



# Secondary and tertiary treatments for multiple sclerosis patients with urinary symptoms

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Multiple sclerosis patients with refractory urinary symptoms after treatment with behavioral therapy and medications still have treatment options. Prior to starting treatments, baseline symptoms should be assessed and treatment goals thoroughly discussed. Catheterization, botulinum toxin, and reconstructive surgery all can play a role in improving both safety and quality of life for these patients. Newer modalities, such as neuromodulation, may also have an increasing role in the future as more data develop regarding efficacy. Risks need to be weighed against any perceived benefit and disease status before more aggressive therapy is initiated.

**Keywords:** Multiple sclerosis; Neurogenic urinary bladder; Urinary incontinence

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## INTRODUCTION

Multiple sclerosis (MS) is the most common neuro-inflammatory disease of the central nervous system. It is an auto-immune disease which targets the myelin sheath of neurons throughout the central nervous system and affects between 80–135 per 100,000 people, with a 2:1 females to male incidence ratio [1,2]. Like many autoimmune diseases, the exact cause of MS is unknown but is likely a mixture of genetic predisposition and poorly understood environmental risk factors [3]. MS can be subclassified as either clinically isolated syndrome, relapsing remitting, secondary progressive, or primary progressive disease (Fig. 1).

Urinary symptoms are highly prevalent among patients with MS and run the gamut from urinary incontinence to urinary retention, with sometimes both incontinence and retention occurring concomitantly [4]. According to data from the North American Research Committee on

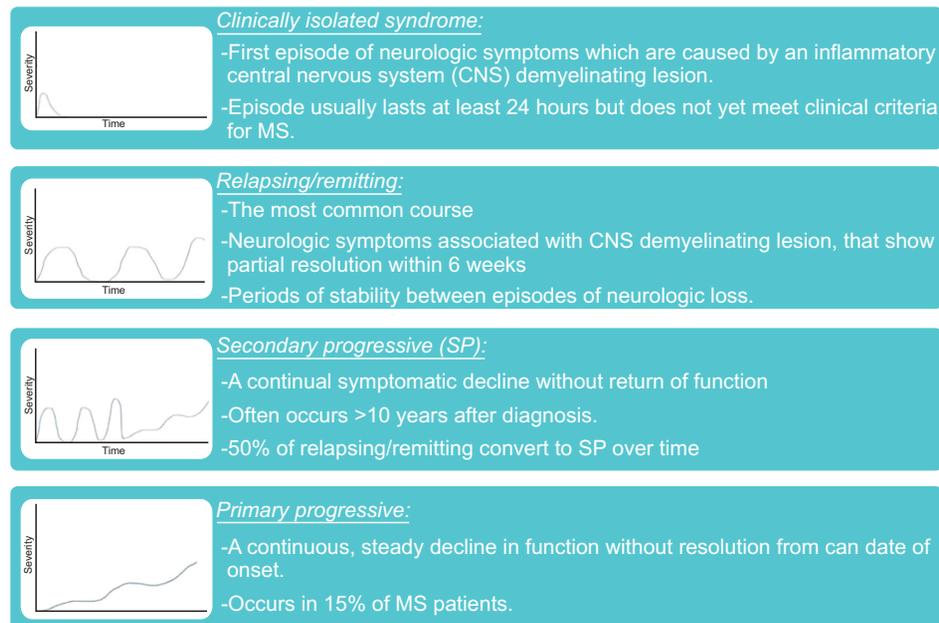
Multiple Sclerosis (NARCOMS) survey, 65% of patients reported at least one moderate to severe urologic symptom and 79% of the patients reported urge incontinence (UI) as a dominant symptom. However, only 32% of the responders had specifically seen a provider to treat urinary symptoms within the last year [5,6]. Magnetic resonance imaging (MRI) studies suggest that MS lesions in the corticospinal tract can be associated with urinary urgency/frequency, urinary hesitancy, and progressive lower urinary tract bother [7]. Cervical lesions are associated with findings of detrusor sphincter dyssynergia (DSD) [8]. Weak stream, urinary incontinence symptoms have also been associated with lesions in the cerebellum/pons [9].

