
Age Related Pathogenesis of Nocturia in Patients With Overactive Bladder

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on behalf of the 037 Study Group

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Purpose: Nocturia is caused by increased nocturnal urine output (nocturnal polyuria) and/or diminished nocturnal bladder capacity. We retrospectively evaluated the causes of nocturia in patients with overactive bladder and nocturia.

Materials and Methods: A total of 850 patients (18 years or older) with symptoms of overactive bladder (8 or more micturitions per 24 hours and urgency or urgency urinary incontinence) and nocturia (mean of 2.5 or more episodes per night) were enrolled in a 12-week study of tolterodine ER (4 mg QD) vs placebo. Of this total 845 patients (417 men and 428 women) completed 7-day bladder diaries. Patients were stratified post hoc by sex and age groups (less than 50, 50 to 70, more than 70 years). Indices of nocturnal urine production (nocturia index, nocturnal polyuria index and nocturnal bladder capacity index) were compared using ANOVA (α level 0.05). Higher nocturia index and nocturnal polyuria index values suggest that nocturia occurs because of nocturnal urine overproduction. Higher nocturnal bladder capacity index values suggest that nocturia occurs because of decreased nocturnal bladder capacity.

Results: There were no statistically significant gender or age related differences in baseline nocturnal micturitions. Nocturia index increased significantly with age ($p < 0.0001$), and values were significantly higher among men than women for all age groups ($p = 0.0064$). Nocturnal polyuria index increased significantly with age ($p < 0.0001$) and there were no gender differences. For nocturnal bladder capacity index there was a significant decrease with advancing age among men (1.75 greater than 1.16 greater than 0.90) and women (1.53 greater than 1.42 greater than 1.08, $P_{interaction} = 0.0148$).

Conclusions: In younger patients with overactive bladder, decreased nocturnal bladder capacity has a greater role in the pathogenesis of nocturia symptoms, whereas in older patients increased nocturnal urine output has a greater role.

Key Words: urination disorders, age factors, bladder, pathology

It is well established that the prevalence of LUTS, including the storage symptoms of urgency, frequency, UUI and nocturia, increases with age. Although the development of LUTS is not strictly dependent on age, age related changes in renal function and bladder capacity likely contribute to their emergence. However, this is not to say that such conditions are inevitable or untreatable. Available treatments should be selected based on the underlying pathophysiology, which in most cases can be determined using simple and validated diagnostic criteria that do not involve complex or invasive procedures.

Of the storage LUTS, nocturia, which is defined by the International Continence Society as waking 1 or more times

during the night to urinate,¹ shows the most precipitous increase in prevalence with age.^{2,3} It is also one of the most common reasons for interrupted sleep in the general population.⁴ The underlying pathophysiology of nocturia can be attributed to urological and/or nonurological causes, as well as primary sleep disorders—all of which are influenced by age. Age related changes in renal function that compromise water and sodium conserving mechanisms contribute to the well documented increase in urine production at night (nocturnal polyuria) among older individuals.^{5,6} In addition, age related reductions in functional bladder capacity⁷ can lead to increased micturition frequency and urgency, especially during nighttime hours.^{6,8} In this instance nocturia is generally associated with a decreased NBC. In both cases, NBC and NP can be derived from information recorded in 24-hour voiding diaries.

Previous research has validated the usefulness of 2 complementary indices of nocturia, the nocturia index, a measure of nocturnal urine overproduction relative to FBC, and NBCi, which reflects NBC.⁹ Together, these indices provide quantitative information about the relative contributions of nocturnal urine overproduction and reduced NBC to the etiology of nocturia. In this study we evaluated the causes for nocturia in symptomatic younger vs older men and women with OAB and nocturia. This is the first study to evaluate the etiology of nocturia as a function of age in

Submitted for publication December 8, 2006.

Supported by Pfizer Inc and the Institute for Prostate and Bladder Research.

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† Financial interest and/or other relationship with Pfizer, Ferring and Aventis.

‡ Financial interest and/or other relationship with Pfizer, Novartis and Johnson & Johnson.

§ Financial interest and/or other relationship with Pfizer.

See Editorial on page 378.

For another article on a related topic see page 710.

patients with OAB who were otherwise matched for their frequency of nocturia. As previously mentioned determining the cause of nocturia is important for making appropriate treatment decisions.

