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FEMALE UROLOGY (L COX, SECTION EDITOR)

Combination Pharmacotherapy for Treatment of Overactive Bladder (OAB)

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Abstract
Overactive bladder syndrome (OAB) negatively affects the quality of life of patients and their interactions with society. Treatment of OAB starts with behavioral modification and then pharmacotherapy using monotherapy with either antimuscarinics or β3 agonists. The third-line more invasive approaches are the next treatment option currently recommended. Both antimuscarinic agents and β3 agonists work through a different molecular pathway. This brings up the potential of having an additive effect when using a combination treatment for patients with OAB. Currently, the potential for using combination therapy to treat OAB in patients who had no improvement with a monotherapy approach before we attempt a more invasive approach is being explored. Several studies have shown the benefits of combination therapy which will be an additional option to the tools to treat OAB.

Keywords Overactive bladder (OAB) · Urinary urgency · Combination therapy for OAB

Introduction

Overactive bladder syndrome (OAB) is defined by the International Continence Society as urinary urgency accompanied by day time frequency and/or nocturia with or without urgency urinary incontinence [1]. Urgency is defined as "the complaint of a sudden compelling desire to pass urine, which is difficult to defer" [2]. OAB is associated with urgency urinary incontinence in about 30% of patients [3] and OAB is expected to affect about 20% of people in 2018 [4]. OAB is a chronic problem which can negatively affect the quality of life of affected patients. Economically, it is associated with decreased productivity and higher health care cost [5]. Socially, OAB can lead to social isolation and depression [6]. Multiple comorbidities may be associated with OAB especially in elderly such as increased risk of falls and fractures [7, 8]. Thus, treatment of OAB helps these patients to avoid morbidity and improve quality of life.

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Treatment of OAB

The American Urologic Association (AUA) guidelines recommend pharmacotherapy as a second line in the treatment of OAB after a trial of conservative therapy before proceeding to more invasive third-line therapy [9•]. Antimuscarinic medications have been the mainstay of pharmacotherapy treatment for many years. Antimuscarinics act through inhibition of the muscarinic receptors improving the bladder storage and hence improve OAB symptoms [10]. However, the compliance and adherence rates with antimuscarinics are low because of its side effects and/or lack of efficacy [11]. The most common systemic side effects that lead patients to quit treatment are dry mouth, constipation, and visual disturbances. Increasing the dose of antimuscarinics, switching to different antimuscarinics, or combination of antimuscarinics was attempted to manage lack of efficacy before switching to β3 agonists [12]. Wang et al. [13] reported improvement of OAB symptoms with adding an additional dose of oxybutynin ER (5–15 mg) to patients who were treated with other antimuscarinics. They noticed the improvement of symptoms in about 20% of patients. However, more than 75% of the patients discontinued the therapy due to lack of efficacy or development of side effects.

β3 agonist, mirabegron, has been in clinical use since 2012 and has a similar clinical efficacy to antimuscarinics [14].

However, treatment with β3 agonist, mirabegron, was reported to be better tolerated and was associated with better compliance and adherence rates over 12 months [15–17]. In a meta-analysis by Kelleher et al. [18], they reviewed a total of 64 studies to assess mirabegron 50 mg efficacy and tolerability when compared to placebo, or antimuscarinics excluding combination treatment with solifenacin 10 mg. In 42 studies, mirabegron 50 mg was found to have similar efficacy in improving urinary frequency when compared to other treatments excluding solifenacin 10 mg and combination of mirabegron 25 mg and solifenacin 5 mg. In 37 studies, mirabegron 50 mg had similar efficacy compared to other antimuscarinics in treating urgency urinary incontinence except for combination therapy of solifenacin and mirabegron. In addition, mirabegron was well tolerated by the patients.

If pharmacotherapy treatment with a monotherapy approach did not achieve satisfactory results, the patients will proceed a more invasive 3rd-line therapy as recommended by the AUA guidelines. However, there may be additional benefits using a combination therapy of β3 agonist mirabegron and antimuscarinic agents before proceeding to the 3rd-line therapy. Several trials have been conducted to investigate the efficacy and safety of combination treatment.

