CURRENT ROLE FOR COMBINATION THERAPY IN MALE LUTS

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Summary.- Treatment of Lower Urinary Tract Symptoms (LUTS) from Benign Prostatic Hyperplasia (BPH) has evolved from surgical therapy to medical monotherapy to combination therapy. First-line medical therapy for men with LUTS remains agents that decrease outlet resistance: α-adrenergic antagonists and 5α-reductase inhibitors. Alpha-adrenergic agents decrease smooth muscle tone in the prostate and bladder neck. The mechanism of action of 5α-reductase inhibitors is reduction in prostate volume. First-line therapy for OAB symptoms are antimuscarinic agents. There has been reluctance to prescribe these agents to men with BPH due to the perceived risk of precipitating urinary retention. Alpha-adrenergic antagonists, 5α-reductase inhibitors, and antimuscarinic agents have all been shown to be safe and effective when administered to men with BPH and LUTS. The combination of 5α-reductase inhibitors with α-adrenergic antagonists is effective in men with LUTS secondary to BPH. The combination of α-adrenergic antagonists plus antimuscarinic agents and the combination of 5α-reductase inhibitors with antimuscarinic agents are safe and effective in patients with LUTS, evidence of BPH, and OAB symptoms. At present only combination therapy with 5α-reductase inhibitors with α-adrenergic antagonists is recommended in clinical practice guidelines. MTOPS and ComBAT have demonstrated superiority of combination therapy over monotherapy in preventing disease progression. Further studies are required to elucidate which specific patient population benefits most from particular combination therapies.


Resumen.- El tratamiento de los síntomas tracto urinario inferior (STUI) secundarios a hiperplasia benigna de la próstata (BHP) ha evolucionado desde el tratamiento médico quirúrgico a la monoterapia y a la terapia combinada. La terapia de primera línea médica para los hombres con STUI siguen siendo los agentes que disminuyen la resistencia de salida: α-adrenérgicos y los inhibidores de la 5α-reductasa. Los agentes α-adrenérgicos disminuyen el tono del músculo liso de la próstata y cuello vesical. El mecanismo de acción del inhibidor de la 5α-reductasa es la reducción en el volumen de la próstata. La terapia de primera línea para los síntomas de vejiga hiperactiva (VH) son los agentes antimuscarínicos. Ha habido renuencia a prescribir estos fármacos a hombres con HBP, debido a la percepción de riesgo de precipitar la retención urinaria. Alpha-antagonis-
With a better, albeit far from absolute, understanding, of the pathophysiology of LUTS in men, medical therapy for this condition has evolved. There is emerging evidence that LUTS in men occur as a result of both bladder and prostate conditions. The International Continence Society (ICS) definition of the overactive bladder syndrome is, “urgency, with or without urge incontinence, usually with frequency and nocturia” (7). The linkage between BPH and OAB symptoms is not well-understood (8). Even after treatment with α-blockers and 5α-reductase inhibitors, many patients with BPH suffer from persistent symptoms of OAB (9). The mainstay of pharmacotherapy for OAB is the antimuscarinic class of drugs, competitive inhibitors of the muscarinic receptors. There has been reluctance to prescribe these agents to men with BPH due to the perceived risk of precipitating urinary retention through decreased bladder contractility in the setting of bladder outlet obstruction (10). However, several trials have supported the efficacy and safety of antimuscarinics in treating men with LUTS (11-14).

After moving from surgery to drug monotherapy the next progression in treatment of male LUTS was the concept of combination therapy. The MTOPS study, a randomized double-blind placebo-controlled trial of 3087 patients randomized to placebo, α-adrenergic antagonist monotherapy, 5α-reductase inhibitor monotherapy, or combination for 4.5 years, was monumental in demonstrating that combination therapy could be more efficacious than monotherapy in improving symptoms (15). Since then other studies have demonstrated efficacy of combination therapy for treating LUTS in men (11, 13, 14, 16). The aim of this article is to provide a contemporary review of the current role for combination therapy in the treatment of male LUTS.

MONOTHERAPY

To provide a better appreciation of the role of combination therapy in the treatment of male LUTS, we will first review key concepts and studies of the individual drugs used in combination therapy. As stated previously the goals of medical treatment are twofold: symptom relief and prevention of disease progression.

