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Systematic Review of the Epidemiology of Urinary Incontinence and Detrusor Overactivity among Patients with Neurogenic Overactive Bladder

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Key Words

Neurogenic overactive bladder · Neurological bladder dysfunction · Urinary symptoms · Detrusor overactivity · Urinary incontinence · Epidemiology · Systematic review

Abstract

Background: The prevalence and incidence of neurogenic overactive bladder (nOAB) are poorly defined. This systematic literature review identified nOAB epidemiological data and estimated the incidence and prevalence of urinary incontinence (UI) and detrusor overactivity (DO) in patients with multiple sclerosis (MS), spinal cord injury (SCI), Parkinson's disease (PD), stroke and spina bifida. An initial search of MEDLINE, Embase, PubMed, and the Cochrane library was supplemented by an internet search for grey literature and manual searching of the bibliographies of retrieved articles. Additional study selection identified comparable studies for statistical analysis. A descriptive statistical analysis, single-arm meta-analysis and stratified analysis were conducted using predefined criteria. ***Summary:*** Initial selection identified 189 articles containing prevalence data. Secondary selection for statistical analysis identified 39 and 52 articles with prevalence of UI and DO, respectively. Random-effect meta-analysis found the prevalence of UI was 50.9% in patients with MS, 52.3% with SCI, 33.1% with PD and 23.6% with stroke. Spina bifida was excluded due to insufficient data. The prevalence of DO may be biased and artificially elevated because it can only be measured with urodynamic investigations. ***Key Messages:*** A substantial proportion of patients with neurological conditions develop UI that may be attributable to nOAB.

Introduction

Overactive bladder syndrome (OAB), also known as urge syndrome or urgency-frequency syndrome, is characterized by urgency (with or without urgency urinary incontinence, UI), frequency and nocturia [1]. Patients who suffer from symptoms of OAB, where the cause is neurogenic, are often referred to as having neurogenic OAB (nOAB). The symptoms of OAB usually stem from

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overactivity of the detrusor muscle of the bladder (detrusor overactivity, DO) but may also be caused by other forms of urethrovesical dysfunction [1]. Where the cause of DO is neurogenic, the condition is known as neurogenic DO (nDO) [1, 2]. nOAB is most commonly seen in patients with multiple sclerosis (MS), spinal cord injury (SCI), Parkinson's disease (PD), cerebrovascular accident/stroke and spina bifida [3–7]. In the majority of cases in the literature, UI among patients with underlying neurological conditions was found to be associated with nOAB and attributable to DO [8, 9].

The clinical presentation, symptoms and course of nOAB vary depending on the nature of the underlying neurological condition. The diagnosis is made based on the history, examination and urodynamic assessment [10].

A range of terms are used in published literature to describe bladder dysfunction caused by neurological disorders. The most common term used is 'neurogenic bladder,' which describes bladder dysfunction due to neurological dysfunction which may be caused by trauma, disease or injury [11]. Neurogenic bladder is a nonspecific term that may describe conditions ranging from areflexic noncontractile bladder to DO. The range of terms used causes difficulties in evaluating the literature to assess the prevalence and incidence of nOAB [12].

In the absence of any systematic reviews of the epidemiology of this condition, a systematic literature review was undertaken to estimate the incidence and prevalence of UI and DO in patients with 5 neurological conditions: MS, SCI, PD, stroke and spina bifida. These 5 conditions were selected as being conditions in which bladder dysfunction is well documented.

Methods

Search Strategy

The PICOS (population, interventions, comparisons, outcomes and study designs) Systematic Reviews [13] elements were as follows: population, patients with nOAB or with conditions considered to be alternate terms for nOAB (online suppl. table A; for all online suppl. material, see www.karger.com/doi/10.1159/000353274; alternative terms were considered because of the wide variation in terminology used for neurogenic bladder disorders), UI and/or DO associated with either MS, SCI, PD, stroke or spina bifida, and outcomes of prevalence or incidence data. The search was divorced from interventions, comparisons and study design. Relevant papers were identified through electronic searches of MEDLINE, Embase, PubMed and the Cochrane library. The searches were performed on June 25, 2010 and were not limited initially by date or language. In addition, an internet search was undertaken for grey literature, and relevant articles were searched manually for further references.

Selection Criteria

Citations/abstracts of identified studies were reviewed and assessed for relevance. Full paper copies of studies considered to be relevant were reassessed for inclusion against predefined criteria. This systematic literature review was intended to be exhaustive; therefore, various types of studies were initially included (e.g. studies assessing prognostic factors or quality of life) in addition to population-based epidemiological studies. This study selection based on the predefined criteria has been termed 'study selection 1' and the criteria for selection are listed in table 1.

