Nocturia and chronic kidney disease; systematic review and nominal group technique consensus for primary care assessment and treatment

Alex Ridgway[1]; Nikki Cotterill[1, 2]; Shoba Dawson[3]; Marcus J. Drake[1,4]; Emily Henderson[3,5]; Alyson L. Huntley[3]; Jonathan Rees[6]; Eddie Strong[3]; Christopher Dudley[7]; Udaya Udayaraj[8,9]

1. Bristol Urological Institute, North Bristol NHS Trust, Bristol, UK
2. School of Health and Social Wellbeing, University of the West of England, Bristol, UK

3. Population Health Sciences, Bristol Medical School, University of Bristol, UK

4. Translational Health Sciences, Bristol Medical School, University of Bristol, UK

5. Older Person's Unit, Royal United Hospital NHS Foundation Trust Bath, Combe Park, Bath, UK

6. Tyntesfield Medical Group, North Somerset, Bristol, UK

7. Nephrology Department, Southmead Hospital, North Bristol NHS Trust, Bristol, UK

8. Nuffield Department of Medicine, University of Oxford, Old Road Campus, Oxford, OX3 7BN;

9.Oxford Kidney Unit, Churchill Hospital, Oxford, OX3 7LE.

Correspondence

Marcus Drake, Bristol Urological Institute, L&R Building, Southmead Hospital, Bristol, BS10 5NB, UK

Word count 4204 (including abstract and main text, excluding tables, figures and references)

Key words; Nocturia, Lower urinary tract symptoms, Chronic Kidney Disease, Systematic review, Nominal Group Technique

Abstract

Context: Reduced renal function impairs salt and water homeostasis, which can drive nocturnal or 24-hour polyuria. Nocturia can arise early in chronic kidney disease (CKD). Evidence-based recommendations can facilitate management outside nephrology clinics.

Objective: systematic review (SR) of nocturia in CKD, and expert consensus for management in primary care and in specialist clinics outside nephrology.

Evidence Acquisition: Four databases were searched from January 2000-April 2020. 4011 titles and abstracts were screened, and 108 studies underwent full-text screening. Seven met the inclusion criteria and two were identified through other sources. Consensus was derived from an expert panel with public involvement using Nominal Group Technique (NGT).

Evidence Synthesis: Several plausible mechanisms contribute to nocturnal or 24-hour polyuria in CKD, but there is little evidence on interventions to improve nocturia. NGT assessment recommendations for nocturia (at least twice per night) in patients with CKD or at risk of CKD being assessed in a non-nephrology setting were: history (thirst, fluid intake), medication review (diuretics, lithium, calcium channel antagonists, non-steroidal anti-inflammatory medications), examination (oedematous state, blood pressure), urinalysis (haematuria and albumin: creatinine ratio) blood tests (blood urea, serum creatinine and electrolytes, eGFR), bladder diary. Renal ultrasound follows local CKD guidelines. Treatment options include optimising blood pressure control, dietary adjustment to reduce salt intake, fluid advice, medication review. Referral to specialist nephrology services should follow local guidelines.

Conclusion: CKD should be considered when evaluating patients with nocturia. Assessment aims to identify mechanisms and instigate therapy, but the latter may be more applicable to reducing wider morbidity associated with CKD than nocturia itself.

Patient Summary. People with kidney disease can suffer severe sleep disturbance from passing urine overnight. We looked at published research and found some useful information about mechanisms. A group of experts was able to develop practical approaches for assessing and treating the situation.

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 can be due to nocturnal polyuria (2, 3), defined as more than 20% (in younger age groups) and more than 33% (in older people) of daily urine volume being passed during the main sleep period (1). Alternatively, 24-hour polyuria (defined as daily urine output of > 40 ml/kg/day (1)) may be responsible. In health, there is circadian rhythm in urine output, and evidence of circadian rhythmicity in some diuretic and anti-diuretic hormones (4). Age-related changes in these circadian rhythms contribute to nocturia by impairing the overnight regulation of urine production, giving rise to nocturnal polyuria (5). In addition, 24-hour polyuria can increase voiding frequency during both daytime and night-time.