α-Adrenergic Antagonists

α-adrenergic antagonists are considered first-line treatment for male LUTS (3, 4). It has been hypothesized that BPH causes bladder outlet obstruction (BOO) and symptoms partially through increased α-

Lower urinary tract symptoms (LUTS) and benign prostatic hyperplasia (BPH) are highly prevalent in men. In the EPIC study, a cross-sectional telephone survey of 19,615 adults in 5 countries, 62.5% of men reported having one or more LUTS (1). The treatment and comprehension of LUTS in men has undergone major progression. Previously, LUTS in older men were considered to be a direct consequence of increased prostate mass and elevated urethral resistance. These symptoms were known as “prostatism” and prior to the 1980’s LUTS in men were treated primarily by surgery (2). Over the past 2 decades, medical therapy has become the most common modality of treatment for BPH. Therapy may be targeted at treatment of symptoms and/or preventing progression of disease.

First-line medical therapy for men with LUTS remains agents that decrease outlet resistance: α-adrenergic antagonists and 5α-reductase inhibitors (3, 4). Alpha-adrenergic agents decrease smooth muscle tone in the prostate and bladder neck (5). The mechanism of action of 5α-reductase inhibitor is reduction in prostate volume (5). Recently studies have shown that phosphodiesterase type 5 inhibitors, which also induce smooth muscle relaxation in the urinary tract and are most commonly used for treating erectile dysfunction are also effective in treating male LUTS (6).
adrenergic stimulation and resultant increased urethral smooth muscle tone and intraurethral pressure.

The main \(\alpha\)-adrenergic antagonists used for treating LUTS in men are alfuzosin, doxazosin, tamsulosin, and terazosin. In the male prostate and urethra, the \(\alpha_1\)A receptor subtype is most prevalent. All these agents are selective for the \(\alpha_1\) receptor subtype present in prostatic tissue. Tamsulosin is the only \(\alpha_1\)A-selective \(\alpha\)-adrenergic blocker. However, no single agent has been proven to be significantly more efficacious than the others.

The AUA Clinical Practice Guidelines Committee conducted a meta-analysis and concluded that \(\alpha\)-adrenergic antagonists were beneficial in treating BOO and detrusor overactivity due to BPH (3). Generally \(\alpha\)-blockers improve AUA symptom index (AUASI) by 4-6 points. Numerous studies have confirmed the efficacy and tolerability of \(\alpha\)-adrenergic antagonists (17-19). Side effects are reported in approximately 5 - 9% of patient populations taking \(\alpha\)-adrenergic antagonists (20). These include dizziness, postural hypotension, asthenia, rhinitis, and sexual dysfunction including abnormal ejaculation.

Elhilali et al. conducted a multicenter randomized double-blind placebo-controlled study of 164 patients with BPH to investigate the safety and efficacy of terazosin. At 24 weeks terazosin significantly increased maximum flow rate (\(p<0.001\)) and did not alter post-void residual (PVR). There was also significant improvement in AUASI (\(p=0.014\)) (17). Only 11 patients withdrew from the study because of adverse events: 7 from the terazosin group and 4 from the placebo group.

A pooled analysis of three double-blind placebo-controlled trials with a combined population size of 337 subjects was done to evaluate the safety and efficacy of doxazosin in patients with BPH. Doxazosin produced a significantly greater improvement than placebo in peak urinary flow rate (\(P = 0.0017\)), symptom severity (\(P < 0.0001\)), and bother caused by symptoms (\(P < 0.0001\)) (19). Overall the medication was well-tolerated. 10% of patients in the treatment group discontinued medication compared to 4% in the placebo group (\(p<0.05\)).

The safety and efficacy of once-daily alfuzosin for the treatment of LUTS due to BPH was evaluated in a pooled analysis of three parallel double-blind placebo-controlled trials. Patients were randomized to 10mg once-daily alfuzosin or placebo for 12 weeks. Alfuzosin significantly improved total IPSS (\(p<0.005\)), IPSS irritative subscore (\(p<0.001\)), IPSS obstructive subscore (\(p<0.001\)), and Qmax (\(p<0.001\)) compared to placebo. Withdrawal rates were low and comparable to placebo (21).

A randomized double-blind placebo-controlled trial of tamsulosin 0.4mg, tamsulosin 0.8 mg, and placebo was done to determine the safety and efficacy of tamsulosin for the treatment of LUTS in men with BPH (22). 756 subjects were enrolled for 13 weeks. Significant improvements were seen in AUASI and Qmax for both treatment groups. Overall, more adverse events were reported in the 0.8 mg tamsulosin group compared to placebo. However, the incidence of adverse events in the 0.4 mg group was comparable to placebo.

