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Antimuscarinics for neurogenic overactive bladder in multiple sclerosis: real-life data

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Abstract

Background: Antimuscarinics (AMs) represent the mainstay of treatment for storage lower urinary tract symptoms (LUTS) but few data are available on their impact in multiple sclerosis (MS) patients.

Objective: To assess effectiveness and tolerability of AMs in MS patients with neurogenic detrusor overactivity (NDO).

Methods: Sixty consecutive outpatients, who started treatment with AMs at one centre, were recruited. The primary endpoint was change in Patient's Perception of Intensity of Urgency Scale (PPIUS) at 6 months; secondary endpoints were post-void residual urine (PVR) and pads used daily. Incidence and severity of adverse events (AEs) were recorded.

Results: Significant reduction ($p < 0.001$) of mean PPIUS and pads use were detected, as well as a significant increase ($p < 0.001$) of PVR (143 $\pm$ 42 ml).

AEs, recorded in 53% of patients, were frequently multiple and caused suspension of AM in 10% of cases, mainly for xerostomia, which has been the commonest AE (26.6%). Neurological AEs appeared in 11.7% of subjects, mostly with oxybutynin. Worsening/onset of voiding LUTS, reported by 8.3% of MS, resulted to be the unique AE correlated to AM dosage.

Conclusion: This study suggests that AMs are effective in MS patients, but their use should be tailored on every patient as even low dosages can be poorly tolerated. AEs, including neurological ones, are common.

Keywords: antimuscarinics, lower urinary tract symptoms, multiple sclerosis, neurogenic detrusor overactivity, urgency urinary incontinence

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Introduction

Multiple sclerosis (MS) is a chronic inflammatory and neurodegenerative disease of the central nervous system, more often affecting young women.[1] Although its aetiology is not clear, autoimmunity, influenced by environmental and/or genetic factors, is known to play a major role in disease pathogenesis.[1–3] Patients may experience a wide range of symptoms during the course of the disease, including lower urinary tract symptoms (LUTS). LUTS have been reported in 75–100% patients affected by MS and over 40% of cases can be present at disease onset.[4] Most often LUTS result from the involvement of the spinal cord[5] and patients may suffer from storage phase LUTS – as urinary urgency, increased urinary frequency, and urgency incontinence, due to neurogenic detrusor overactivity (NDO) with or without detrusor sphincter dyssynergia– as well as voiding phase LUTS. LUTS in MS may be considered the worst symptom of the disease[6] and are associated with significant morbidity, which may result in harmful psychological and economic consequences, impairment of patients' Quality of Life (QoL), and severe complications requiring hospitalisation. Moreover, LUTS may change over time, paralleling the dynamic course of MS, as well as the response to treatment.[4,6]

The management of LUTS in MS patients focuses, primarily, on improving patients' symptoms and QoL while avoiding urological complications as urinary tract infections (UTIs), bladder stones and the infrequent renal impairment.[7] The first-line treatment of neurogenic storage LUTS includes antimuscarinics (AMs), which may reduce the frequency and intensity of NDO by blocking muscarinic receptors distributed throughout the detrusor and suburothelium, and the parasympathetic-mediated activation of the detrusor. The long-term efficacy and safety of AMs therapy for NDO is well documented (Level of Evidence 1a) and AMs are strongly recommended as the first-line medical treatment for NDO.[8]

Six AMs are currently marketed worldwide with small, but sometimes significant, individual differences in their efficacy and tolerability profiles.[9] AMs are not selective and can lead to systemic anticholinergic effects. Storage LUTS are commonly more difficult to treat and evaluate in MS than in other conditions. In fact, MS patients may need several symptomatic therapies, which can interact with AMs, making the treatment challenging for the risk of additive side-effects. Furthermore, disability can progress, LUTS can change over time and, finally, patients can be reluctant to take medications. AMs in MS patients have also been associated with a relatively high risk of urinary retention and current guidelines do not recommend AM in subjects with an increased post-void residual (PVR) and advise monitoring it when AM therapy is applied, with the combination of intermittent catheterisation if appropriate.[10–12]

As scarce evidence on the use of AMs to treat NDO in patients affected by MS has been published,[13] in this study, we aimed to assess the efficacy, tolerability and safety of AM agents in a group of MS patients with storage LUTS.