An initial review of the data from the citations identified in study selection 1 yielded a wide range of point estimates within the data because of the significant heterogeneity of the patient populations across the studies. To produce a more accurate estimate of the prevalence of UI and DO, a second study selection was performed (termed 'study selection 2') in order to identify the most comparable studies for statistical analysis. Inclusion/exclusion criteria used for study selection 2 are also listed in table 1.

Two independent researchers performed all stages of study selection. Any disagreements between reviewers were resolved by discussion until consensus was reached.

Data Collection and Analysis

Two researchers extracted incidence and prevalence data from included articles after study selection 1 into a data extraction table according to a predefined set of parameters. Incidence was defined as the number of new cases of nOAB or equivalent indication within each of the patient populations, with the neurological conditions of interest occurring during a specific time. Prevalence was defined as the total number of cases of nOAB or equivalent indication within the general patient population with each neurological condition of interest at a certain time.

Following study selection 2, a descriptive statistical analysis was conducted, followed by single-arm meta-analysis and stratified analysis using predefined criteria. The outcomes of interest in this analysis were the rates of UI and DO in patients with each of the conditions of interest (MS, SCI, PD and stroke). Results for spina bifida were not included in the statistical analysis because insufficient data were found. All analyses were performed in Stata SE version 8.2. (Stata Corp LP, College Station, Tex., USA).

UI and DO Meta-Analyses

The rates of DO and UI and their precisions in each study were calculated. These were then combined to produce a pooled estimate of the rate of DO and UI in patients with each neurological disease of interest. Pooling was done using both fixed-effect and random-effect models. The fixed-effect model was run using the inverse variance method, and the random-effect model was run using the DerSimonian and Laird methods [14]; the estimate of heterogeneity was taken from the inverse variance model. Heterogeneity was assessed using Cochran's Q test and the I^2 statistics [15, 16].

For each outcome, additional random-effect models were run within prespecified subgroups of interest, which included year of publication, geographical location, sample size, urinary symptoms assessment method, use of urinary symptoms as criteria for study inclusion, and study type as stratification factors (online suppl. table B).

Table 1. Inclusion and exclusion criteria: study selection rounds 1 and 2

Selection stage	Inclusion criteria	Exclusion criteria
Study selection 1	– Studies reported in English of human subjects conducted in any country – Studies evaluating the epidemiology of nOAB (or alternate terms[1]), UI or DO associated with MS, SCI, PD, stroke or spina bifida – Studies reporting epidemiology end points of incidence and/or prevalence – Epidemiology studies [cohort (prospective), case-control (retrospective), or cross-sectional (prevalence) in design], systematic reviews or meta-analyses.	– In vitro or other preclinical studies – Editorials, letters, case reports, commentaries, interview-based market research, legal cases, newspaper articles or patient education materials – Studies reporting epidemiology data for nOAB (or alternate terms), UI or DO associated with conditions other than the neurological conditions of interest – Studies assessing disease management strategies or treatments as the primary aim or end point
Study selection 2	– Studies reporting data from unselected patient populations only – Original research in form of observational studies (prospective or retrospective cohort, or cross-sectional) – Studies exploring rates[2] of any type of incontinence and/or DO[3] – Studies reporting relevant data in patients with MS, SCI, PD, stroke or spina bifida – Adults (>17 years) – UI only: assessed using validated incontinence instruments, patient questionnaires, medical evaluation or review of medical charts – DO only: diagnosed and assessed urodynamically	– Studies reporting data from selected patient populations, i.e. data from: – Disease subgroups – Disease severity subgroups – Subgroup of patients experiencing a particular symptom – Patients who had undergone a particular treatment or management strategy – Patients reviewed in only 1 medical department – Studies including patients specifically stated to have surgically altered bladder, prostate enlargement or preexisting history of any kind of urinary symptoms – Studies including patients specifically stated to have SCI of nontraumatic origin – Stroke studies in which patients were assessed at or prior to 3 months after stroke

[1] See online supplementary appendix A for a list of alternative terms.
[2] Outcomes had to be reported as the number of patients who had UI and/or DO as a fraction of the total number of patients with the neurological condition assessed.
[3] Also termed detrusor hyperplasia or detrusor hyperactivity in older literature.

