Assessment and treatment of nocturia in neurological disease in a primary care setting; systematic review and nominal group technique consensus

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Abstract

Context, Neurological disease can affect rate of urine production and bladder storage function, increasing nocturia severity, with additional risks if mobility or cognition is impaired.

Objective, Systematic review (SR) of nocturia in neurological diseases, and expert consensus for management in clinics without neurologist input.

Evidence Acquisition, Four databases were searched from January 2000-April 2020. 6262 titles and abstracts were screened and 43 studies were included for full-text screening. 11 met the inclusion criteria and two studies were identified through other sources. Nominal Group Technique (NGT) was used to develop consensus in an expert/ public panel.

Evidence Synthesis, 13 studies (seven Parkinson's disease, five multiple sclerosis) were included, all undertaken in secondary care. Neurological disease severity was incompletely described, and nocturia severity was generally measured subjectively. NGT consensus supported basic neurological assessment, and the use of bladder diaries where neurological impairment permits. Treatments include pelvic floor muscle training, medications review, risk mitigation, improving bowel function, overactive bladder syndrome therapy (if urgency is reported in association with nocturia episodes), treatment of post void residual and desmopressin according to licence. Measures to improve mobility and mitigate risk when using the toilet overnight should be considered. Multifactorial issues such as obstructive sleep apnoea and hypoventilation must be considered.

Conclusion, Nocturia in neurological disease is complex and lacks a robust evidence base, with very little research done in the primary care context. Guidance should be pragmatic, with reduction of risk a key requirement, until a multidisciplinary evidence base can be developed.

Patient Summary, People with neurological disease can suffer severe sleep disturbance from passing urine several times overnight. We looked at published research and found very little information to help general practitioners manage this. We assembled a group of experts, to develop practical approaches for assessing and treating nocturia in neurological disease.

Introduction

Nocturia is the number of times urine is passed during the main sleep period. Having woken to pass urine for the first time, each urination must be followed by sleep or the intention to sleep (1). This results in sleep disturbance associated with a significant negative impact on health, well-being and traumatic accidents (e.g., falls) (2). Nocturia is a multifactorial condition, with a range of relevant contributors, such as systemic disease (3), sleep disorders and behavioural factors (4).

Neurological disease can increase the prevalence and severity of nocturia (5), by affecting rate of urine production or storage function. This is compounded by wider influences, especially impaired mobility and cognition. The principal medical therapy is desmopressin, which has mainly been evaluated in patients with multiple sclerosis (MS) (6). Unfortunately, desmopressin can cause hyponatraemia that limits its use in older adults (7, 8). Hence, assessment and treatment of nocturia needs to factor in both the neurological disorder and overall health influences in individual patients. Practical recommendations on these issues have been developed in the secondary care setting (5). However, initial management of nocturia is generally undertaken in primary care. The PLANET study (PLanning Appropriate Nocturia Evaluation and Treatment) was established to support healthcare practitioners undertaking the initial assessment of nocturia. It aims to rationalise the initial management of nocturia for particular use in non-specialist settings. This applies principally to primary care but potentially also to secondary care (for example urology departments where there is no subspecialist neuro-urology expertise). The study incorporates a series of systematic reviews in a variety of medical conditions and uses multidisciplinary panels with general practitioner and applicable specialist membership to synthesise assessment and treatment recommendations. The current paper reports the systematic review of published evidence relating to nocturia in neurological diseases, and the derived expert consensus for primary care management. The protocol for the systematic review was registered on PROSPERO (CRD42019157821).

Evidence acquisition

Systematic review methodology

Search strategy

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement was followed (9). A comprehensive search strategy was developed by two authors (SD, MD) and the research team (Appendix 1, see example search strategy). Search terms for nocturia covering all-cause neurological disease were identified. Several scoping searches using a combination of two main blocks of terms [nocturia and specific neurological condition] NOT [desmopressin or children] were run in MEDLINE to maximise the sensitivity and specificity of the developed search strategy. Desmopressin was not included due to the availability of contemporaneous SR (6, 7).

