

Prevalence of Lower Urinary Tract Symptoms in People with Multiple Sclerosis

A Systematic Review and Meta-analysis

Hawra B. Al Dandan, PT, M App Mngt (Health); Susan Coote, PT, PhD; Doreen McClurg, PT, PhD

CME/CNE Information

Activity Available Online: To access the article, post-test, and evaluation online, go to <http://www.cmscscholar.org>.

Target Audience: The target audience for this activity is physicians, physician assistants, nursing professionals, and other health care providers involved in the management of patients with multiple sclerosis (MS).

Learning Objectives:

- 1) Describe the most prevalent lower urinary tract symptoms (LUTSs) and LUTS types in the general MS population according to International Continence Society (ICS) classification.
- 2) Identify limitations in the current evidence base and recommendations for conducting significant future studies.

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Background: No published study, to our knowledge, has systematically reviewed the prevalence estimates of lower urinary tract symptoms (LUTSs) and LUTS types in the general multiple sclerosis (MS) population. Therefore, a systematic review and a meta-analysis were conducted to determine the totality of literature investigating the prevalence of LUTSs and LUTS types in the general MS population according to International Continence Society definitions.

Methods: Various electronic databases were searched between January 4, 2018, and February 12, 2018. This review included observational studies involving adults (18 years or older) with a confirmed diagnosis of MS recruited from the general MS population using self-report and/or objective outcome measures for LUTSs.

Results: Twelve studies were included in the meta-analysis. The results showed that LUTSs were prevalent in people with MS, with a pooled prevalence of 68.41% using self-report and 63.95% using the objective measure of urodynamics. When considering LUTS types, urinary frequency was the predominant symptom, with a pooled prevalence estimate of 73.45%, followed by urgency assessed using self-report measures at 63.87%. Detrusor overactivity was found to be the most prevalent urodynamic symptom, with a pooled prevalence estimate of 42.9%, followed by detrusor sphincter dyssynergia at 35.44%.

Conclusions: This systematic review revealed that LUTSs are highly prevalent in MS. There is a need for improvement in the conduct and reporting of prevalence studies of LUTSs in MS and for the use of validated self-report outcome measures to enable pooling of data in the future. *Int J MS Care.* 2020;22: 91-99.

Lower urinary tract symptoms (LUTSs) are common in people with multiple sclerosis (MS) and result primarily from demyelinating lesions that affect the spinal cord, disturbing neural connections from the pontine micturition center to the parasympathetic sacral micturition center.^{1,2} Many studies have demonstrated that worsening of urinary symptoms is correlated with increasing spinal cord involvement in people with MS.²⁻⁴

Definitions and terminology in lower urinary tract function recommended by the International Continence Society (ICS) that include signs, symptoms, and urodynamic observations⁵ were followed in this review. Symptoms are defined as subjective indicators perceived by the patient or caregiver that motivate him or her to seek medical advice. They are possibly suggestive of a health problem or a disease. Signs are the self-report measures used to verify and quantify symptoms, including validated questionnaires, frequency-volume charts,

pad tests, or bladder diaries, that are usually stated by the patient or caregiver and observed by the physician as an indication of lower urinary tract dysfunction. Urodynamic observations, including urodynamic studies (UDSs), are performed in urodynamic laboratories and are used as objective outcome measures of lower urinary tract function.^{5,6}

The ICS categorizes LUTSs into 1) storage symptoms, 2) voiding symptoms, or 3) postmicturition symptoms.⁵ Storage symptoms include failure to store urine, which can lead to overactive bladder (OAB), a symptom-based condition defined as a “[u]rinary urgency, usually accompanied by frequency and nocturia, with or without urgency urinary incontinence, in the absence of urinary tract infection or other obvious pathology.”⁷ Urinary urgency is a storage symptom with the complaint of a sudden desire to pass urine that is difficult to defer. Similarly, urgency urinary incontinence is a storage symptom that results in an involuntary loss of urine that is accompanied by urgency; frequency is defined as voiding too often throughout the day, and nocturia is the need to wake up at night one or more times to void.⁵ In UDSs these symptoms present as detrusor overactivity and/or increased or decreased bladder sensation.

