

# **Association of sleep disorders with nocturia; systematic review and nominal group technique consensus on primary care assessment and treatment**

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## Abstract

*Context,* Sleep disorders affect responsiveness to sensory information and can cause nocturnal polyuria and reduced sleep depth, hence are potentially influential in understanding mechanism of nocturia.

*Objective,* systematic review (SR) and expert consensus for primary care management of nocturia in sleep disorders.

*Evidence Acquisition,* Four databases were searched from January 2000-April 2020. 1658 titles and abstracts were screened and 23 studies potentially applicable were included for full-text screening. Nominal Group Technique was used to derive consensus on recommendations for management using an expert panel with public involvement.

*Evidence Synthesis,* 13 studies met the SR inclusion criteria, all of which studied obstructive sleep apnoea (OSA), with 10 evaluating the effect of continuous positive airway pressure. NGT consensus discussed the assessment of OSA with other key sleep disorders, notably insomnia, restless legs syndrome/ periodic limb movements of sleep and parasomnias, including non-REM parasomnias and REM sleep behaviour disorder (RBD). The NGT considered that use of screening questions to reach a clinical diagnosis is sufficient basis for offering conservative therapy within primary care. Reasons for referral to a sleep clinic are suspected sleep disorder with substantially-impaired daytime function despite conservative treatment. Suspected RBD should be referred and, if confirmed, neurology opinion is indicated. Referrals should follow local guidelines. Persisting nocturia is not currently considered an indication for referral to a sleep clinic.

*Conclusion,* Sleep disorders are potentially highly influential in nocturia, but are often overlooked.

*Patient Summary,* People with sleep disorders can experience nocturia due to easy waking or increased bladder filling. We looked at published research and information was limited to one form of sleep disturbance, obstructive sleep apnoea. We assembled a group of experts, to develop practical approaches for assessing and treating nocturia in the potentially-relevant sleep disorders.

## Introduction

Repeated sleep disruption is highly problematic, with those affected having significantly impaired quality of life, health, relationships and work lives (1, 2). Along with primary sleep disorders, behavioural and environmental influences, and medical and psychological factors can all contribute to sleep quality. Nocturia is a cause of sleep disruption, reflecting 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 (3). Nocturia is multifactorial (4-6), and one factor is sleep impairment, which may make waking to pass urine more likely.

The relationship between sleep disruption and nocturia can be hard to ascertain, largely because determining why an individual awoke or was awoken is often challenging. On one hand, nocturia can arise when the signals from the bladder indicating the need to pass urine are sufficient to wake the patient to initiate toileting behaviour. For example, obstructive sleep apnoea (OSA) causes nocturnal polyuria and hence increased bladder signals. On the other hand, likelihood of response to the signals may be influenced by depth of sleep. For example, restless legs syndrome (RLS) and periodic limb movements of sleep (PLMS) will cause lighter sleep and more frequent arousals, and hence more awareness of bladder sensation leading to convenience voids. It is recognised that the nocturnal polyuria caused by OSA is generally explained by natriuretic peptide release in response to negative intrathoracic pressure, and treatment with continuous positive airway pressure (CPAP) can reduce nocturia (7-8). However, nocturia mechanisms are less well defined for other potential sleep disorders.

Under-diagnosis of concurrent sleep disorders may limit nocturia treatment efficacy, but recommendations about how to identify and treat sleep disturbances in these patients are lacking. The PLANET study (PLanning Appropriate Nocturia Evaluation and Treatment) was established to support healthcare practitioners responsible for initial management of nocturia. The current paper reports the systematic review of published evidence relating to nocturia in primary sleep disorders, and the expert consensus for primary care management derived from a multidisciplinary group, incorporating general practitioner and sleep specialist input. The protocol of the systematic review was registered on PROSPERO (CRD42019157821).

## Methods

### Systematic review

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 sleep and related diseases were identified. Desmopressin was not included due to prior publications covering its role in nocturia comprehensively (2). Several scoping searches using a combination of two main blocks of terms [nocturia and sleep and related conditions] NOT [desmopressin or children] were run in MEDLINE to maximise the sensitivity and specificity of the developed search strategy (Appendix 1).

A combination of free-text terms and thesaurus headings for each block of terms 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 relevant citations from January 2000-April 2020: MEDLINE; Embase; The Cochrane Library and PsycINFO. Forward and backward referencing of included papers were undertaken 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.

