# *Effective treatment of neurogenic detrusor overactivity in multiple sclerosis patients using desmopressin and mirabegron*

Athanasios Zachariou, MD,[1] Maria Filiponi, MD,[2] Dimitrios Baltogiannis, MD,[1] John Giannakis, MD,[1] Fotios Dimitriadis, MD,[3] Panagiota Tsounapi, MD,[4] Atsushi Takenaka, MD,[4] Nikolaos Sofikitis, MD[1]

[1]Urology Department, School of Medicine, Ioannina University, Ioannina, Greece
[2]Urology Department, Elpis Hospital, Volos, Greece
[3]1st Urology Department, Aristotle University, Thessaloniki, Greece
[4]Urology Department, School of Medicine, University of Tottori, Yonago, Japan

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***Introduction:*** *Multiple sclerosis (MS) is the commonest progressive neurological disease affecting young people. With advancing disease, management of neurogenic detrusor overactivity (NDO) based on antimuscarinics may prove inadequate and if based on botulinum toxin, may necessitate clean intermittent self-catheterization. The aim of the study was to evaluate the effectiveness of combined mirabegron and desmopressin administration in the treatment of NDO in patients with MS.*

***Materials and methods:*** *Sixty patients diagnosed with MS and NDO were evaluated. All had received treatment with solifenacin 10 mg/daily for 3 months and were displeased with the results. Patients were divided in four groups. In Group A (n = 15) patients continued receiving solifenacin 10 mg/daily; in Group B (n = 15) patients received mirabegron 50 mg/daily; in Group C (n = 15) patients received desmopressin 120 mcg/daily and in Group D (n = 15) patients received mirabegron 50 mg/daily and desmopressin 120 mcg/daily. All patients were assessed with a 3 day bladder diary at the beginning and at the end of the treatment.*

***Results:*** *All patients in Groups A, B and C did not demonstrate statistically significant changes at the end of the treatment period in their 3 day bladder diary and in the presence of urinary infections. In Group D, a statistically significant improvement was noted in the mean change from baseline to end of treatment in micturition episodes (3.5 ± 0.4 micturition/24h), in urgency episodes (2.3 ± 0.2) and mean number of urinary incontinence (1.0 ± 0.2 episodes/24h).*

***Conclusions:*** *Treatment with mirabegron and desmopressin revealed both effectiveness and safety in patients with NDO and MS.*

**Key Words:** neurogenic detrusor overactivity, mirabegron, desmopressin, multiple sclerosis

## Introduction

Multiple sclerosis (MS) is an inflammatory disorder of the central nervous system that affects over 400,000 people in North America and 2.1 million worldwide.[1] Patients with MS often have neurogenic detrusor overactivity (NDO), which frequently results in urgency, frequency, nocturia and urgency incontinence.[2] This is well reflected by urodynamic findings showing that detrusor overactivity is the most common sign, presented in up to 81% of patients.[3] Bladder dysfunction in MS can be socially disabling, have negative psychological and economic consequences and impair patients' quality of life. Proper identification of bladder dysfunction and associated problems combined with appropriate management to prevent upper tract complications, results in improved quality of life and is therefore essential to the comprehensive care of MS patients.

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Address correspondence to Dr. Athanasios Zachariou, 3 Spyridi Street, Volos 38221, Greece

Oral anticholinergic medications for NDO have been a mainstay for medical therapy for decades in MS patients. Unfortunately, they are either inefficacious or poorly tolerated in up to 30% of patients.[4] An important adverse effect of anticholinergic therapy to consider in MS patients is decreased sweating, which prevents cooling and exacerbates overheating in patients already suffering from heat intolerance. Moreover, dry mouth rates are shown to be significantly higher, resulting in withdrawals in several studies.[5-7]

