# Effect of Mirabegron Versus Solifenacin in Treatment of over Active Bladder

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**Abstract: Purpose:** to compare effect of β-3 Androreceptor agonist (Mirabegron) versus M3 Antimuscarenic (Solifenacin) in patients with over active bladder symptoms. **Materials and methods:** From jun 2017 to jun 2018 60 consecutive patients range from 20 to 60 years old with Over Active Bladder syndrome were enrolled in this prospective, randomized, controlled study. patients were divided into 2 groups of 30 patients each using a randomized 1:1 method, In group A, the patient received mirabegron 50 mg once a day for 12 weeks. In group B, the patient received solifenacin succinate 5 mg once a day for 12 weeks Patients was followed up for 12 weeks by clinical examination & OABSS Score & Urodynamic Study. **Results:** Day time frequency of Mirabegron arm was 40% <7, 40% from 8-14 and 20% >15. Day time frequency of Solifenacin arm was 40% <7, 46% from 8-14 and 13.3 % >15. Night time frequency of Mirabegron arm was 10% zero, 50% one, 26.7% two and 13.3 % three times per night, Night time frequency of Solifenacin arm was 6.7% zero, 46.7 % one,26.7 two and 20 % three. Urgency of Mirabegron arm was 30% less than one per week, 46% one a week or more, 13.3% once a day, 6.7% Two to four times a day. Urgency of Solifenacin arm was 40% less than one per week, 40% one a week or more, 13.3% once a day, 6.7% two to four times a day. Urge incontinence of Mirabegron arm was 50% less than one per week, 30% one a week or more, 13.3% once a day, 6.7% two to four times a day. Urge incontinence of Solifenacin arm was 46.7% less than one per week, 33.3% one a week or more, 13.3% once a day, 6.7% two to four times a day. After treatment**:** Day time frequency of Mirabegron arm becomes 86.7% <7, 13.3% from 8-14 and 0% >15. Day time frequency of Solifenacin arm becomes 53.3% <7, 46.7% from 8-14 and 0% >15. Night time frequency of Mirabegron arm becomes 80% zero, 20% one, 0% two and 0 % three times per night**,** Night time frequency of Solifenacin arm was 46.7% zero, 46.7 % one 6.7% two and 0% > three. Urgency of Mirabegrone arm becomes 60% not at all, 40% less than one per week, 0% one a week or more, 0% once a day, 0% Two to four times a day. Urgency of Solifenacin arm becomes 33.3% not at all, 46.7% less than one per week, 0% one a week or more, 0% once a day, 0% two to four times a day. *P* value is 0.012 which is significant. Urge incontinence of Mirabegron arm becomes 40% not at all, 60% less than once per week, 0% one a week or more, 0% once a day, 0% two to four times a day. Urge incontinence of Solifenacin arm becomes 40% not at all, 40% less than one per week, 20% one a week or more, 0% once a day, 0% two to four times a day **Conclusion:** Both solifenacin and mirabegron were effective in improving Over Active Bladder symptoms. Mirabegron showed greater tolerability with fewer patients discontinuing therapy because of side effects.

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**Key words:** over Active Bladder, Mirabegron, Solifenacin.

## 1. Introduction

Overactive bladder (OAB) is a syndrome characterized by the presence of urgency, with or without urinary incontinence usually with increased daytime or night-time frequency. OAB is a very prevalent condition in both female and male patients, and it is more common in older adults compared with the general population. Moreover, OAB syndrome adversely affects patient's health-related quality of life inducing depression, social isolation and decreased levels of activity, especially in presence of urgency incontinence **(Abrams et al., 2009).**

The prevalence of overactive bladder (OAB) is high, with 12–16% of adults in Europe, USA affected by this symptom syndrome. **(Milsom et al., 2001)**

Urinary bladder smooth muscle is enriched with muscarinic receptors, the majority of which are of the M2 subtype whereas the remaining minority belong to the M3 subtype. Antimuscarinic agents, such as Solifenacin, are first-line pharmacotherapy for the treatment of OAB symptoms. However, some patients have a suboptimal response to antimuscarinics and some may experience intolerable side-effects, such as dry mouth and constipation.

Recent advances in the understanding of OAB have identified three β-adrenoceptor subtypes, β1, β2 and β3, in the detrusor muscle and urothelium.

The β3-adrenoceptor is the predominant β-receptor subtype in the human urinary bladder. β3-adrenoceptor agonists relax detrusor smooth muscle during the bladder storage phase and increase bladder

capacity without negatively affecting voiding parameters, including maximum urinary flow rate (*Q*max), detrusor pressure at *Q*max (*P*det*Q*max), and residual volume.

