# 23. Real-Life Data

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# Real-Life Data on Mirabegron in Neurogenic Bladder Dysfunction

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**Keywords**
Multiple sclerosis · Incontinence · Neurogenic detrusor overactivity · Overactive bladder · Persistence

**Abstract**
***Aims:*** To determine factors for treatment persistence in a real-life cohort of adult neurogenic lower urinary tract dysfunction. ***Methods:*** We reviewed records of patients with neurogenic lower urinary tract dysfunction and mirabegron prescriptions. Exclusion criteria were indwelling urethral or suprapubic catheters and implanted neurostimulators. We extracted demographic data, indication for prescription, concomitant use of other agents with possible anticholinergic effect, beta blockers, duration of treatment and reason of discontinuation. ***Results:*** We included 110 subjects in this study. Neurologic diagnoses included multiple sclerosis, Parkinson's disease, and other diagnoses (dementia, paraplegia, and tetraplegia). Previous usage of antimuscarinics was found in 78 patients (71%). Mirabegron was combined with antimuscarinics in 15 patients (14%). Drugs with any anticholinergic activity were taken by 94 subjects (86%). Mirabegron was taken for a median of 497 days and 60 patients discontinued the medication within the study period. Main reasons of discontinuation were lack of effect (44/110), side effects (10/110), and non-reimbursement (6/110). There were no differences in mirabegron discontinuation by neurological disease, beta blocker usage, or anticholinergic burden. ***Conclusions:*** Mirabegron is continued in more than half of patients with neurogenic lower urinary tract dysfunction for more than 6 months. Further research is needed to identify eventual predictive factors.
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## Introduction

Adult neurogenic lower urinary tract dysfunction (ANLUTD) often leads to overactive bladder symptoms such as frequency, urgency, urgency incontinence, and nocturia [1, 2]. Oral medical treatment can offer symptomatic relief to patients with multiple sclerosis (MS), stroke, Parkinson's disease, and dementia. ANLUTD underlying these symptoms is mainly treated with antimuscarinics [3]. These agents have high discontinuation rates in idiopathic overactive bladder as well as neurogenic etiology, 57.8% and 32.5% at 1 year, respectively [4].

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Mirabegron is the first beta-3 agonist that has been approved since 2013 as treatment for overactive bladder [5]. The difference in mechanism of action results in a lower rate of dry mouth, which is the most prevalent adverse effect. Mirabegron improves cystometric capacity and bladder compliance and reduces maximum detrusor pressure in neurogenic bladders [6–8]. A recent placebo-controlled randomized trial of mirabegron in ANLUTD reported that mirabegron treatment improves patient-reported symptoms and quality of life at the end of 4 weeks therapy [8]. Improved patient compliance and persistence with mirabegron have been reported compared to other medications for overactive bladder [9–12]. However, longer durations of observation have not been reported for patients with neurogenic etiology. Data are important as ANLUTD require lifelong treatment for the prevention of potentially life-threatening complications. The aim of this study is to report long-term real-life data of mirabegron in patients with neurological disease and to identify factors for treatment persistence.

## Materials and Methods

This is a retrospective study of tertiary care patients of a single urological department. The study protocol was approved by the hospital Ethics Committee. We included all patients aged ≥18 years with neurogenic lower urinary tract dysfunction who were prescribed mirabegron 50 mg between 2013 and 2017. Individual patient records were reviewed to determine eligibility. We excluded patients with indwelling urethral and suprapubic catheters, implanted neurostimulators and no follow-up visits.

The primary outcome of this study was time to discontinuation of mirabegron, which was defined as number of days between the first date of prescription and final record of mirabegron intake in medical record from any health care provider. Explicit stop or absence in medication list is coded as mirabegron discontinuation. Data extracted were patient demographics, neurogenic disease, comorbidities, medication history, prescribing indication, symptom improvement, and duration of mirabegron treatment. At follow-up visits, symptom improvement was assessed by the question "When compared to the time you started the treatment, how would you rate your symptoms now?" Drugs with anticholinergic side effect were recorded according to the Anticholinergic Cognitive Burden scale [13] and a list compiled from a systematic review of anticholinergic risk scales [14].