### *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 outcome). 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 sleep-related causes of nocturia. Reference lists of relevant identified systematic reviews were searched to identify additional relevant primary studies.

Timeframe: To ensure compliance with International Continence Society standardisation terminology for nocturia (3, 10, 11), we limited the search to studies published since 2000.

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/>) by SD. Post de-duplication, selection of studies was completed in two stages. First, two review authors (EP, 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 (83%) between the reviewers both at title and abstract, and 91% at full-text screening stage. Any disagreements were resolved through discussion or involvement of the 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 (EP and SD). Any disagreements were resolved through discussion and where necessary, consultation with the third reviewer (MD).

*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

Nominal Group Technique (NGT) is a semi-quantitative structured group interview process (12, 13) for developing consensus. It was used to consider the relationship between sleep disorders and nocturia, in terms of assessment and therapy in primary care. Management of comorbid conditions was not covered, since a separate NGT process was undertaken for nocturia of multifactorial aetiology. The NGT was run with an expert panel including specialists in sleep disorders, 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 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, 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. Nominal groups were conducted until saturation was reached.

## Results

### Systematic review

1658 titles and abstracts were screened after deduplication. 23 studies were included for full-text screening, of which 13 studies were identified as relevant. No additional studies were identified through forward and backward screening (Figure 1).

INSERT FIGURE 1 ABOUT HERE

Of the 13 studies included, there were 9 cohort studies, 3 cross-sectional studies and a case control study. The number of participants in the included studies ranged from 44 to 1970. 10 of the studies assessed the impact of CPAP on nocturia in OSA, there was one study which evaluated the impact of Uvulopalatopharyngoplasty on nocturia in OSA (Table 1). The SR found no published research into the assessment of nocturia in association with other sleep disorders.

INSERT TABLE 1 ABOUT HERE

Endeshaw and colleagues (14) recruited 72 adults aged 64 and over, of whom 58 completed the study. Subjects completed a 72 hour voiding diary, followed by overnight ambulatory sleep recording. The Oxygen Desaturation Index (ODI), defined as the number of desaturations per hour of sleep, was used. ODI-1 referred to any fall in oxygen saturation by 3% or more; ODI-2 referred to a fall in oxygen saturation by 3% or more and to less than 90%. The mean nocturia episodes were 1.76+/-1.06, 1.38/-0.74, and 3.00 /- 2.00 for subjects with ODI-2 of 0.0 to 4.9, 5.0 to 14.9, and 15.0 or more per hour, respectively (P= 0.039). The difference in nocturia episodes between those with different levels of ODI when the oxygen saturation remained 90% or greater at the time of desaturation (ODI-1 definition) could have occurred by chance. Subjects with an AHI of 25 or greater per hour had a greater number of nocturia episodes, higher BMI, higher MAP, and marginally higher Epworth Sleepiness Scale. The correlation between AHI and nocturia was inconsistent (Pearson correlation = 0.395,P) Guillenminault et al. (2004) conducted a prospective evaluation of 87 men 65 years and older with suspected OSA. Group A consisted of patients with OSA and two or more episodes of nocturia (n=31). Group B consisted of patients with OSA and <2 episodes of nocturia (n=29). Group C consisted of patients with long sleep latencies (sleep onset insomnia), absence of OSA and <2 episodes of nocturia (n=27). All of the subjects underwent a minimum of 8 h of nocturnal polysomnogram. Nocturia severity was based on report of frequency during the week prior to the evaluation and frequency on the night of polysomnography. OSA patients

were treated with nasal CPAP after calibration with polysomnography. The other patients were treated with 5 mg Zolpidem at bedtime for a maximum of 15 days, with simultaneous referral to a behavioural program for the treatment of insomnia. Group A had a mean of 3.8 +/- 0.4 episodes of nocturia per night before treatment; Group B, 0.7 +/- 0.25; and Group C, 0.68 +/- 0.29. After treatment, the mean episodes of nocturia were 0.7 +/- 0.27, 0.67 +/- 0.21 and 0.68 +/- 0.25 for Groups A, B and C, respectively. After treatment, all of the groups had less than two episodes of nocturia per night. Epworth Sleep Score also changed significantly for Groups A and B ( $p = 0.0001$ ) but not for Group C. Pre and post treatment Beck Depression Index significantly improved in all of the groups (15).

