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Current role of treatment in men with lower urinary tract symptoms combined with overactive bladder

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Lower urinary tract symptoms (LUTS) and benign prostatic hyperplasia (BPH) are highly prevalent in older men. The storage subcategory of LUTS is synonymous with overactive bladder (OAB) syndrome, which is an empirical diagnosis. Traditionally, alpha-blockers are widely prescribed to manage the LUTS of BPH, although storage symptoms may persist in many men despite treatment. Therefore, because therapies that target the prostate often fail to alleviate storage symptoms, they may not be the appropriate therapy for OAB. In past years, most physicians appeared to give more weight in elderly men to voiding symptoms than to storage symptoms and to be more concerned with initial treatment with anticholinergics for males with storage symptoms. Considering the recent increase in data on the efficacy and safety of combination treatment with alpha receptor antagonists and antimuscarinic agents, the standard pharmacologic treatment of patients with LUTS combined with OAB should be an alpha receptor antagonist and an antimuscarinic agent. Beta-3 adrenoreceptor agonists may also potentially be useful for the treatment of male LUTS combined with OAB.

Keywords: Prostatic hyperplasia, Overactive urinary bladder, Pharmacology

INTRODUCTION

Lower urinary tract symptoms (LUTS) and benign prostatic hyperplasia (BPH) are highly prevalent in older men. The prevalence and severity of LUTS increase with age [1]. In the EPIC study, a cross-sectional survey of 19,615 adults in 5 countries, 62.5% of men reported having one or more LUTS [2]. The LUTS of BPH that relate to voiding tend to be most prevalent, and the symptoms related to storage are embarrassing and disruptive to daily life and tend to be more bothersome [3].

The storage subcategory of LUTS is synonymous with overactive bladder (OAB) syndrome, which is defined by the International Continence Society as "urgency, with or without urge incontinence, usually with frequency and nocturia" [4]. International differences in OAB prevalence have been observed. A multinational study in six European countries demonstrated significant variation in prevalence, with Spain reporting the highest (22%) prevalence and France reporting the lowest (12%) prevalence [5]. However, in Asian samples, the prevalence of OAB has been reported to be even higher. An OAB prevalence of about 30% was observed in the Asian male population (range, 14%–84%). Frequency and urgency were the most commonly reported symptoms, whereas 13% of individuals examined reported urge incontinence [6].

Traditionally, alpha-blockers are widely prescribed to manage the LUTS of BPH, although storage symptoms may persist in many men despite treatment [7]. Therefore, because therapies that target the prostate often fail to alleviate storage symptoms, they may not be the appropriate therapy for OAB. Addi-

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tionally, in clinical practice, it is difficult to treat patients who have BPH and OAB symptoms with an anticholinergic agent because of the possibility of acute urinary retention (AUR) [8]. The aim of this article was to provide a contemporary review of the current role of anticholinergic therapy in the treatment of male LUTS combined with OAB.

TREATMENT OPTIONS FOR MEN WITH LUTS AND OAB

LUTS in men are often treated first with agents that target the prostate or bladder outlet obstruction (BOO; dynamic obstruction), such as 5-alpha reductase inhibitors (5-ARIs) and alpha receptor antagonists [9]. Men with LUTS/OAB are usually treated with BPH drugs rather than those specific for OAB, despite the high prevalence of coexistent storage symptoms in men with LUTS [10]. Many physicians are still reluctant to prescribe anticholinergics owing to concern about urinary retention, especially in men with BOO. However, several studies have reported that prescribing anticholinergics to men with LUTS or even BOO does not seem to elevate the risk of AUR [11,12].

ALPHA RECEPTOR ANTAGONISTS

Alpha receptor antagonists are considered the first-line treatment for LUTS [13]. Alpha receptor antagonists decrease smooth muscle tone in the prostate and bladder neck [14]. Because LUTS in men have traditionally been attributed to BPH and obstructed urinary flow, pharmacological therapies have been aimed at improving urinary flow rates rapidly and optimizing voiding efficiency [15]. According to the European Association of Urology guidelines, alpha-blockers should be offered to men with moderate to severe LUTS and are considered the first-line drug treatment for these patients [16]. The American Urologic Association Clinical Practice Guidelines Committee determined that alfuzosin, doxazosin, tamsulosin, and terazosin are all appropriate treatment options for patients with LUTS secondary to BPH [13]. Placebo-controlled studies have shown that α1-blockers typically reduce the International Prostate Symptom Score (IPSS) by approximately 35% to 40%. Furthermore, the maximum urinary flow rate (Qmax) increases by approximately 20% to 25% [17-19].

