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First Line Therapy for Multiple Sclerosis Related Urinary Symptoms for the Non-Urologist: Behavioral Therapy and Oral Pharmacologic Treatment

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Abstract

Patients with multiple sclerosis are frequently bothered by urinary symptoms, including urinary urgency, incontinence and retention. Although referral to a urologic provider is frequently needed to treat these symptoms, the number visits can be reduced or even potentially avoided when treatment for urinary symptoms is initiated by the primary care team. First line therapy for urinary symptoms includes classifying urinary symptoms as a storage or emptying problem, measuring impact of the problem, reviewing behavioral therapy options, and discussing appropriate pharmacologic interventions.

INTRODUCTION

Urinary symptoms are highly prevalent in among multiple sclerosis (MS) patients. According to cross sectional questionnaire data from the North American Research Committee on Multiple Sclerosis (NARCOMS) survey, 65% of patient report at least one moderate to severe urologic symptom, 79% report any degree of urge incontinence (UI), while only 32% specifically see a provider to address these symptoms in the last year [1,2]. The perception of bladder symptom severity also impacts daily living among MS patients. Zecca et al., recently reported quality of life outcomes from 403 stable multiple sclerosis patients from Switzerland and Rome and found approximately 50% of the patients had at least 1 episode of incontinence per week and over 30% felt that urinary incontinence impacted everyday life and caused moderate to severe living problems [3]. This impact on quality of life may cause avoidance of activities which can then result social isolation and reduction in social support networks.

Bladder management is a crucial component in maintaining the health of MS patients. Jick et al., followed a MS cohort between 1993 and 2006 and reported that UTI was associated with a 4.1 adjusted HR (2.7-6.3) for all cause mortality for these patients [4]. The goals of managing MS related urinary symptoms focus on two principles: 1) maintain a safe urinary system which minimizes risk of urinary tract infection and provides protection of kidney function and 2) promote a stable urinary specific quality of life. As multiple sclerosis progresses, patients need to be reassessed for both urinary specific safety and quality of life issues and treatment strategies should be re-evaluated. Consequently, a plan of increasing intervention is usually employed address the evolving care needs for multiple sclerosis patients with urinary symptoms.

The focus of this article will be on office based behavioral and pharmacologic management strategies for symptomatic multiple sclerosis patients. There are considerable data examining efficacy of endoscopic botulinum toxin injections, minimally invasive procedures such as sacral neuromodulation and posterior tibial nerve stimulation, and reconstructive surgeries for treating refractory MS related urinary symptoms [5,6]. However, the majority of multiple sclerosis patients with urinary symptoms are not seen by urologists but by clinicians who need a conservative arsenal of treatment options to offer these patients as first line therapy. This review paper will discuss treatment options clinicians could potentially discuss and implement prior to referral to a urologist.

When to refer to a urologist

Over the past few years, team based care has become more prevalent for complex medical conditions with goal of reducing patient hospital visits, interventions, and hospitalizations. As a result, office based primary care providers of patients with MS (neurologists, physical medicine and rehabilitation physicians, etc.) are increasingly asked to address bladder dysfunction concomitantly when managing other manifestations of the disease. As more education regarding urological management of MS patient permeates these team care networks, the number of urological visits can be reduced for the MS patient. Figure (1) represents which types of treatments can be reasonable started by primary care teams (Figure 1). A good example is found in DeRidder et al., algorithm which recommends when neurologists should make a referral to a neuro-urologist based on consensus guidelines that is specific for different stages of Multiple sclerosis [7]. An additional example of a symptom based decision algorithm was published by Amarenco et al. [8].

