Published in final edited form as:

Sleep Med. 2014 October ; 15(10): 1276–1278. doi:10.1016/j.sleep.2014.05.013.

INCREASES IN DURATION OF FIRST UNINTERRUPTED SLEEP PERIOD ARE ASSOCIATED WITH IMPROVEMENTS IN PSQI-MEASURED SLEEP QUALITY

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Abstract

Objective—Urology clinical trials assessing bladder function have relied on the self-reported duration of the first uninterrupted sleep period (FUSP) as a proxy outcome for sleep, but the relationship between this measure and more conventional self-reported measures of sleep is unknown. In this study, we examined the association between changes in FUSP and a widely used self-reported measure of sleep, the Pittsburgh Sleep Quality Index (PSQI).

Methods—We conducted post-hoc (secondary) analyses of unpublished data from a previously published randomized clinical trial (NCT00477490) of desmopressin (a medication used to treat nocturia) and examined relationships between Baseline to 4-week change in FUSP and PSQI Global and subscale scores for participants (N = 580 to N = 606) having complete data.

Results—Data indicated strong associations between change in PSQI Global score and FUSP change in and in 6 of 7 subscale scores. A reduction of 1.8 points in PSQI Global score was associated with a 72 minute lengthening of FUSP.

Conclusions—Results suggest that FUSP is a potentially valuable metric that correlates with changes in perceived sleep duration, depth, quality for the entire night, efficiency, latency and daytime function. An increase in FUSP was related to improvement in nearly all PSQI subscales. The validity of this measure in the general population remains to be determined.

Keywords

sleep; nocturia; self-report; PSQI; first uninterrupted sleep period; clinical trial

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INTRODUCTION

The first uninterrupted sleep period (FUSP) has been used as a self-reported outcome in studies of various urological conditions including benign prostatic obstruction (BPO) (1) overactive bladder (OAB) (2) and nocturia (3). How this outcome relates to other, better recognized measures of sleep quality remains unclear. In this post-hoc analysis, we compared data on FUSP from a phase III trial of a nocturia medication (4), which also included previously unpublished data on the Pittsburgh Sleep Quality Index (PSQI) (5), to determine how closely changes in FUSP related to changes in various aspects of self-reported sleep on PSQI.

METHODS

Data were derived from a registered phase III trial (www.clinicaltrials.gov: NCT00477490) of the orally dispersible tablet (ODT) formulation of desmopressin in nocturia patients who reported two or more voids/night. This was an Institutional Review Board-approved, 4-week, randomized, placebo-controlled study of four doses of desmopressin ODT (10, 25, 50 and 100 µg), and details of inclusion criteria are described in the primary manuscript presenting data from this trial (4). Sedative/hypnotic medications and OAB medications were permitted as long as the patient had been on a stable dose for 3 months prior to screening. Initiation of these medications or any change in dose or discontinuation of therapy for subjects who entered the trial on these medications constituted a protocol violation and data were excluded from the current analyses. Patients with renal disease, male patients with BPO or prior history of urological malignancies and female patients with history of pelvic prolapse were excluded. FUSP was defined as the elapsed time in minutes from turning off the light intending to go to bed to the time of first nocturnal void, or until the time of final awakening (if no void occurred), minus the time in minutes it took the subject to fall asleep. FUSP was recorded in a 3-day voiding and sleep diary completed at baseline, and immediately prior to the Week 4 visit at the end of the double-blind period. The average FUSP over the 3-day voiding and sleep diary was summarized for the baseline and 4-week time periods. Similarly, the PSQI (utilizing the customary 30-day time frame) was completed at baseline and at the end of the 4-week double-blind period.

A post-hoc analysis of a subgroup of patients who completed both the diaries and PSQI at baseline and at week 4 visit was performed pooling all treatment groups. The change from baseline in PSQI components and FUSP were analyzed using Analyses of Covariance (ANCOVA) adjusting for age and baseline value. The relationship between the change in FUSP and change in PSQI was analyzed using an ANCOVA model of the change from baseline on respective PSQI scale components, controlling for baseline PSQI score, age, and baseline FUSP, with change in FUSP as a covariate.

RESULTS

The Intent-to-Treat (ITT) population comprised of 757 patients (416 men, 341 women; mean age = 62.0; SD = 13.1; range 20-89) who awakened an average of 3.3 times per night to void. A subgroup of patients (n = 580 to n = 606), who provided data both on FUSP and

on the PSQI global or subscale scores both at baseline and Week 4, were included in the current analyses. The subgroup had similar demographics (gender and age) and baseline values for FUSP and PSQI as the entire ITT population.

At baseline the mean FUSP was 116.0 (SD = 62.8) minutes and mean baseline Global PSQI was 8.2 (3.8). During the 4-week study, patients experienced an average increase of 72.4 minutes (95% CI 64.3, 80.5; $p < 0.0001$) in FUSP, after adjusting for baseline value and age. The adjusted mean reduction from baseline to Week 4 in PSQI global score was -1.8 (95% CI $-2.0, -1.6$) ($p < .0001$). As shown in Table 1, a one hour increase in FUSP was associated with a highly significant changes in the PSQI global score and 6 out of 7 component scores. The direction of those changes uniformly indicated improved sleep associated with increased FUSP.