Statistical analysis was done using Graphpad Prism 7.0. Continuous variables were expressed as the mean ± SD, and categorical data were expressed as absolute number and percentages in parentheses. Continuous variables were compared using the Mann-Whitney U test. Categorical variables were compared using Fisher's exact test. Differences in survival curves were determined by log-rank (Mantel-Cox) test. A 2-sided value of $p < 0.05$ was considered statistically significant.

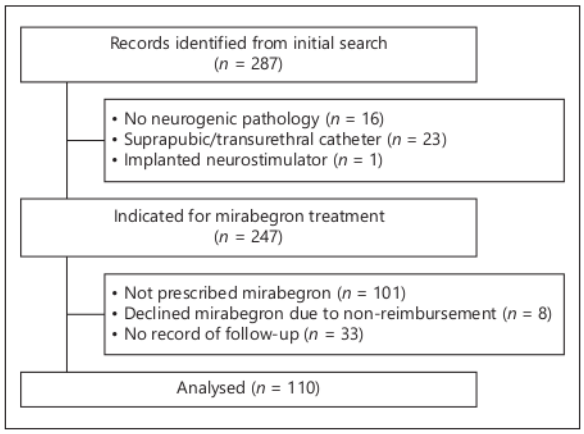


**Fig. 1.** Flow diagram of subjects.

## Results

Searching of electronic medical record database identified 287 patients with adult lower urinary tract dysfunction and indication for mirabegron in the medical record. After applying exclusion criteria, 16 patients had no record of neurologic disease, 24 patients had indwelling catheters and implanted stimulators. Mirabegron was not prescribed to 109 patients and 33 patients were lost to follow-up. We included 110 subjects for final analysis as detailed in Figure 1.

Patient characteristics are described in Table 1. The most frequent neurologic diagnoses were MS (42/110 [38.2%]) and Parkinson's disease (27/110 [24.5%]). Prescribing indications were treatment failures with antimuscarinics, specifically persistent urgency (40/110), persisting incontinence (52/110) and intolerance to side effects (37/110). A minority of patients also complained of frequency (27/110), nocturia (27/110), and stress urinary incontinence (19/110). All patients with residual urine of more than 150 mL (10/110) were treated with intermittent catheterization. Mirabegron was prescribed in combination with antimuscarinics in 15 out of 110 patients (13.6%). Patients were concurrently taking one or more medications with possible anticholinergic side effects in 94 out of 110 (85.4%).

Mirabegron was discontinued by 60 out of 110 patients (median duration of intake of 497 days, minimum-maximum 3–1,540 days). The reason of discontinuation was lack of effect in 44 out of 110 patients, side effects in 10 out of 110, and non-reimbursement in 6 out of 110. We



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**Table 1.** Distribution of patient characteristics by discontinuation of mirabegron