MATERIALS AND METHODS

In this post hoc analysis, we used baseline data collected from patients with OAB (8 or more micturitions in 24 hours and UII) and nocturia (a mean of 2.5 or more episodes per night) who completed a randomized, double-blind, placebo controlled trial of tolterodine ER conducted at multiple centers throughout the United States and Chile.¹⁰ Key exclusion criteria included polyuria (more than 3,000 ml per 24 hours), stress incontinence, and post-void residual urine volume more than 200 ml. Patients were not specifically excluded for peripheral edema or cardiovascular disease.

Of the 850 patients (older than 18 years) enrolled, 845 (417 men and 428 women) completed 7-day bladder diaries at the baseline visit. Patients were instructed to record their sleep cycle (ie night, which was defined as the time the patient intended to fall asleep, until the time the patient intended to awaken or actually awakened¹) and the time of each micturition during the day and at night. For 2 of the 7 days, patients used a standardized graduated measuring receptacle to record the volume (ml) voided per micturition with every micturition. Patient data were stratified by sex and age group (younger than 50, 50 to 70, older than 70 years).

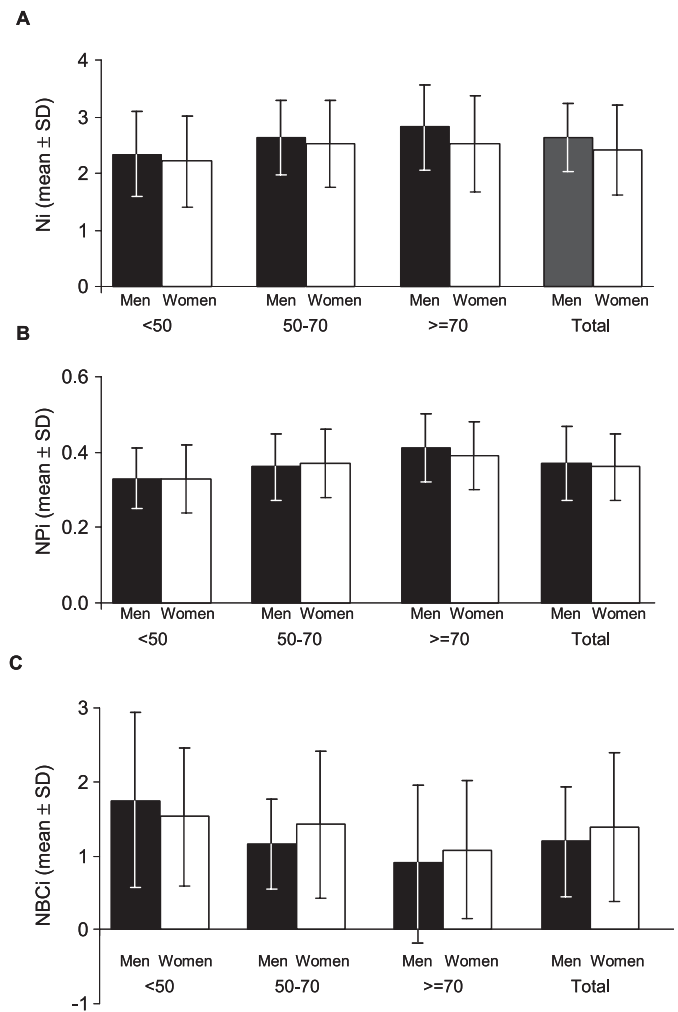
Consistent with International Continence Society guidelines,¹ NUV was defined as the total volume of urine voided during the night, including the first morning void (ie the first micturition after waking with the intention of awakening). The 24-hour voided volume was defined as the total volume voided during a 24-hour period. MVV was defined as the largest single voided volume measured in a 24-hour period, which is also a measure of FBC.

Bladder diary data were used to derive the Ni, NPi and the NBCi.⁹ Ni was defined as NUV divided by MVV. If the Ni was greater than 1, nocturia was deemed due to nocturnal urine output in excess of FBC, which in turn, may have been due to increased NP, reduced NBC, or both. NP was defined as an NPi (NUV per 24-hour urine output) greater than 35%. The Appendix summarizes the formulas and the interpretation of the resulting values. In essence, the higher the Ni and the NPi, the more nocturia occurs owing to nocturnal urine overproduction. The higher the NBCi, the more nocturia occurs because of diminished NBC.

