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Nocturnal Polyuria in Older Women with Urge Urinary Incontinence: Role of Sleep Quality, Time in Bed, and Medications Used

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Abstract

Purpose—Nocturia is common and bothersome in older adults especially those who are also incontinent. Since nocturnal polyuria (NP) is a major contributor, we examined factors associated with NP in this population to identify those possibly amenable to intervention.

Method—We analyzed baseline data from two previously-completed studies of urge urinary incontinence (UUI). The studies involved 284 women (mean 72.9 ± 7.9 years) who also completed 3-day voiding diaries. Participants with nocturnal polyuria index (NPi) of $> 33\%$ were categorized as having NP (NPi = nocturnal urinary volume/24-hour urine volume). Associations between NP and various demographic, clinical, and sleep-related parameters were determined.

Results—Fifty-five percent of the participants had NP. Multivariable regression analysis revealed that age, body mass index (BMI), use of angiotensin-converting-enzyme inhibitor (ACE-I)/angiotensin receptor blocker (ARB), time spent in bed, and duration of first uninterrupted sleep (DUS) were independent correlates of NP. Participants with larger nocturnal excretion reported shorter DUS and worse sleep quality despite spending similar time in bed.

Conclusion—BMI, use of ACE-I/ARB, time in bed and DUS are independently associated with NP in older women with UUI, and are potentially modifiable. These findings also confirm the association between sleep and NP. Further studies should explore whether interventions to reduce NP and/or increase DUS help to improve sleep quality in this population and thereby reduce or eliminate the need for sedative hypnotics.

Keywords

Nocturia; Nocturnal polyuria; Elderly; Duration of uninterrupted sleep before first void

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INTRODUCTION

Nocturia is one of the most common and bothersome lower urinary tract symptoms (LUTS).¹ It is defined by the International Continence Society (ICS) as waking at least once nightly to void, with each void preceded and followed by sleep.² The prevalence of nocturia increases significantly with age, affecting approximately 70% among individuals > 60 years of age.³

Studies identify four pathophysiologic mechanisms for nocturia: nocturnal polyuria (NP), 24-hour polyuria, decreased bladder capacity, and sleep disorders.^{1, 4} Of these, NP is the most common,⁵ and it is defined as nocturnal output that exceeds 33% of total daily urine production.² Its pathophysiology among older adults remains poorly understood and is a major impediment to improving therapy.² Nocturnal mobilization of peripheral edema, sleep apnea, or fluid overload conditions, such as poorly controlled diabetes and heart failure, contribute to NP in the elderly, but its etiology in the absence of these is not clear.^{4, 6}

NP is inextricably related to sleep but the nature of this relationship in the elderly is complex and not fully understood. NP is related to time spent in bed; people spending prolonged time in bed have a proportionately higher nocturnal urinary volume (NUV), but most studies of NP lack information about the duration of time spent in bed. In addition, the role of sleep quality on nocturnal urine production in the elderly is not known. Studies in young adults have revealed that nocturnal urine production is strongly influenced by sleep stages: excretion of water, electrolytes and other osmotically active substances declines substantially during the deepest stage of sleep (non-rapid eye movement sleep [NREM] or “slow wave sleep”). NREM predominates in the first 3–4 hours of sleep, and sleep interruption during NREM alters renal water/salt excretion and increases nocturnal urine volume (NUV).^{7–10} Such disruption may contribute to insomnia which is prevalent in the elderly, especially sleep-maintenance insomnia. At the same time the impact of poor sleep quality and frequent sleep interruptions on nocturnal urine production among the elderly is not known.

In addition to sleep, several other age-related factors, such as comorbidity, medications, and renal sodium handling, may impact NP in the elderly but this has never been studied in this population. To address these knowledge gaps, we conducted a secondary analysis of two recently completed studies of urge urinary incontinence (UUI).^{11, 12}

METHODS

Study Design

This is a secondary analysis of baseline data from two NIH-funded prospective studies of older women with UUI. The parent studies were designed to identify the factors that predict and mediate the therapeutic response to biofeedback (BFB) and to evaluate brain responses to bladder filling before and after intervention.

