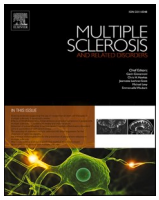
Multiple Sclerosis and Related Disorders 91 (2024) 105884

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard



Review article

Algorithms for the first-line management of bladder, bowel and sexual dysfunction in multiple sclerosis: Present and future

Vito Tota [a,b,*], Giovanni Briganti [c], Laurence Ris [b]

[a] HELORA Hospital Network, Mons, Belgium
[b] Department of Neuroscience, Research Institute for Health Science and Technology, Université de Mons, Belgium
[c] Department of Computational Medicine and Neuropsychiatry, Faculty of Medicine, Université de Mons, Belgium

ARTICLE INFO

Keywords:
Algorithms
Multiple sclerosis
Neurogenic lower urinary tract dysfunction
Neurogenic bowel disorders
Sexual dysfunction

ABSTRACT

Introduction: Neurogenic lower urinary tract (NLUTD), bowel (NBD), and sexual dysfunction (SD) are commonly observed in patients with (pw) multiple sclerosis (MS) and diminish the patients' quality of life (QoL). This systematic review aim to evaluate and discuss the current algorithms for the management of these issues.
Methods: A systematic review was conducted on the PubMed in June 2024. The primary search criterion was the presence of the term 'algorithm/s' or 'management/ing' in the title and/or abstract, followed by the MeSH term 'multiple sclerosis' and a combination of free-text keywords referring to NLUTD, NBD or SD.
Results: Fifteen articles regarding NLUTD were considered eligible, only one regarding SD while none addressed NBD.
Discussion: Numerous studies emphasize the profound impact of urinary and bowel symptoms on the QoL and morbidity in pwMS. Few algorithms addressing NLUTD are designed for first-line physicians and addresses the key priorities in MS care. Specific approaches to NBD management in pwMS are lacking. Screening for SD requires a structured assessment to deliver appropriate solutions.
Conclusion: NLUTD, NBD, and SD are underdiagnosed and undertreated. The implementation of straightforward algorithms for first-line physicians could enhance the management of these common issues, improve the QoL, reduce costs, and ensure appropriate referral to specialists.

1. Introduction

Multiple sclerosis (MS) is one of the most common causes of non-traumatic disability among young adults (Thompson et al., 2018). Neurogenic lower urinary tract dysfunction (NLUTD), bowel dysfunction (NBD), and sexual dysfunction (SD) are commonly observed in patients with MS (pwMS), representing a substantial burden of the disease.

NLUTD typically appears approximately 6 years after MS onset, with nearly all patients experiencing bladder symptoms within 10 years (Panicker et al., 2015). While there is a direct correlation among NLUTD, disease duration, and neurological disability (evaluated with the Expanded Disability Status Scale - EDSS) (Wang et al., 2016; Seddone et al., 2021), in certain cases some symptoms may already be present at the time of diagnosis. The most common clinical presentation is overactive bladder (OAB), characterized by urgency, urinary frequency, nocturia and/or urge incontinence. Voiding dysfunction (VD) is also frequently reported, independently or in association with OAB (Abrams et al., 2002). These symptoms significantly diminish the patient's quality of life (QoL) (Khalaf et al., 2016; Ziadeh et al., 2022) and have a profound impact on their social interactions (Browne et al., 2015). Persistent and untreated NLUTD can lead to complications such as hydronephrosis, vesico-ureteral reflux, recurrent urinary tract infections (UTI), kidney stones, and ultimately renal failure (Castel-Lacanal et al., 2015). Neurological symptoms can deteriorate rapidly during infections and fever, making it challenging to differentiate between an acute worsening due to MS relapse or a rise in body temperature. Moreover, exacerbations associated with systemic infections seem to lead to more sustained neurological worsening compared to those occurring in other contexts (Buljevac et al., 2002). Although NLUTD frequency in pwMS, the risk of developing upper urinary tract damage (UUTD) is generally lower compared to individuals with spinal cord injury or spina bifida (Musco et al., 2018; Lawrenson et al., 2001).

* Corresponding author.
E-mail address: vito.tota@helora.be (V. Tota).

https://doi.org/10.1016/j.msard.2024.105884
Received 30 April 2024; Received in revised form 14 August 2024; Accepted 8 September 2024
Available online 14 September 2024

Between 39 % and 73 % of pwMS suffer from either constipation, fecal incontinence, or both, depending on the population studied (Preziosi et al., 2018). The presence of bowel disturbances appears to be correlated with the severity and duration of the disease (Munteis et al., 2006). Hemorrhoids, abdominal pain, fecal impaction, rectal bleeding, rectal prolapse, anal fissure, abdominal bloating, nausea, and prolonged evacuation, can complicate NBD and further lower the QoL of pwMS. Some patients need to plan their outings in advance, search for restroom locations as soon as they are away from home, and use protective measures daily, both during the day and at night. All of this leads to stress and avoidance behavior, resulting in social withdrawal among patients who are already emotionally fragile due to the disease and its impact on their mobility, vision, and cognition (Norton and Chelvanayagam, 2010).

It has been estimated that 50–90 % of men and 40–80 % of women will experience some form of SD related to MS in their life (Kessler et al., 2009). It can develop at various stages of the disease, starting at an early stage (Donzé and Hautecoeur, 2009; Tzortzis et al., 2008), with growing prevalence during the following disease course (Darija et al., 2015). The etiology of SD in MS is still a matter of discussion. It is suggested that factors such as advancing physical disability, psychological elements, and potential side effects of medications contribute to the prevalence of SD (Bronner et al., 2010) in pwMS. Despite its frequency, it does not appear to be the primary issue affecting the QoL of pwMS compared to bowel and bladder dysfunction (15.8 % versus 60.4 %) (Khan et al., 2006), likely because patients with progressive or relapsing forms of MS have different priority concerns (Barin et al., 2018). SD seems to have a more significant impact on mental health aspects than severity of physical disability (Schairer et al., 2014).

While the majority of studies addressing sphincter and sexual dysfunction in pwMS may be daunting for physicians who lack experience in managing these conditions, algorithms can simplify the pathway to address these common issues by condensing them into straightforward visual decision trees. This review aims to evaluate current algorithms for diagnosing and managing bladder, bowel, and sexual dysfunction in pwMS and to discuss priorities for future first-line management algorithms.