A combination free-text terms and thesaurus headings for each concept were combined with terms in the title and abstract fields and translated as appropriate for each database. The following electronic bibliographic databases were searched for potential primary studies from January 2000-April 2020: MEDLINE; Embase; PsycINFO; and the Cochrane Library. Forward and backward referencing of included papers were undertaken to supplement the database searches to identify any further relevant papers for inclusion.

Eligibility criteria

Population: Patients in any setting (globally) aged 18 and over.

Interventions: Any intervention focusing on the reduction of nocturia episodes

Comparators: Inactive (placebo, no treatment, standard care) or active (conservative, medication or interventional) control interventions.

Outcomes: The change in the number of episodes of nocturia per night. Secondary outcome(s): nocturnal urine volume, nocturnal polyuria index, time/number of hours of sleep to first nocturia episode, safety data, sleep quality, insomnia, daytime sleepiness, patient problems, well-being or self-reported health status, patient reported quality of life and adverse effects.

Types of studies: Primary studies of any design discussing assessments, mechanisms or treatments for neurological causes of nocturia. The SR did not discriminate whether a study was performed at primary or secondary care level; this interpretation was applied during the nominal group technique (NGT) consensus (see below). Those studies which required assessments not directly available in primary care (e.g., urodynamics) were not included. Likewise, therapies not directly accessible to primary care were excluded (e.g., deep brain stimulation), but those potentially available were retained (e.g., Percutaneous Tibial Nerve

Stimulation: PTNS). Reference lists of systematic reviews were searched to identify relevant primary studies.

Timeframe: Papers published since 2000 were included. We limited studies by date to ensure that the search identified all relevant studies using International Continence Society standardisation terminology (1, 10, 11).

Language: No language restrictions were applied, provided an English language abstract was available for initial screening.

Screening

References were managed in Rayyan (https://rayyan.qcri.org/). SD exported search results from the different databases to Rayyan. Post de-duplication, selection of studies was completed in two stages. First, two review authors (NVM, SD) independently screened titles and abstracts; next the full text articles were screened to identify potentially relevant studies for inclusion. There was a high level of agreement (88%) between the reviewers both at title and abstract and full-text screening stage. Any disagreements were resolved through discussion or involvement of a third reviewer (MD).

Data extraction and quality assessment

Data extraction was undertaken using a customised table in Word and was completed independently by two reviewers (NVM and SD). Any disagreements were resolved through discussion and, where necessary, consultation with a third reviewer (MD).

Deviation from the protocol SR was undertaken to ascertain what published studies are available in this subject area, all of which were communicated to the NGT panel, where members scrutinised evidence for applicability to the consensus according to quality and relevance. Quality assessment was not done at the SR stage due to the lack of a generalisable tool suited to the wide range of potential study designs permitted for inclusion. Given the nature of the review question, it was not deemed relevant.

Nominal Group Technique methodology

NGT (12, 13), a semi-quantitative structured group interview process, was used to establish the principal elements of nocturia mechanism, assessment and therapy in neurological disease and for prioritisation to achieve consensus on primary care management. Management of the potential for undiagnosed neurological disease (14) or comorbid conditions were not covered (a separate NGT process was undertaken for multifactorial

nocturia). Participants received the studies identified in the SR in advance of the NGT meeting. Online meetings (audio recorded and transcribed) were structured to include; 1. Introduction and explanation, 2. Silent generation of ideas (as individuals), 3. Sharing ideas, where each participant shared their ideas in a round-robin format, until no new responses emerged, with the facilitator (NC) recording each idea on an online editable whiteboard (Jamboard, https://jamboard.google.com/), 4. Group discussion, 5. Voting and ranking, in which participants ranked the three most important responses. Group sessions lasted approximately 2 h and ranged in size from 3 to 6 participants. Nominal groups were conducted until saturation was reached.

Results

Systematic review results

We identified 9289 titles and abstracts, and, after deduplication, we screened 6262 titles and abstracts. 43 studies were included for full-text screening of which 11 studies were identified as relevant. Two additional studies were included through forward and backward screening (Figure 1).