Recently, (Mirabegron) a new class of oral drug has emerged, which induces a direct relaxation of detrusor smooth muscle via stimulation of bladder β3-adrenoceptors and has been approved by the USA Food and Drugs Administration (FDA) and European Medicines Agency (EMEA) for treatment of OAB. In the USA and Canada, the recommended starting dose is 25 mg once daily, with an option to increase to 50 mg. In Europe and Japan, the recommended dose is 50 mg once daily with 25 mg dose reserved for special populations (e.g. those with renal or hepatic impairment).**(Kullmann et al., 2011)**

## 2. Patient and Methods

From jun 2017 to jun 2018 60 consecutive patients range from 20 to 60 years old with Over Active Bladder syndrome were enrolled in this prospective, randomized, controlled study.

All patients underwent a detailed clinical evaluation, including.

- A complete history, physical and neurological examination.
- Urinary symptoms related to OAB were evaluated with OAB Symptom Score (OABSS).

Patients underwent urodynamic investigation with .

- Filling cystometry.
- Pressure/flow study.

The study was performed with a transurethral 6-Fr, double-lumen catheter into the bladder and a balloon catheter inserted into the anus to measure abdominal pressure, with a filling rate of 50 ml/min and patients in sitting position.

We considered only the urodynamic parameters obtained during filling cystometry and pressure/flow study:

- Maximum cystometric capacity (MCC: ml) .
- Maximum flow rate (Qmax: ml/s).
- Post void residual volume (PVR: ml).
- Detrusor pressure at open (pdet.open: cm H 2O ).
- Detrusor pressure at maximum flow (pdet. Qmax: cm H 2 O).

Patients with urinary tract infection, neurological disease, bladder lithiasis, genital prolapse, uncontrolled narrow angle glaucoma, patients with cognitive impairments, severe cardiac disease, hypertension, pelvic tumors, were excluded.

In each arm of the study any patient who discontinued the treatment or missed the follow up was replaced by another patient.

patients were divided randomly into 2 groups of 30 patients each using a randomized 1:1 method,

- In group A, the patient received mirabegron 50 mg once a day for 12 weeks.
- In group B, the patient received solifenacin succinate 5 mg once a day for 12 weeks.

**End Points**

Improvement in OAB symptoms, including day time frequency, night time frequency, urgency and urge incontinence was considered the primary efficacy end point in this study.

The effect of the drugs on storage and voiding functions was the secondary end point.

The primary efficacy end point was evaluated with OABSS. It consisted of 4 items related to OAB syndrome symptoms.

The score of the first item (day time frequency) ranges from 0 to 2, the score of the second item (night time frequency) ranges from 0 to 3, the scores of the third and fourth items (urgency and urge incontinence respectively) range from 0 to 5.

A greater score represents a worsening of symptoms.

The secondary end point was evaluated with urodynamic study: fillingcystometry and pressure flow study.

OABSS and urodynamic study were performed before and after drugs administration.

Symptoms and urodynamic parameters were used according to the standardized terminology of the International Continence Society.

**Statistical analysis**

Data were coded and entered using the statistical package SPSS (Statistical Package for the Social Sciences) version 25. Data was summarized using mean, standard deviation, median, minimum and maximum in quantitative data and using frequency (count) and relative frequency (percentage) for categorical data. Comparisons between quantitative variables were done using the non-parametric Mann-Whitney test. For comparison of serial measurements within each patient the non-parametric Wilcoxon signed rank test was used For comparing categorical data, Chi square ($\chi 2$) test was performed. Exact test was used instead when the expected frequency is less than 5.

## 3. Results

Sixty consecutive patients ( 37 female, 23 males) with Over Active Bladder syndrome were enrolled in this prospective, randomized, controlled study.

They were divided randomly into 2 groups of 30 patients each using a randomized 1:1 method,

- In group A, the patient received mirabegron 50 mg once a day for 12 weeks.

- In group B, the patient received solifenacin succinate 5 mg once a day for 12 weeks.

Their age ranged from 20 to 60 years old.

Mean age of Mirabegron group was 36.63, SD: 11.36.

Mean age of Solifenacin group was 36.27, SD: 10.47.

19 female patients (63.3%), 11 male patients (36.7%) received Mirabegron.

18 female patients (60%), 12 male patients (40) received Solifenacin.

All patients filled the Over active bladder symptoms score (OABSS Table 1) before receiving the treatment.

