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When to Treat the Prostate, the Bladder, or Both?

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Article info

Keywords:

5 α -reductase inhibitor
 α_1 -adrenoceptor antagonist
Antimuscarinic agent
Benign prostatic hyperplasia
Combination therapy
Erectile dysfunction
Lower urinary tract symptoms
Overactive bladder
Phosphodiesterase-5 inhibitor

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Abstract

Context: Pharmacological therapy for relieving lower urinary tract symptoms suggestive of benign prostatic hyperplasia (LUTS/BPH) has evolved during the past years. The possible benefits of combination therapies to prevent disease progression or to treat LUTS/BPH with concomitant overactive bladder (OAB) or erectile dysfunction (ED) are currently studied.

Objectives: To review the evidence provided in clinical trials and to assess the current medical practice concerning the pharmacological treatment of men suffering from LUTS/BPH.

Evidence acquisition: This paper is based on a presentation during the symposium “The future of LUTS/BPH: management beyond the prostate” at the European Association of Urology’s 2008 annual meeting. The results of a Web survey evaluating the opinion of urologists about treatment of LUTS/BPH patients were discussed and an update lecture on medical therapy for LUTS/BPH was given.

Evidence synthesis: Men who are highly bothered by their symptoms but with a low risk of disease progression can achieve fast relief of symptoms with α_1 -adrenoceptor (α_1 -AR) antagonist monotherapy. Those patients at risk for LUTS/BPH progression can benefit from additional 5 α -reductase inhibitor therapy. Concomitant OAB symptoms in LUTS/BPH patients can be treated with a combination of an α_1 -AR antagonist and an antimuscarinic agent. An α_1 -AR antagonist combined with a phosphodiesterase-5 inhibitor might improve symptoms in men with lower urinary tract symptoms (LUTS) and concomitant ED.

Conclusions: The pharmacological treatment of LUTS/BPH patients should be adapted to their individual risk of progression and their individual symptom profile.

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1. Introduction

When bothersome lower urinary tract symptoms suggestive of benign prostatic hyperplasia (LUTS/BPH) start to interfere with normal activities and

thus reduce quality of life (QoL), men often seek treatment for these symptoms. Treatment options for LUTS/BPH include watchful waiting, pharmacological therapy, and (minimally invasive) surgery [1]. At low risk of disease progression, the target of

treatment is fast and continued relief of symptoms with minimal treatment morbidity. However, in patients with an increased risk of LUTS/BPH progression, treatment should additionally delay or even prevent disease progression and the development of complications [1,2]. According to the particular symptoms, the degree of bother, and the risk of disease progression, a patient-tailored therapy should be introduced taking into account the best available evidence as well as the patient's perspective [3]. For the majority of men, pharmacological therapy has become the initial treatment of choice [4,5].

2. Evidence acquisition

Recent studies have broadened the insight into the efficacy of pharmacotherapy in terms of relieving symptoms and improving QoL. Furthermore, possible treatment-related adverse events have been studied extensively. The implications of these studies in selecting the appropriate therapy for particular subgroups of men with LUTS/BPH were addressed during an update lecture at the symposium "The future of LUTS/BPH: management beyond the prostate" at the 2008 annual meeting of the European Association of Urology.

A Web survey, in which 408 urologists participated, was conducted to get an idea about the management of LUTS/BPH in current clinical practice. The responses from those who spent >25% of their time on patient care (ie, 382 urologists) were analysed.

This review reports on the available evidence of (principally) randomised controlled trials and discusses the outcomes of the Web survey, as presented at the symposium.

3. Evidence synthesis

3.1. Monotherapy with α_1 -adrenoceptor antagonists

Monotherapy with an α_1 -adrenoceptor (α_1 -AR) antagonist is the current standard for patients with mild-to-moderate LUTS/BPH at low risk of disease progression [6]. The onset of action is rapid—within 2 wk—especially for those α_1 -AR antagonists that can be initiated at full therapeutic dose. This therapy results in effective relief of urinary symptoms as shown in various studies by the improvement in total International Prostate Symptom Score (IPSS) and in maximum urinary flow rate (Q_{max}). Typically, trials with a placebo run-in period report symptomatic improvement in the range of 30–50% and an improvement in Q_{max} of 15–30% after 3 mo of α_1 -AR

antagonist treatment [7]. This improvement is sustained in the long-term, demonstrated up to 4.5 yr in randomised controlled trials as well as up to 6 yr in open-label extension studies [8–10].