Voiding symptoms include failure to empty urine and may present with a variety of clinical manifestations, including hesitancy, poor stream, intermittency, straining, terminal dribble, dysuria, and need to immediately

From the School of Allied Health, Faculty of Education and Health Sciences (HBAD, SC), and Health Research Institute (SC), University of Limerick, Limerick, Ireland; Imam Abdulrahman Bin Faisal University, Dammam, Saudi Arabia (HBAD); and Nursing, Midwifery, and Allied Health Professions Research Unit, Glasgow Caledonian University, Glasgow, UK (DM). Correspondence: Hawra B. Al Dandan, PT, M App Mngt (Health), School of Allied Health, Faculty of Education and Health Sciences, University of Limerick, Limerick, Ireland V94 T9PX; e-mail: Hawra.Aldandan@ul.ie.

void again, that contribute to reducing the normal functional capacity of the bladder. Common urodynamic findings include detrusor-sphincter dyssynergia, which involves loss of coordination between detrusor muscles and the external sphincter during the storage phase² and/or detrusor underactivity. Postmicturition symptoms include postmicturition dribble and a feeling of incomplete emptying. The latter is often associated with postvoid residue on UDS or ultrasound.

Early diagnosis of LUTSs in patients with MS is important to prevent possible complications and guide the management pathway. This could be obtained through specific diagnostic measures, including self-report and/or objective outcome measures. There is debate among experts for undertaking UDSs in people with MS. The European Association of Urology and UK National Institute for Care and Clinical Excellence guidelines recommend using UDSs with symptomatic neurologic patients when conservative treatment has failed, whereas the American Urological Association guidelines recommend using UDSs for all neurologic patients with or without LUTSs.⁸ According to the ICS, UDSs are defined as measurements of all physiologic function and dysfunction of the lower urinary tract that help in diagnosing the cause and nature of the lower urinary tract abnormalities. It involves two principal methods of investigation: conventional UDSs and ambulatory UDSs. It generally requires an individual to have a full bladder for uroflowmetry and postvoid residual measurement before filling cystometry and pressure-flow study.^{5,6}

Several studies have shown that LUTSs in MS can be the source of a significant reduction in health-related quality of life.⁹⁻¹¹ A qualitative study was conducted of people with MS to explore and discuss participants' experiences of living with LUTSs and how these symptoms affect their quality of life. This study revealed that bladder dysfunction in MS results in major disturbances to activities of daily living, which can affect their lifestyle.¹² Fear of leaking urine in public among people with MS was identified as a barrier to engaging in physical activities, which might reduce their health-related quality of life.¹³ Also, bladder incontinence has been found to be associated with increased risk of falling in people with MS aged 45 to 90 years.¹⁴ Therefore, increased focus on understanding the prevalence of LUTSs and LUTS types in the MS population may help improve therapeutic interventions that could potentially

improve the health-related quality of life of people with MS.

Previous reviews of LUTSs in people with MS have tended to use samples of people with bladder problems and investigate the prevalence of each type of LUTS. One such systematic review aimed to investigate the incidence and prevalence of urinary incontinence and detrusor overactivity in people with neurogenic OAB. That review found that urinary incontinence in people with MS ranged from 6.9% in an Italian single-center study to 95% in a Japanese study. The review revealed detrusor overactivity prevalence estimates of 27% to 91%.¹⁵ Other reviews¹⁶⁻¹⁹ reported that the storage symptoms of urgency, frequency, and urgency urinary incontinence were the predominant symptoms in people with MS and ranged from 32% to 86%, 32% to 83%, and 19% to 83%, respectively. The lack of studies sampling from a general MS population, together with the small sample sizes and lack of reporting of detailed methods, affects the reliability of these results.

In 2002, the ICS subcommittee issued standardized terminology and definitions of LUTSs that are recommended to be followed.⁵ However, the lack of consistency in terminology weakens previous studies' results and limits the ability to draw strong conclusions from their results. To investigate the burden of LUTSs in people with MS, there is a need for researchers to apply the standardized terminology of LUTSs that has been established by the ICS.

