Implications of cardiovascular disease for assessment and treatment of nocturia in primary care; systematic review and nominal group technique consensus

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Word count 3859 (including abstract and main text, excluding tables, figures and references)

Key words; Nocturia, Lower urinary tract symptoms, Cardiovascular, Systematic review, Nominal Group Technique

Abstract

Context, Heart conditions affect salt and water homeostasis as a consequence of the underlying condition, compensatory processes and therapy, hence nocturnal polyuria can result. These processes need to be identified as part of a full evaluation of nocturia.

Objective, systematic review (SR) of nocturia in cardiovascular disease, and expert consensus for primary care management. Primary care was stipulated as a healthcare setting in which the expertise did not include specialist cardiology.

Evidence Acquisition, Four databases were searched from January 2000-April 2020. 3524 titles and abstracts were screened and 27 studies underwent full-text screening. Eight studies overall were included. Nominal Group Technique (NGT) was used for consensus with an expert panel incorporating public involvement.

Evidence Synthesis, Most SR papers focused on nocturia related to blood pressure (BP), whilst one investigated leg oedema. Hypertension, particularly overnight blood pressure above normal, corresponds with increased risk of nocturia. NGT identified fluid and salt overload, non-dipping hypertension and some therapeutic interventions to be key nocturia contributors. History taking and examination should identify raised JVP/ ankle swelling, with relevant investigations including measurement of BP, resting electrocardiogram (ECG) and B-type natriuretic peptide. Treatment recommends reducing salt (including substitutes), alcohol and caffeine. Heart failure is managed according to local guidance, and controlling fluid intake to 1-2L daily. If there is no fluid retention, reduce or discontinue diuretic or calcium channel blocker, following up to reassess condition. Target clinic blood pressure is 140/90 mmHg

Conclusion, Cardiovascular disease and its treatment is influential for understanding nocturia. Management aims to identify and treat heart failure and/ or hypertension.

Patient Summary, People with cardiovascular disease can suffer severe sleep disturbance from passing urine due to increased overnight blood pressure or heart failure. Following a detailed evaluation of published research, a group of experts recommended practical approaches for assessing and treating these issues.

Introduction

The range of contributory factors in population assessments of nocturia indicates the importance of considering medical conditions affecting water and salt balance when evaluating individuals (1-4). Cardiovascular disease is characterised by alterations in both water and salt handling, which reflect the underlying deficit, compensatory responses or therapy. For some patients, this may result in peripheral oedema. Fluid shifts when lying supine, along with endocrine responses, mean that rate of urine production from the kidneys may increase. This can result in nocturnal polyuria.

Generally, the over-riding importance of cardiac function means that nocturia is considered a subordinate and relatively minor issue in the clinical picture. Nonetheless, the sleep disturbance associated with nocturia can contribute a significant part of the quality-of-life impairment, to the detriment of the patient's overall health status. Furthermore, it is conceivable that persisting nocturia might reflect an aspect of the cardiovascular disease status, for example a diurnal variation in cardiovascular parameters, or suboptimal therapy.

Both nocturia and cardiovascular disease increase in prevalence with age, along with a range of morbidities that can affect salt and water handling. This means that assessment and therapy are complex, and generally not achieved with a single-specialty approach (5,6). The first healthcare professional reviewing a patient's nocturia may encounter clinical factors with which they may have comparatively little familiarity. Thus, equipping healthcare professionals

to manage and refer nocturia necessitates a viewpoint that can incorporate specialty aspects in the non-specialist context. The PLANET project (PLanning Appropriate Nocturia Evaluation and Treatment) aims to rationalise specialist elements for the initial management of nocturia to the primary care setting. It comprises a sequence of overlapping specialty consultations covering the range of common influences on nocturia, with the current review reporting the specialty consensus for primary care management of cardiovascular diseases in nocturia and the underpinning systematic review. The protocol of the systematic review was registered on PROSPERO (CRD42019157821).

