Nocturia: A Highly Prevalent Disorder With Multifaceted Consequences

Donald L. Bliwise, Adrian Wagg, and Peter K. Sand

Nocturia is a bothersome, multifactorial condition with many underlying causes and contributing factors. Nocturnal polyuria (NP; overproduction of urine at night) is a frequent component. The prevalence of nocturia increases with age; specific estimates of prevalence are influenced by frequency thresholds used to define it. There is a tendency toward higher prevalence in young women than young men, which is reversed in later life.

The association between frequency of nocturnal voiding and sleep disruption is well-documented. Nocturia correlates strongly with shorter sleep during the first part (2-4 hours) of the night, during which the first nocturnal void often occurs. A short time to first void after sleep onset (often referred to as "first uninterrupted sleep period") is associated with increased daytime dysfunction and decreased sleep quality and/or sleep efficiency.

Adverse health consequences related to nocturia include poor sleep, depression, reduced quality of life, and increased risk of morbidity, mortality, falls, and fractures; studies have been able to establish a causal role for nocturia in only some of these.

The potential impact of nocturia on health increases with age. By age 80, 80% of people will rise at least once per night to void. Despite its associated bother, nocturia is often accepted as a natural consequence of aging and many people do not seek help. Women, in particular, may be reluctant to report nocturia.

This article reviews the prevalence of nocturia, possible impact on sleep, mortality and morbidity, and falls, and its importance in the elderly/frail population and women. UROLOGY 133: 3–13, 2019. © 2019 Elsevier Inc.

Nocturia has been defined by the International Continence Society (ICS) as "the complaint that the individual has to wake at night one or more times for voiding." Each void is preceded and followed by sleep.[1] Although the ICS definition of nocturia is clear, few people are bothered or affected by one nightly nocturic episode, and this does not seem to be either harmful and/or bothersome.[2] Nevertheless, nocturia is considered one of the most bothersome lower urinary tract symptoms (LUTS).[3] The majority of people with nocturia report moderate bother associated with 2 nocturnal voiding episodes or major bother with 3 or more,[4] although the degree of bother from a similar number of nocturia episodes may vary from person to person.[5]

Nocturia is a multifactorial condition with many possible contributing etiological factors of which nocturnal polyuria (NP; overproduction of urine at night [greater than 20%-33% of total 24-hour urine volume depending on age]) is a frequent contributor,[1,6] albeit one which is often overlooked. NP is present in most patients with nocturia (76%-88%).[6,7] The ICS defines NP as a nighttime urine volume (NUV) that is greater than 20% of total daily urine output in young people and more than 33% of total daily urine output in elderly people (>65 years of age).[1] NUV is "the total volume of urine passed between the time the individual goes to bed with the intention of sleeping and the time of waking with the intention of rising." Thus, NUV does not include the last void before going to bed, but it does include the first morning void.[1] In an effort to provide further clarity and user-friendly definitions to aid clinical practice and research, an ICS draft report on the terminology for nocturia and nocturnal lower urinary tract function published in 2019 suggests that NP be redefined as "excessive production of urine during the individual's main sleep period"; the threshold used to quantify "excessive" will need to be highlighted in clinical and research settings and derived from a bladder diary.[8]

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The multifactorial etiology of nocturia complicates the diagnosis and treatment of nocturia. Numerous potential factors underlying nocturia have been identified including sleep disorders, bladder outlet obstruction, overactive bladder (OAB) syndrome, sleep apnea syndrome, amongst others.[1,6,9] Given the myriad of possible contributors to nocturia, the use of a frequency-volume chart, which provides an accurate assessment of nocturia, is fundamental to the identification of the underlying mechanisms, such as NP, and may help identify the appropriate treatment.

In this article, one of a series of articles published in this supplement that summarizes the presentations and discussions from a roundtable meeting focused on nocturia and NP, we examine the prevalence of nocturia, its potential impact on sleep, mortality, morbidity, quality of life (QoL), and its importance in the elderly/frail population and women.

PREVALENCE OF NOCTURIA AND NP

Using a clinically meaningful definition of nocturia as two or more voids/night, its prevalence in women in their second or third decades was 4.4%-18%, whilst in their seventh and eighth decades it was 28.3%-61.5%. In men, the corresponding age groups demonstrated a prevalence of 2%-16.6% and 29%-59.3%, respectively. Prevalence increased with age in both sexes in all studies.[6] Illustrative data from a systematic review by Cornu et al are shown in Figure 1.[10]

Irrespective of the varying classifications, 3 epidemiological properties of nocturia persist: (1) it is common; (2) the prevalence increases with age; and (3) it affects a significant proportion of younger individuals. For example, in the epidemiology and incontinence survey, a population-based, cross-sectional telephone interview of 19,165 adult men and women in 5 countries (Canada, Germany, Italy, Sweden, and the UK), 13% of men and 17% of women aged <40 years reported 2 or more nocturnal voids, which increased to 20% and 21% of middle-aged (aged 40-59 years), and to 35% and 36% of men and women aged ≥60 years. Unsurprisingly, when nocturia was defined as one or more voids, the prevalence of nocturia increased in all ages.[11]

A similar pattern was reported in the USA. Data from the 2005 to 2006 and 2007 to 2008 cycles of the National Health and Nutrition Examination Survey, a cross-sectional survey of the United States noninstitutionalized population, demonstrated an overall prevalence of nocturia (2 or more voids per night) of 21% (weighted 95% confidence interval [CI] 19.3-23.0) and a linear progression with age (P <.001) from 8.2% (CI 6.6-10.2) in men aged 20-34 years to 55.8% (CI 51.3-60.2) in men aged ≥75 years.[12]

Although usually considered a predominantly male condition, the prevalence of nocturia in women in the 5 countries participating in the epidemiology and incontinence survey was 54.5% compared with 48.6% in men.[11] As noted by Bosch and Weiss in their review, there appears to be a tendency toward a higher prevalence of ICS-defined nocturia in young women than in young men, a trend which is reversed in later life.[6] In a Finnish study, higher rates of nocturia were observed for women than for men in younger populations; this gender difference disappeared between the ages of 50-59 years and the prevalence was higher among men aged >60 years (Fig. 2).[13]