Several systemic diseases cause nocturia (6,7). Along with chronic kidney disease (CKD), there are many causes of nocturnal polyuria, including behavioural factors in healthy people, cardiovascular disease, endocrine dysfunction and sleep disorders. Hence, the initial assessment of nocturia should identify contributory conditions (8). However, a practical approach to evaluating potential renal diseases contributing to nocturia is lacking outside a specialist setting. The PLANET study (PLanning Appropriate Nocturia Evaluation and Treatment) aims to rationalize the initial management of nocturia. A systematic review (SR) and evidence-based expert consensus for nocturia in renal disease is reported in this paper. It was run alongside equivalent reviews for other medical conditions, which converge with the overall aim of developing a generalised management approach to be published elsewhere. The protocol of the systematic review was registered on PROSPERO (CRD42019157821).

Methods

Systematic review methodology

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) in consultation with AH. Search terms for nocturia covering renal diseases were identified. Desmopressin was not included due to prior publications covering its role in nocturia comprehensively (10). Scoping searches using a combination of two main blocks of terms [nocturia and nephrological conditions] NOT [desmopressin or children] were run in MEDLINE to maximise the sensitivity and specificity of the developed search strategy (Appendix 1).

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; The Cochrane Library and PsycINFO. Forward and backward referencing of included papers were undertaken to supplement the database searches to identify any further relevant papers for inclusion. While we excluded systematic reviews, we scanned reference lists of these reviews and also conducted forward citation searches to identify any studies relevant to our review.

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 mechanisms, assessments or treatments for renal 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). 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 standardised terminology (1, 11, 12).

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 and after de-duplication, selection of studies were completed in two stages. First, two review authors (MD, SD) independently screened titles and abstracts; next, full text articles were screened to identify potentially relevant studies for inclusion. There was a high level of agreement (89%) between the reviewers both at title and abstract and full-text (91%) screening stage. Disagreements were resolved through discussion.

Data extraction was undertaken using a customised table in Word and was completed independently by two reviewers (MD and SD).

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.

Nominal Group Technique methodology

Nominal Group Technique (NGT) is a semi-quantitative structured group interview process for developing consensus (13, 14). It was used to consider the relationship between CKD and nocturia for clinical management outside the setting of a specialist nephrology clinic. The NGT panel included specialists in nephrology, urology and primary care, with public involvement. Participants received the studies identified in the SR in advance of the NGT to help familiarise themselves with the existing evidence base. This evidence base formed the knowledge base to handle deficiencies which needs addressing in the future. Online meetings (audio recorded and transcribed) were structured to include; 1. Introduction and explanation, 2. Silent generation of ideas (as individuals), 3. Sharing ideas (round-robin format), until no new responses emerged, with the facilitator (NC) recording concepts using 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 5 to 7 participants. Nominal groups were conducted until saturation was reached.

Results

4011 titles and abstracts were identified and after deduplication 3940 titles and abstracts were screened. 108 studies were included for full-text screening of which 7 studies were identified as relevant. Two studies were identified through forward and backward screening (Figure 1). Nine papers met the inclusion criteria.

INSERT Figure 1 about here

Of the nine studies, eight were observational (15, 17-23) using either cross-sectional, case control or cohort design, and one was a pilot study (16). Four studies were from Japan (15, 20-22), three from the USA (16, 17, 19) and two from Taiwan (18, 23). Seven studies focused on the prevalence and mechanisms of nocturia (15-21), one on treatment (22) and one on assessment (23) (Table 1).

INSERT Table 1 about here

Yoshimura et al. (15) undertook a population level cohort study of 6517 individuals, who were invited to health screening and asked to complete self-report questionnaires and bladder diaries. Renal impairment was defined as serum creatinine above the laboratory reference range (> 1.1 mg/dL for male subjects and > 0.8 mg/dL for female), and was associated with a higher prevalence of nocturia on univariate analysis. However, on multivariate analysis it was not associated with nocturia of severity twice per night or worse.

