

# Hormonal manipulation of lower urinary tract symptoms secondary to benign prostatic obstruction

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## ABSTRACT

Although the etiology of lower urinary tract symptoms (LUTS) is often multifactorial, a significant proportion of men over the age of 50 suffer from benign prostatic obstruction (BPO) secondary to benign prostatic hyperplasia. Prostate, being an androgen responsive organ is dependent on the male sex hormone, testosterone, for growth. Thus, treatment strategies that manipulate the levels of circulating hormones that influence the level of testosterone and/or prostatic growth represent an important potential option for patients suffering with troublesome LUTS due to BPO. Despite this, the only hormonal treatment that is currently used in daily clinical practice is the 5-alpha reductase inhibitor. In this article, we review the current evidence on the use of the 5-alpha reductase inhibitors finasteride and dutasteride. We also discuss new emerging hormonal manipulation strategies for patients with LUTS secondary to BPO.

**Key words:** 5-alpha reductase inhibitors, benign prostatic hypertrophy, benign prostatic obstruction, gonadotropin hormone releasing hormone, growth hormone releasing hormone, lower urinary tract symptoms, luteinizing hormone releasing hormone

## INTRODUCTION

Benign prostatic hyperplasia (BPH) is the most common cause of benign prostatic obstruction (BPO) and subsequent lower urinary tract symptoms (LUTS) in men over the age of 50.<sup>[1]</sup> BPH is the pathological proliferation of glandular and stromal tissues within the prostate and results in one of the most common clinical problems in urology and its symptoms can have severe adverse effects on the quality-of-life of patients. Whilst the exact etiology of LUTS is complex and multifactorial<sup>[2]</sup> [Figure 1], sex steroids, neuropeptides and inflammatory cytokines have

been implicated in the development and progression of BPH.<sup>[1,3]</sup> BPH may cause symptoms if the enlarging prostate impinges upon the prostatic urethra causing BPO. Broadly, symptoms can be classified into either obstructive (weak stream, hesitancy, intermittency, incomplete bladder emptying) or storage (frequency, urgency, nocturia) in nature.<sup>[4,5]</sup> A number of questionnaires have been developed and validated to allow urologists to objectively monitor disease progression and regression following treatment of which, the most common in clinical use today is the International Prostate Symptom Score.<sup>[6]</sup>

For men with BPO who develop bothersome LUTS or complications such as urinary retention, there are a number of therapeutic options, which include watchful waiting, medical and surgical approaches. Medical treatments using pharmacological agents such as alpha-1 adrenoreceptor antagonists (alpha blockers) and 5-alpha reductase inhibitors are the cornerstone of treatment of men with LUTS secondary to BPO. Surgical management, for example transurethral resection of the prostate or Holmium laser enucleation of the prostate, is generally reserved for men who experience complications or have LUTS, which are refractory to medical treatment.

In this article, we review the current hormonal manipulation strategies that exist to control LUTS secondary to BPO and

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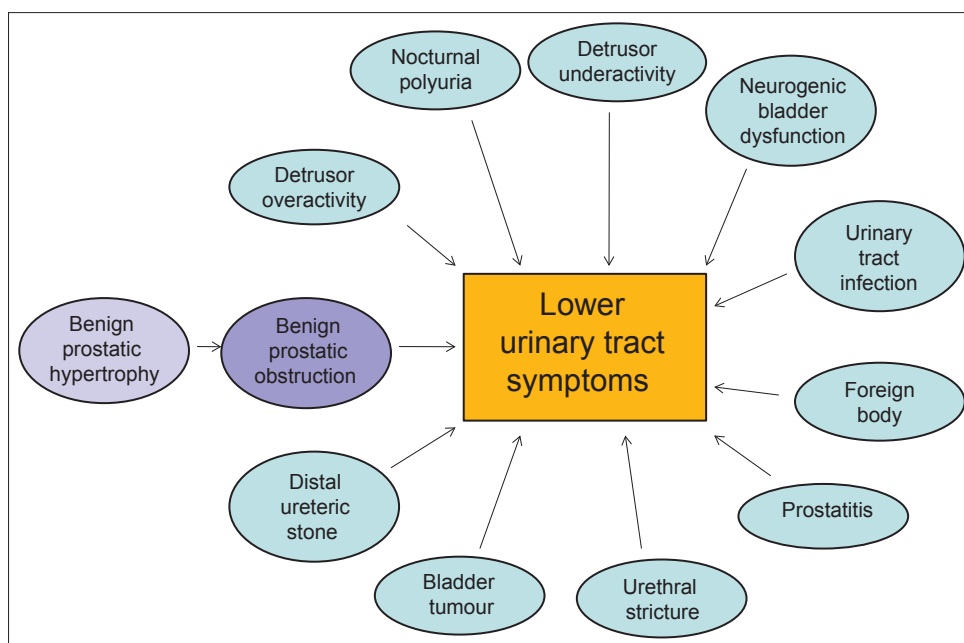