By blocking α_{1A} -ARs in the prostate, the urethra, and the bladder neck, the α_1 -AR antagonists can inhibit smooth-muscle contraction and reduce the dynamic component of bladder outlet obstruction, thereby relieving lower urinary tract symptoms (LUTS). Inhibition of α_{1D} -ARs, predominately present in the smooth muscle of the bladder, may improve storage symptoms [11]. The α_1 -AR antagonists are effective in LUTS/BPH patients irrespective of prostate size [12].

This treatment is generally well tolerated, especially tamsulosin or alfuzosin therapy [7]. Tamsulosin has low affinity for the α_{1B} -ARs in the vasculature compared with the nonselective α_1 -AR antagonists, which might explain its low incidence of vasodilatory adverse events [13].

3.2. Combination therapy: α_1 -adrenoceptor antagonist plus 5 α -reductase inhibitor

3.2.1. Clinical evidence

In 2003, Kirby et al evaluated the efficacy of an α_1 -AR antagonist, a 5 α -reductase inhibitor (5-ARI), and their combination in a 1-yr, randomised, double-blind, placebo-controlled PROspective European Doxazosin and Combination Therapy (PREDICT) trial with 1095 men with benign prostatic hyperplasia (BPH) [14]. The baseline parameters of patients and study characteristics of this trial are listed in Table 1. The improvement in IPSS from baseline to end point was statistically significant in both the α_1 -AR antagonist group (–8.3) and the combination therapy group (–8.5) versus the placebo group (–5.7), and the 5-ARI group (–6.6). Neither the IPSS nor the Q_{max} significantly improved in the combination therapy group versus the α_1 -AR antagonist group. The addition of the 5-ARI did not provide additional benefit to α_1 -AR antagonist therapy in this short-term study among patients with a rather small prostate size.

In the four-arm Medical Therapy Of Prostatic Symptoms (MTOPS) trial (Table 1), combination of an α_1 -AR antagonist and a 5-ARI was significantly superior in improving the symptom score and in preventing clinical BPH progression compared with either drug alone [8]. Secondary subgroup analysis revealed that in patients with a prostate <25 ml, combination therapy was not better than α_1 -AR antagonist monotherapy. However, in patients with a prostate size between 25 ml and 40 ml, and even more so in those with a prostate size >40 ml,

Table 1 – Baseline characteristics of the clinical trials

| | PREDICT [14] | MTOPS [8] | CombAT [16] | TIMES [22] | LUTS/BPH + ED pilot [28] |
|-------------------------|---|---|--|--|--|
| No. of patients | 1095 | 3047 | 4844 | 879 | 62 |
| Age, years | 64 | 62.6 | 66.1 | 62 | 63.4 |
| IPSS | 17.2 | 16.9 | 16.4 | 19.9 | 17.4 |
| Prostate size, ml | 36.3 | 36.3 | 55.0 | ND | ND |
| Q _{max} , ml/s | 10.5 | 10.5 | 10.7 | 12.9 | 9.5 |
| Comorbidity | – | – | – | OAB | ED |
| Study duration | 52 wk | 4.5 years [*] | 2 yr [†] | 12 wk | 12 wk |
| Treatment arms | Placebo Doxazosin (1 → 8 OD) Finasteride (5 mg OD) Combination | Placebo Doxazosin (4 → 8 OD) Finasteride (5 mg OD) Combination | Tamsulosin (0.4 mg OD) Dutasteride (0.5 mg OD) Combination | Placebo Tamsulosin (0.4 mg OD) Tolterodine ER (4 mg OD) Combination | Alfuzosin (10 mg OD) Sildenafil (25 mg OD) Combination |

PREDICT = PRospective European Doxazosin and Combination Therapy; MTOPS = Medical Therapy Of Prostatic Symptoms; CombAT = Combination of Avodart and Tamsulosin trial; TIMES = Tolterodine and tamsulosin In Men with lower urinary tract symptoms including overactive bladder: evaluation of Efficacy and Safety; LUTS/BPH + ED = lower urinary tract symptoms suggestive of benign prostatic hyperplasia and concomitant erectile dysfunction; IPSS = International Prostate Symptom Score; Q_{max} = maximum urinary flow rate; ND = no data reported; OAB = overactive bladder; ED = erectile dysfunction; OD = once daily; ER = extended release.

