) recruited men with a normal digital rectal examination, a PSA of <3.0 ng/ml and AUA symptom score <20, and was designed to examine the effect of finasteride versus placebo on the risk of prostate cancer, it also confirmed that finasteride treatment was associated with a lower risk of AUR and need for TURP.[17] The efficacy of dutasteride has been examined in double-blind, placebo-controlled phase III studies.[18] Dutasteride reduced symptom score by 4.5 points, increased Qmax by 2.2 ml/s and reduced the risk of AUR by 57% and surgery by 48%. Both finasteride and dutasteride are generally well-tolerated. Withdrawals due to adverse events were similar to placebo except for sexual adverse events. Compared to placebo, 5 ARIs have significantly higher incidence of sexual side effects in terms of decreased lipids, impotence, ejaculation disorders, reduced ejaculate volume and gynecomastia.

Phytotherapy. Phytotherapeutic agents have become a popular treatment for LUTS/BPH. These agents are employed extensively in Europe, where their use is more prevalent than α–blockers and finasteride

combined.[19] In the USA, consumers often purchase herbal medications over the counter to supplement traditional treatment or as a substitute.[19] Herbal treatment for BPH has been extensively reviewed.[19-23] and a detailed discussion of this topic is beyond the scope of the present review. The mechanism of action of phytotherapeutic agents is poorly understood and difficult to ascertain as plant extracts are of variable contents. Nevertheless, same studies suggest that intracellular inhibition of 5 AR is a mechanism of action.[19]

A recent study has demonstrated that phytotherapy with permixon improves LUTS due to BPH with no negative impact on the sexual function.[24] Another recent study has shown that permixon 320 mg/day is slightly superior to tamsulosin 0.4 mg/day in reducing LUTS in severe BPH patients.[21] A recent meta-analysis of all available published trials of permixon for treating men with BPH showed a significant improvement in peak flow rate and reduction in nocturia above placebo a 5-reduction in IPSS.[20] Several recent studies have suggested a potential benefit of phytotherapy for BPH. In addition, there have been few side effects reported. The role of these agents in the treatment of BPH may be in those patients who seek alternative medications with minor symptoms and with no absolute indications for medical or surgical management.[19,20]

Anticholinergics. Bladder outlet obstruction (BOO) caused by BPH will result in detrusor instability and overactive bladder. A substantial proportion of men with LUTS/BPH will have irritative bladder symptoms resulting from an overactive bladder commonly associated with BPH. There is, therefore, a rational basis for treating such symptoms with anticholinergic drugs.[25] It is a common perception that using an anticholinergic in men with BOO runs the risk of AUR, because of the inhibitory effect of anticholinergics on bladder contraction in the presence of BOO, and so these drugs tend not to be used. Nevertheless, some recent studies specifically determined the safety of anticholinergic drugs in this situation.[26] Large tolerability and safety studies of anticholinergic drug treatment, which includes many men (many of whom are likely to have BOO) suggest that anticholinergic medications is likely to be safe in men with LUTS /BPH.[27] Preliminary recent data from men with urodynamically proven BOO support this assertion.[28] Larger studies are required to determine the safety and therapeutic role of anticholinergic medication in men with LUTS/BPH.

Combination of α–blockers plus 5 ARIs. The rational basis of combination of both α–blockers and 5 ARIs is the fact that this combination theoretically should have dual synergetic effect against both the dynamic and the static components of obstruction in patients with LUTS/BPH. Herein, we will present the most important prospective randomized trials that studied this issue.

The ALPHIN Study. The most relevant among the non-controlled trials is the Alphin Study involving more than 1000 patients, which compared alfuzosin or finasteride alone and a combination of alfuzosin and finasteride over 6 months. From this study it was clear that alfuzosin and the combination did significantly better on the IPSS, however, the combination did not provide any additional benefit over alfuzosin alone.[29]

The Veterans Affairs Study. The oldest placebo-controlled study was the Veterans Affairs Study comparing terazosin or finasteride alone with a placebo or a combination of both drugs.[30] From this study terazosin and the combination did better than finasteride alone or the placebo and there was no additional benefit in administering the combination over terazosin alone. One of the drawbacks of this study was the small volume of the prostate included, which did not allow finasteride to act optimally.

The Prospective European Doxazosin and Combination Therapy (PREDICT) Study. The second placebo-controlled study was recently published:[31] the PREDICT Study. This trial compared doxazosin or finasteride alone with a placebo or a combination of both drugs. More than 1000 patients were included in this one year study. The results are quite similar to the Veterans Affairs Study. Doxazosin and the combination did better on IPSS improvement than finasteride alone or the placebo. There was no additional benefit in administering the combination over doxazosin alone.

The Medical Therapy of Prostatic Symptoms (MTOPS) Study. The design of the MTOPS was recently published[32] and preliminary results have been given.[29] A total of 3047 BPH patients were randomized into 4 arms to receive doxazosin (4 or 8 mg) alone, finasteride (5 mg) alone, a placebo, or a combination of both drugs. The primary goal of this prospective study was to determine if medical treatment could prevent or delay the clinical progression of BPH, defined as AUR, renal insufficiency due to BPH, recurrent UTIs or urosepsis, incontinence or a rise of more than 4 points on the IPSS. In contrast to the previous combination therapy studies, many patients enrolled in the MTOPS study fulfilled the conditions for maximal efficacy of finasteride: 31% had a PSA

Table 1 - Summary of the results of Medical Therapy of Prostatic Symptoms (MTOPS) study.

Results of MTOPS	Combination	Doxazosin	Finasteride	Placebo
↓ AUA score (points)	7	6	5	4
↑ Qmax (ml/s)	3.7	2.5	2.2	1.4

AUA - American Urological Association, Qmax - maximum flow rate

above 1.4 mg/ml. At 4 years, change in symptom score was 7 points for combination, 6 points for doxazosin, 5 points for finasteride and 4 points for placebo; the median baseline symptom score being 17. These improvements were paralleled by changes in Qmax: 3.7 ml/s for combination, 2.5 ml/s for doxazosin, 2.2 ml/s for finasteride and 1.4 ml/s for placebo; the median baseline Qmax being 10.6 ml/s. A summary of the results of MTOPS study is given in **Table 1**. The combination therapy was more effective in relieving and preventing the progression of symptoms than either of the 2 drugs alone. The addition of finasteride to doxazosin significantly reduced the risk of AUR, and the need for BPH-related surgery. The overall risk of progression was reduced by 39% for doxazosin, 34% for finasteride and 67% for combination therapy. The risk of retention was reduced by 31% for doxazosin, 67% for finasteride and 79% for combination therapy, while the risk of surgery was reduced by 64% and 67% for finasteride and combination therapy, with no significant change in the risk for the doxazosin group compared with placebo.[33]

Should all BPH patients receive combined therapy? Certainly not, and for many reasons. The daily cost of the treatment is a matter of concern, but more important is the risk of adverse effects: patients receiving a combination therapy experience the adverse effects resulting from both agents.[8] Patients selection has to be defined so that combination therapy is administered only to those patients who will get maximal clinical benefit. Patients most likely to benefit from combination therapy are those in whom baseline risk of progression is significantly higher, generally patients with larger glands (>30g) and higher PSA (>1.6 mg/ml).[11]

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