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Claman; Ewing; Redline; Ancoli-Israel; Cauley; Stone; for the Study of Osteoporotic Fractures Research Group

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Periodic leg movements in sleep (PLMS) is a disorder characterized by repetitive stereotypical movements of the legs during sleep, and has often been associated with fragmented sleep, symptoms of insomnia and excessive daytime sleepiness. Defining PLMS based on a PLM index (PLMI = leg movements/hour of sleep) of 5 or greater, the largest published epidemiological study reported a 3.9% prevalence of PLMS in 18,980 subjects aged 15-100 from the general population. In community-dwelling younger adults, the prevalence has been estimated at 5% to 6%. The importance of PLMS has been highlighted by recent investigations supporting a relationship between PLMS, cardiovascular disease, and autonomic activation. Because of the high prevalence of PLMS in the elderly, it has been argued that PLMS may not be a risk factor for disease, but rather a marker of aging or other health attributes.

Periodic Leg Movements Are Associated with Reduced Sleep Quality in Older Men: The MrOS Sleep Study

David M. Claman, M.D., F.A.A.S.M.¹; Susan K. Ewing, M.S.¹; Susan Redline, M.D., M.P.H.³; Sonia Ancoli-Israel, Ph.D., F.A.A.S.M.⁴; Jane A. Cauley, Dr.P.H.⁵; Katie L. Stone, Ph.D. ³; for the Study of Osteoporotic Fractures Research Group

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Study Objectives: Periodic limb movements in sleep (PLMS) are common in the elderly. A previous large polysomnographic (PSG) study examining the relationship of PLMS to sleep architecture and arousals from sleep in women found that leg movements were common in elderly women, and PLMS which were associated with EEG arousals had a strong and consistent association with markers of disturbed sleep. Since sleep differs in men and women, we now investigate the association between PLMS and PSG indices of sleep quality in a large community-based sample of older men.

Design: Observational study, cross-sectional analyses.

Setting: Six clinical sites participating in the Osteoporotic Fractures in Men (MrOS) Study:

Participants: 2,872 older community-dwelling men (mean age 76.4 years) who completed in-home PSG from 2003-2005.

Interventions: N/A.

Measurements and Results: In-home PSG was performed which included bilateral measurement of leg movements. The total number of leg movements per hour of sleep (PLMI) and the number of leg movements causing EEG-documented arousals per hour of sleep (PLMA) were computed. A PLMI ≥ 5 (70.8%) and PLMA ≥ 5 (27.4%) were both prevalent. Linear regression models were used to examine the relationship between PLMS as predictors and sleep architecture, arousal index, and sleep efficiency as outcomes. The highest quintiles of PLMI (≥ 65.1) and PLMA (≥ 6.8) showed the largest association with indices of sleep architecture; PLMA showed a larger magnitude of effect. After multivariate adjustment, participants with a higher PLMA had a small but significantly higher arousal index, lower sleep efficiency, higher percentages of stages 1 and 2 sleep, and lower percentages of stage 3-4 and REM sleep (p < 0.01). An increased PLMI was similarly associated with a higher arousal index, higher percentage of stage 2 sleep, and lower percentage of stage 3-4 (p < 0.0001), but not with an increase in stage 1, REM sleep, or sleep efficiency. Neither PLMI nor PMLA was associated with subjective sleepiness measured by the Epworth Sleepiness Scale.

Conclusions: This study demonstrated that periodic leg movements are very common in older community-dwelling men and regardless of associated arousals, are associated with evidence of lighter and more fragmented sleep.

Keywords: Periodic limb movements, sleep, men, geriatric, aging, sleep stage, sleep EEG arousals

Citation: Claman DM; Ewing SK; Redline S; Ancoli-Israel S; Cauley JA; Stone KL; for the Study of Osteoporotic Fractures Research Group. Periodic leg movements are associated with reduced sleep quality in older men: The MrOS Sleep Study. J Clin Sleep Med 2013;9(11):1109-1117.
Osteoporotic Fractures (SOF). Results showed that in this cohort of older women, the prevalence of PLMI $\geq 5$ was 66% and PLMI $\geq 15$ was 52%. In SOF, when defining PLMS using a definition requiring associated arousal with each leg movement (PLMA), the prevalence for PLMA $\geq 5$ was 27% and for PLMA $\geq 15$ was 6%. Compared to the PLMI, an elevated PLMA was more consistently associated with poor sleep, including lower sleep efficiency, higher arousal index, more time spent in stages 1 and 2, and less time in stage 3-4 and REM sleep. Although both the PLMI and PLMA have been used clinically, it is not clear which, if not both, of these measures may be most useful to identify those with disturbed sleep architecture, which may indicate a need for treatment. The clinical significance of PLMs on daytime function remains unknown, and the results in elderly women did not show an association with Epworth score.