^{*} Mean follow-up.

[†] Results of preplanned analysis (total study duration is 4 yr).

combination therapy led to a superior improvement in Q_{max} and symptoms compared with either monotherapy [15]. The larger the prostate, the more the combination of an α_1 -AR antagonist and a 5-ARI was beneficial.

The 2-yr analysis of the Combination of Avodart and Tamsulosin (CombAT) trial (Table 1) showed that combination therapy resulted in a significantly greater improvement in symptoms versus a 5-ARI from month 3 and versus an α_1 -AR antagonist from month 9 onwards in patients with moderate-to-severe LUTS and an enlarged prostate (≥ 30 ml) [16]. At 2 yr after treatment initiation, a reduction of 6.2 in IPSS versus baseline was observed in the combination therapy group, while a reduction of 4.9 and 4.3 was seen in the 5-ARI and the α_1 -AR antagonist group, respectively ($p < 0.001$). There was no placebo group included in this study.

Current evidence suggests that combination therapy with an α_1 -AR antagonist and a 5-ARI should be considered in patients at risk of LUTS/BPH progression (eg, with prostatic enlargement, elevated prostate-specific antigen (PSA) levels, and moderately or severely bothersome LUTS) [17]. These patients need continuous treatment resulting in effective delay or prevention of the development of serious complications such as acute urinary retention (AUR) or BPH-related surgery [1].

3.2.2. Clinical practice

The Web survey included a case of a patient at high risk of LUTS/BPH progression (Fig. 1). More than 60% of the urologists suggested combination therapy for this man. This result illustrates that daily practice is

largely in accordance with clinical evidence in this case. However, 12.9% suggested transurethral resection of the prostate (TURP) as best treatment option for this patient. TURP might be appropriate when combination therapy fails to improve LUTS or for

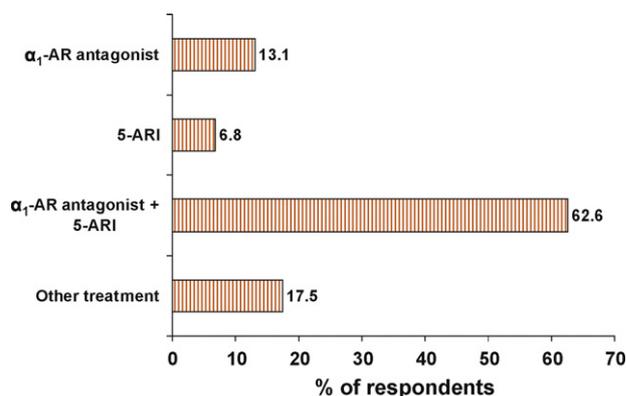


Fig. 1 – Opinions of 382 urologists participating in a Web-based survey regarding the following case: How would you treat a man aged 70 yr presenting with complaints of daytime frequency, nocturia, urgency, and terminal dribbling? He started noticing the symptoms about 4 yr ago, but they had worsened considerably in the last year. Symptom score evaluation shows that the patient has a total International Prostate Symptom Score (IPSS) of 28 with a high bother score (IPSS quality of life: 5). Additional examinations show that he has a prostate volume of 80 ml, a maximum urinary flow rate (Q_{max}) of 9 ml/s, postvoid residual of 50 ml, and a prostate-specific antigen (PSA) level of 2.2 ng/ml. He has a history of hypertension and is being treated with an angiotensin-converting enzyme (ACE) inhibitor.

α_1 -AR = α_1 -adrenoceptor; 5-ARI = 5 α -reductase inhibitor.

men who request an active intervention with immediate symptomatic relief.

3.3. Lower urinary tract symptoms suggestive of benign prostatic hyperplasia and concomitant overactive bladder symptoms

3.3.1. Clinical evidence

Overactive bladder (OAB) symptoms correspond with storage symptoms such as urgency and daytime and nighttime frequency and are common in LUTS/BPH patients [18]. They have a substantial impact on QoL and are generally considered very bothersome [19]. The population-based European Prospective Investigation into Cancer and Nutrition (EPIC) survey, in which 19 165 men and women aged >18 yr from five countries participated, revealed that 12.8% of women and 10.8% of men report OAB symptoms [20]. Although these rates are similar, treatment often differs: antimuscarinic agents are the preferred drug for women, while in men, storage symptoms are still attributed to the prostate and are therefore often treated with antiobstructive drugs. Another reason for not using antimuscarinic agents in men is the fear of enhancing obstructive symptoms or even driving the patient into AUR due to the inhibitory effect of antimuscarinic agents on detrusor muscle contraction [18,21].

