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Collaborative Review – Bladder Outlet Obstruction

The Role of Antimuscarinics in the Management of Men With Symptoms of Overactive Bladder Associated With Concomitant Bladder Outlet Obstruction: An Update

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Abstract

Context: This review focuses on the contemporary role of antimuscarinics in the management of men with symptoms of bladder outlet obstruction (BOO) and concomitant overactive bladder (OAB). Safety issues of antimuscarinics in this subpopulation of men are also reviewed.
Objective: We reviewed the current literature and performed an analysis of the efficacy, suitability, and the safety of antimuscarinics in this subpopulation of men.
Evidence acquisition: We performed a systematic search of Medline/PubMed, Embase, Scopus, and the Cochrane Database of Systematic Reviews for relevant articles published between 1990 and September 2010, restricted to studies in humans published in English. In addition, published abstracts presented at the annual meetings of the European Association of Urology, the American Urological Association, and the International Continence Society in the last decade (2000–2010) were hand-searched and evaluated. Each article's title and abstract were reviewed for their appropriateness and relevance to the use of antimuscarinics in patients with BOO and concomitant OAB. Relevant articles were fully reviewed and included in the final data acquisition.
Evidence synthesis: Treatment options include combination treatment with α- blockers and antimuscarinics, sequential use of α-blockers and antimuscarinics, monotherapy with antimuscarinics, and a combination of antimuscarinics and 5α-reductase inhibitors. The sequential use of α-blockers and antimuscarinics seems to be the most appropriate approach, and the use of antimuscarinics and α-blockers appears generally to be safe and efficacious. Data are insufficient for a possible stratification of patients for a specific sequence of the drugs reviewed.
Conclusions: This review infers that the existing data confirm the safety of antimuscarinics administered for the treatment of these patients. The efficacy of antimuscarinics has been proven in different trials regarding different storage symptom end points, but not all end points regarding OAB reached significance. All the reported trials are of short duration (4–12 wk) and include only men with low postvoid residual urine volumes at baseline (<200 ml). Overall, the addition of an antimuscarinic to the treatment of a patient with BOO and concomitant OAB seems to offer an amelioration of the symptoms and a moderate improvement in quality of life.

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1. Introduction

Benign prostatic hyperplasia (BPH) is a common condition among elderly men, occurring in up to 70% of men >60 yr of age [1], and is commonly the cause of bladder outlet obstruction (BOO). Although the immediate impact of BOO is on voiding and postvoiding symptoms, lower urinary tract symptoms (LUTS) associated with the disorder include storage symptoms [2]. These symptoms are particularly bothersome to patients, interfere with daily activities, and have a negative impact on patient quality of life (QoL) [3].

Overactive bladder (OAB) is a symptom complex defined by urgency with or without urge urinary incontinence usually associated with increased daytime frequency and nocturia [4]. The most common cause of OAB is detrusor overactivity (DO) in half to two-thirds of patients [5], which is thought to result not only from efferent (motor) hyperfunction/dysfunction but also most likely by afferent (sensory) noise [6–9]. Afferent noise may be generated by local acetylcholine (ACh) release within the detrusor muscle. Moreover, ACh derived from urothelium may stimulate afferent activity (probably via release of adenosine triphosphate) from the bladder, contributing to OAB and DO [8]. It has been suggested that those patients with OAB but without urodynamically demonstrable DO could represent a different part of the same disease spectrum [10]. Interestingly, patients with OAB seem to respond to antimuscarinic treatment irrespective of the presence of DO [11].

DO has been identified in approximately 45–50% of men with BOO and could result from local factors within the bladder, such as denervation hypersensitivity of cholinergic receptors (Cannon's law) and/or structural changes resulting from urinary bladder ischaemia [12]. Not only peripheral problems (BOO and bladder) but even central problems, such as ischaemic brain lesions, can provoke OAB, especially in the elderly population [7]. However, the presence of BOO and DO does not necessarily imply a cause–effect relationship, because OAB symptoms can occur in patients without BOO [12] (Fig. 1), suggesting that it is an age-related phenomenon. Pressure-flow testing is the only way to confirm the presence of BOO in men presenting with one or more LUTS.

Alfa1-adrenoceptor antagonists (α-blockers) remain the most widely used pharmacologic agents for relief of bladder outflow resistance and are targeted at the dynamic component (increased smooth muscle tone) of BPH [13]. Considering the prevalence and severity of storage symptoms in male patients with increasing age, it could be reasonably expected that a combination therapy comprising an α-blocker and an antimuscarinic agent would significantly alleviate storage LUTS after primary treatment with the α-blocker and further improve patient QoL. However, there is the theoretical danger of impairment of already-decompensating bladder activity in the presence of obstruction as a consequence of antimuscarinic action, thereby precipitating acute urinary retention (AUR). For many years, the diagnosis of BPH and BOO has been considered a contraindication to the use of antimuscarinics.

