The Rationale of Combined Antimuscarinics and Alpha-blockers in Patients with LUTS/BPH: Review of the Literature

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INTRODUCTION

Patients with benign prostatic hyperplasia (BPH) might be free of symptoms but often present with lower urinary tract symptoms (LUTS) as a result of difficulties in voiding (e.g. hesitancy, weak stream, dribbling) and irritability of the bladder (e.g. urgency, frequency, urge incontinence) [1]. In the past, this was referred to as "prostatism". However, it has been long known that one third of elderly men with LUTS do not have bladder outlet obstruction (BOO) [2]. In patients who have BOO in addition to detrusor overactivity (DOA), it was reported that storage symptoms persisted in up to 40% of patients even after surgical relief of BOO [3].

Although LUTS and BPH are presumed to be related, the extent to which they are and the nature of the mechanisms linking them are ill-understood. In 1998, the 4th International Consultation on BPH recommended "LUTS suggestive of BPH (LUTS/BPH)" as the preferable term for this condition. Nevertheless, there is no precise definition of LUTS/BPH and it is unclear whether the most relevant target is within the prostate or whether extra-prostatic site are more important [4]. This has created a renewed interest in drugs used for treatment of LUTS/BPH. Traditionally, the initial therapy in men is most often with alpha-blockers, however, combinations of drugs are now being evaluated in clinical trials, and seem to be increasingly prescribed "off label" by physicians [5]. The goal of this review is to briefly discuss the evidence concerning the use of antimuscarics in combination with alpha-blockers in patients with LUTS/BPH.

PREVALENCE OF LUTS/BPH

BPH is a common condition generally associated with aging. The prevalence of BPH has been studied in great detail and results vary from a relatively low prevalence of 13% to a high prevalence of 43% depending on the method of BPH assessment, the country and the age range studied [6]. Berry et al estimated the prevalence of symptomatic BPH was 43% in 50 to 59 year-olds, 70% in 61 to 70 year-olds and 82% in men over 70 year-old [7]. It was presumed to be the most common cause of LUTS in older men. Storage (irritative) symptoms, such as frequency, urgency, nocturia and urge incontinence are commonly seen in patients with LUTS/BPH, but they may also occur in the absence of bladder outlet obstruction from BPH. Storage symptoms are mainly attributable to detrusor instability, which is thought to occur in up to 40% to 60% of patients with benign prostatic obstruction (BPO) or BOO [8]. Eckhardt et al found that the irritative symptoms (e.g. urgency, frequency and nocturia) in 47% of men over 50 years were not caused by BOO, but rather by changes in bladder function [9]. The correlation between BPH and LUTS is still controversial. In 1988, Blaivas proposed that storage symptoms such as frequency, nocturia, and urgency in patients who have BOO may be associated with DOA [10]. Some hypotheses for the potential pathophysiology of DOA in association with male BPH/LUTS were advocated. Based on the histological evidence of denervation and the significant reduction in cholinergic receptors in the obstructed bladder, denervation supersensitivity has been proposed as a possible mechanism for OAB in BOO [11]. But the definitive underlying etiologies of OAB and its relationship with BPO are still not established.

The impact of LUTS/BPH on quality of life (QOL) has been addressed over the past decades, and is an important consideration in LUTS/BPH management. The ICS "BPH" study reported that voiding symptoms are most prevalent in patients with LUTS/BPH, whereas the most bothersome symptoms were storage symptoms [12], because they interfere with daily activities and have a major effect on QOL. Considering the high prevalence of storage symptoms in patients with LUTS/BPH, and the severe impact on patients' QOL, it might be necessary to improve current medical treatment of LUTS associated with or suggestive of BPH.

THE ROLE OF α-BLOCKERS AND 5-α-REDUCTASE INHIBITORS IN LUTS/BPH

Medical therapy for LUTS/BPH aims at alleviation of symptoms as well as beneficial changes in the natural course of the disease. Alpha-blockers are currently the preferred first line medical therapy for men with moderate/severe LUTS. Several α-adrenergic subtypes are present in the human prostate, bladder neck and proximal urethra but the α1 subtype is responsible for contraction [13]. This is based on the hypothesis that LUTS are caused by α-1 adrenergic mediated contraction of smooth muscle cells within the prostate, prostate capsule and bladder neck resulting in BPO. This finding has provided the rationale for the clinical use of α1 adrenergic receptor (α1AR) blocking agents for the relief of LUTS/BPH. Meta-analysis data from the American Urological Association (AUA) Practice Guideline Committee's evidence-based review suggest that the four available α1AR blockers, alfuzosin, doxazosin, tamsulosin, and terazosin are similarly effective in partially relieving symptoms. They produce an average 4 to 6 point improvement in the AUA Symptom Index [14].

