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Review – Neuro-urology

Nocturia and Nocturnal Polyuria in Neurological Patients: From Epidemiology to Treatment. A Systematic Review of the Literature

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Abstract

Context: Nocturia is among the most common and bothersome lower urinary tract symptoms (LUTS), but there is no clear consensus on how to identify and manage this symptom in the neurological population.

Objective: To systematically review the literature about nocturia in neurological patients.

Evidence acquisition: Studies were identified by electronic search of Cochrane and Medline databases. The studies were included if their participants had acquired neurological pathology among multiple sclerosis (MS), Parkinson's disease (PD), stroke, spinal cord injury (SCI), and reported data on the epidemiology, aetiology, diagnosis, or treatment of nocturia. An independent extraction of the articles was performed by two authors using predetermined datasets, including quality-of-study indicators.

Evidence synthesis: A total of 132 studies were included; 46 evaluated the epidemiology of nocturia, 28 the possible aetiologies, 10 the diagnostic tools, and 60 the treatments. Nocturia prevalence ranged from 15% to 96% depending on the pathology and definition used. It was one of the most frequently reported LUTS in PD and stroke patients. Several validated questionnaires were found to screen for nocturia in this population. Causalities were numerous: LUT, renal, sleep, cardiovascular dysfunctions, etc. Treatments targeted these mechanisms, with an overall risk of bias assessed as high or serious. The highest level of evidence was seen in MS patients: pelvic floor muscle training, cannabinoids, and desmopressin were effective, but not melatonin. In stroke patients, transcutaneous sacral and transcutaneous tibial nerve stimulation (TTNS) improved nocturia; in PD patients, TTNS, solifenacin, and rotigotine did not.

Conclusions: Nocturia is highly prevalent in patients with neurological disorders. Causalities and treatments are not different from the general population, but are poorly studied in neurological patients.

Patient summary: In this report, we looked at the published studies about nocturia—the fact of waking to void during the hours of sleep—in patients with neurological diseases. We found that nocturia is very frequent in this population, that the causes are the same as in the general population but may be combined, and that treatments are also the same but have an overall weak level of evidence. We conclude that more research is needed on this topic.

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1. Introduction

Neurological disorders are the leading cause of disability-adjusted life-years and the second leading cause of death [1]. Lower urinary tract (LUT) dysfunction frequently occurs following neurological disorders, and LUT symptoms (LUTS) significantly impact quality of life. Nocturia, defined as the act of waking to void during the hours of intended sleep [2], is among the most common and bothersome LUTS [3]. The epidemiology of LUTS such as overactive bladder (OAB) syndrome and urinary incontinence is well documented in patients with neurological impairment [4]; however, nocturia is poorly described. Nocturia occurs through three main pathological mechanisms: nocturnal urine production (UP), bladder function, and sleep. Abnormal nocturnal UP commonly presents as nocturnal polyuria (NP), which affects up to 88% of adults with nocturia [5]. Indeed, the pathophysiology of nocturia is far more complex [6], with different aetiologies and organ involvement including cardiovascular system (blood pressure [BP] changes, cardiac dysfunction, fluid shift into the lower limbs, etc.), renal function (polyuria, circadian rhythm, diabetes, etc.), sleep (obstructive sleep apnoea [OSA], insomnia, etc.), LUT (OAB, bladder outlet obstruction [BOO], etc.), hormonal changes, and intake (metabolic syndrome, fluid, salt, etc.). In neurological patients, some of these aetiologies, such as OAB, may be over-represented and others may be more frequent depending on the type of pathology. For example, cardiovascular causes are more frequent in patients with dysautonomia in Parkinson's disease (PD), and OSA is frequently found in patients with stroke due to the associated metabolic syndrome. The International Continence Society (ICS) has published guidelines for the management of nocturia in the general population [7]; however, there is no consensus in the neurological population (Supplementary material).