| | Continued mirabegron ($n$ = 50) | Discontinued mirabegron ($n$ = 60) | Significant | Total ($n$ = 110) |
|---|---|---|---|---|
| Gender, $n$ (%) | | | | |
| Female | 29 (58) | 33 (55) | 0.85 | 62 (56) |
| Male | 21 (42) | 27 (45) | | 48 (44) |
| Age, years, median (IQR) | 62 (42–73) | 68.5 (54–74.5) | 0.1 | 66 (47.5–74) |
| Neurogenic disease, $n$ (%) | | | | |
| MS | 21 (42) | 21 (35) | 0.4 | 42 (38) |
| Parkinson's | 10 (20) | 17 (28) | | 27 (25) |
| Dementia | 6 (12) | 9 (15) | | 15 (14) |
| Spinal cord disease | 9 (18) | 5 (8) | | 14 (13) |
| Other | 4 (8) | 8 (13) | | 12 (11) |
| Reason to start mirabegron†, $n$ (%) | | | | |
| Persisting urgency | 14 (28) | 26 (43) | 0.11 | 40 (36) |
| Persisting incontinence | 22 (44) | 30 (50) | 0.57 | 52 (47) |
| Intolerance to side effects of antimuscarinics | 17 (34) | 20 (33) | 0.99 | 37 (34) |
| Pretreatment symptoms†, $n$ (%) | | | | |
| Urgency | 46 (92) | 53 (88) | 0.75 | 99 (90) |
| Urgency incontinence | 42 (84) | 41 (68) | 0.08 | 83 (76) |
| Frequency | 10 (20) | 17 (28) | 0.38 | 27 (25) |
| Nocturia | 10 (20) | 17 (28) | 0.38 | 27 (25) |
| Stress incontinence | 5 (10) | 14 (23) | 0.08 | 19 (17) |
| PVR >150 mL | 6 (12) | 4 (7) | 0.33 | 10 (9) |
| Concomitant therapy†, $n$ (%) | | | | |
| Previous treatment with antimuscarinics | 34 (68) | 44 (73) | 0.84 | 78 (71) |
| Combination treatment with antimuscarinics | 8 (16) | 7 (12) | 0.58 | 15 (14) |
| Any drug with anticholinergic effects | 44 (88) | 50 (83) | 0.59 | 94 (86) |
| Anticholinergic burden score, median (IQR) | 1.5 (0–3) | 1 (0–3) | 0.95 | 2 (0–3) |
| Number of drugs with anticholinergic effect, median (IQR) | 2 (1–3) | 2 (1–3) | 0.78 | 2 (1–3) |
| Beta blocker treatment | 8 (16) | 17 (28) | 0.17 | 25 (22.7) |
| Symptom response, $n$ (%) | | | <0.01 | |
| Improved symptoms | 38 (76) | 16 (27) | | 54 |
| No effect or worsening symptoms | 12 (24) | 44 (73) | | 56 |

† More than one option is possible.
IQR, interquartile range; PVR, post void residual; MS, multiple sclerosis.

could not relate to any serious side effects resulting in hospitalization or need for intervention to the intake of mirabegron in this study population.

Any symptom improvement is associated with higher continuation of mirabegron intake ($p < 0.0001$). There were trends toward a higher rate of urgency and stress incontinence in patients continuing mirabegron, although this difference was not enough to be statistically significant. There were no differences in discontinuation based on the type of neurogenic disease ($p = 0.61$) or beta blockers ($p = 0.23$; Fig. 2). We found no difference in discontinuation by anticholinergic burden both as defined by Anticholinergic Cognitive Burden scale ($p = 0.75$) nor total number of drugs with anticholinergic effect ($p = 0.74$, data not shown).

Figure 3 is an example of cystometry results pre- and post-treatment. Urodynamic study was performed prior to mirabegron initiation in 44 patients. Maximum cystometric capacity was not statistically different between those continuing and discontinuing mirabegron (329 ± 174 vs. 284 ± 185 mL, $p = 0.46$). A similar outcome was found for the first contraction (226 ± 189 vs. 197 ± 130 mL, $p = 0.6$). On follow-up, there was no difference in discontinuation between patients who performed urodynamics and those who did not ($p = 0.19$).



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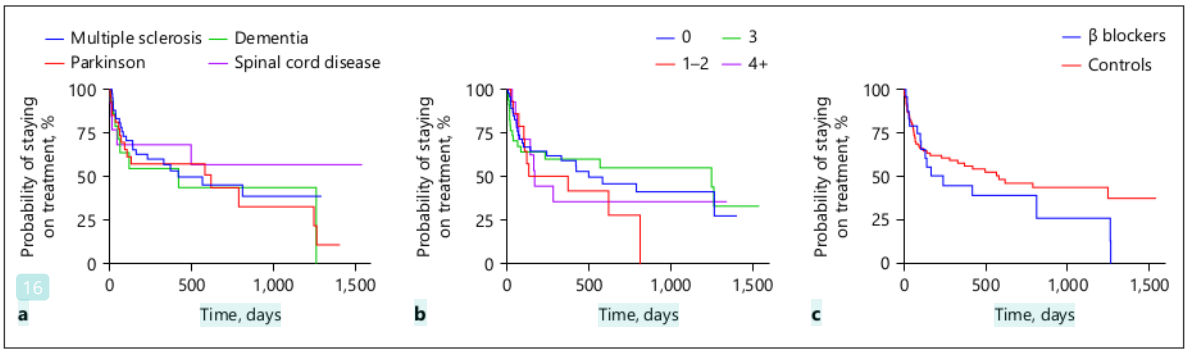