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**Figure 1:** Multifactorial etiology of lower urinary tract symptoms. Benign prostatic obstruction is only one of the many etiologies of lower urinary tract symptoms. Adapted from Oelke M, Bachmann A, Descaseaud A, Emberton M, Gravas S, Michel MC, *et al.* EAU guidelines on the treatment and follow-up of non-neurogenic male lower urinary tract symptoms including benign prostatic obstruction. *Eur Urol* 2013;64:118-40 with permission from Elsevier

also examine some of the novel agents that are currently being developed for use in this field.

## HORMONAL CONTROL OF THE MALE LOWER URINARY TRACT

Before we discuss the various hormonal strategies for treating men with LUTS secondary to BPO, it is worthwhile reviewing the basic hormonal physiology of the male lower urinary tract. Testosterone, the main sex steroid hormone in men is produced primarily in the testes with a small amount also produced from the adrenal glands and is under the regulation of the hypothalamus-pituitary-gonadal axis<sup>[7]</sup> [Figure 2]. Gonadotropin releasing hormone (GnRH) is produced in the hypothalamus and is secreted to the anterior pituitary gland in a pulsatile manner through the hypophyseal portal vein, resulting in the production of luteinizing hormone (LH) and follicle stimulating hormone (FSH). GnRH has a half-life of 5-7 min and is almost completely removed on the first pass through the pituitary gland by receptor internalization or enzymatic breakdown. Known modulators of GnRH secretion include prostaglandins, catecholamines, opioids and feedback regulation by LH, FSH and testosterone.

LH is released into the systemic circulation from the anterior pituitary gland and travels to the testes, resulting in the stimulation of the interstitial cells of Leydig to produce testosterone. In total, a typical healthy adult male would produce approximately 5 g of testosterone per day, of which 2% would be found as the biologically active free or unbound form. The other 98% is bound to the sex hormone binding globulin in blood and is thereby rendered inactive.

In the prostate, testes, epididymis and seminal vesicles, testosterone is converted by the enzyme 5-alpha reductase to the more metabolically potent dihydrotestosterone (DHT). 5-alpha reductase exists in three isoforms, Types I to III and their distribution throughout the body varies with age.<sup>[8]</sup> Reduction of testosterone to the more metabolically active DHT is required for the action of testosterone in most peripheral tissues, but not in the testes.<sup>[9]</sup> In prostate, both testosterone and DHT act on the androgen receptor of prostate cells to induce proliferation.<sup>[3]</sup>