The aim of this study is to systematically review the literature about nocturia and NP in patients with neurological diseases, particularly stroke, PD, multiple sclerosis (MS), and spinal cord injury (SCI).

2. Evidence acquisition

This systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [8].

The Medline and Cochrane library databases were searched with no restriction on the date of publication (date of final search August 2019). The complete search strategy is available in the Supplementary material. English- or French-language comparative (randomised controlled trials [RCTs] and non-RCTs), meta-analysis, or observational studies were included if studying adults (≥ 18 yr old) had acquired neurological pathologies limited to PD, stroke, MS, or SCI. Outcomes were related to the evaluation of nocturia and/or NP: frequency, aetiology, diagnosis, and treatment.

Two review authors independently screened the titles and abstracts of identified records, and the full text of

potentially eligible records were evaluated and extracted using a standardised spreadsheet (Supplementary Tables 1–4). Risk of bias was assessed using the Revised Cochrane Risk-of-Bias (RoB 2) tool for RCTs [9], Risk of Bias In Non-randomized studies of Interventions (ROBINS-I) tool [10], Risk of Bias Assessment tool for Non-randomized Studies (RoBANS) tool [11], the Consensus-based Standards for the selection of health Measurement INstruments (COSMIN) checklist [12], and the quality assessment checklist for prevalence studies [13] when appropriate (Supplementary Tables 1,3, and 4, and Supplementary Fig. 1). Level of evidence (LOE) was assessed according to the Oxford Centre for Evidence-Based Medicine 2011 LOE grading system [14] (Supplementary Tables 1,2, and 4, and Tables 1–3).

3. Evidence synthesis

Of the 132 studies included (Fig. 1), 46 evaluated the epidemiology of nocturia (overall risk of bias: moderate), 28 evaluated the possible aetiologies (overall risk of bias: high for confounding variables, low for measurement of exposure, and unclear for selection of the participants and incomplete outcome data, blinding of outcome assessments, and selective outcome reporting), 10 evaluated the diagnostic tools (see below for the risk of bias), and 60 evaluated the treatments for nocturia or NP (overall risk of bias: high for RCTs, serious for non-RCTs).

Table 1 – Summary: epidemiology of nocturia and nocturnal polyuria among neurological patients.

	Level of evidence
Nocturia seems to be one of the most bothersome LUTS after a stroke	3
Nocturia appears to be as common in women as in men after a stroke	3
Nocturia is frequent among MS patients	3
Nocturia is frequent among PD patients	1
Nocturia is one of the most frequent NMSs in PD patients	3
Nocturia is one of the most frequent LUTS in PD patients	3
Age, late onset of the disease, disease duration, and severity are associated with nocturia in PD	3
Data are conflicting regarding gender-related prevalence of nocturia in PD patients	3
Data are conflicting regarding trends in nocturia prevalence over the course of the disease in PD patients	1
NP prevalence depends on its definition in SCI patients	3
CEBM = Oxford Centre for Evidence-Based Medicine; LUTS = lower urinary tract symptoms; MS = multiple sclerosis; NMS = nonmotor symptom; NP = nocturnal polyuria; PD = Parkinson's disease; SCI = spinal cord injury. The level of evidence was based on CEBM classification.	

Table 2 – Summary: causalities and diagnosis of nocturia among neurological patients.