Pathogenesis of Urgency Sensation

The pathogenesis of urgency sensation in the bladder is important in understanding the mechanism of these medications. Urgency sensation is related to the types of afferent nerves in the bladder. The bladder has 2 types of afferent nerves, myelinated Aδ and non-myelinated C fibers. The Aδ fiber endings are in the detrusor muscle while C fiber nerve endings are found in the urothelium and lamina propria. During the storage phase, while the bladder wall is relaxed, the Aδ fibers are activated which is a part of the sympathetic storage reflex. This reciprocally decreases parasympathetic stimuli to the bladder through stimulation of the β3 adrenoceptors in the bladder wall which will maintain the bladder wall in a relaxed state and the bladder outlet in a contracted state. When the bladder is at full capacity, C fibers become activated causing more nuisance sensation [11]. It is assumed that normal urge sensation of bladder fullness is conveyed by Aδ fiber while the noxious urgency sensation is carried by C fibers [19, 20].

The triggers for urgency seem to be located in the CNS or peripherally in the bladder wall, in the detrusor muscle (myogenic), or in the urothelium [21]. Chemical mediators, such as adenosine triphosphate, neurotropic factors, serotonin, prostaglandins, histamine, and bradykinin, may be released during bladder distention and initiate signaling within and between urothelial cells, bladder nerves, and other cells within the bladder. Inappropriate signaling could lead to flawed bladder control and hence urgency sensation [22, 23]. Bladder aging may be a factor as well, which can lead to changes in neuronal and non-neuronal acetylcholine within urothelial cells leading to bladder dysfunction and the urgency sensation [19].

Antimuscarinic Treatment

Antimuscarinics agents have been the primary pharmacotherapy for OAB treatment. Antimuscarinics act by inhibition on of the muscarinic receptors in the urothelium and suburothelial myofibroblasts. They act through competitive inhibition of binding of acetylcholine (A.ch) at its receptors. Anticholinergics inhibit the muscarinic receptors (M2 and M3) in the postganglionic synaptic cleft improving the bladder contraction during storage and hence improve OAB [10]. This results in decreased bladder afferent activity in both Aδ and C fibers, and reduced urgency sensation [24–26].

The antimuscarinics have been proven to significantly decrease urgency episodes when compared to placebo. Further improvement was seen with dose escalation at the price of increased systemic side effects such as dry mouth, constipation, and blurred vision [27–35].

β3-Adrenergic Receptors in the Treatment of OAB

β3-adrenergic receptors (β3-AR) are found in the detrusor muscle, in the urothelium, and in the A.ch containing nerve fibers in the human bladder [36–39]. A.ch release from the cholinergic terminals during bladder filling contributes to OAB symptoms. The mechanism of action of β3-AR agonists is through activation of prejunctional β3-adrenoceptors resulting in downregulation of A.ch release in the cholinergic terminal during the storage phase. Decreased A.ch consequently results in inhibitory control of parasympathetic activity to decrease urgency sensation [39, 40].

β3 agonist, mirabegron, was reported to have similar efficacy to antimuscarinics with better tolerability and was approved by the Food and Drug Administration (FDA) in 2012 for treatment of urgency incontinence. Mirabegron was also associated with better adherence and compliance with treatment due to lack of antimuscarinics' deterring side effect profile [14, 16]. In a pooled analysis from 3 large randomized controlled studies [41•], patients received mirabegron 50 mg and 100 mg had a statistically significant reduction in urgency episodes and mean number of voids when compared to placebo. Mirabegron was also well tolerated and showed a good safety profile [41•]. In BEYOND study, patients who had suboptimal response to an antimuscarinic therapy were randomized to mirabegron 50 mg or solifenacin 5 mg. Both medications were found to have similar efficacy in reducing the number of severe urgency episodes per day and the number of

voids per day. The study showed non-inferiority of mirabegron 50 mg compared to solifenacin 5 mg [42•].

There is a theoretical risk of cardiovascular side effects when using β3-AR. However, mirabegron has a high affinity for β3-AR and low affinity to β1-AR and β2-AR in animal models and much more selective for β3-AR in human when compared to both β1-AR and β2-AR and, hence less cardiovascular effects [43].