When anticholinergic medications fail to prove efficacious, the next option is to neutralize the detrusor muscle with intradetrusor injections of botulinum toxin. The majority of MS patients do not use clean intermittent self-catheterization (CISC) prior to treatment. Therefore, the occurrence of urinary retention, initiation of CISC and urinary tract infections are higher post treatment in the MS population than other patients e.g. with spinal cord injury.[8] Unfortunately, some patients do not respond to, or are medically unfit for this treatment and use containment methods such as permanent catheters, condoms, or incontinence pads.[9] Despite the fact that botulinum toxin intradetrusor injections are a cost-effective way to control the symptoms of NDO, the need for anesthesia is one of the largest current cost components.[1]

The β3-adrenergic agonist mirabegron represents a novel class of compounds which have been recently introduced as a new oral treatment for overactive bladder (OAB). Mirabegron improves bladder storage capacity without inducing adverse anticholinergic events. In four large–scale 12 week phase III studies,[10-13] a pooled analysis[10] and 12 month mirabegron study[14] consistently demonstrated superiority over placebo with respect to reductions in incontinence episodes and micturition frequency, with a similar incidence of adverse effects as placebo. The role of mirabegron in the treatment of NDO in patients suffering from MS has not been previously evaluated.

However, it is known that desmopressin administration represents a beneficial treatment option for patients with spinal cord injury or MS to control abnormal nocturnal polyuria and decrease micturition frequency.[15-17] A meta-analysis combining results from five randomized double blind placebo controlled crossover studies had 98 patients available for investigation.[18] All studies showed a statistical reduction in voided volume for 6 hours following administration of desmopressin. None of the studies reported a significant reduction in serum sodium, 0%-8% of patients reported symptoms of fluid retention and 3%-4% of patients reported transient headache.

The aim of the present study was to evaluate the effectiveness of combined mirabegron and desmopressin administration in the treatment of NDO in a population of patients with MS.

## Materials and methods

Between November 2015 and January 2017, 60 patients (20 men and 40 women ≥ 18 years old) with confirmed MS diagnosis according to the criteria stipulated by McDonald et al[19] and symptoms of NDO were eligible for screening and study enrolment. All patients received solifenacin 10 mg/daily for 3 months for NDO with

TABLE 1. **Inclusion and exclusion criteria**

**Inclusion criteria**

1. Classified MS diagnosis for more than 3 years.
2. Treatment with solifenacin 10 mg daily for 3 months with poor results due to NDO.
3. Urodynamic work up.
4. Patients are willing and able to complete the micturition diary correctly.
5. Urgency/frequency (micturition frequency > 8/day).
6. Urge incontinence (involuntary loss of urine after a sensation of urge).
7. Written informed consent has been obtained.

**Exclusion criteria**

1. Significant post void residual volume (PVR > 200 mL).
2. Evidence of a urinary tract infection, chronic inflammation such as interstitial cystitis, bladder stones, previous pelvic radiation therapy, or previous or current malignant disease of the pelvic organs.
3. Non-drug treatment including electrostimulation therapy or start of a bladder training program during the 12 weeks prior to or during the study.
4. Any clinical significant condition, which in the opinion of the investigator makes the patient unsuitable for the trial.

MS = multiple sclerosis; NDO = neurogenic detrusor overactivity; PVR = post-void residual

poor results. Inclusion and exclusion criteria are listed in Table 1. None of the patients experienced a clinical relapse of their MS within 6 months prior to inclusion. Patients were evaluated at the outpatient Urology Clinic for symptoms of NDO by history, urodynamic test and determination of residual urine. All patients were able to walk, most without aids. The urodynamic work up was considered mandatory for inclusion in the protocol because in patients with neurogenic lower urinary tract dysfunction, accurate diagnosis on an individual basis is an absolute prerequisite for effective therapy determination. The research project's protocol has been approved by the institutional Ethics Committee.