Results

Study Selection

An overview of the study selection process and results are summarized in the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow chart in figure 1. A total of 2,742 articles were identified from the electronic database search during study selection 1, of which 186 contained epidemiology data. Analysis and comparison of the epidemiology data identified through study selection 1 proved challenging because of the wide range of terminology used to describe nOAB. Several studies used a variety of terms such as neurogenic bladder, neuropathic bladder and bladder dysfunction, while other studies considered specific clinical conditions such as detrusor hyperreflexia or specific symptoms such as incontinence or urgency. In addition, it was difficult to compare epidemiological data between studies because of the different baseline characteristics of the patient populations such as different disease stages and severity. All of these factors contributed to the heterogeneity of the results of this systematic review. The ranges of prevalence estimates were wide and therefore inconclusive. To address this, a statistical approach was adopted requiring a second study selection to identify suitable data for the statistical analysis.

To perform the analysis on the existing data, additional study selection (study selection 2) was performed to identify studies that were closest to the general patient population and comparable within each neurological condition of interest. Using the criteria for study selection 2 listed in table 1 to assess the 186 studies in-

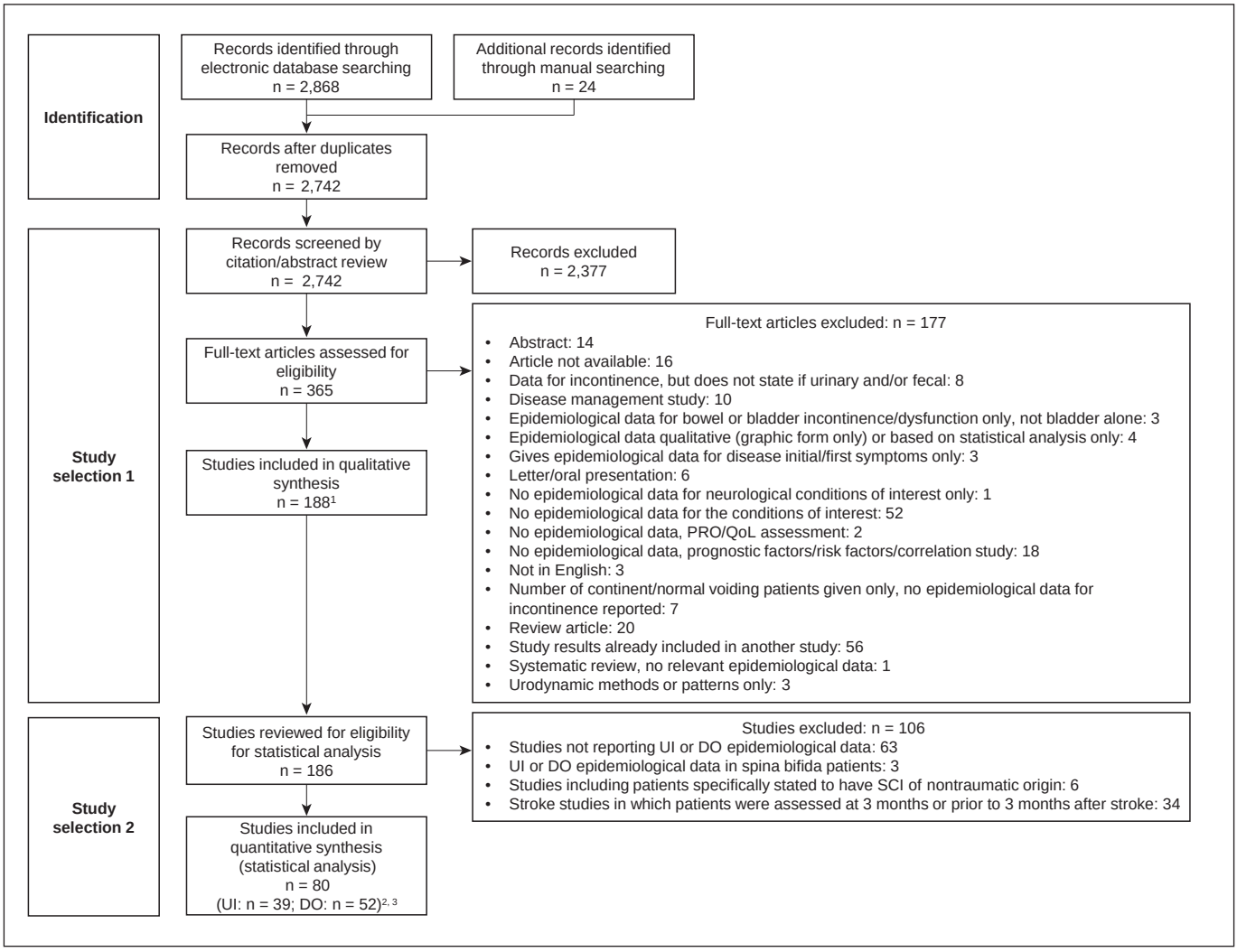

Fig. 1. PRISMA flow chart. PRO = Patient-reported outcomes; QoL = quality of life. [1] 186 epidemiological studies and 2 systematic reviews. [2] 11 studies were included for both UI and DO analysis. [3] 2 studies measured DO in multiple neurological populations.

cluded after study selection 1, 39 articles that reported prevalence of UI and 52 articles that reported prevalence of DO were included for statistical analysis. Details of these articles are given in online supplementary tables C and D.

Evidence Identified (after Study Selection 1)

Systematic Reviews

Two systematic reviews that reported the prevalence of urological problems in patients with MS were identified [17, 18]. Reported clinical symptoms included urgency (32–86%), incontinence or urgency (19–80%), frequency or urgency (31–85%) and incontinence (37–72%). Conditions that were identified urodynamically included DO (34–99%) and detrusor underactivity (0–40%).

Qualitative Assessment of Studies

All 186 epidemiology studies identified by the initial study selection reported prevalence data; however, none of these studies reported the incidence of urological symptoms, including nOAB, for any of the neurological conditions of interest. The earliest study identified was published in 1973 and investigated detrusor areflexia in patients with MS [19].