**Fig. 2.** Kaplan-Meier plots of time to discontinuation of mirabegron by (**a**) neurogenic disease (Mantel-Cox log-rank test $p = 0.61$), (**b**) anticholinergic burden score ($p = 0.75$), (**c**) beta-blocker usage ($p = 0.23$). MS, multiple sclerosis; ACB, Anticholinergic Cognitive Burden.

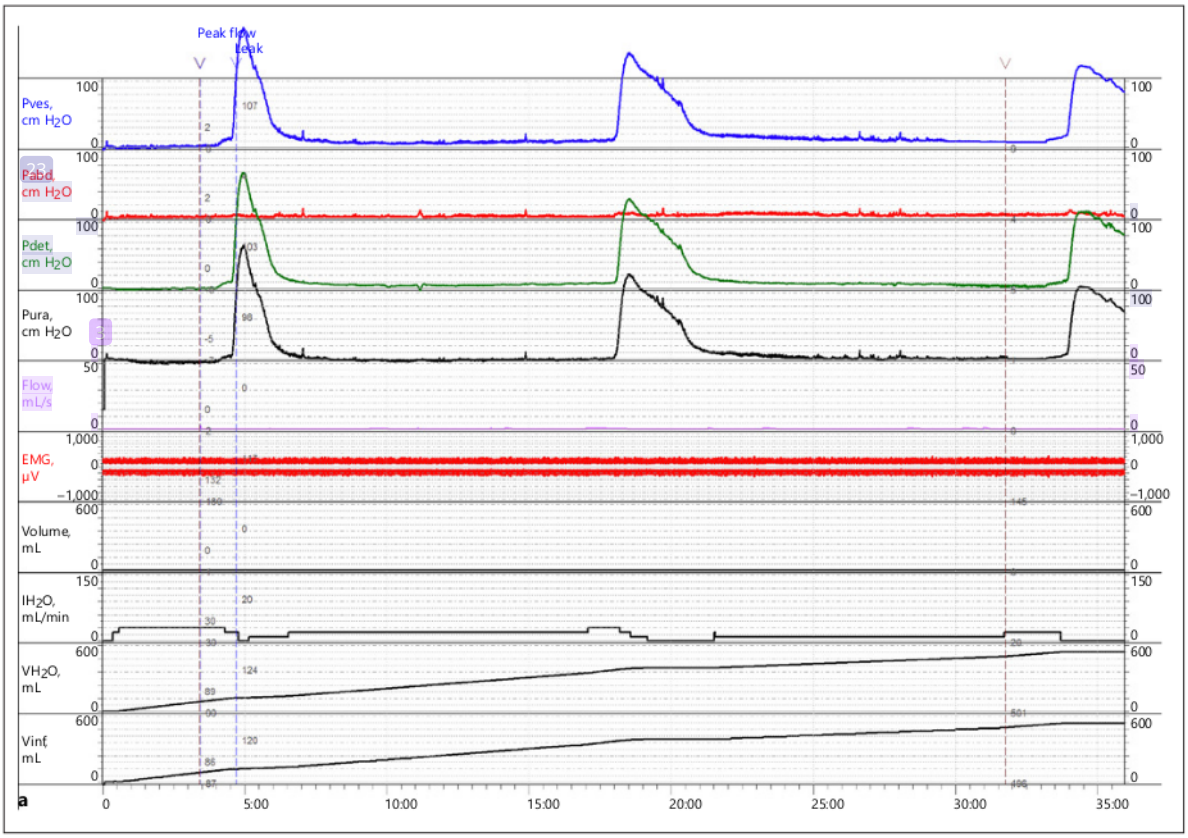


**Fig. 3.** Urodynamic examination in patient with NLUTD due to spinal cord injury (**a**) pre-treatment with mirabegron and (**b**) under combination treatment of mirabegron and solifenacin.