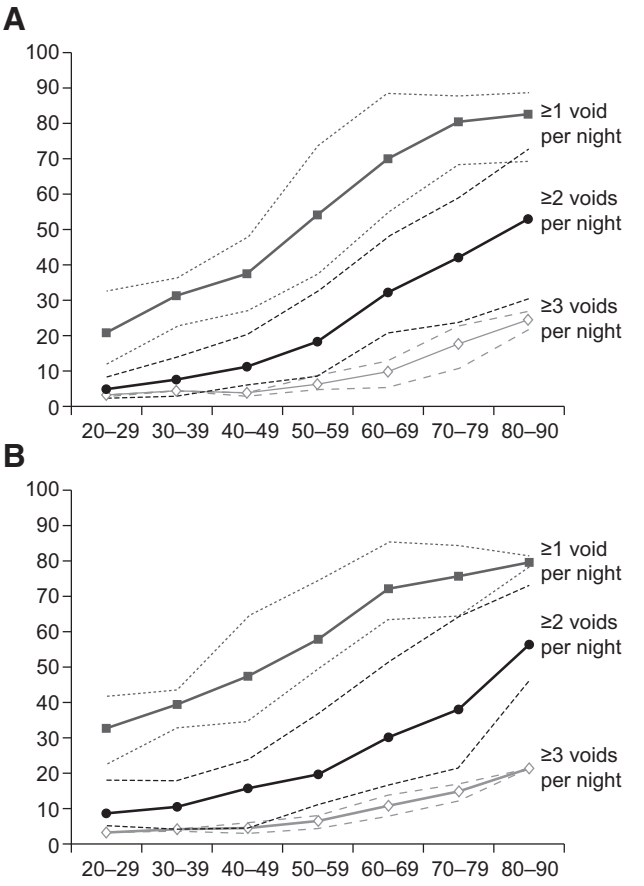

Figure 1. Trends in prevalence of nocturia stratified by number of voids per night and age intervals in (**A**) men and (**B**) women, represented by continuous lines. Square markers on continuous lines are the mean values of the prevalence for each category in each age interval. Dotted lines represent the minimal and maximal values in the literature for each age interval.[10]Reprinted from Cornu et al.[10] Copyright 2012, with permission from Elsevier B.V.

THE POTENTIAL IMPACT OF NOCTURIA AND NP ON SLEEP

A large number of observational studies demonstrate a relationship between the frequency of nocturnal voiding and the negative effect on QoL and well-being. Foremost, nocturia is associated with disruption of sleep that can result in daytime fatigue, cognitive impairment, mood alterations, increased susceptibility to disease, decreased work performance, dizziness, an increased risk of falls, depression, and mortality.[14] The effect of disturbed sleep *per se* can be best understood in the context of the normal physiology of sleep.

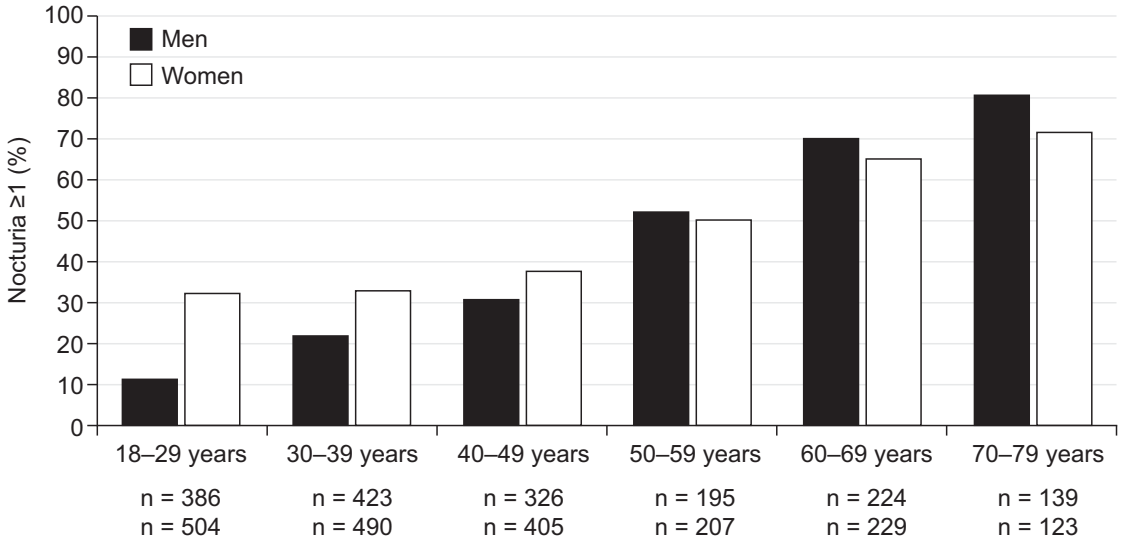

Figure 2. Prevalence by age and sex of nocturia (defined as at least one void per night).[13]Adapted with permission from Wolters Kluwer Health, Inc.: Tikkinen et al.[13]

Sleep Quality

Sleep plays a vital role in physical and mental functioning. It is increasingly recognized that disturbed sleep is a highly prevalent and chronic condition that merits greater awareness due to its associated wide-ranging and serious repercussions. There are many reasons why sleep can be disrupted or shortened at night, including primary sleep disorders, intrinsic lightening of sleep and sleep fragmentation, changes in circadian rhythms, environmental stressors, genetics, or even voluntary curtailment. Patients frequently report sleep impairment associated with nocturia, although it is often overlooked as a cause of sleep problems. Sleep disturbance is significantly bothersome in those with 2 or more nocturnal voids.[15] A National Sleep Foundation survey in the USA in 2003 found that nocturia was the attributed cause of sleep disturbance every night or almost every night in 53% of those aged 55-84 years. Sleep disturbance due to nocturia was more than 4 times more prevalent than pain, cited as the next most frequent attributed cause (Fig. 3).[16]