2. Methods

A systematic review was conducted using the PubMed database with the list of keywords provided in the Appendix, last updated in June 2024. The primary search criterion was the presence of the term 'algorithm/s' or 'management/ing' in the title and/or abstract, followed by the MeSH term 'multiple sclerosis' and a combination of free-text keywords referring to NLUTD, NBD or SD. The retrieved articles were first evaluated based on their titles and abstracts, and those selected underwent further analysis of their content. Only articles in English proposing an algorithm were considered eligible for inclusion in this analysis.

3. Results

Five hundred seventeen articles were initially retrieved, of which 41 were not in English and one was a duplicate. Four hundred seventy-five articles were screened based on their title or abstract, with 384 deemed irrelevant for the analysis. Additionally, 2 articles were excluded because only the abstract was available. Hence, 89 articles were assessed for eligibility. Sixteen articles met the eligibility criteria for analysis, with 15 addressing NLUTD and 1 focusing on SD in MS (Fig. 1). Unfortunately, none of the retrieved articles for NBD met the eligibility criteria for this review.

The different algorithms designed for the diagnosis of NLUTD (Barbalias et al., 2001; De Sèze et al., 2007; Fowler et al., 2009; Di Benedetto et al., 2008; Stoffel, 2010; Ghezzi and Carone, 2011; Yang, 2013; Amarenco et al., 2013; De Ridder et al., 2013; Çetinel et al., 2013; Ghezzi et al., 2016; Phé et al., 2016; Castel-Lacanal et al., 2017; Tornic and Panicker, 2018; Domurath et al., 2020) are summarized and compared in Tables 1 and 2, and are discussed below. The majority of the algorithms rely on medical history (including the number of infections within a specific time frame) and clinical examination to assess patient symptoms, often incorporating questionnaires. Most algorithms prioritize, measuring post-void residual (PVR) urine volume and conducting ultrasound scans of the urinary tract for the diagnosis. The significant PVR range from >70 ml (Domurath et al., 2020) to >200 ml (Yang, 2013). Urinalysis is performed as a first-line investigation in more than half of the cases, while creatinemia and/or creatinine clearance are less frequently required. A bladder diary (BD) is required in most cases either as an initial diagnostic tool or at a later stage. After the initial assessment, the identification of risk factors for complications justifies referral to a neuro-urology specialist more than half of the algorithms (De Sèze et al., 2007; Di Benedetto et al., 2008; Ghezzi and Carone, 2011; Yang, 2013; Amarenco et al., 2013; De Ridder et al., 2013; Castel-Lacanal et al., 2017; Tornic and Panicker, 2018; Domurath et al., 2020). Some algorithms recommend conducting urodynamic studies (UDS) if abnormal results are present during the initial assessment or after poor response to therapy. All algorithms recommend treatment with anticholinergics (AC) for patients with OAB, following the initiation of clean intermittent catheterization (CIC) if the PVR is significant. In the absence of a significant PVR, behavioral therapy and/or pelvic floor muscle training are suggested as first-line non-pharmacological approaches. Alpha blockers for the treatment of VD are mentioned in less than half of the cases. In specific situations (mostly nycturia), few algorithms recommend the use of desmopressin. External neuromodulation is rarely suggested, often when other treatments have failed. Botulinum toxin injections are mostly considered if oral treatment fails. Indwelling catheterization is recommended in patients that are unable to perform CIC. Some algorithms mention additional interventions, ranging from sacral neuromodulation to cystoplasty, for patients with refractory symptoms. Symptom resolution and/or improvement of QoL are considered the therapeutic goals for most algorithms.

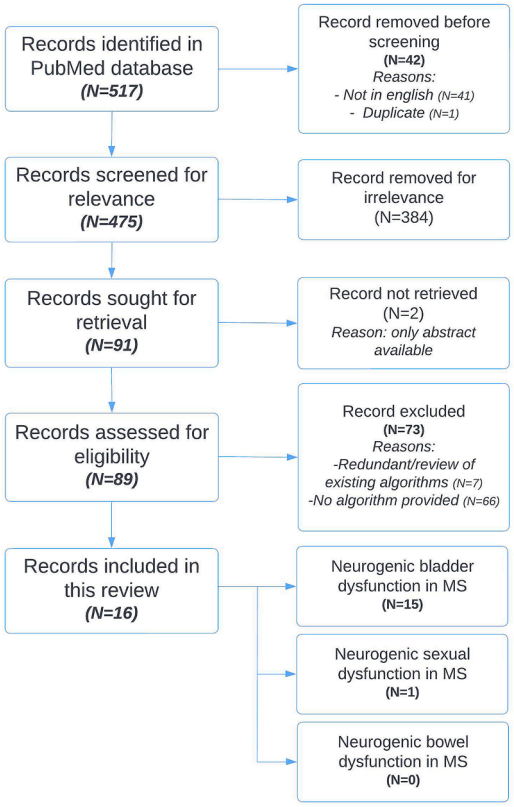


Fig. 1. - Flow-chart.

Table 1
Summary of diagnosis algorithm for NLUTD.

	Symptoms and/or Quality of life questionnaire	Identification of clinical risk factors	Post-void residual	Bladder diary	Ultrasound of the urinary tract	Creatinemia and/or creatinine clearance	Urinalysis	Urodynamic studies
Barbalias 2001[24]	–	–	–	–	–	–	–	First-level
De Séze 2007[25]	First-level [a]	First-level [cd]	First-level [a]	First-level [cd]	First-level [cd]	First-level [cd]	First-level [cd]	First-level [cd]
Fowler 2008[26]	–	–	First-level [c]	–	–	–	First-level [c]	–
Di Benedetto 2008[27]	–	First-level	First-level [c]	–	First-level [c]	First-level	First-level	–
Stoffel 2010[28]	First-level	–	First-level	–	–	–	–	First-level [e]
Ghezzi 2011[29]	First-level [cb]	First-level [c]	First-level [cb]	First-level [cb]	First-level [c]	First-level [c]	First-level [c]	–
Yang 2013[30]	–	–	First-level [c]	–	–	–	First-level [c]	–
Amarenco 2013[31]	First-level	First-level	First-level	Second-level [d]	First-level	Second-level [d]	–	–
De Ridder 2013[32]	First-level	First-level	First-level	First-level	First-level	–	–	–
Cetinel 2013[33]	First-level	–	First-level	First-level	First-level	First-level	First-level	Second-level [f]
Ghezzi 2015[34]	First-level [a]	–	Second-level [a]	Third-level [a]	–	–	–	–
Phé 2016[35]	First-level [c]	First-level [c]	First-level [c]	First-level [c]	First-level [c]	First-level [c]	First-level [c]	First-level [e]
Castel-Lacanal 2016[36]	–	First-level [c]	First-level [c]	–	First-level [c]	First-level [c]	–	Second-level [de]
Tornic 2018[37]	First-level [c]	First-level [c]	First-level [c]	First-level [c]	First-level [c]	–	First-level [c]	–
Domurath 2020[38]	–	First-level [a]	First-level [a]	First-level [a]	–	–	–	–