Baseline continuous variables were analyzed using an ANOVA model with gender, age group, and an interaction term (gender \times age group) included in the model. If the interaction term had a p value greater than 0.10, the ANOVA model was run again without the interaction term to evaluate the significance of the effects of gender and age group. Otherwise, the 95% CI of the baseline variable for each gender and age group combination was compared.

RESULTS

For this subanalysis, both sexes were well represented with 49% men (417, mean age 62 years) and 51% women (428, mean age 56 years). Among all patients the mean age was 59 years and 83% were of white race. There were no sex or age



Summary of results for nocturia index (A), nocturnal polyuria index (B) and nocturnal bladder capacity index (C).

related differences in the baseline prevalence of nocturia in this study population (see figure). Collapsed across age groups, the mean (SD) number of nocturia episodes per night was 3.30 (1.0) and 3.31 (1.0) among men and women, respectively.

Nevertheless, there were statistically significant age and gender related differences in the 3 derived variables. Ni values were greater than 1 in both men and women and for all 3 age groups. The mean Ni in men and women was 2.63 and 2.42, respectively. Moreover, Ni values increased significantly with age ($p < 0.0001$), and values among men were significantly higher than those among women regardless of age ($p = 0.0064$, see figure). For NPi there was a significant effect of age ($p < 0.0001$) but not gender ($p = 0.6325$). That is, NPi increased significantly with age in both men and women. By contrast, the NBCi decreased significantly with age in men and women ($P_{\text{interaction}} = 0.0148$).

DISCUSSION

One of the most common reasons for interrupted sleep in the general adult population is nocturia—waking at least 1 time during the night to urinate.^{4,11} Several epidemiologic studies have shown that nocturia is highly prevalent in both men and women and that prevalence increases with age.^{12–14}

Large numbers of individuals with nocturia also have other LUTS, such as daytime frequency, weak stream, urgency, and incontinence. The present study is the first to evaluate the etiology of nocturia as a function of age in patients with OAB who were otherwise matched for nocturia severity. In this subanalysis, the data were collected from patients with the OAB symptoms of frequency and urgency or UUI as well as nocturia.

Understanding the etiology of nocturia is important for making appropriate treatment decisions, but it can be complex and multifactorial. For example, it can be confounded by the presence of primary sleep disorders that are separate from either lower urinary tract dysfunction or abnormalities of urine production related to cardiovascular, renal, or endocrine diseases. Nevertheless, the underlying pathophysiology that accounts for nocturia in all of these conditions falls into 4 broad categories of NP, reduced NBC (not necessarily exclusive of reduced global bladder capacity), mixed (ie a combination of NP and reduced NBC) and global polyuria (ie increased urine production throughout the day). Symptoms can be categorized based on values derived from 24-hour bladder diaries in which each micturition, volume and corresponding time are recorded.¹ Furthermore, previous studies have shown that the Ni and NBCi are sensitive measures of NP and decreased NBC, respectively.^{9,15}

In this subanalysis, there was a significant effect of age and gender on the derived variable, Ni. Ni increased significantly with age, and values in men exceeded those in women, regardless of age. That Ni was greater than 1 in all patients indicates that the patients' NUV exceeded their FBC (ie MVV), resulting in nocturia. To determine whether their nocturia was due to NP or diminished NBC, 2 other derived variables, NPi and NBCi, also were evaluated. For NPi, there was a significant effect of age but not of gender. By contrast, the NBCi decreased significantly with age in men and women. Because the interaction term was statistically significant ($P_{\text{interaction}} = 0.0148$), understanding the differences between men and women and those that occur because of advancing age are more complex. However, overall, these results suggest that the etiology of nocturia shifted from predominantly diminished NBC (ie NBCi greater than 0) in younger men and women to NP (ie NPi greater than 0.35) in older patients. In fact, the reason we did not observe the expected increase in the number of nocturia episodes with advancing age is because the increase in NP among these older OAB patients nocturia was offset by a decrease in NBC among younger patients.

