Treatment of lower urinary tract symptoms in multiple sclerosis patients: Review of the literature and current guidelines

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This is a followup to the review entitled, "Evaluation of lower urinary tract symptoms in multiple sclerosis patients," published in the February 2017 issue of *CUAJ*.

Abstract

Multiple sclerosis (MS) is a unique neurological disease with a broad spectrum of clinical presentations that are time- and disease course-related. Lower urinary tract symptoms (LUTS) are highly prevalent in this patient population, with approximately 90% showing some degree of voiding dysfunction and/or incontinence 6–8 years after the initial MS diagnosis. Major therapeutic goals include quality of life improvement and the avoidance of urological complications

Owing to the wide divergence of clinical symptoms and disease course, evaluation and treatment differ between patients. Treatment must be customized for each patient based on disease phase, patient independence, manual dexterity, social support, and other medical- or MS-related issues. Ablative or irreversible therapies are indicated only when the disease course is stable. In most cases of "safe" bladder, behavioural treatment is considered first-line defense. Antimuscarinic drugs, alone or in combination with intermittent self-catheterization, are currently the mainstay of conservative treatment, and several other medications may help in specific disease conditions. Second-line treatment includes botulinum toxin A injection, neuromodulation, indwelling catheters, and surgery in well-selected cases.

Introduction

Multiple sclerosis (MS) is a unique neurological disease with a broad spectrum of clinical presentations that are time- and disease course-related. Due to the divergence of patients' symptoms, urologists must have a thorough knowledge of the MS disease process (as we have discussed in a prior article[1]) to correctly evaluate and manage MS-related lower urinary tract symptoms (LUTS). When making clinical decisions, adjustments should be accommodated according to patient mobility, disease phase, manual dexterity, social support, comorbidities, and MS-related urinary symptoms. MS-related LUTS treatment focuses on improving quality of life (QOL) by reducing incontinence and ameliorating storage symptoms and bladder emptying, while avoiding urological complication, such as urinary tract infections (UTIs), bladder and kidney stones, hydronephrosis, and renal function deterioration. Patients should be divided into high- or low-risk for renal function deterioration. Those with indwelling catheters and elevated detrusor storage pressure are at high risk. These factors elicit upper urinary tract (UUT) problems in up to 10% of patients, usually 6–8 years after urinary symptom manifestation.[2] Some authors suggest that the true incidence of UUT deterioration is as low as 0.34%.[3]

Behavioural/physical treatment

Patients with only mild disability and symptoms of overactive bladder (OAB) may benefit from pelvic floor muscle training (PFMT).[4] Such training is helpful only among patients with intact neural pathways to the pelvic floor, who are able to contract it. This kind of treatment is suspected to enhance the inhibitory effect of pelvic floor contraction on the detrusor muscle.[5] Several authors have demonstrated the positive influence of PFMT on disease course.[6-9] However, it is difficult to make general treatment recommendations based on these reports, as they only discuss low-volume, gender-specific methods of outcome assessment. For now, behavioural treatment is indicated only in a minority of patients with mild disability, OAB symptoms, and intact neural pathways to the pelvic floor. Further research is needed to evaluate the effectiveness of such interventions.

Emptying problems are harder to manage with conservative treatment. Timely voiding or double voiding will allow proper emptying without necessitating other interventions, but only in a small group of well-selected patients.[10]

Pharmacotherapy

Treatment of impaired storage

Antimuscarinic drugs, alone or sometimes in combination with intermittent catheterization (IC), are currently the first-line medical treatment in neurogenic LUTS (Level of evidence: 1A).[11-15] When giving anticholinergics without IC, post-void residual (PVR) volume must be monitored before and during the treatment period. Most data on the efficacy and adverse effects of these drugs derive from idiopathic detrusor overactivity (IDO) patients. Only a few trials have investigated neurogenic detrusor overactivity (NDO) patients, and data on MS cases are scarce.

