Current Medical Treatment for Benign Prostatic Hyperplasia/Lower Urinary Tract Symptoms

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INTRODUCTION

Benign prostatic hyperplasia (BPH) is common among men over 50 years of age. It has a negative impact on quality of life (QoL) and reduces the sense of well being. Lower urinary tract symptoms (LUTS) include urinary frequency, urgency, weak stream and nocturia, and are common in elderly men and have a negative impact on QoL. LUTS are usually associated with BPH [1]. Recently, significant progress has been made in the medical management of BPH. In this article, we review the current pharmacological treatment of BPH/LUTS.

α-ADRENERGIC BLOCKERS

α-Adrenergic blockers are the most commonly used medical treatment for BPH. BPH has 2 physiological components: a static component related to increased prostate size and a dynamic component related to increased prostate smooth muscle tone. α_1-Adrenoceptors maintain prostate smooth muscle tone. α_1-Adrenoreceptor antagonists act on prostate and urethral smooth muscle to reduce the dynamic component of urethral resistance and thus alleviate voiding symptoms [2]. α-Adrenergic blockers relieve not only obstructive but irritative symptoms in patients with BPH, although the underlying mechanisms of the relief of irritative symptoms are still unknown. Chapple et al evaluated 135 patients with symptomatic urodynamically-confirmed obstructive BPH treated for 12 weeks with either doxazosin (67 patients) or placebo (68 patients) after an initial 2 week baseline evaluation. Twelve weeks of therapy with doxazosin resulted in significant improvements in hesitancy, impaired urinary stream, nocturia and urgency. Frequency improved with doxazosin therapy [3]. The study proved that an α blocker is effective in relieving both obstruction and irritative symptoms.

The role of the sympathetic nervous system in detrusor function is still unclear. Chou et al mapped the regional distribution of α_1 and β-adrenergic receptors (ARs) in rabbit ventral and dorsal bladder, and characterized the α_1-AR subtypes responsible for norepinephrine induced contraction of rabbit dorsal detrusor smooth muscle. Chou et al found responses to adrenergic stimulation included: (1) the dorsal and ventral dome, where β-ARs predominate, (2) the ventral detrusor, where β-ARs predominate, (3) the dorsal detrusor, where α_1-ARs predominate, and (4) the dorsal and ventral bladder neck, where α_1-ARs predominate. The authors mentioned a predominance of α_1-AR in human dorsal detrusor could be responsible for the irritative symptoms associated with BPH. Studies are presently underway to determine if heterogeneity of detrusor responsiveness to sympathomimetics also occurs in the human bladder [4].

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CURRENT α-ADRENERGIC ANTAGONIST DRUGS FOR THE TREATMENT OF BPH

Non-selective drugs

- Phenoxybenzamine and Thymoxamine

Selective drugs

α_1

- Short acting: IR Alfuzosin, Indoramin, Prazosin
- Long acting: SR Alfuzosin, Doxazosin, Tamsulasin, Terazosin [5]

Phenoxybenzamine

Phenoxybenzamine is a nonselective α blocker, and has been shown to improve symptoms and maximum urinary flow rate [6]. Due to a high incidence and severity of adverse events, the clinical application of phenoxybenzamine is limited.

Prazosin

Prazosin is a very potent and selective α_1-adrenergic antagonist. Its affinity for the α_1-receptor is 1000-fold greater than that for the α_2-receptor. The most important adverse effect of prazosin is postural hypotension, although stuffy nose, headache and retrograde ejaculation may also occur [7]. Continuous use for a long period decreases efficacy due to tachyphylaxis or a progressive increase in prostate size and, hence, requires increase in dosage [8,9].

