



Original Research Article

Comparison of Solifenacin, Mirabegron and Their Combination in the Treatment of Overactive Bladder Syndrome

Article History:

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Received: 21-12-2025

Revised: 28-12-2025

Accepted: 28-12-2025

Published: 31-12-2025

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Abstract: **Objective:** To compare the efficacy and safety of solifenacin, mirabegron, and their combination in patients diagnosed with overactive bladder (OAB) syndrome. **Materials And Methods:** This prospective, randomized, open-label, parallel-group study was conducted at the Department of Urology, DHQ Hospital, Dera Ismail Khan, Pakistan, from January 2023 to December 2024. A total of 180 adult patients (aged 18–75 years) with clinically and urodynamically confirmed OAB were randomly assigned into three groups (n = 60 each): Group A received solifenacin 5mg once daily, Group B received mirabegron 50 mg once daily, and Group C received a combination of solifenacin 5 mg + mirabegron 50 mg once daily. All patients were followed for 12 weeks. Primary outcomes included change in 24-hour micturition frequency, urgency episodes, and nocturia. Secondary outcomes included Overactive Bladder Symptom Score (OABSS), Patient Perception of Bladder Condition (PPBC), and treatment-emergent adverse events (TEAEs). Data were analyzed using SPSS v26.0; $p < 0.05$ was considered statistically significant. **Results:** All three regimens significantly reduced OAB symptoms ($p < 0.001$). The combination therapy (Group C) demonstrated superior reductions in mean micturition frequency (−4.2 vs. −3.1 and −2.9; $p = 0.003$), urgency episodes (−3.8 vs. −2.7 and −2.5; $p = 0.001$), and OABSS (−5.6 vs. −4.1 and −3.9; $p < 0.001$) compared to monotherapies. Dry mouth was more frequent with solifenacin (23.3%) than mirabegron (5.0%) or combination (18.3%; $p = 0.012$). Hypertension was slightly higher in the mirabegron group (8.3%) but not statistically significant ($p = 0.14$). The combination group showed the highest PPBC improvement (78.3% “much/very much better” vs. 60.0% and 58.3%; $p = 0.021$). **Conclusion:** The combination of solifenacin and mirabegron offers significantly greater symptomatic improvement in OAB compared to either monotherapy, with a manageable safety profile. It represents a viable therapeutic option for patients with moderate-to-severe OAB unresponsive to single-agent therapy.

Keywords: Overactive bladder; solifenacin; mirabegron; combination therapy; antimuscarinic; $\beta 3$ -adrenoceptor agonist.

INTRODUCTION

An Overactive Bladder (OAB) syndrome is an extremely common Urological Condition, which can be defined by urinary urgency, with or without Urgency Incontinence, alongside increased daytime frequency of urination and nocturia, with all this occurring without having an associated urinary tract infection or any other identifiable pathology [1]. The International Continence Society (ICS) has categorised OAB as a symptom-based diagnosis that will significantly impact a person's Quality of Life, Sleep and Psychosocial well-being [2]. The worldwide prevalence of OAB is estimated to be between 10% and 17% universally and to be higher among older adults, as well as women [3]. Community-based studies from Pakistan indicate a prevalence of between 12 and 14%; however, under diagnosis of the condition is not uncommon, mainly due to cultural stigma attached to OAB and also due to limited access to skilled urological professionals [4]. Treatments initially attempted for managing OAB include Behavioral Modifications (e.g., Bladder Training, Fluid Management), although Pharmacotherapy is usually needed for the more Moderate-Severe symptoms associated with the syndrome [5].

Antimuscarinic agents have long been considered a first-line treatment for OAB, with solifenacin being one of these agents. Solifenacin is a Premier Selective M3 Muscarinic Receptor Antagonist and works to control Detrusor Overactivity through the prevention of Acetylcholine-induced contractions in the bladder [6]. There are, however, some limitations on the use of Solifenacin due to its side effects associated with anticholinergic agents, particularly for example, in older adults, experiencing Dry Mouth, Constipation and Cognitive Effects [7].

Mirabegron is a β_3 -adrenoceptor agonist which was approved in 2012. This drug works by relaxing the muscle responsible for bladder contraction while the bladder is filling with urine and uses a different method than antimuscarinics (e.g., it utilizes cAMP-type pathways) to achieve this. In patients treated with mirabegron compared to those treated with antimuscarinics, patients treated with mirabegron experience comparable efficacy to antimuscarinics, but mirabegron has a better side effect profile, especially with respect to dry mouth and/or constipation. Unfortunately, high costs and possible increases in blood pressure related to taking mirabegron limit its use in many low-resource settings such as Pakistan.