The Normal Sleep Cycle

The monitoring and staging of human sleep has been well described in the Principles and Practice of Sleep Medicine.[17] The progression of a nightly pattern of sleep comprises multiple sleep cycles in which rapid eye movement (REM) and non-REM (NREM) sleep stages 1-4 alternate. The normal human adult enters sleep through deeper NREM stages (stages 2, 3, and 4 using the classic definitions, or stages N2 and N3 using the updated definitions) before the first episode of REM sleep occurs approximately ≥80 minutes later. Thereafter, NREM sleep and REM sleep alternate through the night, with an approximately 90-minute cycle (Fig. 4).[17]

NREM stages 3 and 4 (or stage N3) concentrate in the early NREM cycles, and REM sleep episodes lengthen across the night. Stage N1 is considered to be a transition between wakefulness and sleep. It occurs upon falling asleep and during brief arousal periods within sleep and usually accounts for 2%-5% of the total sleep time. Stage N2 occurs throughout the sleep period and represents

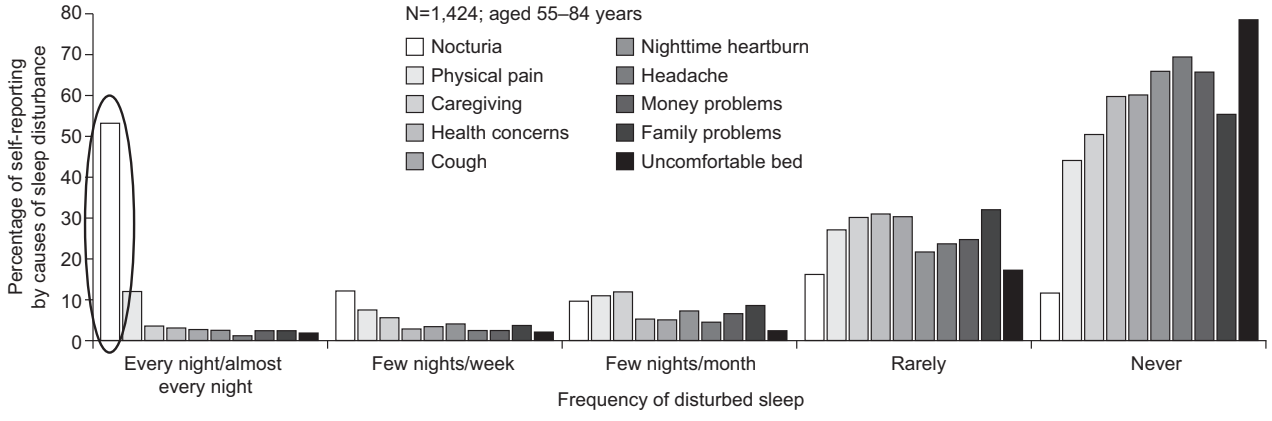

Figure 3. Nocturia is the leading cause of sleep disturbance in older adults.[16]

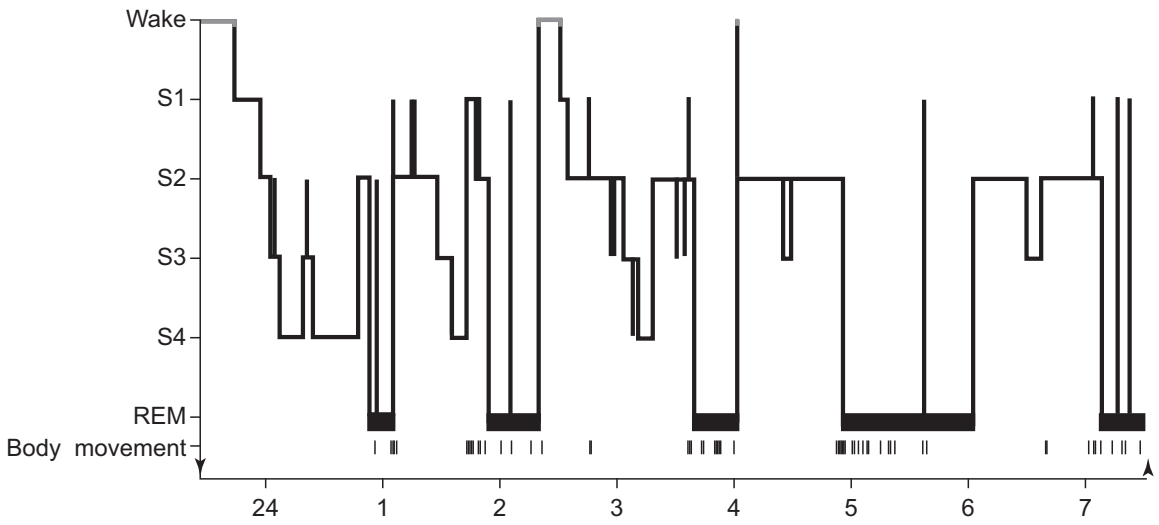

Figure 4. Sequences of states and stages of sleep on a typical night.[17] Permission is granted to reproduce this figure; Carskadon et al.[17]

45%-55% of the total sleep time. Stage N3 (delta or slow-wave sleep [SWS]) occurs mostly in the first third of the night and constitutes 3%-8% of the total sleep time, though this varies widely across studies. Stage N3 sleep decreases with aging and differs widely between women and men, with men showing considerably less N3 sleep in nearly every age group. REM represents 20%-25% of total sleep time and usually occurs in 4-6 episodes throughout the night.[17]

Effects of Sleep Disruption

Interruption of Stage N3 or restorative SWS—even without a reduction in the total quantity of sleep—leads to fatigue, increased discomfort, and a decreased pain threshold,[18] suggesting that sleep during the first 2-4 hours of the night, in particular, should be minimally disturbed. The duration of uninterrupted sleep until the first void may be useful in measuring the impact of nocturia on the patient's QoL.[19] The importance of SWS deprivation is suggested by the preemptive recovery of SWS during undisturbed subsequent sleep, which may be either within the same sleep episode or during the next sleep episode. Furthermore, the association of SWS with sleep continuity (as assessed by the number of awakenings), suggests that enhancement of SWS may lead to an improvement in sleep continuity and may contribute to improved daytime function, noting that loss of SWS early in the sleep period may not be recovered in later sleep periods.[20] SWS reduction increases morning plasma glucose and serum insulin responses and reduces postprandial insulin sensitivity, thus playing a key role in the impairment of glucose tolerance associated with disturbed sleep.[21] Interruption of SWS is linked with impaired glucose metabolism with abnormalities in glucose intolerance, insulin resistance, and impaired β-cell function.[22]