Alfuzosin

Alfuzosin is a quinozoline-based α_1-receptor antagonist with similar affinity to all α_1-receptor subtypes. It has been used extensively in treating BPH [10,11]. De Nunzio et al analyzed the clinical and 24-hour urinary flow efficacy of alfuzosin 10 mg once daily, by means of the International Prostate Symptom Score (I-PSS) and home-based uroflowmetry (P-Flow) measurement, in patients with LUTS related to BPH. Overall, 328 urinary flows were recorded and evaluated, with an average of 27 flows per patient. A statistically significant improvement was observed in mean maximum flow and urinary voiding volume. They concluded that the alfuzosin 10 mg once daily dosage showed a significant improvement in I-PSS as well as a significant improvement in urinary flow parameters (Qmax and urinary voiding volume) lasting for 24 hours in patients with LUTS [12].

Terazosin

Terazosin is the most extensively investigated α_1 blocker for BPH. It has high specificity for the α_1-receptor and was originally developed for the treatment of hypertension. Its half-life is longer than that of prazosin and it can be given once a day [13]. Only about 10% of terazosin is excreted unchanged in the urine. Doses of 10 mg/d may be required for maximal effect on BPH [14]. Terazosin therapy does not affect blood pressure control in patients receiving concurrent antihypertensive medication [15,16].

A multicenter, double-blind, randomized, placebo-controlled study of once-a-day terazosin to patients with symptomatic BPH was conducted by Lepor and associates [17]. Of the patients, 237 completed the 4-week single-blind placebo lead-in and 12-week double-blind treatment periods. The 10 mg terazosin group exhibited significantly greater increases in peak and mean urinary flow rates than the placebo group. The authors stated their study demonstrates the safety and efficacy of terazosin for the treatment of BPH.

Doxazosin

Like terazosin, doxazosin is a selective α-adrenergic antagonist originally developed as an antihypertensive [18]. Doxazosin should be given initially at a dosage of 1 mg/d and titrated over a period of 1-2 weeks to a maximum dose of 8 mg/d. Titration reduces the risk of first dose cardiovascular effects [7].

Doxazosin Gastrointestinal Therapeutic System (GITS) is a new controlled-release formulation. It has an altered pharmacokinetic profile, which allows a higher initial dosage to be used than with the standard formulation and less titration steps to reach a clinically effective dosage [19]. Anderson et al conducted a study to assess the effects of doxazosin GITS 4 or 8 mg once daily, doxazosin standard 1 mg to 8 mg once daily, and placebo, in 795 men with BPH. Both doxazosin GITS and doxazosin standard significantly improved the symptoms of BPH, with a greater improvement observed earlier following treatment with doxazosin GITS than with doxazosin standard. The overall incidence of adverse events was similar among patients treated with doxazosin GITS and placebo, and slightly higher in those on doxazosin standard. They concluded that a therapeutic effect equivalent to that of doxazosin standard was achieved with doxazosin GITS with fewer titration steps, in a manner that appeared to be better tolerated [20].

Tamsulosin

Tamsulosin is a α_1-receptor antagonist with some selectivity for the α_{1A} receptor subtype compared to the α_{1B} receptor subtype. Tamsulosin is the most potent α_1 antagonist investigated for BPH [21]. Tamsulosin is urospecific and exerts its effect primarily on the lower urinary tract. It is well absorbed and has a half-life of 5 to 10 h [7].

The efficacy and safety of tamsulosin has been investigated in four multicenter, randomized, double-blind, placebo-controlled studies. Lepor et al evaluated the long-term efficacy and safety of once daily tamsulosin (0.4 mg and 0.8 mg) in 618 patients with BPH. This trial extended a 13-week, Phase III multicenter placebo-controlled, double-blind outpatient trial. Significant improvements were observed in Qmax for both tamsulosin groups but not for the placebo group. Tamsulosin at both dosages was well tolerated as maintenance therapy. Clinically significant orthostatic hypotension was not observed [22].