In a cohort of 98 outpatients aged >60y with estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2 and hypertension treated with diuretics, prevalence of nocturia at least twice per night was seen in 79.6% of men and 54.5% of women (16).

Amongst 9110 participants in the National Health And Nutrition Examination Survey (NHANES) 2005-2008 who completed a sleep questionnaire, Plantinga et al. (17) found that the proportion of study participants urinating once per night or less reduced with increasing severity of CKD (no CKD 79%, CKD G1-2 65%, CKD G3-4 56%) and the proportion urinating twice or more per night rose correspondingly (no CKD 21%, CKD G1-2 35%, CKD G3-4 44%). Diuretic use was not significantly associated with nocturia in multivariate analysis. The authors point out that a self-report survey could be at risk of limitations such as inconsistent responses. For example, 44% of patients with CKD 3-4 reported urinating twice or more per night, but only 23% reported waking frequently at night.

Hsu et al. (18) evaluated 50 men aged <50 years with CKD (eGFR < 60 ml/min/1.73 m^2) and 187 age-matched men without CKD (mean age for both groups was 44 years), and men who regularly took alpha-blockers, diuretics or anticholinergics were excluded. Men with CKD had higher scores for nocturia (1.3 vs. 0.8, p=0.02) but had significantly less daytime urinary frequency and relatively lower urgency scores. Multivariate regression identified low eGFR as a significant risk factor for nocturia (OR 3.04, 95% CI 1.5-6.17).

Nocturia prevalence is increased in patients with diabetes (41.4% vs 23.4%, p<0.0001) in the NHANES study (19). Diabetes biomarkers, such as HbA1c, were not predictive

of nocturia. However, biomarkers that indirectly reflect diabetic disease progression could be predictive for nocturia, such as raised protein: creatinine ratio (UPC; adjusted odds ratio 2.74, 95% confidence interval 1.28-5.85). Serum creatinine concentration was not associated with nocturia.

Fukuda et al. (20) found that worsening renal function is associated with increasing nocturnal polyuria. There was inverse relationship with creatinine clearance and night/day ratio of urine volume and urine sodium excretion rates but no correlation with free water clearance or urea excretion rates. They concluded that physiological changes in patients with CKD lead to disturbances in circadian rhythms of diuresis, natriuresis and blood pressure control, resulting in nocturnal polyuria.

Matsuo et al. (21) used a validated formula to estimate daily salt intake from spot urine samples on sodium excretion. 728 study participants were categorised into high and low salt intake groups around the overall median salt intake. There were significant differences in nocturia, at 2.2 ± 1.3 episodes per night in the high salt group (>9.3 g/day), compared with 1.4 ± 1.3 episodes per night for the low salt group (<9.3 g/day). Nocturnal urine production in the high salt group was 518 ± 241ml, whereas in the low salt group it was 154 ±147ml. Multivariate analysis showed high salt intake, as indicated by high salt excretion, was an independent risk factor for nocturia. 37% of participants had renal dysfunction, defined as an eGFR of between 15-60 ml/min/1.73 m^2 ; this was also found to be an independent predictor of nocturia. There was no subgroup analysis of association of salt intake and nocturia reported in the CKD group.

Liu et al. (22) found raised serum creatinine to be an independent risk factor for nocturia in a population of men with type 2 diabetes mellitus. eGFR was 72.0 ± 22.1 mL/min/1.73 m^2 for people with nocturia no more than once per night, 64.7 ± 22.6 for people with nocturia two or more episodes per night and 61.9 ± 23.8 for people with nocturia three or more episodes per night. During a 3.5 year follow up, mortality rate was higher for worse nocturia, at 6.2% for severe nocturia (≥3 times per night) and 1.7% for mild nocturia (≤once per night).