Evaluation and classifying urinary symptoms

All clinicians should have a basic understanding of how to classify and measure urinary symptoms in MS patients. To begin, evaluation of the urological patient should include a detailed history regarding voiding habits. A 3 day voiding diary is extremely helpful in correlating the frequency of urinary symptoms with daily fluid intake and volume of urine. Panicker et al., noted that a good bladder diary should include daily fluid intake, frequency of urination, volume of urination, and documentation of episodes of incontinence and urinary urgency [9]. Physical exam should document neurological function, particularly regarding mobility and balance. Hand function and mobility is also particularly important to assess since it may impact choice of urological treatment. The genitourinary tract also should be examined if the patient is performing intermittent catheterization or has an indwelling catheter. Multiple sclerosis patients who use indwelling urethral catheters, particularly female, are at particular risk for urethral erosion and urethral fistula. Post void residual can be measured with via intermittent catheterization or a bladder ultrasound. Ghezzi recommends using a cut off value of post void residual >100 ml as abnormal [10], but the relationship between post void residual values and urinary symptoms has not been well defined in multiple sclerosis patients [5].

Additionally, multiple sclerosis patients should be initially evaluated for urinary tract infections as a source of urinary symptoms. Cox et al., screened 118 patients referred to a urology clinic for treatment of urinary symptoms and found that 31% met definition of chronic urinary tract infection, with equal distribution between relapsing/remitting and secondary progressive subtypes [11]. Urine analysis with a dipstick test is usually sufficient to identify a urinary tract infection. However, practitioners should keep in mind that urine analysis may be falsely positive in patients performing intermittent catheterization. Patients with an indwelling catheter should have urine tested via straight catheterization from a sterile catheter. Urine cannot be tested from a urine collection bag for these patients. Practitioners should follow established recommendations for identifying urinary tract infections for patients with indwelling catheters [12].

Urinary symptoms among MS patients are less frequently associated with chronic renal injury once chronic pyelonephritis is excluded. Fletcher et al., screened 173 people with multiple sclerosis who were referred to a urology clinic and found upper tract changes on ultrasound in on 6%. Over extended follow

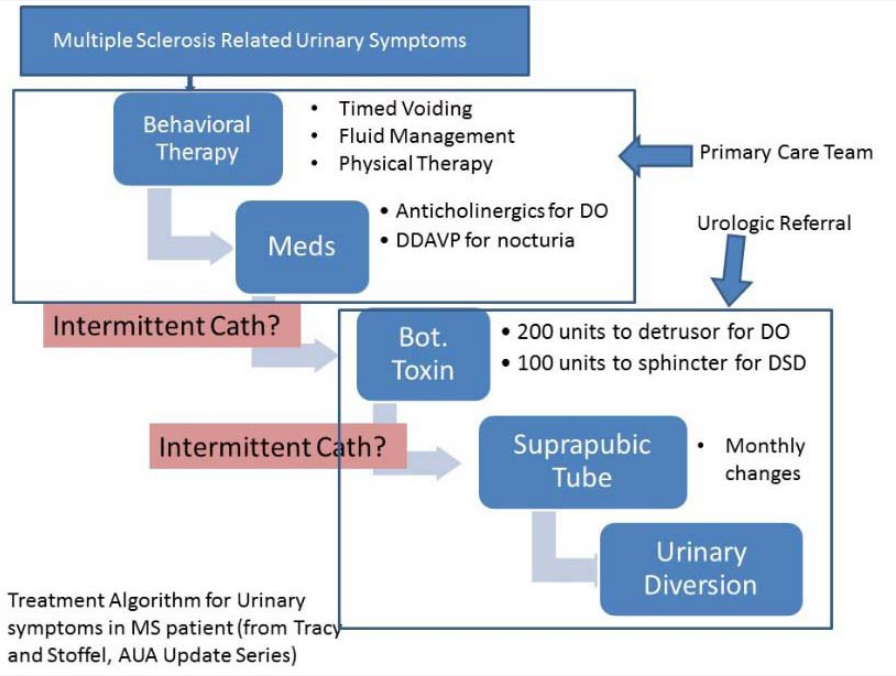

Figure 1 Treatment Algorithm for Urinary Symptoms in the MS Patient.

up, only 12% developed subsequent upper tract changes. Risk factors for renal injury were low bladder compliance and age over 49 [13].