Sleep Disturbances and Nocturia

Several studies have reported that nocturia is associated with disrupted sleep although the relationship is likely bidirectional. A polysomnographic analysis of patients with nocturia indicates that nocturnal voiding was associated with poor sleep across the entire night of sleep.[23] In a multivariate analyses of a large, elderly population (≥60 years) adjusted for potential confounding factors (such as age, sex, body mass index (BMI), medication use, renal function, bedtime, rising time, daytime physical activity, endogenous melatonin levels, and bedroom light levels), an increased nocturnal voiding frequency (0, 1, 2, 3 or more), was significantly associated with poorer objective sleep quality. An increase in nocturnal voiding frequency was significantly associated with lower sleep efficiency (SE; duration of time asleep as a proportion of intended sleep time) and longer wake after sleep onset (WASO) (mean SE, 86.3, 84.8, 83.6, and 81.2%, respectively; mean WASO: 42.6, 48.9, 53.6, and 66.1 minutes, respectively; both P_{trend} <.001).[24] Polysomnographic data from the Sleep Heart Health Study demonstrated that patients with nocturia had less total sleep time, sleep efficiency and proportion of REM sleep, but had a higher arousal index and were more hypoxemic, the latter indicating a higher likelihood of sleep apnea. They also were subjectively more sleepy on the basis of their Epworth Sleepiness Score.[25]

An association between nocturia and sleep disturbance is further supported by objective measures of sleep quality and clinically validated questionnaires, although this is often not queried on traditional sleep diaries. Sleep diaries completed by elderly volunteers with poor sleep report that nightly awakenings are frequently accompanied by bathroom trips for urination.[26] Actigraphic measurements confirm an association between a higher number of awakenings after sleep onset and wake bouts with a greater number of voids. Wake bouts were a mean of 11.5% (±23.5%) longer on nights on which there was a trip to the bathroom (P <.05, paired t test). WASO was also longer on nights on which there was a trip to the bathroom (20.8% ± 33.0%; P <.05, paired t test). There were no differences in total sleep time (P = .18), the length of sleep

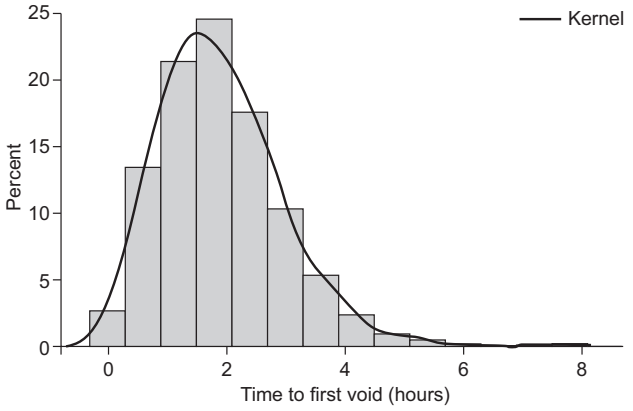

Figure 5. Frequency distribution of time to first void (*Also called first uninterrupted sleep period, FUSP) in untreated nocturia.[28]Republished with permission Bliwise et al.[28]

bouts ($P = .52$), or the number of sleep ($P = .12$) or wake ($P = .15$) bouts.[27]

Nocturnal voiding is negatively related to the occurrence of the restorative N3 stage of sleep, which can have a potentially deleterious impact on daytime alertness, health, and well-being.[23] A patient's first nocturnal void often occurs within 2 to 3 hours of sleep onset, likely disrupting SWS (Fig. 5).[28] This time to first void after sleep onset (or the first uninterrupted sleep period; FUSP), is an important indicator of overall sleep quality in people with nocturia. A shorter FUSP is associated with increased daytime dysfunction and a decrease in sleep quality, sleep efficiency, and total sleep duration.[28]

The duration of FUSP is drastically reduced with increasing severity of nocturia. Compared with those with 1 or 2 nocturnal voids, FUSP was significantly shorter than in those with 3 or 4 nocturnal voids (150.4 [104.9] minutes vs 57.4 [34.1] minutes, respectively; $t = 2.37$, $P < .05$).[23] Improvements in nocturia are associated with lengthening of FUSP and result in longer total sleep duration[29] and improvements in scores on the Pittsburgh Sleep Quality Index—a clinically-validated tool for measuring sleep quality.[28,30]

NOCTURIA, NP, AND POTENTIAL HEALTH IMPACTS

A wide range of potential adverse consequences upon health have been reported as being related to the presence of nocturia and its associations with poor sleep. Although a number of primarily observational, cross-sectional studies demonstrate relationships between nocturia and these conditions, it is important to note that these studies have been unable to establish causality and a direct link. Some of the most convincing evidence that nocturia is a *cause* for at least some health consequences has been obtained from clinical trials that demonstrate improvement in parameters such as QoL as a result of treatment for nocturia. For example, desmopressin, a selective vasopressin receptor 2 (V2) agonist, has been shown to be effective, well-tolerated and to improve QoL in adults with nocturia due to NP. Two formulations, an orally disintegrating tablet and a low-dose intranasal spray, showed treatment effects corresponded with significant improvements in patient QoL based on the Nocturia QoL questionnaire scores for bother/concern and sleep/energy; $P < .05$[31] and the Impact of Nighttime Urination QoL questionnaire scores for overall impact and the nighttime domain; $P \leq .0255$.[32]