Further, recent evidence suggests that combining antimuscarinics with β_3 -agonists may have synergistic benefits. When using combination therapy, you would be simultaneously targeting both efferent and afferent pathways for bladder overactivity. Randomized trials that have been performed in Western countries provide strong evidence for the superiority of combined therapy compared to monotherapy; however, this type of data

from South Asian populations (particularly Pakistan) remains sparse.

The purpose of this study is to evaluate and compare the efficacy and safety of solifenacin monotherapy, mirabegron monotherapy and combination therapy in treating patients who have an overactive bladder in Pakistan, and specifically in this population of patients from a public-sector tertiary care hospital in Dera Ismail Khan. To the best of our knowledge, this study represents the first study of this type conducted in Khyber Pakhtunkhwa Province.

MATERIALS AND METHODS

Study Design and Setting: A prospective, randomized, open-label, parallel-group clinical trial was conducted at the Department of Urology, District Headquarter Teaching Hospital (DHTQH), Dera Ismail Khan, Pakistan, from January 2024 to December 2025, after approval by the Institutional Review Board. Written informed consent was obtained from all participants. **Inclusion Criteria:** Age 18–75 years, Diagnosis of OAB per ICS criteria: urgency ≥ 3 times/day, with or without incontinence, plus ≥ 8 micturitions/24h, Confirmed by 3-day bladder diary and OABSS ≥ 5 , Failure or intolerance to behavioral therapy alone. **Exclusion Criteria:** Urinary tract infection, bladder outlet obstruction (BOO), neurogenic bladder, or urothelial carcinoma, History of bladder surgery, Concomitant use of other OAB medications, Uncontrolled hypertension (SBP >160 mmHg), severe cardiac disease or hepatic/renal impairment (eGFR <30 mL/min), Pregnancy or lactation. **Sample Size Calculation:** Based on a pilot study ($n = 30$), a mean difference of 1.5 in micturition frequency reduction between groups, with SD = 2.0, $\alpha = 0.05$, and power = 80%, a minimum of 52 patients per group was required. Accounting for 15% dropout, we enrolled 60 per group (total N = 180). **Randomization and Intervention:** Patients were randomized using computer-generated block randomization (block size = 6) into three groups: Group A: Solifenacin 5 mg orally once daily, Group B: Mirabegron 50 mg orally once daily, Group C: Solifenacin 5 mg + Mirabegron 50 mg orally once daily, all medications were provided free of cost. Dose escalation (solifenacin to 10 mg) was not permitted per protocol. **Outcome Measures, Primary:** Change from baseline to week 12, Mean 24-hour micturition frequency, Mean urgency episodes/day, Nocturia episodes/night. **Secondary:** OABSS (range 0–15; higher = worse), PPBC (7-point scale: 1 = “no problem” to 7 = “very severe problem”),

Treatment-emergent adverse events (TEAEs). **Data Collection:** Patients maintained a 3-day bladder diary at baseline, week 4, and week 12. OABSS and PPBC were administered at each visit. Vital signs, including blood pressure, were recorded at every visit. **Statistical Analysis:** Data were analyzed using SPSS v26.0. Continuous variables were expressed as mean $\pm$ SD; categorical as frequencies (%). ANOVA with post-hoc Tukey test compared intergroup differences. Paired t-

tests assessed intragroup changes. Chi-square or Fisher's exact test evaluated categorical outcomes. $p < 0.05$ was

considered statistically significant.

RESULTS

A total of 180 patients were enrolled; 171 completed the 12-week follow-up (dropout rate = 5%). Baseline characteristics were comparable across groups (Table 1).

Table 1: Baseline Demographics and Clinical Characteristics (N = 180)

Variable	Group A (Solifenacin)	Group B (Mirabegron)	Group C (Combination)	p-value
Age (years), mean $\pm$ SD	54.2 $\pm$ 9.1	55.7 $\pm$ 8.6	53.9 $\pm$ 9.8	0.48
Female, n (%)	38 (63.3)	40 (66.7)	37 (61.7)	0.83
BMI (kg/m ²)	26.4 $\pm$ 3.2	25.9 $\pm$ 3.0	26.8 $\pm$ 3.5	0.31
Baseline micturition/day	11.3 $\pm$ 2.1	11.5 $\pm$ 1.9	11.2 $\pm$ 2.3	0.72
Baseline OABSS	9.4 $\pm$ 1.8	9.6 $\pm$ 1.7	9.3 $\pm$ 2.0	0.65

All $p > 0.05$, indicating no significant baseline differences.

Primary Outcomes (Table 2), All groups showed significant within-group improvement ($p < 0.001$). The combination group achieved significantly greater reductions in micturition frequency, urgency, and nocturia vs. both monotherapies ($p < 0.01$).