NLUTD: Neurogenic lower urinary tract dysfunction. a, Asymptomatic patients; b, Asymptomatic patients with long term disease, signs of spinal cord involvement and/or moderate to severe disability (EDSS > 3); c, Patients with lower urinary tract symptoms; d, Upon referral to a neuro-urologist specialist; e, In case of severe or refractory symptoms or in patients with risk factors for upper urinary tract damage; f, If signs of upper urinary tract damage are detected

The only algorithm available for SD in MS targets men with erectile dysfunction (Li et al., 2020). After enquiring the factors contributing to SD and excluding other etiologies (urological, vascular, …), phosphodiesterase-5 (PDE5) inhibitors are proposed as first line therapy. If first-line treatment fails, second-line treatments (vacuum constriction devices or intracavernosal injections) or third-line treatments (penile prostheses) can be considered upon referral to an appropriate specialist.

4. Discussion

This systematic review reveals a significant effort to provide straightforward management strategies for NLUTD in pwMS. On the other hand, NBD remains significantly underaddressed. SD in pwMS has received increased attention in the scientific literature in recent years, indicating growing awareness. Nonetheless, further time and research are required to fully integrate SD management into clinical practice.

Most authors rely on symptom-based screening, with or without validated questionnaires, for detecting NLUTD in pwMS. The only exception is the algorithm proposed by Barbalias et al. (2001), which relies solely on UDS. Identifying risk factors for complications and assessing PVR are key priorities for most algorithms. Some risk factors, such as the number of UTIs or the severity of disability, can be easily detected through clinical history and examination, while others require additional tests, such as urinary tract ultrasound or creatinine clearance, for assessment. A BD might be considered in the initial assessment as an indicator of clinical severity (Domurath et al., 2020) or used to monitor the efficacy of therapeutic interventions. Urinalysis can be a useful tool for identifying potential irritants that may cause or exacerbate urinary symptoms in pwMS. However, asymptomatic bacteriuria may occur, especially in individuals with indwelling catheters or those undergoing CIC. Efforts by the scientific community to define UTI in the context of NLUTD (Dinh et al., 2019) and MS (Donzé et al., 2020) suggest that urinalysis results should be interpreted critically, and antibiotic use should be limited to specific situations. With few exceptions (Barbalias et al., 2001; Phé et al., 2016), UDS generally require a prior neuro-urological evaluation. Although urological symptoms poorly correlate with abnormalities found in UDS (Tadayyon et al., 2012), some practitioners advocate for conducting UDS in all pwMS presenting with urinary symptoms. Others believe it's only necessary in specific situations, such as in cases of refractory OAB, recurrent UTI or when bladder anomalies are identified through ultrasound imaging. The assessment of clinical predictors of UUTD should be conducted before considering UDS (Beck et al., 2022). Due to the low incidence of UUTD in the MS population, indiscriminate use of invasive diagnostic procedures may be inappropriate, as they are uncomfortable and increase costs without offering additional patient benefit (Fletcher et al., 2013). The management of NLUTS in pwMS should prioritize patients' symptoms and QoL.

Most algorithms suggest as AC a first-line treatment for OAB. Their use is associated with a moderate efficacy in alleviating symptoms and reducing detrusor overactivity in MS despite the increase of PVR and a significant incidence of adverse effects (Andretta et al., 2022). Recent studies have highlighted a dose-dependent relationship between chronic use of AC and an increased risk of dementia (Zheng et al., 2021; Morrow et al., 2018), raising concerns about the risk-benefit ratio of their use in this population. Pelvic floor rehabilitation programs and external neuromodulation are non-pharmacological interventions that have been proven to be both safe and effective for the OAB (Tulek et al., 2021; De Sèze et al., 2011; Marzouk et al., 2022) and should be considered as a first-line approach. The use of beta-3-adrenergic receptor agonists might represent an effective alternative to AC in pwMS (Glykas et al., 2021), where symptoms management is prioritized over the suppression of uninhibited detrusor contractions. Combination treatment using different pharmacological and non-pharmacological therapies may enhance effectiveness and reduce the side effects associated with higher doses of medications for OAB. Alpha-blockers may be considered as first-line treatment for VD (Schneider et al., 2019) in the absence of

Table 2
Summary of treatment algorithm for NLUTD.

	Behavioral therapy and/or pelvic floor muscle training	Anticholinergics	Desmopressin	External peripheral neuromodulation	Alpha-blockers	Botulinum toxin injections	Clean intermittent catheterization	Indwelling catheterization	Other treatments mentioned
Fowler 2008[26]	–	First-line [a]	–	–	–	–	First-line [b]	–	No
Di Benedetto 2008[27]	First-line	First-line	–	–	First-line	–	First-line [b]	–	No
Stoffel 2010[28]	First-line	First-line	First-line	Second-line	First-line	Second-line	First-line [b]	Third-line	Yes
Ghezzi 2011[29]	First-line	First-line	–	First-line	First-line [a]	–	First-line [b]	Second-line [g]	No
Yang 2013[30]	First-line	First-line	–	–	–	–	First-line [b]	First-line [g]	No
Amarenco 2013[31]	–	First-line	–	–	First-line	–	–	–	No
De Ridder 2013[32]	First-line [acd]	First-line	First-line [cde]	–	First-line [e]	First-line [ef]	First-line [ef]	First-line [ef]	Yes
Cetinel 2013[33]	First-line	First-line	First-line [a]	–	–	Second-line	First-line [b]	First-line [bg]	Yes
Phé 2016[35]	First-line	Second-line	–	Third-line	–	Third-line	First-line [b]	Second-line [g]	Yes
Castel-Lacanal 2016[36]	–	First-line [a]	–	–	–	–	–	–	No
Tornic 2018[37]	–	First-line [a]	–	Second-line	–	Second-line	First-line [b]	Third-line [g]	Yes