	Level of evidence
<i>Causalities</i>	
Lower urinary tract dysfunction	
DO is frequent in PD patients with nocturia	3
DO is frequent in MS patients with nocturia	3
White matter brain lesions are associated with nocturia severity in stroke patients	3
Brain volume is associated with nocturia in PD patients	3
Sleep disorders	
OSA is frequent after a stroke and is a plausible cause of nocturia	3
Hypnotics intake is associated with nocturia in stroke patients	3
Data are conflicting regarding the role of RBD in PD patients	3
Cardiovascular dysfunction	
Abnormal BP circadian pattern, especially reverse dipping pattern, is associated with NP in SCI patients	3
Abnormal circadian pattern of solute and water clearance could be driven by abnormal BP in SCI patients	4
Renal dysfunction	
Nocturnal polyuria seems to be frequent in PD patients with nocturia	3
Abnormal circadian pattern of solute (sodium and urea) and water clearance is associated with NP in SCI patients	3
Abnormal circadian pattern of solute and water clearance could be driven by abnormal BP or fluid shift due to fluid retention in SCI patients	4
<i>Diagnosis</i>	
In stroke patients, DAN-PSS is a validated PROM	3
In PD patients, NMSQuest, NMSS, PDSS-2, NSDQ, and SCOPA-AUT are validated PROMs	3
In MS patients, UDI and NBSS are validated PROMs	3
In SCI patient, NBSS is a validated PROM	3
BP = blood pressure; CEBM = Oxford Centre for Evidence-Based Medicine; DAN-PSS = Danish Prostatic Symptom Score; DO = detrusor overactivity; MS = multiple sclerosis; NBSS = Neurogenic Bladder Symptom Score; NMSQuest = Non Motor Symptoms Questionnaire; NMSS = Non-Motor Symptoms Scale; NP = nocturnal polyuria; OSA = obstructive sleep apnoea; PD = Parkinson's disease; PDSS 2 = Parkinson's Disease Sleep Scale version 2; PROM = patient-reported outcome measure; RBD = rapid eye movement sleep behaviour disorder; SCI = spinal cord injury; UDI = Urge-Urinary Distress Inventory. The level of evidence was based on CEBM classification.	

Table 3 – Summary: treatment of nocturia and nocturnal polyuria among neurological patients.

	Level of evidence
<i>Interventions targeting cardiovascular dysfunction</i>	
In SCI patients with lower limb oedema, multilayer compressive bandages are efficient	3
In SCI patients, locomotor training may be efficient	3
<i>Interventions targeting lower urinary tract dysfunction</i>	
In MS patients with OAB, PFMT is efficient	2
In stroke patients with OAB, TENS applied to sacral dermatomes or TTNS is efficient	1
In PD and MS patients with OAB, PTNS is efficient	3
In PD, MS, and SCI patients with OAB, oxybutynin is efficient	3
In PD patients with OAB, mirabegron is efficient	3
In MS patients with OAB, cannabinoids are efficient	2/3
In PD and MS patients with refractory OAB, botulinum toxin detrusor injections are efficient	3
In incomplete SCI and MS patients with OAB, SNM test implantation is efficient	3
<i>Interventions targeting renal dysfunction</i>	
In MS patients, oral or intranasal desmopressin is efficient	1
In SCI and PD patients, oral or intranasal desmopressin is efficient	3
<i>Interventions targeting sleep</i>	
Melatonin is not efficient in PD patients	2
CPAP is effective in reducing NP only in stroke patients	3
CEBM = Oxford Centre for Evidence-Based Medicine; CPAP = continuous positive airway pressure; MS = multiple sclerosis; NP = nocturnal polyuria; OAB = overactive bladder syndrome; PD = Parkinson's disease; PFMT = pelvic floor muscle therapy; PTNS = percutaneous tibial nerve stimulation; SCI = spinal cord injury; SNM = sacral neuromodulation; TENS = transcutaneous electrical nerve stimulation; TTNS = transcutaneous tibial nerve stimulation. The level of evidence was based on CEBM classification.	

3.1. What is the epidemiology of nocturia and NP in patients with neurological diseases?

3.1.1. Idiopathic PD

Nocturia was one of the most frequently reported nonmotor symptoms (NMSs) in PD, with a prevalence ranging widely between 15% [15] and 86% [16], depending upon the

definition and assessment tool used. Most studies did not use a threshold to define the presence of nocturia [16–38]. This was the case for studies using the Non Motor Symptoms Questionnaire (NMSQuest) [17–29] in which prevalence of nocturia ranged between 26% and 83%; the Non-Motor Symptoms Scale (NMSS) [30–33], showing a prevalence from 38% to 67%, or the International Prostate

Fig. 1 – Flow diagram. MS = multiple sclerosis; NP = nocturnal polyuria; PD = Parkinson's disease; SCI = spinal cord injury.