Participants

Study procedures have been described previously.^{11, 12} Participants were cognitively intact, functionally independent, community-dwelling women aged 60 and older. All had at least

five UUI episodes per week for at least 3 months despite correction of potentially reversible causes. All were able to complete a voiding diary accurately, and to understand instructions in BFB sessions. Both studies were approved by the University of Pittsburgh institutional review board and all participants provided written informed consent.

Women with significant mental or cognitive impairment (Mini-Mental State Examination score < 24) that could have prevented them from adhering to the study protocol were excluded, as were women with a history of bladder cancer, spinal cord lesion, multiple sclerosis, pelvic radiation, interstitial cystitis, urethral obstruction, urinary retention (PVR > 200 ml after non-instrumented void), clinically apparent neurological lesion, and those who were medically unstable.

Clinical Assessment

All participants who completed baseline evaluation were included in the current analysis. Baseline evaluation had included detailed medical and voiding/incontinence history and a comprehensive physical examination including neurological, cognitive and stress incontinence testing.

For this analysis we reviewed data from the baseline 3-day bladder diary completed by each participant. Diaries included the times and volumes of each void, as well as the times the subjects awoke and went to sleep each day. The first void after waking was included in the nocturnal urine volume (NUV). The nocturnal polyuria index (NPi) was calculated by dividing NUV by 24-hour urine volume. To categorize the participants with NP we not only used the ICS definition of NPi of >33%,² but also an alternative threshold of NPi of > 53%.¹³ Participants with a 24-hour urine volume >40 ml/kg body-weight were classified as having 24-hour polyuria.² Time in bed was defined as the interval between going to bed with the intent of sleeping and getting up for the day, and it was obtained using the times recorded in the 3-day bladder diary. Duration of uninterrupted sleep before first awakening to void (DUS) was defined as the interval between times marked in the bladder diary as going to bed with the intent of sleeping and the first awakening to void.

The short form of the Center for Epidemiologic Studies Depression Scale (CES-D) was completed by participants at baseline. Because the focus of the parent study was incontinence, and there were no specific sleep-related questionnaires, we used the sleep restlessness question from CES-D as a proxy measure for sleep quality. This question assessed sleep restlessness over the past week; scores ranged from 0 to 3 for “rarely” (<1 day), “some of the time” (2–3 days), “occasionally” (3–4 days), and “all of the time” (5–7 days), respectively.

Statistical Analysis

We used the independent sample t-test and chi-square test, respectively, to compare continuous and categorical data among participants with and without NP. Multiple regression analysis with a stepwise selection approach was used to obtain a parsimonious set of variables correlated with NPi. Candidate predictor variables included age, BMI, tobacco and alcohol use, albumin level, creatinine, presence of peripheral edema, and bladder diary variables including 24-hour urine volume, mean awake-voided volume, functional bladder

capacity, time in bed, and DUS. Medications were also considered, including use of angiotensin-converting-enzyme inhibitor [ACE-I]/angiotensin receptor blocker [ARB], diuretics, calcium channel blockers, anti-cholinergics, anti-depressants, and non-steroidal anti-inflammatory drugs [NSAIDs].

Using a subset of participants with available CES-D scores, we compared NPi, DUS, and time in bed across self-rated categories of restless sleep ratings using analysis of variance. SAS[®] version 9.3 (SAS Institute, Inc., Cary, North Carolina) was used for all statistical analyses.

RESULTS

Demographic and 3-day bladder diary data are displayed in Table 1 and Table 2 respectively. Participant age ranged from 60–93 years.

In this cohort of elderly women with UUI, 65% had > 1 nocturnal void/night and 55% met the ICS definition of NP. Demographic factors were comparable between those with and without NP as were bladder diary variables such as 24-hour urine output and daytime functional bladder capacity (FBC); however, the nocturnal bladder capacity (NBC) was significantly higher in those with NP (Table 2). Despite a higher NBC, the first nighttime voided volume among those with NP was significantly less (226 ± 80 vs 282 ± 90 , $p = .0004$, Figure 1).

Compared to those without NP, participants with NP spent significantly more total time in bed and had shorter duration of uninterrupted sleep before first awakening to void (DUS).

Multivariable stepwise regression revealed that increased NPi was associated independently with advancing age, higher BMI, longer time in bed, shorter DUS and non-use of an ACE-I/ARB (Table 3). Results remained the same regardless of the NPi threshold used to define NP.