Urological evaluation should next focus on identifying the type of voiding dysfunction: failure to store and failure to empty urine. Both types of symptoms can be present within the same patient. Validated questionnaires can help measure severity and impact of urinary symptoms. Tsang et al., performed a systematic review of neurogenic bladder validated questionnaires and identified 14 viable instruments available for examining multiple sclerosis patients [14]. MRI findings should be reviewed to help understand disease burden and location of lesion, although the lesion location inconsistently predicts urinary symptoms in multiple sclerosis patients. Figure (2) represents an aggregate summary of relationships between MRI findings and urinary symptoms [6].

However, some urinary symptoms can be difficult to differentiate even when using post void residual measurements and validated questionnaires. These patients can be referred for urological evaluation for urodynamic testing. By placing a small (7 french) pressure sensing catheter per urethra and instilling volume at a set rate, urologists can directly assess bladder capacity, bladder compliance (change in pressure/volume), bladder over activity, outlet obstruction, and urethral competency. The distribution of specific urodynamic findings among MS patients are well established in published literature. Detrusor over activity, with or without incontinence is the most common finding. Detrusor sphincter dyssynergia is found in approximately 25% of MS urodynamic studies. Urinary retention from underactive bladder is detected in approximately 20% of studies and elevated bladder pressures (low compliance) in less than 10% [11,15]. Stress incontinence is relatively uncommon among MS women. Dillon et al., reported only a 14% incidence of stress incontinence in a cohort of 280 women with a mean age of 50 years old [16]. In the authors' experience, urodynamics is most helpful in determining if urinary symptoms are related to bladder over activity, bladder outlet obstruction or underactive bladder.

Behavioral and pharmacologic strategies to treat urinary incontinence in multiple sclerosis patients

Once safety issues have been ruled out as a source of urinary symptoms, primary should start treatment of MS related urinary symptoms. As mentioned previously, multiple sclerosis patients can be greatly impacted by urinary incontinence. Tapia et al., performed a systematic review of the impact of urinary incontinence and concluded that patients with neurogenic detrusor overactivity have a lower health related quality and have greater economic impact from symptoms when compared to overactive bladder patients without a neurological disease [17]. Concern over urinary symptoms can subsequently cause MS patients to drink less fluid, which may cause additional health related co-morbidity. Cincotta et al., evaluated 50 people with MS and found a relationship between patients with low hydration status, bladder dysfunction, and elevated self reported fatigue scores [18]. Consequently, MS patients with urinary incontinence should be immediately started on a treatment pathway to help mitigate the impact of these symptoms on overall quality of life.

Behavioral therapy/physical therapy

Behavioral modifications should be included as part of first-line treatment for all multiple sclerosis patients with urinary incontinence. Practitioners can use a patient's voiding diary to make recommendations regarding fluid intake changes. Although there is no best practice regarding optimal fluid intake volumes for MS patients, we have found that recommendations of limiting intake to less than 64 oz/day is a reasonable goal, keeping in mind underlying hydration needs. The diary can also be used to start a progressive time voiding schedule in which the patient voids at a set interval during the day and increases the interval weekly.