Score Symptom [16,34,35], with a prevalence ranging from 64% to 86%; and the International Continence Society Male Short Form questionnaire [36] in which prevalence was found to be 81%. Studies using a threshold of more than one void per night to define nocturia suggested a prevalence of 38% [39], whereas in those using two or more voids per night [40–43], the prevalence ranged between 35% and 57.5%. Little was found about the evolution of nocturia with the course of the disease, and results of two studies were conflicting: one reporting an increase of nocturia frequency over time [44], whereas the other did not show significant differences [28].

3.1.2. Multiple sclerosis

When the threshold of one or more episodes per night was used, the prevalence of nocturia ranged between 53.3% [45] and 94% [46]. Using the threshold of two voids per night, the prevalence ranged between 31.7% [47] and 82% [46]. Four studies did not define any threshold [48–51].

3.1.3. Stroke

Nocturia has been found to be significantly more frequent amongst stroke survivors compared with the nonstroke population [52]. When the threshold of one or more episodes per night was used, nocturia prevalence ranged from 45.7% [53] to 82.2% [54]. Using the threshold of two voids per night, the

prevalence ranged between 49% [52] and 50.6% [54]. Four studies did not define a threshold [55–58]. One study reported an increase in nocturia over time after stroke, but statistical significance was not tested [53].

3.1.4. Spinal cord injury

Only two studies have investigated the epidemiology of nocturia and NP in patients with SCI. NP was a reason for referral in 7.4% of patients referred for the management of a BP disorder [59], but the exact prevalence of NP or nocturia is unknown, and only mean values of Nocturnal Polyuria index (NPI) were described. However, the mean NPI was significantly greater in acute SCI patients when compared with chronic SCI; no difference was found between complete and incomplete SCI. Viaene et al [60] reported a 57.4–100% prevalence of NP in 47 SCI patients hospitalised in rehabilitation, depending on the definition and cut-off used. In this study, NP occurred regardless of age, level of injury, and completeness of the lesion.

3.2. What are the validated diagnostic tools in this population?

3.2.1. Idiopathic PD

Many patient-reported outcome measures (PROMs) with validated psychometric properties have been developed to screen for NMSs in PD patients, and some of these include a

specific question on nocturia: the Parkinson's disease sleep scale (PDSS-2) [61], NMSQuest [62], and NMSS [63]. The Scale for Outcomes in Parkinson's Disease and the Autonomic Dysfunction Severity Questionnaire, although validated, presented gender biases [64]. A specific sleep questionnaire that assessed nocturia, the Neurodegenerative Disease Sleep Questionnaire [65], has been developed, but the assessment of its psychometric qualities is limited to its structural validity. The systematic assessment of the risk of bias of these PROMs has shown the overall quality of assessment of psychometric properties to range from adequate to very good. Other tools specific to sleep evaluation, such as sleep log and wrist actigraphy, have been tested [66], but only nocturnal activity measured by wrist actigraphy was significantly related to nocturia.

3.2.2. Multiple sclerosis

Two PROMs assessing nocturia among other LUTS were considered reliable in patients with MS: the Urge-Urinary Distress Inventory [67] and the Neurogenic Bladder Symptom Score; the latter was also validated in SCI patients [68]. The overall quality of assessment of the psychometric properties of these PROMs ranged from adequate to very good.

3.2.3. Stroke

The Danish Prostatic Symptom Score (DAN-PSS) questionnaire has also been validated in stroke patients [69,70]. However, only the assessment of reliability and relevance by experts was of adequate quality.