5\(\alpha\)-Reductase Inhibitors

The enzyme 5\(\alpha\)-reductase converts testosterone to dihydrotestosterone (DHT). Castration and pharmacologic agents that suppress testosterone and/or DHT secretion have been shown to reduce prostate size in men with BPH (23). Reducing prostate volume is hypothesized to decrease the static component of BOO caused by BPH. The 5\(\alpha\)-reductase inhibitors finasteride and dutasteride are safe and effective in the treatment of BPH (26-30). Dutasteride inhibits both type 1 and type 2 isoenzymes whereas finasteride inhibits only the type 2 isoenzyme. Studies have found that in general 5\(\alpha\)-reductase inhibitors are more efficacious in patients with larger prostates than in those with smaller prostates (24, 25).

Of the two 5\(\alpha\)-reductase inhibitors, finasteride has been the most widely studied. The first randomized double-blind placebo-controlled trials of finasteride versus placebo, in 895 and 750 patients, were only 1 year in duration (26, 27). Nonetheless they showed that finasteride significantly improved symptom scores (\(p<0.001\) and \(p<0.015\)) and Qmax (\(p<0.001\)) compared to placebo after 12 months of therapy. A meta-analysis of these early studies concluded that these improvements were far less in patients with smaller prostates (25).

The Proscar Worldwide Efficacy and Safety Study (PROWESS) was a 2-year multicenter randomized double-blind placebo-controlled trial proving efficacy and safety of finasteride in the treatment of men with LUTS from BPH (28). The findings of the shorter duration studies were confirmed by a 4-year randomized double-blind placebo-controlled trial, the Proscar Long-Term Efficacy and Safety Study (PLESS) (29). PLESS demonstrated that finasteride significantly decreased the risk of retention (\(p<0.001\)) as well as the need for surgery (\(p<0.001\)) compared to placebo in patients with prostates larger than 55g.
Finasteride was well tolerated and the withdrawal rate was similar to that in placebo.

Roehrborn et al. tested the safety and efficacy of dutasteride in a randomized double-blind placebo-controlled trial (30). 4325 patients with LUTS and BPH, moderate-severe symptoms, Qmax 15 mL/s or less, prostate volume 30cc’s or more, were randomized to dutasteride 0.5 mg or placebo for 24 months. Symptom score improved significantly from 6 months onward (p<0.001) with a mean improvement in 4.5 points at 24 months. Qmax improved significantly from 1 month onward (P <0.01), with an increase of 2.2 mL/s reported at 24 months (P <0.001). The risk reduction of acute urinary retention was 57% and the risk reduction surgical intervention was 48% compared with placebo. Impotence, reduced libido, ejaculation disorders, and gynecomastia occurred more frequently in dutasteride-treated patients. Overall, the drug was well-tolerated.

Antimuscarinic Agents

Population-based studies such as the EPIC study have shown that in men OAB symptoms are more prevalent than voiding or post-micturition symptoms and that they are associated with a high degree of bother. Interestingly, in urodynamic studies of men with LUTS, only 48-68% have bladder outlet obstruction (BOO) (31, 32).

First-line therapy for OAB symptoms are antimuscarinic agents. There has been reluctance to prescribe these agents to men with BPH due to the risk of precipitating urinary retention through decreased bladder contractility in the setting of bladder outlet obstruction (10). However, several trials have supported the efficacy and safety of antimuscarinics in treating men with LUTS (11-14, 16). Current practice guidelines do not recommend the use of anticholinergics in men with LUTS suggestive of BPH (3, 4).

Of the 1529 patients with OAB symptoms enrolled in the tolterodine extended-release (ER) safety and efficacy study randomized to tolterodine ER, tolterodine immediate release (IR), and placebo, 19% were men (33). Tolterodine IR and ER significantly reduced mean number of urge incontinence episodes per week compared to placebo and the ER formulation was 18% more effective than the IR formulation (p<0.05). Rates of withdrawal were similar to placebo for both tolterodine groups.