Methods

Systematic review methodology

Search strategy: The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement was followed (7). A comprehensive search strategy was developed by two authors (SD, MD) in consultation with AH. Search terms for nocturia covering cardiovascular disease were identified. The role of desmopressin was not included as this has been covered in previous comprehensive publications (2). Several scoping searches using a combination of two main blocks of terms [nocturia and cardiovascular disease] NOT [desmopressin or heart valve disease 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 and 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 relevant studies.

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 (primary). 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 cardiovascular 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).
Timeframe: Papers published since 2000 were included. The date limitation was to bring consistency with International Continence Society standardised terminology (8).
Language: No language restrictions were applied, provided an English language abstract was available for initial screening.

Screening: SD exported search results from the different databases to Rayyan (https://rayyan.qcri.org/). Post de-duplication, selection of studies was completed in two stages. First, two review authors (PBGR, SD) independently screened titles and abstracts; next the full texts were screened to identify potentially relevant studies for inclusion. There was a high level of agreement (93%) between the reviewers at each stage. Any disagreements were resolved through discussion or involvement of a third reviewer (MD).

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

Deviation from the protocol 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. 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.

Nominal Group Technique methodology

NGT is a qualitative method for developing consensus through concept generation and prioritisation (9, 10). The specific directive was to consider primary care management of nocturia in cardiovascular disease, in which primary care was stipulated as a healthcare setting in which the expertise did not include specialist cardiology (for example, general practice or secondary care urology clinics (11). Participants received the studies identified in the SR in advance of the NGT to help familiarise themselves with existing evidence base. This evidence base formed the knowledge base to handle deficiencies which need addressing in the future. Online meetings (audio recorded and transcribed) were structured in a standardised process comprising: individual generation of ideas; dialogue to share ideas under the direction of a facilitator (NC); group discussion to prioritise concepts with visual structure (jamboard, https://jamboard.google.com/); concluding with voting to develop ranking.

Results

Systematic review

We identified 5311 titles and abstracts and after deduplication we screened 3524 titles and abstracts. 27 studies were included for full-text screening, of which 7 studies were identified as relevant. An additional study was included through forward and backward screening (Figure 1).

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Eight papers were finally included (Table 1): five from Japan, two from the United States and one from Denmark, and all were published in English. Three studies were observational (12, 15, 19) and five papers did not specify the design (13,14, 16-18). In total, 3906 males and 4188 females were analysed, with half of the studies including men only. Most articles focused on

populations > 50-years-old, except Victor et al. (12) who included 35–49-year-old men. The majority of papers focused on nocturia related to blood pressure (BP), whilst one investigated leg oedema. Five studies described mechanisms of nocturia associated with cardiovascular disease (13-17), two focussed on assessment (12, 18) and one on treatment (19).

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Mechanisms of nocturia

There were five studies which described mechanisms of nocturia (13-17). An observational study addressed leg oedema (13), evaluating the relationship with urinary levels of the anti-diuretic hormone arginine vasopressin (AVP) and nocturnal urine volume (NUV) in male inpatients in Japan who had benign prostatic enlargement and prostate cancer and were scheduled for surgery. They found that AVP was the only independent predictive variable for nocturnal polyuria, and that leg oedema decreases the secretion of AVP, thus indirectly increasing nocturnal urine volume. Brain natriuretic peptide, which can be a marker for cardiac overload, was measured and was not found to be related to NUV but had a positive correlation to leg oedema, suggesting that patients with leg oedema and high brain natriuretic peptide levels might have subclinical heart failure.