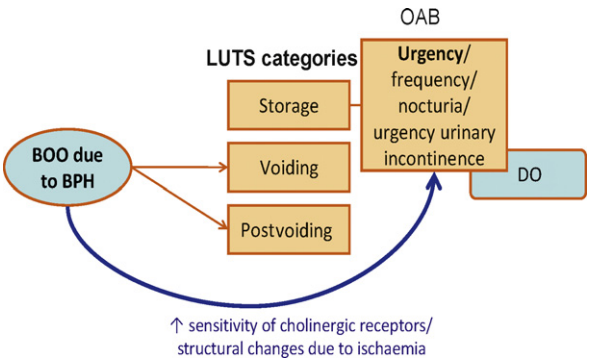

Fig. 1 – Lower urinary tract symptoms (LUTS) involved in benign prostatic hyperplasia (BPH)–associated bladder outlet obstruction (BOO) and overactive bladder (OAB). BOO resulting from BPH can lead directly to voiding and postvoiding LUTS. OAB symptoms are often associated with detrusor overactivity (DO) identifiable on urodynamic testing.

Although traditionally, antimuscarinic therapy at therapeutic doses has been assumed to work via motor pathways, there is an increasing body of evidence that the mechanism of action of antimuscarinics on OAB symptoms could be on bladder sensory pathways rather than on motor pathways [8,14,15]. Accordingly, antimuscarinics administered at clinically recommended doses have little effect on voiding pressures [8,16].

There is some evidence that muscarinic acetylcholine receptors located in the urothelium/suburothelium and on afferent nerves may contribute to the pathophysiology of OAB. Blockade of these receptors may also contribute to the clinical efficacy of antimuscarinic agents [8,17]. Muscarinic receptors are also known to be expressed on sympathetic nerve endings, where they play a regulatory role in the release of norepinephrine [18,19]. Moreover, it has been proposed that there is an activation of C-fibres in pathologic situations without having a significant role in the physiologic sensation of bladder filling. The non-neuronal release of neurotransmitters may also represent another mechanism of a direct stimulatory effect on C-fibres [20,21]. In support of this hypothesis, Hedlund et al [22] showed in an animal study that tolterodine did not decrease the contractile effects of apomorphine-induced detrusor contractions at the doses used, suggesting that the drug had no effect on efferent neurotransmission during voiding. It is of interest also that in a recent study, Fullhase et al [23] concluded that urodynamic changes in obstructed rats can be normalised by intrathecal 5-hydroxymethyl tolterodine and by intrathecal doxazosin. When the two drugs were combined at the doses used, only small additional effects were observed. The central pathways on which the two drugs act seem to be upregulated in rats with partial urethral obstruction, but the effect appears to be less relevant under physiologic conditions (nonobstruction).

A further important consideration is the direct action of antimuscarinics on possible antimuscarinic receptors of the prostate. Witte et al [24] reported the existence of dense cholinergic innervations in the prostate within both the stromal and epithelial compartments of the prostatic gland. Interestingly, the muscarinic receptors of the human

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prostate, which have been shown to be functional in signal transduction assays, are expressed at greater densities than α1-adrenoceptors. The M1-subtype receptors predominate and are located on epithelial cells; low levels of M2 receptors are found on stromal cells. Contractile responses of the prostate to M2 receptor stimulation are small. It has also been suggested that, in humans, muscarinic receptors may promote the growth of the prostate. Based on these data, it seems that a direct effect on the prostate has to be considered when muscarinic receptor antagonists are used in men. It appears that they could act not only on glandular secretion but also on prostatic growth [24–27].

Antimuscarinics now represent first-line treatment of OAB. Therefore, given the prevalence of combined voiding and OAB (storage) symptoms as well as the finding that the QoL of these patients is mainly affected by the symptoms of OAB, it is important to ascertain whether obstruction is a contraindication for the use of antimuscarinics. Many studies have now addressed this question as well as testing the efficacy of different treatment regimens [28]. This review attempts to summarise the findings of these investigations.

2. Evidence acquisition

A systematic search of National Centre for Biotechnology Information PubMed, Embase, Scopus, and the Cochrane Database of Systematic Reviews for relevant articles published between 1990 and September 2010 was performed using the following Medical Subjects Headings terms: *combination treatment and OAB, alpha-blockers plus anticholinergics, alpha-blockers plus antimuscarinics, alpha adrenoreceptor antagonist plus antimuscarinics, alpha adrenoreceptor antagonist plus anticholinergics, OAB and BPH, OAB and BOO, Lower Urinary Tract Symptoms, muscarinic receptors and prostate, oxybutynin, tolterodine, propiverine, darifenacin, trospium chloride, solifenacin,* and *fesoterodine*. The search was restricted to studies of humans published in English. Each article's title and abstract were reviewed for their appropriateness and relevance to the use of antimuscarinics in patients with BOO and concomitant OAB. Furthermore, published abstracts presented at the annual meetings of the European Association of Urology, American Urological Association (AUA), and International Continence Society (ICS) in the past decade (2000–2010) were hand-searched and evaluated. The initial list of selected papers was further enriched by suggestions from co-authors of the present review, some of whom are international opinion leaders on this topic (Fig. 2).