Materials and methods

A prospective uncontrolled study on a consecutive series of MS patients, who presented at one single centre in Italy over the course of one year and began a therapeutic regimen with AMs, has been carried out. Patients who had experienced a MS clinical relapse within 6 months before enrolment or who changed any MS-related disease modifying or symptomatic treatment were excluded. Patients received extensive counselling on behavioural modifications and were evaluated prior to the start of treatment and at 6 months of follow-up. All patients completed a 4-day bladder diary before the start of the treatment and at 6-month follow-up, the diary also incorporated the Patient's Perception of Intensity of Urgency Scale (PPIUS) – which describes the degree of urgency on a scale from 0 (no urgency) to 4 (urge-urinary incontinence).[14] All patients received urological and neurological evaluation at baseline and at 6 months of follow-up and could contact the physicians by e-mail for any query. Disability was assessed according to Expanded Disability Status Scale (EDSS).[15] Moreover, all patients received a post-void residual (PVR) evaluation by office ultrasound prior to starting the treatment and by ultrasound or self-catheterisation around 14 days after AMs start, to guarantee a possible adjustment of AM dosage or type or formulation. PVR was also re-assessed at 6 months of follow-up or before whenever deemed necessary. Patients with a PVR greater than 100 ml or more than 50% of the estimated bladder capacity, were advised to start a clean intermittent catheterisation regimen. UTIs were excluded in all patients at baseline and at each control, or patients were treated with antibiotics and then re-assessed after the resolution of the infection. Urinary tract anomalies, such as stones and hydroureteronephrosis, were excluded by ultrasonography performed at each control. Invasive urodynamics were not included in the routine diagnostic work-up, as they were used only in complicated cases, namely after the failure of first- line treatments or prior to surgical treatments, as suggested by guidelines.[11]

The primary endpoint was the change in PPIUS at 6 months; secondary endpoints at 6 months were the changes of PVR, voided volumes at the bladder diary and pads used daily. Also subjective assessment of the improvement of QoL (single question, Likert-type scale) was investigated at 6 months.

Treatment was regarded as effective if a resolution or amelioration of NDO-related symptoms was detected at PPIUS and reflected by a reduction or abolition of pads usage with increased voided volumes at bladder diary. Therapy with AMs would be considered as ineffective if no changes or a worsening of symptoms occurred during the therapeutic regimen.

Safety assessment included the incidence and severity of AEs over the study period.

Continuous variables were described by mean and standard deviation when normally distributed or by median and range, categorical variables were described by absolute frequencies and percentages. A paired *t*-test was utilised to assess differences among paired measurements, a p-value < 0.05 was deemed statistically significant.

Results

Baseline data

Sixty patients were recruited, 75% were women, with a median age of 53 ± 12 years. At baseline, the average duration of MS was 17.6 ± 8.8 years and mean EDSS score was 4.7 ± 1.5.

AMs were prescribed for storage LUTS (OAB-Dry) in 34 cases (56.7%) and for urge-urinary incontinence (OAB-Wet) in 26 (43.3%). The mean voided volume was 240 ml and the average PPIUS was 3.4 with an average use of 1.3 pads/day (range 0–6). The average PVR was 100 ± 32 ml (range 0–350 ml) with 24 patients (40%) who performed intermittent catheterisation at an average of 3.7/day (range 1–8).

Most patients (48, 80%) started with Oxybutynin (Ox) immediate release 2.5 mg twice daily (bid) (being the only AM historically reimbursed by the Italian National Healthcare System) and reached the mean dosage of 8.2 mg/day. Two patients (3%) used Ox extended release 10 mg, 4 (7%) trospium chloride extended release 60 mg/day, 3 (5%) solifenacin 5 mg/day, 2 (3%) propiverine 15 mg/day and 1 (2%) tolterodine 4 mg/day.

At any follow-up, kidney and bladder ultrasounds were normal in all cases and no change in EDSS score was observed.