Matsuo et al. (23) categorised 321 participants into whether they managed to reduce salt intake in response to dietary advice and low salt diet. Overall, 69.5% were successful in reducing salt intake. Reduction of daily salt intake reduced nocturnal urinary volume and nocturnal polyuria index in patients with excessive salt intake. Baseline night-time urinary frequency of 2.3±0.9 improved to 1.4±1 at 12 weeks. The proportion of the patients with renal dysfunction was significantly higher in the group who failed to reduce salt intake (44.9% vs 30.9%, p=0.022).

Nominal Group Technique

Mechanisms

The NGT panel agreed that nocturia in patients with CKD is predominantly due to nocturnal polyuria, but could also be due to 24-hour polyuria. Relevant processes were considered to include;

1. Loss of the normal nocturnal dipping of blood pressure and emergence of hypertension. Nocturnal hypertension can cause pressure-natriuresis, causing increased urine production.

2. Fluid and salt retention. In health, excess dietary fluid and salt are preferentially excreted during waking hours. This effect may become blunted in CKD, resulting in compensatory nocturnal natriuresis and polyuria. Furthermore, redistribution of retained fluid related to positional and hydrostatic changes may explain nocturnal increase in urine output, particularly as CKD becomes more advanced.

3. Alteration of the nocturnal increase of antidiuretic hormone (ADH), which generally reduces overnight urine production, with nocturnal polyuria the consequence. There may also be insensitivity to ADH in chronic interstitial renal diseases, in which case 24-hour polyuria could result.

4. Loss of medullary hypertonicity in chronic interstitial renal diseases causing 24-hour polyuria.

5. Inherited or acquired defective tubular sodium reabsorption (e.g. Barter syndrome) and solute driven osmotic diuresis in proximal tubular disorders such as Fanconi syndrome cause 24-hour polyuria.

6. Medications.

a) Diuretics, depending on duration of action and timing of doses (for example, a long acting diuretic, such as a thiazide, administered later in the day)

b) Lithium causes nephrogenic diabetes insipidus due to ADH insensitivity

c) Antihypertensive medications that cause oedema and redistribution of retained fluid at night causing nocturia, notably Calcium Channel Antagonists (CCAs) (e.g. Amlodipine)

d) Long term use of Non-steroidal anti-inflammatory drugs (NSAIDs) causing tubulointerstitial damage.

Assessment

The NGT did not recommend detailed CKD evaluation for patients with nocturia once per night. However, nocturia twice or more per night may warrant further evaluation to assess the severity of CKD in those already known to have it, or to identify the development of CKD in those who may be at risk of it. Risk factors for CKD include diabetes, hypertension, previous acute kidney injury, cardiovascular disease, multisystem diseases, gout, medications, hereditary kidney disease, and urological causes (24).

History. Discussion of thirst, along with fluid intake (volume/ timing/ type), and urine volume. This can be facilitated by scrutiny of a completed bladder diary.

Medication review. Type and timing of diuretics, lithium, CCAs, NSAIDs.

Examination. Looking for pitting oedema of dependent regions (e.g. swelling of the ankles), with the caveat that fluid retention could be present without overt clinically manifest oedema.

Blood pressure. Assessed as per local or national guidance (e.g. National Institute of Health and Care Excellence (NICE) guidelines for Hypertension in adults: diagnosis and management) (25).

Urinalysis. Spot urine albumin: creatinine ratio (ACR) and urine dipstick for haematuria
Blood tests. blood urea and serum creatinine and eGFR. NT-proBNP should be tested if there is suspicion of subclinical oedematous state. If elevated, pathways for management of heart failure should be consulted (e.g. NICE guidelines for Chronic heart failure in adults: diagnosis and management) (26).

Renal Ultrasound. As per local or national guidance applicable to CKD (e.g. NICE guidelines Chronic kidney disease: assessment and management) (24).

Treatment

Diet advice. Diet adjustments to reduce salt intake should be considered. Patients should be directed towards information on how to reduce salt intake using local or national guidelines (e.g. guidance from the UK Association of Dietitians) (27). Fluid advice is also appropriate, in particular avoidance of caffeine and alcohol in the evening.