Sleep

Participants with shorter DUS reported worse sleep quality (Table 4, Figure 2). Across the scale of worsening sleep restlessness, an inverse relationship was seen between DUS and NPi. Participants with shorter DUS reported worse sleep quality and had higher NPi despite similar time in bed. (Table 4, Figure 2).

DISCUSSION

NP affected more than half of these fairly healthy, cognitively intact, older women with UUI. It was independently associated with advancing age, higher BMI, longer time in bed, shorter DUS and non-use of an ACE-I/ARB medication. Additionally, after controlling for time in bed, longer DUS correlated with better sleep quality and lower NPi. To our knowledge, this is the first study to concurrently examine the impact on NP of sleep, fluid excretion, and lower urinary tract function. By focusing on the independent contribution and the relative importance of common and potentially modifiable clinical factors, the study also sets the stage for a prospective evaluation of a multifaceted intervention.

Association of NP with age and BMI was not surprising. NP in the elderly arises from a complex interaction of several pathophysiological processes involving the lower urinary tract, renal function and sleep. Aging adversely impacts each of these systems to different degrees and the circadian rhythm of urinary excretion is disrupted with age.¹⁴ Higher BMI has also been associated with increased frequency of nocturia and higher NP independent of underlying sleep apnea.^{15, 16}

Our study also confirmed time in bed as an independent predictor of NP.^{17, 18} Prolonged time in bed is associated with insomnia in this age group.¹⁹ The increased time in bed likely reflects an effort by the individual with frequent awakenings to “catch up” on sleep, but the increased attention and effort to sleep may increase brain activity and perpetuate insomnia.²⁰ Physiological and sensory hyperarousal in older adults with insomnia²¹ may also make them more aware of bladder fullness and lead to frequent awakenings to void. Thus the interplay of nocturia and sleep could lead to increased time in bed, and proportionately the volume of urine produced while in bed may increase. In such cases, nocturia and NP may be a consequence of poor sleep. Additionally, smaller volume of first nighttime void among nocturics with NP in our cohort suggests that the awakening may be related to poor sleep rather than to the volume in the bladder.

Another interesting finding of our study is the difference in DUS between those with and without NP. DUS was an hour shorter among those with NP. With similar time in bed, participants with shorter DUS reported worse sleep quality and had a higher NP. Thus, DUS may explain the relationship between NP and sleep quality, and increasing DUS through decreasing NP could be a potential target for improving sleep quality and decreasing nocturia burden among older adults.^{22, 23} These findings suggest a bidirectional relation between sleep and nocturia. So, too, does our earlier study, which revealed that behavioral approach to insomnia reduced nocturia.²⁴

Physiologic rhythm of urine production is governed by a variety of hormones that regulate salt and water excretion, including vasopressin, renin, aldosterone, angiotensin, and atrial natriuretic peptide. Studies in young adults have shown that secretion of these hormones is strongly influenced by sleep stages, especially slow wave sleep which predominates in the first half of the night.^{7, 8} Sleep deprivation and disruption of slow wave sleep blunts the nocturnal surge in secretion of these hormones and thereby contributes to natriuresis and diuresis.^{9, 10} Our results, which show an association between early awakenings, poor sleep quality, and higher NP support the argument that sleep and NP may have a bidirectional relationship in the elderly as well; however, we were unable to assess formal sleep, electrolyte or hormonal levels in the available dataset.

We also found evidence that use of ACE-I/ARB is associated with lower NP. A possible reason for this observation may be the benefit of ACE-I/ARB to renal health. An age-related decrease in renal function and urine concentrating ability is thought to contribute to NP.²⁵ The renin-angiotensin-aldosterone system (RAAS) plays a major role in renal function and RAAS blockade with ARBs and ACE-I slows the progression of renal disease.²⁶ Although one of the direct effects of angiotensin II blockade is natriuresis, the overall renal protective effect of ACE-I/ARB may have long-term beneficial effects on older adults with nocturia. A

large NIH survey recently reported benefits of ACE-I/ARB in urge incontinent men, but not in women, but the study did not assess the effect of ACE-I/ARB on NP or its impact on nocturia.²⁷

Our study has several strengths. First, the primary studies collected detailed demographic and clinical data on every participant and thus provide a unique opportunity to analyze the objective bladder diary data combined with detailed clinical information. Second, we used both the internationally standardized definition of NP as well as an alternative one; both yielded the same results. We did not use other possible definitions of NP, for example nocturnal urine production (NUP) > 90 ml/hour, or nocturia index > 1¹³ since each has limitations. For instance, the NUP criterion ignores urine production during the day and presumes that urine output is constant between 1 am–6 am. Yet, studies have shown that nighttime urine output is not constant but varies depending on sleep stage which, in turn, regulates the rhythm of renal regulatory hormones.^{7, 8} Similarly, the definition of nocturia index >1 reflects the association between bladder capacity and NUV rather than NP.