DEPRESSION

Nocturia is frequently cited as a cause of mood disturbance, although it may be equally likely that the disturbed sleep associated with depression makes nocturnal voiding more likely to occur. It is difficult to establish a temporal link between nocturia and depression to determine which is primary. A systematic review focused on the relationship between nocturia and depression/anxiety revealed that depression and nocturia frequently coexist. Overall, nocturia increased the odds of reporting depression (odds ratio [OR] 1.20-20.24), while depression similarly increased the odds of reporting nocturia (OR 1.20-7.73). The findings of this systematic review suggested a bidirectional association of depression and anxiety with nocturia.[33] Nocturia appears to carry a greater risk of depression in men than in women. Results from the Boston Area Community Health (BACH) Survey indicate the risk of depression symptoms in patients with nocturia was almost 3 times higher in men with versus without nocturia, and almost twice as high in women (OR 2.79, 95% CI 1.81-4.31, and 1.80, 95% CI 1.29-2.51, respectively). Increased odds of depression were also observed with an increasing number of nightly voids. Among women who reported sleep interference due to urological symptoms, nocturia was associated with a threefold increase in the odds of depression.[34] Earlier BACH data showed that mean mental health scores were lower in those with nocturia than in those without nocturia[35] and that statistically significant associations were observed between depression and nocturia of any degree of severity among both men and women.[36]

MORTALITY

Some studies have shown an association between nocturia and mortality. Increased mortality in individuals with nocturia might be related to sleep disruption and concomitant health issues. Nevertheless, some studies suggest that nocturia may be an independent predictor of mortality and indicate a correlation with the number of voiding episodes. For example, the National Health and Nutrition Examination Survey III data indicate that nocturia predicted mortality in men and women after accounting for major confounding factors. A multivariate analysis showed a statistically significant trend of increased mortality risk with increased number of nocturnal voiding episodes in men and women. The association was strongest in men and women younger than 65 years. Increased mortality risk was observed with an increase in the number of nocturnal voids.[38] Similarly, in a community-based sample of Japanese individuals 70 years old or older, the 5-year mortality rate in individuals with nocturia (2 or more voids per night) was significantly higher than in those without nocturia (35/359 [9.7%] vs 18/425 [4.2%], respectively). In patients with nocturia, the mortality hazard ratio (HR), adjusted for age, sex, and BMI, was 1.91 (95% CI 1.07-3.43, $P = .03$). This relationship was unchanged (HR: 1.98, 95% CI 1.09-3.59, $P = .03$) when adjusted for comorbidities and associated pharmacologic treatments.[39] Neither of these studies controlled for disturbed sleep in their models, thus allowing for the possibility that sleep disruption from causes other than nocturia was ultimately the relevant predictor.

In an attempt to overcome some of the limitations of earlier observational studies, nocturia was examined as a mortality risk factor based on the baseline data in a large, well-characterized male population (participants in the Reduction by Dutasteride of Prostate Cancer Events [REDUCE] trial), controlling explicitly for a wide range of comorbidities and risk factors for nocturia, including disturbed sleep.[40] Nocturia was associated with a risk of increased mortality (HR = 1.72; 95% CI 1.15-2.55) when controlled for age, sex, and medical comorbidities. Inclusion of disturbed sleep in the model reduced the magnitude of the association (HR = 1.43; 95% CI 0.93-2.19), arguing for at least partial mediation by disturbed sleep. These results, although limited to men aged 50-75 years, suggest that nocturia may be associated with all-cause mortality, even after adjusting for confounding comorbidities.[40]

QoL

It is well-recognized that nocturia is associated with poorer QoL and may affect the ability to carry out normal activities of daily living. In 2003-2004, a survey in Finland designed to evaluate the associations of nocturia and health-related quality of life (HRQoL) identified that the presence of at least two voids per night was associated with impaired HRQoL, as measured by the generic 15D instrument. Nocturia was statistically significantly associated with lower scores in 14 of the 15 domains reported by men and women in the HRQoL questionnaire (Fig. 6). For every increase in nocturnal voids above one, further reductions in HRQoL scores were seen. The mean age-adjusted 15D score for men (and women) without nocturia was 0.953 (0.950) compared with 0.925 (0.927), 0.898 (0.890), and 0.833 (0.840) for those with 1, 2, and 3 or more voids per night, respectively.[4] In the LUTS Disease-Specific Program, a noninterventional survey of real-life clinical practice patients with a diagnosis of nocturia reported a significantly higher impact on their QoL than did patients with a diagnosis of daytime LUTS only. The underlying causes of bother were related to sleep problems.[41] In 2 studies of desmopressin formulations in adults with nocturia due to NP, treatment effects corresponded

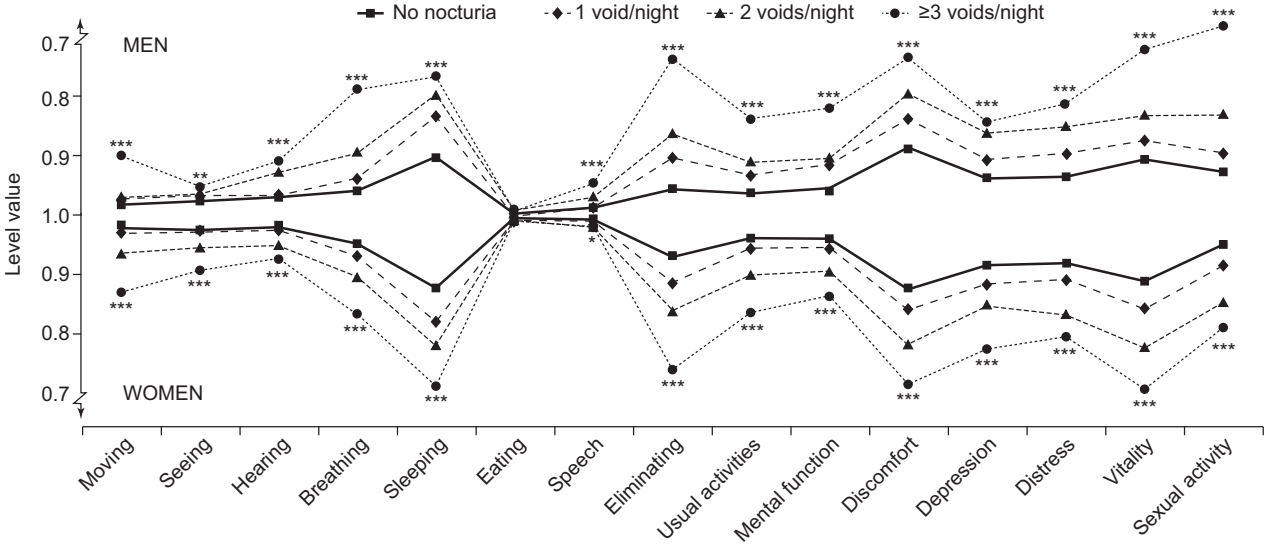

Figure 6. Nocturia was associated with significantly lower scores on 14/15 dimensions of HRQoL.[4] Reprinted from Tikkinen et al.[4] Copyright 2010, with permission from Elsevier B.V.