Medication review. Review the timing and type of relevant medications that could be causing nocturia. This may need support of the relevant specialty that initiated the prescription.

Hypertension management. If BP is elevated, hypertension treatment needs review, with follow up to assess response. It would be logical to consider bedtime administration of medication in those already taking antihypertensive medications. Referral should be considered according to established guidelines (e.g. NICE guidelines for Hypertension in adults: diagnosis and management) (25).

Discussion

Our systematic literature review has mostly identified studies demonstrating the association between nocturia and CKD and plausible mechanisms for this association, but there was paucity of interventional studies addressing the management of nocturia in the CKD population.

Most studies demonstrating the association of CKD and nocturia defined nocturia as episodes of waking up twice or more during the main sleep period. The NGT panel therefore felt CKD evaluation amongst patients with nocturia of one episode per night was not indicated. The prevalence of nocturia is high in CKD, especially amongst those with GFR < 60 mL/min/1.73 m^2 (CKD stage 3 and above) and increased with the severity of CKD. However, in the study by Plantinga et al. (17), 21 % of patients with nocturia twice or more had no CKD. In addition, the majority of older patients, where nocturia is highly prevalent, are likely to have early stages of CKD that does not progress to end stage renal disease (28). Early diagnosis of mild CKD in this population may not necessarily alter life expectancy. Therefore, CKD screening of all patients with nocturia twice per night or more may lead to unnecessary investigations.

The occurrence of nocturia as a new symptom could be an indication of deterioration of renal function in those with known CKD. The NGT panel therefore felt that further evaluations to assess current kidney function and proteinuria, and to review BP management and medications in this patient group was warranted. Current guidelines within the UK (NICE guidelines Chronic kidney disease: assessment and management) recommend screening for CKD using eGFR and urine ACR for those patients who are

at risk of CKD (24). A new presenting symptom of nocturia in those at risk of CKD could be an indication of development of CKD. Accordingly, it would seem logical to offer opportunistic screening for CKD according to established guidelines, if it has not been undertaken already. Further referral to specialist nephrology services should be considered if patients meet local or national referral criteria to reduce CKD progression.

There are several plausible mechanisms for nocturia in patients with CKD, as described above. Nocturnal polyuria and essential hypertension share some of the same pathophysiological determinants (5). Nocturnal polyuria is associated with non-dipping of blood pressure at night in patients with CKD, and appears to be mediated by increased nocturnal activity (29). Urinary sodium excretion during the night is enhanced as renal function deteriorates (20) and as the circadian rhythm of BP becomes non-dipper type (30). The panel is not aware of evidence to suggest existence of a normotensive non-dipper phenotype prevalent in the nocturia population, but was unable to rule it out. Posture is also relevant in influencing natriuresis (31), raising a possibility that nocturnal polyuria may be based on pressure natriuresis during the night. Assessment recommendations in the NGT included standard BP measurement as per established guidelines on hypertension diagnosis and management (25). The NGT consensus considered that a finding of normal BP on standard management would usually mean that ambulatory BP to look for nocturnal hypertension would not be done, since antihypertensive treatment would be unlikely. Furthermore, the group considered there was insufficient evidence to estimate likelihood of positive findings. Nonetheless, they acknowledged that further research or different clinical perspectives could shift that opinion. Home-directed readings, guided by an information leaflet, might be considered in some situations, but cannot be considered routine practice. It is not clear that treating night-time hypertension, or attempting to restore dipping BP, reduces nocturia. However, this is established practice on grounds of general health. Therefore, a trial of switching antihypertensive medications to bedtime dosing could be considered for those with nocturnal polyuria who are already established on antihypertensive medications.