Effectiveness

At 6 months of follow-up, 58 patients were evaluable (two stopped Ox immediate release for early intolerance to AMs). Frequency and urgency, as reported in the bladder diaries, resulted unchanged in 26.3% of cases, improved in 57.9% and solved in 15.8%. As first therapy, Ox immediate release resulted effective in 38 patients (79.2%) – 9 of them solved completely the LUTS – and ineffective in 10 (20.8%). The other AMs showed the following rate of effectiveness: trospium chloride extended release 60 mg 75%, solifenacin 5 mg 66.7%, Ox extended release 10 mg and propiverine 15 mg 50%, tolterodine extended release 4 mg 0% in 1 patient.

A significant reduction ($p < 0.001$) of the mean PPIUS and pads use by day and significant increase ($p < 0.001$) of PVR were observed, with one patient who had to start intermittent catheterisation (Figures 1–3). A mean increase of voided volumes of 120 ml (range 0–310) was also recorded. Improvement in QoL was reported by 57% of patients (Likert-type score 4–5 in the QoL assessment question).

At the end of follow-up, five types of outcomes were observed (Table 1): 14 (23.3%) continued the same AM at the same dosage; 12 (20%) adjusted the dosage of the same AM (6 increased the dose to obtain a better control of storage LUTS while 6 reduced the dose to control side effects); 23 (38.4%) changed AM; 6 (10%) suspended the therapy and 5 (8.3%) switched to invasive therapies.

Tolerability

A total of 39 AEs were observed in 32 cases (53%, Table 2): 23% of AEs were immediate (within 24 h), 64% at early assessment (within 1 week) and 13% delayed (within 1 month). Most AEs (36/39) regarded the most used AM in our series (Ox immediate release) and were multiple in six patients without any correlation with the dosage of Ox and the degree of disability according to EDSS. Two AEs were reported in two out of four patients treated with trospium chloride extended release 60 mg (one early constipation and one worsening of voiding LUTS) and in one out of three patients treated with solifenacin 5 mg (drowsiness).

Two patients stopped Ox immediate release 2.5 mg bid before the 6-month follow-up (at around 48 h from the start of the treatment), one for severe xerostomia plus blurred vision and one for mental confusion, dizziness and blurred vision.

Xerostomia regarded 26.6% of patients and was severe in 10%. It was the main cause of suspension of AM therapy. This AE was observed with Ox immediate release and also solifenacin in subsequent therapies.

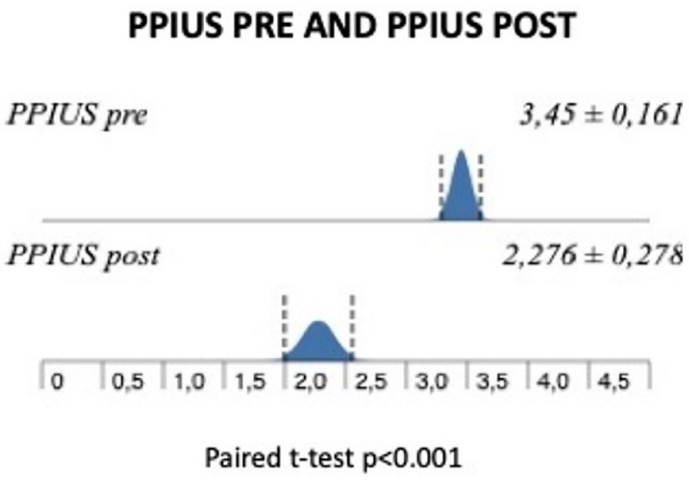

Figure 1. Patient's perception of intensity of urgency scale (PPIUS) changes at 6 months.

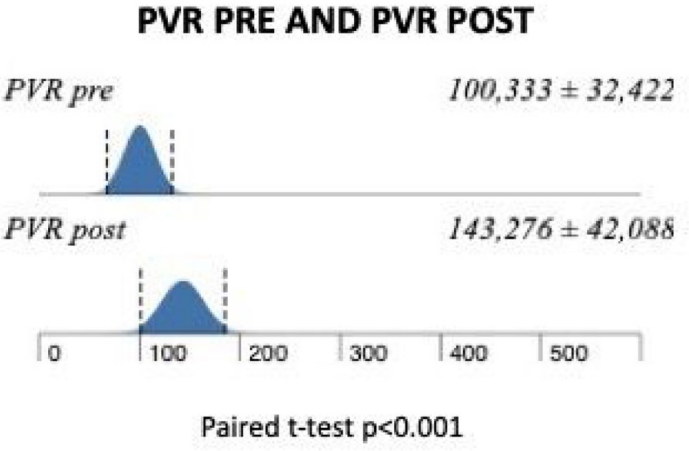

Figure 2. Post-void residual (PVR) changes at 6 months.