with significant improvements in patient QoL.[31] Nocturia is one of a range of symptoms associated with OAB. The MATRIX study assessed HRQoL and safety with transdermal oxybutynin in patients with OAB syndrome, more than 80% of whom were affected with nocturia. In patients with OAB syndrome, the MATRIX study assessed HRQoL and safety with the transdermal oxybutynin. A significantly greater proportion of participants reported improvement rather than worsening on all individual item responses for the majority of the King's Health Questionnaire domains (range: −4.3% to −29.5%; $P \leq .001$). The greatest proportionate changes were for the domains of Role Limitations (−29.5%), Emotions (−29.3%), and Personal Relationships (−29.1%).[37]

WORK PRODUCTIVITY AND ACTIVITY IMPAIRMENT

Alongside the well-documented associations with QoL impairment, the presence of bothersome or frequent nocturia is also associated with impaired physical activity and work productivity. For example, data gathered for the LUTS Disease-Specific Program, revealed that 60% of patients diagnosed with night-time LUTS reported being tired "always" or "usually"; this proportion was significantly lower for patients with daytime problems only (37%; $P < .0001$).[42]

Overall work productivity impairment associated with nocturia was between 14% and 39% in a systematic review which estimated productivity impairment as measured by the work productivity and activity impairment instrument. This level of impairment was similar to that observed in conjunction with other common chronic diseases (eg, GERD, asthma/allergies, sleep problems, OAB syndrome, and gout).[43]

Data from other studies support the findings of the review by Miller et al.[43] For example, a cross-sectional study investigated the relationship between nocturia and productivity, vitality and utility in a group of working individuals in Sweden. Here, the presence of nocturia was associated with a significant impairment in daytime activity and work productivity. Overall work impairment statistically significantly increased with increasing severity of symptoms (impairment increased on average 2% with each additional void). The overall impairment was related to reduced productivity as a possible consequence of nocturia (13% in the nocturia group vs 8.6% for controls). In addition, a higher proportion of people with nocturia reported sick leave for any reason (21% vs 12.5% in the control group).[44] The relationship between nocturnal voids and sick leave was confirmed by data from a postal survey in Sweden. Seven or more days of sick leave during the past year was reported by 13.4% of the men and 24.7% of the women with no nocturnal voids, and by 19.9%, 20.4%, and 55.6% of the men ($P = .001$) and 25.4%, 44.6%, and 50% of women ($P = .001$) with 1, 2, and 3 or more nocturnal voids, respectively.[45]

FALLS AND FRACTURES

An association between nocturia and falls was reported in ambulatory elderly participants in 1992.[46] Since then several retrospective, population-based studies have suggested that nocturia may be a risk factor for falls and fractures. A study to evaluate the relationship between hip fractures and nocturia in elderly people in Finland found that the occurrence of hip fractures increased in relation to the number of nocturnal micturition episodes and with an increased nocturnal urine output. The risk of hip fractures was independently increased by 3 or more nocturia episodes/night vs ≤2 episodes/night (OR 1.8, 95% CI 1.1-3.0).[47] An association of nocturia with fracture risk was also observed in Japanese individuals ≥70 years old. For all fractures and fall-related fractures with nocturia the HR was 2.01 (95% CI 1.04-3.87; $P = .04$) and 2.20 (95% CI 1.04-4.68; $P = .04$).[39]

Additionally, in a prospective, cohort study of community-dwelling, elderly people, nocturia (≥3 voids/night) was associated with an approximately 28% increased risk of falling. The increase in the risk of an incident fall associated with nocturia was 1.27 (95% CI 1.01-1.60). The effect was similar following adjustment for age, sex, race, and length of follow-up. The authors suggested that their study supported the notion that repeatedly arising from bed, perhaps in a sleepy state, to walk to the bathroom in a dark or dimly lit room may be the contributing factor associated with these falls. Daytime falls may also be related to sleep deprivation resulting from numerous awakenings in connection with nocturia/NP.[48] There are, however, significant limitations of these data. Although nocturia has been consistently associated with an increased risk of falls and fractures, in a similar fashion to urinary urgency and urgency incontinence by day. Data on this temporal association are few and limited to falls, regardless of timing, in community-dwelling elderly women, which failed to demonstrate a strong association with LUTS[49] and to falls where a relationship to toileting in hospital inpatients has been demonstrated.[50-52] Likewise, there are no clinical trials that have addressed the impact of any nocturia intervention with falls or falls risk as a primary outcome. The relatively low absolute incidence of falls, even in a population at risk, makes this a daunting task.

NOCTURIA IN THE FRAIL ELDERLY

As previously discussed, the prevalence of nocturia and its considerable negative impact on QoL and health increases with age and is associated with social isolation, depression, and increased risk of morbidity and mortality. It is practically axiomatic that nocturia in the elderly is related to NP; hence the need for a discussion on the nexus among nocturia, NP, and frailty.

Frailty is a distinct clinical syndrome, associated with the aging process, in which multiple body systems gradually lose their physiological reserve. Consequently, frail

people are, by definition, particularly vulnerable to functional decline or death, often after an apparently minor challenge to their health. Frailty carries an increased risk for poor health outcomes, including falls, incident disability, hospitalization, and mortality.[53,54]

What is Frailty?