3.3. What are the causalities of nocturia in patients with neurological disease?

3.3.1. Lower urinary tract

Detrusor overactivity (DO) was found in up to 79% of PD patients [39] and in 57.8% of MS patients [45] with nocturia. In comparison, the prevalence of DO ranged from 32% [45] to 61% [50] in MS patients without nocturia. These urodynamic changes were supported by brain modifications: white matter reduction in both hemispheres and reduction of cortical surface on the left hemisphere pre- and post-central areas in PD [71], and deep white matter hyperintensities in stroke [54]. In MS, the presence and size of pontine lesions were not associated with nocturia [72]. Detrusor sphincter dyssynergia was frequently reported in SCI and MS patients with spinal cord lesions [73], and was associated with urinary retention and post-void residual (PVR) volume. However, in a population of 102 patients with MS, the volume of a single PVR was not associated with the severity of nocturia [74]. Although detrusor underactivity and BOO were rarely described in patients with stroke or PD, these were common urodynamic diagnoses in such patients when they complained of LUTS [75–78]. However, the presence of prostatic enlargement was not associated with nocturia in patients with PD [79]. In addition, the posterior surface area of the prostate gland was not a predictor of nocturia in patients with a cardiovascular risk factor, including a history of stroke [80].

3.3.2. Renal

The loss of the normal circadian pattern of UP can be driven by a primary vasopressin or brain natriuretic peptide (BNP) secretion disorder, or by a nocturnal fluid shift. When compared with controls, 119 SCI patients showed no circadian rhythms in the diuresis rate or in the renal clearance of creatinine, free water, solutes, sodium, or urea [81]. Loss of circadian sodium clearance was specific of patients with SCI compared with controls with NP. In PD patients with nocturia, NP has been poorly reported, and only two small studies [82,83] described this mechanism, with a prevalence varying between 56% and 66%, depending on the definition used. In one of the most important cohorts of MS patients with nocturnal LUTS, the authors did not observe NP in the voiding diaries of patients [45]. In stroke patients, NP was described in one case series, in which 100% of four patients with nocturia had NP and all were found to have an abnormal circadian rhythm of vasopressin secretion [84].

3.3.3. Sleep

In stroke patients, sleep disorder breathing symptoms [85], severe OSA [86], and use of hypnotics [85] were associated with nocturia. Nevertheless, NP and OSA were not associated with nocturia in these patients [86]. In PD patients, nocturia severity and bother were associated with lower sleep efficiency and total sleep time [87], however not with OSA [87,88]. The association of nocturia with rapid eye movement sleep behaviour disorder (RBD) was inconsistent; one study found an association between enuresis and RBD [89] and another found no significant association with possible RBD [90]. Although sleep disorders are extremely common in patients with MS and SCI [91], no studies evaluating the impact of sleep disorders on the occurrence of nocturia have been found.

3.3.4. Cardiovascular

Abnormal BP circadian pattern (nondipping and reverse dipping) is hypothesised as a mechanism for nocturia and NP. Cardiovascular autonomic failure is known to occur in PD [92]; however, no study was found to demonstrate an association. Moreover, one small study that assessed the link between autonomic symptoms and nonautonomic NMSs [93] did not find any significant association with nocturia. In acute SCI patients, BP circadian pattern was largely found to be abnormal, persisted for a long time over the 12 mo period after injury, and was correlated with a loss of circadian pattern of UP in patients with tetraplegia [94]. In a study with more "chronic" patients, the reverse dipping pattern was associated with a significant increase in nocturnal UP, particularly in tetraplegic patients [95].

Cardiovascular risk factors and decreased physical activity are associated with nocturia in the general population [7]. Whereas these are important in patients with stroke or SCI, no studies examining an association with nocturia in neurological patients were found.

3.3.5. Intake

Only one cross-sectional study assessed the association between nocturia and hydration status, which was

significant in MS patients [46]. The association between nocturia and increase of calorie and protein intake in SCI patients [96] have not yet been studied to our knowledge.