The remaining mechanism papers focused on the role of blood pressure with nocturia (14-17). Graugaard-Jensen et al. (14), published an experimental study in 18 healthy older males with seven or fewer episodes of nocturia in one week. These individuals had an increase in 24 hour urine output and NUV when there were nocturia episodes. The nocturnal voided volume (NVV) was larger than the maximum bladder capacity (MBC) on nocturia nights and 81% of MBC on nights with no nocturia. There were no differences in average voided volumes or fluid intake on days before the nocturia episodes. The subjects were hospitalized for 36 hours and mean arterial BP (measured half hourly during the daytime and hourly overnight) in patients who had nocturia was higher than patients without a nocturia episode; this difference was significant during the night-time. In the group without nocturnal voiding, there was an increase in AVP in plasma overnight compared to daytime, although the difference in nocturnal AVP levels was not significant between groups. There was a trend of lower levels of angiotensin II throughout the day in men with nocturia. Since AVP and angiotensin II were decreased, the rise in BP was not thought to be caused by these hormones and could be a compensatory response. Total urine output was the same between groups, but NUV was higher in patients with nocturia episodes. The reported observations may have been influenced by the effect on sleep pattern resulting from taking blood samples and BP measurement during hospitalization. The authors conclude that in healthy older men with occasional nocturia, an increase in BP overnight may be associated with intermittent nocturnal polyuria, implying a possible baroregulatory mechanism for nocturia.

A cross sectional study conducted by Matsumoto et al. (15), included 5959 Japanese participants aged between 30-74 years old. BP was measured at home during both daytime and night-time. Oximetry was monitored and a sleeping diary was completed. They described nocturia as an independent and strong determinant for BP change, with smaller nocturnal BP drop in subjects with frequent urination during the night, with the conclusion that nocturia can cause abnormalities in circadian BP. They suggest a possible mechanism involving salt

sensitivity, which would increase BP overnight by facilitating sodium excretion and diuresis and increasing nocturnal urination.

Natsume (16, 17) published two experimental studies in Japanese men and women with nocturnal polyuria. In the first study, AVP was monitored in 29 hospitalized patients; 25 patients lacked a primary diurnal rhythm of AVP and 38% had a low nocturnal AVP according to plasma osmolality (pOsm). 5% hypertonic saline was infused and AVP measured; this led to an upward shift in the osmotic threshold in nocturnal polyuria patients compared to healthy volunteers. This was considered potentially related to an abnormal osmotic regulation and to secondary resetting that alters volume-pressure regulation. An abnormal diurnal variation in AVP secretion appeared to be prevalent in nocturnal polyuria patients. Mean nocturnal voided volumes were higher than the diurnal. Mean BP correlated with nocturnal polyuria index (NPI) and mean daytime-to-night-time single voided volume ratio (16). The second publication, including 33 adults with nocturia, used a similar methodology involving hypertonic saline infusion and AVP monitoring (17). Increasing BP was associated with worse nocturnal polyuria and had a negative relation with daytime diuresis. Plasma AVP was not an independent variable for a rise in nocturnal diuresis rate or a decrease in daytime diuresis rate. BP, but not age, was related to nocturnal diuresis rate, perhaps reflecting a hypervolaemic state or increased sympathetic activity.

Assessment and treatment of nocturia

Two studies investigated assessment (12,18), and one paper described management of nocturia with cardiovascular disease (19). Victor et al. (12) determined that uncontrolled hypertension is an independent variable of clinically significant nocturia (defined as 2 or more nightly voids) in non-Hispanic black men aged 35-49 years. Men with hypertension were 56% more likely to have nocturia. If hypertension was treated and controlled, nocturia rate was the same as with normotensives. Treated but uncontrolled hypertensive patients had worse nocturia than untreated patients. They determined that nocturia in patients with treated high BP can be a symptom of uncontrolled hypertension. Explanations for the fact that treated uncontrolled patients had worse nocturia than untreated were: men treated and uncontrolled are likely to have had a higher BP before treatment; long-standing hypertension could lead to dysregulation of renal Na^+ transporters and altered nocturnal dip in BP; systolic and diastolic values for the uncontrolled patients were higher, suggesting an exponential instead of linear relation between BP and nocturia; medication for BP could have side effects including nocturia.