Oztura et al. (2005) assessed 1970 patients referred with suspected sleep disordered breathing (SDB) (16). Nocturia was assessed using a 'standard questionnaire' to evaluate frequency of urination per night. Polysomnography was conducted for minimum of 8 hours. Respiratory disturbance index (RDI) was established as the number of all obstructive type respiratory events per hour of sleep including apnoeas, hypopnoeas and flow limitations. The frequency of nocturnal urination showed significant variation according to the severity of SDB ( $P < 0.001$ ). Nocturnal urination of more than three times per night was reported significantly more by severe SDB patients (those with RDI  $> 40$ ) than by other groups of SDB patients (5.3% in mild SDB, 17.7% in severe,  $p < 0.001$ , positive predictive value = 0.73, negative predictive value = 0.52). For the group as a whole, correlations were found between the frequency of nocturnal urination and mean age ( $r = 0.27$   $P < 0.001$ ), BMI ( $r = 0.20$   $P < 0.001$ ), RDI ( $r = 0.26$   $P < 0.001$ ), Apnoea Hypopnea Index (AHI;  $r = 0.26$   $P < 0.001$ ), Respiratory Event Index (REI;  $r = 0.10$   $P < 0.001$ ) and lowest oxygen saturation ( $r = 0.26$   $P < 0.001$ ).

Fitzgerald et al. (2006) evaluated 200 sleep studies including 100 men and 96 women. 137 patients had OSA and 59 patients had a normal sleep study. Patients diagnosed with other sleep disorders ( $N = 4$ ) were excluded. If diagnosed with OSA, a second sleep study was performed using CPAP. Sleep technicians documented the episodes of nocturia. Among patients with OSA and nocturia who had CPAP studies ( $n = 46$ ), nocturia episodes significantly decreased from a median of 3 episodes to 0 episodes per notional 8 hour sleep time ( $P < 0.001$ ). In 29 patients (60%) the rate of nocturia episodes per hour decreased to zero. All indices of oxygenation improved significantly when CPAP was used. In patients with OSA and nocturia, increasing severity of OSA, measured as AHI, was related to increasing nocturia frequency (17).

Margel et al. (2006) studied 97 patients (75 men and 22 women) who were referred for polysomnography due to suspected OSA. 50 had mild to moderate OSA (RDI less than 35/hr) and 47 had severe OSA (RDI greater than 35/hr). Patients diagnosed with OSA were treated with CPAP, and those continuing therapy for at least 1 month were included in the study. The mean SD number of awakenings to void at home before CPAP was 2.5 +/- 2.4/night; during CPAP, it was 0.7 +/- 0.6/night ( $p < 0.001$ ). The mean SD number of awakenings to void in the laboratory was 1.1 +/- 0.9 before CPAP and 0.5 +/- 0.6 during CPAP treatment ( $p < 0.001$ ). The improvement in nocturia after CPAP was significant in both mild to moderate and severe OSA, but it was more prominent in the patients with severe OSA (18).

Miyauchi et al. (2014) studied 98 patients referred with suspected OSA. 9 patients dropped out, 3 were lost to follow up, and final data was collected for 51 patients. Night-time frequency reduced following one month of CPAP from 2.0 +/- 1.1 to 1.0 +/- 1.2 ( $p = 0.014$ ) and night-time urine volume reduced from 542.4 +/- 289.9ml to 354.0 +/- 217.4ml ( $p = 0.005$ ), with significant improvement of total IPSS and QOL scores (19).

Maeda et al. (2016) prospectively recruited 150 men who were planned to receive CPAP for moderate to severe OSA. Nocturia was measured using Question 7 from the IPSS questionnaire, and was defined as  $\geq 2$  urinations in a single night. After 3 months of CPAP, nocturia severity fell from  $1.4 \pm 1.3$  to  $0.7 \pm 0.9$  ( $p < 0.01$ ). Among the 56 patients with nocturia pre-treatment, CPAP significantly reduced the number of awakenings from  $2.8 \pm 0.9$  times/night to  $1.2 \pm 1.1$  times/night ( $p < 0.01$ ) (20).

