



COMPARATIVE EFFECTS OF MIRABEGRON AND SOLIFENACIN COMBINATION VERSUS MIRABEGRON MONOTHERAPY FOR OVERACTIVE BLADDER IN WOMEN

Mudassar Saeed Pansota¹, Farheen Hameed², Sama Ul Haque³, Muhammad Ali Zubair⁴, Shazia Begum Shahani^{5*}, Mujeeb-Ur-Rehman Sahito⁶

¹MBBS, MS (Urology), Assistant Professor, Department of Urology, Shahida Islam Medical & Dental College, Lodhran, Pakistan

²Associate Professor, MBBS, MPhil (Pharmacology), Department of Pharmacology, Shahida Islam Medical & Dental College, Lodhran, Pakistan

³MBBS, MPhil (Anatomy), Associate Professor, Anatomy, Fazaia Ruth Pfau Medical College, Karachi, Pakistan

⁴MBBS, MPhil (Pharmacology), Assistant Professor, Department of Pharmacology, Shahida Islam Medical and Dental College, Lodhran, Pakistan

^{5*}MBBS, MPhil (Anatomy), Professor, Department of Anatomy, Liaquat University of Medical & Health Science, Jamshoro, Pakistan

⁶MBBS, MS (General Surgery), MS (Urology), MPhil (Anatomy), Associate Professor, Department of Anatomy, Peoples' University of Medical & Health Sciences for Women, Shaheed Benazirabad, Pakistan

***Corresponding Author:** Prof. Dr. Shazia Begum Shahani

*MBBS, MPhil (Anatomy), Professor, Department of Anatomy, Liaquat University of Medical & Health Sciences, Jamshoro, Pakistan, Email: shazia.shahani@lumhs.edu.pk

ABSTRACT

Introduction: Management of Overactive bladder (OAB) continues to present significant challenges. Mirabegron, β_3 adrenergic agonist recent approval has captured much attention in specialists, of course, who care for patients with OAB. Most Clinicians prefer antimuscarinic agent as first line therapy for the OAB patients which can be titrated to a higher dose or may be switched to another parasympatholytic or mirabegron. It has been proven by studies that mirabegron added to antimuscarinic therapy enhances treatment efficacy without a loss in tolerability and, with that, improves long-term adherence.

Objectives: To evaluate and compare the effectiveness of combination therapy of mirabegron and solifenacin with the monotherapy of mirabegron for the treatment of overactive Bladder (OAB) in women.

Material and Method: 480 women with diagnosis of overactive bladder (OAB) with age range of 20 to 50 years were included in the study. Patients with urinary tract infections, bladder stones, pelvic malignancies, spinal injuries, multiple sclerosis, diabetic neuropathy and Parkinson's disease were excluded from the study. The patients were divided into 2 groups. Patients in Group A received mirabegron 25 mg once daily and solifenacin 5 mg once daily for 12 weeks. For the same duration of 12 weeks, patients allocated to Group B received only mirabegron 25 mg once daily. Urinary incontinence was monitored at both pre-treatment and after a treatment duration of 12 weeks by the patient history. OABS score baseline and after 12 weeks was also taken. Cases were

followed for 12 weeks through contact numbers with assessment of efficacy of intervention at the end of follow-up based on the said operational definition.

Results: The mean Overactive Bladder Symptom (OABS) score in Group A (mirabegron + solifenacin) was 10.33 ± 3.12 at baseline and was improved to 4.43 ± 1.32 after 12 weeks while in Group B (mirabegron alone), it was 10.13 ± 2.98 at baseline and decreased to 6.87 ± 2.76 after 12 weeks. The efficacy of the combination therapy in Group A was observed in 143 patients (59.58%), compared to 117 patients (48.75%) in Group B, with a p-value of 0.017 which is statistically significant.

Conclusion: Results of this study established that combination therapy of mirabegron and solifenacin was found to be more effective in treating overactive bladder in women than the monotherapy of mirabegron.

Keywords: Overactive Bladder, Solifenacin, Mirabegron.