Multiple Sclerosis. A total of 45 studies reported rates of urological symptoms in patients with MS. The prevalence of these symptoms ranged from 6.9% (defined as incontinence) in an Italian single-center study of 101 unselected patients [20] to 95% (defined as symptomatic voiding dysfunction) in a Japanese study of 32 patients referred for neurourological evaluation [21]. The prevalence of detrusor hyperreflexia ranged from 27% in a sample of consecutive patients admitted to 2 neurological centers in Italy [22] to 91% among 70 patients who underwent cystometric evaluation in a UK study [9]. The highest estimate of detrusor hyperreflexia for a relatively unselected group of patients was 70% among 113 patients treated at a medical center in Los Angeles, Calif., USA [23].

Spinal Cord Injury. A total of 35 studies reported prevalence data for urinary symptoms in patients with SCI. Studies were divided into traumatic and nontraumatic SCI studies. The prevalence of urinary symptoms in patients with traumatic SCI ranged from 20% in a study of Medicare beneficiaries admitted to inpatient rehabilitation facilities [24] to 88.3% in a Brazilian study of 60 patients [25]. The prevalence of urinary symptoms in patients with nontraumatic SCI ranged from 5.9% at 6-month follow-up in a UK study of 25 patients with newly diagnosed non-Hodgkin's lymphoma [26] to 90% in a Pakistani study of 20 patients with a principal diagnosis of acute transverse myelitis [27]. The most frequent condition identified urodynamically was detrusor hyperreflexia. Its prevalence ranged from 11% among 70 patients referred to the Brazilian National Spinal Cord Injury Centre [28] to 85% among 42 men with thoracic lesions admitted to an SCI center in India [29].

Parkinson's Disease. The prevalence of urinary symptoms in patients with PD, reported in 28 studies, ranged from 3% for detrusor hyperreflexia with detrusor-sphincter dyssynergia in a Japanese study of 70 patients [30] to 94% for urge incontinence in a US study of 17 women referred to a urodynamic laboratory for evaluation [31]. The prevalence of detrusor hyperreflexia alone ranged from 7.7% among a sample of 52 consecutive patients in an Italian study [22] to 93% among 30 patients referred for urodynamic evaluation for symptomatic urinary dysfunction [32].

Stroke. Data on the prevalence of urological symptoms in stroke patients were reported in 61 studies. The prevalence of such symptoms ranged from 11.1% (UI) in a Dutch study of 143 patients with first-time unilateral hemispheric stroke assessed 36–43 days after stroke onset [33] to 70% (urgency) and 76% (nocturia) in a Danish single-center study of 407 patients [34]. The prevalence of bladder dysfunction identified urodynamically ranged from 3% (reported as storage disorder with hypoactive detrusor) in a Turkish study of 33 patients [35] to 90% (reported as DO) in a study of 40 patients referred for urodynamic evaluation in India [4].