Our study also has some limitations. First, although various studies exploring the etiology of LUTS in elderly have shown similar results,^{5, 17, 18} because our study included only older women with UI, its applicability is unknown for the older population in general, i.e. women without UI or men. Second, since UI was the focus of the primary study, the effect of underlying detrusor overactivity (DO) on nocturia cannot be excluded. The impact of DO on nocturia is controversial. Krystal *et al.* showed that DO contributed to nocturia pathophysiology²⁸, but nocturnal DO preceding nocturia was demonstrated in less than half of the nocturia events. The limited response of nocturia to treatment with anticholinergic medications²⁹ further suggests that even in patients with UI and nocturia, it is likely that nocturia is more often related to an etiology other than DO. Third, sleep apnea is a known risk factor for poor sleep and NP.^{1, 5} Since the primary study focused on UI, formal sleep apnea assessments were not completed. However, a detailed medical history was obtained from each participant and none had a diagnosis of sleep apnea or used continuous positive airway pressure treatment. Higher BMI is a risk factor for obstructive sleep apnea, and BMI was comparable among nocturics with and without NP. Finally, since the primary studies were not designed to examine sleep duration, state, or quality, we cannot determine whether participants with prolonged time in bed or self-reported poor sleep quality had sleep-related difficulties. Nevertheless, our findings concur with previous studies suggesting prolonged time in bed as a prominent cause of geriatric insomnia.³⁰

CONCLUSION

Our study of urge incontinent older women suggests that advancing age, higher BMI, and prolonged time spent in bed are independently associated with higher NP_i, and that longer DUS and use of ACE-I/ARB are independently associated with lower NP_i. In addition, longer DUS correlates with better sleep quality in this population. Future studies of NP should assess the impact of utilizing simple interventions to increase DUS and consolidate sleep (e.g. mild restriction of bed time) as part of the therapeutic approach to such patients.

Definition for abbreviations

NP	Nocturnal polyuria
NPi	Nocturnal polyuria index (nocturnal urinary volume/24-hour urine volume)
NUV	Nocturnal urinary volume
DUS	Duration of uninterrupted sleep before first awakening to void
ACE-I/ARB	Angiotensin-converting-enzyme inhibitor / angiotensin receptor blocker

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Figure 1.
Comparing first nighttime void volume (ml) among those with and without NP

Figure 2. Comparing duration of uninterrupted sleep before first awakening to void, NPi, and time in bed with sleep restlessness as scored in CES-D questionnaire

Table 1

Characteristics of the participants with and without NP

Characteristics	All (n=284)	With NP (n=186)	Without NP (n=98)	p-value
Age, yr [sd]	72.9 [7.9]	73 [7.9]	72 [7.8]	.12
BMI, [sd]	29.8 [6.5]	30.3 [6.6]	29.9 [6.4]	.17
Smoking, % (n)-				
none	57 (161)	58 (108)	54 (53)	.26
Past	38 (107)	34 (64)	43 (43)	
Current	4 (12)	5 (10)	2 (2)	
Alcohol, % (n)	4 (12)	6 (11)	6 (6)	.91
Edema, % (n)	32 (90)	33 (61)	29 (29)	.46
Albumin, [sd]	4.2 [0.3]	4.2 [0.3]	4.2 [0.3]	.43
Creatinine, [sd]	0.9 [0.2]	0.9 [0.2]	0.9 [0.2]	.85
Medication use, % (n)				
ACE/ARB	31 (87)	29 (54)	34 (33)	.39
Diuretic	28 (78)	27 (50)	29 (28)	.72
CCB	14 (39)	16 (30)	9 (9)	.11
Anti-cholinergic	13 (38)	11 (21)	17(17)	.14
Anti-depressant	17 (48)	18 (33)	15 (15)	.61
NSAIDS	24 (67)	25 (46)	21 (21)	.49
Comorbidities, % (n)				
Cardiovascular	36 (104)	39 (72)	32 (32)	.11
Neurological	13 (37)	14 (26)	11 (11)	.14
Respiratory	26 (74)	29 (54)	20 (20)	.12
Musculoskeletal	54 (154)	62 (116)	38 (38)	.07
Diabetes	16 (45)	17 (32)	13 (13)	.42
Psychiatric	20 (56)	23 (43)	13 (13)	.20
Cancer	11 (34)	6 (11)	23 (23)	.10