INTRODUCTION

Overactive bladder (OAB) syndrome is expressed as an urgency with or without involuntary urination, often accompanied by nocturia and increased urinary frequency, in the absence of an identifiable pathological cause.¹ The typical underlying mechanism is detrusor overactivity, as confirmed by urodynamic studies, although urethra-vesical dysfunctions can present with similar clinical features. (- et al., 2021) Several epidemiological studies have reported a positive correlation between advancing age and the prevalence of OAB symptoms (Makhani et al., 2020). In a large population-based study, OAB symptoms were reported by 8.7% women aged 40-44 years, and the prevalence increased to 31.3% aged ≥ 75 years. Another thing is that it is more frequent in older adults and also, over 80% of patients aged 80 to 90 years have at least one nocturnal voiding. (Mueller et al., 2019)

There is 9 to 43% prevalence of OAB in adult women. The well known risk factors for OAB include cardiovascular disease, obesity, arthritis, depression, irritable bowel syndrome and smoking. Common risk factors in women include diabetes, pregnancy, urinary tract infections, menopause, uterine prolapse, hysterectomy and neurological conditions such as multiple sclerosis. (Hsu et al., 2019).

Overactive bladder ranges from behavioral therapy and pharmacologic intervention to minimally invasive procedures and surgical options.⁶ The frontline pharmacologic treatment is through the use of antimuscarinic agents, particularly solifenacin, which acts in relaxing the detrusor muscle and modulating bladder function in the storage phase. However, persistence of antimuscarinic therapy is limited by suboptimal efficacy and the occurrence of atropine like adverse effects such as blurred vision, dry mouth and constipation that predispose patient for discontinuation in many patients. (Wang et al., 2019)

Another class of oral pharmacotherapy that is also used in the management of OAB includes β_3 -adrenergic receptor agonists.⁸ This new class of drugs, which comprises mirabegron, is a β_3 -adrenergic receptor agonist that prevents the contraction of the detrusor muscle for the facilitation of urine storage. Its new mechanism of action is believed to be equivalent in effectivity to antimuscarinics but with better side effects profiles that eliminate or significantly reduced the risks of such common antimuscarinic adverse side effects as blurred vision, dry mouth, constipation, and cognitive decline. Tolerability and improved safety of mirabegron result in a high compliance rate among patients and low discontinuation rates over long-term treatment. (Özkidik et al., 2019)

As mirabegron acts through a distinct mechanism of action compared with antimuscarinics, the combination of mirabegron with an antimuscarinic, like solifenacin, might lead to an improved tolerability without loss of therapeutic efficacy, contrary to an increase in the dose of an antimuscarinic monotherapy. The combination of two oral agents with different mechanisms is aimed at the treatment and the persistence increase of OAB symptoms without enhancement of known side effects due to antimuscarinics. This may reduce the need for dose escalation of

antimuscarinics or even more invasive interventions. Clinical data reported at 12 weeks after start of treatment, showed an efficacy rate of 65.2% of mirabegron and solifenacin, compared with 54% of the treatment using mirabegron.¹⁰

Overactive bladder symptoms often severely and negatively impact health-related quality of life, usually bringing about conditions such as depression, anxiety, and sleep disturbances. These complaints can hinder daily activities and social as well as professional functioning, especially in women. Despite the progress made in treatment, managing OAB continues to be difficult for urologists. Currently, there are no local data regarding the comparison of the various treatment modalities in women. In this way, the purpose of my research is to fill this gap, bringing very important insights to improve the future management strategies for OAB in women.

MATERIALS AND METHODS

The clinical trial included 480 women diagnosed with overactive bladder (OAB), which is defined as urinary urgency minimum of one episode per week, either with or without incontinence and nocturia more than once per night. Symptomatic OAB was evaluated using the Overactive Bladder Symptom Score, a validated measure of symptoms. The OABS questionnaire consists of four questions with score range of 0 to 15, higher scores indicating the severity of the disease.

It included women aged 20-50 years who presented at the Urology department of Shahida Islam Medical College and Teaching Hospital, Lodhran. From May 2024 for 3 months, The sample size calculation was done with WHO sample size calculator for two proportions, with a 5% level of significance, 80% power, P1 = 54%, and P2 = 65.2%. Patients with urinary tract infections, bladder stones, pelvic malignancies, spinal injuries, multiple sclerosis, diabetic neuropathy and Parkinson's disease were excluded from the study.