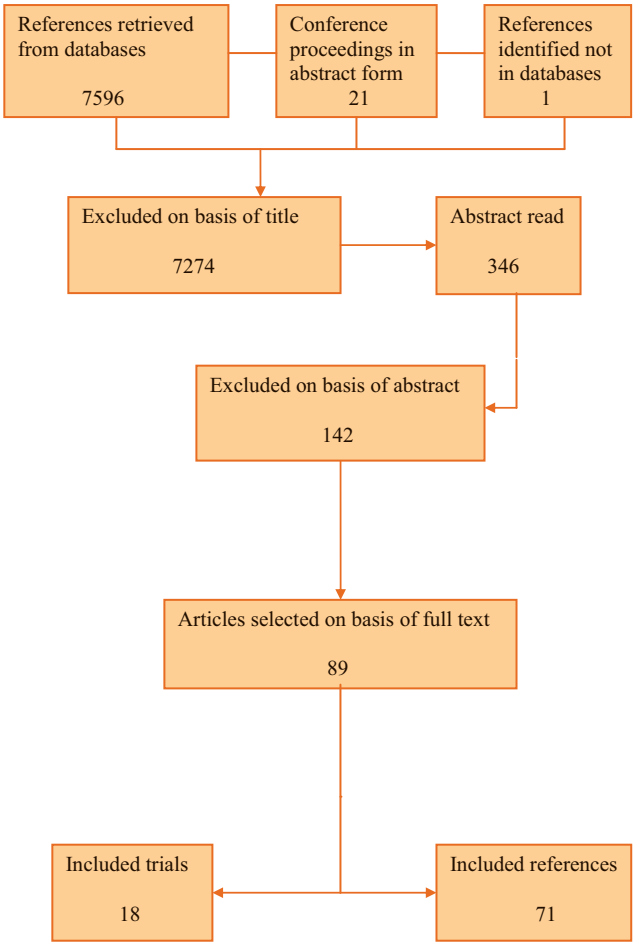

Fig. 2 – Flow diagram of the search results.

3. Evidence synthesis

3.1. Monotherapy with antimuscarinics

For many years, antimuscarinics were used only in women, and the trials usually included female patients. Rather recently, antimuscarinics have been used in men presumed not to have BOO. In three large trials that included women and men without presumed BOO, a post hoc analysis in each study focused on the group of men [29–31]. All three studies concluded that treatment with antimuscarinics (two trials with tolterodine extended release [ER] and one with solifenacin 5 mg) was efficacious, while symptoms suggestive of urinary retention were absent or not significantly different from the placebo group. An interesting study by Ronchi et al [32] investigated the influence of solifenacin in men with underactive detrusor. This trial concluded that treatment did result in changes in urodynamic parameters but that these changes seemed not to be of clinical significance, as suggested by the lack of subjective deterioration in voiding difficulties and the low incidence of AUR.

Few studies have investigated the effects of monotherapy with antimuscarinics for male patients with BOO and OAB symptoms. The efficacy findings from these studies have not been encouraging. For example, in a post hoc analysis of the TIMES study, tolterodine alone had no significant effect on measures of urgency in patients with both BOO and OAB, although this finding was in contrast to the results of a previous study [30]. However, safety results from monotherapy studies confirm the finding from combination studies that acute AUR is probably an issue only for patients with prominent storage symptoms and

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severe concomitant BOO [33]. Nishimatsu and colleagues [34] did not report any episodes of AUR in 26 patients with obstruction and OAB treated with propiverine.

The results of the few clinical trials in this area support this lack of effect of antimuscarinic monotherapy on voiding pressures. In a study by Abrams and co-workers [35], 149 men with BOO and urodynamically verified OAB received tolterodine 2 mg twice daily. Of the 149 patients, 87% completed the 12-wk treatment. There were no changes in urodynamic parameters suggestive of safety concerns, and only a mild increase in residual volume was noted (+25 ml). In addition, there was only one reported case of AUR. In this study, there were improvements in storage symptoms favouring tolterodine.

A small study [36] and a small group of patients in another study [37] suggested a positive effect of monotherapy with antimuscarinics in patients with OAB and concomitant BOO. In the first study, mean 24-h micturition frequency decreased from 9.8 to 6.3 voids, and nocturia decreased from 4.1 to 2.9 episodes nightly. Significant changes in mean AUA symptom scores (−6.1) were also noted. In this trial, no patient reported AUR [36], while in the second study, urinary frequency improved significantly, but postvoid residual (PVR) urine volumes also increased

Table 1 – Studies investigating the use of an α-blocker and antimuscarinic combination therapy for men with bladder outlet obstruction and overactive bladder symptoms