Mirabegron 25 mg daily and mirabegron 50 mg orally daily were not associated with any significant increase in heart rate. There was a slight increase in heart rate in patients receiving mirabegron 200 mg daily [44]. In the TAURUS trial, it showed the presence of slight changes in the systolic and diastolic blood pressure which were not clinically significant. The changes were about + 0.2/− 0.3 mmHg for mirabegron 25 mg daily and + 0.4/+0.4 mmHg for mirabegron 100 mg/day [45]. A systemic review and meta-analysis confirmed these results. Mirabegron 50 mg did not show any increase of cardiovascular events of hypertension or cardiac arrhythmias when compared to placebo while mirabegron 100 mg was associated with slightly increased risks of both hypertension and arrhythmias [43].

Combination Therapy of OAB

It seems that β3-adrenoceptors agonists and antimuscarinics have significant improvement of urgency and urgency incontinence when used as a monotherapy. However, both act through a different molecular mechanism to relax the bladder, and it appears theoretically that a combination therapy may uphold the potential of obtaining an additive effect in patients who failed treatment with monotherapy. So, would combination therapy provide a superior clinical response? Will they provide better tolerance and adherence from the patient and have fewer systemic side effects?

Three large clinical trials were designed to study the potential benefits of combination treatment. The SYMPHONY trial [46••] was a phase 2 multicenter, randomized, double-blind dose-ranging trial of a combination treatment of mirabegron and solifenacin in patients with overactive bladder. The aim of the study was to evaluate the efficacy and safety of the combination therapy compared to solifenacin monotherapy or placebo over 12 weeks. Patients were randomized to 12 different treatment groups where 6 groups had combination therapy (different doses of solifenacin, 2.5/5/10 mg, and mirabegron, 25/50 mg), monotherapy with solifenacin (2.5/5/10 mg), monotherapy with mirabegron (25/50 mg), or placebo.

The combination therapy arms were found to have significant improvements in mean voided volume per day, the frequency of voiding per day, number of urgency episodes, and urgency urinary incontinence per day when compared to monotherapy [46••]. The combination treatments with solifenacin 5 or 10 mg significantly improved mean voided volume with adjusted differences ranging from 18.0 ml (95% confidence interval [CI], 5.4–30.0) to 26.3 ml (95% CI, 12.0–41.0). Most of the combination therapies significantly reduced urinary frequency when compared with monotherapy with solifenacin 5 mg. Five of six combinations significantly reduced urgency episodes compared with solifenacin 5 mg, ranging from − 0.98 (95% CI, − 1.78 to − 0.18) to − 1.37 (95% CI, − 2.03 to − 0.70). Overall, the combination of mirabegron 50 mg with solifenacin 5 mg or 10 mg was associated with better outcomes when compared to any monotherapy alone.

The investigators also observed better tolerability when compared to other antimuscarinic medications with less dry mouth. When it comes to the safety of the combination therapy, during the study, there were no significant side effects or major adverse effects. There were no significant changes in blood pressure, pulse rate, or ECG parameters. There were no significant changes in post-void residual (PVR) volume or urinary retention episodes between combination and monotherapy groups; however, the incidence of constipation was noted to be slightly higher with combination therapy [46••].

In a further analysis of the SYMPHONY trial [47••], the authors explored the benefits of the combination therapy on patients' reports of clinical improvement and improved health-related quality of life. They compared the combination therapy versus placebo and monotherapy (solifenacin 5 mg) using questionnaire OAB-q [Symptom Bother/total HRQoL] and Patient Perception of Bladder Condition (PPBC) score. There were statistically significant improvements in patient-reported outcomes and efficacy of combination therapy, solifenacin 10 mg and mirabegron 25 mg ($p = 0.023$) and with solifenacin 5 mg and mirabegron 50 mg ($p = 0.015$) when compared to solifenacin 5 mg. This substantiates that the improvement with combination treatment was, in fact, helping to improve patients' perception which was clinically significant.