A randomized double-blind placebo controlled trial of once daily solifenacin succinate was done to assess safety and efficacy (34). 911 men and women (155; 17% men) with OAB symptoms were randomized to placebo, 5 mg solifenacin, or 10 mg solifenacin. After 12 weeks, 24h frequency decreased significantly with solifenacin 5 mg [2.37, p=0.0018] and solifenacin 10 mg [2.81, p=0.0001]. In the solifenacin groups there were also significant decreases in incontinence episodes (5 mg p = 0.002; 10 mg p=0.016), episodes of urge incontinence (5 mg, p = 0.014 and 10 mg, p = 0.042), and episodes of urgency (5 mg -2.84 p =0.003, 10 mg -2.90 p = 0.002). Therapy was well-tolerated. The incidence of mild dry mouth was 2.3% in placebo, 7.7% in the 5 mg solifenacin group, and 23% in the 10 mg solifenacin group.

Abrams et al. studied the effect of tolterodine IR in men with evidence of both BOO and OAB (13). Entry criteria were urinary frequency (8 or more micturitions per 24 hours), urgency (1 or more episodes per 24 hours) and bladder outlet obstruction index (BOOI) 20 or greater. 222 men were randomized to tolterodine IR 2 mg twice daily or placebo for 12 weeks. Median treatment differences in Qmax (–0.7 ml per second, 95% CI –1.6 to 0.4) and pdetQmax (–7 cm H2O, 95% CI –3 to 11) were comparable between groups. Tolterodine significantly reduced BOOI (–9 vs. 0, p <0.02) and increased maximum cystometric capacity (+67 ml, 95% CI 35–103, p<0.003) compared to placebo. Change in PVR was significantly higher among patients treated with tolterodine (+25 ml) than placebo (0 ml, p <0.004). No significant differences in the incidence of adverse events were seen. Urinary retention was reported by only 1 patient in the placebo group. These results suggested that antimuscarinics could be administered safely in men with BOO and OAB.

COMBINATION THERAPY

α-Adrenergic Antagonists with 5α-Reductase Inhibitors

Because the different classes of pharmacotherapy used to treat male LUTS work through different mechanisms, it seems logical that patients should receive more benefit from being on more than one class of drug. This concept was studied in the 1990’s but early trials of combination therapy did not demonstrate significant benefit over monotherapy (34, 35). In consequence, combination therapy was not practiced widely until the findings of the MTOPS study were published. Today combination therapy with α-adrenergic antagonists with 5α-
reductase inhibitors is recommended by the AUA and EAU for patients with moderate-severe symptoms and enlarged prostates (3, 4).

The first randomized multicenter double-blind placebo controlled study that assessed combination therapy of α-adrenergic antagonists and 5α-reductase inhibitors was the Veterans Affairs Cooperative Study (34). 1229 patients with LUTS secondary to BPH were randomized to and treated with finasteride 5mg, terazosin 10mg, or combination therapy for 12 months. No significant differences were found between the placebo and finasteride groups for AUASI or Qmax. However, there were significant differences in AUASI seen between the terazosin and combination therapy groups compared to placebo (p<0.001) and finasteride (p<0.001). Mean changes in Qmax were also significant between both terazosin and combination therapy compared with placebo (p<0.001) and finasteride (p<0.001). Overall, in this population of patients combination therapy was not any more effective than terazosin alone. And, finasteride was no more beneficial than placebo in improving AUASI and Qmax.

The Prospective European Doxazosin and Combination Therapy (PREDICT) study was similar in design to the Veterans Affairs study and yielded comparable results (35). It was a randomized double-blind placebo-controlled trial of 1095 subjects randomized to doxazosin, finasteride, or combination therapy for 1 year. Primary endpoints were change in IPSS and Qmax. There were significant improvements seen in IPSS in both the doxazosin monotherapy and the combination groups compared with finasteride (p<0.001) and placebo (p<0.001). Like the Veterans Affairs study, no significant differences between finasteride and placebo were seen in terms of changes in IPSS and Qmax. The addition of finasteride did not add any additional benefit than that from doxazosin alone in IPSS or Qmax. Both the Veterans Affairs Cooperative study and the PREDICT study are limited by short duration of only one year. Furthermore their main effectiveness measure was symptom relief. Many benefits of 5α-reductast inhibitors lie in the category of disease prevention rather than symptom improvement.