**Before treatment:**

- Day time frequency of Mirabegron arm was 40% <7, 40% from 8-14 and 20% >15.
- Day time frequency of Solifenacin arm was 40% <7, 46% from 8-14 and 13.3 % >15.

P value was 0.758 which is not significant.

- Night time frequency of Mirabegron arm was 10% zero, 50% one, 26.7% two and 13.3 % three times per night.
- Night time frequency of Solifenacin arm was 6.7% zero, 46.7 % one,26.7 two and 20 % three.

P value was 0.92 which is not significant.

- Urgency of Mirabegron arm was 30% less than one per week, 46% one a week or more, 13.3% once a day, 6.7% Two to four times a day.
- Urgency of Solifenacin arm was 40% less than one per week, 40% one a week or more, 13.3% once a day, 6.7% two to four times a day.

P value was 0.974 which is not significant.

- Urge incontinence of Mirabegron arm was 50% less than one per week, 30% one a week or more, 13.3% once a day, 6.7% two to four times a day.
- Urge incontinence of Solifenacin arm was 46.7% less than one per week, 33.3% one a week or more, 13.3% once a day, 6.7% two to four times a day.

**After treatment:**

- Day time frequency of Mirabegron arm becomes 86.7% <7, 13.3% from 8-14 and 0% >15.
- Day time frequency of Solifenacin arm becomes 53.3% <7, 46.7% from 8-14 and 0% >15.

P value is 0.005 and it's significant

- Night time frequency of Mirabegron arm becomes 80% zero, 20% one, 0% two and 0 % three times per night.
- Night time frequency of Solifenacin arm was 46.7% zero, 46.7 % one 6.7% two and 0% >three.

P value is 0.019 which is significant.

- Urgency of Mirabegrone arm becomes 60% not at all, 40% less than one per week, 0% one a week or more, 0% once a day, 0% Two to four times a day.
- Urgency of Solifenacin arm becomes 33.3% not at all, 46.7% less than one per week, 0% one a week or more, 0% once a day, 0% two to four times a day.

P value is 0.012 which is significant.

- Urge incontinence of Mirabegron arm becomes 40% not at all, 60% less than once per week, 0% one a week or more, 0% once a day, 0% two to four times a day.
- Urge incontinence of Solifenacin arm becomes 40% not at all, 40% less than one per week, 20% one a week or more, 0% once a day, 0% two to four times a day.

| | | Sofenacin before | | Sofenacin after | | *P* value |
|---|---|---|---|---|---|---|
| | | Count | % | Count | % | |
| **DAY time frequency** | **≤7** | 12 | 40.00% | 16 | 53.30% | 0.021 |
| | **from 8 to 14** | 14 | 46.70% | 14 | 46.70% | |
| | **≥15** | 4 | 13.30% | 0 | 0.00% | |
| **Night time frequency** | **zero** | 2 | 6.70% | 14 | 46.70% | <0.001 |
| | **one** | 14 | 46.70% | 14 | 46.70% | |
| | **two** | 8 | 26.70% | 2 | 6.70% | |
| | **>3** | 6 | 20.00% | 0 | 0.00% | |
| **Urgency** | **Not at all** | 0 | 0.00% | 10 | 33.30% | <0.001 |
| | **Less than once a week** | 12 | 40.00% | 14 | 46.70% | |
| | **Once a week or more** | 12 | 40.00% | 6 | 20.00% | |
| | **About once a day** | 4 | 13.30% | 0 | 0.00% | |
| | **Two to four times a day** | 2 | 6.70% | 0 | 0.00% | |
| | **Five times a day or more** | 0 | 0.00% | 0 | 0.00% | |
| **urge incontinence** | **Not at all** | 0 | 0.00% | 12 | 40.00% | <0.001 |
| | **Less than once a week** | 14 | 46.70% | 12 | 40.00% | |
| | **Once a week or more** | 10 | 33.30% | 6 | 20.00% | |
| | **About once a day** | 4 | 13.30% | 0 | 0.00% | |
| | **Two to four times a day** | 2 | 6.70% | 0 | 0.00% | |
| | **Five times a day or more** | 0 | 0.00% | 0 | 0.00% | |

