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ARTICLE

# The safety and effectiveness of mirabegron in Parkinson's disease patients with overactive bladder: a randomized controlled trial

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**ABSTRACT**

**Purpose:** To assess the safety and effectiveness of mirabegron in patients with PD complaining of overactive bladder (OAB).

**Patients and methods:** From January 2017 to November 2020, we performed a prospective randomized, double-blind, placebo-controlled trial that enrolled PD patients with symptoms of OAB. The total duration of the study was 13 weeks, comprising a 1-week screening period and a 12-week treatment period. A total of 110 patients were randomized in one of two groups: treatment group (mirabegron 50 mg) or placebo group. The primary outcomes of our study were the change from baseline in OAB symptom score (OABSS) and the overactive bladder questionnaire short form (OAB-q SF) score. The secondary outcomes were the change from baseline in the mean number of micturitions/24 hours, the mean number of urgency episodes/24 hours, the mean number of urgency incontinence episodes/24 hours and the mean number of nocturia episodes/night, volume voided/micturition (ml) as recorded on a 3-day bladder diary. Safety assessments included adverse events, electrocardiogram, QT corrected for heart rate using Fridericia's correction (QTcF) interval and blood pressure and pulse rate measurements.

**Results:** There was a significant improvement in the primary outcome and secondary outcome measures in the treatment group compared to the placebo group. Adverse events were mild and the same in the two groups. The cardiovascular safety profile was high. This study is limited by its sample size and its short follow-up period.

**Conclusions:** Mirabegron is a promising drug to control OAB symptoms in patients with PD with an excellent safety profile.

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Mirabegron; overactive bladder; Parkinson's disease

## Introduction

Parkinson's disease (PD) is a common movement disorder associated with the degeneration of dopaminergic neurons in the substantia nigra. Bladder dysfunction is one of the most common autonomic disorders in PD [1]. OAB (overactive bladder) symptoms can occur in early and untreated PD patients. Both storage symptoms and voiding symptoms were reported [2]. Nocturia is the most prevalent storage symptom reported by patients with PD (>60%). Patients also complain of urinary urgency (33–54%) and daytime frequency (16–36%) [3]. Pharmacologic interventions, especially anticholinergic medications, are the first-line option for treating OAB in patients with PD [4]. However, it is important to balance the therapeutic benefits of these drugs with their potential adverse effects. Intradetrusor Botulinum toxin injections and electrical stimulation were also used to treat OAB in those patients with variable efficacy [5]. Mirabegron is a β3-agonist that was approved for the treatment of idiopathic OAB. Its efficacy seems comparable to that of anticholinergic drugs, with superior tolerability. Mirabegron improved both the urodynamic and patient-reported outcomes in patients with neurogenic detrusor overactivity arising from spinal cord injury or multiple sclerosis. Treatment with mirabegron was tolerated well in those patients [6].

There is a paucity of well-designed prospective studies that assess the clinical use of mirabegron for OAB in patients with PD. Therefore, this study aimed to evaluate the efficacy and safety of mirabegron for the treatment of OAB in patients with PD.

## Materials and methods

### *Study design and participants*

This study was a prospective trial of adult patients with PD in a single tertiary care referral institution between January 2017 and November 2020. Patients are referred to our

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hospital from a large number of primary and secondary care centers. The study was a randomized, double-blind placebo-controlled trial that enrolled patients with PD and with symptoms of OAB (urgency, urinary frequency, and/or urgency incontinence). The total duration of the study was 13 weeks, comprising a 1-week screening period and a 12-week treatment period. The study was performed in accordance with the Declaration of Helsinki and was approved by our Institutional Review Board (N.18/2016).

Inclusion criteria for this study were patients with a clinical diagnosis of PD according to UK Brain Bank Criteria [7]. The diagnostic criteria were tested by a movement disorders specialist in the 12 months before receiving mirabegron therapy. Patients should be aged between 40 and 70 years, have a stable dose of anti-Parkinsonian drugs 8 weeks before study entry and be stage 1–3 on modified Hoehn and Yahr scale [8]. Patients received mirabegron 50 mg once daily, had post-void residue less than 100 ml on an ultrasound of the bladder performed before study entry and were taking only levodopa or dopamine agonist at stable doses before entering the study. In this study, all participants had an urgency score of $\geq$ 2 and a total score of $\geq$ 3 on the OAB symptom score (OABSS) (discussed later on).