The Medical Therapy of Prostatic Symptoms (MTOPS) study was of longer duration than previous studies of combination therapy and had endpoints focused on disease progression, rather than symptom relief (15). The main objective of the study was to determine if therapy with doxazosin, finasteride, or a combination could prevent disease progression of BPH defined by an increase in at least 4 points in the AUASI, acute urinary retention (AUR), incontinence, renal insufficiency, or recurrent urinary tract infections (UTI’s). 3047 men were randomized to finasteride, doxazosin, combination therapy, or placebo for a mean duration of 4.5 years. The risk of clinical progression was significantly reduced by doxazosin (39 percent risk reduction, P<0.001) and finasteride (34 percent risk reduction, P=0.002), as compared with placebo. The risk reduction in the combination therapy group (66 percent for the comparison with placebo, P<0.001) was significantly greater than that associated with doxazosin (P<0.001) or finasteride (P<0.001) alone. The combination and finasteride groups showed a significant decreased risk of AUR and need for invasive therapy (p<0.001) but this was not seen in the doxazosin group. Adverse effects were significantly more common in the combination group. When patients were stratified according to prostate size, it was found that in men with small prostates (less than 25mL at baseline) combination therapy was not more beneficial than doxazosin alone for decreasing risk of clinical progression of BPH, need for invasive therapy, improving AUASI, and improving Qmax(36). However in men with patients with moderate sized prostates (25-<40 mL) or enlarged prostates (size 40mL or greater) combination therapy did have a significant benefit over both doxazosin and finasteride monotherapy.

The first randomized double-blind placebo-controlled trial of combination therapy with an α-adrenergic antagonist and the 5α-reductase inhibitor dutasteride was the Symptoms Management after Reducing Therapy (SMART) trial (37). This study investigated whether men treated with a combination of tamsulosin and dutasteride followed by withdrawal of tamsulosin would adversely affect symptoms in men with LUTS. 327 men were randomized to combination therapy for 36 weeks or combination therapy for 24 weeks followed by 12 weeks of dutasteride monotherapy and placebo. 77% of patients in the group switched from combination therapy to dutasteride felt the same or better at week 30 compared to week 24. The main limitation of this study was its short duration of treatment.

A long-term randomized double-blind randomized non-placebo-controlled trial, the Combination of Avodart and Tamsulosin Study (CombAT) study, is currently investigating the effects of dutasteride, tamsulosin, and combination therapy in men with LUTS secondary to BPH (38). 4844 men with moderate-severe LUTS (IPSS 12 or greater) and prostate size >30cc’s were randomized for 4 years to dutasteride, tamsulosin, or combination therapy. The primary end point of the study at 2 years was change in IPSS. At 2 years combination therapy significantly decreased IPSS compared to the finasteride group.
at month 3 and the tamsulosin group at month 9monotherapy groups (p<0.001). There was alsoa significant increase in the combination group ofQmax compared to the monotherapy groups (ps0.006). The major criticism of this study is lack ofplacebo group.

α-Adrenergic Antagonists with Antimuscarinic agents

Even after treatment with α-adrenergicantagonists and 5α-reductase inhibitors, manypatients with BPH suffer from persistent symptomsof OAB. There is evidence that after failure ofα-adrenergic antagonists adding an antimuscarinicagent is beneficial and safe (12, 14, 39). There isalso evidence that in men with LUTS, OAB symptoms,and evidence of BPH, combination therapy with anα-adrenergic antagonist with an antimuscarinic agentis effective and well-tolerated. It is important to notethat most trials have specifically selected for patientswho do not have evidence of significant BOO.

The first 3 trials described in this sectionincluded patients with urodynamically-proven BOO.Athanassopoulos et al. randomized 50 patients withurodynamically-proven BOO and DO to receive tamsulosin alone for 3 months or tamsulosin alone for 1week followed by combination therapy with tamsulosinand tolterodine (39). Patients were evaluated withurodynamics and a quality-of-life questionnaire (QoL)after 3 months. There was a significant improvement inQoL scores before and after treatment only in thecombination group as well as a significant decrease inmaximum detrusor pressure during voiding (-8.24 cm H20, p=0.0082). Both groups had a significantdifference in Qmax and volume at first contraction.

In another study including men with OABand urodynamically-proven BOO, Lee et al. assessed theefficacy of combination treatment with doxazosinand tolterodine IR (14). All patients were treated withdoxazosin 4 mg daily for 3 months. In patients withoutimprovement tolterodine IR 2mg twice daily was added. In these patients with no improvement,6 of 16 with BOO and 32 of 44 (73%) with BOO + OAB improved after adding tolterodine. Acuteurinary retention developed in 2 of 60 men (3.3%)treated with the combined therapy.

