

**Original article:**

## Medical Management of Benign Prostatic Hyperplasia

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### Abstract:

Benign prostatic hyperplasia (BPH) is a common condition among older male population. Histologically it is characterised by the presence of discrete nodules in the periurethral zone of prostate gland. Lower urinary tract symptoms (LUTS) are a group of symptoms due to a number of diseases may be urological and non urological other than an enlarged prostate that present with these symptoms. Watchful waiting is appropriate among those patients who have low AUA symptoms score (0-7) as literature evidences show no significant benefit of medications over placebo. NX-1207 is a new drug under investigation for treatment of symptomatic BPH. NX-1207 has been suggested to elicit a proapoptotic effect on the prostate. With better understanding of pathophysiology of BPH the line of management has improved. The medical management has come down to two established options at present time i.e. either monotherapy with  $\alpha$ -blockers or combined therapy of  $\alpha$ -blockers and 5 ARIs. Both these modalities have shown to reduce the disease progression and improve symptomology significantly.

Keywords : Benign prostatic hyperplasia , NX-1207

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### Introduction

Benign prostatic hyperplasia (BPH) is a common condition among older male population. Histologically it is characterised by the presence of discrete nodules in the periurethral zone of prostate gland (1). This involves both the stromal and the glandular elements of prostate. The enlarged gland is associated with lower urinary tract symptoms in the form of obstructive due to extrinsic compression of prostatic urethra leading to impaired voiding while increased smooth muscle tone and resistance within the enlarged gland leads to detrusor overactivity contributing to storage symptoms. When a symptom of urinary obstruction interferes with quality of life, treatment is warranted. However the severity of symptoms do not correlate to degree of hyperplasia and other conditions can simulate such symptoms. Lower urinary tract symptoms (LUTS) are a group of symptoms due to a number of diseases may be urological and non urological other than an

enlarged prostate that present with these symptoms.(2)

The prevalence of both BPH and LUTS rises markedly with increased age. BPH affects 70% of US men 60–69 years of age and 80% of those 70 years of age or older (3). In the Boston Area Community Health survey, LUTS prevalence increased from 8% in men 30–39 years of age to 35% in men 60–69 years (4). In the Rancho Bernardo study, 56% of men 50–79 years of age, 70% of men 80–89 years of age, and 90% of men 90 years of age or older reported LUTS. Other population-based studies have demonstrated similar trends (5, 6).

The Agency for Health care policy and Research (AHCPR) now the Agency for Healthcare Research and Quality published guideline for BPH. The diagnosis of the condition is based on patient's symptomatology. The symptoms include urinary frequency, nocturia, urgency, hesitancy, intermittency, weak stream, straining

to void, and sensation of incomplete evacuation (7). The assessment of severity of symptoms is done by urinary symptom scoring system developed by American Urological association(AUA).The total score ranges from 0-35.This point score is graded into mild(0-7), moderate (8-19) and severe (20-35) (8).

In addition to the symptoms the patient is evaluated in terms of quality of life or bothersome severity of the problem.

The contribution to the symptomatology can be physiologically understood by dividing the hyperplastic gland into two components – dynamic and static. The dynamic component is contributed by the fibromuscular elements and the static part is contributed by the glandular or epithelial elements (10). On the modification of these parts is the medical management of BPH based. The disease is progressive in the sense that there is increase in the size of the prostate gland as well as the severity of the symptoms. This may lead to acute retention of urine, one of most significant complications of BPH. The other complications are bladder decompensation, recurrent urinary tract infections, bladder calculi and obstructive nephropathy(9).

In last two decades lot of work has been done in the field of management of BPH. New forms of medical and minimal invasive modalities have come up. Leaving aside the cases where there are absolute indications of surgery in rest of cases one has the option of medical management.

Primary goal of treatment has been to alleviate symptoms as a result of prostatic enlargement, however recently treatment has additionally focused on alteration of disease progression and prevention of complications that can associated with BPH/LUTS. (10) Benign Prostatic Hyperplasia Guideline Panel has put forward clinical practice guidelines for management of

LUTS associated with BPH. (10)

#### **Watchful waiting**

Watchful waiting is appropriate among those patients who have low AUA symptoms score (0-7) as literature evidences show no significant benefit of medications over placebo. However regular follow up and monitoring is essential and to look for spontaneous exacerbations and remissions of BPH (even without treatment) (7). As per the panel the standard watchful approach is encouraged for those individuals with mild symptoms of LUTS secondary to BPH (AUA –SI score <8) and patients with moderate or severe symptoms (AUA-SI score > 8) who are not bothered by their LUTS. Watchful waiting patients are usually re-examined yearly, repeating the initial evaluation and measures to reduce risk such as medical interventions, may be offered depending on the circumstances. Patients with higher AUA symptoms cores should be given information on appropriate treatment options.