In a meta-analysis by Nicholas et al, the authors could not advocate the use of anticholinergics in MS.[16] Ethans et al observed that tolterodine was effective in a group of 48 NDO patients, 10 of whom suffered from MS.[17] Tolterodine 2 mg twice daily was significantly superior to placebo in enhancing catheterization volume and reducing the number of incontinence events. Its efficacy was comparable to that of oxybutynin, with significantly improved side effect profile (dry mouth).

Recently, van Rey and Heesakkers described the beneficial impact of solifenacin on urinary urgency incontinence (UUI) events and symptomatic improvement in 30 MS patients.[18] UUI episodes/24 hours decreased from 1.3 to 0.2, number of pads per day dropped from 2.0 to 1.0, frequency/day diminished to 9.5 from 11.7, and micturition volume rose from 121.9 to 155.3 cc.

As in other NDO patients, Bennett et al demonstrated oxybutynin dose-escalation tolerability in a combined neurogenic population, including MS patients (22 out of 39).[19] High oxybutynin doses (up to 30 mg) engendered statistically significant decreases in the number of voids in 24 hours, nocturia, and incontinence episodes. Oxybutynin doses higher than 15 mg were requested by 74.4% of patients at the end of the study. No patient experienced serious adverse events and none dropped out during the 12-week course, although previous work has raised concerns about the cognitive effect of oxybutynin in populations with potential cognitive impairment.[20] Albeit anticholinergics administration in MS is not supported by strong evidence, they still remain the most prevalent first-line treatment for OAB symptoms. Oxybutynin, trospium, tolterodine, and propiverine are all well-established (Level of evidence: 1A),[13] efficient, long-term treatment options in NDO. Recent data from MS patients support the prescription of darifenacin and solifenacin with similar effectiveness and favourable adverse event profile.

Desmopressin is widely administered to address nocturnal polyuria in both men and women.[21,22] The data on MS patients are limited, not up-to-date, and not gender-specific. A meta-analysis revealed that 20 µg of desmopressin reduced nocturia episodes by 0.5–1.5 per night and increased uninterrupted sleep by an average of two hours.[23] Although β3 agonists were shown to be effective in OAB patients,[24] data on NDO and especially MS populations are scant. Ongoing studies are currently evaluating them alone and in combination with anticholinergics in these patients. Some promising results have come from cannabis-based extracts and phosphodiesterase inhibitors. Preliminary clinical trials have demonstrated favourable outcomes of these treatments on muscle spasticity[25] and storage symptoms.[26,27]

Treatment of voiding symptoms

Alpha-blockers are first-line pharmacological treatments (Level of evidence: 1B)[13] aimed at reducing bladder outlet resistance in NDO patients. Abrams et el evaluated tamsulosin efficacy in 263 patients with neurogenic lower urinary tract dysfunction secondary to supra-sacral spinal cord lesions.[28] Four-week, placebo-controlled treatment produced no statistically significant diminution of its primary endpoint — maximal urethral pressure. However, a one-year, open-label extension study disclosed increased mean voided volume (based on micturition diary) and improved QOL, as assessed by the International Prostate Symptom Score questionnaire (IPSS) and the severity of autonomic dysreflexia symptoms. Data of its use in MS patients are sparse, especially in women. However, many European consensuses[12,14,15] still recommend it for voiding symptoms, mainly in men with suspected contribution of benign prostatic obstruction.