INSERT FIGURE 1 ABOUT HERE

General characteristics of included studies

Of the 13 studies (15-27) included, one (21) focused on assessment and 12 (15-20, 22-27) evaluated treatment of nocturia in neurological patients. Participants were recruited through secondary care (Neurology or Urology) in all studies included we identified no studies in primary care. Six studies (16-22) investigated treatment in Parkinson's disease (PD), five studies evaluated MS (15, 23-26) and one (27) study combined patients with either MS, PD or spinal cord injury (SCI) (Table 1). Four studies focused on PD-related medication (levodopa, dopamine receptor agonist and adenosine receptor antagonist) (16-19), three OAB treatment (Mirabegron, Solifenacin, Oxybutynin) (20, 22, 27), two PTNS (23-24), one melatonin (15), one cannabinoid (25), and one pelvic floor muscle training (PFMT) (26). Seven were interventional (15-17, 22, 24-26), three were observational (18, 20, 27) and three did not specify the design (19, 21, 23).

INSERT TABLE 1 ABOUT HERE

With one exception (21), all studies measured nocturia using subjective patient reported outcome scores (International Prostate Symptom Score (IPSS); International Consultation on Incontinence Nocturia Quality of Life (ICIQ-NQoL) (28); 8-item OAB Questionnaire (OAB-v8); OAB Symptom Score (OAB-SS)). A bladder diary to assess the number of nocturia episodes objectively was used in 8 studies. No physical examinations or questionnaires were reported taking into account co-morbidities which may contribute to nocturia (i.e., factors such as peripheral oedema, or sleep apnoea).

Vaughan et al. (21) was the only study to obtain objective data on episodes of nocturia and sleep disturbance, using a sleep laboratory to evaluate ambulatory patients with PD. 93% of participants reported at least one episode of nocturia on IPSS. Patients with a high nocturia frequency and high bother scores experienced worse sleep, as detailed by sleep efficiency and total sleep time. PD patients with ≥2 episodes of nocturia were more likely to have hypertension compared to those with ≤1 episodes. Greater motor impairment was associated with more frequent nocturia episodes. Cognition, as measured by the mini-mental state exam (MMSE) and total dopaminergic therapy dose, was not linked to the nocturia frequency.

Parkinson's disease pharmacological interventions

A large cohort study enrolling 68 people showed reduction of nocturia episodes following two months of treatment with extended-release levodopa in patients with PD, and improvement of ICIQ-NQoL. No correlation was found between nocturia related quality of life and Hoehn and Yahr PD stage, but the staging information was not clearly stated. Compared to baseline, extended-release levodopa did not yield significant changes on the UPDRS-III-score (16).

In three female PD patients, switching from Bromocriptine to Pergolide alongside levodopa, reduced the number of nocturia episodes (19). The transdermal dopamine agonist, Rotigotine reduced the number of episodes of nocturia in 52 patients (17). The recognised side effects of application site reaction and nausea were reported. Initial treatment with Istradefylline (adenosine A2A receptor antagonist) showed a significant reduction in nocturia episodes (3.0 ± 1.6 to 2.0 ± 0.9, $P<0.05$) along with motor improvement, however, this improvement was not sustained at one year. Motor symptoms significantly improved throughout the course of

the study compared to baseline (MDS-UPDRS part III at baseline 30.0 ± 12.9 vs 13.5 ± 7.0 after one year) (18).

OAB pharmacological treatment

Controlled release oxybutynin was assessed in one study including patients with PD, MS and SCI (27). The study did not specify whether symptoms suggesting OAB were present. A significant decrease in number of nocturia episodes per night (from 1.8 at baseline to 1.2 after 12 weeks, P=0.006) was found. Oxybutynin side-effects most consistently reported were dry mouth and constipation.

The efficacy of Mirabegron was evaluated in a retrospective study of PD patients with a mean Hoehn and Yahr stage of 2.7 ± 0.9 (20). The diagnosis of OAB was made in a urology out-patient clinic. Mirabegron significantly decreased the mean number of nocturia episodes per night from 3±2.2 to 2.6±0.4 (p=0.02). 23 patients (46%) persisted on Mirabegron after a median follow-up of 19 months.