#### **Alpha Blockers.**

Alpha adrenergic blockers are appropriate and effective treatment alternatives for patients with bothersome, moderate to severe LUTS secondary to BPH (AUA-SI score>8). Alpha 1 receptor antagonists i.e. doxazosin, prazosin, and terazosin, improve the luts by promoting smooth muscle relaxation. These agents improve BPH symptoms in a short span of action. (7) Symptom improvement is typically noted within two to four weeks of initiating alpha blocker therapy (12).

As per the 2003 guidelines, all the 4 alpha blockers appear to have similar efficacy and effectiveness.

Alpha blockers are associated with stromal element of the prostate and have a major influence on prostatic smooth muscle tone which is the major

contributor to pathophysiology of LUTS secondary to BPH, thus theoretically it acts at the site with greatest benefit with fewer side effects. A randomised trial comparing terazosin, finasteride and placebo showed significant symptom reduction in patients receiving terazosin compared to other two groups. Alpha Blockers have shown to delay BPH related surgery and incidence of AUR (13). The side effects of this class of drugs such as fatigue, asthenia, retrograde ejaculation and postural hypotension remain but these can be managed with dose titration and bed time administration (14). Though older less costly generic alpha blockers remains reasonable choice although dose titration and blood pressure monitoring is essential. To overcome the effects that are due to the global alpha blockade, new drugs have come up that are receptor specific. Alpha I receptors are present in the prostate, bladder neck and lower ureters. These urospecific drugs-tamsulosin, alfuzosin have less systemic side effects. These drugs have a clear advantage of single daily dose and less of hypotensive side effects. Thus drugs are better placed in view of their therapeutic activity as well as side effect profile in comparison to older class of alpha blockers.

### **5 Alpha Reductase Inhibitors.**

Prostate growth is stimulated by androgenic hormones especially dihydrotestosterone (15, 16). The active hormone is dihydrotestosterone (DHT) that is formed by the conversion of testosterone by 5 alpha Reductase enzymes. There are two isoenzymes I and II and type II predominates in the prostate accounting for generation of DHT in prostate (17). The 5-alpha-reductase inhibitors (5ARI) act on the glandular component of the prostate gland i.e. the static component. The two 5ARIs currently available are finasteride and dutasteride. Finasteride is

selective type II 5ARI while as dutasteride inhibits both type I and type II 5alpha reductase isoenzymes. This difference in activity leads to a reduction in serum level of DHT by approximately 70 percent with finasteride compared to approximately 95 percent with dutasteride (18). Although an early study showed similar efficacy for finasteride and placebo, the larger Proscar Safety Plus Efficacy Canadian Two Year Study (PROSPECT) found that treatment with finasteride led to significant improvement in urinary symptoms and flow rates. However, in the PROSPECT study, the improvements with finasteride were significant less than those with any alpha blockers (19). Analysed together, the results of multiple studies suggest that finasteride may work best in men with large gland, whereas alpha blockers are effective across the range of prostate sizes.

In a placebo controlled study Finasteride treatment showed that it reduces the risk of AUR and the need for surgery but >50% and significantly improves the symptom score, improve urinary flow rates and reduce prostate volume (all  $P < 0.001$ ) compared to placebo. (21) The side effects are sexual dysfunction which are reversible on cessation of therapy and the incidence of newly reported events decreased after first year. (22)

Dutasteride demonstrated efficacy in reducing the risk of AUR and BPH related surgery. In a double blind placebo controlled trial of dutasteride in BPH there has been 57 percent risk reduction for AUR and 48 percent risk reduction for surgery (23).

5-Alpha reductase inhibitors may be used to prevent progression of LUTS secondary to BPH in individuals with demonstrable prostatic enlargement and to reduce the risk of urinary retention and future prostate related surgery. It should not be used in men with LUTS secondary

to BPH without prostatic enlargement.