NLUTD: Neurogenic lower urinary tract dysfunction. a, Non-significant post-void residual; b, Significant post-void residual; c, Walking unaided; d, Walking with aid; e, Chair bound; f, Bedbound; g, Clean intermittent catheterization unfeasible. The algorithm proposed by Barbalias has been omitted because it is based on pathophysiology rather than symptoms. The algorithms by De Seze, Ghezzi, and Domurath have not been included because they do not provide a therapeutic flowchart.

significant PVR. Most algorithms use a PVR of 100 ml as the threshold for initiating CIC. Although this cut-off is debated (Ingram et al., 2024), it provides a consistent criterion for clinical decision-making. These first-line treatments for OAB and VD are well-suited for integration into algorithmic approaches, as their standardized nature facilitates clear and systematic application. Invasive treatments should be considered only after a multidisciplinary evaluation by specialists. For patients with severe motor and/or cognitive disabilities, suprapubic indwelling catheterization can be discussed. The decision to adopt these interventions is complex and cannot be easily simplified through a decision tree.

Among the algorithms discussed, only a few have undergone a validation process (Amarenco et al., 2013; Ghezzi et al., 2016; Domurath et al., 2020). While this process is crucial for ensuring a tool's accuracy, reliability, and effectiveness, it is not sufficient on its own to establish its suitability in a clinical context. Ghezzi et al. (2016) designed an algorithm for screening urinary symptoms in asymptomatic pwMS in order to determine who may benefit from treatment. The first-level analysis consists of the International Prostate Symptom Score, which primarily focuses on voiding symptom screening rather than storage symptoms. The algorithm created by Domurath et al. (2020) suggest to stratify the patients in four groups based on PVR, micturition frequency and UTI rate, each of which could benefit from a different diagnostic and therapeutic approach. Although its utility, the authors do not provide a visual flowchart suitable for first-line physicians. Amarenco et al. (2013) present a straightforward algorithm that addresses the key priorities in the management of NLUTD in MS. However, it does not include the non-pharmacological approaches. Ongoing evaluation and continuous updates are necessary to ensure that the tool remains relevant and effective in clinical practice over time. Additionally, it is essential to conduct external validation in the specific settings where these algorithms are intended to be employed.

NBD is widespread among people with MS and is undoubtedly multifactorial in nature. Both constipation and fecal incontinence can profoundly affect these individuals, significantly impacting their QoL and overall health (Dibley et al., 2017). Anorectal hyposensitivity could be considered a common factor contributing to both symptoms, justifying their coexistence (Preziosi et al., 2018). Furthermore, constipation may exacerbate other MS symptoms, such as spasticity or bladder dysfunction (Panayi et al., 2011), amplifying the burden of the condition on affected individuals. The co-occurrence of bladder and bowel dysfunction suggests a reciprocal modulation between the two organs. This phenomenon, known as 'pelvic cross-talk,' may be attributed to their common embryological origin, similarities in function (storage and evacuation), innervation, and anatomical proximity, although its mechanism is yet to be clarified (Panicker et al., 2019). This cross-organ sensitization underscores the importance of a multimodal management approach when addressing bladder and bowel dysfunction. Currently, there is no specific algorithm for the management of these issues in pwMS. The existing algorithms addressing NBD (Cotterill et al., 2018; Kurze et al., 2022) are mostly tailored to patients with spinal cord injury (SCI), yet evidence-based treatments specifically addressing NBD in pwMS are notably lacking. Although NBD in MS and SCI may present similar symptoms such as incontinence and constipation, it differs in several key aspects: patients with SCI may face autonomic dysreflexia risks that are absent in pwMS, whereas pwMS tend to experience progressive accumulation of physical and cognitive disability over time, unlike patients with SCI. For this reason (Miget et al., 2022), a questionnaire specifically designed for anorectal disorders in pwMS has been created and validated to characterize symptoms, monitor the effectiveness of interventions, and evaluate their impact on the QoL (Tan et al., 2023). In terms of treatment, assessing diet and nutritional status, including fluid intake, is essential, as is taking a detailed drug history. Polypharmacy may cause constipation (e.g., AC drugs and baclofen), while some medications, such as antibiotics or statins, may lead to loose stools. Patients with mild neurological disability should adopt the

squatting position during defecation to enhance stool evacuation. The use of laxatives and/or constipating agents may be considered if dietary measures are ineffective. Suppositories and enemas can enhance the effect of laxatives by stimulating a reflex contraction of the rectum in patients primarily affected by anorectal dysfunction. Abdominal massage (McClurg et al., 2018) and percutaneous posterior tibial nerve stimulation (Sarveazad et al., November 30, 2019) are non-pharmacological approaches that could complement the aforementioned treatments and slightly improve symptoms of NBD; however, additional studies are required to validate their efficacy. Other treatments such as transanal irrigation or sacral neuromodulation should be discussed with a specialist first.