Patients were randomly divided into two groups using computer generated randomizer. Patients in Group A received mirabegron 25 mg once daily and solifenacin 5 mg once daily for 12 weeks. For the same duration of 12 weeks, patients allocated to Group B received only mirabegron 25 mg once daily. Urinary incontinence was monitored at both pre-treatment and after a treatment duration of 12 weeks by the patient history. OABS score was calculated at baseline and after 12 weeks. Cases were followed for 12 weeks through contact numbers with assessment of efficacy of intervention at the end of follow-up which relied on a 50% reduction in episodes of urinary incontinence per 24 hours and at least an improvement of 3 points in the pre-treatment OABS score after 12 weeks.

Data of scores was analyzed using SPSS software Version 25. Mean standard deviation was calculated for age, duration of disease, BMI, number of urinary incontinence at baseline and after 12 weeks, the score of OABS at the baseline and after 12 weeks. Frequency and percentages were calculated for improvement in urinary incontinence, improvement in OABS score and efficacy. Chi-square test was used to compare efficacy between two groups.

RESULTS

This study involved participants aged 20-50 years, with an average age of 36.85 ± 6.61 years. In Group A, mean age was 36.49 ± 7.87 years, and in Group B, it was 35.93 ± 6.19 years. The majority of the participants were between 36 and 50 years, accounting to 257 (53.54%).

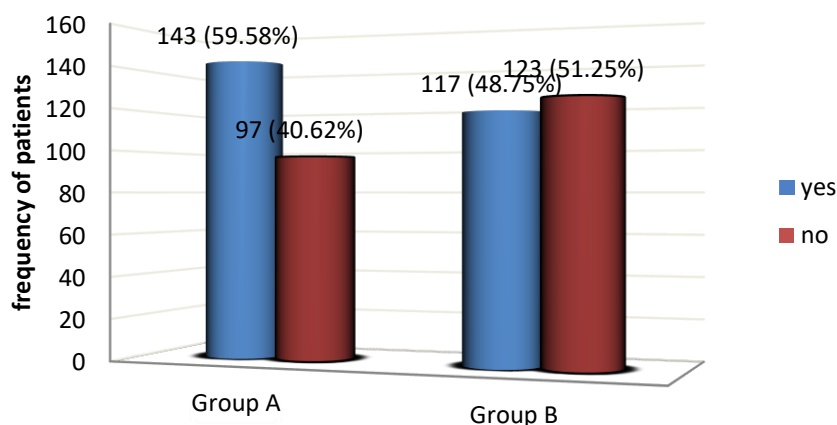
The mean BMI of participants was 28.30 ± 2.20 kg/m² and the mean duration of OAB symptoms was 12.47 ± 2.57 months. In comparison with baseline, the group A patients had mean weekly incontinence episodes 2.44 ± 1.32 that reduced to 1.23 ± 0.89 at the end of 12 weeks of treatment. In Group B, in comparison the baseline mean was 2.65 ± 1.54 episodes/week with a decrease down to 2.01 ± 1.04 at week 12.

In relation to the Overactive Bladder Symptom Score, the mean baseline score in the Group A at the beginning was 10.33 ± 3.12 that became 4.43 ± 1.32 after 12 weeks of intervention. At a mean baseline OABS score of 10.13 ± 2.98 in Group B, the symptom improved to 6.87 ± 2.76 after 12 weeks of the intervention.

Group A (mirabegron + solifenacin) showed efficacy of treatment in 143 patients (59.58%) as it confirmed more than 50% decrease in the number of cases of incontinence with an improvement of more than 3 points in the OABS score on the other hand, Group B-mirabegron alone showed efficacy of treatment in 117 patients (48.75%). The respective p value is 0.017. (Figure I).

		Group A (mirabegron + solifenacin)	Group B mirabegron alone
Mean Age		36.49 ± 7.87 years	35.93 ± 6.19 years
Efficacy		143 patients (59.58%)	117 patients (48.75%).
Overactive Bladder Symptom Score	Baseline	10.33 ± 3.12	10.13 ± 2.98
	12 weeks	4.43 ± 1.32	6.87 ± 2.76
Urinary incontinence/week	Baseline	2.44 ± 1.32	2.65 ± 1.54
	12 weeks	1.23 ± 0.89	2.01 ± 1.04

Figure IX: Comparison of the efficacy of combination of mirabegron and solifenacin with mirabegron alone for overactive bladder in women.