The BESIDE trial [48], was designed to evaluate the efficacy of combination therapy compared to monotherapy in a more difficult-to-treat patient group who continued to have problems with urgency incontinence after 4 weeks of treatment of solifenacin 5 mg. The trial examined whether the addition of mirabegron 50 mg to solifenacin 5 mg (combination therapy) was more effective than solifenacin 5 mg or 10 mg monotherapy in improving patients' symptoms. Patients were randomized 1:1:1 to double-blind daily combination or solifenacin 5 or 10 mg for 12 weeks. Patients receiving the combination treatment were initiated on mirabegron 25 mg increasing to 50 mg after week 4. A total of 2174 patients were included in the trial. At end of treatment, combination therapy was found to be superior to monotherapy solifenacin 5 mg, with significant improvements in daily incontinence episodes, the mean number of voiding per day, and urgency incontinence episodes reported by the patients in a 3-

day voiding diary. The authors concluded that combination therapy was non-inferior to solifenacin 10 mg for urgency incontinence and superior to solifenacin 10 mg for improving the number of voids per day. There were no reports of increasing the bothersome adverse effects associated with antimuscarinic therapy except for constipation. Combination therapy seemed to improve the quality of life of the patients and was well tolerated with no significant side effects.

The third trial was the SYNERGY trial [49••]which included patients who were diagnosed with OAB for at least 3 months. Patients were included based on a voiding diary showing urgency grade 3 and 4 on Patient Perception of Intensity of Urgency Scale (PPIUS) and > 1/day, the urinary frequency was more than 8 times/day, and urgency urinary incontinence. Duration of the study was 18 weeks, 4 weeks of placebo run-in, and 12 weeks of double-blind treatment period then single-blind placebo run-out treatment. Patients were randomized to 6 treatment groups, solifenacin 5 mg and mirabegron 25 mg, solifenacin 5 mg and mirabegron 50 mg, mirabegron 25 mg, mirabegron 50 mg, solifenacin 5 mg, and placebo. Primary endpoints were a change from baseline to the end of treatment in the mean number of urgency incontinence episodes/day, Number of voids/day and nocturia episodes are assessed by electronic diary for 7 days. All primary endpoints were met at the end of the treatment, the combination therapy improved urgency incontinence in all treatment arms when compared to placebo. However, the combination therapy was not superior to mirabegron 50 mg in improving urgency incontinence. The improvement was observed in the number of voids per day, urgency incontinence episodes, urgency episodes per day, and nocturia especially in the combination therapy of solifenacin 5 mg and mirabegron 50 mg, and the response seems to be additive. It was noticed that a greater response was seen in patients who had previous treatment vs patients who were treatment naïve. Overall, combination treatment was superior to monotherapy in the improvement of patients' symptoms.

Improvement of treatment outcomes was reflected by statistically significant improvement of the quality of life of patients as reported using health-related quality of life (HRQoL), Patient Perception of Bladder Condition (PPBC), and Treatment Satisfaction-Visual Analogue Scale (TS-VAS) [49••].

The same results were reproduced in a trial performed in Japan by Yamaguchi et al. [50]. This was a multicenter, open-label, phase IV study which included 223 subjects who met eligibility criteria (≥ 20 years old, an OAB symptom score (OABSS) total of ≥ 3 points, and an OABSS Question 3 score of ≥ 2 points). These patients were initially treated with solifenacin 2.5 or 5 mg once daily for at least 4 weeks and failed to have the optimal response. Subsequently, mirabegron (25 mg once daily) was added to the treatment for 16 weeks and was increased to 50 mg in patients who still had inadequate control of their symptoms. Significant improvements from baseline were seen for the OABSS total score in all treatment groups at the end of treatment. Patients who did not have initial improvement on mirabegron 25 mg reported improvement after increasing mirabegron to 50 mg.

All treatment groups showed statistically significant improvement in the mean number urinary frequency episodes/day, decreased number of urgency episodes/day, decreased the mean number of UI episodes/day, urgency episodes/day, and mean volume voided significantly increased from baseline in all treatment groups. The mean number of nocturia episodes/night decreased numerically from baseline to each visit in all treatment groups. Improvements were seen in the quality of life in all treatment groups using OAB-q SF symptom bother score and mean OAB-q SF total HRQL score [50].

Safety of the combination therapy continues to be evident in all studies with limited adverse effects. The side effects of the combination therapy appear to be minimal with a slight increase in the combined treatment arm. The lowest adverse effects were reported in monotherapy treatment with mirabegron 25 mg and were highest in the combination therapy of solifenacin 5 mg and mirabegron 25 mg [49••]. Minimal side effects were reported including urinary tract infections, increased PVR, dry mouth, constipation, and dyspepsia. However, all of these were not of clinical significance. These were slightly higher in the combined treatment arm. There were no cardiovascular events reported during the treatment period [49••]. These side effects profile was similar as reported by other studies [46••, 48]. Yamaguchi et al. reported similar safety profile with no changes during patients monitoring with laboratory tests, vital signs, 12-lead electrocardiogram, QT corrected for heart rate, and PVR volume [50].