**Combination therapy with  $\alpha$ -blockers and 5 $\alpha$ -reductase inhibitors.**

The relative effectiveness of 5-ARIs and  $\alpha$ -blockers was first evaluated in mid-1990 by Veterans Affairs (VA) Cooperative Studies Group,(14).Combination therapy of terazosin and finasteride was observed to be no better than a placebo. The findings of VA study were replicated by the PREDICT study (24) which substituted  $\alpha$ -blocker doxazosin for terazosin. In the PREDICT study, the baseline prostate volume was 36 g which is virtually identical to the VA study. The Medical Therapy of Prostatic Symptoms (MTOPS) was designed primarily to address disease progression. Combination therapy was significantly more effective than monotherapy at preventing overall disease progression (14). The observed 66%,64%,81% and67% risk reduction of combined therapy for overall clinical BPH progression , symptom progression ,development of AUR and progression to invasive therapy of BPH respectively goes in favour of better outcome with combined therapy. The Combination of Avodart and Tamsulosin (CombAT) study compared the effectiveness of 5-ARI dutasteride, the  $\alpha$ -blocker tamsulosin , and the combination of these drugs .The legitimate conclusion of the CombAT study is that , in a select group of men with large prostates, combination therapy and dutasteride alone are significantly better than tamsulosin at preventing AUR and BPH surgery.

**Phosphodiesterase Type 5 inhibitors.**

Utility of PDE5 inhibitors for treatment of BPH are upcoming .There are several mechanism supporting its use in treatment for BPH-1.Nitric oxide staining nerves are abundant in prostate which means its inhibitors 1.should relax prostatic smooth muscles  
2. endothelin inactivation 3.decrease in autonomic

hyperactivity 4.reducing pelvic ischemia.

Initial data support the clinical benefits of PDE5 inhibitors (sildenafil,tadalafil, vardenafil) for treatment of LUTS secondary to BPH .Four large trials(25-28) have demonstrated that this class of drugs improve LUTS in men with BPH .However none of these studies showed meaningful changes in objective indices of outlet obstruction including uroflowmetric parameters or post void residual volume.

Further investigations are required to assess its utility for primary treatment of BPH/LUTS efficacy of combination with an alpha blocker and or 5ARI and durability of effectiveness.

**Intra prostatic Botulinum Toxin Type A.**

Botulinum toxin type A (BoNT-A)acts irreversibly at cholinergic synapses to block the release of neurotransmitter acetylcholine resulting in decrease of target muscle tone (29) ,thus it may relieve LUTS secondary to BPH by decreasing smooth muscle tone, inhibiting secretory function of prostate and inhibiting sensory afferents that may be mediating LUTS via unrecognised mechanism .Majority of clinical studies with (BoNT-A) in men with LUTS/BPH were small and not randomised or placebo control yet showed statistical significance in both international prostatic symptom scores as well uroflowmetric parameters(30).Long term safety needs to be assessed ,intraprostatic BoNT-A is not yet validated by FDA .It could be useful in patients with BPH/LUTS refractory to medical therapy and not suitable for surgery.

**Gonadotropin -Releasing Hormone (GnRH) Antagonists.**

GnRH agonists reduce the volume of BPE by lowering serum and intraprostatic testosterone and dihydrotestosterone levels. These results in some modest clinical benefits related to improvements in LUTS. The primary disadvantages of GnRH agonists are their

associated immediate and long-term adverse effects due to induction of castrate levels of testosterone. The initial rationale for GnRH antagonists in treatment of BPH/LUTS was the opportunity to titrate serum testosterone to a level that would reduce prostate volume without causing adverse effects.

A small, open-label study with the GnRH antagonist cetrorelix acetate demonstrated that short-term administration of the drug was associated with long-term improvement in LUTS and decreased prostate volume.<sup>35</sup> gm (31). A phase II, randomised, placebo-controlled study in men with BPH/LUTS conducted in Eastern Europe demonstrated promising results (32). The improvement in IPSS and peak flow rate over placebo observed throughout the duration of study was comparable with that observed with  $\alpha$ -blockade. But phase III randomised trial of the drug did not show statistically significant benefit in improving IPSS and peak flow rates (33).

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#### NX-1207.

NX-1207 is a new drug under investigation for treatment of symptomatic BPH. NX-1207 has been suggested to elicit a proapoptotic effect on the prostate<sup>(34)</sup>. The drug is directly injected into prostate as a single administration. In clinical trials it has shown improvement in LUTS exceeding that of all other medical therapies currently marketed for treatment of BPH. Phase III studies are underway to define true efficacy, safety, and mechanism of action of this novel approach.

#### Conclusion.

With better understanding of pathophysiology of BPH the line of management has improved. The medical management has come down to two established options at present time i.e. either monotherapy with  $\alpha$ -blockers or combined therapy of  $\alpha$ -blockers and 5 ARIs. Both these modalities have shown to reduce the disease progression and improve symptomology significantly.