Takayama et al. (18) investigated 242 male adults with treated lower urinary tract symptoms (LUTS). 194 had nocturia (at least twice per night) and 130 had nocturnal polyuria. They did not find differences in subtypes of LUTS or comorbidities between nocturnal polyuria or non-nocturnal polyuria patients. The only significant difference was that there were more patients using 2 or more antihypertensives in the nocturnal polyuria group. In 34 patients (17 with nocturnal polyuria, 17 without), BP was monitored for 24 hrs and categorized according to their blood pressure dipping pattern and presence or not of nocturnal polyuria. There was no difference in systolic BP between nocturnal polyuria and non-nocturnal polyuria patients, but there were more with non-dipping BP in the nocturnal polyuria group. They considered non-dipping BP to be a potential factor for nocturnal polyuria and concluded that treating non-dipping BP might improve nocturnal polyuria.

The study evaluating treatment (19) described how a diet with sodium restriction reduced nocturia episodes from 2.5 to 1 per night in 56 adults, 93% of whom were African American) with various cardiovascular conditions seen in cardiology clinic. There was no change in nocturia episodes in 18 patients who did not follow a low sodium diet. BP and weight did not change in patients who adhered to a low salt diet.

Nominal group technique

Mechanism

Fluid and salt overload may arise in cardiac disease, potentially triggering endocrine responses which counteract the overload via diuresis or natriuresis. Hypertension is another cause of nocturia, notably non-dipping hypertension overnight. The necessity to eliminate excess water or salt is also a therapeutic strategy, with the use of diuretic drugs. Furthermore, calcium channel blockers and ACE inhibitors can have a diuretic effect. Hence, nocturia potentially can be a symptom associated with cardiac dysfunction or its treatment, though this is not widely acknowledged in cardiology guidance. Sleep apnoea and sleep-disordered breathing are associated with cardiovascular disorders, which provides an additional consideration for these patients.

Assessment

Clinical assessment of nocturia should look for features suggestive of cardiac disease in the history. Where cardiac disease is suspected, examination should evaluate the jugular venous pressure (JVP) and look for the presence of peripheral oedema. If it is suspected that heart failure may be contributing to nocturia investigations should include;

- Measurement of BP
- Resting electrocardiogram (ECG)
- Blood test for N-terminal pro B-type natriuretic peptide (BNP)

Where BNP is elevated, echocardiogram can be considered according to local pathways for suspected heart failure.

Treatment

Patients should be provided with general advice, therapy directed at managing fluid retention should be considered and medications should be reviewed.

1. General advice
    a) Encourage the patient to minimise their salt intake, by not adding salt or salt substitutes to food, and avoiding preserved or processed high salt foods and drinks (e.g. sodas and colas).
    b) Consider type and timing of fluid intake, due to diuretic effects (alcohol and caffeine) and cardiomyopathic effects (alcohol). Patients with heart failure are educated to control fluid intake and are advised of a maximum daily fluid intake (usually between 1-2 litres).
2. Managing fluid retention
    a) Confirmed heart failure should be managed according to local guidance
    b) Review of current medications.
        (i) If a patient is taking a diuretic or calcium channel blocker and there are no signs of fluid retention, consider reducing or discontinuing the diuretic or calcium channel blocker with follow up to assess response.

(ii) Medication timing can be adjusted. Intuitively, dosing early in the day should have lower risk of nocturia. However, anecdotal reports suggest that evening dosing of diuretic can be trialled reduce nocturia and this is unlikely to cause harm (20).

3. Improving BP control. In patients with poorly-controlled hypertension, optimised treatment is recommended, with a target clinic blood pressure of 140/90 mmHg.

Discussion

Water and electrolyte balance are affected by cardiac disease and hypertension is a direct cause of nocturia. Hence, assessment of the cardiac status in a patient with nocturia is an important consideration. Unfortunately, the potential association of these processes with nocturia is not widely considered, raising the need for greater discussion of this topic in the context of both primary care and specialist services.