➤ **P-value = 0.017 which is statistically significant**

DISCUSSION

OAB syndrome is defined by the syndrome of urinary urgency, without any infection in the urinary tract or any identifiable disease. The chronic and often bothersome nature of OAB symptoms can significantly impair the quality of life and make patients socially isolated, depressed, and pessimistic.^{13,14} While the backbone of oral pharmacotherapy for OAB has traditionally been antimuscarinics, the use of this class of drugs remains limited by their limited long-term efficacy and adverse effects.¹⁵ The treatment of OAB continues to be challenging; therefore, there is a call for newer therapeutic options.

Mirabegron is an α_3 -adrenoceptor agonist that has garnered much attention among specialists in managing OAB.(O’kane et al., 2022). Most patients with OAB are treated initially by antimuscarinic drugs but Mirabegron can be a better option to its less toxic effects especially in elderly patients (Kuo & Kuo, 2023). Studies have shown that mirabegron can be used in combination with an antimuscarinic without an adverse effect on tolerability but does result in a greater effect that can contribute to more successful treatment persistence.(Jamil et al., 2023) (Salem et al., 2020). It is also considered to be safer and tolerable in comparison to solifenacin after a surgical procedure for SUI after the completion of 6 months of treatment and is considered for long-term treatment of Urgency Urinary Incontinence. (Özkidik et al., 2019)

The age range of participants in this study was 20 to 50 years with an average age of 36.85 ± 6.61 years. The mean ages for Group A and Group B were 36.49 ± 7.87 years and 35.93 ± 6.19 years,

respectively. The majority of participants, 257 (53.54%), belonged to the age group of 36 to 50 years.

The efficacy rate was higher in Group A (mirabegron + solifenacin) with 143 patients that is 59.58%, whereas the efficacy was observed in 117 patients in Group B that is mirabegron monotherapy, at a statistically highly significant p-value of 0.017. This study potentially supports the reduction of urinary urgency, frequency of micturition and nocturia in combination therapy as compared to individual drug in a study with a sample size of 70 patients. (Mahapatra et al., 2022)

The combination of solifenacin + mirabegron is significantly better than using either of these drugs alone as there was a mean decrease of 4 episodes of micturition per 24 hours in comparable to decline of 3.47 episodes with solifenacin alone and 3.67 episodes in the Mirabegron group (Kumar et al., 2023) (Warudkar et al., 2022)

Combination therapy of solifenacin with mirabegron showed significant improvements over solifenacin monotherapy for reduction of OAB symptoms due to double-J stents and improvement of quality of life without producing harmful side effects. (Tang et al., 2022)

Considering the fact that researches have proved mirabegron to be superior to solifenacin therapy with respect in terms of therapeutic effect and treatment-related adverse events so combination therapy can lead to effectiveness and less anti muscarinic effects. (Raj et al., 2024). Some studies justifies mirabegron as a cost effective drug and also suggests that patients with OAB who are treated with mirabegron adhere to the treatment more as compared to other drugs like solifenacin. (Majd et al., 2023).

CONCLUSION

The results of this study indicates that the combination therapy of mirabegron and solifenacin provides superior clinical results in comparison to monotherapy of mirabegron for women suffering from overactive bladder (OAB). This should therefore be considered as routine treatment for women with OAB in attempts to bring out better clinical outcomes.

REFERENCES

1. Faisal, M. S., Opal, S., Nawaz, A., Hassan, M., & Hayat, S. (2021). Comparison between efficacy of solifenacin and oxybutynin for the treatment of overactive bladder in women. *The Professional Medical Journal*, 28(06), 896–901. <https://doi.org/10.29309/tpmj/2021.28.06.6118>
2. Hsu, F. C., Weeks, C. E., Selph, S. S., Blazina, I., Holmes, R. S., & McDonagh, M. S. (2019). Updating the evidence on drugs to treat overactive bladder: a systematic review. *International Urogynecology Journal*, 30(10), 1603–1617. <https://doi.org/10.1007/s00192-019-04022-8>
3. Jamil, M. N., Irum, S., & Islam, E. U. (2023). Comparison Of Solifenacin And Mirabegron For The Treatment Of Overactive Bladder. *Journal of Ayub Medical College, Abbottabad : JAMC*, 35(2), 298–300. <https://doi.org/10.55519/JAMC-02-11795>
4. Kumar, S., Tiwari, V., Chaurasia, D. K., Kumar, S., & Mishra, S. (2023). A Comparative Study of Solifenacin, Mirabegron, and Their Combination as Bladder Relaxants in the Management of Overactive Bladder. *Cureus*, 15(9). <https://doi.org/10.7759/cureus.45612>
5. Kuo, Y. C., & Kuo, H. C. (2023). Comparative study of different combinations of mirabegron and antimuscarinics in treatment for overactive bladder syndrome in elderly patients. *Tzu Chi Medical Journal*, 35(1), 62–68. https://doi.org/10.4103/tcmj.tcmj_209_21
6. Mahapatra, S. K., Dash, R. R., Rath, B., & Hota, P. S. (2022). Solifenacin and Mirabegron Monotherapies Versus Combination Therapy in Overactive Bladder: A Prospective Observational Study. *Biomedical and Pharmacology Journal*, 15(1), 491–497. <https://doi.org/10.13005/bpj/2389>
7. Majd, Z. K., Mohammadnezhad, G., Taheri, S., & Yousefi, N. (2023). Cost-Utility Analysis of Mirabegron Compared to Solifenacin in the Treatment of Overactive Bladder (OAB) in Iran. *Iranian Journal of Pharmaceutical Research*, 22(1), 1–10. <https://doi.org/10.5812/ijpr-136447>
8. Makhani, A., Thake, M., & Gibson, W. (2020). Mirabegron in the treatment of overactive