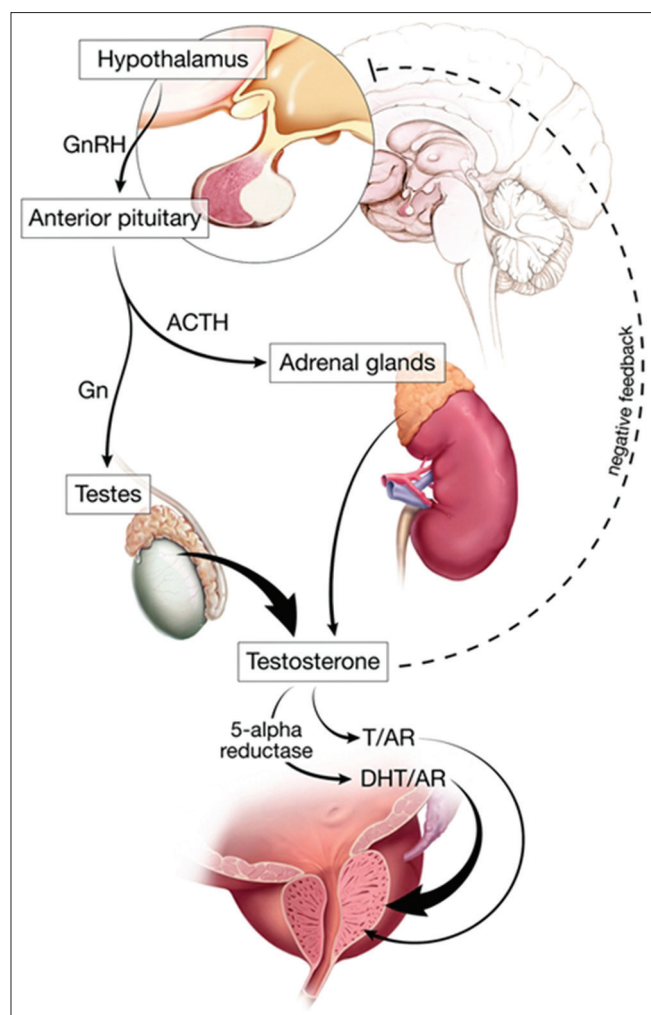
## CURRENT HORMONAL MANIPULATION STRATEGIES OF LUTS SECONDARY TO BPO

### Alpha-1 adrenoreceptor antagonists

Although treatment with alpha-1 adrenoreceptor antagonists (alpha blockers) is strictly speaking not a hormonal treatment, it is worth a brief mention here due to its importance and popularity of use for control of LUTS in men. Alpha-1 adrenoreceptors are the major regulators of smooth muscle contraction and are found concentrated around the male bladder neck and intra-prostatic urethra.<sup>[10]</sup> Alpha-1 adrenoreceptor antagonists work by blocking the binding of catecholamines to the receptor, resulting in the relaxation of the smooth muscle at the bladder neck and prostatic urethra. The most commonly prescribed drugs in this category are terazosin, doxazosin, tamsulosin, alfuzosin and silodosin. Abnormal (retrograde) ejaculation is the most commonly reported side-effect of this class of drug.<sup>[11]</sup>

### 5-alpha reductase inhibitors

In the early 1990s, systemic anti-androgen therapy was shown



**Figure 2:** The Hypothalamus-Pituitary-Gonadal Axis. Gonadotropin releasing hormone is produced in the hypothalamus which in turn stimulates the anterior pituitary gland to produce luteinizing hormone/follicle stimulating hormone and adrenocorticotropic hormone. LH and FSH travel in the systemic circulation to the testes where they are involved in the production of testosterone and spermatogenesis by stimulation of Leydig and Sertolicells respectively. ACTH on the other hand travels to the adrenal gland where it stimulates the production of corticosteroids. Re-used from Aragon-Ching JB, Williams KM, Gulley JL. Impact of androgen-deprivation therapy on the immune system: Implications for combination therapy of prostate cancer. *Front Biosci* 2007;12:4957-71 with permission from frontiers in bioscience

to decrease the size of prostate in men by approximately 30-40%.<sup>[12]</sup> As 5-alpha reductase converts circulating testosterone to the more biologically active DHT, it was postulated that inhibiting 5-alpha reductase would decrease DHT levels within the prostate cells, leading to a decrease in prostatic volume.<sup>[13-15]</sup> In 1992, finasteride became the first 5-alpha reductase inhibitor to be approved by the United States Food and Drug Administration for the treatment of men with LUTS secondary to BPH, followed shortly by dutasteride. Although finasteride has an antagonistic effect solely on the Type II isoenzyme of 5-alpha reductase, dutasteride has antagonistic activity against both Type I and II 5-alpha reductase isoenzymes and also has a longer half-life.

