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Nocturnal Voiding Frequency does not describe Nocturia-Related Bother.

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Abstract

Aim

Nocturia frequency has been used as a measure of treatment efficacy for nocturia even though fluctuation of the symptom over time has been well described in the literature. Additionally, given the multifactorial causal pathway and clinically relevant comorbidities, frequency alone may be an insufficient marker of treatment direction. The aim of this study was to investigate factors associated with nocturia-related bother in order to identify additional variables that may capture the impact of nocturia, direct clinical care and have potential to quantify treatment outcome.

Methods

Prospective data from tertiary hospital Urology and Continence cohorts was matched for identical variables to generate a sample of 204 datasets. Descriptive statistics were obtained to describe the two cohorts. Characteristics of patients were evaluated across levels of nocturia frequency and nocturia-related bother using non-parametric methods; statistically significant differences between groups in each cohort were established.

Results

Nocturia frequency alone does not comprehensively reflect attributable bother. Five sleep variables (poor quality sleep, short time to first awakening to void, less than seven hours of total sleep, primary sleep latency and daytime sleepiness) and daily urinary urgency were significantly associated with high nocturia-related bother.

Attributable bother, despite high frequency nocturia, was minimized by male gender, lack of daily urinary urgency and good sleep quality. Poor health status, urinary urgency and sleep latency were associated with nocturia frequency.

Conclusions

Items of importance to individuals with nocturia have been identified from patient data. These variables have the potential to sit alongside change in nocturia frequency as potential markers of treatment response.

Introduction

Patients rarely present with nocturia as their primary concern, a fact related to perception of the symptom as trivial, a normal part of the ageing process and not worth raising with a doctor.[1] However, strong correlations exist between nocturia and adverse health and wellbeing, likely a result of the multifactorial aetiology of night voiding.[2] Patients report frustration and annoyance at the unpredictability of the symptom and lack of resolution with basic measures such as fluid restriction.[3] Social participation may be limited by a misunderstanding of the unlikely progression of nocturia to incontinence. The inconvenience and trouble caused by nocturia is likely to differ over time and between patients.

It is commonly assumed that the number of times an individual wakes at night needing to pass urine is the appropriate marker of treatment efficacy.[4] However, given the multifactorial aetiology of the symptom and the clinically relevant comorbidities commonly noted this may be an insufficient measure. If, for example, an individual with musculoskeletal pain at night wakes when repositioning in bed and ipso facto is roused and subsequently voids, this will not change with nocturia monotherapy. Similarly, variations in total sleep duration may mask change in nocturia frequency.

A significant relationship has been described between sleep variables and perceived bother of nocturia[5]. Restless sleep, long latency before falling and returning to sleep, and shorter total duration of sleep all correlate with high bother in men with nocturia.[5-6] Furthermore, the link between poor sleep and depression has been well described.[7] Successful treatment of nocturnal polyuria, the most prevalent underlying

cause of nocturia, has been shown to increase time slept before an individual's first nocturia episode (first undisturbed sleep time or FUST).[8]

The importance of evaluating the impact of nocturia on quality of life is understood and clinicians are commonly incorporating this holistic measure into initial assessment.[9-10] However, not all patients waking multiple times report high bother or great impact. Similarly clinical encounters confirm that low frequency nocturia can be perceived as an extreme inconvenience. There is a need to capture factors that mediate adverse mental and physical effects in patients with nocturia. As with many areas of medicine, there may then be an opportunity to incorporate patient priorities into the treatment goal and re-evaluation process for nocturia.

The aim of this study was to investigate predictors of nocturia-related bother in patients seeking help for the symptom and to identify variables that may have the potential to underlie patient-reported outcome measurement. A secondary aim was to identify variables that modify the bother associated with single versus multiple episodes of nocturia.

Materials and Methods

Setting and Participants

Routine data was prospectively collected from two tertiary hospital outpatient clinics over a 6-month period from a consecutive cohort of patients who were ≥18 years of age and reporting nocturia of at least once per night. These Continence and Urology services represented a wide age range, different comorbidities and gender spread. Factors associated with atypical nocturia constituted exclusion criteria and included end-stage renal failure, bladder cancer, previous pelvic radiotherapy, terminal malignancies and urinary catheterisation. Human Research Ethics Committee approval was gained from both sites.