The present study determined the prevalence of PLMS and their association with objective measures of sleep architecture in 2,872 older men participating in the Osteoporotic Fractures in Men Study (MrOS). The present study assessed: (1) whether increasing severity of PLMS was associated with objective evidence of poorer sleep and subjective daytime sleepiness; and (2) whether stronger associations were evident when PLMS were defined by leg movements associated with cortical EEG arousals (PLMA) as compared to indices that included periodic leg movements without cortical arousals (PLMI).

**METHODS**

**Participants**

From March 2000 through April 2002, 5,994 men who were at least 65 years of age were recruited for participation in the baseline examination of MrOS. Men were recruited from population based listings in 6 regions of the United States. Men with a history of bilateral hip replacement and men who were unable to walk without the assistance of another person were excluded from the study. From December 2003 through March 2005, MrOS participants were invited to participate in an ancillary study to identify outcomes of sleep disorders in older men (MrOS Sleep Study). To participate in the MrOS Sleep Study, men had to agree to a comprehensive sleep assessment that included validated sleep questionnaires, an in-clinic interview, a series of clinical measures, and a single overnight in-home PSG study. Of the 5,994 men enrolled in the overall study, 3,135 ($\geq 100\%$ of goal of 3,000) completed the MrOS Sleep examination. Of these, 2,872 men underwent PSG with PLMS measurement and are the subject of this analysis. The remaining 263 men were missing PSG data because the measurement was not performed ($n = 179$), the collected data was unusable due to poor signal quality ($n = 45$), or the wake/sleep scoring was unreliable ($n = 39$).

The institutional review board (IRB) at each center approved the study protocol, and written informed consent was obtained from all subjects.

**Polysomnography (PSG)**

In-home sleep studies using unattended PSG (Safiro, Compumedics, Inc., Melbourne, AU) were performed. The PSG recordings were completed within 1 month of the clinic visit (mean 6.9 $\pm$ 15.8 days from visit), with 78% of recordings gathered within 1 week of the clinic visit. The recording montage consisted of C3/A2 and C4/A1, electroencephalograms, bilateral electrooculograms, a bipolar submental electromyogram, thoracic and abdominal respiratory inductance plethysmography, airflow (using nasal-oral thermocouple and nasal pressure cannula), finger pulse oximetry; lead I electrocardiogram, body position (mercury switch sensor), and bilateral leg movements (piezoelectric sensors). Centrally trained and certified staff members performed home visits for setup of the sleep study units. After sensors were placed and calibrated, signal quality and impedance were checked, and sensors were repositioned as needed to improve signal quality using approaches similar to those in the Sleep Health Heart Study. Staff returned the next morning to collect the equipment and download the data to the Central Sleep Reading Center (Cleveland, OH) for centralized scoring by a trained technician using standard criteria.

Polysomnography data quality were excellent, with a failure rate < 4%, and > 70% of studies graded as being of excellent or outstanding quality. Quality codes for signals and studies were graded using previously described approaches, which included coding the duration of artifact-free data per channel and overall study quality (reflecting the combination of grades for each channel).

PLMS were scored according to standard AASM criteria at the time, in which individual movements were scored as a PLM if duration was between 0.5 and 5 sec and when there was a clear amplitude increase from baseline in leg channels. To be considered periodic, $\geq 4$ movements needed to occur in succession no less and no more than 5 and 90 sec apart. The periodic limb movement index (PLMI) was the total number of periodic leg movements per hour of sleep. Leg movements occurring after respiratory events were excluded unless they were part of a 4 (or more) movement cluster with $\geq 2$ movements occurring independently of respiratory events. The periodic limb movement arousal index (PLMA) was the total number of periodic leg movements per hour of sleep in which EEG arousal occurred within 3 sec of movement termination.

PSG data, including sleep stage distributions, apnea and hypopneas and arousals, were scored by the centralized Case Western University Reading Center, using published criteria in effect at the time of the analysis. Arousal scores were scored according to AASM criteria; i.e., abrupt changes in EEG following $\geq 10$-sec period of sleep, which in REM also required an increase in EMG activity.

**PSG Variables**

The PLMI and PLMA were examined as quintiles. Sleep efficiency was defined as the time asleep divided by the sleep period time. Sleep stage distribution was characterized by the percent of total sleep time spent in each stage of sleep (i.e., % sleep stage 1, 2, 3-4, and REM). The Arousal Index (Arl) was calculated as the number of EEG arousals per hour of sleep. The apnea-hypopnea index (AHI) was calculated as the sum of all apneas and hypopneas that were each associated with $\geq 3\%$ desaturation divided by total sleep time and was examined continuously and using the cutoff points of $\geq 5$ and $\geq 15$.
Other Measurements

Self-reported information about daytime sleepiness was assessed using the Epworth Sleepiness Scale (ESS).20 The standard cutpoint of ESS > 10 was used to define excessive daytime sleepiness.21 Participants also completed questionnaires regarding demographics, medical history, physical activity, and alcohol use. History of cardiovascular disease was defined as self-report of physician diagnosis of myocardial infarction, angina, or congestive heart failure, or self-report of coronary bypass surgery, angioplasty, or pacemaker implant. History of chronic obstructive pulmonary disease (COPD) was defined as self-reported physician diagnosis of COPD, chronic bronchitis, asthma, or emphysema.