In 1998, the finasteride long-term efficacy and safety study

group presented the results of a double-blind, randomized, placebo-controlled study of 3,040 men with moderate to severe LUTS with an enlarged prostate who were treated with 5 mg of finasteride daily or placebo for 4 years.<sup>[16]</sup> The study revealed that men treated with finasteride experienced improved urinary symptoms, reduced prostatic volume, decreased need for bladder outflow surgery and were less likely to develop acute urinary retention compared with the cohort given placebo. In a separate study, finasteride was also shown to be effective at delaying the clinical progression of LUTS secondary to BPH in patients with larger prostates (30 cm<sup>3</sup> and greater) compared with those with smaller prostates.<sup>[17]</sup>

### *Finasteride versus dutasteride*

In 2011, the results of the Enlarged Prostate International Comparator Study was published.<sup>[18]</sup> This study was a large, multi-center, double-blind, randomized control trial of men aged 50 years and above who had a clinical diagnosis of BPH. In total, 1,630 patients enrolled into the study of which 813 patients were randomized to receive dutasteride 0.5 mg daily and 817 patients were randomized to the arm receiving 5 mg finasteride daily. All patients had a 4-week placebo run-in period before randomization and were followed-up for 48 weeks with an optional 24 month open label phase with 0.5 mg dutasteride given once daily. The results showed that both drugs were equally effective in reducing prostatic volume and resulted in a similar reduction in the mean American Urological Association Index Score. Adverse effects were similar between the two types of 5-alpha reductase inhibitors and included erectile dysfunction, decreased libido and ejaculatory dysfunction.

### *Combination therapies using alpha-1 adrenoreceptor antagonists and 5-alpha reductase inhibitors*

The Medical Therapy of Prostatic Symptoms trial was a double-blind, randomized controlled trial, comparing doxazosin, finasteride and a combination of the two against a placebo in 3,047 men of at least 50 years of age with LUTS over a mean follow-up period of 4½ years.<sup>[19]</sup> The study revealed that a combination of finasteride and doxazosin was associated with a significantly better outcome than placebo or either agent alone in reducing the clinical progression of BPH. The combined use of finasteride and doxazosin was therefore shown to decrease the severity of LUTS, risk of developing acute urinary retention and the likelihood of needing a surgical procedure to relieve troublesome LUTS.

In a similar multi-center, double-blind, randomized controlled trial of 4,844 men of age 50 years and above, with a clinical diagnosis of BPH and bothersome LUTS with prostatic volumes above 30 cm<sup>3</sup>, men were randomized to receive daily tamsulosin 0.4 mg, dutasteride 0.5 mg or a combination of both (CombAT trial).<sup>[20]</sup> After 4 years of follow-up in this group of men at high risk of progression of their BPH, combination therapy was shown to be significantly superior to either monotherapy at reducing

the risk of BPH clinical progression and at reducing urinary symptoms. Compared with monotherapy with the alpha-1 adrenoreceptor antagonist tamsulosin, but not dutasteride monotherapy, combination treatment significantly reduced the relative risk of acute urinary retention or BPH related surgery. In keeping with these findings, the European Association of Urology guidelines on non-neurogenic LUTS in men currently recommends the combination therapy approach of an alpha-1 adrenoreceptor antagonist and 5-alpha reductase inhibitor in men with bothersome LUTS and a prostatic volume of greater than 30 cm<sup>3</sup>.<sup>[2]</sup>

## NOVEL HORMONAL THERAPIES FOR TROUBLESOME LUTS DUE TO BPO

Although currently available medical therapies can significantly improve troublesome LUTS due to BPO, not all patients respond well to these therapies. Thus, further novel hormone therapies are currently being developed.

### GnRH antagonists

GnRH antagonists work by directly competing with GnRH for receptors on gonadotroph cell membranes thereby inhibiting gonadotropin secretion with the immediate suppression of testosterone. In addition to the hypothalamus, GnRH receptors have been found to be expressed in two-thirds of BPH tissue samples.<sup>[21]</sup> Initial efforts at developing GnRH antagonists were hampered by the occurrence of severe histamine-mediated anaphylactic reactions in this class of drug. Cetrorelix, a decapeptide analogue of GnRH with a neutral hydrophilic D-ureidoalkyl amino acid at position 6 rendered this compound free of oedematogenic and anaphylactoid reactions and is the most extensively studied GnRH antagonist against BPH to date.