Park et al. (2016) analysed 256 patients diagnosed with OSA on polysomnography. Of these, 66 patients with nocturia  $>1$  were listed for uvulopalatopharyngoplasty (UPPP). Of 66 patients, 37 responded to telephone interviews. Nocturia episodes (captured using IPSS question 7) decreased from  $1.8 \pm 1.1$  to  $0.8 \pm 1.2$  ( $p < 0.001$ ), with total mean IPSS decreasing from  $9.3 \pm 6.9$  to  $5.9 \pm 5.9$  ( $p < 0.001$ ) and QoL score improving from  $1.8 \pm 1.4$  to  $1.1 \pm 1.1$  ( $p = 0.02$ ) (21). The success rate of surgery was 73%; the success group (27 patients) showed a decrease in nocturia episodes (from 1.9 to 0.7,  $P < 0.001$ ). In 15 patients (41%), the nocturia episodes decreased to zero.

Niimi et al. (2016) reviewed 104 patients referred with suspected OSA for polysomnography. 68 continued CPAP therapy for more than 3 months, but only 22 provided post therapy data. In patients with pre CPAP nocturnal polyuria, IPSS score improved from  $2.4 \pm 1.2$  to  $1.6 \pm 0.9$  ( $p = 0.008$ ), and nocturnal urinary frequency improved from  $2.0 \pm 1.7$  to  $0.9 \pm 1.1$  ( $p = 0.042$ ). The mean nocturnal polyuria index improved from  $0.46 \pm 0.13$  before CPAP to  $0.35 \pm 0.17$  after ( $p = 0.023$ ). Despite similar severity of AHI, only patients with pre-existing nocturnal polyuria showed significant improvement in night-time urinary frequency and nocturnal polyuria index after CPAP therapy (22).

Miyazato et al. (2017) studied 53 patients with moderate to severe OSA who were treated with CPAP for 3 months. Night-time frequency changed from 2.1 times to 1.2 times per night ( $p < 0.01$ ). Total nocturnal voided volume decreased from 723.3 ml to 453.6 ml ( $p < 0.01$ ), and nocturnal polyuria index decreased from 37.0% to 28.6% after CPAP treatment ( $p < 0.05$ ). Duration of undisturbed sleep was increased from 193.6 min to 287.3 min. Mean IPSS score fell from 7.6 to 5.0 ( $p < 0.01$ ), and the QOL index improved from 3.4 to 1.9 ( $p < 0.01$ ). Brain natriuretic peptide level did not change with the decrease in nocturnal urine volume (23).

Irer et al. (2018) studied 126 patients aged below 50, referred for polysomnography for suspected OSA. CPAP treatment was recommended for 77 patients, 61 patients accepted treatment, but 54 patients came to the third-month control and completed the questionnaires. Following treatment, frequency of nocturia (baseline  $2.1 \pm 1.3$ , 3 months post CPAP  $0.5 \pm 0.5$  ( $p < 0.001$ )) and nocturnal urine volume (baseline  $547.0 \pm 285.5$  ml, post CPAP  $95.6 \pm 107.8$  ( $p < 0.001$ )) were reduced significantly. Sleep Quality assessed using ICIQ-Nqol was improved (baseline  $12.9 \pm 8.4$ , 3 months post CPAP  $3.7 \pm 3.4$  ( $p < 0.001$ )) (24).

Yu et al. (2019) studied 44 patients with a recent ischaemic stroke diagnosed with OSA. Patients who accepted CPAP ( $N = 25$ ) were compared to those who refused or did not tolerate CPAP ( $N = 19$ ). 9 patients were excluded, and 35 patients completed the study. CPAP therapy significantly decreased nocturnal polyuria index (mean percentage change 9% vs -21% ( $p = 0.005$ )) and nocturnal urine output (mean percentage change 6% vs -26% ( $p = 0.04$ )), but not the nocturia episodes. The authors concluded that CPAP treatment can significantly reduce nocturnal polyuria, but not nocturia frequency, in ischaemic stroke patients with OSA (25).

Vrooman et al. (2020) conducted telephone interviews with 285 patients who had undergone at least 1 year of CPAP treatment for OSA. The authors defined "clinically relevant nocturia" as  $\geq 2$  voids per night. The median nocturia frequency before CPAP was 3 (IQR = 3) and after

CPAP was 2 (IQR = 2). The mean reduction of nocturia with CPAP was  $-1.09$  with a standard deviation of 1.58 ( $p < 0.001$ ). 200 (73.0%) patients had clinically relevant nocturia before CPAP. After treatment with CPAP, the number of patients with clinically relevant nocturia was 141 (51.5%) (26).