All patients were enrolled in a 12 week treatment period and divided into four groups. Group A (n = 15, 5 males, 10 females) included patients who continued receiving solifenacin 10 mg/daily; Group B (n = 15, 5 males and 10 females) included patients who received mirabegron 50 mg/daily; Group C (n = 15, 5 males and 10 females) included patients who received desmopressin sublingually 120 mcg/daily and Group D (n = 15, 5 males and 10 women) mirabegron 50 mg/daily and desmopressin 120 sublingually mcg/daily.

All patients were assessed with a 3 day bladder diary at the beginning and at the end of the treatment. In the voiding diary, the voiding frequency, voided volume per void, the number of incontinence episodes and the number of pads used were recorded. All methods, units, and definitions used in the urodynamic evaluation were done according to ICS standards.[20]

Adverse events were evaluated and serum electrolytes, blood pressure and pulse rate were measured. To assess the presence of urinary infection, a combined rapid test of urine was used.

Primary endpoint was the change from baseline to end-of-treatment in the mean number of micturition/24h and secondary endpoints were the changes in the mean volume per micturition, the urgency episodes, the mean number of urinary incontinence episodes and the presence of urinary infection.

Changes from baseline to endpoint were subjected to the Wilcoxon signed-ranks test. Our data were evaluated with the use of SPSS software, USA, release 13.0. The statistical analysis was done using the percentage, paired t-test. Statistical significance was accepted $p < 0.05$. Data are presented as the mean ± standard deviation (range).

## Results

The study characteristics, including age, weight, symptoms duration, median frequency/day, mean volume voided per urination, median incontinence episodes per day and median number of pads used daily were not significantly different between four groups, Table 2. All patients had received treatment with

TABLE 2. **Demographic characteristics in the beginning of observation**

| | **Group A Solifenacin 10 mg daily** | **Group B Mirabegron 50 mg daily** | **Group C Desmopressin 120 mcg/daily** | **Group D Mirabegron 50 mg daily + Desmopressin 120 mcg/daily** |
|---|---|---|---|---|
| Age (yr) | 42 ± 5.4 yr (27-48 yr) | 43 ± 6.9 yr (29-51 yr) | 42 ± 5.1 yr (26-45 yr) | 40 ± 4.9 yr (31-49 yr) |
| Body weight (kg) | 62.5 ± 8.9 kg (53-75 kg) | 59.5 ± 7.8 kg (48-69 kg) | 60.3 ± 7.6 (50-78 kg) | 62.5 ± 8.9 kg (53-75 kg) |
| Symptom duration (yr) | 9.4 ± 2.5 (5-13) | 9.0 ± 2.9 (5-13) | 9.2 ± 2.8 (6-15) | 9.8 ± 2.9 (5-13) |
| Median frequency/day | 10.6 ± 0.8 (9-13) | 10.8 ± 0.9 (9-13) | 10.5 ± 0.8 (8-13) | 11.0 ± 0.9 (9-13) |
| Median volume voided | 106 ± 10 (90-124) | 102 ± 12 (86-119) | 102 ± 11 (87-120) | 104 ± 10 (89-118) |
| Median urgency episodes/day | 3.8 ± 1.3 (2-6) | 3.5 ± 1.4 (2-6) | 3.5 ± 1.2 (2-5) | 3.6 ± 1.1 (2-6) |
| Median incontinence episodes/day | 1.6 ± 0.4 (1-3) | 1.7 ± 0.3 (1-3) | 1.6 ± 0.2 (1-3) | 1.6 ± 0.4 (1-3) |
| Median number of pads/day | 3.2 ± 1.1 (1-5) | 3.1 ± 1.3 (1-5) | 3.2 ± 1.5 (1-5) | 3.4 ± 1.3 (1-5) |
| Urinary infections during the last 3 months | 3.4 ± 1.2 (2-5) | 3.1 ± 1.1 (2-5) | 3.2 ± 1.2 (2-5) | 3.2 ± 1.1 (2-5) |

solifenacin 10 mg daily for 3 months with poor results and all reported complaints about their continence status.