Spina Bifida. Data on the prevalence of urological symptoms in patients with spina bifida were identified in 25 studies. The prevalence of urological symptoms ranged from 12% (reported as incontinence at long-term follow-up) in an Italian study of 34 children with occult spinal dysraphism [36] to 94.9% (reported as bladder dysfunction) in 39 children with myelomeningocele in Taiwan [37]. The highest prevalence of conditions identified urodynamically was 98% (reported as neuropathic bladder) in an Italian study of 244 patients with myelomeningocele [38]. The prevalence of detrusor hyperreflexia varied from 25% in a US study of 11 patients [39] to 76% in an Italian study of 34 children with occult spinal dysraphism [36]. The prevalence of detrusor areflexia varied from 13.0% in an Italian multicenter study of 46 consecutive patients [22] to 49.5% in a Dutch study of 91 patients followed up for 7 years [40]. Owing to the significant heterogeneity across all studies within each neurological population, these results were not considered conclusive. Therefore, additional criteria were applied (study selection 2) to isolate studies that specifically measured UI and/or urodynamically confirmed DO in the general neurological populations of interest so that these data could be pooled in order to obtain a point estimate.

Statistical Analysis (after Study Selection 2)

Prevalence of UI: Meta-Analysis

The degree of heterogeneity within these data was highly significant ($p < 0.001$, $I^2 > 90\%$) in all 4 neurological diseases. The random-effect model was therefore more appropriate than the fixed-effect model. The results of the meta-analysis are summarized in table 2. Spina bifida was excluded at this stage because of insufficient data. The results of the meta-analysis of studies reporting the UI rate in MS, SCI, PD and stroke patients are shown in online supplementary tables E–H and figures 2–5.

Prevalence of DO: Meta-Analysis

The degree of heterogeneity within these data was highly significant ($p < 0.001$, $I^2 > 75\%$) in all 4 neurological diseases. The random-effect model was therefore more appropriate than the fixed-effect model. The random-effect meta-analysis found that the prevalence of DO was 58.2% (50.5–65.9) in patients with MS, 49.7%

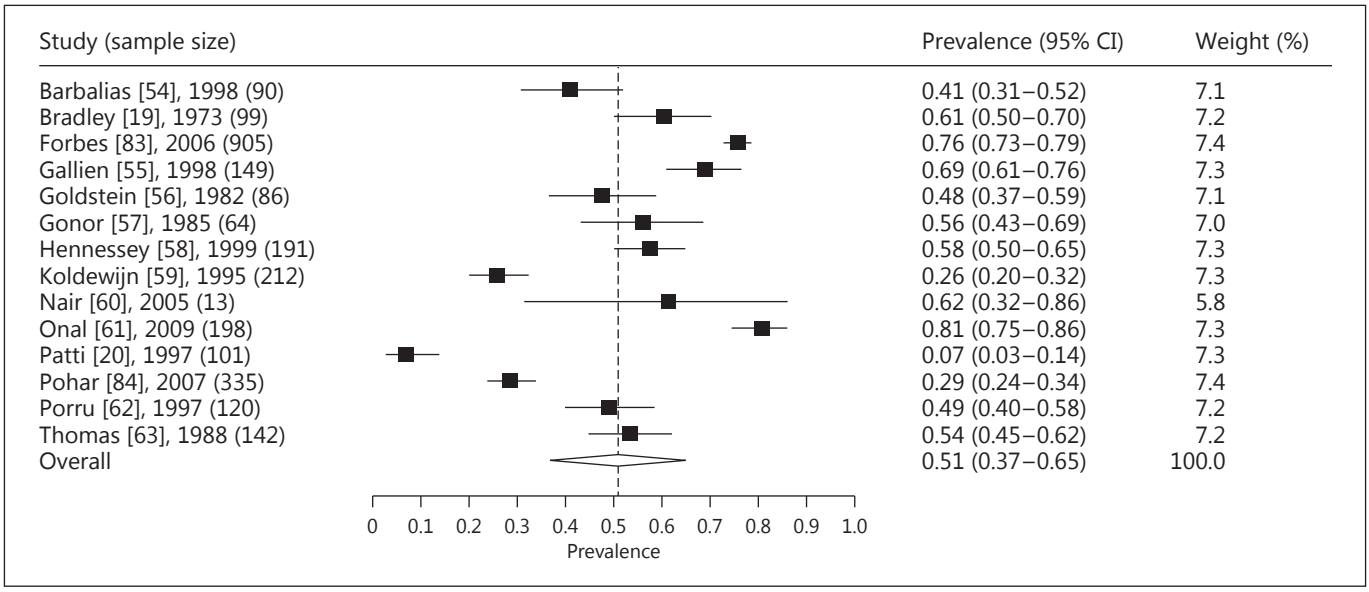

Fig. 2. Prevalence of UI in patients with MS (random-effect model) [19, 20, 54–63, 83, 84]. CI = Confidence interval.