SD is common in both men and women with multiple sclerosis but is often under-reported and undertreated due to challenges patients and healthcare professionals encounter in discussing and managing these issues in clinical settings (Tudor et al., 2018). In men, the physiology of sexual function can be divided into libido, arousal, erection, ejaculation, orgasm and detumescence. In women, following arousal, the corresponding physiological response to erection is increased vaginal blood flow and lubrication, resulting in clitoral engorgement (Kessler et al., 2009). The most common presentations of sexual dysfunction in men with MS are erectile dysfunction (50 %–75 %), ejaculatory dysfunction (50 %), reduced libido (39 %) and anorgasmia (37 %) (Fletcher et al., 2009). On the other hand, women's most frequent complaints of sexual dysfunction in MS are reduced libido (31 %–64 %), problems with arousal and vaginal lubrication (33 %–52 %) and failure to orgasm (37 %–38 %) (Bronner et al., 2010). SD in both men and women with MS may arise not only from lesions affecting neural pathways (primary dysfunction) but also from physical disabilities (secondary dysfunction) and psychological and emotional factors (tertiary dysfunction). The knowledge and practices of neurologists and general practitioners who frequently care for pwMS are often insufficient in managing these issues. One fourth of pwMS are not satisfied at all with provider's evaluation and treatment of their sexual issues (Wang et al., 2018). Detailed sexual history and multidimensional questionnaires to assess current sexual function appear to be essential for the diagnostic evaluation of non-neurogenic SD in both genders (Hatzichristou et al., 2016). The Multiple Sclerosis Intimacy and Sexuality Questionnaire (MSISQ-19) is a validated questionnaire designed for the MS population, comprising 19 items related to primary, secondary, and tertiary SD (Sanders et al., 2000).

The algorithm referenced in this article exclusively addresses erectile dysfunction in men with MS (Li et al., 2020). After reasonably excluding other organic causes of erectile dysfunction, PDE5 inhibitors are proposed as a safe first-line treatment. It is important to note that the efficacy of this treatment in people with MS is debated (Fowler, 2005; Safarinejad, 2009; Safarinejad, 2023). The second and third line treatments are the same as those employed in the general population and should be carefully discussed with a specialist first. There is a significant gender disparity in pharmacological treatment options for managing MS-related symptoms, with few of these treatments demonstrating efficacy in pwMS. The lack of algorithms designed for SD in women with MS reflect the complexity of this issue. Sensitivity and proactive measures are essential for primary care physicians managing pwMS. Integrating questionnaires capable to differentiate primary, secondary or tertiary SD into routine MS care could facilitate open discussions about sexual issues and aid to deliver appropriate solutions. By combining pharmacological interventions targeting underlying physiological causes (primary), therapies addressing physical limitations (secondary), and psychological interventions or counseling to address emotional and relational factors (tertiary), healthcare providers can comprehensively address the complex nature of SD in pwMS. This multimodal approach may enhance overall treatment outcomes and QoL. It is advised to engage in multidisciplinary discussions prior to considering invasive or potentially harmful treatments.

Numerous studies have highlighted the significant impact that bladder, bowel and sexual dysfunction have on the QoL of pwMS and how they contribute substantially to the disease's morbidity. Nonetheless, these issues are still frequently underestimated, underdiagnosed, and undertreated. This is partly due to patients' hesitancy in reporting their symptoms and the limited awareness among first-line physicians, including general practitioners and neurologists. Given the prevalence of these disturbances, referring all pwMS to specialists may be neither feasible nor cost-effective. Recognizing and managing uncomplicated urinary and bowel symptoms should be a key goal in MS management for first-line physicians. Routine assessment of SD using validated questionnaires might also enable appropriate care and improve overall patient satisfaction. While few straightforward algorithms exist for managing NLUTD, there is a noticeable lack of algorithms specifically addressing NBD and SD in pwMS. It is crucial for specialists to define the primary priorities in managing these conditions to develop a concise, visually accessible and validated algorithms tailored for first-line physicians. Implementing algorithms in standard MS care could serve as practical tools to reduce health costs and improve QoL of pwMS. Moreover, the use of such tools may facilitate the recognition of 'red flags' that warrant referral to a neuro-urologist. An international effort is needed to promptly update these management algorithms whenever new recommendations are published, ensuring that clinical practices remain aligned with the latest evidence and standards of care.

5. Conclusion

Neurogenic bladder, bowel, and sexual dysfunction are common in pwMS. Currently, most of the decision tree algorithms addressing these issues are either dated, unsuitable for first-line physicians, or lacking altogether. Establishing key priorities for developing evidence-based, straightforward, and validated algorithms designed for neurologists and general practitioners is crucial for ensuring their relevance and effectiveness. Implementing these algorithms in standard MS care could reduce healthcare costs, improve QoL of pwMS, and facilitate early identification of conditions necessitating specialist referral.

Role of Funding Source

The funding sources had no role in the design of the study, data collection, analysis, interpretation of results, writing of the manuscript, or decision to publish. This publication acknowledges the financial support of the European Union and Wallonia through the FEDER program for the project titled "MedReSyst_UMONS_AI for Brain".

CRediT authorship contribution statement

Vito Tota: Methodology, Formal analysis, Data curation, Conceptualization. **Giovanni Briganti:** Supervision, Methodology. **Laurence Ris:** Supervision, Resources, Methodology, Funding acquisition.

Declaration of competing interest

The author declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.msard.2024.105884.

References

Abrams, P, Cardozo, L, Fall, M, et al., 2002. The standardisation of terminology of lower urinary tract function: report from the standardisation sub-committee of the International Continence Society. Neurourol. Urodyn. 21 (2), 167–178. https://doi.org/10.1002/nau.10052.

Amarenco, G, Chartier-Kastler, E, Denys, P, Jean, JL, De Sèze, M, Lubetzski, C, 2013. First-line urological evaluation in multiple sclerosis: validation of a specific decision-making algorithm. Mult. Scler. 19 (14), 1931–1937. https://doi.org/10.1177/1352458513489758.

Andretta, E, Finazzi Agrò, E, Calabrese, M, Orecchia, L, Furlan, A, Zuliani, C, 2022. Antimuscarinics for neurogenic overactive bladder in multiple sclerosis: real-life data. Ther. Adv. Urol. 14, 175628722211224. https://doi.org/10.1177/17562872221122484.

Barbalias, GA, Liatsikos, EN, Passakos, C, Barbalias, D, Sakelaropoulos, G., 2001. Urologic manifestations of multiple sclerosis: proposed treatment algorithms. Int. Urol. Nephrol. 32 (3), 345–348. https://doi.org/10.1023/A:1017532631643.

Barin, L, Salmen, A, Disanto, G, et al., 2018. The disease burden of Multiple Sclerosis from the individual and population perspective: Which symptoms matter most? Mult. Scler. Relat. Disord. 25, 112–121. https://doi.org/10.1016/j.msard.2018.07.013.