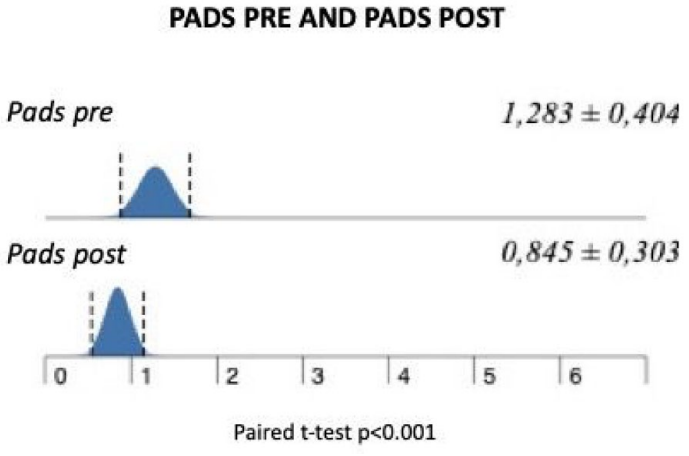

Figure 3. Pads use changes at 6 months.

Neurological AEs appeared in seven patients (11.7%), immediately in five of them. Except for drowsiness, also reported with solifenacin, the neurological AEs were observed exclusively with Ox in any formulation.

Worsening/onset of voiding LUTS were reported within 2 weeks by five patients (8.3%): four were treated with Ox immediate release 5 mg bid and one with trospium chloride extended release 60 mg. In three out of five cases appeared, PVR more than 100 ml and one patient had to start intermittent catheterisation. The reduction of the dosage of Ox to 2.5 mg bid solved the voiding LUTS in four out of five cases.

Constipation was reported by 8.3% of patients and observed only with Ox and trospium chloride extended release. Gastric pyrosis was uncommon (3.3%) and concerned only Ox in any formulation.

Discussion

Considering the few data available about AMs impact on LUTS due to MS, our longitudinal study provides valuable information on the topic, by virtue of repeated observations of a significant number of patients.

Published evidence on the role of AMs in MS is limited. In a meta-analysis by Madhuvrata *et al.*,[16] different dosages or formulations of AMs were evaluated for a short time (maximum follow-up of 6–8 weeks) in NDO due to different conditions; AMs, compared with placebo, were associated with better patient-reported cure/improvement of LUTS and amelioration of urodynamic parameters. The first prospective, open-label study to assess the effectiveness and effects on QoL of solifenacin 5 or 10 mg administered for 8 weeks to 30 MS patients was published by van Rey and Heesakkers[17] in 2011. The authors observed a significant improvement on storage LUTS and global improvement perception on LUTS in 73% of patients.

A 2013 review by Madersbacher *et al.* on efficacy, tolerability and safety of AMs, concluded that only Ox immediate release, propiverine and trospium chloride extended release have been extensively investigated in NDO and are effective with an acceptable profile. But such conclusions are not applicable to MS subjects due to lack of data.[18]

Table 1. Outcomes at 6 months of AM therapy.

Outcome	*n* (% patients)	Outcome reason		
		AM intolerance	AM inefficacy	AM refusal
Change of AMs	23 (38.4)	13/23	10/23	0/23
Continuation same AMs – same dosage	14 (23.3)	NA		
Continuation of same AMs–dose adjustment	12 (20.0)	NA		
Suspension of AMs treatment	6 (10)	5/6	0/6	1/6
Received intradetrusor onabotulinumtoxin A injections	5 (8.3)	0/5	5/5	0/5
Total	60	18/34	15/34	1/34

AM, antimuscarinic; NA, not applicable.