As the disease progresses and becomes more debilitating, MS patients with urinary symptoms need to be reassessed. Frequently, conservative and pharmacological therapy become less effective over time in many of these patient due to physical, cognitive, and physiologic changes. Consequently,

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References 1, 15

Fig. 1. Multiple sclerosis (MS) subtypes.

urinary treatment strategies should be regularly changed to address the urinary safety and quality of life (QoL) issues for the MS patient. When conservative and pharmacologic treatment options have been exhausted, both patients and physicians need to understand the risks, benefits, and outcomes of secondary and tertiary treatments for MS related urinary symptoms.

## DIAGNOSTICS

Prior to initiating secondary or tertiary treatment, it is important to establish a symptom baseline so treatment goals can be clearly understood. This can be accomplished by using QoL questionnaires which can help differentiate between obstructive and irritative symptoms, offer objective longitudinal assessment of symptoms, and measure impact of treatments. Although there are numerous validated tools available to assess generalized urinary symptoms in neurogenic bladder patients [10], there are two validated questionnaires which are more specific to urinary symptoms in MS patients. The Actionable Bladder Symptom and Screening Tool is a good initial screening tool and helps primary care physicians identify MS patients with symptomatic UI who may benefit from initial treatment or referral to a urologist [11]. Similarly, the Neurogenic Bladder Symptom Score is a patient reported outcome measure that assesses impact of neurogenic detrusor overactivity [12]. This questionnaire is also useful for tracking and differentiating changing bladder symptoms over time. In addition to questionnaires, voiding diaries are helpful to both clinician

and patient in examining bladder capacities and how/when bladder symptoms impact daily life. These urologic measure measurements can be combined with an Extended Disability Symptom Score measurement to better appreciate relationship between urinary symptoms and impact of MS across multiple other domains [13].

Prior to starting secondary or tertiary treatments, urodynamic evaluation can likewise be helpful in understanding which bladder physiology to target for treatment. In the United Kingdom National Health System, consensus best practice guidelines for managing MS neurogenic bladder symptoms recommend deferring urodynamics until after first line therapies have been attempted [14]. However, there are no clinical guidelines in the United States which indicate the optimal timing for urodynamics in the MS patient. In our practice, we use urodynamics to help differentiate physiologies of urinary incontinence (primary neurogenic overactive bladder [OAB] versus overflow incontinence) and urinary obstruction (detrusor atony versus DSD) for our symptomatic MS patients. Additionally, urodynamics can identify MS patients with low bladder compliance (<12 cmH<sub>2</sub>O/mL) who present with progressive urinary symptoms or hydronephrosis. Fluoroscopy can also be a useful aid during urodynamics to visually identify DSD, bladder diverticulum, and vesicoureteral reflux [15].

Similar to urodynamic testing, there are no clear guidelines indicating when MS patients best benefit from upper tract imaging. However, upper tract involvement in MS patients is uncommon in the United States population [16] even in long-standing disease and severely disabled

patients. In contrast, other non-United States series suggest that length of time with disease may be associated with increased risk of upper tract changes, with most changes occurring after 6–8 years with the disease [17]. We evaluate upper tracts with imaging routinely in patients presenting for secondary/tertiary therapy.