Exclusion criteria were patients with secondary Parkinsonism syndromes, patients with polyuria with a daily urine volume $>$ 3,000 mL, patients operated on previously by deep brain stimulation, patients taking anticholinergic medications for OAB symptoms, those with a history of benign prostatic hypertrophy (based on documented clinical evaluation by a urologist noted in patient's medical records), patients with stress urinary incontinence, history of severe uncontrolled hypertension (defined as systolic blood pressure(SBP) $\geq$ 180 mm Hg and/or diastolic blood pressure(DBP) $\geq$ 110 mm Hg) and any patients with cognitive impairment during neurologic assessment. More exclusion criteria included: current treatment with digoxin, ketoconazole, patients with a history of QT interval prolongation or taking drugs that prolong the QT interval, patients with severe renal impairment (GFR $<$ 30 ml/min) or moderate-to-severe hepatic impairment (Child-Pugh B&C). If patients were taking previously anticholinergic drugs for OAB, they were allowed to enter the study after a washout period of 4 weeks.

Patients were randomly allocated to two groups, the treatment group and the control group, at a ratio of 1:1. The treatment group received 50 mg of mirabegron daily and the control group received a placebo. Eligible participants were randomly assigned to one of the two groups by a computer-generated lottery. Both the medical team (urologists and neurologists) and the patients were blinded to the treatment assignments until the end of the trial. All the medications were previously prepared by our clinical pharmacists who did not participate in the study enrollment. Medications were preserved in two different containers labeled A and B. Container A contained placebo and container B contained Mirabegron 50 mg tablets. All medications were given by the clinical pharmacist giving the appropriate study treatment as indicated by the computer system. The data collection was performed by the same urologists and neurologists.

Our sample size calculation was based on the required sufficient statistical power to detect a clinically meaningful treatment effect for the total OABSS score. Our input for this calculation was based on: (1) The ability to detect a minimal clinically relevant difference (MCIC) of three points in the mean change from baseline to end of treatment of the OABSS total score, as found in the literature; (2) Equal allocation, where the sample size ratio of treatment to control was set to 1:1; and (3) Information from performed studies. There was an assumption of a 15% dropout rate, achieving an 80% power at the 5% level of significance. The calculation based on this information indicated that 59 patients were required in the treatment group and 59 patients were required in the control group.

We used an indirect multi-measure approach to monitor medication adherence in our trial (pill count, patient education about drug usage, and regular reminders by phone calls and text messages about drug usage).

This trial was registered in the UMIN clinical trial registry (UMIN000043848).

### *Efficacy assessments*

The primary outcomes of our study were the change from baseline in OABSS, overactive bladder questionnaire short form (OAB-q SF) score. The secondary outcomes were the change from baseline in the mean number of micturitions/24 hours, the mean number of urgency episodes/24 hours, the mean number of urgency incontinence episodes/24 hours and the mean number of nocturia episodes/night, volume voided per micturition (ml) as recorded on a 3-day bladder diary before each visit during baseline and the follow-up period.

Patients were instructed to complete OABSS and OAB-q SF and to present their voiding diary at week 0 and 12 weeks after. The study baseline is considered at week 0.

The OABSS is a validated self-assessment questionnaire and consists of four questions on OAB symptoms [9]. Patients respond to each question about their bladder symptoms during the previous week. OABSS subscores included questions on daytime frequency, night-time frequency, urgency and urge incontinence. The total score ranged from 0–15, with greater scores indicating increasing symptom severity.

The overactive bladder quality-of-life short-form questionnaire (OAB-q SF) is a worldwide used questionnaire for health-related quality-of-life in patients with OAB. The OAB-qSF includes 19 items; a six-item symptom bother scale and a 13-item health-related quality-of-life (HRQoL) scale. The recall period is over the previous 4 weeks [10].

All patients were assessed at the urology clinic at week 0 (baseline) and after 12 weeks by two experienced urologists at the same time, urologists were blinded to the study protocol and intervention.

### Neurologic assessment

The severity of motor and non-motor symptoms in patients with PD was assessed using the Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) [11].

The Hoehn and Yahr (H&Y) scale were used to estimate the severity and the progression of PD. The scale is a simple staging assessment that evaluates the severity of overall Parkinsonism dysfunction [8].