Table 2. Description of 39 adverse events observed in 32/60 patients with the first antimuscarinic therapy.

Adverse event	*n* (% of patients with adverse events)
Dry mouth	16 (26.6)[a]
Worsening/comparison voiding LUTS	5 (8.3)
Constipation	5 (8.3)
Blurred vision[b]	4 (6.6)
Dizziness[a]	3 (5.0)
Mental confusion[b]	2 (3.3)
Drowsiness	2 (3.3)
Gastric pyrosis[b]	2 (3.3)

LUTS, lower urinary tract symptoms.
[a]Severe presentation in six cases.
[b]Adverse event reported only with oxybutynin.

The Randomised Controlled Trial 'SONIC Urodynamic study' by Amarenco *et al.* was published in 2015, it included about 100 MS patients treated with solifenacin 5 or 10 mg or Ox immediate release 15 mg or placebo for 4 weeks. It showed an improvement of urodynamic parameters and QoL both with solifenacin 10 mg and with Ox immediate release 15 mg.[19]

In point of fact, the published data on the effectiveness and safety of AMs in MS provide limited evidence and often derive from small and short-term company-sponsored trials, or from studies focused on different causes of NDO with mixed groups of patients.[16–20]

The choice of treatment is not homogeneous in our cohort as 80% of the patients enrolled in our study were treated with Ox immediate release, being the only AM historically reimbursed by the Italian National Healthcare System not requiring to be purchased through patients' own means. While this is recognised as a possible limitation for the generalisability of our results in other healthcare systems, patients treated with other AMs were not excluded from our cohort aiming to present results evaluating the general effectiveness and safety of AMs as a class in MS. The outcomes have been evaluated through simple and objective parameters – bladder diaries, PPIUS, PVR evaluation and pads used by day – checked at follow-up. In our opinion, these parameters represent the gold standard in MS patients, in whom routine invasive examinations should be avoided, also allowing a better adherence to the follow-up programme.

PPIUS is a five-point scale which has been recommended for the assessment of the severity of urgency and urge urinary incontinence in clinical practice. It can be incorporated into bladder diaries allowing the recording of the degree of urgency experienced by the patients at each micturition or catheterisation. The observed mean decrease of PPIUS of more than one point is a simple indicator of the effectiveness of AMs in NDO, considering that urinary urgency is one of

its key symptoms. Besides, the PPIUS improvement can reflect fewer incontinence episodes, therefore fewer pads used and overall better QoL.

Our data demonstrate that storage LUTS improve significantly with AMs in 73.3% of cases, in agreement with another study,[17] with a moderate risk of urinary retention as demonstrated by the average increase of PVR. The primary endpoint of effectiveness – PPIUS – changed significantly at 6 months thanks to AM therapy, together with voided volumes and number of pads used.

These positive outcomes were in some case obtained by titrating different dosages or formulations or types of AMs in the context of a clinical approach. The peculiar condition of MS patients and the unpredictable response to AMs explain the common need of drug adjustments. It should also be emphasised that 15% of the responders to AMs did not report a simultaneous improvement in QoL, probably for an insufficient amelioration of bladder capacity or for the comparison of voiding LUTS.

The tolerability of AMs in MS patients was not adequately investigated in the literature: only dry mouth rates are reported to be significantly higher than placebo in NDO due to different conditions.[16] Amarenco *et al.*[19] reported that 3 out of 189 patients withdrew from the randomised study, but without an indication of the type of AE and if they were affected by MS. Moreover one patient was in treatment with Ox immediate release 15 mg and two were in the placebo group. van Rey and Heesakkers[17] reported that two out of 30 MS patients suspended solifenacin, one for gastrointestinal complaints and one for skin rash. There is above all a lack of long-term data about tolerability of AMS; a drop-out rate of 27% is reported only in one study with fesoterodine, in which the causes of drop-out are not indicated.[21]