### Nominal Group Technique

NGT sessions lasted approximately 2 hours, with 3 to 6 participants, and took place over a six month period at the conclusion of the SR. Members of the panel reviewed the SR findings individually before the first NGT meeting. The findings of the SR were noted to be dominated by papers reporting treatment of sleep disordered breathing, where an improvement of sleep quality and reduction of nocturia was identified in most studies.

The NGT considered that there is generally a long delay between symptom onset and treatment of sleep disorders. Untreated sleep disorders have a substantial economic impact, through lost productivity and increased health care utilisation (e.g. accidents, and worsened diabetes and hypertension).

The presence of severe daytime fatigue, inability to concentrate and negative effects on activities of daily living, i.e. how the patient feels in the day, are strong indicators of sleep disturbance severity. This may be more important symptomatically than factors such as number of times waking or sleep duration. While the pathways for patients from primary care are not well established, severe daytime impact may justify a referral to sleep clinic, even if a causative medical mechanism is identified, particularly if interventions do not improve symptoms.

Nocturia is commonly seen in sleep clinics, with four key contributors;

1. Insomnia. Where nocturia gets better with successful insomnia treatment, the nocturia is probably secondary to going in and out of light sleep.
2. OSA, where nocturia is often a result of nocturnal polyuria, but not invariably. Treatment with OSA may use CPAP, and if nocturia improves in those patients, it probably reflects a reduction in nocturnal polyuria index.
3. RLS/ PLMS. RLS has four key aspects; symptoms are worse at night, they are relieved by movement, they return when the person stops moving, and feelings associated are characteristic. People may describe an uncomfortable creepy crawling feeling and a feeling of needing to move their legs in the afternoon or evening. A high proportion of people with RLS have PLMS, which the person affected may not know about until a bed partner complains of being kicked or disturbed. It only needs to be treated if it is causing sleep disruption or daytime somnolence. Nocturia can be reported if sleep is disturbed by PLMS.
4. Parasomnias are abnormal behaviours and dreams during sleep, or during the transition into sleep or out of sleep. Often they are transient, but in some cases they cause significant sleep disruption or injury.
  - a) Non-REM parasomnias. These reflect incomplete arousals from deep sleep, for example resulting in sleep walking, sleep talking, or sleep sex, and arousal in a confused state. The episodes are more likely to occur in the first half of the night. The patient generally has limited recall for the events, and often has at most vague recall of dreaming. Their eyes are often open during the episode. They can be triggered by sleep deprivation, stress, OSA or excessive alcohol. Non-REM parasomnias often start in childhood and are more likely to affect younger people.

- b) REM sleep behaviour disorder (RBD). This is caused by loss of normal atonia during REM sleep, so people may shout out, kick out or hit. There may be detailed recall of dream contents. RBD is more likely to affect older people, becoming more common after 50 years of age. A significant proportion of people later develop Parkinson's disease or other neurodegenerative disorders, so screening of pre-motor, motor and non-motor symptoms associated with extrapyramidal disorders should be undertaken.

Some patients on questioning may describe nightmares, which are a further sleep disorder area, though sometimes seen in RBD. A nightmare leads to waking up terrified or feeling that something really awful has happened, sufficiently severe that ongoing effects are felt in the day (hangover fear effect), perhaps associated with fatigue, cognitive difficulties and mood change.

In modern practice, screening for sleep disorders is facilitated by accessible technology, such as home pulse oximetry or wearable devices capable of recording oxygen saturation, heart rate, airflow, body position and arterial tone. There are also devices such as accelerometers that can monitor leg movements to facilitate the diagnosis of PLMS. These are increasingly capable of evaluating sleep stage, breathing and PLMS, but currently are generally not used or available in primary care.

#### **Assessment recommendations**

Primary care assessment requires a brief sleep screening history. Initial discussion covers general issues, including detrimental behaviours (working or using electronic devices until bedtime or during the night, and use of stimulants, such as alcohol, caffeine, and recreational drugs) and impaired sleep patterns (factors such as work that includes night shifts). Lack of subjective daytime dysfunction makes insomnia unlikely, and a sleep problem contributing to the nocturia less likely.