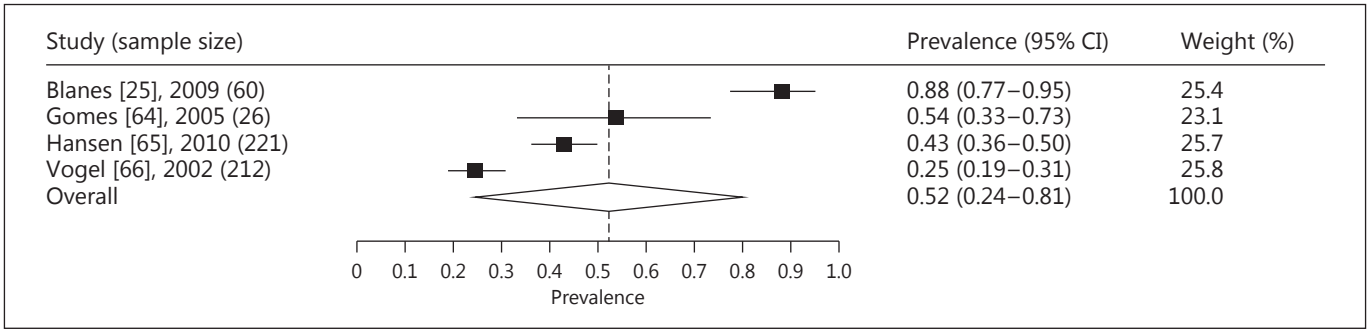

Fig. 3. Prevalence of UI in patients with SCI (random-effect model) [25, 64–66]. CI = Confidence interval.

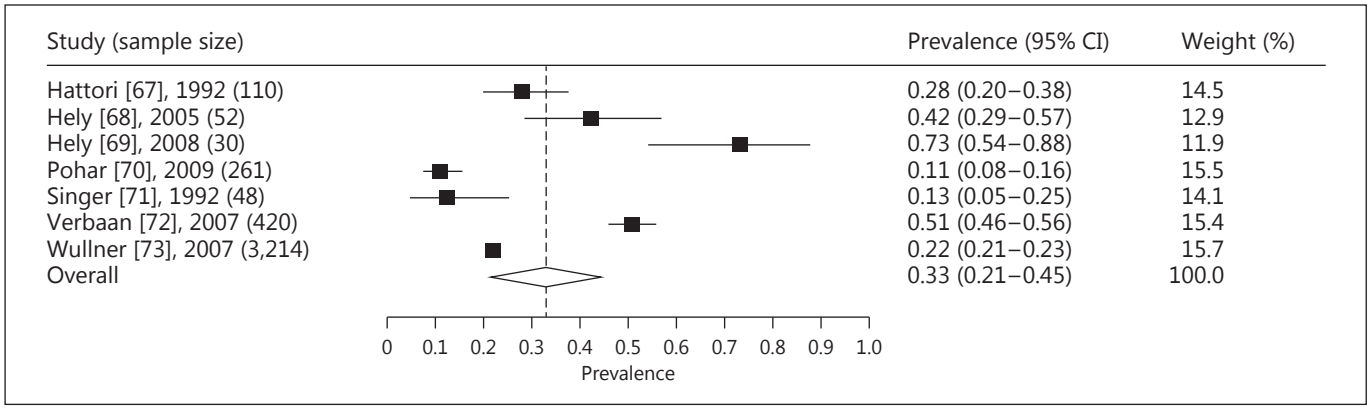

Fig. 4. Prevalence of UI in patients with PD (random-effect model) [67–73]. CI = Confidence interval.