Beck, J, Jaekel, AK, Zeller, FL, et al., 2022. Clinical predictors of neurogenic lower urinary tract dysfunction in persons with multiple sclerosis. Diagnostics 12 (1), 191. https://doi.org/10.3390/diagnostics12010191.

Bronner, G, Elran, E, Golomb, J, Korczyn, AD., 2010. Female sexuality in multiple sclerosis: the multidimensional nature of the problem and the intervention. Acta Neurol. Scand. 121 (5), 289–301. https://doi.org/10.1111/j.1600-0404.2009.01314.x.

Browne, C, Salmon, N, Kehoe, M., 2015. Bladder dysfunction and quality of life for people with multiple sclerosis. Disability Rehabil. 37 (25), 2350–2358. https://doi.org/10.3109/09638288.2015.1027007.

Buljevac, D, Flach, HZ, Hop, WCJ, et al., 2002. Prospective study on the relationship between infections and multiple sclerosis exacerbations. Brain 125 (5), 952–960. https://doi.org/10.1093/brain/awf098.

Castel-Lacanal, E, Gamé, X, Clanet, M, et al., 2015. Urinary complications and risk factors in symptomatic multiple sclerosis patients. Study of a cohort of 328 patients: Urinary Complications and Risk Factors in Multiple Sclerosis. Neurourol. Urodyn. 34 (1), 32–36. https://doi.org/10.1002/nau.22495.

Castel-Lacanal, E, Gamé, X, Clanet, M, et al., 2017. Assessment of a program to encourage the multidisciplinary management of urinary disorders in multiple sclerosis. Neurourol. Urodyn. 36 (3), 706–709. https://doi.org/10.1002/nau.23002.

Çetinel, B, Tarcan, T, Demirkesen, O, et al., 2013. Management of lower urinary tract dysfunction in multiple sclerosis: a systematic review and Turkish consensus report. Neurourol. Urodyn. 32 (8), 1047–1057. https://doi.org/10.1002/nau.22374.

Cotterill, N, Madersbacher, H, Wyndaele, JJ, et al., 2018. Neurogenic bowel dysfunction: clinical management recommendations of the Neurologic Incontinence Committee of the Fifth International Consultation on Incontinence 2013. Neurourol. Urodyn. 37 (1), 46–53. https://doi.org/10.1002/nau.23289.

Darija, KT, Tatjana, P, Goran, T, et al., 2015. Sexual dysfunction in multiple sclerosis: a 6-year follow-up study. J. Neurol. Sci. 358 (1–2), 317–323. https://doi.org/10.1016/j.jns.2015.09.023.

De Ridder, D, Van Der Aa, F, Debruyne, J, et al., 2013. Consensus guidelines on the neurologist's role in the management of neurogenic lower urinary tract dysfunction in multiple sclerosis. Clin. Neurol. Neurosurg. 115 (10), 2033–2040. https://doi.org/10.1016/j.clineuro.2013.06.018.

De Sèze, M, Raibaut, P, Gallien, P, et al., 2011. Intérêt thérapeutique de la stimulation transcutanée tibiale postérieure dans les troubles mictionnels irritatifs de la sclérose en plaques. Résultats d'un programme de recherche clinique hospitalier multicentrique. Pelv. Perineol. 6 (2), 80–88. https://doi.org/10.1007/s11608-010-0354-6.

De Sèze, M, Ruffion, A, Denys, P, Joseph, PA, 2007. Perrouin-Verbe B, International Francophone Neuro-Urological expert study group (GENULF). The neurogenic bladder in multiple sclerosis: review of the literature and proposal of management guidelines. Mult. Scler. 13 (7), 915–928. https://doi.org/10.1177/1352458506075651.

Di Benedetto, P, Delneri, C, Biasutti, E, Bragadin, LM, Giorgini, T., 2008. Vesicourethral dysfunction in multiple sclerosis. Initial assessment based on lower urinary tract symptoms and their pathophysiology. Neurol. Sci. 29 (S4), 348–351. https://doi.org/10.1007/s10072-008-1041-z.

Dibley, L, Coggrave, M, McClurg, D, Woodward, S, Norton, C., 2017. "It's just horrible": a qualitative study of patients' and carers' experiences of bowel dysfunction in multiple sclerosis. J. Neurol. 264 (7), 1354–1361. https://doi.org/10.1007/s00415-017-8527-7.

Dinh, A, Davido, B, Duran, C, et al., 2019. Urinary tract infections in patients with neurogenic bladder. Méd. Mal. Infectieuses 49 (7), 495–504. https://doi.org/10.1016/j.medmal.2019.02.006.

Domurath, B, Kurze, I, Kirschner-Hermanns, R, et al., 2020. Neurourological assessment in people with multiple sclerosis (MS): a new evaluated algorithm. Mult. Scler. Relat. Disord. 44, 102248. https://doi.org/10.1016/j.msard.2020.102248.

Donzé, C, Hautecoeur, P., 2009. Troubles sphinctériens au stade precoce de la sclérose en plaques. Revue Neurol. 165, S148–S155. https://doi.org/10.1016/S0035-3787(09)72127-7.

Donzé, C, Papeix, C, Dinh, A, et al., 2020. Recommandations de la Société française de la sclérose en plaques « infections urinaires et sclérose en plaques » : aspects pratiques. Pratique Neurol. FMC 11 (3), 196–201. https://doi.org/10.1016/j.praneu.2020.07.001.

Fletcher, SG, Castro-Borrero, W, Remington, G, Treadaway, K, Lemack, GE, Frohman, EM, 2009. Sexual dysfunction in patients with multiple sclerosis: a multidisciplinary approach to evaluation and management. Nat. Rev. Urol. 6 (2), 96–107. https://doi.org/10.1038/ncpuro1298.

Fletcher, SG, Dillon, BE, Gilchrist, AS, et al., 2013. Renal deterioration in multiple sclerosis patients with neurovesical dysfunction. Mult. Scler. 19 (9), 1169–1174. https://doi.org/10.1177/1352458512474089.

Fowler, CJ, Panicker, JN, Drake, M, et al., 2009. A UK consensus on the management of the bladder in multiple sclerosis. Postgrad. Med. J. 85 (1008), 552–559. https://doi.org/10.1136/jnnp.2008.159178.