Medications adjustment can be considered in primary care and non-specialist secondary care settings where options allow for maintaining control of the indicated condition. Diuretics are a class of drugs clearly warranting consideration. Thiazide diuretics have a long half-life, and so could result in nocturia if administered later in the day. On the other hand, loop diuretics have a short half-life. Duration of action of furosemide is typically reported to be 6 hours only. Hence, it is conceivable that the risk of nocturia is less with loop diuretics if administered at least 6 hours before bedtime. The potential for calcium channel blockers to contribute to nocturia (32) due to redistribution of fluid at night is not as well known. Switching to alternative antihypertensive medications should be considered in these circumstances. Support of the relevant specialty should be sought where appropriate with regard to other relevant medications, such as lithium or non-steroidal anti-inflammatory medications.

Oedema from salt and water retention is often seen in more advanced stages of CKD but can be seen in those with mild CKD, due to coexisting conditions such as heart failure. Nocturia with reduced daytime voiding frequency and redistribution of fluid at night due to postural changes can cause nocturnal polyuria under these

circumstances (31). Assessment for fluid overload state is important for evaluating nocturia but can be difficult to discern in some patients (subclinical oedema). Indeed, up to 3L of extra fluid may be present in the body before the patient becomes aware of oedema. Sometimes these patients report “their legs feel heavy”. Current guidelines in the UK recommend testing for NT-proBNP for diagnosis of heart failure. The NGT panel felt testing for NT-proBNP could be undertaken if there is suspicion of subclinical oedema, with the caveat that the levels may be raised in patients with renal dysfunction (eGFR< 60 ml/min/1.73 m2) (26). Introducing diuretic therapy or adjusting the dose and frequency to optimize day-time diuresis would be appropriate in these situations. Dietary advice to reduce salt intake is routine clinical practice in patients with fluid retention and may improve nocturia, as shown by Matsuo et al. (23). Fluid advice is a key aspect of treatment. Recommendations to reduce caffeine and alcohol intake are common and appropriate. Nonetheless, effects are not necessarily as simple as is often presumed, given the range of relevant processes identified as factors in CKD that can influence nocturia.

Two small randomised trials published before the time period for our systematic literature search have compared the role of diuretics versus placebo in patients with nocturia. Bumetanide 1mg daily reduced nocturia symptoms by an average of 3.8 episodes per week, but the benefit was seen only in those without prostate hypertrophy, suggesting its role in those with systemic diseases presenting with nocturia (33). Reynard et al. (34) included only patients with nocturnal polyuria and no bladder outflow obstruction. They used furosemide 40 mg given 6 hours before bedtime and demonstrated a modest effect, with reduction in voiding frequency by 0.5 episodes per night and night-time voided volume by 18%. The authors recommend administering furosemide at least 8 hours before retiring for the night to ensure diuresis is complete by bedtime. The study excluded patients with serum creatinine > 150 micromol/l and therefore it is not clear if these benefits will translate to CKD patients with nocturnal polyuria. The panel did feel that diuretic offloading for treating nocturnal polyuria could be considered, but they wanted an updated trial including patients with CKD and incorporating modern-day assessments and phenotyping to ensure suitable patients are chosen for this type of therapy. They did not advocate generalized use of this approach.

Patients who have 24-hour polyuria due to suspected ADH insensitivity or salt losing states from tubular disorders or interstitial renal disease are beyond the scope of this paper and require referral to specialist nephrology services.

Conclusions

Nocturia is common in CKD, but other disease processes such as cardiovascular disease and diabetes that can affect renal function as part of the overall clinical picture may lead to a multifactorial pathophysiology of nocturia. In general, it is important to consider all potential systemic diseases before attributing the nocturia to CKD. Interventions to improve nocturnal polyuria related to CKD are limited. CKD evaluation and referral to specialist nephrology services where appropriate should be considered to reduce CKD-related morbidity and mortality.