The main alpha receptor antagonists used for treating LUTS in men with BPH are alfuzosin, doxazosin, terazosin, tamsulosin, silodosin, and the more recent drug, naftopidil. In the male prostate and urethra, the alpha-1A receptor subtype is most prevalent. These drugs are all selective for the alpha-1 receptor subtype present in prostatic tissue. Silodosin and tamsulosin are the alpha-1A-selective alpha receptor antagonists and naftopidil is the alpha-1D-predominant receptor antagonist.

Direct head-to-head comparisons between alpha receptor antagonists are limited. In a randomized double-blind placebo-controlled study, terazosin significantly increased Qmax ($P<0.001$) and did not alter postvoided residual volume (PVR) at 24 weeks. In a pooled analysis of three double-blind placebo-controlled trials, there was also significant improvement in total IPSS [20]. Doxazosin produced a significantly greater improvement than placebo in Qmax ($P=0.0017$), symptom severity ($P<0.0001$), and bother caused by symptoms ($P<0.0001$) [21]. Another alpha-1 receptor antagonist, alfuzosin, was reported to significantly improve total IPSS ($P<0.005$), IPSS storage subscore ($P<0.001$), IPSS voiding subscore ($P<0.001$), and Qmax ($P<0.001$) compared with placebo [22]. In a meta-analysis of the outcome of 14 different tamsulosin studies, compared with placebo, tamsulosin was superior to placebo with an IPSS improvement of 12% (tamsulosin, 0.4 mg) and 16% (tamsulosin, 0.8 mg) [23]. A more recent drug, silodosin, showed efficacy equal to tamsulosin on study endpoints, but only silodosin significantly reduced nocturia versus placebo (change from baseline was –0.9, –0.8, and –0.7 for silodosin, tamsulosin, and placebo, respectively; $P<0.013$ for silodosin vs. placebo) [24]. Naftopidil, most recently approved in Korea, has distinct characteristics because it has three times greater affinity for the alpha-1D adrenergic receptor subtype than for the alpha-1A subtype [25]. Naftopidil significantly improved the overall IPSS (from 19.2±7.9 to 11.7±5.8, $P<0.001$), QoL score (5.0±0.8 to 3.6±1.3, $P<0.001$), and storage symptom score (8.6±2.9 to 5.8± 3.3, $P<0.001$) from baseline [26].

Several studies have reported that alpha adrenergic receptor antagonists can improve the storage symptoms in male BPH patients [27-29]. Tamsulosin [27,28] and silodosin [29] showed significant improvement in IPSS storage scores. Naftopidil also demonstrated a significant response to improve storage symptoms including daytime frequency and nocturia [30,31]. However, until now, the data were insufficient to support a recommendation for alpha-1 monotherapy for male LUTS combined with OAB.

5-ALPHA REDUCTASE INHIBITORS

The enzyme 5-alpha reductase converts testosterone to dihydrotestosterone [32]. There are two isoforms of 5-alpha reductase: type 1 and type 2. Two 5-ARIs are available for clinical

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use. Dutasteride has a dual mechanism and inhibits type 1 and type 2 5-alpha reductase, whereas finasteride inhibits only 5-alpha reductase type 2. These inhibitors induce apoptosis of prostate epithelial cells, which results in a decrease of prostate size by about 18% to 20% and of prostate-specific antigen levels by about 50% after 6 to 12 months of treatment [33]. Finasteride significantly improves symptom scores ($P<0.001$ and $P<0.015$) and Qmax ($P<0.001$) compared with placebo after 12 months of use [34]. A meta-analysis of these early studies concluded that these improvements were less in patients with a smaller prostate [35]. Dutasteride also showed symptom scores from 6 months onward ($P<0.001$) with a mean improvement of 4.5 points at 24 months [36]. The Qmax improved significantly from 1 month ($P<0.01$) with an increase of 2.2 mL/s reported at 24 months ($P<0.001$). In a head-to-head trial of the two drugs, Qmax, prostate volume, and LUTS variation were similar for both drugs [37]. However, it remains to be elucidated whether 5-ARI monotherapy can improve the storage component of male LUTS, particularly male OAB symptoms.