The following initial screening questions can help identify the possibility of an underlying sleep disorder;

1. Insomnia
  - *'Do you have difficulty falling or staying asleep?'*
  - *'How well do you function during the day?'*
2. OSA
  - *'Do you snore, and sometimes wake up choking?'*
  - *'Does your partner say you stop breathing?'*
  - *'Do you often wake with a headache?'*
3. RLS/ PLMS
  - *'What does it feel like?'*
  - *'Does it vary over the day and is it worse later in the day/evening?'*
  - *'Is it relieved by movement?'*
  - *'Does it come back again a few minutes after you sit or lie back down?'*
  - *'Does your bed partner complain that you have twitchy legs or make kicking movements in your sleep?'*
4. Parasomnias
  - *'Are you aware of, or have you been told about, any odd events at night such as walking around the home, screaming, eating or engaging in sexual activity?'*
  - *'At what age did you first experience the events?'*
  - *'Do you recall the events?'*

- *'If woken from an episode do you recall dreaming?'*
- *'Are your eyes open during the episodes?'*
- *'What time of night do they occur?'*
- *'Do you stay in bed or get out of bed?'*
- *'Have you hurt yourself or someone else?'*
- *'Do you have nightmares, meaning terrifying awful dreams rather than just anxious unpleasant dreams?'*

Positive responses should be followed by additional assessment. This may necessitate usage of more in depth questions or questionnaires for OSA (such as STOP-BANG (27)) or RLS. Local guidance should be followed, for example the National Institute for Health and Care Excellence guidance for OSA (28, 29).

### ***Treatment recommendations***

Initial treatment can be based on clinical diagnoses made in primary care. Relevant guidance for treating sleep disorders should be consulted for specific requirements, for example advice not to drive if feeling sleepy. The following is a list of interventions that can be initiated in primary care;

1. Insomnia;
  - Behavioural interventions suitable for a brief consultation
  - Provision of a leaflet
  - CBT for insomnia programmes within national health systems, including online (region specific)
2. Suspicion of OSA; advice on weight loss, and support with weight loss where indicated by local guidelines
3. Suspicion of RLS/PLMS;
  - Iron deficiency anaemia, or serum ferritin less than 50 to 75 micrograms/L — investigate to identify a cause of iron deficiency and prescribe iron supplements (if appropriate) (29)
  - Reduce alcohol, caffeine and nicotine that can make RLS/PLMS worse. Consider discontinuing antidepressant medication that can exacerbate RLS/PLMS
  - Dopamine agonists (e.g. pramipexole, rotigotine or ropinirole) can be used for treatment, but can be associated with augmentation (paradoxical worsening of RLS symptoms, often starting earlier in the day) and impulse control disorders (30)
  - Pregabalin or codeine in low dose given at night only are treatment alternatives but the risk of developing dependency needs to be considered
4. Suspicion of parasomnia;
  - Discuss general sleep hygiene
  - Advice on avoiding triggers to the non-REM parasomnias
  - Consider safety aspects. Recommend that doors and windows are properly secured, and injury risks, for example staircases and sharp or dangerous objects around the bed, are considered. Ensure the bedpartner is safe and consider sleeping separately
  - In suspected non-REM parasomnias, referral is only needed if the interventions are not helpful, there is injurious behaviour and the patient is concerned
  - If RBD is suspected, sleep hygiene, trigger avoidance and safety should be addressed, and referral should routinely be made to a sleep clinic (to reach diagnosis), and then to neurology if confirmed

## Referral to sleep medicine

1. Referral for assessment of possible RBD (neurology sleep clinic)
2. Suspected or confirmed OSA (respiratory or ENT sleep clinic)
3. Other suspected sleep disorder, where substantially-impaired daytime function persists despite conservative treatment

Persisting nocturia is not considered an indication for referral.

## Discussion

Sleep disorders are common and potentially treatable cause of nocturia, resulting from either increasing likelihood of waking (e.g. insomnia, PLMS) or accelerating bladder filling through nocturnal polyuria (OSA). It is clear that nocturia is often the focus of presentation to primary care, and potentially onward referral, for example to urology clinics. Both primary care doctors and urologists are likely to have only limited knowledge of sleep medicine, hence the current recommendations are intended to be a first step towards facilitating a practical approach to identifying patients with possible sleep disorder in a primary care setting.