| | | Mirabegron before | | Mirabegron after | | *P* value |
|---|---|---|---|---|---|---|
| | | Count | % | Count | % | |
| DAY time frequency | ≤7 | 12 | 40.00% | 26 | 86.70% | <0.001 |
| | from 8 to 14 | 12 | 40.00% | 4 | 13.30% | |
| | ≥15 | 6 | 20.00% | 0 | 0.00% | |
| Night time frequency | zero | 3 | 10.00% | 24 | 80.00% | <0.001 |
| | one | 15 | 50.00% | 6 | 20.00% | |
| | two | 8 | 26.70% | 0 | 0.00% | |
| | >3 | 4 | 13.30% | 0 | 0.00% | |
| Urgency | Not at all | 0 | 0% | 18 | 60.00% | <0.001 |
| | Less than once a week | 10 | 12% | 12 | 40.00% | |
| | Once a week or more | 14 | 12% | 0 | 0.00% | |
| | About once a day | 4 | 4% | 0 | 0.00% | |
| | Two to four times a day | 2 | 2% | 0 | 0.00% | |
| | Five times a day or more | 0 | 0% | 0 | 0.00% | |
| urge incontinence | Not at all | 0 | 0% | 12 | 40.00% | <0.001 |
| | Less than once a week | 15 | 14% | 18 | 60.00% | |
| | Once a week or more | 9 | 10% | 0 | 0.00% | |
| | About once a day | 4 | 4% | 0 | 0.00% | |
| | Two to four times a day | 2 | 2% | 0 | 0.00% | |
| | Five times a day or more | 0 | 0% | 0 | 0.00% | |

All patients undergo Urodynamic study before and after treatment and the results was

**Before treatment:**

- Mean Maximum cystometric capacity of Mirabegrone arm was 334.03 while Solifenacin arm was 301.45.

P value was 0.279 which is not significant.

- Mean Maximum flow rate of Mirabegrone arm was 18.92 while Solifenacin arm was 16.22.

P value was 0.929 which is not significant.

- Mean post voiding residual volume of Mirabegron arm was 19.3 while Solifenacin arm was 21.13.

P value was 0.623 witch is not significant.

- Mean detrusor pressure at open for Mirabegron arm was 27.09 while Solifenacin arm was 24.73.

P value was 0.076 witch is not significant.

- Mean detrusor pressure at maximum flow for Mirabegron arm was 31.17 while Solifenacin arm was 27.68.

**After treatment**

- Mean Maximum cystometric capacity of Mirabegron arm becomes 420 while Solifenacin becomes 317.47.

P value was 0.004 which is significant.

- Mean Maximum flow rate of Mirabegrone arm becomes 16.65 while Solifenacin arm becomes 14.

P value is 0.965 which is not significant.

- Mean post voiding residual volume of Mirabegron arm becomes 16.5 while Solifenacin arm becomes 21.8.

P value is 0.031 which is significant.

- Mean detrusor pressure at open for Mirabegron arm becomes 27.42 while Solifenacin arm becomes 22.6.

P value is 0.033 which is significant.

- Mean detrusor pressure at maximum flow for Mirabegron arm becomes 30.67 while Solifenacin arm becomes 25.33.

| | Solifenacin Group | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Before | | | | | After | | | | | *P* value |
| | Mean | SD | Median | Minimum | Maximum | Mean | SD | Median | Minimum | Maximum | |
| maximum cystometric capacity (MCC: ml) | 301.45 | 85.58 | 301 | 145 | 512 | 317.47 | 84.7 | 320 | 155 | 515 | <0.001 |
| maximum flow rate (Qmax: ml/s) | 16.22 | 6.02 | 17.2 | 6.2 | 31.7 | 14 | 4.57 | 14.3 | 6 | 25.8 | <0.001 |
| post void residual volume (PVR: ml) | 21.13 | 16.51 | 19 | 5 | 70 | 21.8 | 14.89 | 23 | 5 | 65 | 1 |
| Detrusor pressure at open | 24.73 | 12.32 | 16.5 | 13.2 | 50.4 | 22.6 | 11.74 | 14.2 | 12.2 | 45.2 | <0.001 |
| Detrudor pressure at maximum flow | 27.68 | 12.56 | 20.2 | 13.4 | 55.4 | 25.33 | 11.22 | 18.2 | 12.6 | 48.2 | <0.001 |

| | Mirabegron Group | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Before | | | | | After | | | | | *P* value |
| | Mean | SD | Median | Minimum | Maximum | Mean | SD | Median | Minimum | Maximum | |
| **maximum cystometric capacity (MCC: ml)** | 334.03 | 127.4 | 321 | 117 | 672 | 420.1 | 158.37 | 430 | 122 | 677 | <0.001 |
| **maximum flow rate (Qmax: ml/s)** | 18.29 | 9.82 | 14.85 | 6.5 | 34.7 | 16.65 | 9.25 | 12.65 | 6.4 | 33.7 | <0.001 |
| **post void residual volume (PVR: ml)** | 19.3 | 12.96 | 16.5 | 5 | 50 | 16.5 | 10.92 | 15 | 5 | 45 | <0.001 |
| **Detrusor pressure at open** | 27.09 | 5.45 | 24.9 | 18.2 | 37.2 | 27.42 | 5.55 | 28.95 | 19.3 | 35.1 | 0.015 |
| **Detrudor pressure at maximum flow** | 31.17 | 5.95 | 30.5 | 21.2 | 44.6 | 30.76 | 6.43 | 32.75 | 20.7 | 39.2 | 0.253 |