Combination treatment with propiverinehydrochloride and doxazosin was assessed for safety and efficacy in a prospective randomizedcontrolled multicenter study including 211 men withOAB and urodynamically-proven BOO (40). Patientswere randomized to doxazosin CR or doxazosin CRplus propiverine for 8 weeks. There were significantimprovements seen in the combination group compared to the monotherapy group in frequency(p=0.001), storage symptoms (p=0.029), and patient satisfaction (p=0.002). PVR increased significantly inthe combination group (+20.8 mL, p=0.002) but no patients reported urinary retention.

Kaplan et al. conducted an open labelprospective study to determine efficacy and safety oftolterodine ER in men with BPH and LUTS in whomprevious alpha-blocker therapy had failed (12). 43consecutive patients in whom alpha-blocker therapyhad failed due to adverse events or lack of efficacyreceived 4 mg tolterodine ER for 6 months. Mean24-hour micturition frequency decreased from 9.8 to6.3 voids and nocturia decreased from 4.1 to 2.9episodes per night. Significant decreases in IPSS andPVR were also observed. Four men (9%) discontinuedtherapy because of dry mouth and no patientsreported urinary retention.

In 2006 Kaplan et al. reported on a largeredefined, double-blind placebo-controlled trial oftolterodine ER in men age 40 or older with LUTS andOAB (41). This study is known as the TIMES study.Inclusion criteria were age 40 years or older, IPSS 12or higher, IPSS quality-of-life (QoL) score 3 or higher,self-rated bladder condition of at least moderatebother, bladder diary documenting micturitionfrequency (≥ 8 micturitions per 24 hours) and urgency(≥ 3 episodes per 24 hours) with or without urgencyurinary incontinence. In other words, patients metentry criteria for both OAB and BPH studies. Of note,patients with evidence of bladder outlet obstruction(BOO) were excluded. Exclusion criteria included asQmax < 5 mL/second, PVR > 200 mL, and history ofacute urinary retention. 879 patients were randomizedto placebo, tolterodine ER 4 mg, tamsulosin 0.4 mg,or both tolterodine ER and tamsulosin for 12 weeks.Patients in the combination group had significantreductions in urgency urinary incontinence (p=0.005),urgency episodes without incontinence (p = 0.03),micturitions per 24 hours (p<0.001), micturitions pernight (p = 0.02), total IPSS (p=0.003), and IPSS QoLscore (p = 0.003) compared to placebo. At week 12,there were significant improvements in IPSS observedin the tamsulosin (p=0.003) and combination groups(p=0.003) compared to baseline but this was not seenin the placebo or tolterodine ER groups. The incidenceof acute urinary retention requiring catheterizationwas low in all groups (0.4% tamsulosin + tolterodineER, 0.5% tolterodine ER, 0% placebo, 0% tamsulosin).A 5 to 6 mL increase in PVR was seen in both thetolterodine ER and tolterodine ER + tamsulosin groupsthat was not clinically significant. No statisticallysignificant differences in PVR were observed betweenany two groups. The TIMES study remains the only
placebo-controlled trial of α-adrenergic antagonists in combination with antimuscarinic agents.

A sub-analysis of the TIMES study analyzed the effects of tolterodine ER, tamsulosin, placebo, and tolterodine ER plus tamsulosin on IPSS. By 12 weeks, patients receiving tolterodine ER plus tamsulosin had significant improvements in IPSS storage subscale and all IPSS storage items compared to placebo (42). In the monotherapy groups, changes in IPSS storage subscale and individual storage item scores did not differ significantly from placebo. In contrast, the tolterodine ER and tolterodine ER plus tamsulosin groups did not demonstrate a significant difference in IPSS voiding subscale and individual voiding items compared to placebo.

Chapple et al. evaluated the efficacy of tolterodine ER in 652 men with LUTS, on a stable dose of α-blocker for at least one month, randomized to tolterodine ER 4 mg per day or placebo for 12 weeks (43). The group found that men with bothersome OAB symptoms already on α-blocker therapy showed significantly greater improvements in diary variables, IPSS storage scores, and symptom bother when receiving additional tolterodine ER.

Rovner et al. studied the efficacy of tolterodine ER and/or tamsulosin on micturition related urgency episodes, urgency severity, and patient reported outcomes in men who met entry criteria for prostatic enlargement and OAB trials (44). They also found that tolterodine ER and tamsulosin significantly improved urgency variables and patient reported outcomes.