ANTIMUSCARINIC AGENTS

Antimuscarinic agents are considered the first-line treatment for patients with OAB. These agents act by blocking acetylcholine binding at muscarinic receptors on the detrusor muscle, thereby reducing the ability of the detrusor to contract during the voiding phase [38]. Antimuscarinic agents improve the storage symptom of urgency and increase bladder capacity, whereas their effects decrease during the voiding phase when a massive release of acetylcholine from cholinergic nerves is present [39].

In clinical practice, many physicians are reluctant to prescribe antimuscarinic agents in male patients with LUTS combined with OAB owing to the concern of urinary retention. However, several studies have reported that prescribing antimuscarinic agents to men with LUTS or even BOO does not seem to elevate the risk of AUR [11,40]. The results of several studies support the efficacy and safety of antimuscarinics in treating men with LUTS and OAB [41-44]. For example, Abrams et al. [11] reported the efficacy of tolterodine immediate-release in men with both BOO and OAB. Tolterodine significantly reduced the BOO index (–0.9 vs. 0, $P<0.02$) and increased maximal cystometric capacity (+67 mL; 95% confidence interval, 35–103; $P<0.003$) compared with placebo. No significant differences in the incidence of adverse events were seen, whereas the change in PVR was significantly higher among patients treated with tolterodine (+25 mL) than in those given placebo (0 mL, $P<0.004$). In another study, fesoterodine 4 or 8 mg resulted in significantly greater improvements in micturition frequency, urgency episodes, and urgency urinary incontinence episodes compared with placebo in men with OAB [45].

Although studies in elderly men with LUTS and OAB symptoms were exclusively carried out with tolterodine or fesoterodine, it is likely that similar efficacy and adverse events will also be shown with other antimuscarinic agents. Long-term studies on the efficacy of muscarinic receptor antagonists in men with LUTS are still lacking; therefore, these drugs should be prescribed with caution, and regular re-evaluation of IPSS and PVR urine is advised [13,16].

COMBINATION TREATMENT: ALPHA RECEPTOR ANTAGONISTS + ANTIMUSCARINIC AGENTS

Even after treatment with alpha receptor antagonists and 5-ARIs, many patients with BPH/LUTS suffer from persistent symptoms of OAB. In recent years, a number of studies have reported on the combination treatment of alpha receptor antagonists and antimuscarinic agents [12,41-47]. In a 2006 study by Kaplan et al. [48] named the TIMES study, tolterodine extend release (ER) and tamsulosin combination treatment resulted in significant improvement in urgency episodes, number of micturitions, nocturia, and IPSS. The medication was well tolerated with no significant differences in voiding pattern, PVR, or episodes of AUR. A subanalysis of the TIMES study combination treatment with tamsulosin and tolterodine ER showed significant improvements in IPSS storage symptom scores compared with placebo. A recent phase II study [49], a dose-finding study of solifenacin and tamsulosin in males with LUTS associated with BPH (the SATURN study), was designed to investigate the combination of tamsulosin and solifenacin versus tamsulosin alone and placebo in the treatment of men with LUTS. Combination therapy was associated with significant improvements in micturition frequency and voided volume versus the tamsulosin oral controlled absorption system alone. In addition, significant improvement was found in the IPSS storage subscore in all the combination groups compared with tamsulosin alone. In another recent study [50], the combination of solifenacin 6 mg and the tamsulosin oral controlled absorption system significantly improved storage and voiding symptoms, as well as QoL parameters, over placebo. In the ADAM study [51], combination therapy with alpha receptor antagonists and tolterodine sustained release resulted in significantly

greater improvements versus placebo plus alpha-blocker in 24-hour micturitions, daytime micturitions, 24-hour urgency episodes, daytime urgency episodes, nocturnal urgency episodes, frequency–urgency sum, IPSS storage subscale, OAB-q symptom bother scale, and OAB-q coping domain at week 12.