Scores were calculated by experienced neurologists with competence in movement disorders blinded to study protocol and results.

### Safety assessment

Patients were asked to measure their BP, pulse rate (PR) daily in the morning and evening by an automated device given to them before entering the study.

BP and pulse rate measurements (at rest), 12-lead ECG, QT corrected for heart rate using Fridericia's correction (QTcF) interval calculation, were performed at the beginning of study and 12 weeks after by an experienced cardiologist who was blinded to the study protocol.

### Statistical analysis

Baseline data and adverse events were compared using independent *t*-tests for continuous measures and Pearson's Chi-square or Fisher's exact tests for categorical measures.

Changes in primary and secondary efficacy outcome measures were compared between treatment and placebo groups using analysis of covariance (ANCOVA), adjusting for the baseline value. Changes in safety outcome measures from baseline or week 1 to week 12 were calculated and compared between treatment and placebo groups using analysis of covariance (ANCOVA).

In each treatment and placebo group, changes in efficacy or safety outcome measures from baseline or week 1 to week 12 were assessed using the Wilcoxon signed-rank test (continuous outcomes) for paired data. All analyses were performed using IBM SPSS software, version 20.0. Statistical tests were two-sided and $p < 0.05$ was defined as statistically significant.

## Results

### Demographic and baseline characteristics

A total of 130 patients were initially screened. Twenty patients were excluded due to the eligibility criteria, protocol violation and withdrawal issues. The common reasons related to withdrawal from our trial are the change in location, loss to follow-up and other personal reasons. There were no treatment related withdrawals from the trial. The final randomized sample consisted of 95 patients (53 received Mirabegron 50 mg, 42 received the placebo) (Figure 1). Most of the patients in both groups had an age between 60 and 70 years. Fifty-seven percent and 21% of the patients were males in the treatment and placebo group, respectively. Most of the patients in both group had PD for more than 5 years, Hoehn and Yahr stage 2.5 and 3. When comparing the MDS-UPDRS subscales in both groups, there are no statistically significant differences in part I and III subscales.

For OAB symptoms, most of the patients in both groups reported symptoms duration of $>$ 24 months and were using previous anticholinergic therapy. Table 1 shows the demographic data of the patients and their clinical characteristics.

### Efficacy

Table 2 summarizes the difference from baseline in treatment and placebo groups for results of OABSS, voiding diary parameters and OAB-q SF. The mean OABSS total score at baseline was $10.2 \pm 1.2$ and $10.7 \pm 1$ in the treatment and the placebo group, respectively. This means it decreased significantly to $6.9 \pm 1.4$ in the treatment group compared to the placebo group ($10.5 \pm 1.1$) at the end of the trial. Significant improvements from baseline were seen in the OABSS total score in the treatment group compared to placebo at 12 weeks. A reduction of $\geq$ 3 points from total OABSS was estimated as a minimally clinically important change (MCIC) [12]. In the placebo group the OABSS remain almost the same between baseline and the end of trial ($10.7 \pm 1$ versus $10.5 \pm 1.1$). At 12 weeks, 72% of patients from the treatment group reached the MCIC of total OABSS, while none of the patients from the placebo group reached this MCIC (Table 3).

In the treatment group, the mean number of micturition episodes/24 hours decreased significantly from baseline to the end of treatment (from $11 \pm 1.2$ to $8.7 \pm 1.1$, respectively, $p < 0.001$), also the mean number of micturition/night, the mean number of urgency episodes/24 hours and the mean number of leaks/24 hours decreased significantly from baseline to the end of treatment (from $1.5 \pm 0.6$ to $1.1 \pm 0.7$; from $2.4 \pm 1.1$ to $0.6 \pm 0.6$; and from $2.2 \pm 1.2$ to $0.4 \pm 0.6$, respectively, $p < 0.001$). In the placebo group, all bladder diary parameters remained almost the same and did not reach any statistically significant differences between baseline and week 12 of the trial.

It is important to note that the volume voided/micturition significantly improved from baseline to the end of the trial in the treatment group (from $122.1 \pm 16$ ml to $141.3 \pm 17.7$ ml, $p < 0.001$). In the placebo group, the volume voided/micturition remained stable at 112 ml at the end of the trial.