Process

Variables collected were derived from commonly used validated questionnaires available in both English and Dutch: the Pittsburgh Sleep Quality Index (PSQI), ICIQ-Overactive Bladder Quality of Life Module (ICIQ-OAB), ICIQ-Female Lower Urinary Tract Symptoms Long Form (ICIQ-FLUTS), ICIQ-Male Lower Urinary

Tract Symptoms Long Form (ICIQ-MLUTS) and the Nocturia Quality of Life (NQoL) measure. Questionnaires utilised were in keeping with each site's usual practices; two items, 'general health status' and 'walking status' were collected at a single site only.

Nocturia frequency was gathered by patient report. For one site this was through an open-ended question derived from Item 2 of the Overactive Bladder Symptom Score (OABSS): "How many times do you typically wake up to urinate from sleeping at night until waking in the morning? The other site extracted the average number of nocturia episodesfrom a 3-day Frequency Volume Chart (bladder diary).

For the variable 'nocturia bother', one site utilised Item 12 of the NQoL: 'Overall how bothersome has having to get up at night to urinate been during the past 2 weeks?' with five options to respond ranging from "no bother" to extreme bother". The other site used Item 3b of the ICIQ-F/MLUTS: 'How much does nocturia bother you?' with a visual analogue scale ranging from 0-10 and representing "not at all" to "a great deal" of bother.

Key sleep variables were derived from patient report and the bladder diary. Sleep efficiency was calculated by dividing the number of hours spent sleeping by total time in bed attempting to sleep. This information was derived from Item 1 (usual bed time), Item 3 (usual get up time) and Item 4 (hours of sleep) of the Pittsburgh Sleep Quality Index (PSQI). First undisturbed sleep time (FUST) was calculated from the duration between falling asleep to the first nocturia episode expressed in hours. This information was derived from Items 1 and 2 of PSQI**:** usual bed time, duration (in minutes) taken to fall asleep each night and the time of first wakening to void.

Statistical analysis

Data was entered into SPSS Version 24. Descriptive statistics were obtained to describe the two cohorts. Characteristics of patients were evaluated across varying levels of nocturia frequency and nocturia-related bother using non-parametric methods. Nocturia-related bother was collapsed into a binary variable: "No to little bother" versus "Moderate to great/extreme bother". For categorical data, frequencies and percentages were calculated and Fisher's exact test used to assess statistically significant differences between groups. For continuous data, median values and interquartile ranges were calculated and the Mann Whitney U test performed to assess statistically significant differences between groups. Logistic regression, adjusting for

age and gender, was used to identify variables predictive of (i) nocturia-related bother of moderate to extreme nature and (ii) nocturia severity of ≥2/night.

Results

Demographic and clinical characteristics of the 113 Continence and 91 Urology participants are reported in *Table 1*. There were statistically significant differences between the cohorts on all key variables except marked nocturia-related bother. Compared to the Continence Clinic, the Urology cohort was on average 6 years younger; more likely to be male (53% versus 38%); had a BMI 4kg/m^2 lower and a smaller proportion of participants with nocturia ≥2/night. In both cohorts, moderate-severe nocturia-related bother was reported by over 50% of study participants.

Table 2 shows the association of variables with nocturia-related bother. In both cohorts, daily urinary urgency, frequency of nocturia and poor quality of sleep were significantly more common in participants who reported higher bother ($p<0.05$). A short FUST was significantly more prevalent in Urology patients experiencing higher bother ($p<0.001$); this approached statistical significance in the Continence Cohort ($p=0.058$). A total sleep time of 7 hours or less showed a trend toward being more prevalent in participants with higher bother (Continence Clinic $p=0.062$; Urology Clinic $p=0.057$). In the older Continence Cohort, poor sleep efficiency was statistically more common in the higher bother group ($p=0.010$); with the presence of impaired walking ability (0.061) and lower perceived general health status ($p=0.084$) approaching significance. A finding unique to the Urology Cohort was a greater proportion of participants with high bother citing “low enthusiasm to get things done” (PSQI item 9) as a problem ($p=0.032$) and using sleep medications at least weekly ($p=0.059$). In both cohorts, sleep latency, sleep disordered breathing and daytime sleepiness was unaffected by nocturia-related bother.