Reference	No. of patients	Treatment	Type of study	Follow-up, wk	Efficacy end points	No. of retention cases	Level of evidence
Lee et al [46]	142	Propiverine plus doxazosin	ProspectiveRandomised Controlled Double-blind Multicentre	8	Bladder diary (+) IPSS (+ storage) Patient satisfaction (+)	0	1b
Kaplan et al [38]	225	Tolterodine plus tamsulosin	Prospective Randomised Controlled Double-blind	12	PPTB (+) Bladder diary (+) IPSS (+ total)	2	1b
MacDiarmid et al [54]	203	Oxybutinin plus tamsulosin	Prospective Randomised Placebo-controlled Double-blind	12	IPSS (+ storage) QoL (+) Uroflowmetry and PVR	0	1b
Chapple et al [55]	283	Tolterodine ER plus α-blocker	Prospective placebo-controlled Double-blind	12	IPSS (+) Symptom bother (+) Bladder diary (+) Uroflow & PVR	3	1b
Kaplan et al [56]	398	Solifenacin plus tamsulosin	Prospective Placebo-controlled Double-blind	12	Bladder diary (+) IPSS (total) Uroflowmetry and PVR	7	1b
Athanasopoulos et al [43]	25	Tolterodine plus tamsulosin	Prospective Randomised	12	Urodynamics (+ storage) Pressure flow study QoL (+)	0	2b
Lee et al [53]	68	Tolterodine plus doxazosin	Prospective Observational	12	IPSS (+)	2	2b
Maruyama et al [50]	51	Propiverine or Oxybutinin plus naftopidil	Prospective Randomised Controlled	12	IPSS (total) QoL Uroflowmetry and PVR	0	2b
Yang et al [51]	33	Tolterodine plus terazosin	Prospective Randomised	6	IPSS (+ storage) Uroflowmetry and PVR	0	2b
Yokoyama et al [37]	23	Propiverine plus naftopidil	Prospective Randomised Controlled	4	IPSS (+ storage) Bladder diary (+)	0	2b
Mohanty et al [49]	38	Tolterodine plus tamsulosin	Prospective Randomised	12	Urodynamics (+) Pressure flow study QoL (+) Bladder diary (+) IPSS (total)	0	2b
Wiedemann et al [57]	4382	Trospium plus α-blocker	Prospective Multicentre Open Noninterventional	4	IPSS (+ total) QoL (+) Bladder diary (+) Pads requirement (+)	N/A	3b
Kang et al [52]	70	Propiverine plus tamsulosin	Prospective	12	QoL (+) IPSS Uroflowmetry and PVR	0	3b
Aldemir et al [58]	45	Tolterodine plus alfuzosin	Prospective	12	IPSS (total) Uroflowmetry and PVR	0	3b

ISPP = International Prostate Symptom Score; PPTB = Patient Perception of Treatment Benefit; QoL = quality of life; PVR = postvoid residual; ER = extended release; N/A = not applicable.
(+) = Favouring combination treatment with an antimuscarinic plus an α-blocker

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significantly, while one patient presented with AUR and one with more difficulty in voiding [37]. In contrast, in a well-contacted study [38], a large group of patients treated with monotherapy did not show any significant effects on measures of urgency, the International Prostate Symptom Score (IPSS), and the overall percentages of patients reporting treatment benefit. One patient presented with AUR.

A recent study focusing on acute urinary retention in men concluded that those using antimuscarinics experienced a 2.9-fold increase in relative risk, but that risk was greatest in the first 30 d of use [39]. In this study, the specific demographic and urodynamic characteristic of this subpopulation are not clear. As the results of this study have not yet been published as a full paper, they should be considered with scepticism. In contrast, another recent small study concluded that long-term antimuscarinic use (>1 yr) was a risk factor for increasing the PVR urine volume by >50 ml. Prostate-specific antigen (PSA) levels and prostate volumes were not risk factors in this study [40].

These studies suggest a minimal influence of antimuscarinics on the likelihood of developing AUR, although it is not clear which patients would experience the best efficacy. It seems likely that patients with mild obstruction, smaller prostates, low PSA levels, and OAB symptoms are most likely to benefit from monotherapy with antimuscarinics [41].

3.2. Combination treatment with α-blockers and antimuscarinics

In 1994, Chapple and Smith referred to the theoretical possibility of combination treatment with α-blockers and antimuscarinics for BPH [42]. Since then, a variety of such combinations have been evaluated in patients. The existing trials literature reported in English that used the combination of an antimuscarinic and an α-blocker (AA treatment) are presented in Table 1. The earliest publication in Medline that discusses this type of therapy for the treatment of BOO in men with concomitant OAB is that of Athanasopoulos et al [43]. This prospective, randomised, controlled study evaluated the effect of tolterodine 2 mg twice daily combined with tamsulosin 0.4 mg once per day compared with tamsulosin monotherapy on QoL in 25 patients with BOO and concomitant DO. The patients were >50 yr of age and had mild or moderate BOO and concomitant detrusor overactivity as urodynamically proven in a pressure flow study (Schafer's nomogram). The follow-up period was 3 mo. Urodynamic measures improved in both groups, but only the combination therapy group achieved a better QoL. Furthermore, no instances of AUR were reported, and tolterodine did not affect urine flow or residual volume. This was a small prospective, randomised study that emphasised the conceptual benefit of this combination treatment.

These data supported earlier findings published in Japanese from Saito et al [44] in a nonindexed journal describing combination treatment with an α-blocker and an antimuscarinic agent, although the only available information in English from that study comes indirectly from citations [45,46]. In this Japanese randomised, single-blind, multicentre, 4-wk study, the authors assessed the efficacy of the combination of propiverine 20 mg/d and tamsulosin 0.2 mg/d in 67 BPH patients. In the combination group, the improvement in storage symptoms was greater, with particularly significant improvement seen in nocturia. The residual volume was unchanged in both groups, and there was only one case (1.5%) of AUR with the combined treatment.

Subsequently, in a prospective, randomised, double-blind, controlled, multicentre trial, Lee et al [46] compared the efficacy and safety of combination therapy with propiverine and doxazosin in a group of patients with urodynamically confirmed BOO and concomitant OAB symptoms. For 8 wk, 142 patients received combination treatment. Compared with the doxazosin arm, the patients in the combination therapy group showed greater improvement in urinary frequency; average micturition volume; and scores for items 2, 4, and 7 of the IPSS questionnaire. Patient satisfaction was significantly higher in the combination treatment group. There was also a significant increase in PVR urine (+20.7 ml) in the combination treatment group, but no case of AUR was recorded. This is a study with a high level of evidence and a substantial number of included patients, but it has a short follow-up.