Lee et al. [43,44] recently reported that initial combined treatment with alpha receptor antagonists plus an antimuscarinic agent showed improvement in not only storage symptoms but also QoL scores without increasing the risk of AUR. In recognition of the growing body of evidence for the use of antimuscarinics for storage symptoms in men, the 6th International Consultation on New Developments in Prostate Cancer and Prostate Disease recommended the use of combination therapy with alpha-blockers for men with BOO mixed with OAB [52]. However, there seems to be a discrepancy between the awareness of urologists and their actual practice patterns in the treatment of men with BOO mixed with OAB owing to fear of AUR [10].

5-ARIs AND ANTIMUSCARINIC AGENTS

Recently, Chung et al. [53] reported that combination therapy with 5-ARIs and antimuscarinic agents is safe and effective in men with LUS/BPH. Tolterodine ER with 0.5 mg dutasteride was given to men with persistent OAB symptoms and LUTS that were unsuccessfully treated with dutasteride alone. All patients were given 4 mg tolterodine ER daily for 12 weeks and maintained on dutasteride. The total IPSS decreased with dutasteride treatment from 19.3 to 14.3 and further decreased with the addition of tolterodine to 7.1 ($P<0.001$). Storage symptoms decreased from 9.8 to 4.5 after tolterodine ($P<0.001$). In this study, the combination of tolterodine ER and dutasteride was effective, safe, and well-tolerated in men with large prostates (≥30 mL) with persistent OAB symptoms and LUTS/BPH.

BETA-3 ADRENORECEPTOR AGONISTS

The beta-3 adrenoreceptor subtype is the predominant form of beta adrenoceptor in the bladder [54]. Its stimulation is associated with increased bladder capacity without a change in micturition pressure, PVR, or voiding contraction [55,56]. Nitti et al. [57] reported that 40 mg mirabegron showed a statistically significant decrease in urgency episodes and micturition frequency without adversely affecting voiding urodynamics. Although these findings showing the urodynamic safety of mirabegron in men with LUTS and BOO are very promising, more randomized controlled trials are needed for positioning a new therapy for LUTS and OAB.

CONCLUSION

The treatment of BPH/LUTS combined with OAB is slowly but constantly evolving. In past years, most physicians appeared to give more weight in elderly men to voiding symptoms than to storage symptoms, and they are more concerned with initial treatment with anticholinergics for males with storage symptoms. However, antimuscarinic therapy alone or in combination with alpha receptor antagonists improves OAB symptoms in men with or without BOO. The concern regarding antimuscarinic use leading to an increased incidence of urinary retention appears to be unfounded. Therefore, the standard pharmacologic treatment of patients with LUTS combined with OAB should be an alpha receptor antagonist and an antimuscarinic agent. Beta-3 adrenoreceptor agonists may also be potentially useful for the treatment of male LUTS combined with OAB.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

REFERENCES

1. Rosen R, Altwein J, Boyle P, Kirby RS, Lukacs B, Meuleman E, et al. Lower urinary tract symptoms and male sexual dysfunction: the multinational survey of the aging male (MSAM-7). Eur Urol 2003;44:637-49.
2. Irwin DE, Milsom I, Hunskaar S, Reilly K, Kopp Z, Herschorn S, et al. Population-based survey of urinary incontinence, overactive bladder, and other lower urinary tract symptoms in five countries: results of the EPIC study. Eur Urol 2006; 50:1306-14.
3. Witjes WP, de la Rosette JJ, Donovan JL, Peters TJ, Abrams P, Kay HE, et al. The International Continence Society "Benign Prostatic Hyperplasia" Study: international differences in lower urinary tract symptoms and related bother. J Urol 1997;157:1295-300.
4. Abrams P, Cardozo L, Fall M, Griffiths D, Rosier P, Ulmsten U, et al. The standardisation of terminology in lower urinary tract function: report from the standardisation subcommittee of the International Continence Society. Urology 2003;61:37-49.
5. Milsom I, Abrams P, Cardozo L, Roberts RG, Thuroff J, Wein AJ. How widespread are the symptoms of an overactive blad-