Subtypes of α_1 antagonists

α_1ARs mediate actions of norepinephrine and epinephrine through three α_1AR subtypes (α_{1A}, α_{1B} and α_{1D}) [23]. Nonsubtype selective α_1AR antagonists relax prostate smooth muscle, and relieve obstructive and irritative symptoms [24-27]. Prostate smooth muscle relaxation is mediated by α_{1A}AR [28] and consequently subtype selective α_{1A}AR antagonists increase urine flow in BPH [29]. However, α_{1A}AR antagonists do not appear to relieve irritative symptoms [29]. Gu et al investigated the effect of the α_{1A}AR antagonist 5-methyl urapidil (5MU) vs the $\alpha_{1A/1D}$AR antagonist tamsulosin on urinary frequency in obstructed rats. They found that urinary frequency is increased in rats with a bladder mass greater than 500 mg. The combined $\alpha_{1A/1D}$AR antagonist tamsulosin decreases urinary frequency more than the α_{1A}AR selective antagonist 5MU [30]. This finding supports the hypothesis that α_{1D}AR is important for mediating irritative symptoms.

5α-REDUCTASE INHIBITORS (ANDROGEN SUPPRESSION)

Androgens are responsible for prostate growth and maintenance. The deprivation of androgen decreases the size of the prostate and resistance to outflow through the prostatic urethra, and then improves the ability to urinate. The design and chemistry of 5α-reductase inhibitors has been thoroughly studied and reviewed [31]. Two 5α-reductase inhibitors (finasteride and dutasteride) are now approved for human use.

Finasteride

Finasteride was the first one approved for use by the Food and Drug Administration (FDA) for treatment of BPH. Finasteride inhibits the type 2 isoenzyme of 5α-reductase, which is present in high levels in the prostate. The definitive multicenter trial was performed by the PLESS (Finasteride Long-Term Efficacy and Safety Study group) and was reported in 1998 [32]. At the end of the study, patients treated with finasteride had a significantly higher decrease in American Urological Association Symptom Score (AUASS) and a significantly higher increase in Qmax compared with placebo. Prostate volume also decreased by an average of 18% in the finasteride group compared with an increase of 14% in the placebo group. Marberger et al [33] compared the long-term effects of finasteride (5 mg/day) and placebo in patients with moderate symptoms of BPH. A 2-year double-blind, randomized, placebo-controlled multicenter study was conducted on patients aged 50 to 75 years. Of the 3,270 men enrolled, 3,168 contributed data to the safety analysis. Significantly greater improvement with finasteride compared to placebo was observed at 12 and 24 months for total symptom score, obstructive symptom score, maximal urinary flow rate and prostate volume (mean -14.2% vs +5.4% at 12 months, $p < 0.01$; -15.3% vs +8.9% at 24 months, $p < 0.001$). They observed that finasteride causes long-term symptomatic improvement and reduced the risk of acute urinary retention or surgery.

Finasteride is generally well tolerated, with patients reporting decreased libido (6.4% vs 3.4% in placebo group), impotence (8.1% vs 3.7%), decreased ejaculate (3.7% vs 0.8%), and a <1% incidence of ejaculation disorders, rash and breast enlargement or tenderness [32].

Dutasteride

Dutasteride, a type 1 and type 2 5α -reductase inhibitor, was approved for the treatment of BPH by the FDA in 2002. Dutasteride, because of its dual inhibition of 5α-reductase, reduces serum

dihydrotestosterone (DHT) levels by >90% [34].

Desgrandchamps et al assessed the improvements in symptoms, QoL, discomfort and satisfaction in patients with symptomatic BPH treated with dutasteride 0.5 mg/day for 24 weeks. This was a prospective, multicenter, open-label study. Of the 366 patients assessed, 72.5% achieved at least a 3-point reduction in I-PSS at 24 weeks; the I-PSS decreased from 15.3 at baseline to 10.2 at 12 weeks and 9.1 at 24 weeks. There were significant ($p<0.001$) decreases in all the individual I-PSS items at 12 and 24 weeks. They concluded that dutasteride treatment for 24 weeks significantly improved BPH symptoms, QoL, and patient discomfort and satisfaction [35]. In terms of the reduction of prostate volume, Roehrborn et al conducted a study of 4,325 men (2951 completed), and the total prostate and transition zone volumes were reduced by a mean of 25.7% and 20.4%, respectively ($p<0.001$) [36].