There was always a concern about combination therapy with risks of increased PVR or urinary retention; however, this was not found to be true. There were no increased events of urinary retention or other significant adverse effects during the study. Drake et al. [51] reviewed the effect of combination therapy on PVR in BESIDE trial. They found that the actual changes in PVR from the baseline were 5.5 ml, 3 ml, and 7.4 ml in the combination therapy group of mirabegron 50 mg and solifenacin 5 mg, solifenacin 5 mg and solifenacin 10 mg respectively. This is clinically insignificant changes in all treatment groups.

The above trials were focused on adding β3-adrenoceptors agonists to antimuscarinics. Shin et al. [52] reported on adding antimuscarinics to patients who had suboptimal response to β3 agonists. They reported a good response to adding low-dose antimuscarinics to patients who had suboptimal response to mirabegron 50 mg daily for 4 weeks. They included 30 patients who reported suboptimal response in PPBC (≥ 4). Patients had an additional low dose of antimuscarinics (propiverine HCl, 10 mg) for 8 weeks. They showed improved PPBC response as the primary endpoint. These

patients exhibited an improved frequency of voiding, episodes of urgency, and episodes of urgency incontinence which were secondary endpoints. Adverse effects of dry mouth were reported to be minimal and were limited only to dry mouth in 3 patients and no reported urinary retention problems [52]. The number of patients in this trial was limited; however, it continues to show improvement of OAB symptoms in patients who received combination therapy.

Safety in Elderly Patients

OAB increases in prevalence and severity with aging. It is estimated that up to 20% of people aged 65 years or more will have symptoms of OAB and up to 40% in those who are more than 75 years of age [53]. Treatment of elderly patients requires additional consideration since there are multiple factors affecting decision making. Most often these patients have other morbidities, such as cognitive issues and constipation, and are often on multiple medications which require additional attention. Elderly patients may have problems with impaired attention, memory loss, and somnolence [54]. There is a theoretical risk of dementia and impaired cognitive function associated with increased usage of antimuscarinics in the elderly [55, 56]. Previously, it was shown that treatment with oxybutynin was associated with deterioration of cognitive function when compared to placebo [57]. Using a lower dose of antimuscarinics in combination with β3 agonists (mirabegron) could be a good alternative to improve symptoms with decreasing side effects of antimuscarinics. Gibson et al. [58] performed a subgroup analysis on elderly patients who were enrolled in BESIDE study to determine efficacy and safety of combination treatment in elderly patients. They included 2110 patients (83% women) and about 31% of patients were > 65 and about 9% were older than 75 years of age. They found that patients benefited from treatment in general; however, combination therapy was better than monotherapy with solifenacin 5 mg and 10 mg in reducing the number of daily incontinence episodes/24 h, daily frequency of voiding, average daily urgency, and urgency incontinence episode in all age groups [58]. Side effects were similar between all treatment groups during the treatment period in all ages and the most common side effect was dry mouth which was higher in solifenacin 10 mg and was well tolerated. Constipation was slightly higher in older age groups with all treatments. There were trivial and no clinically significant changes in blood pressure in all patients across all ages [58].

Conclusion

Having combination therapy of 2 classes of medications, antimuscarinics and β3 agonists (mirabegron), acting through different molecular pathways to modify bladder dysfunction, seems to offer advantages over monotherapy alone. Multiple trials provided evidence that this combination offers additive outcomes to monotherapy alone in improving OAB symptoms. This improvement extended to affect the quality of life to these subjects. The combination therapy was safe and was tolerated by patients with minimal side effects. Successful treatment of patients who failed monotherapy seems to provide an extra treatment option for refractory cases. It seems logical in a step-by-step treatment algorithm to start with monotherapy then if failed proceed to combination treatment prior to proceeding to a more invasive line of treatments. The combination treatment seems to be safe and well tolerated by elderly patients.

Compliance with Ethical Standards

Conflict of Interest Ahmed El-Zawahry each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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