In our experience, AEs were quite common, mainly moderate and sometimes simultaneous. A direct correlation between AE and the dosage of Ox immediate release was not found, to indicate that also low dosages can be poorly tolerated in MS patients. Worsening/comparison of voiding LUTS is the only AE correlated to the dosage of AM. It is known that these drugs present in MS patients a relatively high risk of urinary retention, as demonstrated by the mean increase of PVR detected, and current guidelines advise PVR monitoring when AM therapy is applied.[10–12] So it is appropriate to start AM therapies at low dosages with early checks of PVR to avoid or reduce the risk of urinary retention. We acknowledge that the increase of PVR could represent an improvement of storage LUTS in patients who already perform intermittent catheterisation, as the AMs solve urinary losses with an increase of bladder capacity. Contrarily, the occurrence of voiding LUTS and even of high PVR requiring intermittent catheterisation may cause a worsening of QoL in patients who were not used to the intermittent catheterisation manoeuvre.

In our case series, xerostomia is more common than reported in the literature[19] and has been the main cause of suspension of AMs, especially when associated with blurred vision, which never presented alone. Also neurological AEs are not unusual and occurred mainly with Ox in any formulation.[22] Constipation, due to the anticholinergic effect of AM that worsens the motility in the gastrointestinal system, is already prevalent in MS patients and is usually tolerated.

The rare and late onset of dyspepsia has been observed only with Ox and should be carefully investigated at every follow-up.

We found that the effectiveness of AMs on storage LUTS can mitigate the impact of AEs, making the treatment acceptable in most cases. Hence, AM therapy is advisable in storage LUTS due to MS but it is necessary to tailor the treatment and to regularly check the patients, as even low dosages can be poorly tolerated. When Ox is utilised, therapy should start with low doses of immediate release formulation such as Ox immediate release 2.5 bid, to ameliorate the tolerability. The dosage can, therefore, be modified to reach the best balance between efficacy and tolerability. AMs blood–brain barrier penetration should always be kept into account when treating MS patients, especially in consideration of the significant penetration shown by oxybutynin, solifenacin and tolterodine, which should warrant caution primarily in cases of elderly patients at risk for cognitive decline.[23,24]

AMs that do not cross the blood–brain barrier, as trospium chloride,[25] should be preferred in case of neurological AEs, a complete drug-class shift might also be considered in such cases, with regard to the beneficial neurological safety profile of beta 3-adrenoceptor agonists for storage LUTS in MS.[26]

Conclusion

MS is a complex and multifaceted neurological disease with a broad spectrum of symptoms including storage LUTS, which may change over time and whose treatment is challenging. Although AMs administration in MS is not supported by strong evidence, in our series, AMs resulted significantly effective in most cases thanks to a prudent titration and to a tailored therapy.

AEs, sometimes simultaneous, were not correlated to the dosage of AMs, except the comparison/worsening of voiding LUTS. Xerostomia is the commonest cause of suspension of AMs and neurological AEs are not unusual.

Efficacy, tolerability and LUTS evolution should be investigated periodically, preferably by the same physicians to reach a good compliance.

Finally, we underline the need of good-quality comparative and randomised controlled trials and, above all, real-life studies with an adequate follow-up exclusively focused on MS patients.

Declarations

Ethics approval and consent to participate

This study qualified as a service evaluation of the natural history of MS patients treated by a neuro-urology service without any deviation from standard clinical practice. Ethics committee approval was granted by 'CESC della Provincia di Venezia e IRCSS San Camillo' (reference 231A/CESC). Written informed consent for anonymised data collection for scientific purposes was obtained from each patient at first encounter. The study was conducted in accordance with the principles of the World Medical Association Declaration of Helsinki and national standards of Good Clinical Practice.

Consent for publication

Not applicable.

Author contributions

Elena Andretta: Conceptualisation; Investigation; Methodology; Writing – original draft.

Enrico Finazzi Agrò: Conceptualisation; Writing – review & editing.

Massimiliano Calabrese: Conceptualisation; Writing – review & editing.

Luca Orecchia: Conceptualisation; Writing – review & editing.

Antonietta Furlan: Conceptualisation; Writing – review & editing.

Cristina Zuliani: Conceptualisation; Investigation; Methodology; Writing – review & editing.

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Competing interests

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Availability of data and materials

The anonymised data that support the findings of this study are available upon reasonable request from the corresponding author.

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