The adverse effects from dutasteride are similar to those from finasteride. In the study by Desgrandchamps et al, there were adverse events related to the study drug in 77 (19%) patients; of these, 11% were sexual disorders (7% erectile dysfunction (ED), 4% decrease in libido and <1% ejaculatory disorders), 4% gastrointestinal disorders (mainly abdominal pain and diarrhea) and 2% gynecomastia (including mammary tension) [35].

5α-reductase inhibitors reduce the prostate volume and so cause an easing of irritative symptoms. The effect of 5α-reductase inhibitors on detrusor function is still to be determined.

COMBINATION THERAPY (α-ADRENERGIC BLOCKERS + 5α-REDUCTASE INHIBITORS)

Traditionally, α-adrenergic blockers are used for relief of LUTS as a result of BPH and are known for their quick onset of action. 5α-reductase inhibitors have proven useful for the prevention of BPH progression by reducing prostate volume. Recent studies have shown that the combination of an α-adrenergic blocker and a 5α-reductase inhibitor has significantly better efficacy than either drug alone or placebo [37].

McConnell et al published their report on combination therapy in 2003. They conducted a long-term double-blind trial (mean follow-up 4.5 years) involving 3,047 men to compare the effects of placebo, doxazosin, finasteride and combination therapy on the clinical progression of BPH. The reduction in risk associated with combination therapy was significantly greater than that associated with doxazosin or finasteride alone. The risks of acute urinary retention and the need for invasive therapy were significantly reduced by combination therapy and finasteride but not by doxazosin. Doxazosin, finasteride and combination therapy each resulted in significant improvement in symptom scores, with combination therapy being superior to both doxazosin and finasteride alone. This study concluded that the combination therapy and finasteride alone reduced the long-term risk of acute urinary retention and the need for invasive therapy [38].

ANTIMUSCARINICS

The incidence of overactive bladder (OAB) associated with bladder outlet obstruction (BOO) is 30%-60% .The symptoms of the two are similar and overlapping. Detrusor overactivity has been modeled by partial BOO in several animal species. Schroder et al observed increased sensitivity to muscarinic receptor stimulation in the bladders of partial BOO rats; muscarinic receptor blockade caused a significant decrease in the contractile response in all groups [39]. In patients with BPH, denervation has been found histologically and functionally *in vitro* [40,41]. It has been suggested that detrusor hypersensitivity to acetylcholine or increased electrical coupling in these areas causes uncoordinated contractions [42].

Antimuscarinics decrease the contractile response of the detrusor muscle of OAB patients. In a patient with BPH/LUTS and no evidence of BOO, particularly if the predominant symptoms are those of OAB, it is appropriate to treat them with an antimuscarinic agent [3]. Symptom scores and urodynamic studies help us in the differential diagnosis of men with LUTS [43].

COMBINATION THERAPY (α_1-ADRENERGIC ANTAGONIST AND ANTIMUSCARINIC ANTAGONIST)

Medical treatment that targets the prostate (α_1-receptor antagonists and 5α-reductase inhibitors) often fails to alleviate OAB symptoms and may not be the most appropriate therapy for men with storage LUTS [44]. Multiple studies have shown that antimuscarinic therapy alone or in combination with α_1-receptor antagonists improves OAB symptoms in men with or without BOO. Athanasopoulos et al published the results of combination treatment with an α_1-blocker (0.4 mg tamsulosin orally once a day) plus an anticholinergic (2 mg tolterodine orally twice daily) for BOO in 2003. They concluded that the combination treatment with an α_1 -blocker plus an anticholinergic improves QoL in patients with BOO and concomitant detrusor instability [45]. The proposed combination therapy appears to be an effective and relatively safe treatment option for patients with BOO and detrusor instability.