Our results are similar to those reported by Rembratt et al,¹⁶ who examined diary data from more than 200 age matched elderly (more than 70 years) men and women with and without nocturia. Among nocturics the NPi was 0.45 compared with 0.31 in nonnocturics. In addition, those with nocturia had a greater NUV than those without nocturia (700 and 417 ml, respectively) and had smaller functional bladder capacities (325 vs 400 ml). The most dramatic distinction between nocturics and nonnocturics was for the Ni, which was 2.1 for nocturics and 1.0 for nonnocturics. Together with our findings, these results suggest that the most significant reason for nocturia in the elderly is a mismatch between volume of urine ex-

creted and the bladder's capacity to hold adequate urine volumes during the hours of sleep.¹⁶

In parallel with our finding that elderly people tend to arise owing to NP,¹⁷ Swithinbank et al concluded that NP increased disproportionately to nocturia alone as women age.¹⁸ Further, it should be emphasized that the nocturia parameters Ni, NPi and NBCi are gradations within a continuum. That is, there are young individuals whose NPi exceeds the 0.35 threshold, and older patients who have lower NPi than their younger counterparts. There are also nocturics who have both high NPi and high NBCi, which portends the most bothersome and challenging cases of nocturia.

One shortcoming of this analysis is that only patients with OAB symptoms were included in the study. Further studies of subjects without OAB should be conducted to determine whether these findings are applicable to them as well. A second shortcoming is that only patients with 2.5 or more nocturia episodes per night (as recorded in 7-day baseline diaries) were compared, and there was not an increase in the number of nocturia episodes with advancing age as reported in some other nocturia studies. Accordingly, our results may not be generalizable to the population at large.

CONCLUSIONS

In this subanalysis of data from a large population of patients with OAB and nocturia, the contribution of reduced NBC and NP to this bothersome condition differed by age. In younger patients (younger than 50 years), nocturia likely resulted from reduced NBC as measured by the NBCi. In older patients (older than 70 years) nocturia likely resulted from NP as measured by the NPi. Importantly, these are not mutually exclusive categories. Many patients may have decreased NBC and NP. These are 2 extremes of a continuum and there is likely a gradual shift from one to the other with advancing age. Nevertheless, determining the underlying etiology of nocturia has important implications for treatment, and such treatments should be highly individualized.

ACKNOWLEDGMENTS

Linda A. Goldstein, Complete Healthcare Communications, Inc., provided assistance.

APPENDIX

Formulas for Evaluation of the Etiology of Nocturia		
Variable	Formula	Interpretation
Nocturia index	$Ni = NUV \div MVV$	$Ni > 1 \rightarrow$ nocturia due to NP and/or \downarrow NBC
Nocturnal polyuria index	$NPi = NUV \div 24\text{-hr Vol}$	$NPi > 35\% \rightarrow$ diagnosis is NP
Predicted number of nightly voids	$PNV = Ni - 1$	Assumes NBC is maximal (NBC = MVV)
Nocturnal bladder capacity index	$NBCi = \text{Actual No. nightly voids} - PNV$	$NBCi > 0 \rightarrow$ NBC $<$ MVV

Abbreviations and Acronyms

ER	=	extended release
FBC	=	functional bladder capacity
LUTS	=	lower urinary tract symptoms
MVV	=	maximum voided volume
NBC	=	nocturnal bladder capacity
NBCi	=	nocturnal bladder capacity index
Ni	=	nocturia index
NP	=	nocturnal polyuria
NPi	=	nocturnal polyuria index
NUV	=	nocturnal voided volume
OAB	=	overactive bladder
PNV	=	predicted number of nightly voids
UUI	=	urgency urinary incontinence

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EDITORIAL COMMENT

The study by Weiss et al demonstrates, through the analysis of void diaries in patients with OAB, that elderly patients with nocturia have higher nocturnal urine production and younger patients have a decrease in nocturnal bladder capacity. However, the case for widespread adaptation of urinary indices is not convincing. There is significant variability in void diaries, and the 7-day diary, as used in this investigation, is usually required for more accurate results.^{1, 2} However, poor compliance and bother can be substantial.³ In addition, the patient population for whom these indices may prove most beneficial, the elderly, is more often affected by limited mobility, cognitive impairment and by adverse effects of polypharmacy. Thus, derivative data from void diaries are only as accurate as the raw data that have been provided by the patient and readers are urged not to over-emphasize these indices.

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