Logistic regression to identify associations with high nocturia-related bother (*Table 3)* revealed four significant variables common to both cohorts: nocturia frequency, short FUST, daily urinary urgency and fair to very bad sleep quality ($p<0.05$). The greatest odds ratios for marked nocturia-related bother in the Urology cohort was impaired sleep quality (OR 11.8 95% CI 3.14-44.64) followed by daily urinary urgency and

low enthusiasm. In the Continence cohort, impaired quality of sleep and daily urinary urgency were associated with double the risk of high nocturia-related bother.

Less than a quarter of patients from the Continence clinic (23.9%) and 38.5% of patients from the Urology service reported mild nocturia (<2/night). Table 4 shows that in this subset of participants, participants who reported high bother with mild nocturia (<2/night) admitted to significantly more daytime sleepiness than participants attributing minimal bother. Impaired health (Continence cohort) and poor sleep quality (Urology cohort) also significantly amplified nocturia-related bother. The report of low bother despite higher severity nocturia was observed in the Urology Cohort only. Protective factors were: perceived good quality sleep (p=0.015), urgency less than daily (p=0.008) and male gender (p=0.015).

Patient characteristics were stratified by severity of nocturia (<2/night versus ≥2/night) (see Appendix). In both cohorts, daily urgency was significantly more prevalent in in the higher severity nocturia sub-group (Continence p<0.001; Urology p=0.003). Median sleep time before first nocturia episode was significantly shorter when nocturia occurred ≥2/night compared to only 1/night (Continence 1.5 hours shorter (p<0.001); Urology 1.2 hours less (p<0.001). Primary sleep latency and trouble sleeping because of uncomfortable breathing was significantly more common with frequent nocturia in the Urology cohort (p<0.004 and p<0.044 respectively). Poor health status was significantly more prevalent in the Continence cohort reporting ≥2 nocturia episodes compared to only one void per night. Neither sleepiness during the day nor the use of sleep-inducing medication changed with higher frequency nocturia.

Logistic regression to identify associations with high frequency nocturia *(Table 5)* revealed that for both cohorts, those with nocturia ≥2/night were over 8 times more likely to report moderate to extreme nocturia-related bother and 4 times more likely to experience daily urinary urgency as compared to those voiding only once per night. A longer FUST was significantly protective for frequent nocturia in both cohorts (Continence OR 0.36, 95% CI 0.23-0.60; Urology OR 0.11, 95% CI 0.04-0.28). In the Urology cohort delayed sleep onset independently predicted high frequency nocturia (OR 3.82 95% CI 1.24-11.83).

Discussion

This study has shown that in order to understand aspects of importance to individual patients with nocturia, clinicians should clarify urinary urgency, overall sleep quality, ease of sleep onset, time before first arousal to void and total sleep time. The interconnectedness of factors associated with severity of nocturia is reflected in the mix of variables generating patient bother. Findings from this study suggest that capturing the number of times a patient wakes to void at night may not adequately summarise the consequences or pinpoint the most bothersome issues. Different ways of expressing and capturing nocturia-related bother in standard consultation are warranted.

Data from this study has highlighted that whilst factors associated with frequent nocturia overlap with variables that compound bother generated by the symptom, there is a clear deleterious effect from concurrent sleep dysfunction. Patients who reported bother disproportionate to nocturia severity all disclosed truncated sleep duration before initial night void. This intuitive finding is in agreement with other reports,[5,12] but does not necessarily inform routine practice. Recent longitudinal work suggests that self-perceived sleeping difficulties and nocturia may be bi-directional.[13] The importance of sleep disruption is likely to be clinically relevant, having been implicated in increased diuresis, slow return to health, risk for anxiety, depression and falls.[14-17]

Clearly the screening and diagnostic process for nocturia should include aspects of sleep onset, initial duration of restorative sleep and events that may disturb sleep (such as pain, uncomfortable breathing and efforts to achieve thermoregulation). A measure that would be helpful in identifying factors contributing to sleep dysfunction in nocturia patients has recently been described.[18] Ideally assessment will also capture the impact of regular nocturia on day to day function. Quality of life tools ask about sleepiness, productivity, behavioural change and worry.[10] Patient responses may suggest further inter-specialty investigation should precede nocturia treatment, providing an opportunity to tailor intervention toward unmet needs.