Significant improvements from baseline were noted for the mean of OAB-q SF symptom bother score and the mean of OAB-q SF total HRQoL score in the treatment group. The OAB-q SF symptom bother score decreased from $39.8 \pm 8.1$ to $22.2 \pm 7.4$ at the end of the trial ($p < 0.001$). The OAB-q SF total HRQoL score increased from $64.4 \pm 7.4$ to $83.8 \pm 7.7$ at the end of the trial ($p < 0.001$). In the placebo group, the mean of OAB-q SF symptom bother score and the mean of OAB-q SF total HRQoL score did not change from the baseline values. At 12 weeks, 90% of patients from the treatment group reached the MCIC of OAB-q SF HRQoL, while only 7% of patients from the placebo group reached this MCIC (*p*-value $<$ 0.001) (Table 3). The recommendation of a 10-point

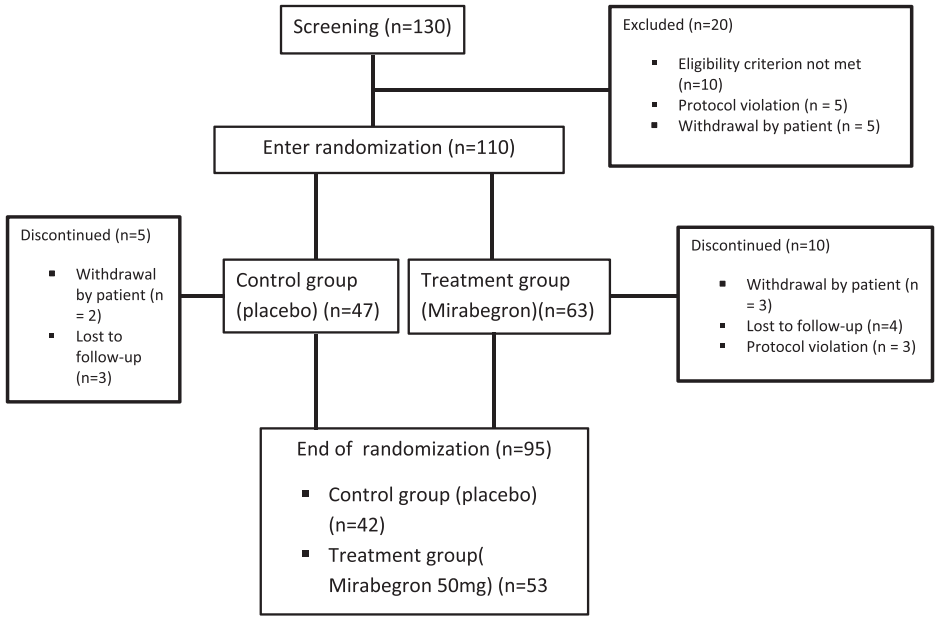


Figure 1. Flowchart for patients included in our study.

Table 1. Patient demographic and other baseline characteristics.

| | Treatment | Placebo | *p*-value |
|---|---|---|---|
| Age group, *n* (%) | | | 0.3** |
| 40–50 years | 5 (9) | 1 (2) | |
| 50–60 years | 12 (23) | 13 (31) | |
| 60–70 years | 36 (68) | 28 (67) | |
| Sex, *n* (%) | | | 0.001* |
| Male | 30 (57) | 9 (21) | |
| Female | 23 (43) | 33 (79) | |
| Duration of PD, *n* (%) | | | 0.02* |
| < 2 years | 2 (3) | 9 (22) | |
| 2–5 years | 21 (40) | 11 (26) | |
| > 5 years | 30 (57) | 22 (52) | |
| PD severity (Hoehn and Yahr staging), *n* (%) | | | 0.6** |
| Stage 1.5 | 2 (4) | 1 (2) | |
| Stage 2 | 5 (9) | 2 (5) | |
| Stage 2.5 | 21 (40) | 22 (52) | |
| Stage 3 | 25 (47) | 17 (41) | |
| Severity of motor and non-motor symptoms in PD patients, Mean (SD) | | | |
| Part I – Non-motor experiences of daily living | 12.94 (3.8) | 12.69 (2.6) | 0.7*** |
| Part II – Motor experiences of daily living | 15.51 (3.9) | 13.43 (2.6) | 0.003*** |
| Part III – Motor examination | 40.45 (12.4) | 40.98 (7.9) | 0.8*** |
| Duration of OAB symptoms (months), *n* (%) | | | 0.6* |
| 3–12 months | 4 (7) | 5 (12) | |
| 12–24 months | 18 (34) | 11 (26) | |
| > 24 months | 31 (59) | 26 (62) | |
| Previous use of anticholinergic drug for OAB symptoms, *n* (%) | | | 0.6 |
| Yes | 44 (83) | 35 (83) | |
| No | 9 (17) | 7 (17) | |

PD, Parkinson's disease; OAB, overactive bladder.
* Pearson's Chi-square test; ** Fisher's Exact Test; *** Independent *t*-test.

minimally important difference for all OAB-q subscales is supported by the convergence of anchor-based and distribution-based methodologies [13].