Kaplan et al [38] published the results of an important randomised, controlled, double-blind trial (the TIMES study) in which 225 patients were enrolled in the combination treatment arm (tolterodine ER 4 mg plus tamsulosin). After 12 wk of treatment, the Patient Perception of Treatment Benefit (PPTB) questionnaire, bladder diary variables, and IPSS were assessed, and the combination group showed significant improvements in all measured parameters. There was no effect on voiding pattern and no significant difference in urinary flow or the PVR urine among any groups. Two patients taking tolterodine ER plus tamsulosin presented with AUR, and the authors concluded that the use of an antimuscarinic is a safe option for the treatment of BPO. This study did not look at the addition of antimuscarinics in symptomatic patients. This study included an adequate number of patients and was well designed, offering a high level of evidence.

A subanalysis [47] of data from the TIMES study [38] focused on the urgency perception scale and concluded that the group of 217 men who received tolterodine plus tamsulosin showed significantly improved urgency variables and patient-reported outcomes. Moreover, this group of patients reported increased satisfaction with the treatment as well as a willingness to continue the treatment [30]. Another subanalysis [48] of data from the TIMES study [38] looked at effects on urinary symptoms assessed by the IPSS. This subanalysis concluded that tolterodine ER plus tamsulosin were significantly more effective than placebo in treating storage LUTS, including OAB symptoms. Tamsulosin alone also produced significant improvements in voiding LUTS. It is important to underline that the results of the TIMES subanalysis should be considered with caution, as it is a post hoc analysis.

Accordingly, Mohanty et al [49] reported another prospective study of tolterodine ER plus tamsulosin in

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which patients in the combination group had a significantly better response to treatment than patients in the tamsulosin monotherapy group for the majority of the main urodynamic variables studied as well as QoL end points. In this study, the degree of obstruction was evaluated with a pressure flow study (ICS nomogram). The number of patients in this study was rather limited, but the results are of value.

In 2006, Maruyama et al [50] published a prospective, randomised, controlled study in which either 25–75 mg/d of naftopidil (an α_1D-AR blocker) alone (monotherapy group) or combination therapy using 25–75 mg/d of naftopidil and an antimuscarinic agent (10–20 mg/d of propiverine hydrochloride or 2–6 mg/d of oxybutynin hydrochloride; cotherapy group) were administered for 12 wk to 101 BPH patients with storage symptoms. In this study, the IPSS and QoL index improved significantly in both groups, with no marked differences between groups. Maximum flow rate (Q_{max}) and residual urine volume tended to improve in both groups, again with no marked differences between groups. However, median post-therapeutic residual urine volume was significantly worse in the combination therapy group (45.0 ml) than in the monotherapy group (13.5 ml; $p = 0.021$). The authors noted that the ratio of patients with increased residual urine volume to unchanged residual urine was also significantly worse for combination therapy (22.9%) than for monotherapy (5.0%; $p = 0.038$). They concluded that naftopidil is a useful agent as the first choice in BPH patients with storage symptoms. With the low-dosage antimuscarinic, the combination therapy group did not present any superiority regarding efficacy. Moreover, although they did not encounter any cases of AUR, the percentage of patients with increased residual urine volume was also significantly worse for the combination therapy group. It is worth mentioning here that a statistically significant increase in PVR (45 ml) probably has no clinical significance. This study had adequate follow-up and value.

The 2009 prospective, randomised, controlled study from Yokoyama et al [37] investigated similar treatment groups. Sixty-six men >50 yr of age with IPSS scores >8, BPH, and concomitant OAB were randomised into three groups: naftopidil (50 mg once daily) only or propiverine hydrochloride (20 mg once daily) or naftopidil (50 mg once daily) plus hydrochloride (20 mg once daily). The use of antimuscarinics in this study did improve storage symptoms. This is a small study with short follow-up but is of some value.

In 2007, Yang et al [51] reported on the effectiveness and safety of the combination of terazosin and tolterodine for LUTS/BPH patients with dominant storage symptoms. A total of 69 patients were enrolled; the main exclusion criteria were prostatic volume >50 ml, Q_{max} <10 ml/s, and residual urine >50 ml. After initial treatment with terazosin for 1 w, the patients were randomly assigned to two groups. One group (33 patients) received terazosin plus tolterodine in combination. After 6 wk of treatment, the results showed significantly greater reductions in IPSS after treatment in the combination group compared with the monotherapy (terazosin) group, mainly because of storage IPSS items. There was no difference in Q_{max} or PVR urine between the two groups after treatment, and no case of AUR was recorded in this prospective but sort-term study. The authors suggested that the profile of patients in their study might be used as the indication for such combined therapy for LUTS associated with BPH without urodynamic evaluation. This is another study with a limited number of patients and short follow-up but with a good level of evidence.

Kang et al [52] reported the results of their clinical trial at the end of 2009, which had evaluated the efficacy and safety of combined therapy of an α-blocker (tamsulosin 0.2 mg) and a low-dose antimuscarinic (propiverine HCl 10 mg) compared with tamsulosin monotherapy in patients with BPH accompanied by OAB symptoms. This prospective study included male patients with LUTS, a prostate volume ≥20, and an IPSS score >8. Patients with PVR volume >100 ml pretreatment were excluded. In total, 115 patients completed the study. After 3 mo, both groups showed significant improvements in IPSS, QoL score, voided volume, Q_{max}, and PVR, but only the QoL score was significantly different between the groups (in favour of the AA treatment group). No cases of AUR were recorded in the low-dose study. This trial had adequate follow-up and included a good number of patients but has a low level of evidence.