Pharmacological treatment of failure to empty (detrusor sphincter dyssynergia [DSD] and/or detrusor underactivity [DU]) remains a significant problem with insufficient remedy. No major breakthroughs have occurred in the field in the last 20 years. In patients with adequate manual dexterity, the most reasonable approach, to decrease the rate and frequency of involuntary detrusor contractions, would include initiation of IC.[29,30] Unfortunately, no class of pharmacological agents can selectively relax the external urinary sphincter. Several drugs, including benzodiazepines, dantrolene, baclofen, and α-adrenergic antagonists, have been given to treat external sphincter dyssynergia (DESD).[31,32] Baclofen and diazepam exert their actions predominantly within the central nervous system (CNS), whereas dantrolene directly impacts skeletal muscles. Although these drugs are capable of providing variable relief of muscle spasticity, their efficacy is far from complete. Troublesome adverse events, especially muscle weakness and severe fatigue, mainly in younger patients, minimize their overall utility. Some promising results have arisen from cannabis-based extracts. Preliminary clinical trials have demonstrated the favourable effects of these treatments on muscle spasticity[25] and storage symptoms.[26]

Botulinum toxin (BT)

Intrasphincteric BT injection

Data on BT for the treatment of DESD are very limited. A systemic review found only a small number of articles with mixed patient populations, different injection methods, volume, and dosage.[33] Gallien et al failed to confirm the significant effectiveness of botulinum toxin A (BoNTA) 100 units over placebo via transperineal injections in the first trial conducted on MS patients.[34] The short, transient effect, with the need for repeated injections every 3–4 months, are all contributing to the limitation of BT in this situation.

Intradetrusor BT injections

Since its introduction in the treatment of spinal cord injury (SCI) patients,[35] data on BT in NDO cases are accumulating. Today, intradetrusor BoNTA injection is considered to be the most effective, minimally-invasive treatment to reduce NDO (Grade A recommendation).[13] Several multicentre, randomized, double-blind, placebo-controlled studies, all with very similar methodologies, have determined that BoNTA curbs the UUI rate, improves maximal cystometric capacity (MCC), and enhances urinary-related QOL.[36-39]

In a multicentre, double-blind study, 275 NDO patients (154 with MS) were randomized to placebo vs. intradetrusor BoNTA injection.[37] UUI events/week, QOL (measured by the Incontinence Quality of Life questionnaire), MCC, and maximum detrusor pressure at involuntary detrusor contraction (IDC) were all significantly improved.

Herschorn et al followed 57 NDO patients (19 with MS) randomized to placebo or BoNTA 200 or 300 units, in a prospective, double-blind, multicentre study.[38] Mean daily UUI, Health-related QOL questionnaire scores, and treatment satisfaction improved in comparison to placebo-treated patients, with no clinically relevant differences between BoNTA doses.

BoNTA injection duration was estimated to be 42 weeks,[37] which necessitated repeated injections. Tested in two small cohorts of MS patients,[40,41] repeated injections delivered around 56% improvement, with up to 76% complete continence. Both studies demonstrated a significant decline of patients returning for repeated injections without providing any explanation for this phenomenon.

Another common finding from the above studies,[37,38,40,41] was that the toxin's effect was dose-dependent, and dose-escalation from 200 to 300 units resulted in a higher degree of de novo need for IC without significant clinical improvement. These results standardized treatment to 200 units for NDO management.

In general, MS patients differed greatly from SCI patients, with the majority still preserving their ability to void.[37] Initiation of IC could have serious implications for patients' daily lives and should be addressed while offering this treatment to patients who are still urinating by themselves. In these cases, patients should be evaluated for their ability to perform self-catheterizations and informed about the risk of becoming temporarily IC-dependent. However, Gamé et al showed that IC initiation had no negative impact on QOL.[42] Mehnert et al tried to address the risk of de novo IC in a case study by reducing BoNTA injection dosage to 100 units.[43] They noted similar improvement in MCC and lowered maximal detrusor pressure, with about 33% reduction of de novo need for IC. Table 1 summarizes studies of de novo IC and BoNTA dose levels.

Second- and third-line non-pharmacological options

Neuromodulation

Neuromodulation is another option after conservative treatment failure.