Acknowledgements

This project is funded by the National Institute for Health Research (NIHR) under its Research for Patient Benefit (RfPB) Programme (Grant Reference Number NIHR RfPB PB-PG-1217-20034). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

The authors would like to thank Dr Charles Tomson, Department of Renal Medicine, Freeman Hospital, Newcastle upon Tyne, UK; Professor Christopher Pugh, Nuffield Department of Medicine, University of Oxford, Oxford, UK, and Dr Christopher Dudley, Southmead Hospital, Bristol, UK for their valuable contribution to the NGT consensus session.

MD declares the following potential conflicts of interest; Ferring (Advisory Board member), Astellas and Pfizer (Speaker).

References

1. Hashim H, Blanker MH, Drake MJ, Djurhuus JC, Meijlink J, Morris V*, et al.* (2019). International Continence Society (ICS) report on the terminology for nocturia and nocturnal lower urinary tract function. Neurourol Urodyn 38**:** 499-508.
2. Weiss JP, Bosch JL, Drake M, et al. Nocturia Think Tank: focus on nocturnal polyuria: ICI-RS 2011. *Neurourol Urodyn*. 2012;31(3):330-339.
3. Hofmeester I, Kollen BJ, Steffens MG, et al. The association between nocturia and nocturnal polyuria in clinical and epidemiological studies: a systematic review and meta-analyses. *J Urol*. 2014;191(4):1028-1033.
4. Duffy JF, Scheuermaier K, & Loughlin KR (2016). Age-Related Sleep Disruption and Reduction in the Circadian Rhythm of Urine Output: Contribution to Nocturia? Curr Aging Sci 9**:** 34-43.
5. McKeigue PM, Reynard JM. Relation of nocturnal polyuria of the elderly to essential hypertension. Lancet. 2000;355(9202):486-488.
6. Gulur DM, Mevcha AM, & Drake MJ (2011). Nocturia as a manifestation of systemic disease. BJU Int 107**:** 702-713.
7. Drake MJ. Should nocturia not be called a lower urinary tract symptom?. *Eur Urol*. 2015;67(2):289-290.
8. Marshall SD, Raskolnikov D, Blanker MH, Hashim H, Kupelian V, Tikkinen KA*, et al.* (2015). Nocturia: Current Levels of Evidence and Recommendations From the International Consultation on Male Lower Urinary Tract Symptoms. Urology 85**:** 1291-1299.
9. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71.
10. Sakalis VI, Karavitakis M, Bedretdinova D, Bach T, Bosch J, Gacci M, et al. Medical Treatment of Nocturia in Men with Lower Urinary Tract Symptoms: Systematic Review by the European Association of Urology Guidelines Panel for Male Lower Urinary Tract Symptoms. Eur Urol. 2017.
11. Van Kerrebroeck P, Abrams P, Chaikin D, Donovan J, Fonda D, Jackson S, et al. The standardization of terminology in nocturia: report from the standardization subcommittee of the International Continence Society. BJU Int. 2002;90 Suppl 3:11-5.
12. Hofmeester I, Kollen BJ, Steffens MG, et al. Impact of the International Continence Society (ICS) report on the standardisation of terminology in