## TREATMENT

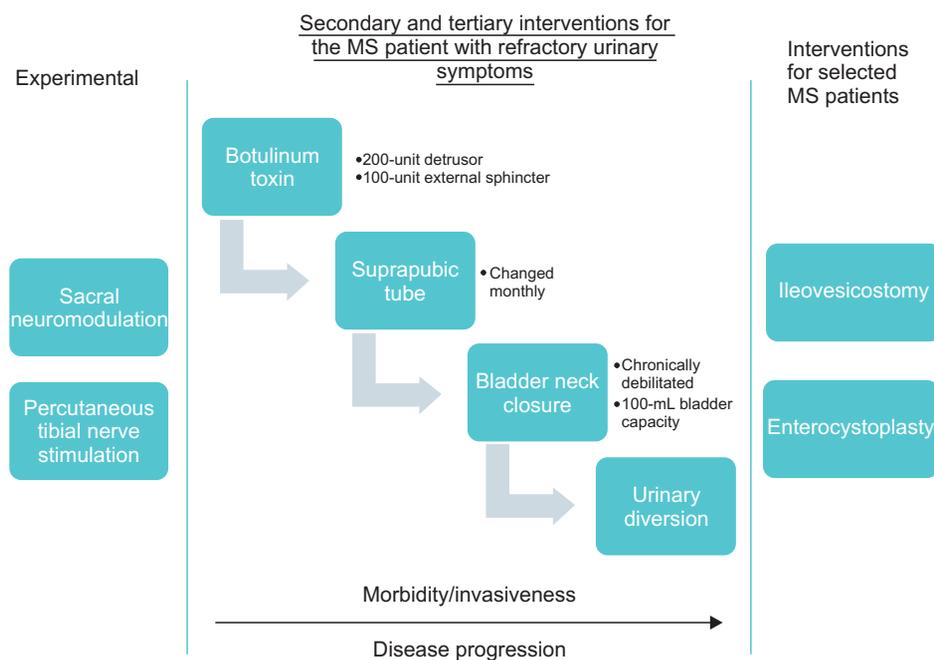
It is helpful to understand which primary/conservative therapies have been attempted before initiating secondary or tertiary treatments. First line therapy should include addressing modifiable factors which could be contributing to urinary symptoms. These interventions include decreasing fluid intake to less than 64 oz (as appropriate), reduction of caffeine and alcohol intake, and weight loss for BMI over 25. Physical therapy can be offered to improve pelvic floor function and facilitate urine storage and emptying. Additionally, voiding diaries can be used to start progressive timed voiding in which the patient increases the interval between voids by 15 minutes/week with target goal of voiding every three hours during the day. Physicians should also review which medications have been previously attempted to treat bladder symptoms. Common pharmacologic agents used to treat urinary symptoms include anticholinergics or beta 3 agonists for OAB, although there are few dedicated studies examining the efficacy of these medications in MS patients [18]. Desmopressin, in contrast, has some evidence supporting its

use for treating nocturia in MS patients, particularly those with high maximum bladder capacity [19]. Although alpha blockers can be considered for treating urinary retention in MS patients, data is extremely limited. The authors have had some anecdotal success using alpha blockers to treat symptomatic retention in MS men and concomitant BPH.

If patients continue to be symptomatic after attempting these initial therapies, secondary and then tertiary therapies should be considered. When treating MS patients with urinary symptoms, both patient safety and QoL should be correlated with risks and benefits of the intervention. Fig. 2 summarizes a common progression of secondary/tertiary treatments for MS patients with urinary symptoms, organized by invasiveness and risk: Botulinum toxin, catheterization/suprapubic tube, bladder neck closure, urinary diversion. The figure also notes experimental therapies (neuromodulation) which may have a future place in the treatment progression as data develops. Finally, the figure also summarizes selected surgical interventions for selected MS patients (enterocystoplasty, ileovesicostomy). Treatments are discussed below.

## CATHETERIZATION

Clean intermittent catheterization (CIC) has been a staple treatment for neurogenic bladder patients with urinary retention and incomplete emptying. In the NARCOMS survey of over 9,000 MS patients, 11%–15% of people reported currently using or past use of a catheter.



**Fig. 2.** Treatment algorithm for managing urinary symptoms for multiple sclerosis (MS) patients.

Of these patients, over 80% performed intermittent catheterization [20]. However, patients with MS can have poor manual dexterity from weakness, tremor, rigidity or spasticity, decreased visual acuity and cognitive impairment which can limit their ability to perform intermittent catheterization over time. Vahter et al. [21] followed 23 MS patients and found that while 83% successfully completed training, only 14 patients continued to catheterize for more than 3 months. Complication data regarding CIC and MS are limited, although the urinary tract infection is the most commonly reported morbidity associated with the technique [22,23].