Table 2: Change in Primary Efficacy Parameters at Week 12

Outcome	Group A	Group B	Group C	p-value (A vs C)	p-value (B vs C)
Micturition/day (mean)	-3.1 $\pm$ 1.2	-2.9 $\pm$ 1.1	-4.2 $\pm$ 1.0	0.003	0.001
Urgency episodes/day	-2.7 $\pm$ 1.0	-2.5 $\pm$ 0.9	-3.8 $\pm$ 0.8	0.001	<0.001
Nocturia/night	-1.4 $\pm$ 0.6	-1.3 $\pm$ 0.5	-1.9 $\pm$ 0.4	0.002	<0.001

Secondary Outcomes (Table 3), OABSS and PPBC improved most in Group C ($p < 0.01$ vs. others).

Table 3: Secondary Outcome Measures at Week 12

Measure	Group A	Group B	Group C	p-value (overall)
Δ OABSS	-4.1 $\pm$ 1.3	-3.9 $\pm$ 1.2	-5.6 $\pm$ 1.1	<0.001
PPBC "Much/Very Much Better" (%)	60.0	58.3	78.3	0.021

Adverse Events (Table 4), Dry mouth was significantly more common with solifenacin and combination therapy. Hypertension incidence was low and non-significant.

Table 4: Treatment-Emergent Adverse Events (TEAEs)

Adverse Event	Group A (n=60)	Group B (n=60)	Group C (n=60)	p-value
Dry mouth	14 (23.3%)	3 (5.0%)	11 (18.3%)	0.012
Constipation	8 (13.3%)	2 (3.3%)	7 (11.7%)	0.068
Hypertension	3 (5.0%)	5 (8.3%)	4 (6.7%)	0.14
Headache	5 (8.3%)	6 (10.0%)	5 (8.3%)	0.92
Discontinuation	3 (5.0%)	2 (3.3%)	2 (3.3%)	0.84

Defined as SBP ≥ 140 mmHg or >20 mmHg increase from baseline.

Subgroup Analysis by Gender (Table 5), Women showed greater symptom reduction across all groups, but the combination remained superior in both genders ($p < 0.05$).

Table 5: Efficacy by Gender – Δ Micturition Frequency at Week 12

Group	Men (n=63)	Women (n=108)	p-value (Men vs Women within group)
A	-2.8 ± 1.1	-3.3 ± 1.2	0.08
B	-2.6 ± 1.0	-3.0 ± 1.1	0.12
C	-3.9 ± 0.9	-4.4 ± 1.0	0.03

Table 1 confirms randomization success. Table 2 demonstrates the combination's superior efficacy on core OAB symptoms. Table 3 shows greater patient-perceived improvement with dual therapy. Table 4 highlights the expected anticholinergic side effect profile, with dry mouth significantly higher in solifenacin-containing regimens. Table 5 suggests women may benefit more, particularly with combination therapy.

DISCUSSION

Our study shows that the combination of solifenacin and mirabegron is significantly more effective in improving the symptoms of OAB than monotherapies, which is consistent with results from international studies, such as SYNERGY [12] or BESIDE trial [13]. The mean decrease in the number of micturitions per day (-4.2) and urgency episodes per day (-3.8) with combination therapy also exceeded the minimum clinically important difference > 1.5–2 for these end points [14].

The underlying mechanistic hypothesis for synergy is clear: solifenacin suppresses parasympathetic detrusor contraction and mirabegron increases bladder storage capacity by way of smooth muscle relaxation mediated through β_3 [15]. This dual pathway strategy targets both efferent (motor) and afferent (sensory) aspects of OAB pathophysiology. Significantly, this doublet was not associated with a disproportionate increase in serious adverse events.

Group C experienced dry mouth more often than Group B, with rates of 18.3% compared to 5.0%. However, this was a bit lower than the 23.3% seen with solifenacin alone. This might be because mirabegron helps relax the bladder, which could make the antimuscarinic effects less intense. This finding matches up with what Nitti *et al.* reported, showing that people tolerate combination therapy well. The low rate of stopping treatment, between 3.3% and 5.0%, indicates that people are sticking with their medications, which is impressive considering the challenges of cost and access in the public health system in Pakistan. Offering free medications probably played a big part in this positive outcome. While our results do differ a bit from some meta-analyses that say the benefits of combination therapy are slight, those studies often looked at different patient groups and lower doses. In our study group, made up of patients with moderate to severe overactive bladder (average OABSS score over 9), the benefits of the combination therapy were clearly evident.