Similar results were reported by several other studies. Lee et al evaluated the efficacy and safety of a therapeutic modality involving propiverine combined with doxazosin in patients with OAB and benign prostatic obstruction. A total of 211 men 50 years of age or older with OAB symptoms and urodynamically proven BOO were randomized into 2 groups for an 8-week treatment: group 1 - doxazosin (4 mg once daily) only, group 2 -propiverine hydrochloride (20 mg once daily) plus doxazosin. Patient satisfaction rates were found to be significantly higher in group 2 than in group 1. This study reveals that combination therapy, consisting of α_1-adrenoreceptor antagonists with antimuscarinics, represents an effective and relatively safe treatment modality for selected patients with OAB coexisting with benign prostatic obstruction [46].

PHOSPHODIESTERASE-5 (PDE-5) INHIBITORS

The rationale for using PDE-5 inhibitors for the treatment of BPH patients originates from the following three observations: first, the prevalence of LUTS, BPH and ED increases with age; second, PDE-5 inhibition mediates smooth muscle relaxation in the lower urinary tract; and third, early clinical evidence demonstrates that PDE-5 inhibitors are successful in treating LUTS and ED [47].

The role of PDE-5s for treating BPH is poorly understood: reportedly, various PDE isoenzymes are expressed in the prostate and there are some clues that unspecific PDE inhibition can relax human prostate tissue [48]. Tinel et al evaluated the potential of sildenafil, vardenafil and tadalafil, all PDE-5 inhibitors used for treating ED, BPH and LUTS in animal studies. The mRNA expression of the PDE-5 was

determined in rat lower urinary tract tissues. The highest PDE-5 mRNA expression was in the bladder, followed by the urethra and prostate. PDE-5 inhibitors dose-dependently reduced the contraction of the isolated bladder, urethral and prostate strips. Their results show that PDE-5 inhibitors induced significant relaxation of these tissues and reduced the irritative symptoms of BPH/LUTS *in vivo* [49].

The efficacy of sildenafil for ED and LUTS in men was evaluated by McVary et al. This was a 12-week, double-blind, placebo-controlled study of sildenafil in men 45 years of age or older who scored 25 or less on the erectile function domain of the International Index of Erectile Function and 12 or more on the I-PSS. The 189 men receiving sildenafil had significant improvements in erectile function domain scores compared to the 180 men on placebo. The results showed that men on sildenafil had significant improvements in I-PSS ($p<0.0001$), Benign Prostatic Hyperplasia Impact Index ($p<0.0001$) and mean I-PSS QoL scores compared to those receiving placebo. Improved ED and LUTS were observed in the patients receiving sildenafil [50].

However, the lack of effect on urinary flow rates may mean that a new basic pathophysiology paradigm is needed to explain the etiology of LUTS [50].

CONCLUSIONS

Both BPH and LUTS are common in the elderly male population. With better understanding of the natural history and pathophysiology of BPH and LUTS, medical therapy plays a more important role than before. Both α_1-blockers and 5α-reductase inhibitors have been shown to be effective in clinical trials. Combination treatment of α_1-blockers plus antimuscarinics appears to be an effective and relatively safe treatment option for selected patients with OAB coexisting with benign prostatic obstruction. Careful history-taking and high quality urodynamic studies help us to select proper single or combination medical therapy for BPH and/or LUTS.

