



ORIGINAL ARTICLE

## To assess the effectiveness of Mirabegron in reducing urodynamic detrusor overstimulation in patients with Overactive Bladder Syndrome (OAB).

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**ABSTRACT... Objective:** To investigate the efficacy of mirabegron in treating overactive bladder by assessing its impact on urodynamic detrusor overactivity (DO). **Study Design:** Cross-sectional study. **Setting:** Center for Urology and Transplantation in Sindh. **Period:** April 6, 2022, to October 4, 2022. **Methods:** Sixty-four individuals presenting OAB symptoms and without prior OAB medication use were included after obtaining informed consent and conducting relevant medical evaluations. Patients demonstrating signs of detrusor overactivity were evaluated through urodynamic assessments. Collected data, including patient history and study outcomes, were recorded using a standardized Proforma (Annexure I). Patient demographics, age, and gender distribution were documented. Patients with urodynamic detrusor overactivity were administered 50.0 mg mirabegron tablets once daily for a period of 13 weeks. A noteworthy percentage of patients reported substantial success after three months of treatment. **Results:** The average age of study participants was 50 years. The mean duration of OAB symptoms was  $20.22 \pm 15.38$  months. Of the total 64 patients, 41 were female (64.06%) and 23 were male (34.94%). Notably, successful treatment outcomes were observed in 49 cases (76.56%). **Conclusion:** Mirabegron emerges as a valuable therapeutic option for individuals dealing with overactive bladder. This study underscores its efficacy in managing OAB symptoms, with a notable success rate of 76.6%. These findings contribute to the growing body of evidence supporting mirabegron as an effective treatment for overactive bladder syndrome.

**Key words:** Antimuscarinic Drugs, Detrusor Overactivity (DO), Mirabegron, Nocturia, Overactive Bladder Syndrome (OAB), Urodynamic Urinary Frequency.

### INTRODUCTION

Overactive bladder dysfunction is characterized by prevalent symptoms that include frequent urination (up to eight times a day), nocturia (waking up at least once during the night to urinate), urgency, and urgency leakage, collectively diminishing the quality of life. This condition can be caused by various factors, including neurogenic, myogenic, or idiopathic origins. Despite antimuscarinic drugs being the conventional approach to overactive bladder (OAB) therapy, their effectiveness is limited for some individuals due to inadequate results or bothersome side effects, leading to a significant rate of treatment discontinuation. Mirabegron, a selective  $\beta_3$ -adrenoceptor agonist, presents a distinctive mechanism of action and a favorable

side-effect profile, offering a promising alternative to antimuscarinic treatment for OAB. Previous studies by Schiavi et al. reported a 79.3% success rate in treating OAB with mirabegron, while he found a success rate of 70.5%. Therefore, this research aims to investigate the efficacy of mirabegron in the context of overactive bladder syndrome.<sup>1</sup>

### Rationale

The primary goal of this research is to validate that patients suffering from overactive bladder syndrome and receiving treatment with mirabegron tablets yield comparable outcomes. Traditionally, antimuscarinic medications like solifenacin were employed for OAB treatment; however, numerous patients ceased their usage

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due to adverse side effects. As a result, this study seeks to explore the potential of mirabegron as an alternative treatment option with improved tolerability. Should the study uncover less favorable outcomes, it will necessitate the exploration of alternative therapeutic avenues that can effectively alleviate symptoms and lower the overall burden of the condition on patients. The insights gained from this study could lay the foundation for more extensive investigations, building upon the current findings to further enhance the management of OAB.

### Objectives

The core objective of this research is to ascertain the efficacy of mirabegron as a treatment for overactive bladder (OAB) by evaluating its impact on urodynamic detrusor overactivity.

### Operational Definitions

#### Effectiveness

The term “effectiveness” pertains to the advantageous outcomes observed with the administration of mirabegron tablets. The reduction in instances of urodynamic detrusor overactivity aligns with the efficacy of Mirabegron. Detrusor overactivity signifies the involuntary contractions of the detrusor muscle during the bladder’s filling phase. This research utilizes standard cystometry procedures, where patients are positioned supine and subjected to controlled bladder filling using room-temperature saline at a consistent rate. Maximal cystometric capacity (MCC) measurements are followed by provocative maneuvers, including coughing in supine and sitting positions. Involuntary detrusor contractions during these maneuvers indicate detrusor overactivity.