3.3. *Sequential use of α-blockers and antimuscarinics*

Studies investigating the combined use of α-blockers and antimuscarinics have shown that patients can benefit from this treatment strategy. However, a more pragmatic approach to therapy that mirrors what is likely to be real-life clinical practice is to use sequential therapy, where the patient is first treated with an α-blocker, and those with continuing OAB symptoms at follow-up have an antimuscarinic agent added to their therapy. This strategy has the important benefit of minimising the number of medications the patient receives to achieve improved QoL (Table 1). In 2004, Lee et al [53] published the results of a prospective observational study assessing the efficacy of combination treatment (doxazosin and tolterodine) in men with BOO and DO. PVR urine >150 ml or severe obstruction according to the Abrams–Griffiths nomogram were exclusion criteria, and all patients completed the IPSS. Only 35% of patients with BOO and DO showed symptomatic improvement with doxazosin as monotherapy. Of the 68 nonresponders, 73% had a symptomatic improvement 3 mo after the addition of tolterodine. Two men receiving combined therapy experienced AUR, which resolved with insertion of an indwelling catheter overnight and cessation of tolterodine therapy. This study was the first to use the sequential technique with a substantial number of patients and a representative follow-up period, offering a good level of evidence.

MacDiarmid et al [54] reported the results of a large randomised, double-blind, placebo-controlled study in 2008 that showed that men with LUTS who demonstrated incomplete symptom remission with tamsulosin alone experienced significant improvement—particularly with

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respect to storage symptoms—with the addition of 10 mg/d of oxybutynin ER. In this well-conducted study, 203 patients received the combination of oxybutynin ER and tamsulosin for 12 wk; none reported AUR. Eligibility requirements included a maximum flow rate ≥8 ml/s and a PVR ≤150 ml. The criteria for excluding about half of the screened population from randomisation in this study are not provided. This is a study with a high level of evidence and large number of patients, and it has adequate follow-up.

In 2009, Chapple et al [55] published a well-designed prospective, double-blind, placebo-controlled trial in men ≥40 yr of age with frequency, urgency, and at least moderate problems reported on the Patient Perception of Bladder Condition (PPBC) score, despite being on a stable dose of an α-blocker for ≥1 mo. Multiple α-blockers were used in this study. Patients were randomised to tolterodine ER 4 mg or placebo once daily for 12 wk while continuing their prescribed α-blocker therapy. At baseline and week 12, subjects completed the PPBC, IPSS, OAB Questionnaire, and 5-d bladder diaries using the five-point Urinary Sensation Scale (USS). *Frequency–urgency sum* was defined as the sum of USS ratings for all micturitions. The use of bladder diary outcomes is the important difference between this trial and earlier trials. A total of 292 patients in the placebo arm and 283 in active drug treatment completed the study. Significantly greater improvements in diary variables, IPSS, and symptom bother were achieved by patients receiving additional tolterodine ER versus placebo plus an α-blocker. Regarding safety issues, acute AUR requiring catheterisation occurred in <1% of patients in both groups. There were no clinically meaningful changes in PVR volume or Q_{max}. This trial had a large number of patients, adequate follow-up, and a high level of evidence.

In 2009, Kaplan et al [56] reported their results using solifenacin as the antimuscarinic combination treatment. This was a 12-wk, double-blind, placebo-controlled trial assessing the safety and tolerability of solifenacin plus tamsulosin in men with residual OAB symptoms after tamsulosin monotherapy and included a tamsulosin plus placebo group. A total of 398 men having taken tamsulosin for ≥4 wk were randomised in this study. Inclusion criteria were (1) ≥45 yr of age, (2) ≥8 micturitions and ≥1 urgency episode per 24 h, (3) IPSS ≥13, (4) PPBC score ≥3, (5) PVR ≤200 ml, and (6) Q_{max} ≥5 ml/s. The authors concluded that at week 12, solifenacin plus tamsulosin decreased daily micturitions and urgency episodes. However, only changes in urgency episodes reached statistical significance versus placebo plus tamsulosin. There was a low incidence of AUR requiring catheterisation. Of the patients on solifenacin plus tamsulosin, seven (3%) reported retention and three required catheterisation. No patients on placebo plus tamsulosin reported retention. This study included a large number of patients with adequate follow-up and has a high level of evidence.

In the same year, Wiedemann et al [57] published a large, multicentre, open, noninterventional, prospective study performed in private urology practices. Only patients with OAB and LUTS resulting from benign prostatic enlargement/BPH who were insufficiently treated with α-receptor blockers were eligible to participate. Patients received trospium chloride–coated tablets as oral add-on therapy. The dosing and duration of treatment were not predetermined, but a minimal treatment period of 4 wk was suggested. Core symptoms of LUTS (urgency, frequency), IPSS, OAB, and QoL score were assessed at the beginning and end of the observation period. In total, 4104 cases fulfilled the predetermined criteria for the evaluation of efficacy, and all 4382 cases were included in the safety analysis. After a mean (standard deviation) treatment period of 40 (17.9) d with trospium chloride as add-on therapy, all primary end points had improved: The mean daily micturition frequency was reduced from 11.8 (3.5) to 8.5 (2.5) events. The percentage of continent patients increased from 66.6% to 83.1%, and the proportion of patients requiring incontinence pads was almost halved, from 19.9% to 11.7%. The median IPSS was reduced from 18 to 12, and the QoL score improved from 4 to 2. Treatment tolerability was assessed according to a questionnaire as very good or good by 94.2% of the doctors. There were 121 (2.8%) early treatment withdrawals, and 35 (0.8%) patients experienced adverse events. This study has a short follow-up but probably reflects the everyday clinical situation. This trial has the largest number of patients and the shortest follow-up, therefore providing a low level of evidence.