nocturia on the quality of reports on nocturia and nocturnal polyuria: a systematic review. *BJU Int*. 2015;115(4):520-536.
13. Jones J, Hunter D. Consensus methods for medical and health services research. BMJ 1995 Aug 5;311(7001):376-80.
14. McMillan SS, King M, Tully MP. How to use the nominal group and Delphi techniques. *Int J Clin Pharm*. 2016;38(3):655-662.
15. Yoshimura K, Terada N, Matsui Y, Terai A, Kinukawa N, & Arai Y (2004). Prevalence of and risk factors for nocturia: Analysis of a health screening program. Int J Urol 11**:** 282-287.
16. Patel M, Potluri K, Leehey D, Bansal V, Brubaker L, Flanigan R, et al. Urinary incontinence and diuretic avoidance among adults with chronic kidney disease. Int Urol Nephrol. 2016 May 21;48.
17. Plantinga L, Lee K, Inker LA, Saran R, Yee J, Gillespie B, et al. Association of sleep-related problems with CKD in the United States, 2005-2008. Am J Kidney Dis Off J Natl Kidney Found. 2011 Oct;58(4):554–64. Hsu
18. Hsu CK, Wu MY, Chiang IN, Yang SS, & Chang SJ (2015). Are Middle-Aged Men with Chronic Kidney Disease at Higher Risk of Having Nocturia than Age-Matched Controls. Low Urin Tract Symptoms 7**:** 133-137.
19. Tam CA, Helfand BT, Erickson BA. The Relationship Between Diabetes, Diabetes Severity, Diabetes Biomarkers, and the Presence of Lower Urinary Tract Symptoms: Findings From the National Health and Nutrition Examination Survey. Urology. 2017 Jul;105:141–8.
20. Fukuda M, Motokawa M, Miyagi S, Sengo K, Muramatsu W, Kato N, et al. Polynocturia in chronic kidney disease is related to natriuresis rather than to water diuresis. Nephrol Dial Transplant. 2006 Aug 1;21(8):2172–7.
21. Matsuo T, Miyata Y, Sakai H. Daily salt intake is an independent risk factor for pollakiuria and nocturia. Int J Urol. 2017;24(5):384–9.
22. Liu H-Y, Chung M-S, Wang H-J, Liu R-T, Chuang Y-C. Nocturia indicates a poor health status and increases mortality in male patients with type 2 diabetes mellitus. Int Urol Nephrol. 2016 Aug;48(8):1209–14.
23. Matsuo T, Miyata Y, Sakai H. Effect of salt intake reduction on nocturia in patients with excessive salt intake. Neurourol Urodyn. 2019;38(3):927–33.
24. NICE Chronic kidney disease: assessment and management [NG203]. NICE guideline. 2021.https://www.nice.org.uk/guidance/ng203/history. Accessed 10th December 2021.
25. NICE Hypertension in adults: diagnosis and management [NG136]. NICE guideline. 2019. https://www.nice.org.uk/guidance/ng136. Accessed 10th December 2021.
26. NICE Chronic heart failure in adults: diagnosis and management [NG106]. NICE guideline. 2018 https://www.nice.org.uk/guidance/ng106. Accessed 10th December 2021.
27. British Dental Association. The Association of UK Dietitians. Food Fact Sheet: Salt. https://www.bda.uk.com/resourceDetail/printPdf/?resource=salt. Accessed 10th December 2021.
28. Ellam T, Twohig H, Khwaja A. Chronic kidney disease in the elderly people: disease or disease label ? BMJ 2016;352:h6559 doi: 10.1136/bmj.h6559.
29. Agarwal R, Light RP, Bills JE, Hummel LA. Nocturia, nocturnal activity, and nondipping. *Hypertension*. 2009;54(3):646-651.
30. Fukuda M, Munemura M, Usami T, Nakao N, Takeuchi O, Kamiya Y*, et al.* (2004). Nocturnal blood pressure is elevated with natriuresis and proteinuria as renal function deteriorates in nephropathy. Kidney Int 65**:** 621-625.

31. Uzu T, Takeji M, Yamauchi A, & Kimura G (2001). Circadian rhythm and postural change in natriuresis in non-dipper type of essential hypertension. J Hum Hypertens 15**:** 323-327.
32. Tikkinen KA, Auvinen A, Johnson TM, 2nd, Weiss JP, Keranen T, Tiitinen A*, et al.* (2009). A Systematic Evaluation of Factors Associated With Nocturia--The Population-based FINNO Study. Am J Epidemiol. 170(3), 361–368.
33. Pedersen PA, Johansen PB. Prophylactic treatment of adult nocturia with bumetanide. Br J Urol 1988; 62: 145–7
34. Reynard JM, Cannon A, Yang Q, Abrams P. A novel therapy for nocturnal polyuria: a double-blind randomized trial of frusemide against placebo. Br J Urol. 1998 Feb;81(2):215-8.

Figure 1: PRISMA Flow diagram

Table 1: Study characteristics