After 3 months treatment with solifenacin 10 mg, seven out of fifteen patients in Group A stopped treatment. The main complaint was the low efficacy of treatment and the poor continence status. They also reported minor adverse effects (dry mouth and constipation) and were excluded from the study.

In Group B, after 3 months treatment with mirabegron 50 mg, four out of fifteen patients stopped treatment and were excluded from the study. The main complaint was the low efficacy of treatment and the poor continence status. Tachycardia was the only side effect that was reported by one participant. The bladder diary characteristics of patients in Group A and B are shown in Tables 3 and 4 accordingly.

In Group C, after 3 months treatment with sublingually desmopressin 120 mcg/daily, four out of fifteen patients stopped treatment complaining about low efficacy of treatment and were excluded from the study. Its bladder diary characteristics are depicted in Table 5.

In Group D, a statistically significant improvement was estimated in the mean change from baseline to end-of-treatment in micturition episodes (3.5 ± 0.4 micturition/24h), in urgency episodes (2.3 ± 0.2)

TABLE 3. **Bladder diary characteristics with solifenacin 10 mg/daily**

| | **Group A before treatment** | **Group A after treatment** | **p value** |
|---|---|---|---|
| Median frequency/day | 10.6 ± 0.8 (9-13) | 10.1 ± 0.6 (9-13) | p > 0.05 |
| Median volume voided | 106 ± 10 (90-124) | 111 ± 15 (91-128) | p > 0.05 |
| Median urgency episodes/day | 3.8 ± 1.3 (2-6) | 3.1 ± 0.9 (2-6) | p > 0.05 |
| Median incontinence episodes/day | 1.6 ± 0.4 (1-3) | 1.6 ± 0.3 (1-3) | p > 0.05 |
| Median no of pads/day | 3.2 ± 1.1 (1-5) | 2.9 ± 1.1 (1-5) | p > 0.05 |
| Urinary infections during the last 3 months | 3.4 ± 1.2 (2-5) | 3.1 ± 1.0 (2-5) | p > 0.05 |

TABLE 4. **Bladder diary characteristics with mirabegron 50 mg/daily**

| | **Group B before treatment** | **Group B after treatment** | **p value** |
|---|---|---|---|
| Median frequency/day | 10.8 ± 0.9 (9-13) | 9.9 ± 0.6 (9-12) | p > 0.05 |
| Median volume voided | 102 ± 12 (86-119) | 119 ± 15 (96-149) | p > 0.05 |
| Median urgency episodes/day | 3.5 ± 1.4 (2-6) | 3.2 ± 0.9 (2-6) | p > 0.05 |
| Median incontinence episodes/day | 1.7 ± 0.3 (1-3) | 1.5 ± 0.3 (1-3) | p > 0.05 |
| Median no of pads/day | 3.1 ± 1.3 (1-5) | 2.7 ± 1.1 (1-4) | p > 0.05 |
| Urinary infections during the last 3 months | 3.1 ± 1.1 (2-5) | 2.1 ± 1.0 (1-4) | p > 0.05 |

TABLE 5. **Bladder diary characteristics with desmopressin 120 µg/daily**

| | **Group C before treatment** | **Group C after treatment** | **p value** |
|---|---|---|---|
| Median frequency/day | 10.3 ± 0.9 (9-13) | 9.1 ± 0.3 (8-11) | p > 0.05 |
| Median volume voided | 105 ± 9 (88-120) | 117 ± 18 (92-125) | p > 0.05 |
| Median urgency episodes/day | 3.5 ± 1.3 (2-6) | 3.2 ± 0.4 (2-5) | p > 0.05 |
| Median incontinence episodes/day | 1.5 ± 0.4 (1-3) | 1.4 ± 0.2 (1-3) | p > 0.05 |
| Median no of pads/day | 3.3 ± 1.2 (1-4) | 2.8 ± 1.2 (1-5) | p > 0.05 |
| Urinary infections during the last 3 months | 3.1 ± 1.3 (2-5) | 3.3 ± 0.9 (2-5) | p > 0.05 |

