The Fluctuation of Nocturia in Men with Lower Urinary Tract Symptoms Allocated to Placebo during a 12-Month Randomized, Controlled Trial

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Abbreviations and Acronyms

AUA-SI = American Urological Association symptom index

LUTS = lower urinary tract symptoms

VA CSP BPH = Veterans Affairs Cooperative Studies Program Benign Prostatic Hyperplasia

Purpose: We determined the fluctuation of nocturia in a 12-month period in men with lower urinary tract symptoms.

Materials and Methods: Men with lower urinary tract symptoms were allocated to the placebo arm of the United States Department of Veterans Affairs Cooperative Studies Program Benign Prostatic Hyperplasia Study. Reported nocturia frequency using the American Urological Association Symptom Index was collected at 6 time points (2, 4, 13, 26, 39 and 52 weeks). Repeat measurements of nocturia during a 1-year period were analyzed using a generalized mixed linear model.

Results: Of the 305 men allocated to the placebo group 256 participants (84%) gave answers for all 6 time points. In the entire sample the mean nocturia count did not significantly vary from baseline (week 2) after adjusting for covariates ($p = 0.542$). However, there was considerable fluctuation in nocturia during 1 year. Of the 93 men with 3 or 4 episodes at baseline 47% had improvement and 12% had worsening at 1 year. Of the 184 men who reported 2 or greater nocturia episodes at baseline 15% reported 0 or 1 at 52 weeks. Depending on the case definition during followup the probability of nocturia progression varied between 8% and 54% while nocturia regression varied between 2% and 33%.

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Conclusions: Using repeat questionnaire based assessments we observed considerable fluctuation in nocturia. However, overall there was no significant increase in prevalence in a 1-year period. These findings may be reassuring to providers and patients who elect to delay interventions for nocturia.

Key Words: prostate, prostatic hyperplasia, lower urinary tract symptoms, nocturia, United States Department of Veterans Affairs

NOCTURIA (waking from sleep at night to void[1]) is one of the most bothersome LUTS associated with benign prostatic enlargement.[2,3] However, little is known about the natural history of nocturia.[4]

Community based longitudinal studies of older men showed variable rates of incident and remitting nocturia during multiyear followup with no information on short-term fluctuation in nocturia.[5–9] Short-term night-to-night fluctuation may obscure true incidence and remission in studies with 2 time points. This may be especially relevant for prevalent symptoms such as nocturia.[10] However, repeat assessment and modeling may give more accurate estimates.

The definition of nocturia used in previous longitudinal studies may also account for variability in the calculated incidence rates because previous studies differed in whether nocturia was defined as at least 1 or at least 2 episodes per night. The standard definition suggests that nocturia is present if an individual has even 1 episode per night.[1] However, recent epidemiological data suggest that 1 nocturia episode is most often associated with no or minimal bother and no measurable impact on health related quality of life.[3,11] In contrast, 2 nightly voids typically result in slightly impaired quality of life and 3 or more voids moderately affect well-being.[3]

Even more limited data are available to guide decisions about the initiation of therapy in men with LUTS.[12] Thus, understanding the fluctuation of nocturia within a year has implications at the population level to understand the natural history and at the individual level to guide clinical management of nocturia. Clinical trials with a placebo arm, such as the VA CSP BPH Study of men with LUTS, provide an opportunity to observe fluctuation in self-reported nocturia in an untreated population.[13] In this post-hoc analysis of the VA CSP BPH Study we characterized fluctuations in nocturia frequency in a 1-year period in an untreated sample of men with LUTS.

MATERIALS AND METHODS

The VA CSP BPH trial evaluated the effects of terazosin and/or finasteride vs placebo in 1,229 men 45 to 80 years old by comparing changes in AUA-SI scores[14] and peak urinary flow rates. Study inclusion criteria were an AUA-SI score of 8 or greater, urine flow rate 4 to 15 ml per second with a voided volume of 125 ml or more and a post-void residual volume of 300 ml or less.

This analysis was based on data from 305 men who were randomized to the placebo arm of the study. Only the 256 men (84%) with complete nocturia data at all assessment points were included in the final analysis. Informed consent was obtained at the time of the VA CSP BPH trial. The study protocol was approved by the Cooperative Studies Evaluation Committee and Human Rights Committee of the Cooperative Studies Program Coordinating Center, Department of Veterans Affairs, Perry Point, Maryland.[13] These secondary data analyses were done on a de-identified data set, which included data on study weeks 0 through 52.

Nocturia Assessment

Nocturia frequency data were obtained at weeks 0, 2, 4, 13, 26, 39 and 52 after randomization. Participants were asked, "In the last week, how many times did you most typically get up to urinate from the time you went to bed at night until the time you got up in the morning?"[14] Participants responded by categorizing nocturia frequency as 0, 1, 2, 3, 4 or 5 or more episodes per night. We observed a significant decrease in reported nocturia between weeks 0 and 2, consistent with the initiation of placebo treatment. An average $\pm$ SD of 0.23 ± 1.02 fewer nocturia episodes were reported at week 2 ($p = 0.0004$). Therefore, to assess the natural history we evaluated subsequent nocturia fluctuation using week 2 as the baseline.

Analysis

We used 3 analytical techniques to assess the fluctuation in reported nocturia. In the first set of analyses nocturia at 52 weeks was compared to that at week 2. Only men reporting between 1 and 4 episodes of nocturia at week 2 were included in the evaluation. Few men reported 0 (9) or 5 or more (5) episodes at week 2.

In the second set of analyses we examined the risk of nocturia progression and regression using week 2 as the baseline. Progression was examined in participants who reported 0 or 1 nocturia episode at week 2. Because nocturia at weeks 2 and 4 correlated highly (Spearman rank correlation 0.76, table 1), week 4 data were not included in analyses of the case definitions for the risk of nocturia progression. We used 5 case definitions at 52 weeks, including 1) 2 or greater episodes at all 4 subsequent visits (weeks 13 to 52), 2) 2 or greater episodes at 3 or greater subsequent visits (weeks 13 to 52), 3) 2 or greater episodes at 2 or greater subsequent visits (weeks 13 to 52), 4) 2 or greater episodes at 1 or greater subsequent visits