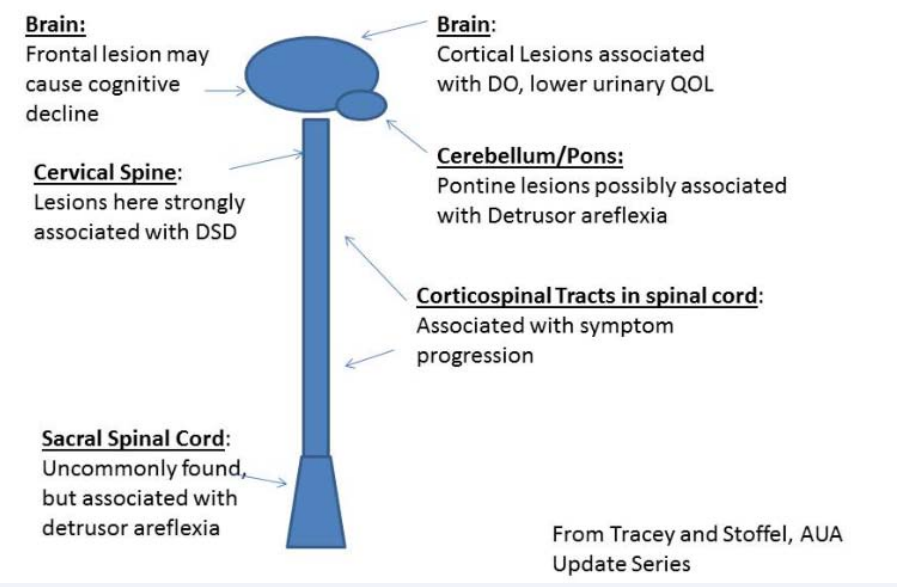

Figure 2 Relationships between location of MS lesions and urinary symptoms.

There are good randomized, placebo controlled trials demonstrating the pelvic floor therapy as effective treatment option for people with multiple sclerosis. Mc Clurg et al., randomized MS patients with urinary incontinence into two groups: 1) Pelvic Floor Muscle Training, Electromyography Biofeedback and Placebo Neuromuscular Electrical Stimulation, and 2) Pelvic Floor Muscle Training, Electromyography Biofeedback, and Active Neuromuscular Electrical Stimulation. The group found that both groups demonstrated a reduction in number of incontinence episodes over a 24 week follow up, but the active neuromuscular stimulation group had greater improvement (85% reduction in incontinence episodes versus 47% reduction, p = 0.001)(19). Incontinence episodes were reduced in Group 2 by 85% (p = 0.001) whereas in Group 1 a lesser reduction of 47% (p = 0.001). These results were confirmed by Lucio et al. In this study, 35 female MS patients were randomized into pelvic floor training and sham groups. After 12 weeks of therapy or sham, the pelvic floor train group demonstrated a 75% reduction in overactive bladder questionnaire scores compared to a no change in the sham group [20]. Some data exists that non-traditional therapies such as yoga [21] and electro-acupuncture [22] may also offer some improvement of urinary symptoms for selected multiple sclerosis patients.

Pharmacologic management

Anti-cholinergic medications reduce urinary urgency and urge incontinence by blocking muscarinic receptors expressed in the detrusor muscle. Though M2 receptors make up the majority of receptors in the bladder, M3 receptors more acutely regulate detrusor function and their blockade produces the therapeutic effect [23]. Side effects of muscarinic blockade include dry mouth, constipation, and cognitive impairment. Cruce et al., examined cognitive impairing among multiple sclerosis patients using anticholinergic medications and found that the patients had significantly lower symbol digit modality test and selective reminding test scores, compared to baseline [24]. Consequently, cognitive side effects, in particular, need to be considered prior to starting these medications for MS patients with prominent brain lesions. We have found that extended release anticholinergic medications are generally more tolerable in MS patients compared to immediate release medications. A post void residual prior to initiation of therapy can also be helpful in monitoring for incomplete bladder emptying and reducing the risk of exacerbating urinary retention when using these medications. If oral anticholinergic medications are effective in reducing lower urinary tract symptoms but cause intolerable side effects, a transdermal anticholinergic medication can be offered instead. Since the transdermal delivery system bypasses hepatic activation of the anticholinergic compound, there may be fewer anticholinergic side effects such as dry mouth or constipation [25].

With the exception of small case series [26] there are little data specifically examining the use of anticholinergic medications for treating multiple sclerosis neurogenic bladder overactivity. However, a meta-analysis demonstrated that anticholinegic treatment was generally effective across multiple types of neurogenic bladder etiologies. Madhuvrata et al., examined 960 patients from 16 randomized controlled trials and found anticholinergic treatment resulted in significantly higher patient-reported cure/ improvement of overactive bladder symptoms (risk ratio: 2.80) and a higher maximum cystometric capacity (weighted mean difference: 50cc) when compared with placebo. The meta-analysis did not find any differences in outcomes between oxybutynin and other antocholinergic medications [27].