3.3.6. Comorbidities and demographics

In PD, disease duration [41,97], age at onset [23,24,32], gender [19,41,79,89,98], and disease severity [41,42,87,99] were associated with nocturia and its severity.

3.4. Which treatments of nocturia have been assessed in patients with neurological disease?

The treatments that have been evaluated in this population target the underlying mechanisms of nocturia.

3.4.1. Lower urinary tract

3.4.1.1. Pharmacological treatments

3.4.1.1.1. *Antimuscarinics*. Oxybutynin was assessed in two small studies including patients with MS, PD, or SCI, and was efficient in reducing nocturia frequency [100] and severity [101]. Tolerance was poor due to the anticholinergic

side effects. Solifenacin has been evaluated in one RCT including PD patients [102], but its efficacy was demonstrated in the open-label phase only.

3.4.1.1.2. *Mirabegron*. Its efficacy was assessed in PD patients only [103,104], with a significant reduction in nocturia frequency.

3.4.1.1.3. *Cannabinoids*. Synthetic cannabinoid [105] or cannabis medical extracts (whole plant or Sativex) [106,107] have been reported to improve nocturia significantly, with a greater size effect for more severely affected patients [107]. The most frequently reported side effects were xerostomia and central nervous system-related symptoms: dizziness, headache, hallucinations, etc.

3.4.1.2. Surgical treatments

3.4.1.2.1. *Sacral neuromodulation*. Only one study conducted in incomplete SCI patients provided data on postimplantation results on nocturia [108]. As with studies reporting only

Fig. 2 – Summary of nocturia in neurology diagnosis and treatment pathways. PM&R = physical medicine and rehabilitation.

test-phase data [109,110], there was an improvement in nocturia.

3.4.1.2.2. OnabotulinumtoxinA intradetrusor injections. In PD patients, the results of studies using 100 U were contradictory: one demonstrated a significant improvement of nocturia at 6 mo [111], while the other did not [112]. Both reported an increase in PVR, requiring intermittent catheterization [111] or alpha-blocker use [112]. With the dose of 200 U, a significant decrease in nocturia was observed after 1, 3 [113], and 4 [114] mo, and no requiring-treatment PVR was reported [113]. Only three non-RCTs have published data on nocturia in MS patients. In two studies using 300 U, nocturia reduced significantly after the first injection [115,116], maximally by 72% at 3 mo [116]. With the dose of 100 U, efficacy was reported at 1 mo only [117]. The rate of side effects ranged from 6.2% to 66%, and the most frequently reported event was the necessity to perform self-catheterization.

3.4.1.3. Nonpharmacological nonsurgical treatments

3.4.1.3.1. Electrical nerve stimulation. Results of transcutaneous electrical nerve stimulation with sacral electrodes on nocturia in various neurological populations were inconsistent [118,119], as were those of transcutaneous tibial nerve stimulation (TTNS) in stroke patients [119]. In PD patients, one RCT evaluating TTNS versus sham stimulation did not find any significant difference [120]. Percutaneous tibial nerve stimulation was found to be effective and well tolerated in the short- [121,122] and long-term [123,124] treatment of nocturia in MS patients. Similar results have been reported at 12 wk in PD patients with DO [125]. In SCI patients, only one case series is available [126], in which continuous pudendal electrical stimulation failed to lead to a permanent decrease in nocturia episodes.

3.4.1.3.2. Pelvic floor muscle therapy. In MS patients, four RCTs demonstrated the efficacy of pelvic floor muscle therapy (PFMT) in reducing nocturia frequency and/or severity, but they did not show any evidence about the usefulness of adding electromyographic (EMG) biofeedback, neuromuscular electrical stimulation, or TTNS [127–130]. In PD [131] and stroke [119] patients, PFMT alone, or with EMG biofeedback and behavioural therapy showed little or no difference in reducing nocturia.