Zesiewicz et al. performed a double-blind pilot study of Solifenacin to manage symptoms of OAB in PD (22). OAB included symptoms of nocturia and was defined as at least 8 voids per 24 hours and at least daily urinary urgency. During the double-blind phase, no significant improvement of nocturia was seen. Contrary to the double-blind phase, statistically significant improvement in nocturia (effect size 0.82, p=0.01) was seen during the open label phase.

Drugs to ameliorate symptoms

Drake et al. performed a randomized, double-blind, placebo-controlled crossover trial of sustained-release melatonin in patients with relapsing and progressive MS (15). At baseline, the mean number of nocturia episodes was 1.78/night. After treatment, nocturia was 1.4 episodes per night for the melatonin group, compared to for the placebo group, a difference which may have occurred by chance (p=0.85, standard deviations not provided).

A small, open-label study of Sativex® (*delta-9-tetrahydrocannibinol and cannabidiol*) improved urinary symptoms in people with advanced MS (25). A subsequent multicentre, randomised, double-blind, placebo-controlled study evaluated the use of Sativex as an add-on therapy in people with MS who had failed first line therapy (generally anticholinergics) for OAB. This study failed to meet its primary endpoint of reduction in daily number of urinary

incontinence episodes but there was a significant reduction in number of episodes of nocturia (adjusted mean=-0.52, p=0.01), a secondary outcome measure. Frequent adverse events were reported, including nausea, vomiting, diarrhoea and weakness and central nervous system-related complaints such as dizziness, headache, disorientation, dissociation, impaired balance and paraesthesia.

Pelvic floor muscle training

In a study including female patients with MS and Expanded Disability Status Scale (EDSS) score less than 6.5 (walking with bilateral aids), pelvic floor muscle training reduced the number of nocturia episodes (2.38 to 0.46, P<0.0001) compared to a sham intervention (26).

Percutaneous tibial nerve stimulation

Two small, open-label studies of PTNS reported significant reduction (from 3 to 1 episode/night, p=0.002; decrease in nocturia by 2.6 episodes/night, p<0.001) in the number of nocturia episodes in patients with MS diagnosed with neurogenic overactive bladder (23-24). With 12 weekly treatment sessions, the effect of PTNS in ambulatory patients with MS, was maintained up to 12 months in responders (23).

Nominal group technique results

Use of bladder diaries (4), need for conservative measures such as fluid advice (29), and the use of desmopressin according to its licenced indications (6, 29) are established expectations of assessment and therapy, and the NGT supported the expectation that these be applied for this patient group. Employing the SR findings, the NGT discussions considered mechanisms, and developed assessment and therapy recommendations for primary care application. Established practice for assessment of nocturia and evaluations relevant to detecting non-neurological factors were not reviewed.

A range of potential mechanisms and contributory factors was identified, due to direct effects, and indirectly resulting from the wider effects of neurological disease (Table 2). Enuresis, defined as a complaint of intermittent incontinence that occurs during periods of sleep (30, 31), was additionally considered.

INSERT TABLE 2 ABOUT HERE

Relating to assessments, the discussion focussed on evaluation that could be undertaken in primary care, subject to local skills and guidelines. Recommendations for assessments that could facilitate understanding of mechanism or selection of treatment, and potential safety considerations in the neurological context, are given in Table 3.

INSERT TABLE 3 ABOUT HERE

Treatments are listed in Table 4 and are contingent on the findings of prior assessment.

INSERT TABLE 4 ABOUT HERE

Discussion

A major publication by the International Continence Society (ICS) led by a panel of urologists evaluated the complexity of medical causes of nocturia and developed a detailed specialist algorithm (1). The current study complements the ICS report by focussing on primary care and running an NGT process with a multidisciplinary panel. The initial medical consultation for managing nocturia usually takes place in a primary care setting, and needs to consider possible mechanisms, so that assessments can be selected with a view to specific treatment. PLANET is undertaking an overarching evaluation for a generalised management approach in primary care, following systematic review and NGT for cardiovascular, endocrine, renal, sleep medicine conditions and multimorbid presentations, alongside the current review for neurological disease.