*In vitro*, work by Siejka *et al.* demonstrated that cetrorelix inhibited the proliferation of BPH prostate cells (BPH-1 cell line) by decreasing growth factor levels of insulin-like growth factor (IGF)-1, IGF-2 and fibroblast growth factor-2 (FGF-2), resulting in the inhibition of the activation of transcription factor signal transducer and activator of transcription 3 (STAT3) and down regulation of the expression of the GnRH and alpha-1 adrenoreceptors in prostatic tissue.<sup>[22]</sup> *In vivo*, work conducted on rat models of BPH demonstrated that cetrorelix given at doses lower than required to induce castration levels of testosterone still significantly reduced the weight of the prostate. Furthermore, in the prostate of experimental rats, the levels of inflammatory cytokines and growth factors were also found to be reduced at the transcript level (mRNA), supporting the recent notion that BPH has a significant inflammatory component.<sup>[23]</sup>

In clinical studies, Gonzalez-Barcena *et al.*<sup>[24]</sup> evaluated the effect of cetrorelix given twice daily for 4 weeks in 11 patients with bothersome LUTS due to BPH. The authors demonstrated that cetrorelix administration

resulted in a significant reduction in prostatic volume and improvement in clinical symptoms. Furthermore, testosterone levels in these patients also fell below castration levels rapidly, usually within 6-12 h. In a separate study of 13 men with moderate to severe LUTS secondary to BPH, cetrorelix given once a day for 2 months significantly improved IPSS scores and quality-of-life scores, decreased prostatic volume and increased peak urinary flow rate. Sexual function was also found to be enhanced at 18 months.<sup>[25]</sup> Thus, it appears that cetrorelix is well-tolerated and produces long-term improvement in LUTS.

### Growth-hormone-releasing hormone antagonists

GHRH is a human neuropeptide synthesized in the hypothalamus and acts on receptors in the anterior pituitary gland (adenohypophysis) to stimulate the production of somatotropin (growth hormone).

A study by Siejka *et al.*<sup>[26]</sup> demonstrated that GHRH acts as a growth stimulus in a cell line model of BPH (BPH-1 cell line) known to express GHRH receptor. Conversely, GHRH antagonist compounds had an inhibitory effect on the proliferation of BPH-1 cells *in vitro*. Furthermore, Western blot analysis revealed that GHRH acts by phosphorylating the ERK1/2 and JAK/STAT3 intracellular pathways whilst the use of GHRH antagonists reversed this effect. When the authors repeated this same experiment using GHRH receptor null HeLa cells instead, GHRH stimulation failed to induce phosphorylation of ERK1/2 and JAK/STAT3 pathways, confirming that GHRH acts by stimulating the GHRH receptor.

More recently, *in vivo* work on a rat model of BPH has also shown that GHRH antagonists (JMR 132, MIA-313 and MIA 459) reduced the weight of the prostate of laboratory rats significantly.<sup>[27]</sup> This reduction in prostatic weight was associated with significant changes in the expression of genes related to growth factors, inflammatory cytokines and signal transduction. In addition, reduction of inflammatory proteins such as IL-1  $\beta$ , NF- $\kappa$ B/p65, and cyclooxygenase-2 was also noted. Thus, it is postulated that GHRH antagonists lower prostatic weight in experimental BPH by causing direct inhibition of GHRH receptors on prostate cells.

### Combination therapy using GnRH and GHRH antagonists

Due to the potential roles of GnRH and GHRH in BPH development, Rick *et al.*<sup>[28]</sup> evaluated *in vivo* the combined effect of GnRH and GHRH antagonists using a rat BPH model. When GnRH and GHRH antagonists were used in combination, it resulted in a further 10% reduction of prostatic volume compared with using either of these agents on its own. Thus, combination therapy of GnRH and GHRH antagonists may emerge as a novel treatment strategy for men suffering from LUTS due to BPO in the future.



## CONCLUSION

Current hormonal treatment of male LUTS is limited to the use of 5-alpha reductase inhibitors. These have been shown to improve urinary symptoms and to reduce the risk of disease progression. A number of new hormonal treatments are currently being investigated such as GnRH and GHRH antagonists. Although preliminary work has yielded exciting results, so far the vast majority of these have been small and non-randomized studies. Thus, further high quality, multi-center, double-blind randomized controlled trials are urgently required before the true clinical utility of these novel hormonal treatment modalities can be fully established.

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