The NGT discussions highlighted three tests (BP measurement, ECG and BNP) which are available in general practice and comparatively inexpensive. When considered from the perspective of a patient presenting with nocturia, if the patient has a normal ECG and a normal BNP, the likelihood of a significant cardiac abnormality is low. Some patients with heart failure and good systolic function can have a normal ECG, but if retaining salt and water BNP will be elevated. Hence, BNP is particularly pertinent for nocturia assessment. The BP measurement recommended is a daytime standard assessment. Where available, 24-hour BP measurement is more informative, since non-dipping hypertension is particularly pertinent for nocturia. However, issues around availability and cost are such that the NGT discussion did not recommend its routine use for patients with nocturia; instead it may be considered selectively.

Patients with nocturnal polyuria and oedema can have low AVP secretion overnight. However, desmopressin therapy in these patients would increase fluid retention and worsen cardiac function. On this basis, treatment for leg oedema, such as diuretic therapy and restriction of sodium, is deemed reasonable. The cardiovascular benefits of a diuretic are not majorly affected by timing of doses. This allows leeway on when medications can be taken, though there is little evidence relating to the effect of medication timing on nocturia. Two considerations are to avoid the timing of the diuresis overlapping with the patient's bedtime. Additionally, the dehydrating effect of diuretics can cause thirst, leading the patient to drink to an extent that can subsequently increase their urine output; if applicable, this phase should also be completed before the patient's bedtime. Intuitively, these considerations suggest avoiding an evening dose of diuretic, and that dosing earlier in the day might be more appropriate for improving the severity of nocturia. However, evening consumption of liquids and food may counteract the beneficial of earlier dosing with diuretic. Furthermore, anecdotal reports suggest that evening dosing of diuretic can reduce nocturia. Hence, planning and review of response is needed to get recommendations right for the individual patient.

Hypertension treatment has a vital role in reducing the risk of cardiac failure. However, nocturia does not necessarily improve and patients should be counselled accordingly. For those patients already on antihypertensive treatment, a diuretic effect of the medication (including those not generally recognised as diuretics, notably calcium channel blockers (1)) needs to be considered. The influences on dose timing above should be factored in, and the possibility to switch to alternative agents may also be applicable in some cases. This may facilitate achieving the two priorities to maintain BP control and improve nocturia.

Compression stockings were not recommended by the NGT, as cardiologists would generally only advise them for peripheral oedema if it was non-cardiac in origin i.e. dependant in nature (worse at the end of the day due to gravitational effects and resolved by the morning having laid flat in bed). Hence they are more usually used to treat venous insufficiency. Elevation of the legs in the evening is also usually recommended for dependant oedema, but may be considered in patients with heart failure and peripheral oedema.

The limited literature base identified in the SR indicates that the relationship between cardiovascular disease and nocturia is under-researched. It is possible that nocturia could develop early in the clinical progression of heart failure, before the onset of JVP elevation, shortness of breath, oedema and exercise limitation. Class 2 cardiac failure indicates a person who becomes short of breath on strenuous effort, and diagnosis may not be made until further progression of cardiac failure. At this stage, it is possible that compensatory processes may affect rate of urine production. Hence, nocturia might precede typical heart failure symptoms, bringing the possibility of making the initial diagnosis earlier in the clinical course. This may enable an opportunity to intervene with a view to preventing progression, an area the NGT considered worth further research. They also discussed that encouraging results from a clinical trial in 1998 (21) suggest that research into the effect on nocturia of a trial of diuretic might be considered (unless contraindicated) for patients without oedema. The evidence synthesised in this work has emphasised the need for a robust trial that could test the efficacy of a diuretic on nocturia and provide insight into the underlying mechanisms. A short-term course (e.g. for seven days) of 40 milligrams of furosemide daily may help establish whether a patient has subclinical salt and water retention, with weight (fluid) loss over the course of a week indicating a positive response.

Conclusions

Cardiovascular conditions affect nocturia as a result of heart failure and/ or hypertension. This should be assessed by clinical examination and investigation with BP and BNP measurement, and ECG. Treatment should focus on therapy of hypertension or heart failure according to local guidance, along with dietary advice, and review of medications.

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.

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

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Figure 1: PRISMA Flow chart

Table 1: Study characteristics

Appendix 1: Sample search strategy