To date there are few reports of the change in nocturia frequency after intervention for clinically relevant sleep disturbance, aside from sleep-disordered breathing (SDB). Following continuous positive airway pressure (CPAP) treatment for SDB a reduction

of up to 2.28 nocturia episodes per night has been reported.[19-21] Of interest, given the high risk for frequent nocturia with urinary urgency, is a recent report of women with moderate or severe SDB who experienced a reduction in overactive bladder symptoms after 3 months of CPAP therapy.[22] Similarly, in a CPAP trial controlled for type 2 diabetes mellitus, 90% of participants across both groups evidenced improved nocturia.[23]

Nocturia is currently classified by the number of night voids. It is a problematic variable for patients to report due to recall and the fact that episodes can change night to night.[24] Furthermore, there is a potential floor effect in patients presenting with low frequency nocturia. This study has identified additional variables associated with attributable bother and frequent nocturia. The six variables, short FUST, poor quality of sleep, <7 hours total sleep, primary sleep latency, daytime sleepiness and daily urinary urgency, are measurable and potentially modifiable. It is likely that as smart devices interface more easily with data storage systems patients will collect sleep, waking and night voiding parameters electronically. This improved accuracy and reduced burden will support early identification of direction of treatment response. The study has several limitations. Firstly, data collection was confined to standardised tools specific to LUTS that were routinely used in the participating clinics. To minimise variation between the sites medical history data was not included in the analysis. The expectation was that not all clinicians would document the range of comorbidities that underlie nocturia, thus skewing analysis of factors such as heart failure, sleep disordered breathing or third space sequestration. Secondly, the measure of nocturia frequency was by self-report or bladder diary data. Although Homma and colleagues showed similar values on both measures, with a good strength of agreement (weighted kappa coefficient of agreement of 0.68-0.77) [25], there may have been some differences in reporting of nocturia episodes. The difference in baseline nocturia frequency between the sites is likely related to demographic differences between the cohorts rather than measurement method. Lastly, the measure of bother from both cohorts was collapsed into a binary variable, “No to little bother” versus “Moderate to great/extreme bother”. This is a similar categorisation to that described by Vaughan et al[26] and independent of nocturia frequency. The subjectivity of the construct of bother may have been a study limitation, although it was collected using standardised metrics.

Future work is needed to establish the sensitivity of these nocturia-related variables when captured using current validated questionnaires and diaries. Ultimately a suite of items from which an individual can select variables that matter to them most, would be clinically helpful and facilitate targeted treatment that meets the care needs of patients with nocturia.

Conclusions

This study has identified variables associated with moderate to severe nocturia-related bother. When developed into a framework, these items have the potential to sit alongside nocturia frequency as indicators of both care needs and treatment efficacy.

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Table 1: Demographic and Clinical Characteristics

	Continence Clinic n=113	**Urology Clinic n=91**	**p-value**
Age in years median (IQR)	70 (60-79)	64 (51-69)	<0.001*
Gender n (%) male	43 (38)	48 (53)	0.047*
Body Mass Index in kg/m^2 median (IQR)	28.7 (25.1-33.1)	24.7 (22.9-27.1)	<0.001*
Nocturia Frequency median (IQR)	2.5 (2.0-3.5)	2.0 (1.0-3.0)	<0.001*
Nocturia Frequency n (%) ≥2/night	86 (76)	56 (62)	0.032*
Nocturia Bother n (%) moderate-severe	66 (58)	56 (62)	0.665

Categorical Data: n (%) & Fisher's exact test; Continuous Data: median (IQR) & Mann Whitney U test**.**