β_3-adrenergic receptor agonist

Mirabegron facilitates detrusor relaxation through stimulating adrenergic receptors in the detrusor and urothelium [28]. There are no data demonstrating efficacy in multiple sclerosis treating neurogenic overactive bladder. However, pooled data from 3 randomized, placebo-controlled, double blind trials demonstrate that mirabegron is effective in decreasing frequency of incontinence episodes for idiopathic overactive bladder patients. This study utilized a dose of 50 mg and showed a significant reduction of number of voids/24 hours compared to placebo, but did not show changes in volume per void [29]. These findings have lead some physicians to advocate for mirabegron use in patients adversely affected by anticholinergic side effects. It should be noted that safety studies have also demonstrated that mirabegron is associated with minor rises in systolic blood pressure and heart rate [30].

Desmopressin: Nocturia can significantly impact of quality of life among MS patients. It has been shown to produce "disruptions and loss" in MS patients, meaning daily activities were disturbed resulting in lost experiences [31]. Desmopressin is a synthetic analogue of anti-diuretic hormone that decreases frequency or nocturia by stimulating increased water reabsorption by the collecting tubules. It has an effective treatment length of up to 6 hours. There are significant data supporting efficacy among MS patients with symptomatic nocturia. In these studies, MS patients experienced a decrease in nocturia by a mean 0.5 – 1.5 episodes/ night and an increase of sleep by a mean of 2 hours [32,33]. A high bladder capacity at baseline may predict better outcomes for desmopressin in MS patients [34]. This medication should be prescribed with caution in elderly patients or when patients have dependent leg edema that mobilizes at night due to the risk of hyponatremia and exacerbation of congested heart failure. Patients should be made aware of these risks and instructed to limit fluid intake at night and not use this medication more than once in a 24h period. Prescribers should check sodium levels within a week of starting this medication and then periodically on their patients using desmopressin.

Cannabinoids: Late last century, government officials in the United Kingdom proposed exploration into the medicinal properties of cannabis for multiple sclerosis patients since the illegal use of cannabis had become commonplace by patients with this condition. Two large placebo controlled trials were undertaken. Wade et al., prospectively studied 160 MS patients in a double blinded, randomized placebo controlled trial that examined the efficacy of whole plant cannabis medicinal extracts in mitigating multiple different MS symptoms, including bladder dysfunction. The data did not demonstrate significant bladder symptom improvement in either questionnaire based assessment of symptoms or visual analog reporting of improvement [35]. The second trial was the Cannabis in Multiple Sclerosis (CAMS) trial. This multicenter, placebo-controlled trial assessed the effect of

oral cannabis extract and delta (9)-tetrahydrocannabinol (THC) on patients with MS with various symptoms, including bladder dysfunction. In contrast to Wade et al., a subset analysis of the CAMS study showed that urge incontinence episodes decreased in patients taking cannabis extract and THC, compared to placebo (38% vs 33% vs 18%, p <0.001) [36]. In the United States, the American Academy of Neurology released a report of guideline development which examined the efficacy and safety of medical marijuana in selected neurological disorders. The findings of this report concluded that smoked THC and oral cannabinoids were likely ineffective in reducing MS related bladder overactivity [37]. Oral extracts of cannabis are not currently approved for treatment of multiple sclerosis LUTS in the United States.