Overactive Bladders (OAB) Syndrome: Diagnosis of OAB is established through clinical history assessment. Individuals exhibiting the following symptoms are categorized under the overactive bladder umbrella<sup>2</sup>:

- Urgent need for urination, with or without urgency incontinence
- Frequent urination exceeding eight times within 24 hours

- Nocturia (awakening one or more times during the night for urination)
- Absence of identifiable biological causes

### Successful Treatment

Successful treatment refers to the complete resolution of detrusor overactivity during urodynamic evaluations. A marked improvement is observed after three months of treatment.

### METHODS

This cross sectional study was conducted at Hospital for Urology and Transplantation in Sindh from April 2022 to October 2022. The ethical approval for this study was given by institutional ethical committee (10-01-23).

#### Sample Size

The sample size of 64 patients was determined based on a success rate assumption of 79.3% for mirabegron, a desired precision level of 9%, and a confidence interval of 95%, using the formula:  $N = (Z^2 \times P(100-P))/e^2$

#### Sample Technique

The sampling method employed was non-probability consecutive sampling.

#### Inclusion Criteria

Patients meeting the following criteria were included:

- OAB symptoms persisting for at least three months, including acute urinary incontinence
- No prior OAB medication use
- Both male and female individuals aged between 20 and 60 years
- Willingness to provide informed consent

#### Exclusion Criteria

Exclusion criteria encompassed patients with:

- Neurological conditions identified through clinical examination or historical records
- Urinary tract infections based on urine examination reports
- Severe heart conditions, as indicated by medical histories (e.g., coronary artery diseases, valvular heart diseases)
- Refusal to provide informed consent

## Quantitative Research

After securing ethical clearance, 64 outpatient clinic (OPD) patients who met inclusion criteria were enrolled following thorough history, examinations, and informed consent procedures (Annexure-II and III). Patients suspected of detrusor overactivity underwent urodynamic testing. Data, along with study findings, were meticulously recorded using a standardized Proforma (Annexure-I). Demographic data including age and gender were documented. Patients with diagnosed urodynamic detrusor overactivity received 50 mg of mirabegron orally once daily for three months. Significant success rates were noted after the treatment duration. The primary outcome assessed the percentage of patients with persistent urodynamic overactivity at the three-month treatment endpoint.

## Data Analysis

Statistical analysis employed the SPSS program. Continuous data such as age and OAB duration were analyzed for mean and standard deviation. Gender-stratified success rates were presented with frequencies and percentages. Stratification was utilized to control confounding variables such as age, gender, and OAB duration. Subsequent to stratification, a chi-square test was performed.

## RESULTS

The mean age of participants ranged from 20.23 to 60.70 years, with eligibility criteria encompassing individuals aged between 20 and 60 years (Table-I). The average duration of overactive bladder (OAB) symptoms among participants was  $20.22 \pm 15.38$  months, with a range spanning from 3 to 60 months (Table-II). Among the cohort, a predominant representation of female patients was observed, with a smaller proportion of male participants seeking medical attention. Specifically, the study encompassed 41 women (64.06%) and 23 men (34.94%) (Figure-1).

The outcomes of OAB treatment were marked by a successful resolution in 49 patients (76.56%), while 15 patients (23.44%) did not experience such success (Figure-2). Subsequent analysis revealed that treatment success for OAB did not demonstrate a discernible correlation with age.

Within the age group of 20 to 50, 23% of patients exhibited positive treatment outcomes, while a slightly higher percentage of 26% within the age group of 51 to 60 also experienced improvement. Notably, the calculated p-value for this disparity stood at a non-significant 0.637 (Table-III).

Regarding gender-based investigations into OAB treatment efficacy, the results were inconclusive. Among male participants, 20 individuals responded positively to treatment, while in the female group, 29 individuals exhibited favorable outcomes. The p-value calculated for this difference was similarly non-significant at 0.142 (Table-IV).

Furthermore, the investigation of the relationship between OAB duration and treatment efficacy revealed no significant associations. Specifically, among OAB sufferers with a symptom duration of three to twelve months, 22 participants displayed positive treatment responses. Comparably, among those with OAB lasting between thirteen and sixty months, 27 participants experienced favorable outcomes from treatment. The resulting p-value of 0.738 indicated a lack of statistical significance in this regard (Table-V).

| Age (Years) |       |
|-------------|-------|
| Mean        | 50.23 |
| S.D.        | 8.70  |
| Minimum     | 20    |
| Maximum     | 60    |

**Table-I. Descriptive statistics in term age.**

The mean age of the participants was 50.23 years, with a standard deviation of 8.70. The age range varied between 20 and 60 years, with the youngest participant being 20 years old and the oldest being 60 years old. This distribution reflects the diversity of ages within the study population.