In 2010, Aldemir et al [58] published a prospective trial assessing the efficacy and reliability of alfuzosin 10 mg alone or in combination with tolterodine 2 mg in patients with BPH accompanied by LUTS. This is the first trial to use alfuzosin as the α-blocker component of AA treatment. In this study, 45 males >40 yr of age were included for evaluation. Pretreatment examination included IPSS, Q_{max} in uroflowmetry, and PVR volume. Those with PVR >200 ml, Q_{max} <5 ml, or PSA values >4 ng/ml were excluded from the study. Treatment was started with 10 mg alfuzosin, and at the end of the third month, tolterodine 2 mg taken twice daily was added for another 3 mo. Thirty-seven patients were able to complete the 6-mo study. Significant improvements were seen in both groups when compared with baseline. Interestingly, when the two treatments were compared at 6 mo, no statistical differences between the α-blocker monotherapy group and the AA treatment group were found. It is worth mentioning that in this trial, the average PSA value of the patients was 1.4 ng/ml, and the average prostate volume was not large (34.8 ml). No cases of AUR were encountered. This study included a moderate number of patients with adequate follow-up, providing a low level of evidence.

In addition to the full papers that have been reviewed, our literature search also found abstracts published in journal supplements that have yet to be published as full papers [59–61]. All the work in these abstracts concluded that combination therapy with an antimuscarinic and α-blocker is effective and that the risk of urinary retention is minimal.

3.4. *Antimuscarinics and 5α-reductase inhibitors*

Chung and co-workers [62] were the first to publish a work on the combination of an antimuscarinic agent (tolterodine

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4 mg at bedtime) with dutasteride (0.5 mg). The safety and efficacy of this combination was assessed in 51 men with persistent OAB LUTS unsuccessfully treated with ≥6 mo of dutasteride monotherapy. In this 12-wk, open-label study, inclusion criteria were IPSS ≥12, IPSS QoL item ≥3, significant bother, frequency (eight or more voids in 24 h), and urgency (three or more episodes in 24 h). Efficacy was assessed by changes in diary end points and IPSS (total, storage, and voiding), while safety was assessed by changes in PVR, Q_{max}, adverse events, and AUR. The baseline prostate volume was 54.3 ml. At 12 wk, treatment with tolterodine significantly reduced frequency (24-h micturition frequency: −3.2; $p < 0.02$), urgency (OAB episodes: 19.2%; $p < 0.03$; severe OAB episodes: 71.4%; $p < 0.05$), and nighttime voiding (−0.9; $p < 0.003$). 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 ($p < 0.001$). Decreased sexual potency was observed in two patients (3.9%), while PVR increased by 4.2 ml, Q_{max} decreased by 0.2 ml/s, and no patients went into retention. The authors concluded that the combination of tolterodine and dutasteride was effective, safe, and well tolerated in men with large prostates (≥30 ml) having persistent OAB symptoms and LUTS secondary to BPH. This is a low-evidence study with adequate follow-up and without a large number of patients.

3.5. Safety of combination therapy with antimuscarinics

The growing body of literature investigating the use of combination treatment with antimuscarinic agents and an α-blocker or 5α-reductase inhibitor (5-ARI) indicate that these strategies introduce no additional side-effects other than those known for each individual drug. Overall, despite the side-effects, it seems that the impact of these undesirable actions is not particularly clinically significant (eg, dry mouth, constipation, hypotension). The main concern regarding the possibility of AUR has not been evident in practice as long as patients with elevated PVR urines (usually >200 ml) are excluded. Indeed, all the works to date have found that the risk of retention is minimal [28,63].

In addition, a recent study in animals has found that the impact of antimuscarinics on the voiding phase is small, further supporting the safety of antimuscarinics in treating obstructed bladders [64]. Another recent study looking at the safety and urodynamic characteristics of treatment with tolterodine or tolterodine plus tamsulosin in men with LUTS concluded that both options are safe in men with BOO. The inhibitory effect of antimuscarinic agents on detrusor muscle contractions is unlikely to aggravate the voiding difficulties of men with BOO [65]. Although none of the reviewed studies noted central nervous system (CNS) safety signals associated with antimuscarinic therapy, this should be specifically evaluated in future trials. Some of the antimuscarinics—those that can easily pass the blood–brain barrier—may worsen cognition [66]. The risk of CNS impairment is of particular concern for vulnerable populations such as the elderly and CNS-compromised neuropathic bladder patients such as those with multiple sclerosis or Parkinson's disease [66]. Therefore, the use of CNS-active drugs in patients with cognitive impairment should be avoided.