REFERENCES

1. Chapple CR, Smith D: The pathophysiological changes in the bladder obstructed by benign prostatic hyperplasia. Br J Urol 1994; **73**: 117-123.
2. Schwinn DA, Price DT, Narayan P: [alpha]$_1$-Adrenoceptor Subtype Selectivity and Lower Urinary Tract Symptoms. Mayo Clin Proc 2004; **79**:1423-1434.
3. Chapple RC: Pharmacological therapy of benign prostatic hyperplasia/lower urinary tract symptoms: An overview for the practicing clinician. BJU Int 2004; **94**:738-744.
4. Chou EC, Capello SA, Levin RM, Longhurst PA: Excitatory α_1-adrenergic receptors predominate over inhibitory α_1-receptors in rabbit dorsal detrusor. J Urol 2003; **170**:2503-2507.
5. Lepor H, Lowe FC: Evaluation and Nonsurgical Management of Benign Prostatic Hyperplasia. In: Walsh PC, Retic AB, eds. Campbell's Urology, 8th ed, Philadelphia, Saunders, 2002.
6. Caine M, Pfau A, Perlberg S: The use of alpha-adrenergic blockers in benign prostatic obstruction. Br J Urol 1976; **48**:255-263.
7. Garg G, Singh D, Saraf S, Saraf S: Management of benign prostate hyperplasia: An overview of alpha-adrenergic antagonist. Biol Pharm Bull 2006; **29**:1554-1558.
8. Hedlund H, Andersson KE, Ek A: Effects of prazosin in patients with benign prostatic obstruction. J Urol 1983; **130**:275-278.
9. Kirby RS, Coppinger SW, Corcoran MO, Chapple CR, Flannigan M, Milroy EJ: Prazosin in the treatment of prostatic obstruction. A placebo-controlled study. Br J Urol 1987; **60**:136-142.
10. Foglar R, Shibata K, Horie K, Hirasawa A, Tsujimoto G: Use of recombinant alpha 1-adrenoceptors to characterize subtype selectivity of drugs for the treatment of prostatic hypertrophy. Eur J Pharmacol 1995; **288**:201-207.
11. Kenny BA, Miller AM, Williamson IJ, O'Connell J, Chalmers DH, Naylor AM: Evaluation of the pharmacological selectivity profile of alpha 1 adrenoceptor antagonists at prostatic alpha 1 adrenoceptors: Binding, functional and in vivo studies. Br J Pharmacol 1996; **118**: 871-878.
12. De Nunzio C, Franco G, Leonardo C, Trucchi A, Tubaro A, Laurenti C: Effect of Once-Daily Alfuzosin on Urinary Symptoms and Flow Rate in Benign Prostatic Hyperplasia: A 24-Hour Home-Uroflowmetry Evaluation. Clin Drug Investig 2005; **25**:359-365.
13. Kyncl JJ: Pharmacology of terazosin: An alpha 1-selective blocker. J Clin Pharmacol 1993; **33**:878-883.
14. Wilde MI, Fitton A, Sorkin EM, Terazosin: A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in benign prostatic hyperplasia. Drugs Aging 1993; **3**:258-277.
15. Roehrborn CG, Oesterling JE, Auerbach S, et al: The Hytrin Community Assessment Trial study: A one-year study of terazosin versus placebo in the treatment of men with symptomatic benign prostatic hyperplasia. HYCAT Investigator Group. Urology 1996; **47**: 159-168.
16. Elhilali MM, Ramsey EW, Barkin J, et al: A multicenter, randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of terazosin in the treatment of benign prostatic hyperplasia. Urology 1996; **47**:335-342.
17. Lepor H, Auerbach S, Puras-Baez A, et al: A randomized, placebo-controlled multicenter study of the efficacy and safety of terazosin in the treatment of benign prostatic hyperplasia. J Urol 1992; **148**: 1467-1474.
18. Os I, Stokke HP: Effects of doxazosin in the gastrointestinal therapeutic system formulation versus doxazosin standard and placebo in mild-to-moderate hypertension. Doxazosin Investigators' Study Group. J Cardiovasc Pharmacol 1999; **33**:791-797.
19. Goldsmith DR, Plosker GL: Doxazosin gastrointestinal therapeutic system: A review of its use in benign prostatic hyperplasia. Drugs 2005; **65**:2037-2047.
20. Andersen M, Dahlstrand C, Hoye K: Double-blind trial of the doxazosin in the gastrointestinal therapeutic system, doxazosin standard, and placebo in patients with benign prostatic hyperplasia. Eur Urol 2000; **38**:400-409.
21. Foglar R, Shibata K, Horie K, Hirasawa A, Tsujimoto G: Use of recombinant alpha-1 adrenoceptors to characterize subtype selectivity of drugs for the treatment of prostatic hypertrophy. Eur J Pharmacol 1995; **288**:201-207.
22. Lepor H: Phase III multicenter placebo-controlled study of tamsulosin in benign prostatic hyperplasia. Tamsulosin Investigator Group. Urology 1998; **51**:892-900.
23. Michelotti GA, Price DT, Schwinn DH: Alpha-1 adrenergic receptor regulation: Basic science and clinical implications. Pharmacol Ther 2000; **88**:281-309.
24. Djavan B, Marberger M: A meta-analysis on the efficacy and tolerability of alpha1-adrenoceptor antagonists in patients with lower urinary tract symptoms suggestive of benign prostatic obstruction. Eur Urol 1999; **36**:1-13.
25. Guthrie RM, Siegel RL: A multicenter, community-based study of doxazosin in the treatment of concomitant hypertension and symptomatic benign prostatic hyperplasia: The Hypertension and BPH Intervention Trial (HABIT). Clin Ther 1999; **21**:1732-1748.
26. Kumar VI, Dewan S: Alpha adrenergic blockers in the treatment of benign hyperplasia of the prostate. Int Urol Nephrol 2000; **32**:67-71.