| Duration of Overactive Bladder (OAB) (Months) |       |
|---|-------|
| Mean  | 20.22 |
| S.D.  | 15.38 |
| Minimum                                       | 03    |
| Maximum                                       | 60    |

**Table-II. Descriptive statistics of Overactive Bladder Illness Severity over Time (OAB)**

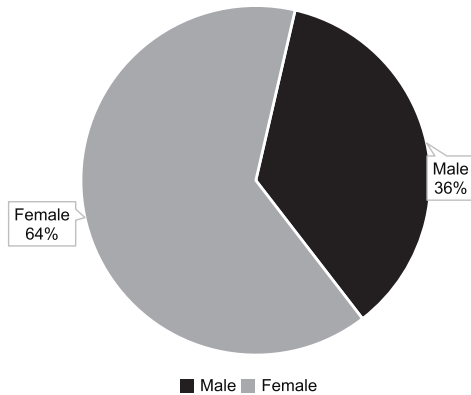


Figure-1. Gender-wise distribution

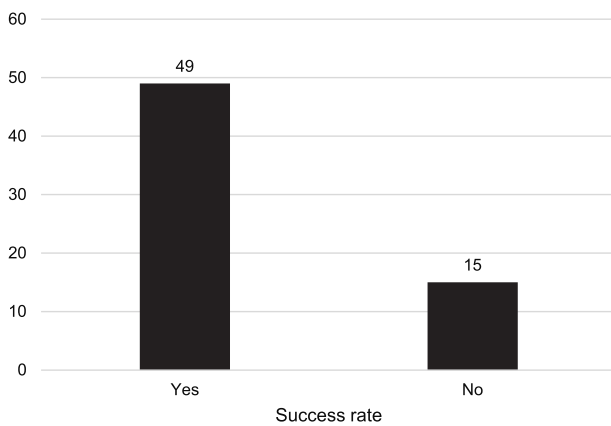


Figure-2. Frequency of success treatment of OAB

| Age Group   | Treatment Success |    | P-Value |
|-------------|-------------------|----|---------|
|             | Yes               | No |         |
| 20-50 Years | 23                | 06 | 0.637   |
| 51-60 Years | 26                | 09 |         |

Table-III. Stratification of age to determine the association of age with treatment success

The calculated p-value for the difference in treatment success rates between the two age groups was found to be 0.637. This p-value indicates that the observed variations in treatment success rates between the age groups were not statistically significant.

| Gender | Treatment Success |    | P-Value |
|--------|-------------------|----|---------|
|        | Yes               | No |         |
| Male   | 20                | 03 | 0.142   |
| Female | 29                | 12 |         |

Table-IV. Stratification of gender to determine the association of gender with treatment success

Upon statistical analysis, the calculated p-value for the gender-based difference in treatment success rates was determined to be 0.142. This p-value indicates that the observed variations in treatment success rates between males and females were not statistically significant.

| Duration of Overactive Bladder (OAB) | Treatment Success |    | P-Value |
|--------------------------------------|-------------------|----|---------|
|                                      | Yes               | No |         |
| 03-12 Months                         | 22                | 06 | 0.738   |
| 13-60 Months                         | 27                | 09 |         |

Table-V. Stratification of duration of overactive bladder (OAB) to determine the association of duration of overactive bladder (OAB) with treatment success

### DISCUSSION

Oversensitive bladder (OAB) syndrome significantly impacts the population, presenting with symptoms of urinary frequency, urgency, and/or excessive urination. Epidemiological studies indicate that OAB syndrome affects approximately 12% of adults, irrespective of gender, with a prevalence that increases with age. This trend is observable globally, including in Asian countries like Pakistan, India, Singapore, South Korea, Japan, China, as well as in other regions such as Argentina and the Bahamas.<sup>4</sup> Notably, the incidence of OAB in individuals under 40 years old in European countries is reported to be around 16.6%. In the United States, the prevalence of OAB is roughly equal among men and women (16.0% vs. 16.9%), and it is well-documented that the severity of symptoms escalates with advancing age.<sup>5</sup>

Standard first-line pharmacological therapy for OAB syndrome often consists of antimuscarinics. Several mechanisms, such as direct suppression of bladder afferent transmission at the level of the urothelium and suburothelium, have been proposed to explain how these agents can decrease detrusor activity and increase bladder capacity. However, antimuscarinics don't work well for everyone, and they might have unwanted side effects, including dry mouth and constipation. As a result, less than 25% of patients continue taking antimuscarinic medication after 1 year.<sup>6</sup>