A variety of models have been described in an attempt to explain the physiological, biological, and molecular pathways of the syndrome. The phenotypic model[53] and the accumulated deficit model[55] are the 2 best established international frailty models. In the phenotypic definition, frailty is postulated to be a "biologic syndrome of decreased reserve and resistance to stressors, resulting from cumulative declines across multiple physiologic systems". In this model a frailty phenotype is defined by 5 physical characteristics: reduced grip strength, slow walking speed, low level of physical activity, self-reported exhaustion, and unintentional weight loss. People with 1 or 2 characteristics are identified as prefrail; those with 3 or more are identified as frail.[53]

The accumulated deficits model identifies frailty based on the number of deficits accumulated, including clinical signs, symptoms, diseases, physical and cognitive impairments, psychosocial risk factors, and common geriatric syndromes, which are combined to form a frailty index. An individual's frailty index (FI) score is based on a simple count of the number of deficits present expressed as a proportion of potential deficits and indicates the likelihood that frailty is present.[55] An integral conceptual model of frailty has been proposed that includes physical, psychological, and social domains of frailty extend to include a fourth domain, cognitive frailty (Fig. 7).[56,57]

Mortality, Morbidity, and Frailty

Whichever frailty model is considered when examining the complex and heterogeneous scenario of frailty in older persons, there is no doubt that frailty correlates with mortality. An evaluation of the prevalence and 10-year outcomes of frailty in older adults in relation to deficit accumulation indicates that the prevalence of frailty increases with age and at any age frailty lessens survival. The mean FI increases with age, as does the mortality rate. The correlation coefficient (r) between age and the mean FI value was high for both men (r = .989, P = .001) and women (r = .992, P = .001). The mean FI was significantly higher (P <.001) in people who died (0.195 ± 0.135) than in those who survived (0.119 ± 0.102).[58] Similarly, in a representative Canadian population survey (N = 66,589) the proportion of accumulated deficits in FI showed a linear relationship with mortality. On average, although women accumulated more deficits than men of the same age, their risk of mortality is lower.[54] A systematic review and meta-analysis has demonstrated the FI is a significant predictor of mortality; a higher FI was significantly associated with higher mortality risk (pooled HR for 13 cohorts: 1.039, 95% CI 1.033-1.044, P <.001).[59] The FI is a sensitive predictor of survival; personal biological age (which can be estimated from the FI), is a stronger correlate of mortality than chronological age.[60] The dependence of the mortality rate on the FI supports its use as a simple and accessible tool for estimating individual risks of mortality.

Data from the Cardiovascular Health Study show modest concordance between frailty and disability. Of those who were frail, 46% had comorbid disease, 6% had

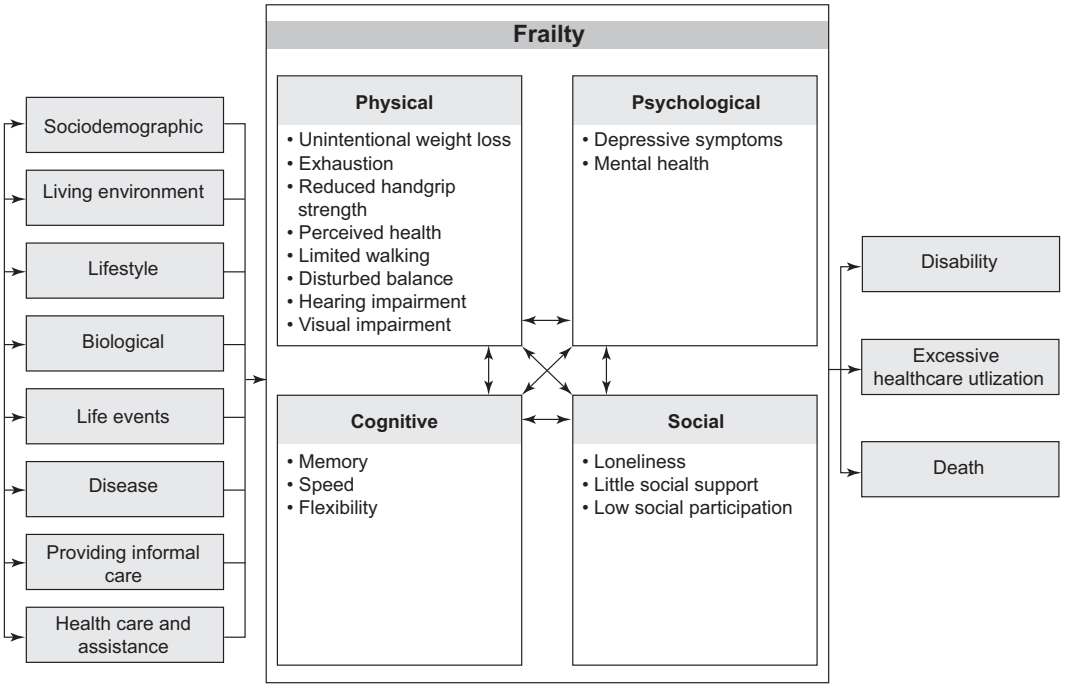

Figure 7. Adapted version of the integral conceptual model of frailty, based on Gobbens, 2010.[56]Adapted from van Oostrom et al.[56]

activities of daily living (ADL) disability, 22% had both comorbid disease and ADL disability, and 27% had neither ADL disability nor comorbidity.[53] Around 15% (95% CI 14-16%) of the older non-nursing home population were frail, and 45% (95% CI 44-47%) were prefrail; chronic disease and disability prevalence increased with frailty; >50% of frail people had had a fall in the previous year.[61] The incidence of frailty and LUTS both increase with age, but there is limited information available on frailty and associated nocturia. A Brazilian cross-sectional urban study in an independent elderly population showed that incontinence doubled in the frail vs nonfrail (42.9% vs 20.8%, respectively).[62] Similarly, in a Taiwanese study from veterans' nursing homes, the presence of frailty was more common among people with urinary incontinence than those without (60.7% vs 32.3%, P <.001)[63] but, as in the Brazilian study, nocturnal LUTS were not expressed separately from overall incontinence.