Antimuscarinic agents do, however, have a place for men with LUTS and OAB symptoms. The so-called (Tolterodine and tamsulosin In Men with lower urinary tract symptoms including overactive bladder: evaluation of Efficacy and Safety) study, a recent randomised, placebo-controlled study demonstrated a beneficial effect when combining an antimuscarinic drug with an α_1 -AR antagonist (Table 1) [22].

Significantly more men (80%) with LUTS, micturition frequency (≥ 8 micturitions per 24 h), and urgency (≥ 3 episodes per 24 h) receiving an α_1 -AR antagonist plus an antimuscarinic agent reported treatment benefit by week 12 over placebo (62%; $p < 0.001$), while neither monotherapy could demonstrate a significant difference versus placebo. Only the combination therapy resulted in significant reduction versus placebo in both urgency episodes per 24 h and micturitions per 24 h. Urinary retention was reported in 1.3% of patients on placebo, 0.9% of patients on antimuscarinic monotherapy, 0% of patients on α_1 -AR antagonist, and 0.9% of patients on combination therapy provided that the residual urine (RU) does not exceed 200 ml or a quarter of the bladder capacity. Patients with RU >200 ml were excluded from this study [22]. These low rates accord with an earlier study of 50 patients with bladder outlet obstruction and detrusor instability [23].

These data suggest that the combination of an antimuscarinic agent and an α_1 -AR antagonist is safe and more effective in reducing bothersome storage symptoms in patients with LUTS/BPH than are α_1 -AR antagonists alone. Of course, larger and longer placebo-controlled studies are needed to confirm these findings.

3.3.2. Clinical practice

The Web survey also included a case of a LUTS/BPH patient with explicit storage symptoms (Fig. 2). More than three out of four physicians suggested treating this man with α_1 -AR antagonist monotherapy. Only 12.5% of those who choose “other treatment,” or 1.3% in total, opted for the combination of an antimuscarinic drug and an α_1 -AR antagonist. However, if the α_1 -AR antagonist failed to resolve the severe storage symptoms, about half of the physicians would treat the man with an antimuscarinic agent plus an α_1 -AR antagonist, while one-third of the responders would choose surgery (Fig. 3).

3.4. Lower urinary tract symptoms suggestive of benign prostatic hyperplasia and concomitant erectile dysfunction

LUTS/BPH and erectile dysfunction (ED) are both highly prevalent in older men and have a large impact on QoL. Moreover, several studies including

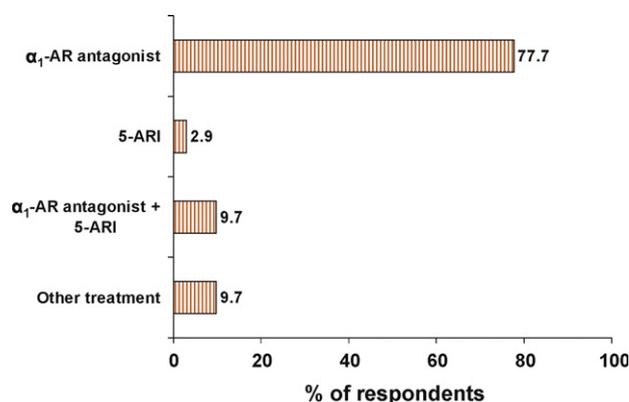


Fig. 2 – Opinions of 382 urologists participating in a Web-based survey regarding the following case: How would you treat a man aged 67 yr presenting to your office with the complaint that he has very bothersome lower urinary tract symptoms (urgency, frequency, nocturia, and weak stream) for more than 6 mo? International Prostate Symptom Score (IPSS) evaluation shows that he has a total IPSS of 27 and a high bother score (IPSS quality of life: 5). Further examinations show that he has a prostate volume of 29 ml, a maximum urinary flow rate (Q_{max}) of 11 ml/s, a postvoid residual of 62 ml, and a prostate-specific antigen (PSA) level of 1.1 ng/ml. He is currently taking ramipril for hypertension.