## 4. Discussion

Many studies were performed to evaluate the efficacy of Solifenacin and Mirabegron alone and more recently in combination with other drugs on over active bladder.

As regarding studies demonstrated that Solifenacin is effective in treatment of patients with OAB. There was no difference in therapeutic efficacy between the OAB wet and OAB dry groups. The Urgency, daytime frequency and nocturia improved significantly after treatment. Voided volume and FBC were also noted to have significant improvement without affecting voiding efficacy**.(Chen, Chen, & Kuo, 2010)**

And this is similar to our study, solifenacin shows improvement in Day and Night time frequency, urgency and urge incontinence.

Solifenacin is considered to be a better Antimuscarinic agent than other Antimuscarinics because of its higher affinity to M2 and M3 muscarinic receptors, which might play a major role in bladder contractility. One previous study has shown that the mean frequency of micturition decreased by 21% and 19.5% in patients receiving Tolterodine and Oxybutynin, respectively, for 12 weeks**(Chen et al., 2010)**

In Our study we choose Solifenacin 5 mg as the best antimuscarinic agent to be compared with the new drug Mirabegron.

Mirabegron is a selective b3-adrenergic receptor agonist recently developed for the treatment of patients with overactive bladder (OAB), which offers an alternative pharmacological option to the well-established treatment with Antimuscarinics.**(Leone Roberti Maggiore et al., 2014)**

Mirabegron is the progenitor of b3-AR agonists, and it is currently approved in all Western countries and Japan for the symptomatic treatment of urgency, increased micturition frequency, and/or urgency incontinence occurring in adults with OA**(Leone Roberti Maggiore et al., 2014)**

Studies demonstrated that mirabegron was effective and safe in treating patients with OAB. It should be noticed that patient perception of bladder condition (PPBC) after treatment and the number of 'responders' were significantly higher among patients treated with mirabegron than with placebo, although with a minimal difference in terms of absolute numbers. Based on these findings, the real clinical efficacy of mirabegron may be questioned, in many RCTs on OAB, the effects of the placebo are quite high; this may be explained by an actual active treatment that patients in the placebo group usually receive: a bladder retraining. All patients have to fill in a bladder diary during the trial recording the voided volume, the urgency, as well as the incontinence episodes. This is, by all means, a form of bladder retraining that has a level of evidence with a grade of recommendation A according to the 2012 International Consultasion on Incontinence. **(Leone Roberti Maggiore et al., 2014)**

In comparison between the two drugs few researchers evaluated the effect of these drugs on urodynamic parameters.

In our study, both solifenacin and mirabegron were observed to be effective in the treatment of OAB symptoms with significant improvements in day- and night- time frequency, urgency and in the number of episodes of urge incontinence. Urodynamic findings showed improvements of the parameters evaluated in the storage phase, both with solifenacin and with

mirabegron with a significant increase in MCC but significant increase with Mirabegronthan sofenacineand with a reduction in the number of patients with DO. However, important differences between the 2 drugs were found in the voiding phase of pressure flow study with a significant decrease of Qmax, pdet.open and pdet.Qmax and with a significant increase of PVR in patients treated with solifenacin. Whereas, the same urodynamic findings did not produce significant changes following therapy with mirabegron.

In line with results obtained by other authors who have shown how mirabegron can increase bladder capacity without decreasing the amplitude of the voiding contraction. **(Kaidoh et al., 2002)**

## 5. Conclusion

Both solifenacin and mirabegron were effective in improving Over Active Bladder symptoms. Mirabegron showed greater tolerability with fewer patients discontinuing therapy because of side effects. Both solifenacin and mirabegron were effective in improving the storage function in the pressure flow study, but solifenacin showed a reduction in the effectiveness of the detrusor pressure in the voiding phase. Therefore, at present, mirabegron can be considered as the drug with the better balance between efficacy and tolerability in the treatment of OAB.

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