http://dx.doi.org/10.12954/PI.14045

der and how are they managed? A population-based prevalence study. BJU Int 2001;87:760-6.
6. Moorthy P, Lapitan MC, Quek PL, Lim PH. Prevalence of overactive bladder in Asian men: an epidemiological survey. BJU Int 2004;93:528-31.
7. Lemack GE. Defining the role of overactive bladder treatments in men with lower urinary tract symptoms. Nat Clin Pract Urol 2007;4:174-5.
8. Chapple CR, Khullar V, Gabriel Z, Muston D, Bitoun CE, Weinstein D. The effects of antimuscarinic treatments in overactive bladder: an update of a systematic review and meta-analysis. Eur Urol 2008;54:543-62.
9. 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;49:651-8.
10. Lee SH, Kim DK, Kim JC, Lee KS, Lee JG, Park CH, et al. The urologist's view of male overactive bladder: discrepancy between reality and belief in practical setting. Yonsei Med J 2010;51:432-7.
11. Abrams P, Kaplan S, De Koning Gans HJ, Millard R. Safety and tolerability of tolterodine for the treatment of overactive bladder in men with bladder outlet obstruction. J Urol 2006;175(3 Pt 1):999-1004.
12. Kaplan SA, Walmsley K, Te AE. Tolterodine extended release attenuates lower urinary tract symptoms in men with benign prostatic hyperplasia. J Urol 2005;174:2273-5.
13. McVary KT, Roehrborn CG, Avins A, Barry MJ, Bruskewitz RC, Donnell RF, et al., editors. American Urological Association Guideline: management of benign prostatic hyperplasia (BPH). Revised 2010. Linthicum: American Urological Association; 2010.
14. Chapple CR. Pharmacological therapy of benign prostatic hyperplasia/lower urinary tract symptoms: an overview for the practising clinician. BJU Int 2004;94:738-44.
15. Dmochowski RR, Gomelsky A. Overactive bladder in males. Ther Adv Urol 2009;1:209-21.
16. Oelke M, Bachmann A, Descazeaud A, Emberton M, Gravas S, Michel MC, et al. Guidelines on the Management of Male Lower Urinary Tract Symptoms (LUTS), incl. Benign Prostatic Obstruction (BPO). Arnhem: European Association of Urology; 2012.
17. MacDonald R, Wilt TJ. Alfuzosin for treatment of lower urinary tract symptoms compatible with benign prostatic hyperplasia: a systematic review of efficacy and adverse effects. Urology 2005;66:780-8.
18. Wilt TJ, Howe RW, Rutks IR, MacDonald R. Terazosin for benign prostatic hyperplasia. Cochrane Database Syst Rev 2002;(4):CD003851.
19. van Kerrebroeck P, Jardin A, Laval KU, van Cangh P. Efficacy and safety of a new prolonged release formulation of alfuzosin 10 mg once daily versus alfuzosin 2.5 mg thrice daily and placebo in patients with symptomatic benign prostatic hyperplasia. ALFORTI Study Group. Eur Urol 2000;37:306-13.
20. Elhilali MM, Ramsey EW, Barkin J, Casey RW, Boake RC, Beland G, 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;47:335-42.
21. Roehrborn CG, Siegel RL. Safety and efficacy of doxazosin in benign prostatic hyperplasia: a pooled analysis of three double-blind, placebo-controlled studies. Urology 1996;48:406-15.
22. Roehrborn CG, Van Kerrebroeck P, Nordling J. Safety and efficacy of alfuzosin 10 mg once-daily in the treatment of lower urinary tract symptoms and clinical benign prostatic hyperplasia: a pooled analysis of three double-blind, placebo-controlled studies. BJU Int 2003;92:257-61.
23. Wilt TJ, Mac Donald R, Rutks I. Tamsulosin for benign prostatic hyperplasia. Cochrane Database Syst Rev 2003;(1):CD002081.
24. Chapple CR, Montorsi F, Tammela TL, Wirth M, Koldewijn E, Fernandez Fernández E, et al. Silodosin therapy for lower urinary tract symptoms in men with suspected benign prostatic hyperplasia: results of an international, randomized, double-blind, placebo- and active-controlled clinical trial performed in Europe. Eur Urol 2011;59:342-52.
25. Masumori N. Naftopidil for the treatment of urinary symptoms in patients with benign prostatic hyperplasia. Ther Clin Risk Manag 2011;7:227-38.
26. Sakai H, Igawa T, Onita T, Furukawa M, Hakariya T, Hayashi M, Efficacy of naftopidil in patients with overactive bladder associated with benign prostatic hyperplasia: prospective randomized controlled study to compare differences in efficacy between morning and evening medication. Hinyokika Kiyo 2011;57:7-13.
27. Lepor H. Phase III multicenter placebo-controlled study of tamsulosin in benign prostatic hyperplasia. Tamsulosin Investigator Group. Urology 1998;51:892-900.
28. Abrams P, Schulman CC, Vaage S. Tamsulosin, a selective alpha 1c-adrenoceptor antagonist: a randomized, controlled trial in patients with benign prostatic 'obstruction' (symptomatic BPH). The European Tamsulosin Study Group. Br J Urol 1995;76:325-36.
29. Kawabe K, Yoshida M, Homma Y; Silodosin Clinical Study Group. Silodosin, a new alpha1A-adrenoceptor-selective antagonist for treating benign prostatic hyperplasia: results