Fowler, CJ., 2005. A double blind, randomised study of sildenafil citrate for erectile dysfunction in men with multiple sclerosis. J. Neurol. Neurosurg. Psychiatry 76 (5), 700–705. https://doi.org/10.1136/jnnp.2004.038695.

Ghezzi, A, Carone, R, et al., The Multiple Sclerosis Study Group, Italian Society of Neurology, 2011. Recommendations for the management of urinary disorders in multiple sclerosis: a consensus of the Italian Multiple Sclerosis Study Group. Neurol. Sci. 32 (6), 1223–1231. https://doi.org/10.1007/s10072-011-0794-y.

Ghezzi, A, Mutta, E, Bianchi, F, et al., 2016. Diagnostic tools for assessment of urinary dysfunction in MS patients without urinary disturbances. Neurol. Sci. 37 (3), 437–442. https://doi.org/10.1007/s10072-015-2415-7.

Glykas, I, Fragkoulis, C, Mitsikostas, DD, et al., 2021. B3 agonists or anticholinergics in the treatment of the lower urinary tract dysfunction in patients with multiple sclerosis?—A randomized study. World J. Urol. 39 (8), 3049–3056. https://doi.org/10.1007/s00345-020-03555-8.

Hatzichristou, D, Kirana, PS, Banner, L, et al., 2016. Diagnosing sexual dysfunction in men and women: sexual history taking and the role of symptom scales and questionnaires. J. Sex. Med. 13 (8), 1166–1182. https://doi.org/10.1016/j.jsxm.2016.05.017.

Ingram, CF, Lincoln, JA, Khavari, R., 2024. Voiding phase dysfunction in multiple sclerosis. Urol. Clin. North Am. 51 (2), 177–185. https://doi.org/10.1016/j.ucl.2024.01.005.

Kessler, TM, Fowler, CJ, Panicker, JN., 2009. Sexual dysfunction in multiple sclerosis. Expert Rev. Neurother. 9 (3), 341–350. https://doi.org/10.1586/14737175.9.3.341.

Khalaf, KM, Coyne, KS, Globe, DR, et al., 2016. The impact of lower urinary tract symptoms on health-related quality of life among patients with multiple sclerosis. Neurourol. Urodyn. 35 (1), 48–54. https://doi.org/10.1002/nau.22670.

Khan, F, McPhail, T, Brand, C, Turner-Stokes, L, Kilpatrick, T., 2006. Multiple sclerosis: disability profile and quality of life in an Australian community cohort. Int. J. Rehab. Res. 29 (2), 87–96. https://doi.org/10.1097/01.mrr.0000194393.56772.62.

Kurze, I, Geng, V, Böthig, R, 2022. Guideline for the management of neurogenic bowel dysfunction in spinal cord injury/disease. Spinal Cord 60 (5), 435–443. https://doi.org/10.1038/s41393-022-00786-x.

Lawrenson, R, Wyndaele, JJ, Vlachonikolis, I, Farmer, C, Glickman, S., 2001. Renal failure in patients with neurogenic lower urinary tract dysfunction. Neuroepidemiology 20 (2), 138–143. https://doi.org/10.1159/000054774.

Li, V, Haslam, C, Pakzad, M, Brownlee, WJ, Panicker, JN., 2020. A practical approach to assessing and managing sexual dysfunction in multiple sclerosis. Pract. Neurol. 20 (2), 122–131. https://doi.org/10.1136/practneurol-2019-002321.

Marzouk, MH, Darwish, MH, El-Tamawy, MS, Morsy, S, Abbas, RL, Ali, AS., 2022. Posterior tibial nerve stimulation as a neuromodulation therapy in treatment of neurogenic overactive bladder in multiple sclerosis: A prospective randomized controlled study. Mult. Scler. Relat. Disord. 68, 104252. https://doi.org/10.1016/j.msard.2022.104252.

McClurg, D, Harris, F, Goodman, K, et al., 2018. Abdominal massage plus advice, compared with advice only, for neurogenic bowel dysfunction in MS: a RCT. Health Technol. Assess. 22 (58), 1–134. https://doi.org/10.3310/hta22580.

Miget, G, Tan, E, Pericolini, M, et al., 2022. The Neurogenic Bowel Dysfunction score (NBD) is not suitable for patients with multiple sclerosis. Spinal Cord 60 (12), 1130–1135. https://doi.org/10.1038/s41393-022-00837-3.

Morrow, SA, Rosehart, H, Sener, A, Welk, B., 2018. Anti-cholinergic medications for bladder dysfunction worsen cognition in persons with multiple sclerosis. J. Neurol. Sci. 385, 39–44. https://doi.org/10.1016/j.jns.2017.11.028.

Munteis, E, Andreu, M, Téllez, MJ, Mon, D, Ois, A, Roquer, J., 2006. Anorectal dysfunction in multiple sclerosis. Mult. Scler. 12 (2), 215–218. https://doi.org/10.1191/135248506ms1254oa.

Musco, S, Padilla-Fernández, B, Del Popolo, G, et al., 2018. Value of urodynamic findings in predicting upper urinary tract damage in neuro-urological patients: a systematic review. Neurourol. Urodyn. 37 (5), 1522–1540. https://doi.org/10.1002/nau.23501.

Norton, C, Chelvanayagam, S., 2010. Bowel problems and coping strategies in people with multiple sclerosis. Br. J. Nurs. 19 (4), 220–226. https://doi.org/10.12968/bjon.2010.19.4.46783.

Panayi, DC, Khullar, V, Digesu, GA, Spiteri, M, Hendricken, C, Fernando, R., 2011. Rectal distension: the effect on bladder function. Neurourol. Urodyn. 30 (3), 344–347. https://doi.org/10.1002/nau.20944.

Panicker, JN, Fowler, CJ, Kessler, TM., 2015. Lower urinary tract dysfunction in the neurological patient: clinical assessment and management. Lancet Neurol. 14 (7), 720–732. https://doi.org/10.1016/S1474-4422(15)00070-8.

Panicker, JN, Marcelissen, T, Von Gontard, A, Vrijens, D, Abrams, P, Wyndaele, M., 2019. Bladder-bowel interactions: do we understand pelvic organ cross-sensitization? International Consultation on Incontinence Research Society (ICI-RS) 2018. Neurourol. Urodyn. 38 (S5). https://doi.org/10.1002/nau.24111.