## *Safety*

Table 4 summarizes the difference of safety measures from baseline in the treatment and the placebo groups. In the treatment group, there was no increase in the office measured SBP, DBP and PR from baseline to the end of the trial. The difference of the mean of self-measured SBP and DBP from baseline were $+1.1 \pm 4.5$ mm Hg and $+0.5 \pm 5.6$ mm Hg, respectively. There were no notable changes from baseline in self-measured PR. The mean change in the QTcF interval from baseline to the end of the trial was $0.9 \pm 1.3$ ms. In the placebo group, changes from baseline to the end of the trial in SBP, DBP, PR and QTcF were minimal and unremarkable.

The incidence and type of DRAEs were similar in the treatment and placebo groups, except for constipation, arthralgia and high PVR. There were no serious adverse events and no

Table 2. The difference from baseline in treatment and placebo groups for results of OABSS, voiding diary and OAB-q SF.

| | Treatment group | | | Placebo group | | |
|---|---|---|---|---|---|---|
| | Baseline | Week 12 | *p*-value[a] | Baseline | Week 12 | *p*-value[a] |
| OABSS (Mean ± SD) | | | | | | |
| Total OABSS | 10.2 ± 1.2 | 6.9 ± 1.4 | *<0.001* | 10.7 ± 1 | 10.5 ± 1.1 | *0.03* |
| Daytime frequency score Q1 | 1 ± 0 | 1 ± 0.1 | 0.3 | 1 ± 0 | 1 ± 0 | 1 |
| Nighttime frequency score Q2 | 1.6 ± 0.7 | 1.1 ± 0.7 | *<0.001* | 1.8 ± 0.6 | 1.8 ± 0.7 | 0.4 |
| Urgency Score Q3 | 3.8 ± 0.4 | 2.4 ± 0.9 | *<0.001* | 2.4 ± 0.8 | 2.2 ± 0.8 | *0.02* |
| Urge incontinence score Q4 | 3.7 ± 0.5 | 2.4 ± 0.6 | *<0.001* | 2.4 ± 0.8 | 2.3 ± 0.9 | 0.1 |
| Bladder diary measures (Mean ± SD) | | | | | | |
| No. of micturition/24 h | 11 ± 1.2 | 8.7 ± 1.1 | *<0.001* | 10.4 ± 1 | 10.2 ± 1.1 | *0.01* |
| No. of micturition/night | 1.5 ± 0.6 | 1.1 ± 0.7 | *<0.001* | 1.8 ± 0.6 | 1.8 ± 0.7 | 0.6 |
| No. of urgency episodes/24 h | 2.4 ± 1.1 | 0.6 ± 0.6 | *<0.001* | 2.4 ± 0.8 | 2.2 ± 0.8 | *0.03* |
| No. of leaks/24 h | 2.2 ± 1.2 | 0.4 ± 0.6 | *<0.001* | 2.4 ± 0.8 | 2.3 ± 1 | 0.4 |
| Volume voided per micturition (ml) | 122.1 ± 16 | 141.3 ± 17.7 | *<0.001* | 112 ± 19.7 | 112.6 ± 13.5 | 0.7 |
| OAB-qSF (Mean ± SD) | | | | | | |
| OAB-qSF symptom bother | 39.8 ± 8.1 | 22.2 ± 7.4 | *<0.001* | 51.3 ± 7.7 | 48.7 ± 12 | 0.2 |
| OAB-qSF HRQOL | 64.4 ± 7.4 | 83.8 ± 7.7 | *<0.001* | 68.5 ± 7.4 | 67.6 ± 9.5 | 0.3 |

OABSS, Overactive bladder symptom score; OAB-qSF, Overactive bladder quality-of-life short-form questionnaire; SD, standard deviation.
[a]Wilcoxon Signed-Rank Test to test differences between baseline and week 12 in each group.