of a phase III randomized, placebo-controlled, double-blind study in Japanese men. BJU Int 2006;98:1019-24.
30. Ukimura O, Kanazawa M, Fujihara A, Kamoi K, Okihara K, Miki T, et al. Naftopidil versus tamsulosin hydrochloride for lower urinary tract symptoms associated with benign prostatic hyperplasia with special reference to the storage symptom: a prospective randomized controlled study. Int J Urol 2008;15:1049-54.
31. Oh-oka H. Effect of naftopidil on nocturia after failure of tamsulosin. Urology 2008;72:1051-5.
32. Andriole G, Bruchovsky N, Chung LW, Matsumoto AM, Rittmaster R, Roehrborn C, et al. Dihydrotestosterone and the prostate: the scientific rationale for 5alpha-reductase inhibitors in the treatment of benign prostatic hyperplasia. J Urol 2004;172(4 Pt 1):1399-403.
33. Naslund MJ, Miner M. A review of the clinical efficacy and safety of 5alpha-reductase inhibitors for the enlarged prostate. Clin Ther 2007;29:17-25.
34. The Finasteride Study Group. Finasteride (MK-906) in the treatment of benign prostatic hyperplasia. Prostate 1993;22:291-9.
35. Boyle P, Gould AL, Roehrborn CG. Prostate volume predicts outcome of treatment of benign prostatic hyperplasia with finasteride: meta-analysis of randomized clinical trials. Urology 1996;48:398-405.
36. Roehrborn CG, Boyle P, Nickel JC, Hoefner K, Andriole G; ARIA3001 ARIA3002 and ARIA3003 Study Investigators. Efficacy and safety of a dual inhibitor of 5-alpha-reductase types 1 and 2 (dutasteride) in men with benign prostatic hyperplasia. Urology 2002;60:434-41.
37. Nickel JC, Gilling P, Tammela TL, Morrill B, Wilson TH, Rittmaster RS. Comparison of dutasteride and finasteride for treating benign prostatic hyperplasia: the Enlarged Prostate International Comparator Study (EPICS). BJU Int 2011;108:388-94.
38. Reynard JM. Does anticholinergic medication have a role for men with lower urinary tract symptoms/benign prostatic hyperplasia either alone or in combination with other agents? Curr Opin Urol 2004;14:13-6.
39. Andersson KE. Antimuscarinics for treatment of overactive bladder. Lancet Neurol 2004;3:46-53.
40. Roehrborn CG, Abrams P, Rovner ES, Kaplan SA, Herschorn S, Guan Z. Efficacy and tolerability of tolterodine extended-release in men with overactive bladder and urgency urinary incontinence. BJU Int 2006;97:1003-6.
41. Kaplan SA, Walmsley K, Te AE. Tolterodine extended release attenuates lower urinary tract symptoms in men with benign prostatic hyperplasia. Urol 2008;179(5 Suppl):S82-5.
42. Lee JY, Kim HW, Lee SJ, Koh JS, Suh HJ, Chancellor MB. Comparison of doxazosin with or without tolterodine in men with symptomatic bladder outlet obstruction and an overactive bladder. BJU Int 2004;94:817-20.
43. Lee SH, Byun SS, Lee SJ, Kim KH, Lee JY. Effects of initial combined tamsulosin and solifenacin therapy for overactive bladder and bladder outlet obstruction secondary to benign prostatic hyperplasia: a prospective, randomized, multicenter study. Int Urol Nephrol 2014;46:523-9.
44. Lee SH, Chung BH, Kim SJ, Kim JH, Kim JC, Lee JY. Initial combined treatment with anticholinergics and α-blockers for men with lower urinary tract symptoms related to BPH and overactive bladder: a prospective, randomized, multi-center, double-blind, placebo-controlled study. Prostate Cancer Prostatic Dis 2011;14:320-5.
45. Herschorn S, Jones JS, Oelke M, MacDiarmid S, Wang JT, Guan Z. Efficacy and tolerability of fesoterodine in men with overactive bladder: a pooled analysis of 2 phase III studies. Urology 2010;75:1149-55.
46. MacDiarmid SA, Peters KM, Chen A, Armstrong RB, Orman C, Aquilina JW, et al. Efficacy and safety of extended-release oxybutynin in combination with tamsulosin for treatment of lower urinary tract symptoms in men: randomized, double-blind, placebo-controlled study. Mayo Clin Proc 2008;83:1002-10.
47. Athanasopoulos A, Chapple C, Fowler C, Gratzke C, Kaplan S, Stief C, et al. The role of antimuscarinics in the management of men with symptoms of overactive bladder associated with concomitant bladder outlet obstruction: an update. Eur Urol 2011;60:94-105.
48. Kaplan SA, Roehrborn CG, Rovner ES, Carlsson M, Bavendam T, Guan Z. Tolterodine and tamsulosin for treatment of men with lower urinary tract symptoms and overactive bladder: a randomized controlled trial. JAMA 2006;296:2319-28.
49. Van Kerrebroeck P, Haab F, Angulo JC, Vik V, Katona F, Garcia-Hernandez A, et al. Efficacy and safety of solifenacin plus tamsulosin OCAS in men with voiding and storage lower urinary tract symptoms: results from a phase 2, dose-finding study (SATURN). Eur Urol 2013;64:398-407.
50. van Kerrebroeck P, Chapple C, Drogendijk T, Klaver M, Sokol R, Speakman M, et al. Combination therapy with solifenacin and tamsulosin oral controlled absorption system in a single tablet for lower urinary tract symptoms in men: efficacy and safety results from the randomised controlled NEPTUNE trial. Eur Urol 2013;64:1003-12.
51. Chapple C, Herschorn S, Abrams P, Sun F, Brodsky M, Guan Z. Tolterodine treatment improves storage symptoms suggestive of overactive bladder in men treated with alpha-blockers.