α_1 -AR = α_1 -adrenoceptor; 5-ARI = 5 α -reductase inhibitor.

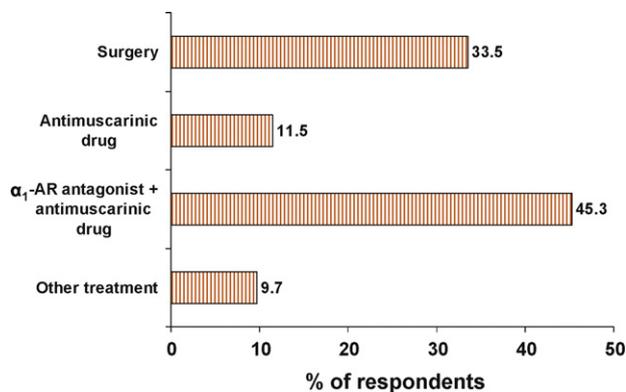


Fig. 3 – Opinions of 382 urologists participating in a Web-based survey regarding the following question: How would you treat this patient if severe storage symptoms (urgency, frequency) did not resolve after treatment with an α_1 -adrenoceptor antagonist?
 α_1 -AR = α_1 -adrenoceptor.

the large Multinational Survey of the Aging Male (MSAM-7), with 12 815 responders between 50 yr old and 80 yr old, showed that both conditions are linked and that LUTS are a crucial risk factor for sexual dysfunction, independent of age and cardiovascular comorbidities [24]. More severe LUTS are associated with more severe sexual dysfunction; while 43.3% of the responders with mild LUTS reported erection problems, 81.9% of the responders with severe LUTS reported erection problems [24]. The biological relationship between LUTS and ED is supported by an increasing body of evidence, although it is not (yet) completely understood. One possible explanation might be that LUTS/BPH patients have a reduction in nitric oxide synthase-containing nerves in the prostate, and lack of nitric oxide can cause ED. This and other theories were recently reviewed by McVary [25].

Since α_1 -AR antagonists are considered to be the most effective monotherapy for LUTS and phosphodiesterase type 5 inhibitors (PDE5-I) are the first-line treatment for ED [26], their combination could provide an interesting therapy for those men suffering from LUTS/BPH and concomitant ED. The α_1 -AR antagonists and PDE5-I have a different mechanism of action, and therefore coadministration might result in synergistic effects on LUTS/BPH and ED. However, both agents can cause vasodilation, and coadministration may lead to hypotension. Selective α_{1A-D} -AR antagonists which have reduced interference with blood pressure (eg, tamsulosin) are therefore probably the best treatment option for combination therapy in this patient population [27].

A recent pilot study of Kaplan et al assessed the efficacy and safety of an α_1 -AR antagonist, a PDE5-I,

and their combination on 62 men with LUTS/BPH and ED (Table 1) [28]. The improvement of the IPSS at 12 wk was significant in all three groups but greatest with the combination therapy group. The combination of the α_1 -AR antagonist and the PDE5-I also improved the International Index of Erectile Function (IIEF) more than either drug alone at 12 wk [28]. The data of this short-term pilot study with a limited number of patients and without placebo control need to be confirmed in large placebo-controlled trials.

4. Conclusions

Management of LUTS/BPH requires careful investigation with respect to symptoms and risk factors for disease progression (eg, prostate volume, PSA level, and age). Medical therapy of LUTS should be tailored to each individual patient. For those patients at high risk of progression, it seems appropriate to add a 5-ARI to the α_1 -AR antagonist to obtain maximum relief of symptoms and to stop the progression of the disease. Coadministration of an α_1 -AR antagonist and an antimuscarinic agent can be considered in the presence of LUTS/BPH and concomitant OAB symptoms. Combining an α_1 -AR antagonist and a PDE5-I might be a good treatment option for men with LUTS and concomitant sexual dysfunction, although additional studies are needed to confirm the current data.

Conflicts of interest

Dr Shahin received an honorarium for presenting the lecture at the European Association of Urology symposium on which this paper was based.

Funding support

The publication of this review was supported by Astellas Pharma Europe.

Acknowledgements

The author is grateful to Ismar Healthcare NV for its assistance with the writing of the manuscript.

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