Table 3. Proportion of patients who reached the MCIC for OABSS and OAB-q SF HRQoL.

| | Treatment group Week 12 | Placebo group Week 12 | *p*-value |
|---|---|---|---|
| Patients who reached MCIC of total OABSS, *n* (%) | 38 (72) | 0 (0) | <0.001 |
| Patients who reached MCIC of OAB-q SF HRQL, *n* (%) | | | |
| OAB-q SF HRQoL | 48 (90) | 3 (7) | <0.001 |

MCIC, minimal clinically important change; OABSS, Overactive Bladder Symptom Score; OAB-q SF, Overactive bladder quality-of-life short-form questionnaire; HRQoL, health-related quality-of-life.

Table 4. The difference from baseline in treatment and placebo groups for safety measures.

| | Treatment Group | | | Placebo Group | | |
|---|---|---|---|---|---|---|
| | Baseline or Week 1 | Week 12 | Change from Baseline | Baseline or Week 1 | Week 12 | Change from Baseline |
| Office measured SBP (mm Hg) | 122.8 ± 10.2 | 121.4 ± 14.2 | −1.3 ± 4 | 116. 2 ± 7.6 | 118 ± 10.3 | 1.9 ± 5.3 |
| Office measured DBP (mm Hg) | 65 ± 8 | 64.5 ± 8.8 | −0.5 ± 5.4 | 59.1 ± 5.8 | 59.5 ± 13 | 0.3 ± 11.6 |
| Office measured pulse rate (bpm) | 69.1 ± 6.7 | 68.9 ± 6.9 | −0.3 ± 1.8 | 66 ± 9 | 65.9 ± 8.9 | −0.1 ± 1.5 |
| Self-measured SBP (mm Hg) | 120.6 ± 10.6 | 121.6 ± 12.2 | 1.1 ± 4.5 | 115. 7 ± 7.5 | 117.3 ± 10.5 | 1.5 ± 7.4 |
| Self-measured DBP (mm Hg) | 65.9 ± 7 | 66.4 ± 8.3 | 0.5 ± 5.6 | 59.4 ± 6 | 60 ± 10 | 0.7 ± 7.7 |
| Self-measured pulse rate (bpm) | 68.1 ± 6.5 | 68 ± 6.7 | −0.1 ± 1.3 | 65.7 ± 9 | 65.1 ± 10 | −0.6 ± 1.7 |
| QTcF interval, ms | 407 ± 18.2 | 408 ± 18.6 | 0.9 ± 1.3 | 410.1 ± 9.2 | 410.4 ± 9.5 | 0.3 ± 1.7 |

All figures are Mean ± SD.
QTcF interval, QT interval corrected with Fridericia's correction; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; SD, standard deviation.

deaths reported during the trial period. Results are summarized in Table 5.

## Discussion

Changes of the central serotonergic system have been suggested to play a relevant role in OAB, irrespective of PD [14]. Anticholinergics are generally used as a first-line treatment for OAB in PD patients. However, it has potential adverse effects [4]. Mirabegron is a long-term treatment option for patients with neurogenic lower urinary tract dysfunction not suitable for antimuscarinics [15]. Mirabegron was an effective treatment in the management of NB unresponsive to antimuscarinics, particularly in patients presenting with storage symptoms [16]. There are only a few trials that test the efficacy of mirabegron in PD patients. Published results were similar to our study, the OABSS scores were substantially lower at the end of each trial where mirabegron therapy was used as second-line therapy and it showed an excellent safety profile. Peyronnet et al. [17] performed a retrospective study including patients with PD who received mirabegron 50 mg once daily for OAB symptoms between 2012 and 2017. Fifty patients were included. After 6 weeks of treatment, 11.4% and 50% of patients reported complete resolution and improvement of their OAB symptoms, respectively. Mirabegron has an excellent safety profile. Gubbiotti et al. [18] conducted a pilot study to assess the effectiveness of mirabegron in patients with PD and OAB symptoms refractory to antimuscarinics. Thirty patients with

Table 5. Summary of drug-related adverse events.

| AE | Treatment group | Placebo group | *p*-value |
|---|---|---|---|
| Total percentage, *n* (%) | 11 (21) | 7 (17) | 0.3* |
| Dry mouth | 4 (7) | 3 (7) | 1** |
| Hypertension | 1 (2) | 2 (5) | 1** |
| Headache | 1 (2) | 1 (2) | 1** |
| PVR > 100 ml | 1 (2) | 0 | 1** |
| Back pain | 1 (2) | 1 (3) | 1** |
| Arthralgia | 1 (2) | 0 | 1** |
| Constipation | 2 (4) | 0 | 0.5** |

AE, adverse event; PVR, post-void residue; * Pearson's Chi-square test; ** Fisher's Exact Test.