The differing mechanisms potentially relevant in neurological disease, as set out in Table 2, are likely to have implications for reducing nocturia episodes, a key factor for improving outcome (34). However, the SR identified that only a few studies discussed mechanism, meaning that the depth of description of causative factors was limited, and interpretation of therapy outcomes was hampered accordingly. Furthermore, even though nocturia is a multifactorial problem, little attempt was made to exclude comorbid disorders. For people with neurological disease, nocturia may reflect a neurologically driven cause (such as endocrine dysfunction, impaired thirst regulation or circadian disruption), or there could be

unrelated causes of nocturia typical of older populations (5). Screening of the study populations for known systemic causes of nocturia, for example OSA or fluid retention, was often not reported. Additionally, symptom score measurement was the principal evaluation for nocturia severity in several studies, rather than more objective approaches, although we acknowledge that completion of a bladder diary may be challenging for some people with neurological impairment. Hence, interpretation of therapy outcomes needs to consider the potential for diluting response due to the complexity of the symptom and methodological factors (7).

One study identified that worse neurological severity (motor impairment, though not cognitive impairment) was associated with more severe nocturia (21). This might lead to a supposition that therapy to improve disease severity could help nocturia. However, the relationship between neurological response and nocturia improvement was inconsistent. Switching from Bromocriptine to Pergolide, alongside use of levodopa was reported to reduce the number of nocturia episodes (19). However, outcomes from only three patients were reported in this study, and ergot-derived agonists are now rarely used in the treatment of PD. In a separate study, the effect of pergolide on nocturia was independent of improvement of parkinsonian symptoms, suggesting a distinct mechanism from that of anti-parkinsonian effects. Thus, the possibility that dopaminergic treatment in PD helps nocturia cannot be excluded. Nonetheless, antiparkinsonian drugs used for night-time control may be valuable more for improving motoric control at night than for reducing nocturia; indeed, movement disorder specialist input regarding optimisation of motor and non-motor symptom complex in PD is invariably warranted.

We identified no evidence to support the statement that disease modifying therapy improves nocturia in people with MS. There was no literature describing response of nocturia to MS disease-modifying therapy. Treatments primarily intended to ameliorate overall health status were identified in the SR, including symptomatic treatment for people with MS. Sativex did not help OAB (primary outcome), but did help nocturia (secondary outcome) (25). This emphasises the importance of proper evaluation of nocturia mechanism; in OAB, for example, it is valuable to consider whether urgency occurs overnight. Unfortunately, Sativex was associated with noteworthy adverse effects, and use of the medication is generally restricted in practice, hence it could not be recommended for primary care use by the NGT.

PFMT reduced nocturia episodes in MS (patients with EDSS 6.5); this change was presumed to be via an indirect mechanism (26). Melatonin did not reduce nocturia overall, though inclusion of a responder analysis identified a subgroup of patients who did appear to respond (15). This type of analysis is potentially an important consideration in the design of future studies, given the range and complexity of potential mechanisms of nocturia encountered clinically.

Treatments primarily intended to improve LUT function were also evaluated. An effect of OAB drugs in reducing the severity of nocturia implicitly can be expected if the nocturia is driven by urgency, or if the medication has the effect of improving bladder capacity. Use of antimuscarinics and beta-3 adrenergic agonist were reported, though the studies did not specify whether nocturnal urgency was a feature at baseline. In PD, oxybutynin reduced nocturia from 1.8 to 1.2 episodes per night, and mirabegron from 3.0 to 2.6 (27). These apparently small effect sizes for the overall population are discouraging, but the NGT panel suggested that a responder analysis would be needed to identify whether some individuals achieved a greater benefit. The importance of methodology for interpretation is shown by the fact that solifenacin did not improve nocturia in a double-blind setting but did do so in an unblinded context (22). Where antimuscarinics are prescribed, counselling on potential effect on cognition, and maybe gait, is advised. These effects might increase risk of adverse events, such as falls and confusion (35). Mirabegron may be a suitable alternative, especially in older people with neurodegenerative conditions (e.g., PD) (36), provided blood pressure is adequately controlled.