- bladder: Safety and efficacy in the very elderly patient. *Clinical Interventions in Aging*, 15, 575–581. <https://doi.org/10.2147/CIA.S174402>
9. Mueller, E. R., van Maanen, R., Chapple, C., Abrams, P., Herschorn, S., Robinson, D., Stoelzel, M., Yoon, S. J., Al-Shukri, S., Rechberger, T., & Gratzke, C. (2019). Long-term treatment of older patients with overactive bladder using a combination of mirabegron and solifenacin: a prespecified analysis from the randomized, phase III SYNERGY II study. *Neurourology and Urodynamics*, 38(2), 779–792. <https://doi.org/10.1002/nau.23919>
 10. O’kane, M., Robinson, D., Cardozo, L., Wagg, A., & Abrams, P. (2022). Mirabegron in the Management of Overactive Bladder Syndrome. *International Journal of Women’s Health*, 14, 1337–1350. <https://doi.org/10.2147/IJWH.S372597>
 11. Özkidik, M., Coşkun, A., Asutay, M. K., Bahçeci, T., & Hamidi, N. (2019). Efficacy and tolerability of mirabegron in female patients with overactive bladder symptoms after surgical treatment for stress urinary incontinence. *International Braz J Urol*, 45(4), 782–789. <https://doi.org/10.1590/S1677-5538.IBJU.2018.0518>
 12. Raj, M. O., Jose, J., Paul, F., Sreedharan, S., & Uthaman, N. (2024). Therapeutic effectiveness and adverse drug reactions of mirabegron versus solifenacin in the treatment of overactive bladder syndrome. *Perspectives in Clinical Research*, 15(3), 147–151. https://doi.org/10.4103/picr.picr_166_23
 13. Salem, A. A. M., Kamhawy, O. M., Salem, E. A. E., & Elsayed, I. I. (2020). Mirabegron versus solifenacin in treatment of overactive bladder in female patients in zagazig university hospitals. *Egyptian Journal of Hospital Medicine*, 81(5), 2078–2083. <https://doi.org/10.21608/EJHM.2020.126406>
 14. Tang, Q. lai, Zhou, S., Liu, Y. qing, Wu, J., & Tao, R. zhen. (2022). Efficacy and safety of combination of mirabegron and solifenacin in patients with double-J stent related overactive bladder: a prospective study. *Scientific Reports*, 12(1), 1–7. <https://doi.org/10.1038/s41598-022-23795-5>
 15. Wang, J., Zhou, Z., Cui, Y., Li, Y., Yuan, H., Gao, Z., Zhu, Z., & Wu, J. (2019). Meta-analysis of the efficacy and safety of mirabegron and solifenacin monotherapy for overactive bladder. *Neurourology and Urodynamics*, 38(1), 22–30. <https://doi.org/10.1002/nau.23863>
 16. Warudkar, S., Jain, A. B., Dave, N. S., & Chaturvedi, A. R. (2022). Meta-analysis of efficacy and safety of Mirabegron plus Solifenacin combination therapy in comparison with Solifenacin monotherapy in overactive bladder. *European Urology*, 81(4), S662–S663. [https://doi.org/10.1016/s0302-2838\(22\)00526-7](https://doi.org/10.1016/s0302-2838(22)00526-7)