3.4.2. Renal

Since NP in neurological patients is caused by disorders in the secretion or action of vasopressin, administration of its analogue, desmopressin, at bedtime may reduce nocturnal UP by decreasing free water clearance. This treatment, which has been studied most widely in patients with MS, was shown to have a moderate effect on the number of nocturnal voids and a large effect on the mean difference in urine volume in a meta-analysis including five RCTs [132]. In four out of these five studies, no statistically significant differences of the plasma sodium levels were seen between the placebo and desmopressin groups. Other studies [133–136] have reported similar results on nocturia and plasma sodium levels.

Commonly reported adverse events were headache, nausea, fluid retention, and rhinitis/epistaxis (range rate: 5–68.5%). Only two studies were available in SCI patients, totalling 15 participants [137,138]. Intranasal desmopressin was effective in decreasing the number of nocturia episodes in the long term [137], and the number of night-time intermittent catheterisation and nocturnal UP episodes in the short term [138]. No change in serum electrolytes was seen in these two studies. Evidence in PD is limited to eight patients [139], in whom the dose of 20 µg was effective, but one of them had a delirium related to hyponatraemia.

3.4.3. Cardiovascular

Lower leg oedema (LLE) is highly prevalent in SCI patients, and a recent study [140] assessed the effects of intermittent pneumatic compression (IPC) and multilayer compressive bandage (MCB) on both legs' volume and NP. IPC showed a trend to increase UP during bed rest, with higher bladder volume at midnight. MCB significantly decreased LLE and UP during bed rest and sleep, and increased UP during the day when patients were in their wheelchair.

Another treating factor could be performing a prolonged physical activity that is known to lead to changes in UP [95]. To date, only one study involving eight SCI patients showed a decrease in the percentage of participants complaining of nocturia after 80 d of locomotor training [141].

3.4.4. Sleep

Though OSA appeared to be prevalent in a variety of neurological disorders, the effect of continuous positive airway pressure (CPAP) on nocturia or NP has been assessed only in 35 patients hospitalised in rehabilitation for ischaemic stroke [142]. CPAP therapy significantly decreased the NPi and nocturnal UP, but not the number of nocturia episodes.

Melatonin—a key hormone circadian control—has its secretion altered in a range of neurological diseases. Only one RCT is available about the effects of melatonin on nocturia, which failed to prove its efficacy in MS patients [143].

3.4.5. Comorbidities: PD-specific treatments

With regard to levodopa, the results of its effects on nocturia are still contradictory, as some studies found a detrimental effect [42,99] and others a favourable one [144]. The effects of dopamine agonists (pergolide [145] or rotigotine [146–148]) and STN-DBS [149–152] were also conflicting. Subcutaneous apomorphine infusion therapy has also been reported in a small number of patients but with positive effects [153,154]. Istradefylline [155] and rasagiline [156] were ineffective in case of nocturia or NP.

4. Conclusions

4.1. Summary of evidence

Nocturia is highly prevalent in patients with neurological diseases. It is considered as one of the most frequent and bothersome LUTS in stroke patients, and one of the most frequent NMSs in PD patients. However, information on NP and other neurological disorders such as SCI is scarce.

Fig. 3 – Implications for research: perspectives in nocturia and nocturnal polyuria in neurology. CPAP = continuous positive airway pressure; MS = multiple sclerosis; NP = nocturnal polyuria; OSA = obstructive sleep apnoea; PD = Parkinson's disease; PROM = patient-reported outcome measure; SCI = spinal cord injury.

No PROM is designed exclusively for the assessment of nocturia as well as its effects on sleep. Available PROMs include generic scales that measure LUTS, only one tool specific to patients with MS or SCI, and PD-specific scales that cover a variety of NMSs, including nocturia.