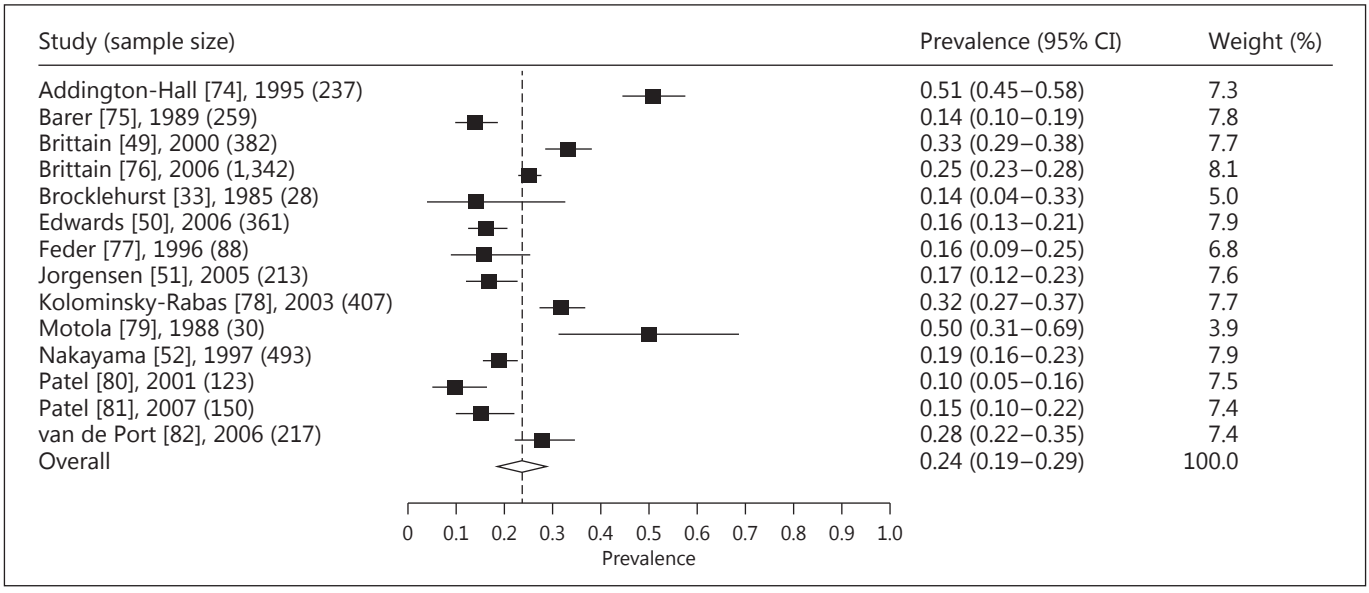

Fig. 5. Prevalence of UI in patients with stroke (random-effect model) [33, 49–52, 74–82]. CI = Confidence interval.

Table 2. Results of meta-analyses for prevalence of urinary incontinence: pooled rates (95% CI)

Neurological disease	Random-effect meta-analysis	Heterogeneity
MS	0.509 (0.367–0.650)	$I^2 = 98.4\%$, $p < 0.001$
SCI	0.523 (0.238–0.807)	$I^2 = 97.8\%$, $p < 0.001$
PD	0.331 (0.213–0.448)	$I^2 = 97.1\%$, $p < 0.001$
Stroke	0.236 (0.185–0.288)	$I^2 = 93.0\%$, $p < 0.001$

The table summarizes the point estimates (%) for each neurological condition. The random-effect model takes into account that the effect size (prevalence) is similar, but not identical, across studies owing to inherent differences across studies. The I^2 statistic is a measure of the inconsistency across study findings and reflects the amount of variance present across studies on a relative scale. p values determined using χ^2 test.

(37.3–62.2) in patients with SCI, 58.6% (34.3–83.0) in patients with PD and 64.7% (54.2–75.3) in patients with stroke. Details of the meta-analysis results by neurological condition are presented in online supplementary tables I–L and online supplementary figures A–D.

For both UI and DO, the stratified analysis did not identify any significant trends. However, the number of studies included in the statistical analysis was limited and was not sufficient for the analysis to produce meaningful results. Detailed results of this analysis are not presented here.

Discussion

Analysis and comparison of the epidemiology data identified proved challenging because of the wide range of terminology used to describe nOAB. Several studies used terms such as neurogenic bladder, neuropathic bladder and bladder dysfunction, while other studies considered specific clinical conditions such as detrusor hyperreflexia or specific urinary symptoms such as incontinence or urgency. The International Continence Society terminology committee has recently provided strict definitions to be used in order to standardize the terminology used in this field; however, such naming conventions are still not being used consistently in the research when describing and studying lower urinary tract symptoms [41]. In fact, 2 large and notable MS studies that focused on urinary symptoms in this patient population [42, 43] were excluded during study selection 2 because, even though they measured the impact of UI symptoms on patients, they did not explicitly ask patients whether symptoms of nOAB with UI were present. Therefore, prevalence estimates could not be extracted from those studies.