The relationship between sleep-disordered breathing and nocturia is complex, and hypoxemia, respiratory effort, and obesity may influence the frequency of nocturnal urination. Subjects with oxygen desaturation to less than 90% have increased episodes of nocturia (14). OSA was the dominant sleep disorder identified in the SR, with several studies evaluating nocturia outcome with OSA therapy. CPAP treatment in patients with OSA under 50 was found to decrease nocturnal polyuria and the frequency of nocturia, with improved quality of life (20). For many patients, nocturia severity drops to a manageable level (15)(26). Improved nocturnal polyuria appears to be the driver for improvement (22), however Yu et al. found that nocturnal polyuria index fell without substantial change in voiding frequency (though the actual results were not stated) (25). Furthermore, take up and persistence with CPAP appears to be incomplete (24), perhaps because the mask may be poorly tolerated.

Despite the clear-cut implications, the SR found no published research into the assessment of nocturia in association with several major sleep disorder issues. Hence, the NGT consensus was the source for primary care assessment recommendations, recognising the limitations of taking such an approach. For example, reliability of history for identifying sleep disorders is hampered by lack of subjective daytime dysfunction in some OSA patients. Nonetheless, in the absence of daytime dysfunction insomnia is unlikely to be present. Hence, the NGT recommendations focussed on relatively straightforward and practical history questions to provide a manageable and realistic broad screening approach.

Published literature on treatment found by the SR was heavily focussed on OSA, where bladder filling resulting from nocturnal polyuria is an important mechanism, though not invariably present. Hence, nocturnal polyuria occurring in conjunction with positive responses to the OSA questions must be considered relevant and sufficient to proceed to the conservative treatments advised and referral to sleep clinic.

There was no indication from the SR of nocturnal polyuria being a factor in other sleep disorders; here the NGT considered increased awareness of sensory stimuli enables a progressive lightening of sleep state that culminates in waking. It is likely that any sensory stimulus could lighten the sleep state; once approaching full wakefulness, emerging awareness of LUT sensation may underpin nocturia, regardless of whether it was contributory to the initial lessening of sleep depth. Positive screening questions combined with nocturia

would support considering the additional assessments and treatment for insomnia, or RLS/PLMS.

At the time many of the studies identified in the SR were undertaken, the ICS defined nocturia as the complaint that the individual has to wake one or more times to void (8). Implicit within this definition was the importance of identifying the need to void as the reason for waking. For sleep disorders, this is not straightforward; they are a wide-ranging group of problems, many of which lead to a lightening of the sleep state and consequent partial waking arousal. In this circumstance, sensory information from any source could further increase arousal. Hence, a sleep disorder could mean that LUT sensation that may not have been significant for someone in a normal sleep state could be sufficient to cause waking. Alternatively, they may wake fully in the absence of a desire to void, and subsequently decide to pass urine, perhaps as part of a routine for attempting to return to sleep. Understandably, these contributors are not easy for patients to discern. In the more recent ICS terminology standardisation, nocturia is defined as 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 (10).

The NGT identified that a clinical diagnosis made in primary care is a valid basis for initiation of conservative therapy. The NGT suggested a directed history for a pragmatic and efficient approach to discerning relevant mechanisms. Symptom assessment tools could be considered, but they may not aid diagnostic certainty without specific expertise. Validated questionnaires such as STOP-BANG are sometimes used in primary care (31), but availability, familiarity and training in interpretation is currently insufficient for the NGT to recommend routine use of these tools. Diagnostic confidence could be strengthened by increasing availability of technology which can provide indications of sleep disorders in the primary care setting (32). At this stage, specialist interpretation is generally necessary for formal diagnosis, but further developments may enable non-specialists to use these tools independently. Cognitive behavioural therapy for insomnia potentially works well if learned from written or online materials, without the necessity for a therapist. Excessive daytime sleepiness is a major determinant of necessity of therapy (33).

The NGT considered suspicion of RBD as requiring referral to sleep medicine and identification of RBD as requiring neurological assessment (due to potential association with neurodegenerative disorder). RBD is uncommon, and considerably less common than non-REM parasomnias, which do not generally necessitate specialist referral. The NGT did not suggest questioning patients whether they think that they act out their dreams, as it does not distinguish between the parasomnias.

## Conclusions

A new presentation with nocturia may reflect a causative sleep disorder, such as OSA, PLMS or insomnia. The evidence base is lacking for specific assessments to screen for sleep disorders in patients with nocturia in a non-specialist setting, so the consensus proposed simple history questions. This was considered sufficient to justify initial conservative therapy in primary care. Suspicion of RBD warrants referral in view of possible neurological implications.

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**Figure 1: PRISMA flow chart**

**Table 1: Study characteristics**

**Appendix 1: Example Search Strategy**