Phé, V, Chartier–Kastler, E, Panicker, JN, 2016. Management of neurogenic bladder in patients with multiple sclerosis. Nat. Rev. Urol. 13 (5), 275–288. https://doi.org/10.1038/nrurol.2016.53.

Polat Dunya, C, Tulek, Z, Kürtüncü, M, Panicker, JN, Eraksoy, M, 2021. Effectiveness of the transcutaneous tibial nerve stimulation and pelvic floor muscle training with biofeedback in women with multiple sclerosis for the management of overactive bladder. Mult. Scler. 27 (4), 621–629. https://doi.org/10.1177/1352458520926666.

Preziosi, G, Gordon-Dixon, A, Emmanuel, A, 2018. Neurogenic bowel dysfunction in patients with multiple sclerosis: prevalence, impact, and management strategies. DNND 8, 79–90. https://doi.org/10.2147/DNND.S138835.

Safarinejad, MR., 2009. Evaluation of the safety and efficacy of sildenafil citrate for erectile dysfunction in men with multiple sclerosis: a double-blind, placebo controlled, randomized study. J. Urol. 181 (1), 252–258. https://doi.org/10.1016/j.juro.2008.09.003.

Safarinejad, MR., 2023. Expression of concern: evaluation of the safety and efficacy of sildenafil citrate for erectile dysfunction in men with multiple sclerosis: a double-blind, placebo controlled, randomized study. J. Urol. https://doi.org/10.1097/JU.0000000000003114. Published online January 10.

Sanders, AS, Foley, FW, LaRocca, NG, Zemon, V., 2000. The multiple sclerosis intimacy and sexuality questionnaire-19 (MSISQ-19). Sex. Disability 18 (1), 3–26. https://doi.org/10.1023/A:1005421627154.

Sarveazad, A, Babahajian, A, Amini, N, Shamseddin, J, Yousefifard, M., 2019. Posterior Tibial nerve stimulation in fecal incontinence: a systematic review and meta-analysis. Basic Clin. Neurosci. J. 419–432. https://doi.org/10.32598/bcn.9.10.290.

Schairer, LC, Foley, FW, Zemon, V, et al., 2014. The impact of sexual dysfunction on health-related quality of life in people with multiple sclerosis. Mult. Scler. 20 (5), 610–616. https://doi.org/10.1177/1352458513503598.

Schneider, MP, Tornic, J, Sýkora, R, et al., 2019. Alpha-blockers for treating neurogenic lower urinary tract dysfunction in patients with multiple sclerosis: a systematic review and meta-analysis. A report from the Neuro-Urology Promotion Committee of the International Continence Society (ICS). Neurourol. Urodyn. 38 (6), 1482–1491. https://doi.org/10.1002/nau.24039.

Seddone, S, Marturano, M, Bientinesi, R, et al., 2021. Lower urinary tract disorders in multiple sclerosis patients: prevalence, clinical features, and response to treatments. Neurourol. Urodyn. 40 (6), 1500–1508. https://doi.org/10.1002/nau.24687.

Stoffel, JT., 2010. Contemporary Management of the Neurogenic Bladder for Multiple Sclerosis Patients. Urologic Clin. North Am. 37 (4), 547–557. https://doi.org/10.1016/j.ucl.2010.06.003.

Tadayyon, F, Etemadifar, M, Bzeih, H, et al., 2012. Association of urodynamic findings in new onset multiple sclerosis with subsequent occurrence of urinary symptoms and acute episode of disease in females. J. Res. Med. Sci. 17 (4), 382–385.

Tan, E, Turmel, N, Kerdraon, J, et al., 2023. A new tool to investigate anorectal disorders in patients with multiple sclerosis: STAR-Q. Progrès en Urologie 33 (7), 362–369. https://doi.org/10.1016/j.purol.2023.02.006.

Thompson, AJ, Baranzini, SE, Geurts, J, Hemmer, B, Ciccarelli, O., 2018. Multiple sclerosis. The Lancet 391 (10130), 1622–1636. https://doi.org/10.1016/S0140-6736(18)30481-1.

Tornic, J, Panicker, JN., 2018. The management of lower urinary tract dysfunction in multiple sclerosis. Curr. Neurol. Neurosci. Rep. 18 (8), 54. https://doi.org/10.1007/s11910-018-0857-z.

Tudor, KI, Eames, S, Haslam, C, Chataway, J, Liechti, MD, Panicker, JN., 2018. Identifying barriers to help-seeking for sexual dysfunction in multiple sclerosis. J. Neurol. 265 (12), 2789–2802. https://doi.org/10.1007/s00415-018-9064-8.

Tzortzis, V, Skriapas, K, Hadjigeorgiou, G, et al., 2008. Sexual dysfunction in newly diagnosed multiple sclerosis women. Mult. Scler. 14 (4), 561–563. https://doi.org/10.1177/1352458508014004090 1.

Wang, G, Marrie, RA, Fox, RJ, et al., 2018. Treatment satisfaction and bothersome bladder, bowel, sexual symptoms in multiple sclerosis. Multiple Scler. Relat. Disord. 20, 16–21. https://doi.org/10.1016/j.msard.2017.12.006.

Wang, T, Huang, W, Zhang, Y., 2016. Clinical characteristics and urodynamic analysis of urinary dysfunction in multiple sclerosis. Chin. Med. J. 129 (6), 645–650. https://doi.org/10.4103/0366-6999.177970.

Yang, CC., 2013. Bladder management in multiple sclerosis. Phys. Med. Rehab. Clin. North Am. 24 (4), 673–686. https://doi.org/10.1016/j.pmr.2013.06.004.

Zheng, YB, Shi, L, Zhu, XM, et al., 2021. Anticholinergic drugs and the risk of dementia: a systematic review and meta-analysis. Neurosci. Biobehav. Rev. 127, 296–306. https://doi.org/10.1016/j.neubiorev.2021.04.031.

Ziadeh, T, Mjaess, G, El Helou, J, et al., 2022. Impact on quality of life in multiple sclerosis patients: which urinary symptoms are to blame? Progrès en Urologie 32 (10), 711–716. https://doi.org/10.1016/j.purol.2022.05.003.