*Considered statistically significant at p<0.05

Table 2: Characteristics by Nocturia Bother

	Continence Clinic			**Urology Clinic**		
	No to Little Bother (n=47)	**Moderate to Extreme Bother (n=66)**	**Sig. *(p)***	**No to Little Bother (n=34)**	**Moderate to Extreme Bother (n=56)**	**Sig. *(p)***
GENERAL MEDICAL						
Age in years (median, IQR)	70 (63.0-80.0)	69.5(59.0-78.3)	0.606	66 (56.0-74.3)	62 (51.0-68.0)	0.102

	Continence Clinic			Urology Clinic		
	No to Little Bother (n=47)	**Moderate to Extreme Bother (n=66)**	**Sig. *(p)***	**No to Little Bother (n=34)**	**Moderate to Extreme Bother (n=56)**	**Sig. *(p)***
Gender (n, % male)	22 (46.8)	21 (32.3)	0.168	21 (61.8)	27 (48.2)	0.277
Body Mass Index in kg/m^2 (median, IQR)	29.0 (25.0-33.4)	28.3 (25.0-33.1)	0.678	24.8 (23.1-27.6)	24.6 (22.5-26.6)	0.538
Hypertension (n, %)	23 (48.9)	34 (53.1)	0.704	11 (32.4)	19 (33.9)	1.000
General Health status (n, % fair to poor)	17 (37.0)	36 (54.5)	0.084	^	^	^
Walking Status (n, % with walking impairment)	28 (59.6)	51 (77.3)	0.061	^	^	^
BLADDER						
Urgency (n, % ≥daily)	31 (66.0)	54 (83.1)	0.045*	7 (20.6)	32 (57.1)	0.001*
Urgency Incontinence (n, % ≥daily)	21 (44.7)	41 (62.1)	0.085	3 (8.8)	9 (16.1)	0.524
Nocturia Frequency (median, IQR)	2.0 (1.0-3.0)	3.0 (2.0-3.5)	0.002*	1.0 (1.0-2.0)	2.0 (2.0-3.0)	<0.0018
SLEEP						
FUST in hrs (median, IQR)	3.4 (2.5-4.0)	2.5 (2.0-3.5)	0.058	3.6 (2.8-5.2)	2.3 (1.7-3.0)	<0.001*
FUST (n, % <3 hours)	16 (34.8)	33 (53.2)	0.078	9 (26.5)	41 (73.2)	<0.001*
Overall sleep quality (n, % fairly to very bad)	13 (27.7)	30 (46.9)	0.049*	3 (8.8)	30 (54.5)	<0.001*
Hours in bed (median, IQR)	8.5 (8.0-9.3)	9.0 (8.1-10)	0.122	8.3 (7.8-8.8)	8.5 (7.6-9.0)	0.806
Hours of sleep (median, IQR)	7.0 (6.0-8.0)	6.0 (5.0-8.0)	0.062	7.5 (7.0-8.0)	7.0 (6.0-8.0)	0.057

	Continence Clinic			Urology Clinic		
	No to Little Bother (n=47)	**Moderate to Extreme Bother (n=66)**	**Sig. *(p)***	**No to Little Bother (n=34)**	**Moderate to Extreme Bother (n=56)**	**Sig. *(p)***
Sleep Efficiency (median, IQR)	84.2 (68.6-94.1)	73.3 (58.0-83.4)	0.010*	90.3 (84.1-94.4)	88.9 (76.8-94.4)	0.150
Trouble sleeping because hot (n, % ≥weekly)	15 (34.1)	26 (44.1)	0.319	5 (15.2)	14 (26.4)	0.289
Trouble sleeping because cold (n, % ≥weekly)	7 (16.3)	15 (25.0)	0.337	3 (8.8)	9 (17.0)	0.352
Night pain (n, % ≥weekly)	18 (41.9)	31 (48.4)	0.556	5 (15.2)	11 (20.8)	0.581
Sleep latency in mins (median, IQR)	17.5 (10.0-32.5)	30.0 (12.5-45.0)	0.189	15.0 (5.0-30.0)	15.0 (10.0-30.0)	0.069
Sleep latency (n, % ≥30mins)	18 (39.1)	36 (57.1)	0.081	8.0 (25.8)	18 (35.3)	0.466
Trouble sleeping because breathing uncomfortable (n, % ≥weekly)	5 (12.2)	14 (24.6)	0.195	1 (3.3)	6 (11.8)	0.250
Trouble sleeping because snore loudly (n, % ≥weekly)	12 (25.5)	17 (25.8)	---	7 (20.6)	11 (19.6)	---
Daytime sleepiness (n, % ≥weekly)	7 (14.9)	18 (27.3)	0.168	1 (2.9)	8 (14.3)	0.145
Low enthusiasm (n, % moderate to big problem)	22 (46.8)	38 (58.5)	0.253	3 (8.8)	16 (29.1)	0.032*
Use of sleep medications (n, % >weekly)	9 (19.6)	20 (30.8)	0.273	3 (8.8)	14 (25.5)	0.059