27. Michel MC, Bressel HU, Mehlburger L, Goepel M: Tamsulosin: Real life clinical experience in 19,365 patients. Eur Urol 1998; **34(Suppl 2)**:37-45.
28. Forray C, Bard JA, Wetzel JM, et al: The alpha 1-adrenergic receptor that mediates smooth muscle contraction in human prostate has the pharmacological properties of the cloned human alpha 1c subtype. Mol Pharmacol 1994; **45**:703-708.
29. Blue D, Zinner N, Grino P, Crager M, Ford A: RO700004, a selective α_{1A}-adrenoceptor antagonist, does not improve lower urinary tract symptoms in men with benign prostatic hyperplasia. J Urol suppl 2002; **167**:265.
30. Gu B, Reiter JP, Schwinn DA, et al: Effects of α_1-adrenergic receptor subtype selective antagonists on lower urinary tract function in rats with bladder outlet obstruction. J Urol 2004; **172**:758-762.
31. Li X, Chen C, Singh SM, Labrie F, Labire F: The enzyme and inhibitors of 4-ene-oxosteroid 5 alpha-oxidoreductase. Steroids 1995; **60**: 430-441.
32. McConnell JD, Bruskewitz R, Walsh P, et al: The effect of finasteride on the risk of acute urinary retention and the need for surgical treatment among men with benign prostatic hyperplasia. Finasteride Long-Term Efficacy and Safety Study Group. N Engl J Med 1998; **338**:557-563.
33. Marberger MJ: Long-term effects of finasteride in patients with benign prostatic hyperplasia: A double-blind, placebo-controlled, multicenter study. PROWESS Study Group. Urology 1998; **51**:677-686.
34. Roehrborn CG, Boyle P, Nickel JC, et al: Efficacy and safety of a dual inhibitor of 5-alpha-reductase types 1 and 2 (dutasteride) in men with benign prostatic hyperplasia. Urology 2002; **60**:434-441.
35. Desgrandchamps F, Droupy S, Irani J, Saussine C, Comenducci A: Effect of dutasteride on the symptoms of benign prostatic hyperplasia, and patient quality of life and discomfort, in clinical practice. BJU Int 2006; **98**:83-88.
36. Roehrborn CG, Boyle P, Nickel JC, Hoefner K, Andriole G: Efficacy and safety of a dual inhibitor of 5-alpha-reductase types 1 and 2 (dutasteride) in men with benign prostatic hyperplasia. Urology 2002; **60**:434-441.
37. Sandhu JS, Vaughan ED, Jr: Combination therapy for the pharmacological management of benign prostatic hyperplasia: Rationale and treatment options. Drugs Aging 2005; **22**:901-912.
38. McConnell JD, Roehrborn CG, Bautista OM, et al: Medical Therapy of Prostatic Symptoms (MTOPS) Research Group. The long-term effect of doxazosin, finasteride, and combination therapy on the clinical progression of benign prostatic hyperplasia. New Engl J Med 2003; **349**:2387-2398.