Table 1. De novo IC and BoNTA injection dosage

	Number of patients	BoNTA dosage	IC-free pre-BoNTA	De novo IC	Indications for IC
Kalsi et al[40]	43 (MS only)	300 units (n=43)	13/43 (30%)	12/13 (92%)	Symptoms & PVR ≥100 cc
Khan et al[41]	137 (MS only)	300 units (n=137)	46/137 (34%)	41/43 (95%)	Symptoms & PVR ≥100 cc
Herschorn et al[38]	57 (19 MS)*	Placebo (n=8) 300 units (n=11)	Placebo 9/28 (32%) 300 units 9/27 (33%)	Placebo 2/9 (22%) 300 units 5/9 (56%)	N/A**
Cruz et al[37]	275 (154 MS)	Placebo (n=50) 200 units (n=53) 300 units (n=51)	Placebo 39/50 (78%) 200 units 39/53 (74%) 300 units 42/51 (82%)	Placebo 2/39 (5%) 200 units 16/39 (41%) 300 units 27/42 (64%)	Clinical judgment
Mehnert et al[43]	12 (MS only)	100 units (n=12)	12/12 (100%)	3/12 (25%)	Clinical judgment

*No specific data available for the MS subgroup; **not applicable. BoNTA: botulinum toxin A; IC: intermittent catheterization; MS: multiple sclerosis; PVR: post-void residual.

Sacral neuromodulation (SNM)

Ever since the U.S. Food and Drug Administration (FDA) approved SNM for refractory UUI in 1997, data on its efficacy in NDO patients have been accumulating.[44,45] In MS patients, neuromodulation manages storage problems and pelvic floor/sphincter overactivity. The data on MS patients are limited to case series, with mixed treatment indications. This lack of sufficient evidence has prevented its inclusion in expert panel consensus recommendations.

Marinkovic and Gillen determined that 12 of 14 patients were free of the need for IC after SNM,[46] while Minardi and Muzzonigro saw a trend towards decreasing number of catheterizations per day after SNM.[47] Given the fact that MS is a changing neurological condition, ongoing magnetic resonance imaging may be needed, but may limit the deployment of chronic metallic implants. Non-implantable neuromodulation would be preferable in such populations.

Transcutaneous posterior tibial nerve stimulation (PTNS)

PTNS has been shown to improve storage symptoms in two recent studies.[48,49] The patient population differed, to some extent, from the CNS study, as only 13% were on IC,[48] and DSD was an exclusion criterion.[49]

Intermittent catheterization

Self- or third-party IC is the preferred management strategy for NDO patients with related bladder-emptying dysfunction. In order to perform IC, patients must have enough manual dexterity to hold the catheter and expose the urethral meatus. Other pre-IC necessities are sufficient sight, cognition, and body position (a matter of equilibrium and general motor function). Many international consensuses advise on the utility of IC in MS,[4,11] but no strong evidence supports these recommendations, which include the use of 12–16 Fr catheters, 4–6 times per day, with bladder volume at catheterization limited to 400–500 cc.

Few European consensuses [4,14,15] have recommended IC initiation whenever PVR exceeds 100–150 cc. However, not all MS patients will benefit from a rigid PVR cutoff for initiation of IC (100–150 cc). IC should not be initiated hastily, as it is not complication-free. Clinical judgment is preferred on rigid cutoffs and should be based on patient age, gender, type and duration of MS, Extended Disability Status Scale (EDSS) scores, symptoms, and ability to perform IC. Other important information includes several PVR measurements, patient symptoms (recurrent UTIs, cystolithiasis, incontinence, etc), and risk of UUT deterioration and bladder capacity, as evaluated by urodynamic study (UDS) or voiding diary.

Indwelling urinary drainage

When IC-dependent patients cannot catheterize themselves or are unwilling to do so, indwelling catheters are an option.