To our knowledge, no study has been conducted to systematically review and summarize existing data to obtain a summary estimate of the prevalence of LUTSs and LUTS types in the general MS population using only the standardized ICS terminology. Therefore, the purpose of this study was to systematically review the literature to determine the totality of literature investigating the prevalence of LUTSs and LUTS types in a general MS population according to ICS recommendations.

Methods

The conduct and reporting of this study are in accordance with the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines.²⁰

Search Strategy

The search strategy was discussed with the faculty librarian to optimize retrieval of relevant studies. The searches were started January 4, 2018, and concluded February 12, 2018, and were not limited by date. The literature was searched for peer-reviewed original articles using the following individual electronic databases: AMED (Allied and Complemen-

tary Medicine), CINAHL (Cumulative Index to Nursing and Allied Health Literature), MEDLINE, PsycARTICLES, Embase, Scopus, PubMed, and The Cochrane Library database. The search terms used were *multiple sclerosis AND neurogenic bladder OR urinary dysfunction OR urinary bladder OR overactive bladder OR incontinence OR bladder dysfunction OR bladder OR detrusor OR lower urinary tract OR urinary OR catheter* OR enuresis OR nocturia*. All identified studies were imported into bibliography management software (EndNote X8; Clarivate Analytics, Philadelphia, PA). The reference lists of full-text screened articles and other systematic reviews on the prevalence of LUTSs in people with MS were hand searched for potentially relevant articles. We contacted authors to clarify missing data and ordered interlibrary loans for any remaining articles unobtainable through author contact.

Eligibility Criteria

The inclusion criteria for the studies were as follows: 1) population—people with a confirmed diagnosis of MS, 18 years and older, recruited from the general MS population in a random/consecutive way that suggests they would be representative of the population; 2) the study provided an estimate of the prevalence of LUTS categories according to ICS definitions⁵; 3) outcome measures—any means of establishing the presence of LUTSs, including self-report and/or objective measures; and 4) study design—baseline data that are first estimate values of a longitudinal study design or observational study design, including cross-sectional studies, baseline data of prospective or retrospective cohort studies, or case-control studies. Studies were excluded if the population of interest was limited to pregnant women or if studies with mixed neurologic populations did not separate results for people with MS. Two reviewers (H.B.A.D., N.O'M.) independently screened abstracts and full texts to determine the eligibility of the included studies. Any disagreements between reviewers were resolved by consulting with a third reviewer (D.M.) until consensus was achieved.

Data Extraction and Quality Assessment

Each study identified was screened in detail to extract author(s) name, year, title, study design, settings, study population, age, sex, type(s) of MS, severity of MS, disease duration, outcome measure(s), and key findings. Two independent reviewers reviewed the data extraction table to confirm the accuracy and clarity of the extracted information.

Methodological quality and risk of bias were assessed using the Newcastle-Ottawa Scale adapted for cross-sectional studies.²¹ We extracted cross-sectional data from one case-control study and one longitudinal study, and thus they were considered as cross-sectional studies for quality appraisal. This tool comprises three key domains: selection, comparability, and outcome. A star system was used to allow a semiquantitative assessment of study quality, with a maximum of ten stars awarded depending on the criteria level that the study meets in each section. The process was performed independently by two reviewers (H.B.A.D., N.O'M.), and disagreements were resolved by discussion.

Statistical Analysis

The prevalence estimates of LUTSs and LUTS types are reported as percentages extracted from each study. We pooled the prevalence estimates for self-report measures and UDSs. Statistical analysis was performed using Review Manager software, version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) for meta-analysis, and a random effect model with 95% CIs was applied. Standard error was obtained using the following formula: $\text{SQRT}(p*(1-p)/n)$, where p indicates prevalence; n , sample size. Heterogeneity was assessed using I^2 statistics. We used the Cochrane interpretation of these values where an I^2 value of 30% to 60% indicates moderate heterogeneity; 50% to 90%, substantial heterogeneity; and 75% to 100%, considerable heterogeneity.^{22,23}

Results

Figure S1 (published in the online version of this article at ijmsc.org) shows the flow diagram of the literature search and results. After screening of 15,274 abstracts, 22 studies met the inclusion criteria, and 12 studies were included in the meta-analysis: 11 cross-sectional studies and one case-control study.