 http://dx.doi.org/10.12954/PI.14045

Eur Urol 2009;56:534-41.
52. Abrams P, Chapple C, Khoury S, Roehrborn C, de la Rosette J; International Consultation on New Developments in Prostate Cancer and Prostate Diseases. Evaluation and treatment of lower urinary tract symptoms in older men. J Urol 2013;189(1 Suppl):S93-101.
53. Chung DE, Te AE, Staskin DR, Kaplan SA. Efficacy and safety of tolterodine extended release and dutasteride in male overactive bladder patients with prostates >30 grams. Urology 2010;75:1144-8.
54. Yamaguchi O, Chapple CR. Beta3-adrenoceptors in urinary bladder. Neurourol Urodyn 2007;26:752-6.
55. Leon LA, Hoffman BE, Gardner SD, Laping NJ, Evans C, Lashinger ES, et al. Effects of the beta 3-adrenergic receptor agonist disodium 5-[(2R)-2-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]-1,3-benzodioxole-2,2-dicarboxylate (CL-316243) on bladder micturition reflex in spontaneously hypertensive rats. J Pharmacol Exp Ther 2008;326:178-85.
56. Tyagi P, Tyagi V. Mirabegron, a β_3-adrenoceptor agonist for the potential treatment of urinary frequency, urinary incontinence or urgency associated with overactive bladder. IDrugs 2010;13:713-22.
57. Nitti VW, Rosenberg S, Mitcheson DH, He W, Fakhoury A, Martin NE. Urodynamics and safety of the β_3-adrenoceptor agonist mirabegron in males with lower urinary tract symptoms and bladder outlet obstruction. J Urol 2013;190:1320-7.