NOCTURIA AND NP IN WOMEN

Nocturia in women is a notable health concern, associated with significant morbidity and decreases in HRQoL. Nocturia and NP are common among women; among young adults, the prevalence of nocturia is generally greater in women, except in very late life.[6,10] The prevalence of nocturia is more common in parous women and shows a linear increase with age, occurring in more than 50% of women aged ≥80 years.[10] Studies also suggest that nocturia is more frequent during pregnancy and postpartum, as well as postmenopausally.[9] The proposed link between nocturia and menopause has been challenged, and recent nomenclature ("genitourinary syndrome of menopause") describing the genitourinary symptoms associated with menopause does not explicitly include nocturia.[64] Although data are limited regarding the exact etiology of nocturia in women, a number of studies have identified risk factors for its occurrence, including urgency and snoring,[6] high BMI,[65] age, hypertension, and heavy smoking.[66]

A survey of 3,669 40- to 64-year-old Swedish women analyzed the relationship between nocturnal micturition and health. Poor health was 8 times more common in women with 3 or more nocturnal voiding episodes than in women with no such episodes; poor health was reported by 4.7% of the women without nocturnal micturition, and by 11.2%, 20.1%, and 39.0% (P <.0001) of the women with 1, 2, and 3 or more nocturnal voiding episodes, respectively.[67] In addition, the profound effects of nocturia on perceived state of health was independent of heart disease, diabetes, age, and menopausal status.[67] Furthermore, data drawn from a survey of physicians and patients in France, Germany, Spain, UK, and USA to assess the impact of nocturia, revealed that women with nocturia and daytime symptoms had the worst outcomes of all the diagnostic subgroups on 3 PRO scales (the OAB Questionnaire Short Form, the Nocturia Impact Diary, and the Work Productivity and Activity Impairment Questionnaire).[42]

Women with regular nocturia report a pronounced deterioration in their sleep, QoL, and general health.[68] Possible associations between excessive daytime sleepiness and nocturia were investigated in a group of Brazilian women undergoing screening for cervical cancer. In these women (aged 18-89 years), the prevalence of excessive daytime sleepiness was 31.3% and the majority of respondents (56.7%) reported having nocturia; 32.4% of the women reported nocturia once a night and 24.3% had 2 or more nocturnal voids. The relative risk of excessive daytime sleepiness was 1.58 (CI 1.06-2.37) in women with 2 or more nocturnal voids, independent of time in bed (P = .030). In addition, women with a higher nocturnal voiding frequency had worse quality of sleep (P <.001) and a higher prevalence of daytime sleepiness (P = .016).[69] Effective pharmacologic treatment of urgency urinary incontinence is associated with a decreased frequency of incontinence and nocturia, and an improvement in overall sleep quality, sleep duration, and sleep efficiency. A secondary analysis of the data from a multicenter, double-blind, 12-week randomized trial (4-8 mg fesoterodine [antimuscarinic] therapy daily versus placebo) found a greater improvement in sleep quality (total Pittsburgh Sleep Quality Index score 0.48; P = .02) and a greater improvement in sleep duration and sleep efficiency subscales (P <.05), although intervention did not affect daytime sleepiness. The improvement in nighttime voiding frequency was found to explain 13% of the treatment association with sleep quality.[70]

The lower estrogen levels that occur in relation to the menopause and beyond are associated with urinary frequency, urgency, and nocturia. Postmenopausal women are often prescribed vaginal estrogen to help combat vaginal and lower urinary tract symptoms such as dryness, dyspareunia, urgency, frequency and recurrent urinary tract infections. A systematic review, conducted by the Society of Gynecologic Surgeons, compared the efficacy and safety of vaginal estrogens with placebo, systemic estrogen, and nonhormonal vaginal alternatives in the management of genitourinary syndrome of menopause. In addition to relieving common vulvovaginal atrophy-related symptoms, vaginal estrogens offered substantial improvement in symptoms of urinary urgency, frequency, nocturia, stress urinary incontinence, and urgency urinary incontinence.[71]

CONCLUSIONS AND FUTURE LINES OF INVESTIGATION

Nocturia and NP are common and deserve attention. Anyone can be affected but it is most prevalent in later life and affects both men and women. Nocturia disturbs sleep and can seriously affect QoL and health.

Nocturia develops against a background of age-related changes in the renal and urinary systems, sleep disturbances, and concurrent disease states, and with pharmacologic interventions. In particular, sleep interruption may have numerous negative consequences for those with

nocturia, including daytime fatigue, difficulty concentrating, mood alterations, and decreased workplace productivity. The detrimental effects of sleep fragmentation are especially difficult for those with active lifestyles and demanding work schedules.

Nocturia may be responsible for significant morbidity and increased risk of falls and fractures, and is a strong predictor of mortality, with a dose-response pattern of increased mortality risk with increasing number of nocturnal voids. The consequences of nocturia, as demonstrated by their improvement in randomized clinical trials, are: a lower QoL, increased depression, and poorer sleep quality. Nocturia is associated with poor concentration at work and can lead to a loss of productivity. Despite its impact, nocturia is often accepted as a natural consequence of aging; many people do not seek help and are less likely to do so with increasing age.[31] In the elderly, frailty may be useful concept for risk assessment that can be applied to the elderly population in care settings as well as in the community.

Progress in the treatment of nocturia and NP will be aided by research initiatives aimed at better understanding the pathophysiological basis of nocturia. Identifying an independent relationship between nocturia and sleep disturbance represents a challenge. However, more detailed measurements of sleep need to be employed to fully understand the complex relationship between sleep disorders and nocturnal urine production and to characterize the various chronobiological components of excess nocturnal urine production. Additionally, it is unclear which factor (nocturia or sleep disturbance) is the biggest detriment to QoL.

Although falls are undoubtedly associated with the presence of nocturia, and also represent a significant economic burden, further investigations are needed to determine the underlying mechanisms of the observed association. Institution-wide fall-rate studies may help to characterize the extent of the problem, and in addition there is a need to better understand the relationship between the frailty and nocturia.

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