Study and Patient Characteristics

Of the 22 studies that met the inclusion criteria, nine were not included in the meta-analysis because the methods of data collection were not described in sufficient detail to allow accurate interpretation of the findings,²⁴⁻³² and one additional study provided prevalence estimates of OAB with no details given for single symptoms to enable pooling of the data for meta-analysis.³³ Some urinary symptoms in two studies were not included in the final analysis because the terminology was inconsistent with the ICS classification or the urinary symptoms were combined, making prevalence estimates for individual ICS categories not possible.^{34,35}

Descriptive characteristics of included studies are provided in Table S1. The 12 studies³⁴⁻⁴⁵ in the final analysis included 2507 MS participants, including 1799 women (71.8%), with sample sizes ranging from 21 to 1047 and age ranging from 18 to 89 years. There were 1554 participants (62.0%) with relapsing-remitting MS, 108 (4.3%) with primary progressive MS, and 155 (6.2%) with secondary progressive MS; 690 participants (27.5%) did not have descriptive characteristics presented in the included studies. Outcome measures used to estimate the prevalence of LUTSs in the MS population are presented in Table 1. Nine studies administered nine different self-report measures, and six studies investigated the prevalence based on objective measures (five using UDSs and one using portable ultrasound).

Table 1. Outcome measures used in included studies

Measure type and study	Outcome measure
Self-report measures	
Akkoç et al, 2016 ³⁶	Overactive Bladder Symptom Score
de Almeida et al, 2013 ³⁴	Kurtzke Functional System Scale for Bladder
Khalaf et al, 2015 ³⁸	Lower Urinary Tract Symptoms tool
Nortvedt et al, 2007 ⁴¹	International Prostate Symptom Score–Norwegian
Murphy et al, 2012 ³⁹	Urogenital Distress Inventory-6
Zecca et al, 2016 ⁴³	International Consultation of Incontinence Questionnaire
Hall et al, 2012 ³³	Boston Area Community Health Survey
Kale et al, 2009 ³⁷	Self-report measure (developed by author)
Vieira et al, 2015 ⁴²	Composite Autonomic Symptom Score (Portuguese)
Objective measures	
Akkoç et al, 2016 ³⁶	Ultrasound, catheterization (postvoid residue)
de Almeida et al, 2013 ³⁴	Urodynamic studies
Nakipoglu et al, 2009 ⁴⁰	Urodynamic studies
Porru et al, 1997 ³⁵	Urodynamic studies
Weinstein et al, 1988 ⁴⁴	Urodynamic studies
Bemelmans et al, 1991 ⁴⁵	Urodynamic studies

Urodynamic studies were performed according to ICS standards⁴⁶ in four studies, with three using liquid cystometry^{35,40,45} and one using gas cystometry including carbon dioxide.⁴⁴ The UDS procedure in one study was not described in sufficient detail.³⁴

Prevalence

The pooled prevalence of general LUTSs using self-report measures from four studies^{34,37,38,42} was 68.41% (95% CI, 45.24%-91.58%) (Figure 1A) and detected by UDSs from three studies^{34,40,45} was 63.95% (95% CI, 57.78%-70.12%), with significant heterogeneity ($I^2 = 100\%$) (Figure 1B).

The prevalence estimate of each type of LUTS was detected through self-report measures in seven studies and by UDSs in three studies. Prevalence ranges and meta-analyses are presented in Table S2. The 95% CIs for most estimates were wide. Sensitivity analysis was not appropriate in this review owing to the small number of studies included in the meta-analyses.

The pooled prevalence of storage symptoms detected by self-report measures showed that frequency was the predominant symptom, followed by urgency and nocturia (Figure S2). The pooled prevalence estimates

using objectively measured UDSs showed that detrusor overactivity is the predominant symptom, followed by reduced bladder sensation (Figure S3).