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Hormonally based medical therapy for BPH began after the discovery that 5-α-reductase inhibitor (5ARI) which can arrest prostatic growth and target the static component of obstruction. Studies have shown that 5ARIs have significant efficacy in clinical improvement, especially in men with glands larger than 40 g [15]. However, they are less effective than alpha blockers in improving LUTS and are not an appropriate treatment for men with LUTS who do not have prostatic enlargement, whereas they do reduces the risk of acute urinary retention and the need for BPH-related surgery [16].

The data from the Medical Therapy of Prostate Symptoms (MTOPS) Study showed that combined therapy with finasteride, a 5-alpha-reductase inhibitor, and doxazosin, an alpha-1 adrenergic receptor antagonist, provided greater long-term improvement of LUTS/BPH than finasteride or doxazosin alone. The combination therapy reduced the risk of overall BPH progression, which in that study was defined as an increase in the international prostate symptom score (IPSS) ≥ 4 points, acute urinary retention, urinary incontinence, renal insufficiency or recurrent urinary tract infection [17].

EFFICACY AND SAFETY OF COMBINED ANTIMUSCARINICS IN LUTS/BPH

It has been estimated that up to half of men with BOO secondary to BPH have involuntary detrusor contractions and symptoms of overactive bladder. Moreover, in patients who have BOO in addition to DOA, it was reported that storage symptoms persisted in up to 40% of patients even after surgical relief of BOO [3]. Overactive bladder symptoms may coexist with BPH or BOO without being caused by the prostate condition, thus pharmacotherapies that target only the prostate - and not the bladder - may not alleviate overactive bladder symptoms [18].

Although, treatment with either an α1 adrenergic receptor antagonist or a 5-α-reductase inhibitor provides some improvement, many patients with LUTS associated with BPH still suffer from irritative symptoms (urgency, frequency, urge incontinence) affecting their quality of life. What are the benefits of adding antimuscarinics to the treatment regimen in men who have LUTS and persistent OAB symptoms? We reviewed the literature of available studies and evidence concerning the use of antimuscarinics drugs - alone or in combination with α-blocker - in patients with LUTS/BPH (Table 1).

Lee et al [19] enrolled 144 men who had LUTS with urodynamically proven with BOO only (n=76) or with BOO plus DOA (n=68). Lack of symptomatic improvement after an initial 3 months of doxazosin monotherapy prompted a switch to combination treatment with tolterodine. They found that the majority of men with BOO (79%) had symptomatic improvement with an α-blocker alone. Conversely, the majority of men with BOO + DOA (65%) did not. In patients who did not respond to α-blockers, antimuscarinics were effective in achieving symptoms relief in 37.5% of patients with BOO only and 73% of patients with BOO + DOA. They concluded that the combination treatment, based on urodynamic diagnosis, can be started early and circumvents the need for an evaluation period for α-blocker monotherapy.

Athanasopoulos et al [20] studied 50 men with LUTS and urodynamically confirmed BOO and DOA. They were given either a combination of tolterodine 2 mg twice daily and tamsulosin 0.4 mg (n=25), or tamsulosin alone (n=25). After 3 months, there was a significant reduction in the maximum detrusor pressure during micturition (from 70 to 61 cm H_2O) in those on combined alpha blocker and anticholinergic treatment and a statistically significant increase in the maximum flow rate (Qmax). However, the increase of the Qmax in patients receiving combination therapy was equivalent to those who received monotherapy with an α-blocker (from 10.5 to 11.8 mL/s and from 10.3 to 11.5 mL/s respectively). Analysis also revealed statistically significant improvement in QOL scores only in combination group patients (mean scores 525.0 and 628.4 before and after treatment, respectively, interestingly, p=0.0003).

Interestingly, no acute urinary retention was observed and tolterodine did not affect the quality of urine flow or residual urine volume. They concluded that combination treatment can significantly improve storage symptoms without compromising urine outflow and can improve QOL in patients with BOO and concomitant DOA.