*(Figure continued on next page.)*



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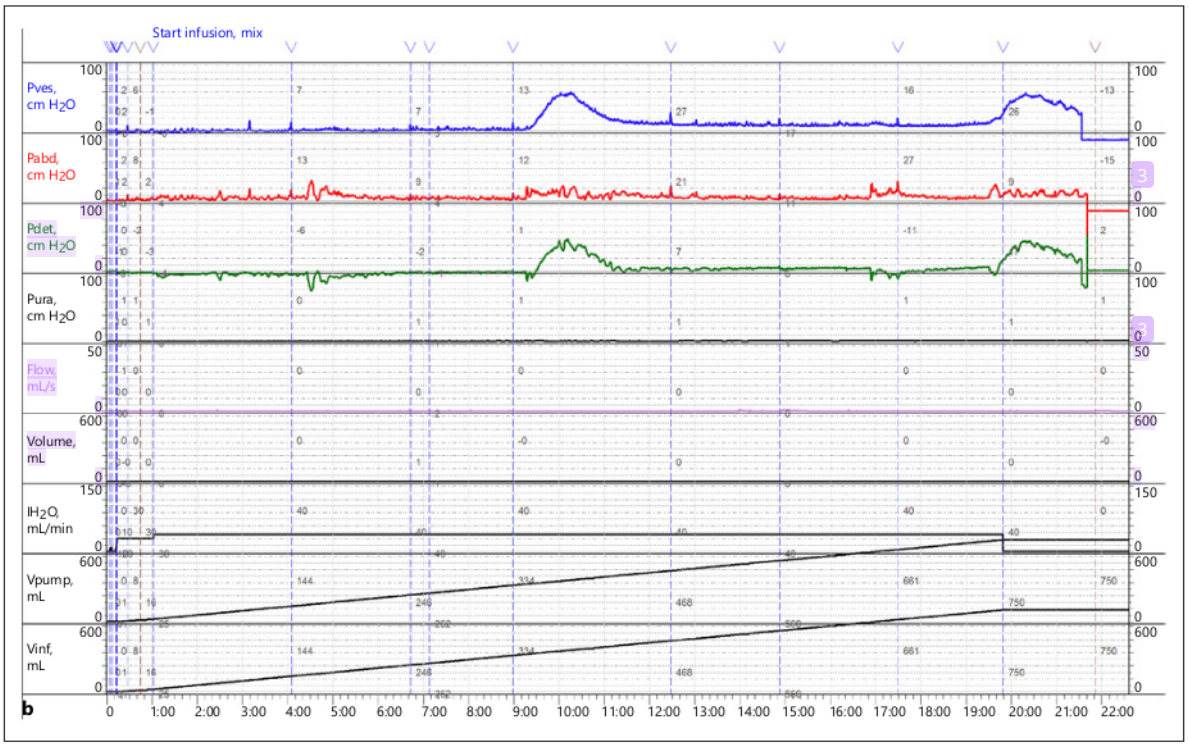


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## Discussion/Conclusion

This study revealed that in patients with ANLUTD mirabegron was continued for more than 1 year in 41% of patients. These were patients who did not benefit from oral antimuscarinic therapy either due to lack of efficacy or side effects (Table 1). The most frequent reason for discontinuation was lack of effect and side effects. Both of these characteristics were similar to antimuscarinic treatment [4, 15].

We assessed whether patient factors can predict the discontinuation of treatment, including neurologic disease, total anticholinergic effect of all medications taken, and intake of beta blockers. There is no difference in discontinuation between the different types of neurologic pathology. Patients enrolled in this study have neurogenic etiology, which frequently necessitates concomitant medications with varying anticholinergic effect. Longer-term clinical data has shown that anticholinergics initially alleviate symptoms; however, a subset of patients subsequently discontinue with lack of efficacy being the most frequent reason [4]. In elegant animal studies, chronic administration of anticholinergics show similar initial reduction in voids, which normalized at 4 weeks along with reduced expression of M3 receptors [16, 17]. We hypothesized that overall anticholinergic effects of all medications taken in our patient population may determine response to mirabegron treatment. Two separate methods for quantifying anticholinergic use were used but no correlation with mirabegron treatment persistence was identified by either method [13, 14]. Finally, theoretical interference of beta-blockers such as metoprolol on the beta-3 receptor was considered. However, we found no statistically significant difference in persistence with mirabegron treatment ($p = 0.23$) [18].