If an indwelling catheter is needed, United Kingdom MS treatment guidelines suggest using a suprapubic tube rather than a urethral catheter for long term care [14]. QoL of MS patients with an indwelling catheter has not been thoroughly examined in the literature. James et al. [24] examined the QoL of 1,201 MS patients using catheters (intermittent catheterization, urethral catheter, suprapubic tube) and found that 25% respondents reported catheterization negatively impacting QoL, 52% reported a positive impact on QoL, and 19% reported neutral QoL. If a suprapubic tube is utilized, the tube should be changed monthly and patients monitored for chronic urinary tract infections. Urodynamics should be considered to monitor for loss of bladder compliance. Patients unable to perform intermittent catheterization over time can be bridged with a indwelling urethral catheter until neurologic symptoms return to baseline (relapsing-remitting) and they can resume intermittent catheterization. Indwelling catheter can also be used as temporary treatment until a suprapubic tube can be placed (primary or secondary progressive). If a urethral catheter is used over a long term, patients should understand risk of potential urethral injury [25].

## NEUROMODULATION

Neuromodulation is a secondary/tertiary intervention which can be used to treat refractory urinary incontinence and urinary retention. Although it is best studied in the neurologically intact population, there is a growing interest in studying the outcomes of neuromodulation for treating urinary symptoms in MS patients.

Peripheral tibial nerve stimulation (PTNS) is a minimally invasive technique in which the posterior tibial nerve is electrically stimulated via small gauge needle placed near the medial malleolus. Stimulation of this mixed sensory-motor nerve potentiates somatic afferent branches that pass through the L4–S3 spinal roots. These stimulated afferent

nerves then, in theory, inhibit the central reflex pathways which may cause uninhibited detrusor contractions. Individual prospective series studied PTNS in MS patients with lower urinary tract symptoms refractory to medical therapy [26]. Outcomes demonstrated a reduction in daytime frequency of voiding (9 voids to 6) and nocturia (3 voids to 1). An additional 21 patients study showed that when maintenance PTNS treatments extended for over a year in this cohort of MS patients decreased by 5.4 voids daily, UI decreased by 3.4 episodes daily, urgency episodes decreased by 7.4 episodes daily, nocturia decreased by 2.6 voids/night, and voided volume improved by a mean of 72.1 mL [27]. PTNS may be a promising therapy for MS patients since it has no metallic implant limiting MRI use, and transcutaneous patches have been recently developed which may lead to home based therapies. However, more studies with longer follow-up are needed to identify MS phenotypes which may best benefit from this modality.

Sacral nerve stimulation (SNS) (InterStim, Medtronic, Fridley, MN, USA). SNS is indicated for refractory OAB, nonobstructive urinary retention and fecal incontinence. Similar to PTNS, there are limited data examining outcomes of this treatment with progressive neurologic diseases like MS. Limited sample sizes have shown significant improvement in well selected MS patients [28]. However, the adoption of neuromodulation use has been limited in MS due concerns over the frequent need for body MRI in the MS patient. Because of this concern and unknown long term efficacy in the MS population, it may be prudent to limit sacral neuromodulation to MS patients with clinically isolated syndrome or stable relapsing-remitting disease. Secondary progressive patients may be a poor group for sacral neuromodulation since the patients experience significant functional and cognitive loss and have difficulty articulating symptoms and response to programmatic changes to the stimulation patterns.

Pundental nerve stimulation is an alternative method of neuromodulation in which the pundental nerve, rather than the S3 nerve root, is stimulated. In theory, this pattern of stimulation may improve afferent signaling and decrease proximal urethral sphincter tone, but there are no large series demonstrating efficacy in the MS population.

## ONABOTULINUM A

Treatment of refractory neurogenic UI with 200 units of onabotulinum toxin has been endorsed both the European Union and U.S. Food and Drug Administration. A substantial literature base supports the efficacy of

onabotulinum A for refractory UI in the MS population, including 2 large multicenter, randomized, double-blind, placebo-controlled phase III trials. In these trials, which consisted mostly of a mixed population of MS and spinal cord injury patients, the number of daily UI episodes were decreased by 21 episodes per week (200 unit dose) over a 6-week period. Furthermore, approximately 38% of the treatment patients became completely dry, compared to only 7.6% in the placebo group [29]. BOTOX was also associated with improved patient satisfaction with QoL [30], improved urodynamic bladder compliance, and decreased voiding pressures [29,31]. The mean duration of effect was 37–42 weeks in these studies.