Some types of voiding symptoms were not measured subjectively in any studies (hesitancy and dysuria), and others were measured in only one study (weak stream, intermittency, straining, terminal dribble). Therefore, the pooled prevalence estimates using self-report outcome measures of voiding symptoms in people with MS could not be reported in this review. Pooled prevalence of voiding symptoms using UDSs showed that detrusor-sphincter dyssynergia is the predominant symptom, followed by detrusor underactivity (Figure S4).

For postmicturition symptoms, the pooled prevalence estimates for the feeling of incomplete bladder emptying using self-report outcome measures was 60.56% (95% CI, 60.26%-60.85%) (Figure S5). Using objective outcome measures, one study found prevalence estimates of the feeling of incomplete bladder emptying of 13.3% using ultrasound and 16.2% using a catheter. Postmicturition dribble was not investigated in the studies.

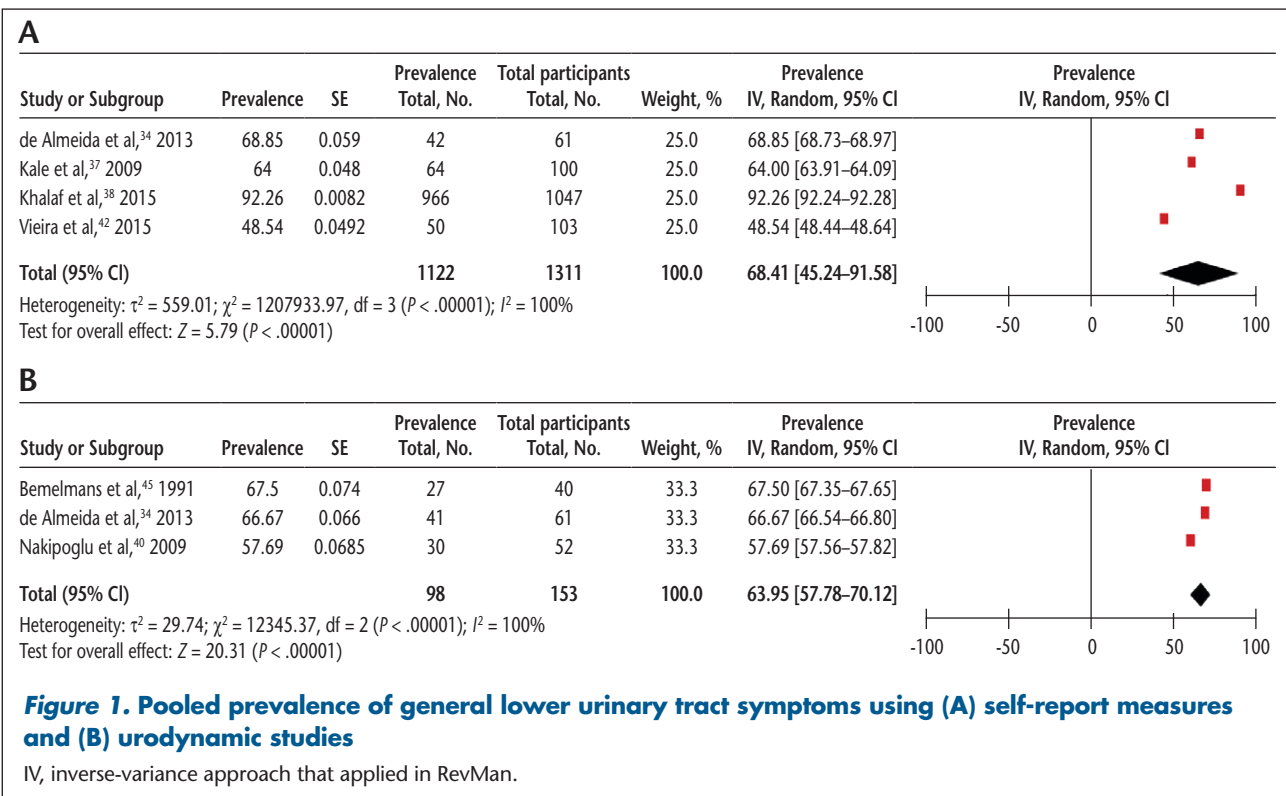
Only one study used a longitudinal study design²⁵ and was not included in the meta-analysis due to insufficient details provided for the self-report outcome measure. The study investigated the prevalence of LUTSs and LUTS types at three time points (baseline and 3- and 6-year follow-up). The prevalence estimate of general LUTSs at baseline was 46.23%. The prevalence of each type of LUTS estimated at baseline was as follows: urgency, 41.93%; hesitancy, 30.1%; urge incontinence, 31.18%; nocturia, 24.73%; and incomplete bladder emptying, 33.3%.