DISCUSSION

This is the first study to investigate the relationship between dynamic changes in FUSP, often reported as a proxy for sleep quality in trials of nocturia, and a widely used index of self-reported sleep encompassing the whole night, the PSQI. The results demonstrated that increasing durations of the period of sleep prior to the first nocturnal void were significantly associated with improvements in the global PSQI score, as well as component scores reflecting sleep quality, latency, duration, efficiency, disturbances and daytime dysfunction. The magnitude of the effect here with the global score (i.e., a change in 1.8 points) is roughly comparable to the magnitude of change seen in a various clinical trials focused on exercise interventions for insomnia (2.1 points) (6), improvements in sleep when treating gastroesophageal reflux with esomeprazole (2.9 points) (7), tai chi effects on sleep (2.1 points) (8), behavioral interventions for improved sleep in osteoarthritis patients (1.5 points) (9), generalized anxiety disorders (1.9 points) (10) or decreased hypnotic drug use (2.8 points) (11), and reduction of sleep symptoms associated with menopause with escitalopram (2.6 points) (12) or gabapentin (2.6 points) (13) in women with nocturnal menopausal symptoms. The fact that in our data, the 4-week change in global PSQI remained above 5 (the commonly accepted threshold for defining poor sleep) (14), suggests that the study population continued to have some problems with sleep, even after their nocturia was successfully treated. Similar results were noted in many of the aforementioned trials as well (6; 8-13). The global PSQI score, relative to the subscale scores, is most typically used in clinical trials, though some intervention studies also report change in subscales (e.g., 6, 8, 10, 13).

Nocturia is among the most frequently cited reasons for disturbed sleep in older adults (15-18) in the general population. Interestingly, nocturia has only been recognized by urologists as a condition in its own right for about a decade, distinct from conditions more commonly thought to be associated with its occurrence, such as bladder outlet obstruction in men, low estrogen in women, and detrusor overactivity or bladder storage capacity, in both men and women (19). Our data suggest that FUSP may serve as a useful measure, not only in trials of bladder medications, but also for sedative/hypnotic trials and for behavioral sleep interventions as well. For example, recent work has shown that obtaining information about nocturia predicted relative success or failure of a behavioral intervention for poor sleep (20).

Ironically, most sleep diaries simply do not ask about nocturia as a component of nighttime awakenings resulting in bathroom trips (21). Data on FUSP could also easily be collected with traditional sleep diaries, although this is not customarily analyzed. The current data suggest that FUSP may be a good measure to include in both interventional and descriptive studies of insomnia. Improvements in FUSP in nocturia treatment also have been associated with improvements in various Quality of Life Measures (22, 23).

Limitations of the current analyses include the fact that the strong relationships between FUSP and PSQI were detected in a clinical population with nocturia that may not translate directly to normal, healthy populations; further research is needed to confirm the correlation between FUSP and PSQI generally. Additionally, the abbreviated diary used in this study to collect data on FUSP did not collect data on other aspects of sleep such as whether the nocturnal voiding trip was perceived as a cause or consequence of the awakening. Finally, the trial generating the data in this report employed randomization with subjects stratified on a 1:1 basis over and under age 65, raising the possibility that, despite controlling for age, associations between FUSP and sleep quality may have been carried by the relative high proportion of older participants in this study. Nonetheless, because nocturia has been shown to be related to poor sleep, lower quality of life and depression across a wide age range in adults (16; 24-26), the robustness of this simple self-report marker suggests consideration of its potential use in other populations as well.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported in part by United States National Institutes of Health grant NS-050595 to Donald L. Bliwise and by the Global Research and Development Division of Ferring Pharmaceuticals. Drs. Bliwise and Holm-Larsen are paid Consultants of Ferring Pharmaceuticals. Dr. Goble is an employee of Ferring Pharmaceuticals. We thank Bjarke Mirner Klein who assisted with statistical analyses.

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Table 1

Associations between FUSP increase and improvement in PSQI component scales

PSQI Scale Component	n	Raw score parameter estimate ^a (1 hr increase in FUSP)	SE	Z-score parameter estimate ^b (1 hr increase in FUSP)	SE	p-value
Global	580	-0.5367	0.0588	-0.1791	0.0196	<0.0001
Sleep Quality	605	-0.1165	0.0133	-0.1634	0.0187	<0.0001
Sleep Latency	582	-0.0828	0.0161	-0.1106	0.0214	<0.0001
Sleep Duration	604	-0.0787	0.0144	-0.1030	0.0189	<0.0001
Sleep Efficiency	604	-0.1253	0.0200	-0.1245	0.0198	<0.0001
Sleep Disturbances	606	-0.0443	0.0130	0.0665	0.0195	0.0007
Sleep Medication	606	-0.0165	0.0178	-0.0198	0.0213	0.3545
Daytime Dysfunction	606	-0.0783	0.0150	-0.0970	0.0186	<0.0001

NOTE: ANCOVAs on respective PSQI scale component changes controlling for respective baseline PSQI score, age, baseline FUSP and change in FUSP as covariate; parameter estimates shown only for 1 hour change in FUSP for each PSQI scale; higher PSQI score indicates poorer sleep; n is sample size at Month 1

^aPSQI raw global scale range: 0–21; subscore scale range: 0–3

^bstandardized z-score based on the population mean and SD