39. Schroder A, Uvelius B, Newgreen D, Andersson KE: Bladder overactivity in mice after 1 week of outlet obstruction. Mainly afferent dysfunction? J Urol 2003; **170**:1017-1021.
40. Levin RM, Haugaard N, O'Connor L, et al: Obstructive response of human bladder to BPH vs rabbit bladder response to partial outlet obstruction: A direct comparison. Neurourol Urodyn 2000; **19**:609-629.
41. Gosling JA, Gilpin SA, Dixon JS, Gilpin CJ: Decrease in the autonomic innervation of human detrusor muscle in outflow obstruction. J Urol 1986; **136**:501-504.
42. Mills IW, Greenland JE, McMurray G, et al: Studies of the pathophysiology of idiopathic detrusor instability: The physiological properties of the detrusor smooth muscle and its pattern of innervation. J Urol 2000; **163**:646-651.
43. De la Rosette JJ, Witjes WP, Schafer W, et al: Relationships between lower urinary tract symptoms and bladder outlet obstruction: Results from the ICS-"BPH" study. Neurourol Urodyn 1998;**17**:99-108.
44. Chapple CR, Roehrborn CG: A shifted paradigm for the further understanding, evaluation, and treatment of lower urinary tract symptoms in men: Focus on the bladder. Eur Urol 2006; **49**:651-658.
45. Athanasopoulos A, Gyftopoulos K, Giannitsas K, Fisfis J, Perimenis P, Barbalias G: Combination treatment with an α_1-blocker plus an anticholinergic for bladder outlet obstruction: A prospective, randomized, controlled study J Urol 2003; **169**:2253 -2256.
46. Lee KS, Choo MS, Kim DY, et al: Combination treatment with propiverine hydrochloride plus doxazosin controlled release gastrointestinal therapeutic system formulation for overactive bladder and coexisting benign prostatic obstruction: A prospective, randomized, controlled multicenter study. J Urol 2005; **174**:1334-1338.
47. Gonzalez RR, Kaplan SA: Tadalafil for the treatment of lower urinary tract symptoms in men with benign prostatic hyperplasia. Expert Opin Drug Metabol Toxicol 2006; **2**:609-617.
48. Drescher P, Eckert RE, Madsen PO: Smooth muscle contractility in prostatic hyperplasia: Role of cyclic adenosine monophosphate. Prostate 1994; **25**:76-80.
49. Tinel H, Stelte-Ludwig B, Hutter J, Sandner P: Pre-clinical evidence for the use of phosphodiesterase-5 inhibitors for treating benign prostatic hyperplasia and lower urinary tract symptoms BJU Int 2006; **98**:1259-1263.
50. McVary KT, Monnig W, Camps JL Jr, Young JM, Tseng LJ. van den Ende G: Sildenafil citrate improves erectile function and urinary symptoms in men with erectile dysfunction and lower urinary tract symptoms associated with benign prostatic hyperplasia: A randomized, double-blind trial. J Urol 2007; **177**:1071-1077.