Behavioral/pharmacologic strategies to treat urinary retention for multiple sclerosis patients

MS patients can develop urinary retention or incomplete emptying from either obstructing detrusor sphincter dyssynergia or an underactive bladder. There is no widely accepted "abnormal" post void residual value for multiple sclerosis patients. The UK consensus statement on management of bladder in multiple sclerosis defined a post void residual greater than 100 ml [38], but there are no data linking volumes above this to increased risk of bladder symptoms or urinary tract infections. We recommend treating an elevated post void residual only in the setting of bothersome urinary symptoms, chronic urinary tract infections, or renal dysfunction. Patients with upper tract changes on renal imaging and/or chronic urinary tract infections should be referred for formal urological evaluation.

Strategies to facilitate bladder emptying in MS patients include self stimulation to induce voiding (Crede voiding), alpha blocker medical therapy, and intermittent catheterization.

Crede/Vibration/Triggered reflex: Some MS patients with urinary retention and urinary symptoms seek to empty the bladder through abdominal straining (Valsalva) or the Crede' maneuver (direct suprapubic abdominal pressure applied by hand or for arm). There are few studies examining safety and efficacy of this voiding technique in the MS population. Prasad et al performed a randomized trial which examined whether a hand held vibratory device would improve emptying in MS patients with PVR > 100ml. The study showed that the combination of abdominal pressure and vibratory device decreased PVR from a 231ml baseline to 126 ml (p = 0.002) [39]. However, we believe that Valsalva voiding or using Credé maneuvers should be discouraged unless the patient is proven with a urodynamic study not to have detrusor sphincter dyssynergia causing bladder outlet obstruction. Data suggest that these maneuvers in the setting of DSD among spinal cord patients can lead to progressive bladder scarring, urinary tract infections, and potentially renal failure with long-term use [40]. De Seze et al., have also reported that MS patients with DSD are at greater risk for potential upper tract changes, although voiding mechanism was not reported in the analysis [41].

Alpha blockers: There is little information regarding pharmacologic treatment of MS related urinary retention. O' Riordan noted a 41% improvement in flow rate and a 26% reduction of post void volume in a limited series of MS patients treated with an alpha blocker for 4 weeks [42]. Stankovich noted a 54% decrease in IPSS scores for 28 MS patients (20 female) with DSD who were treated with tamsulosin 0.4mg for 2 months [43]. Additional studies of mixed DSD pathologies, including MS, also found tamsulosin to be effective in treating obstructive symptoms [44] but longer term, randomized studies are not available. At this time, we recommend that alpha blocker usage in MS patients should be limited to men with concomitant obstructive symptoms from BPH.

Catheterization: Clean Intermittent Catheterization (CIC) has been a staple treatment for patients with neurogenic bladder induced urinary retention and incomplete emptying. Some practitioners and patients have concerns that cognitive or physical limitations make this treatment option not viable for MS patients. However, Vahter et al., demonstrated that 20/23 (87%) of MS patients were able to learn intermittent catheterization after direct instruction. This was independent of function or cognitive status [45]. An additional study showed that MS patients performing CIC do not universally report a negative quality of life [46]. In some cases of progressive disease or rapid debilitation, an indwelling catheter may be needed to facilitate bladder emptying. Patients unable to perform intermittent catheterization can be bridged with a urethral Foley until neurologic symptoms return to baseline (relapsing-remitting) or until a suprapubic tube can be placed (primary or secondary progressive). The UK MS treatment guidelines suggest a suprapubic tube rather than a urethral catheter will limit catheter related complications [38]. The tube should be changed monthly and patients monitored for chronic urinary tract infections. Patients with a suprapubic tube should have bladder physiology studied yearly to identify loss of compliance. When reasonable alternative strategies exist, we strongly discourage long term urethral catheter usage for MS patients due to risk of progressive urethral damage.

CONCLUSION

There are many conservative and pharmacologic treatment options for the primary care team to discuss with MS patients regarding bothersome urinary symptoms. Primary care teams should first identify whether symptoms are related to urine storage or emptying and then follow symptoms over time. Patients with refractory urinary symptoms or safety concerns such as progressive urinary tract infections or renal dysfunction should be referred for urological evaluation and discussion of more invasive treatment options.

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