TABLE 6. **Bladder diary characteristics with mirabegron 50 mg/daily and desmopressin 120 µg/daily**

| | Group D before treatment | Group D after treatment | p value |
|---|---|---|---|
| Median frequency/day | 11.0 ± 0.9 (9-13) | 7.5 ± 0.3 (7-11) | p < 0.01 |
| Median volume voided | 104 ± 10 (89-118) | 189 ± 18 (148-229) | p < 0.01 |
| Median urgency episodes/day | 3.6 ± 1.1 (2-6) | 1.3 ± 0.4 (0-3) | p < 0.01 |
| Median incontinence episodes/day | 1.6 ± 0.4 (1-3) | 0.6 ± 0.1 (0-1) | p < 0.05 |
| Median no of pads/day | 3.4 ± 1.3 (1-5) | 2.2 ± 0.9 (1-4) | p < 0.05 |
| Urinary infections during the last 3 months | 3.2 ± 1.1 (2-5) | 1.1 ± 0.3 (0-2) | p < 0.01 |

and mean number of urinary incontinence (1.0 ± 0.2 episodes/24h). There was a statistically significant increase in mean volume voided per micturition (85 ± 14 mL) as well as a statistically significant reduction of urinary infections. In Group D, both drugs demonstrated good safety and tolerability and only two patients were excluded from the study because they stated that the management of NDO was modest and there was no full resolution of symptoms, Table 6.

## Discussion

The efficacy and safety of desmopressin on the treatment of OAB or NDO and associated problems has already been demonstrated in randomized, double-blind placebo controlled studies.[15-17] However, the efficacy of combined desmopressin and mirabegron administration in the treatment of NDO in patients with MS has not been elucidated. To our knowledge, this is one of the few studies evaluating the efficacy of combination of desmopressin and mirabegron for managing symptoms of NDO in a MS patient population.

NDO affects 50%-80% of patients with MS.[21] The incontinence is often the most bothersome effect of NDO since it leads to more immediately recognizable effects such as poor hygiene, skin breakdown and social isolation. Several studies have shown that urinary incontinence is considered to be one of the worst aspects of the disease, with 70% of a self selected group of patients with MS responding to a questionnaire as classifying the impact bladder symptoms had on their life as "high" or "moderate". The need for NDO treatment is urgent in these patients. First and foremost, the goal is to protect the upper tract from damage, secondly to maintain urinary continence, but all the while maintaining the patient's quality of life.[22] For patients with MS, urodynamic assessments provide the best means of understanding the phenomenon of NDO and its clinically manifested symptoms. Furthermore, in cases of progressive MS, serial urodynamic tests can help tract progressive or adaptive changes in neurologic function that affect urologic symptoms.

There are several oral and intravesical pharmacotherapeutic agents that have been evaluated to treat NDO and diminished bladder compliance in the neurogenic bladder. Oral anticholinergic medications for NDO have been a mainstay of medical therapy for decades in both adult and pediatric patients with MS[21] and their use is recommended for NDO by the UK consensus group for the treatment of MS patients.[23] Antimuscarinic agents for the bladder include oxybutynin (IR, ER, patch, topical gel, intravesical solution), tolterodine (IR, ER), trospium chloride (IR, ER), solifenacin,[24] darifenacin, and fesoteridine. Several studies have shown that adverse events (such as dry mouth and constipation) were significantly higher with anticholinergic drugs, are common and often lead to patient noncompliance.[25]

Few randomized clinical trials have evaluated the effectiveness and safety of desmopressin in patients with MS. There is a wide variation in the indications for application of desmopressin as an additional measure to well known medication in special situations: 1) in case of socially handicapping bladder dysfunction or in case of resistance to other drugs (anticholinergics), 2) when anticholinergic therapy is unfavorable because of significant adverse effects[26] and 3) to gain symptomatic control of nocturnal urine production rates.[27]