Methodological Quality

Results of the quality assessment are presented in Table S3. Study ratings ranged from one to eight of ten stars. Five studies were identified as having high risk of bias for selection, attrition, information, and detection bias.^{26,28,29,35,40} Two studies were found to be at high risk for bias in all areas.^{31,44} All the studies included in meta-analyses were at high risk for attrition bias, which may indicate overestimation of the prevalence of LUTSs in people with MS. Differences in sampling methods and outcome assessments lead to considerable heterogeneity, with wide CI ranges.

Discussion

To our knowledge, no published study to date has systematically reviewed the prevalence estimates of LUTSs and LUTS types in the general MS population.



Therefore, this study was conducted to systematically review and summarize existing data to obtain a summary estimate of the prevalence of LUTSs and LUTS types in the general MS population according to ICS definitions. In people with MS, LUTSs are highly prevalent, with an estimated prevalence of 68.4% for general LUTSs using self-report outcome measures and a prevalence of 63.95% using UDSs. This review showed that the most common symptom when using self-report measures is frequency, with a pooled prevalence estimate of 73.45%, followed by urgency (63.87%), incomplete bladder emptying (60.56%), nocturia (58.95%), and urinary incontinence (42.9%). The most common objectively measured symptoms were detrusor overactivity, with a pooled prevalence estimate of 42.9%, followed by detrusor-sphincter dyssynergia at 35.44%. Voiding symptoms were infrequently reported, and meta-analysis was not possible.

Compared with healthy individuals, LUTSs are predominant in the MS population. The present findings showed that the prevalence estimates of LUTSs and some types of storage symptoms were up to four times higher than those in the general population. A worldwide prevalence estimate⁴⁷ and other population-based surveys among healthy individuals^{48,49} reported the prevalence estimate of general LUTSs at 45.2%, far less than

the pooled prevalence from this review. Some storage symptoms were reported in healthy individuals: 45% to 57.7% for frequency and 36.6% for urgency,⁴⁷⁻⁴⁹ which is much less than the pooled prevalence from the present review. A study of 30,000 healthy individuals⁴⁹ found that nocturia was prevalent, with an estimate of 72.2%, which is greater than the estimates of prevalence for people with MS. This difference could be attributed to methodological issues, including use of the Epidemiology of LUTS (EpiLUTS) survey. The participants were asked to respond to each question related to LUTSs by choosing either *sometimes* or *often*. Different interpretations of each question among participants might lead to variety in reported responses that results in overestimates of the prevalence.

The LUTSs are more prevalent in people with MS than in those with other neurologic diseases. These prevalence estimates suggest that some types of storage symptoms are five times higher in people with MS than in stroke survivors. In a large sample of people with stroke, frequency was estimated to be 15% and urgency 19%,⁵⁰ which are significantly lower than for people with MS. Similarly, a systematic review investigating the estimates of LUTSs in patients with Parkinson disease⁵¹ reported that the prevalence of general LUTSs ranged from 27% to 85%, which is lower than the range of the prevalence

estimates reported in the present review. In addition, the ranges of prevalence estimates for frequency, urgency, and incomplete bladder emptying in patients with Parkinson disease were found to be 32% to 71%, 32% to 68%, and 8% to 28%, respectively, which is far less than the prevalence estimate ranges in people with MS in the present review. In contrast, nocturia in patients with Parkinson disease was the most prevalent storage symptom, with prevalence estimates ranging from 57% to 86%. This prevalence may be attributed to the age-related pathophysiological factors that contribute to Parkinson disease. Age-related physiological, hormonal, and structural factors play an important role in increasing the prevalence of nocturia.⁵²⁻⁵⁴

This systematic review raises issues about the methodological quality of the included studies, and there are learning points for future research in the area. Notably, most of the studies included in this review were conducted using either small groups of patients or larger cross-sectional populations recruited by online survey. Online surveys are typically prone to selection bias,⁵⁵ and this method of data collection may not obtain data from a representative MS sample. Recruitment through neurology clinics or rehabilitation services should be considered. Moreover, all the included studies were affected by attrition bias, and the number of respondents versus nonrespondents was not addressed by statistical analyses and needs to be considered in future studies.