However, MS patients treated with 200 units onabotulinum toxin were at risk for developing urinary retention and urinary tract infections in these randomized studies. The rate of urinary retention requiring initiation of CIC at the 200 U dose was between 30%–42% in those not catheterizing compared to 12% in placebo [29,32]. Urinary tract infections occurred at rate of 31%–35% in the treatment group compared to 16% in the placebo group [32]. The higher rate of UTI in the MS population is thought to be secondary to the higher rate of CIC required in these patients after treatment. Interestingly, one study suggests that up to 23% of MS patients fail to respond to BOTOX. Duration of time MS predicted lack of treatment efficacy in this cohort [33].

There are several small case series examining the efficacy of botulinum toxin injections for treating DSD in neurogenic bladder patients, but long term outcomes for this treatment is lacking. Onabotulinum toxin can be injected into the external sphincter via a cystoscopic or ultrasound guided transperineal approach. The sphincter is usually injected in 2–4 places at the between the 9 to 3 o'clock position across the dorsal aspect of the sphincter with 100 units [34]. There are limited data specifically detailing outcomes in MS patients, but small series suggest that the benefit can last from 2 to 13 months in a generalized neurogenic bladder population [35,36].

## SURGICAL TREATMENT OF URINARY SYMPTOMS IN MULTIPLE SCLEROSIS PATIENTS

Despite the effectiveness of interventions such as onabotulinum toxin treatments, a small number of MS patients eventually develop low capacity/poorly compliant bladders, renal failure, chronic urinary incontinence and/or recurrent urosepsis. The incidence of this urologic phenotype in MS

patients is poorly understood, although it is believed that most MS patients undergoing reconstructive surgery will have advanced, secondary progressive disease.

Bladder neck closure and suprapubic catheter has been reported as a lower risk surgical intervention for the refractory MS patient. The most common indications for this procedure were decubitus ulcers related to incontinence and urethral erosion related to an indwelling catheter [37,38]. Alternatively, an ileovesicostomy with a highly placed stoma can be used instead of a suprapubic tube for patients with poor suprapubic anatomy [25]. The reported complication rate for bladder neck closure ranges from 31%–100% in these series. In our practice, we use bladder neck closure with suprapubic catheter for MS patients who have significant disease related morbidity and do not have an expected long term survival. We have found that a bladder neck closure, particularly in female patients, has less morbidity and a shorter recovery than a continent or incontinent urinary diversion. The short term benefit of continence can outweigh the longer term risk of closure/indwelling catheter for these specific types of MS patients. More comparative studies are needed to determine which MS patients can best benefit from specific types of reconstructive urologic surgery.

Continent stomas and augmentation cystoplasty can be considered for MS patients with refractory urinary symptoms and stable hand function. Multiple surgical techniques have been published, including using ileum [39], ileocecal segments [40], and minimally invasive modalities [41]. There are few dedicated series examining the outcomes specifically in MS patients. The intervention should be used with great care in progressive MS patients due to a high probability of future loss of hand function. It has been the authors' experience that MS patients initially benefit from an enterocystoplasty procedure and are able to perform intermittent catheterization. However, as the disease advances, these patients are unable to independently perform intermittent catheterization and ultimately require an indwelling catheter. Left with undrained bladders, enterocystoplasty patients are at risk for urinary tract infections from urinary retention, increased urinary incontinence, and augment perforation.

Urinary diversion is more commonly utilized, compared to enterocystoplasty, to aggressively treat MS patients who have progression of urinary symptoms despite multiple previous secondary interventions. Urinary diversion has been demonstrated to decrease chronic UTI occurrence and preserve renal function in selected MS patients [42]. A large laparoscopic series showed that only 6.8% of the patients experienced a major complication over a 44-month follow-

up [43]. However, the benefit of this intervention needs to be weighed against the risk disease progression caused by the trauma of surgery.

## CONCLUSIONS

MS patients with refractory urinary symptoms after treatment behavioral therapy and medications still have treatment options. Secondary and tertiary therapies, such as catheterization, botulinum toxin, and reconstructive surgery all can play a role in improving both safety and QoL for these patients. Newer modalities, such as neuromodulation, may also have an increasing role in the future as more data develop. Risks need to be weighed against any perceived benefit before more aggressive therapy is initiated for secondary and tertiary interventions.

## CONFLICTS OF INTEREST

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