Suprapubic catheters (SPCs) are preferred over urethral catheters (UCs) for permanent drainage.[50,51] SPCs avoid known UC complications, such as anterior urethral damage (iatrogenic hypospadias), urethral stricture, fistula formation, epididymitis, and scrotal abscess in men.[52] In women with SCI, UCs have been shown to cause urethral stricture or erosion in 37.2% of patients.[53] SPCs seem especially relevant in MS patients with impaired urethral or perineal sensation who are wheelchair-bound. They eliminate the risk of urethral injury or iatrogenic hypospadias from excessive tension/sitting on catheter tubing. However, SPCs and UCs have similar rates of UUT damage, vesicoureteral reflux, renal or bladder calculi, and symptomatic UTIs.[54]

Third-line treatment alternatives

Failure of conservative and second-line therapies to correct intractable storage symptoms is becoming less frequent in MS patients. Together with the relatively low risk of renal function deterioration, surgical management of bladder dysfunction has a limited role. However, some patients, especially those who are in a stable disease course with long life expectancy, may benefit from surgery. The options include bladder augmentation, as well as continent and non-continent urinary diversion. Although the literature on these techniques is extensive, it is unusual for MS patients to be singled out for separate results analysis.

Women with MS may suffer from stress urinary incontinence (SUI) just like neurologically intact women. Therefore, careful evaluation (including cystoscopy and urodynamic testing) is essential to exclude other possible MS-related findings (cystolithiasis, DU, DSD, recurrent UTIs, etc). Several PVR volume measurements should be obtained as well, and the risk of postoperative retention should be assessed. Only then, should a midurethral sling be offered to patients.

Summary of treatment and levels of evidence

In general, levels of evidence regarding treatment of LUTS in MS are limited. While some data on NDO patients may enable us to achieve Grade A recommendations (based on Level 1–2 evidence studies[55]), most of those concerning MS patients are derived from expert consensuses (Level of evidence: 5, Grade D recommendations). If not indicated otherwise in the text, recommendations are all Grade D.

Table 2 summarizes treatment options for different MS-related urinary symptoms.

Table 2. Treatment options for different MS-related urinary symptoms

		NDO	ND0 & DSD	NDO & DU	DU
First-line treatment	Behavioural/ physical*	PFMT	PFMT + biofeedback	Double-voiding	Double-voiding
	Pharmacological	Anticholinergics	Baclofen/α-blockers	Anticholinergics**	
Second-line treatment	Botulinum toxin injection	Intra-detrusor: refractory NDO and/or risk of UUT deterioration	Intra-sphincteric: refractory DSD and/or Symptomatic high PVR	For catheter bypass	
	Neuromodulation	Refractory NDO	Refractory NDO		
	CIC/indwelling catheters	Refractory NDO and/or risk of UUT deterioration	Refractory NDO/DSD and/or risk of UUT deterioration Symptomatic high PVR	Refractory NDO and/or risk of UUT deterioration Symptomatic high PVR	CIC/indwelling catheter
Third-line treatment	Other/ experimental	Bladder augmentation	Bladder augmentation	Bladder augmentation, diversion	Diversion

*Behavioural/physical treatment is intended as first-line option only in patients without risk factors for UUT deterioration; **in most cases combined with CIC. IC: intermittent catheterization; DSD: detrusor sphincter dyssynergia; DU: detrusor underactivity; NDO: neurogenic detrusor overactivity; PFMT: pelvic floor muscle training; PVR: post-void residual; UUT: upper urinary tract.

Conclusion

MS is a unique neurological disease with a broad spectrum of urological presentations. Urologists play a major role in the evaluation and treatment of these patients. Thorough knowledge of the disease process is needed to choose the right evaluation tool and the right management option for specific subjects. LUTS evaluation and management in MS patients is intended to identify those who are at risk for UUT deterioration and/or QOL impairment. Anticholinergics, with or without IC, are the mainstay of treating OAB symptoms. When conservative therapy fails to reduce the risk of UUT deterioration or improve patient symptoms because of limited efficacy or adverse events profile, second-line therapy is necessary. The introduction of BoNTA intravesical injection has revolutionized treatment in refractory cases. Further research in this specific population is needed to evaluate the real effects of anticholinergic agents, BT, and SNM.

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This paper has been peer-reviewed.

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