In addition to issues of bias, there is a lack of consistency in self-report outcome measures used, with each study using a different measure. Interestingly, none of the studies that investigated frequency symptoms were consistent with the ICS recommendation of using a bladder diary. These factors led to considerable variability in study results, including wide CIs and considerable heterogeneity. The European Association of Urology guidelines recommend using validated questionnaires in future studies,⁸ which, in turn, will enable data synthesis and allow more detailed comparison of results from different studies.

There are limited studies in the literature comparing self-report measures against the reference standard of UDS-based diagnosis.⁵⁶⁻⁵⁸ A correlation has been shown between International Consultation on Incontinence Questionnaire–Short Form (ICIQ-SF) and urodynamic parameters⁵⁶ and between one question dealing with urgency urinary incontinence on the Urogenital Distress Inventory-6 (UDI-6) and UDSs.⁵⁷ These findings

would help reduce UDSs without negatively influencing patient condition. On the other hand, one study found that scores on the symptom scales of the Incontinence Impact Questionnaire-7 (IIQ-7) and UDI-6 were inadequate predictors of eventual urodynamic diagnoses.⁵⁸ Hence, no conclusion could be drawn for the correlation of self-report outcome measures and UDSs due to limited studies in the literature. Further studies are needed in this regard.

The strengths of this study are that the prevalence estimates are derived from studies of the general MS population and not solely from people with MS who had LUTSs. In addition, this review is seemingly the first to classify symptoms according to ICS definitions and to meta-analyze LUTSs across the storage, voiding, and micturition symptoms. Moreover, we used extensive search techniques and made every effort to ensure that the totality of literature was included in this review. A limitation of this review is that we limited it to studies published in the English language. Also, the generalizability of the results is poor because almost all the included studies were of poor quality. A further limitation is that the prevalence of LUTSs in the general MS population was not reported by sex in the included studies. Hence, there is a need for future study to establish the prevalence of LUTSs by sex in people with MS. Also, there is a lack of information in the literature

PRACTICE POINTS

- This review found that lower urinary tract symptoms are prevalent in people with MS using self-report and objective outcome measures.
- The most prevalent symptom using self-report measures was urinary frequency, with a pooled prevalence estimate of 73.45%, followed by urgency at 63.87%.
- Using the objective measure of urodynamic studies, detrusor overactivity was the most prevalent symptom, with a pooled prevalence estimate of 42.9%, followed by detrusor sphincter dyssynergia at 35.44%.
- There is a lack of consistency in self-report measures and methodological issues, such as attrition bias, among included studies. Therefore, there is a need for larger, high-quality studies using validated self-report outcome measures to estimate the prevalence of lower urinary tract symptoms in MS.

related to the prevalence of LUTSs accompanying types of MS. Therefore, we could not consider the prevalence of LUTSs among types of MS in the general MS population. This limitation should be considered in future studies. An additional consideration is whether the prevalence of LUTSs is in a treated or untreated population; it is possible that the prevalence would be reduced if the population included had recently undergone treatment for the condition, and this factor needs to be considered in future studies.

In conclusion, this systematic review revealed that LUTSs are highly prevalent in people with MS when using either self-report or UDSs. Frequency is the predominant symptom, followed by urgency, detected by self-report outcome measures; detrusor overactivity is the predominant symptom, followed by detrusor sphincter dyssynergia, detected by UDSs. There is a need for improved conduct and reporting of prevalence studies of LUTSs, including ICS classification, and for the use of validated self-report outcome measures to enable pooling of data in the future. □

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