Kaplan et al [21] conducted an open study of 43 men with LUTS/BPH who had failed α-blocker therapy (mean 5.7 months), and then received antimuscarinics monotherapy (tolterodine extended-release 4 mg once a day) for 6 months. Comparing baseline and 6-month data, the authors found statistically significant reduction in daytime frequency (from 9.8 to 6.3/day) and nocturia (from 4.1 to 2.9/night). The changes in the mean AUA symptom score (-6.1, $p<0.001$), maximal urinary flow rate (1.9 mL/sec, $p<0.001$), and post-void residual volume (-22 mL, $p<0.03$) were all statistically significant. They suggested that tolterodine is an effective and well tolerated treatment for LUTS secondary to BPH in the absence or presence of BOO.

Abrams et al [22] published an interesting randomized, placebo-controlled trial assessing the role of tolterodine monotherapy in pa-

Table 1.

Authors	Study Materials	Patients Enrolled	Duration	Efficacy
Lee et al	Doxazosin + Tolterodine	144	3 months	Combination therapy improves IPSS score in 6 of the 16 (37.5%) with BOO and in 32 of 44 (73%) with BOO + DOA
Athanasopoulos et al	Tamsulosin vs. Tamsulosin + Tolterodine	50	3 months	Combination therapy increases Qmax (+12 mL/s), decreases PdetQmax (-8 cm H_2O), improves QOL score
Kaplan et al	Tolterodine monotherapy	43	6 months	Tolterodine reduces daytime frequency (form 9.8 to 6.3/d) and nighttime frequency (form 4.1 to 2.9/n), AUA symptom score (17.3 to 11.2) and Qmax (9.8 to 11.7 mL/s)
Abrams et al	Tolterodine vs. placebo	221	3 months	Tolterodine increase volume to first detrusor contraction (+59 mL), maximum cystometric capacity (+67 mL), and decrease BCI (-10) and voiding efficacy (-7%)

tients with BOO. Men (older than 40 years) with BOO and confirmed detrusor overactivity were randomized to tolterodine (2 mg twice daily in 149 men) or a placebo (in 72 men) for 12 weeks. Changes between groups from baseline to week 12 were statistically equivalent in the two groups for the Qmax (-0.7 mL/s) and maximum detrusor pressure (PdetQmax) (-7 cm H_2O). Tolterodine therapy cause a statistically significant increases in volume at the first detrusor contraction (+59 mL, p =0.0026), and maximum cystometric capacity (+67 mL, p=0.0001), as well as decreases in the bladder contraction index (BCI) (-10, p= 0.0045) and voiding efficacy (-7%, p=0.018). Although BCI and voiding efficiency were found to be influenced, these changes had hardly any real clinical significance. They concluded that the inhibitory effect of tolterodine on detrusor contractions did not aggravate voiding difficulties or precipitate urinary retention in urodynamically obstructed patients.

The safety of the use of antimuscarinic drugs can be explained by the fact that these drugs act mainly by decreasing urge during the filling phase, when there is no activity in the parasympathetic nerves releasing acetylcholine. Being competitive antagonists, the action of these drugs can be reduced during the voiding phase, when there is a massive release of acetylcholine [4]. The concerns that antimuscarinics might be associated with impaired voiding and urinary retention do not appear to be supported by the evidence from these assessed studies [23].

CHANGING CONCEPT

The relationship between BPH and LUTS is complex, because not all men with BPH develop LUTS and not all men with LUTS have BPH. Current interest in LUTS has thus focused on additional mechanisms and sites of origin, particularly in the pathogenesis of storage symptoms [5]. Therefore, it is logical to expect that combination therapy with α-blockers and anticholinergics in patients with LUTS/BPH would significantly alleviate symptoms and induce improvement in QOL. However, prescription of these drugs is in conflict with a long-established concept learned in medical school - antimuscarinics are contraindicated in patients with BPH [24]. In 1986, McGuire stated "Approximately 50% of males with obstructive uropathy demonstrate detrusor instability. Treatment of detrusor instability related to obstruction with anticholinergic agents is inappropriate and often precipitates urinary retention [25]. However, Kaplan et al asked us to think again - "are anticholinergics contraindicated in men with LUTS/BPH?" They suggested that antimuscarinic treatment in men with BPH and LUTS may be a reasonable therapeutic option as initial therapy or after failed treatment with an α-blocker [21]. Several studies also revealed that the combination of antimuscarinics and alpha-blockers is an effective and relatively safe option for the management of the bothersome symptoms associated with BPH and detrusor overactivity. However, more randomised controlled trials with a greater number of patients over a longer period are needed to substantiate the rationale of combination therapy.

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