Note: BMI= body mass index, CCB= calcium channel blockers, NSAIDS= non-steroidal anti-inflammatory drugs, SD= standard deviation. Comorbidities included the following: cardiovascular disease (hypertension, atrial fibrillation, congestive heart failure, or heart attack), neurologic (peripheral neuropathy, Parkinson's disease, stroke), respiratory (COPD, asthma, chronic bronchitis), musculoskeletal conditions (arthritis, osteoporosis, or joint replacement), diabetes, psychiatric (depression, anxiety) or cancer.

Table 2

Voiding characteristics of participants with and without NP

Bladder diary measures	With NP (n=186)	Without NP (n=98)	<i>p</i> -value
Nocturia (sd)	2.4 (1.3)	1.4 (1.2)	<.01
FBC, ml (sd)	522 (185)	484 (197)	.09
NBC, ml (sd)	515 (187)	454 (192)	<.01
24 hour voided volume, ml(sd)	1879 (699)	1880 (727)	.90
Mean volume/void while awake, ml (sd)	188 (71)	212 (85)	.01
Mean volume/void while asleep, ml (sd)	327 (170)	152 (162)	<.01
DUV, ml (sd)	1058 (436)	1400 (554)	<.01
NUV, ml (sd)	838 (318)	488 (210)	<.01
NPi, % (sd)	45.7 (7.9)	26 (5.2)	<.01
CES-D score (sd)	5.71 (5.2)	6.03 (3.6)	0.75
Time in bed, min (sd)	532 (71)	470 (69)	.01
Duration of uninterrupted sleep, min (sd)	221 (82)	293 (89)	<.01

Note: FBC= functional bladder capacity, NBC= nocturnal bladder capacity, DUV= diurnal urine volume, NUV= nocturnal urine volume, NPi= nocturnal polyuria index (NUV/24 hour volume *100), CES-D= Center for Epidemiologic Studies Depression Scale, SD= standard deviation. Nocturia: number of voids (averaged over 3 days) during the period between the time the participant noted going to bed for the night and arising for the day.

Table 3

Independent predictors of NP using stepwise multiple regression

Variable	Regression coefficient (SE)	<i>p</i> -value
Age (each year)	0.29 (.08)	<.01
BMI (each kg/m ² unit)	0.27 (.11)	.01
Duration of uninterrupted sleep (each minute)	−0.05 (.01)	<.0001
Time in bed (each minute)	0.06 (.01)	<.0001
ACE-I/ARB (use vs. non-use)	−2.82 (1.5)	.04

Note: BMI= Body mass index, ACE-I/ARB= angiotensin-converting-enzyme inhibitor/angiotensin receptor blocker, SE= standard error

Comparing duration of uninterrupted sleep before first awakening to void, time in bed and NPi with sleep restlessness as scored in CES-D questionnaire

Table 4

Sleep restlessness score	Duration of uninterrupted sleep (minutes)		Time in bed (minutes)		NPi	
	Mean (SD)	Difference (p-value)	Mean (SD)	Difference (p-value)	Mean (SD)	Difference (p-value)
0 (reference)	293 (106)	-----	460 (64)	-----	29.16 (9.33)	-----
1-- some of the time (2--3 days)	297 (73)	6 (.79)	506 (70)	51 (.01)	35.94 (9.39)	5.57 (.07)
2--occasionally (3--4 days)	230 (79)	-64 (<.01)	509 (92)	48 (.02)	40.2 (11.28)	8.28 (<.01)
3--all of the time (5--7 days)	173 (61)	-127 (<.01)	508 (79)	39 (.06)	42.1 (12.26)	10.26 (<.01)