In addition to inconsistency in the terminology used, comparison of epidemiological data between studies proved difficult because of the different baseline characteristics of the patient populations assessed such as underlying neurological disease stage and severity. For example, bladder dysfunction has been shown to correlate

with disability status in patients with MS [20], voiding dysfunction has been shown to develop progressively with advancing disease in patients with PD [30], and the type of bladder dysfunction is significantly associated with the degree of injury in patients with SCI [44]. In addition, patients are often reluctant to discuss symptoms with their health care providers, so it is difficult to assess at what point over the course of the disease they experienced UI and/or DO [45].

This review found that the prevalence of urinary symptoms is likely to increase with the duration of PD and MS. For example, the prevalence of urinary symptoms was 39.3% at a mean disease duration of 4.9 years in a Brazilian study of 61 patients with PD [46] and 64.0% at a mean disease duration of 17.1 years in a Spanish study of 50 patients with PD [47]. In a systematic review of patients with MS, detrusor-sphincter disorders did not appear until an average of 6 years (range 5.0–9.5) after disease onset [17]. Another study of patients with MS also showed that urinary symptoms increase with disease duration [42].

While there is a clear increase in symptoms associated with nOAB as PD and MS progresses over time to more advanced stages of the disease, the trend is less clear among patients with SCI and stroke. Patients with traumatic SCI that affects bladder functioning do not necessarily experience progression in neurological deficits over time, nor are they typically able to regain neurological functioning [48]. In stroke patients, this pattern depends more on the nature and severity of the cerebrovascular insult, as well as the ability of the patients to recover from the incident. While UI may be highly prevalent in the acute phase of a stroke, symptoms may or may not resolve over time as patients regain neurological functioning [49–52]. Nevertheless, the prevalence of UI was notable in each of these patient populations, affecting over half of the patients with MS and SCI (50.9 and 52.3%, respectively), one third of patients with PD (33.1%), and nearly a quarter of all stroke patients at least 3 months after the acute incident (23.6%).

Estimates for the prevalence of DO were also obtained from this study; however, these results should be interpreted with caution as DO can only be measured with urodynamic investigations. Patients are typically only referred for urodynamic workup if they are experiencing bothersome symptoms. Therefore, the DO estimates in this population are likely biased and higher than what would be expected in the population for each neurological condition. In addition, most of these studies had small patient populations (39 out of the 52 identified trials reporting DO prevalence data included less than 100 patients).

One limitation of this review is that the number of articles identified was insufficient for a reasonable stratified analysis. The meta-analysis should be interpreted with caution for this same reason. In addition, non-English language studies were excluded at the study selection stage. It also needs to be noted that no studies were identified reporting incidence data. The review was also limited by the variability in terms used to describe nOAB/nDO in the literature. Moreover, the restriction of the DO analysis to include only urodynamic studies caused the studied patient population to be limited to those with urinary symptoms, which led to smaller sample sizes. Finally, it is important to note that the literature search was conducted in 2010. Since this time, at least 1 study of interest has been published that was not included in this analysis to the authors' knowledge [53].

Despite these limitations, results of this review confirm that a substantial proportion of patients with underlying neurological conditions experience urinary issues. The available data, however, are insufficient to detail the exact proportion of the various urological symptoms at the various stages of the disease. This is partly the result of inconsistent terminology used to describe lower urinary tract symptoms in neurological patients. Future epidemiological studies should consistently adhere to the definitions established in 2002 by the International Continence Society. Finally, registries stratifying urinary symptoms at the various stages of diseases like MS, stroke and SCI are still needed so that clinicians know when inquiry about urinary symptoms is warranted.

Conclusions

This systematic review of the literature did not identify any data on the incidence of neurogenic bladder disorders in patients with PD, SCI, MS, stroke or spina bifida. The prevalence of urological problems varied widely, most likely reflecting the inconsistent terminology used to describe the lower urinary tract symptoms of interest. Future epidemiological studies should consistently adhere to the definitions established in 2002 by the International Continence Society. Despite these limitations, results of the meta-analysis confirm that a substantial proportion of patients with underlying neurological conditions develop nDO and UI.

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Disclosure Statement

Mamuka Teneishvili and Meredith Edwards are employees of PRMA Consulting. Hetal Patel, Kristin Khalaf, Ahunna Onyenwenyi and Denise Globe are employees of Allergan EAME. PRMA Consulting received research funding from Allergan EAME.

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