The second most frequent reason for discontinuation was the prevalence side effects [19]. The favorable side effect profile of mirabegron compared to antimuscarinic agents has been demonstrated both in an idiopathic as well as in a neurogenic overactive bladder [5, 8, 9]. Lastly, discontinuation due to improvement of symptoms has also been reported [19]. Fluctuating symptoms is a feature of certain types of MS, which was the most frequent condition found in our study [20].

The cost of medication is an important factor in treatment choice and decision for discontinuing overactive



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bladder medications [19]. Within the national health care system, no oral medications are reimbursed for overactive bladder. In cases of neurogenic etiology, botulinum toxin is reimbursed. Cost to patients for mirabegron is similar to M-3 selective antimuscarinics and twice the price of nonselective antimuscarinics.

Currently available treatment options for overactive bladder symptoms have similar limitations in long-term results. Oral pharmacotherapeutic options are characterized by low long-term persistence of <40% at 12 months for antimuscarinics [15, 21, 22]. The discontinuation rate of mirabegron is reported as similar or lower compared to antimuscarinics, irrespective of previous antimuscarinic treatment [23]. As alternative to oral treatment, intradetrusor injection of botulinum toxin is efficacious in patients willing to perform intermittent catheterization [24]. In our previously reported experience, 55% of patients treated with onabotulinumtoxin-A discontinued with a mean follow-up of 35 months [25]. Separately, Joussain et al. [26] reports the persistence of botulinum toxin treatment as high as 80.6% at 3 years and 60.8% at 7 years. Patients failing to benefit from one treatment option may still benefit from another agent with the same or a different mechanism of action. These observations point to possible subpopulations that are not identifiable by current investigation methods.

Our study has several strengths. First, patients included have characteristics that commonly exclude them from previously available clinical trial outcomes data. Second, longer term follow-up is important in the care of chronic disease and prevention of possibly life-threatening complications. Finally, the electronic medical record system was connected to other hospitals within the community network. However, we acknowledge the limitations of our study. We excluded 33 patients due to lack of follow-up, which may result in the overestimation of the persistence rate. Symptom assessment was not standardized but was based on history taking by the urologist. Invasive urodynamic examinations were not standard for our patient cohort. If uroflow and postvoid residual did not show significant abnormalities, cystometry was not routinely performed. Repeat urodynamic studies were performed in cases where patients considered botulinum toxin or other invasive treatments. Despite these limitations, we believe that this group of patients demonstrated long-term benefit from mirabegron treatment. Further research should focus to identify predictive factors for treatment benefit and possible role of mirabegron as first-line alternative to antimuscarinic therapy.

In conclusion, Mirabegron is a long-term treatment option for patients with neurogenic lower urinary tract dysfunction not suitable for antimuscarinics. Based on available characteristics, it is not possible to predict which patients will continue treatment.


## Acknowledgment

Gigi Vos assisted in initial data collection.


## Statement of Ethics

The study protocol has been approved by the Ethical Commission of UZ/KU Leuven.

## Disclosure Statement

M.A.S. received non-financial support from Allergan. L.H. reports personal fees from Astellas. F.V.A. reports grants and personal fees from Astellas, grants and personal fees from Allergan, D.D.R. reports grants from Astellas, Ferring, and Medtronic, all outside the submitted work.


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## Author Contribution

M.A.S. was responsible for data collection and management, data analysis, and writing of article; L.H. contributed to study design, data analysis, and interpretation; F.V.A. was in charge of protocol development, data acquisition, and analysis; D.D.R. was involved in protocol development, seeking ethical approval, data collection, management, and analysis, manuscript writing and editing.

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