PTNS may help nocturia in PD (37), and recent research highlights a transcutaneous technique (38). Unfortunately, this is a resource-intensive therapy which is not commonly available and is not generally an option in primary care. Nonetheless, it was retained in the SR since there is the potential for PTNS delivery in this setting. Transcutaneous electrical nerve stimulation with sacral electrodes has been evaluated for nocturia in various neurological populations, but findings are inconsistent (5), and so this is not currently considered suitable for recommendation.

The NGT prioritised evaluations directly relevant to nocturia in the broader setting of people with neurological disease rather than specific types of neurological conditions. It covered potential mechanisms, including co-morbid causes, and environmental factors that could affect the condition or its treatment. These are intended to direct therapy according to

underlying mechanism, and to facilitate response. An aspect the NGT discussions considered important in neurological disease is the identification of enuresis, in particular acquired (secondary) enuresis (30, 31). Childhood (primary) enuresis might be relevant to adult nocturia (39), but the symptom may be driven by rather different mechanisms, e.g., chronic retention, sphincter impairment (40), higher CNS dysfunction or medication (41). Enuresis can co-exist with nocturia, but the description by patients may not be clear, and the enuresis is unlikely to respond to nocturia treatment.

It is important to assess whether a patient's nocturia is driven by nocturnal polyuria (42, 43) rather than factors such as OAB (44). Nocturnal polyuria has been described in conditions such as PD (45, 46), likely associated with autonomic dysfunction, and is under-recognised. Treatment involves conservative measures such as reducing fluid intake but should be balanced against the risk of worsening orthostatic hypotension during this period, with PD patients frequently instructed to stay hydrated to prevent postural symptoms. Treatment with desmopressin has been described, but Parkinson's disease affects an older and potentially frailer population, where the increased risk of hyponatraemia means it should be avoided.

The strengths of the study were the multidisciplinary team, including representation from the appropriate clinical areas, and the formalised qualitative technique for achieving consensus by NGT. Limitations relate to the weakness of the evidence base to inform NGT discussions, notably that all studies were undertaken in secondary care and generally were restricted to patients with MS and PD. Hence, extrapolation of the SR findings to general practice is not necessarily reliable and restricted compared with the potential diversity of neurological disease. Methodologically, problems included small sample sizes and incomplete characterisation of study groups. Hence, a broad view was taken, relying on expert consensus to supplement the evidence base.

Nocturia in neurological disease is an under-researched and under-resourced area requiring additional future research. There is a need to consider more sophisticated description of the neurological situation, alongside exclusion of confounding causes, so that future research can seek to identify predictors of outcome. In therapy studies, description of any change in underlying neurology over the course of the study is important. More widespread use of bladder diaries is also needed to establish important factors such as overnight urgency episodes or nocturnal polyuria; these may need practical adaptations to make their use for a

disabled population easier in primary care. Methodological focus needs to ensure completion of first-line care (such as fluid advice) prior to initiation of investigational treatment, since concurrent delivery will confound interpretation. Ideally, more diverse conditions should be considered for inclusion in research, and a primary care context is desirable.

Conclusions

Nocturia in neurological disease is complex and lacks a robust evidence base, with very little research done in the primary care context. Reduced nocturia is desirable but may not be readily achieved. Hence, guidance has to take a pragmatic line, potentially focussing on reducing risks, such as falls. A multidisciplinary evidence base is needed to improve assessment and therapy.

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Figure 1: PRISMA Flow chart

Table 1: Study characteristics

Table 2: Mechanisms of nocturia in neurological disease (NGT consensus)

Table 3: Primary care assessments for nocturia in neurological disease. ADLs: Activities of Daily Living

Table 4: Primary care therapy of nocturia in neurological disease.

Appendix 1: Sample search strategy