The recent National Institute for Health and Clinical Excellence report [67] presented interesting forest plots. Using data from the TIMES study [38], the researchers compared the adverse events when using antimuscarinics to placebo and found that dizziness, diarrhoea, constipation, and dry mouth were more common on an antimuscarinic therapy. On comparing antimuscarinics to α-blockers, the consequent findings were that the side-effects were those expected using each individual drug. Fewer patients on α-blockers withdrew because of adverse events.

3.6. Predicting who is most likely to respond to the combination treatment

Patients with BOO and concomitant OAB would be suitable for combination treatment with an antimuscarinic agent. However, detailed patient-selection characteristics and appropriate therapy regimens are not yet adequately defined. It is still not completely clear which group of men will benefit most from this strategy [68,69]. Separate analyses of the data used in the TIMES study have demonstrated that tolterodine ER 4 mg was effective in men with smaller baseline prostate volumes (<29 ml) and in those with low baseline PSA levels (<1.3 ng/ml) [70,71].

In a recent post hoc analysis of a 12-wk study performed by Chapple et al [72], the addition of tolterodine ER to α-blocker therapy improved key OAB symptoms and appeared to be well tolerated compared with placebo combined with an α-blocker in men with persistent OAB symptoms, regardless of the subjects' prostate size, as judged by serum PSA concentration. In total, 326 patients received combination treatment with tolterodine ER and an α-blocker, and only two went into AUR. This result was not related to PSA levels.

3.7. Treatments in development

In the future, the combination of an antimuscarinic with a phosphodiesterase type 5 inhibitor (PDE5-I) may be considered. PDE5-Is act by increasing the concentration of nitric oxide in smooth muscle, which relaxes the prostate as well acting on the penis and bladder neck [73,74]. These drugs seem to improve storage and voiding symptoms to a degree in patients with LUTS, although longer-term studies are needed, particularly given the potential cardiovascular safety issues associated with PDE inhibitors. Interestingly, a multicentre, double-blind, placebo-controlled, parallel-group study conducted across 50 centres in North and South America, Europe, and Australia showed no evidence of efficacy for the PDE5-I UK-369003 in the treatment of storage LUTS in men selected based on classic OAB eligibility criteria [75].

Another potential option may be the addition of β_3-agonists to the combination of an α-blocker and an antimuscarinic or the combination of a β_3-agonist with an α-blocker. The combination of β_3-agonists and

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antimuscarinics could maximise the reduction of OAB symptoms, because these drugs have different targets. Indeed, it has been suggested that antimuscarinics affect amplitude and frequency during nonvoiding activity, whilst β_3-agonists affect only frequency [76]. The emerging role of β_3-agonists is important, because these drugs have elicited a potent relaxant effect on the human detrusor muscle in vitro [77], although only data from phase 2 clinical trials have been reported to date [78,79].

4. Conclusions

Our systematic search shows that the use of antimuscarinics in men with BOO and concomitant OAB is safe and, to a degree, efficacious. All other reviews published until now [28,80–88] also infer that the existing data confirm the safety of antimuscarinics administered for the treatment of these patients.

The efficacy of antimuscarinics has been proven in various trials regarding some storage symptom end points, but not all end points regarding OAB reached statistical significance. These studies have included a number of antimuscarinic agents (tolterodine, oxybutynin, propiverine, solifenacin, trospium) with or without an α-blocker. However, all the reported trials are of short duration (4–12 wk) and include only men with low PVR volumes at baseline (<200 ml) [74]. These studies suggest that in men with persistent storage symptoms (OAB symptoms), clinically meaningful improvements can be achieved through the addition of an antimuscarinic therapy to an α-blocker [88].

Monotherapy with an antimuscarinic alone in this patient group is controversial, given the results of the few existing trials. Voiding difficulty and AUR are infrequently reported across all studies, but several trials demonstrated an increase in PVR volume with antimuscarinic therapy [88]. The addition of an antimuscarinic agent to the treatment of a patient with BOO and concomitant OAB symptoms seems to offer a clinical amelioration and an improvement in QoL. The combination of an antimuscarinic agent with an α-blocker seems to be safe according the existing evidence. However, we currently lack sufficient data to formulate criteria (predictors) for which patients would be ideal candidates for this strategy. We would like to suggest, based on existing data, that patients should be selected for addition of an antimuscarinic therapy to existing pharmacotherapy only if they have a residual urine <200 ml and a maximum flow rate >5 ml/s before starting the antimuscarinic treatment. It seems that patients with predominantly storage symptoms and no evidence of an increased PVR can be safely treated with antimuscarinic monotherapy, because in this group, the target would only be the bladder. Patients with persistent storage symptoms after treatment of their voiding symptoms with either α-blockade or combination or monotherapy with a 5-ARI (ie, those with higher PSA levels and larger prostates) can be considered for treatment with the addition of an antimuscarinic agent. Longer-term trials and studies reflecting real everyday clinical practice are needed before definitive conclusions can be drawn.

Author contributions: Anastasios Athanasopoulos had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Athanasopoulos, Chapple, Stief, Gratzke.
Acquisition of data: Athanasopoulos.
Analysis and interpretation of data: Athanasopoulos.
Drafting of the manuscript: Athanasopoulos, Chapple, Stief, Gratzke, Fowler, Tubaro.
Critical revision of the manuscript for important intellectual content: Athanasopoulos, Chapple, Stief, Gratzke, Fowler, Tubaro, Kaplan.
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Supervision: Chapple, Stief, Gratzke, Fowler, Tubaro, Kaplan.
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