Limitations of the study include its open-label design (potential for reporting bias), single-center study, and 12-week duration (long-term safety remains uncertain). However, several strengths of the study are that rigorous diagnostic criteria were used, bladder diaries were implemented, and results are relevant to actual practice

in low-resource Pakistani hospitals. The findings of the study are particularly significant for the care of patients with lower urinary tract symptoms in the Pakistani health care system because many patients do not have access to second-line or advanced treatment options for this condition. Many low- and middle-income countries, including Pakistan, have limited access to advanced therapies for lower urinary tract symptoms because antimuscarinics such as solifenacin are typically the only type of medication available through public sector hospitals due to drug cost and procurement practices. Although mirabegron is becoming more available, it is still a type of premium medication, and the vast majority of patients in low-income countries cannot afford to pay for it without financial assistance. We have demonstrated that when access to both types of medication is available through hospital funding, then the combination of the two will be able to produce clinically meaningful benefits for patients without causing excessive toxicity. This finding emphasizes the need for a review of the medications available to patients in public hospitals and to include β_3 -agonists in the formularies of such hospitals for patients suffering from refractory OAB. In terms of public health, the ramifications of OAB are far more extensive than the symptoms of urinary incontinence alone; they include depression, social isolation and decreased productivity at work factors that are frequently poorly recognized in Pakistani primary care settings.

Women with overactive bladder (OAB) are particularly vulnerable to anxiety related to their condition, with data from a large research study in Pakistan showing that 42% of these women had moderate to severe anxiety levels. However, only 9% of these women consulted a urologist about their symptoms [18]. These results indicate that both psychosocial benefits and improved symptom control can be achieved when suffering from OAB, leading to the potential for lower hidden disability associated with OAB that has not received an appropriate level of treatment.

Cost-effectiveness should also be evaluated. While mirabegron is approximately 3–4 times more expensive than solifenacin in the Pakistani private sector, it may be worth considering for the appropriate patient, especially if the patient has substantial symptoms or has not responded to previous solifenacin treatment. Modelling

of economic cost estimates conducted in India, a low-middle income country (LMIC) with similar demographics, has demonstrated that combination therapy would be cost-effective by preventing one or more additional patients from being treated with the third-line interventions (botox and/or neuromodulation) over the 2 years after treatment initiation [19]. As there are few advanced treatment options for OAB available in the overwhelming majority of Pakistan hospitals, outside of the metropolitan areas, the pragmatic goal of preventing treatment escalation is an important one. Additionally, the fact that women received greater benefit from combination therapy than men further supports research highlighting sex-based differences in the etiologies of OAB.

In postmenopausal women, lack of Estrogen could increase the sensitivity of the bladder afferents, thus enhancing the efficacy of dual-pathway inhibition [20]. This finding supports the need for gender-stratified treatment methods, and points to the importance of sensitivity to gender in the provision of urological care in Pakistan, where cultural expectations can impede timely access to specialist care for women.

The fact that none of the patients experienced any serious cardiovascular events during the 12-week period is also important, in light of concerns regarding the impact of mirabegron on blood pressure. This finding supports previous evidence from large post-marketing surveillance studies showing minimal impact on hemodynamics for normotensive and for well-controlled hypertensive patients [21]. However, due to the high rate of undiagnosed hypertension in rural Pakistan, which may be as high as 35% among adults over 40 years of age [22], regular monitoring of blood pressure should continue before and during the treatment with mirabegron, a practice that was strictly followed in our clinical protocol.

Future studies will examine the durability of response, risk of developing tolerance and/or establishing the long-term safety of mirabegron, including any potential cognitive effects in elderly patients who use a combination of anticholinergic medications. It will also be necessary for future studies to investigate fixed-dose combination formulations (if available in Pakistan) which would promote greater patient adherence and ultimately maximize treatment outcomes.

In conclusion, our results add to an ever-growing body of evidence that favours a personalized approach to treating OAB with drugs that target different underlying mechanisms. Therefore, clinicians in resource-limited settings should see solifenacin and mirabegron as complementary rather than competing options. As in Dera Ismail Khan and areas with similarly limited urological services staffed principally by general surgeons/physicians with minimal specialization training, treatment algorithms combining agents could

lead to a substantial improvement in patient outcomes without the need for extensive diagnostic evaluations or expensive infrastructures to support such treatments.

CONCLUSION

In Pakistani patients with OAB, the combination of solifenacin 5 mg and mirabegron 50 mg once daily provides significantly greater improvement in urinary frequency, urgency, nocturia, and patient-reported outcomes compared to monotherapy with either agent. The safety profile is acceptable, with dry mouth being the most common side effect. Given the high burden of OAB in our population and limited treatment access, this combination represents a valuable therapeutic escalation strategy for patients inadequately controlled on monotherapy.

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