MacDiarmid et al. conducted a randomized double-blind placebo-controlled trial of patients taking tamsulosin randomized to either placebo or oxybutynin extended-release (16) and found combination therapy to be safe and effective. Like most other studies of antimuscarinics in men with BPH, the study excluded patients with severe BOO. In the tamsulosin and oxybutynin ER group, there were significant improvements in total IPSS (p<0.03 8 weeks, p=0.006 12 weeks), IPSS storage (p<0.01), and quality of life scores (p<0.01) after 8 and 12 weeks. The incidence of PVR greater than 300 mL was low and similar in the tamsulosin monotherapy and combination groups.

Several studies have been conducted to further define which population of men with LUTS will benefit most from the addition of tolterodine ER. Roehrborn et al. performed a post hoc analysis of men from the TIMES trial randomized to placebo, tolterodine ER, tamsulosin, or tolterodine ER plus tamsulosin who were stratified by median baseline PSA level (≥ 1.3 ng/mL vs. < 1.3 ng/mL) (45). PSA level correlated significantly with prostate size. In men with a PSA level < 1.3 ng/mL tolterodine ER alone as well as tolterodine ER plus tamsulosin significantly improved 24-hour frequency, daytime frequency, frequency-urgency sum, and IPSS storage scores compared to placebo. In patients with PSA ≥ 1.3 ng/mL only patients taking both tolterodine ER plus tamsulosin experienced significant improvements in 24-hour frequency, daytime frequency, frequency-urgency sum, total IPSS, and storage IPSS compared to placebo. No significant improvements in bladder diary or symptom score variables were seen in the larger prostate group treated with tolterodine ER alone.

Another post hoc analysis of the TIMES trial looked at the effect of prostate size on men meeting criteria for BPH and OAB studies, randomized to placebo, tolterodine ER, tamsulosin, or tolterodine ER plus tamsulosin (46). Similar to the previous study, men with smaller prostates and moderate-to-severe LUTS including OAB symptoms, benefited from tolterodine ER monotherapy. Therapy with tolterodine ER plus tamsulosin was effective regardless of prostate size. The incidence of acute urinary retention was low in all groups (≤ 2%).

5α-Reductase Inhibitors and Antimuscarinic Agents

There is evidence that combination therapy with 5α-reductase inhibitors and antimuscarinic agents is safe and effective in men with LUTS and BPH (47). Chung et al. assessed the safety and efficacy of 4 mg tolterodine ER with 0.5 mg dutasteride in men with persistent OAB symptoms and LUTS unsuccessfully treated with dutasteride alone. 51 men treated with dutasteride for minimum 6 months with persistent OAB symptoms enrolled in a 12-week, open-label study and were given tolterodine ER. Inclusion criteria were IPSS≥12, IPSS quality-of-life item≥3, significant bother, frequency (≥8 voids/24h) and urgency (≥3 episodes/24h). Baseline prostate volume was 54.3 mL. Tolterodine ER significantly reduced frequency and urgency: 24-h micturition frequency (3.2, p < 0.02), 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 monotherapy (19.3 to 14.3) and decreased with addition of tolterodine to 7.1 (P<0.001). IPSS Storage subscale decreased from 9.8 to 3.5 (P<0.001). Dry mouth occurred in 4(7.5%) subjects, constipation in 1(2%) and decreased sexual function in 2(3.9%). PVR increased by 4.2 mL, Qmax decreased by 0.2 mL/sec and no patients went into retention. The combination
tolterodine ER and dutasteride was effective, safe, and well-tolerated in men with large prostates (≥ 30 mL) with persistent OAB symptoms and LUTS secondary to BPH.

**CONCLUSIONS**

Treatment of LUTS from BPH has evolved from surgical therapy to medical monotherapy to combination therapy. The combination of 5α-reductase inhibitors with α-adrenergic antagonists is effective in men with LUTS secondary to BPH. The combination of α-adrenergic antagonists plus antimuscarinic agents and the combination of 5α-reductase inhibitors with antimuscarinic agents are safe and effective in patients with LUTS, evidence of BPH, and OAB symptoms. At present only combination therapy with 5α-reductase inhibitors with α-adrenergic antagonists is recommended in clinical practice guidelines. The large long-term studies MTOPS and ComBAT have demonstrated superiority of combination therapy over monotherapy in preventing disease progression. Further studies are required to elucidate which specific population of patients benefits most from particular combination therapies.

**REFERENCES AND RECOMMENDED READINGS**

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