Categorical Data: n (%) & Fisher's exact test; Continuous Data: median (IQR), & Mann Whitney U test**.** *Difference between groups considered statistically significant at p<0.05. ^ Data not collected by Ghent Urology Clinic. --- = 1 or more cells with expected count <5, therefore significance level not calculated

Table 3: ORs for Predictors of Moderate-Extreme Bother*

	N	OR	95% CI	*p*
Continence Clinic				
Nocturia Frequency	113	1.65	1.16-2.34	0.005
FUST (hrs)	108	0.71	0.52-0.96	0.027
Urgency at least once daily	112	2.49	1.02-6.10	0.046
Overall sleep quality (fairly to very bad)	111	2.34	1.01-5.39	0.047
Sleep Efficiency	112	0.97	0.95-0.99	0.016
Urology Clinic				
Nocturia Frequency	90	2.49	1.44-4.31	0.001
FUST (hrs)	90	0.50	0.35-0.72	<0.001
Urgency at least once daily	90	5.87	2.12-16.27	0.001
Overall sleep quality (fairly to very bad)	89	11.83	3.14-44.64	<0.001
Low enthusiasm (moderate to big problem)	89	4.00	1.05-15.27	0.042

** ORs have been adjusted for age and gender. Table shows only those variables in which the OR was statistically significant at p<0.05.*

Table 4: High versus Low Bother in those Reporting Nocturia <2/night*

	No to Little Bother	Moderate to Extreme Bother	Sig. *(p)*
Continence Clinic (n=27)	**(n=21)**	**(n=6)**	
General Health status (n, % fair to poor)	3 (14.3)	4 (66.7)	0.024
Daytime sleepiness (n, % ≥weekly)	1 (4.8)	4 (66.7)	0.004
Urology Clinic (n=35)	**(n=23)**	**(n=12)**	
Overall sleep quality (n, % fairly to very bad)	2 (8.7)	6 (60.0)	0.004
Daytime sleepiness (n, % ≥weekly)	0 (0.0)	3 (27.3)	0.028

Table shows only those variables in which the OR was statistically significant at p<0.05.

Table 5: ORs for Predictors of Nocturia ≥2/night*

	N	OR	95% CI	*p*
Continence Clinic (n=86)				
Nocturia Bother (moderate to extreme)	113	8.85	3.10-25.30	<0.001
FUST (hrs)	108	0.36	0.23-0.60	<0.001
Urgency at least once daily	112	6.11	2.31-16.15	<0.001
Urgency Incontinence at least once daily	113	3.54	1.36-9.23	0.010
Urology Clinic (n=56)				
Nocturia Bother (moderate to extreme)	90	11.41	3.86-33.71	<0.001
FUST (hrs)	91	0.11	0.04-0.28	<0.001
Urgency at least once daily	91	4.03	1.55-10.47	0.004
Overall sleep quality (fairly to very bad)	90	3.45	1.23-9.66	0.018
Sleep Latency (≥30 minutes)	83	3.82	1.24-11.83	0.020

** ORs have been adjusted for age and gender. Table shows only those variables in which the OR was statistically significant at p<0.05.*