PD and refractory OAB were prospectively included in the study. At 3-month follow-up, seven out of the 30 patients achieved complete urinary continence. Daytime urinary frequency, night-time urinary frequency, frequency of urinary urgency episodes and daily frequency of urge incontinence episodes decreased significantly. No consistent variation in BP or PR was detected during the follow-up period. Recently, Cho et al. [19] published the results of a double-blind RCT that was performed to test the role of mirabegron in PD patients with OAB. They excluded from the trial any patients taking anticholinergic drugs for OAB symptoms. The patients were randomized into placebo and mirabegron groups at visit 2. Visit 3 was performed after 4 weeks of medication. Mirabegron was prescribed to the two groups for the rest of the study period at visit 4. One hundred and seventeen patients were randomized in their trial. In the mirabegron group, the OABSS scores were substantially lower at visit 3 (week 4) and were maintained during the entire study period. No serious adverse event occurred during the study period.

Other randomized controlled trials (RCT) were performed to assess the efficacy of antimuscarinics for the treatment of OAB in patients with PD. An RCT evaluated the efficacy of solifenacin succinate in this setting. Patients were randomized to receive solifenacin succinate 5–10 mg daily or a placebo for 12 weeks followed by an 8-week open-label extension. Results showed that there was an improvement in the number of micturitions per 24 hour period in the solifenacin succinate group compared to placebo at a mean dose of 6 mg/day ($p = 0.01$) with multiple side effects [20]. Yonguc et al. [21] performed another RCT to test the short-term efficacy and safety of fesoterodine fumarate in PD patients with OAB. Sixty-three patients were randomized to receive fesoterodine 4 mg or placebo for 4 weeks. OAB symptoms were significantly improved in older adults with PD under fesoterodine fumarate treatment, even in the open-label period. The cognitive function was not affected in the treatment group.

Typical antimuscarinics adverse events which limit tolerability are less frequent with mirabegron. A large integrated clinical trial database included 11,261 patients in the safety analysis set. More DRAEs were reported for the antimuscarinics group (21.4%) versus the mirabegron group (17.0%). Dry mouth was more frequent in the antimuscarinics group (8.7%) versus the mirabegron (2.7%) and placebo (2.4%) groups. A similar and low frequency was reported between groups for constipation (placebo 1.7%, mirabegron 2.1% and antimuscarinics 2.4%). Urinary retention was $< 1\%$ for all groups [22].

In our study, all patients taking mirabegron 50 mg had a significant improvements in all OAB symptoms. Patient's satisfaction with treatment significantly improved and symptom bothers significantly decreased. Mirabegron therapy was well tolerated and concordant with the known safety profile of mirabegron. The PR did not increase significantly in our patients, while SBP increased by 1 mmHg. Those values were similar to that of previous reports on the safety of mirabegron therapy, where the adjusted mean difference versus placebo for change from baseline to week 12/final visit in SBP was 0.6 and 0.5 for AM and PM measurements, respectively [23]. We targeted to get the highest level of patient adherence to treatment in our study, so we reduced all factors that could affect this adherence. The median level of adherence in our study was 93% during the study period.

Our study has several limitations. First, the sample size was relatively small. Second, the mirabegron therapy was prescribed for 12 weeks and we did not perform a long-term follow-up. Third, mirabegron was used only at 50 mg dosage. Fourth, the study was conducted in a single institution. Fifth, we were looking for upper age limits (not including very elderly patients ($> 70$ years). Sixth, there was some imbalance in baseline characteristics between groups (duration of PD and the severity of motor symptoms) and this may have some impact on the observed outcomes.

## Conclusions

According to our data, mirabegron is a safe and effective therapy for OAB symptoms in patients with PD with minimal adverse events.

## Disclosure statement

No potential conflict of interest was reported by the author(s).

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