Hoverd 1998[16] and Fredrikson 1996[28] showed that the effect of desmopressin has been shown to be only on the voiding frequency and urine volume in the 6 hour period after use of the medication. No other measurements differed between the run in period, placebo treatment and active treatment. Moreover, Kinn et al[29] conducted a placebo controlled trial study using oral desmopressin and showed a reduction in

micturition frequency in the 6 hour period after active treatment. These three studies pointed out that in patients with multiple sclerosis, urinary frequency, urgency and urine production are reduced and voiding is lessened after the administration of desmopressin.

Few studies have referred to the importance of the route of desmopressin administration in MS patients with bladder dysfunction. Kinn and Larson[29] argued that disabled patients with motor dysfunctions confront difficulties with nasal administration. Fredriskon[28] quoted the possible treatment failures in nasal application due to ineffective spraying procedure and depleted nasal absorption. Furthermore, Thumfart et al[30] showed that when treating nocturnal enuresis with intranasal desmopressin formulations, the younger the patient, the higher the risk of the rare but potentially serious side effect of hyponatremia. Moreover, oral administration has the drawback of the slower action onset compared to intranasal application and the oral dose is more than 10 times the dose used for intranasal administration.

This study is one of the few in which the recommended initial dose of 120 mcg/daily of desmopressin was administered sublingually in order to achieve rapid absorption through a parenteral route, avoiding the aforementioned cons of other routes. By being absorbed sublingually, first–pass metabolism is avoided and a faster onset of action (20 minutes) is achieved. Most studies use desmopressin intranasal or in tablets. Importantly, Lottman et al[31] reported that dosages in the range of 120 mcg-360 mcg provided a duration of action of up to 10.2 hours, which is compatible with the average sleep duration of children and adolescents aged 6-18 years old.[32] The sublingual formulation, therefore, represents a better-tolerated alternative to intranasal formulations and a preferred alternative to the oral tablet.

The concern regarding desmopressin use is the development of hyponatremia. Valiquette et al[27] speculated that some patients with MS might have subtle hypothalamic defects in antidiuretic hormone control, making them particularly susceptible to hyponatremia. In the present study, the mean serum sodium concentration of the Groups C and D did not change after desmopressin treatment, suggesting that the development of hyponatremia may be an idiosyncratic response.

Mirabegron is a selective β3-adrenoceptor agonist; the β3 subtype has been identified in bladder smooth muscle tissue (detrusor muscle). In the human bladder, the β3-adrenoceptor subtype was identified to promote detrusor relaxation and urine storage. These observations suggest that drugs acting at β3-adrenoceptors may have therapeutic potential in MS that was confirmed in clinical trials in patients with OAB.[11]

In this study, the combination therapy aimed at decreasing the inconvenient consequences of NDO such as urge incontinence, urgency of urination and higher urinary frequency in patients with MS. Desmopressin was introduced to inhibit the urge to urinate during the night, permitting patients to sleep for intervals ranging from 4 to no more than 7 hours. Desmopressin and mirabegron are administered in MS patients, in a way that both exert physiological activity during an overlapping time period.

The combination therapy resulted in statistically significant improvement in the mean change from baseline to end-of-treatment in micturition episodes, in urgency episodes and mean number of urinary incontinence. There was a statistically significant increase in mean volume voided per micturition as well as a statistically significant reduction of urinary infections. Desirably, administration of desmopressin and mirabegron results in a synergistic effect. It is noteworthy that both drugs demonstrated good safety and tolerability and only two patients were excluded from the study because they stated that the management of NDO was modest and there was no full resolution of symptoms reduction of urinary infections. Obviously, the combined treatment of desmopressin and mirabegron, showed very interesting results in MS patients, suggesting a potential new methodological pattern for the management of NDO. □

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