Causalities are not different from the general population and include LUT, sleep, renal and cardiovascular dysfunctions. These causalities can co-occur in this population. A good example is SCI, in which there are OAB symptoms due to DO [4], NP sustained by impaired vasopressin secretion leading to water diuresis [157], altered circadian rhythms of sodium diuresis and glomerular filtration rate [81], LLE [140], and cardiac dysautonomia [95] leading to nocturnal fluid shift, and more.

Treatments evaluated in patients with neurological disease target these causalities, but the overall LOE is weak and the risk of bias is high. Many of the OAB treatments assessed have been shown to reduce nocturia. Interventions aimed at sleep disorders or cardiovascular mechanisms have rarely been evaluated in this population. Desmopressin is the most studied intervention for NP in these patients, with reported efficacy in nocturia, but also adverse events.

4.2. Importance and limitations

This is the first systematic review of the literature on the epidemiology, aetiology, diagnosis, and treatment of nocturia and NP in patients with neurological diseases. Owing to data heterogeneity, we focused on describing the studies, their results, and their limitations, and on qualitative synthesis rather than meta-analysis. Although the protocol of this review has not been registered and may be exposed to the risk of biased post hoc decisions in review methods, we have followed the PRISMA recommendations step by step.

4.3. Implications for clinical practice

Despite the heterogeneity of the data and the low level of overall evidence, proposals for clinical practice can be made. In practice, it is a matter of targeting the different causalities to be explored and addressed (Fig. 2). Lifestyle modifications, such as control of salt and water intake, encouraged physical activity, and weight management should be considered in these patients, even if robust evidence is still lacking. However, caution should be exercised when

recommending fluid restriction as the patients are often older, sometimes with cognitive impairment, and naturally tend to reduce their water intake [158]. Normalisation rather than restriction of fluid intake should therefore be advised. As water diuresis is one of the main mechanisms of NP, desmopressin could be advised in patients, starting from a low, gender-specific [7] dose to reduce the risk of hyponatraemia. Caution is recommended when using desmopressin in patients who have LLE. This is a risk factor for fluid overload and development of hyponatraemia, especially when advice about fluid restriction is not followed. Moreover, conditions associated with a massive sodium loss due to BNP increase (heart failure, OSA, and important LLE) are contraindications to desmopressin use. Finally, in patients with cognitive impairment in whom fluid restriction is difficult to maintain, desmopressin should not be prescribed. In patients with nocturnal fluid shift and/or sodium diuresis, treatment should be individualised and could be combined depending on the findings from the clinical evaluation: LLE, obesity, physical activity, short-acting daytime loop diuretic, etc.

4.4. Perspectives

Further studies need to be conducted about nocturia and NP in patients with neurological disorders (Fig. 3). Firstly, the evolution of nocturia over time is poorly described, as well as the prevalence of NP in patients with nocturia. There are few or no studies evaluating the impact of patient characteristics on treatment response or on the prevalence of NP or nocturia (eg, voiding mode or treatment of associated DO). Secondly, the validation and translation of PROMs for nocturia are required in different diseases. The diagnostic strategy is not codified, and a TANGO-type detection and guidance tool could be useful in this population [159]. Finally, more robust intervention studies with long-term follow-up are needed. Nonpharmacological and less invasive interventions, such as increasing physical activity, weight management, water or salt intake control, or even water immersion or bed position modifications, are lifestyle interventions that would be of interest to be investigated in the future. Proposals for the management of nocturia should be the subject of a standardised consensus method.

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Study concept and design: Denys, De Ridder, Everaert, Haddad.

Acquisition of data: Haddad, Pauwaert.

Analysis and interpretation of data: Everaert, Haddad, Pauwaert.

Drafting of the manuscript: Everaert, Haddad.

Critical revision of the manuscript for important intellectual content: Arlandis, De Ridder, Del Popolo, Denys, Everaert, Giannantoni, Haddad, Panicker, Van Kerrebroeck.

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Appendix A. Supplementary data

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