On the contrary, a 3-adrenoceptor agonist

changes a particular biochemical cascade. The  $\beta_3$ -adrenoceptor, one of the most common adrenergic receptor subtypes in the urinary bladder, is crucial for releasing the detrusor, which makes it easier to store pee. The only and initial  $\beta_3$ -adrenoceptor agonist to receive FDA approval to treat OAB syndrome is mirabegron (in Tokyo, the US, Taiwan, UK, S. Korea, and Europe).<sup>7</sup> The initial dose is different based on the country; in the US and Ontario, Inclusions, Astellas Pharma Inc., Northbrook, IL, USA, is suggested for specific demographics, while Betanis, Astellas Pharma Inc., Chuo-ku, Tokyo, Japan, and Betmiga, Astellas Pharma BV, Nederland, Finland, both suggest 50 mg initial dosages (e.g., those with severe renal impairment or moderate hepatic impairment). In Taiwan, an inception through completion of 25 mg QD was advised, with a maximal dose of 50.0 mg QD.<sup>8,9</sup>

Women were the primary researchers in this study. OAB is more common among older adults, and previous research has shown that its prevalence is higher among women. However, OAB was more common in males than females as they reached age 60, which may be due to the increased prevalence of bladder outlet obstruction caused by benign prostatic hyperplasia (BPH).<sup>10</sup>

In earlier trials of phase II and III, mirabegrons reduced the urge incontinence episodes and micturition frequency and in a manner similar to that of most antimuscarinic drugs, with adverse effects similar to those of a placebo. The overall mirabegron response rate in our study was 76.6%, whereas it was 70.7% in women and 87.0% in men. Previous research has shown that 68% of female patients get clinically meaningful improvement after receiving mirabegron. The effectiveness of mirabegron was evaluated in a variety of ways, and the results were consistent across all of them: it was as effective as antimuscarinic drugs and better than a placebo.<sup>11,12</sup>

Researchers found a correlation between the degree of incontinence and urgency episodes and the responsiveness to mirabegron in a phase III experiment. The researchers found that women in prospectively progressive cohorts had a

significantly higher response rate to mirabegron when their baseline ICIQ-FLUTS SF (ICIQ-Female LUTS) values were lower.<sup>13</sup> Nonetheless, there is not yet enough information to know whether or not mirabegron will work for a given patient. Animal studies on the effects of  $\beta_3$  adrenoceptor agonists on bladder relaxation found that female rats were less responsive to the drugs than male rats. There are currently no clinical data comparing the efficacy of 25 mg mirabegron between the sexes. Both our univariate and multivariate analyses showed that men had a greater chance of responding to mirabegron. Female patients may have more nuanced causes for LUTS or urge incontinence than their male counterparts.<sup>14</sup>

## CONCLUSION

Our study assessed mirabegron's efficacy in treating Overactive Bladder Syndrome (OAB) by examining its impact on urodynamic detrusor overactivity. We observed that mirabegron effectively treated OAB across various ages and genders without significant differences in treatment success. Specifically, success rates were nearly equal among participants aged 20-50 and 51-60 years, with respective rates of 79.31% and 74.29%, suggesting that mirabegron's effectiveness is not age-dependent ( $p = 0.637$ ). Similarly, treatment efficacy was consistent across genders, with males and females showing success rates of 86.96% and 70.73%, respectively ( $p = 0.142$ ), countering previous claims of gender influence. Additionally, the duration of OAB symptoms prior to treatment did not affect outcomes ( $p = 0.738$ ), indicating mirabegron's reliable performance regardless of symptom longevity.

While the study reported a notable overall success rate of 76.56%, aligning with prior research, limitations include its small sample size and cross-sectional nature. Our research supports mirabegron as a beneficial treatment for OAB, irrespective of patient age, gender, or symptom duration. Further studies, especially longitudinal with larger cohorts, are warranted to reinforce these findings and expand understanding of mirabegron's role in OAB management.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

## SOURCE OF FUNDING







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| 2   | Muhammad Mashkoo Aslam | Methodology.                |  |
| 3   | Muhammad Adnan Sarwar  | Writing-review and editing. |  |
| 4   | Naveed Soomro          | Writing-review and editing. |  |
| 5   | Haider Ali Qureshi     | Writing-review and editing. |  |
| 6   | Hafiz Bilal Murtaza    | Statistical data analysis.  |  |