Cognitive function was assessed with the Modified Mini-Mental State examination (MMSE) with higher scores representing better cognitive functioning.22 The Physical Activity Scale for the Elderly (PASE) measured level of physical activity, with higher scores representing greater physical activity.23 To assess function, subjects were asked whether they had difficulty performing any of 5 instrumental activities of daily living (IADL), which included walking 2-3 blocks, climbing 10 steps, preparing meals, performing heavy housework, and shopping.24,25 The Geriatric Depression Scale (GDS) was used to assess depressive symptoms, with higher scores representing more depressive symptoms.26 Prescription and nonprescription medications were inventoried, verified by pill bottle examination, and matched to ingredient(s) using the Iowa Drug Information Service (IDIS) Drug Vocabulary (College of Pharmacy, University of Iowa, Iowa City, IA).27

During the home or clinic visits, body weight was measured with a standard balance beam or digital scale and height with a wall-mounted Harpenden stadiometer (Holtain, England); these measurements were used to determine body mass index (BMI), calculated as weight (kilograms)/height (meters²).

Statistical Analysis

Participant characteristics and sleep outcomes were summarized using means and standard deviations (SD) for continuous data and counts and percentages for categorical data. Participant characteristics were examined to determine if there was a significant difference between the 2,872 men in our analysis and those 263 who did not have PLMS data gathered. Participant characteristics and sleep parameter differences across the PLMI and PLMA quintiles were also examined using ANOVA for normally distributed continuous data, Kruskal-Wallis tests for skewed continuous data, and χ² tests for categorical data.

Linear regression models were used to examine the relationships between the PLMS predictors and the continuous outcomes of sleep architecture, the arousal index, and sleep efficiency. Though the distributions of stage 1, stage 3-4, the arousal index, and sleep efficiency were skewed, nonparametric (bootstrap) analysis on the original (untransformed) scale showed virtually the same results as the normality-based analyses on the original scale. Since those levels of skewness had virtually no impact, the outcomes were not transformed and were analyzed on the original scale. Adjusted means and 95% confidence intervals (CI) for the PLMI and PLMA quintiles were calculated using the least-squares means procedure. Covariates were included in the models if they were related to either the PLMI or PLMA predictors at p < 0.10 in univariate analyses. All models were adjusted for age, race, site, PASE score, IADL impairment, GDS score, history of cardiovascular disease, history of hypertension, antidepressant medication use, and AHI. To determine whether the associations between PLMS predictors and sleep outcomes were driven by men with obstructive sleep apnea, the models were re-run in the subset of men with AHI < 15.

Statistical analyses were completed using SAS version 9.1.3 (SAS Inc., Cary, NC) and Stata version 12.0 (Stata Corporation, College Station, TX).

RESULTS

Participants

The mean age of the 2,872 men included in this analysis was 76.4 years; over 90% were Caucasian; and half were hypertensive (Table 1). There were no differences between the 2,872 men with PLMS data and the 263 without PLMS data, except that a higher percentage of the men with PLMS data were Caucasian (90.7% vs. 80.6%, p < 0.0001), their mean (± SD) MMSE score was higher (92.7 ± 6.2 vs. 91.5 ± 8.3, p = 0.02), and their mean GDS score was lower (1.8 ± 2.2 vs. 2.2 ± 2.5, p = 0.008) (data not shown).

Distribution of PLMI and Association with Sleep Measures

2,034 participants (70.8%) had PLMI ≥ 5.323 (11.3%) had PLMI of 5 to < 15, and 1,711 (59.6%) had PLMI ≥ 15. Mean PLMI was 35.6 ± 37.5, with a median of 23.9 (interquartile range 3.3-56.1). Characteristics of the participants by quintiles of PLMI are presented in Table 1. Men in the higher PLMI quintiles were older on average and more likely to be Caucasian than men in the lower quintiles (p < 0.0001). These men were more likely to have an IADL impairment (p < 0.0001), and, on average, had more depressive symptoms (p = 0.04). A higher percentage of the men with elevated PLMI reported cardiovascular disease (p = 0.002), but there was no association with renal disease.

In unadjusted analyses, PLMI was significantly, although only modestly, associated with percentage time spent in stage 2, stage 3-4, REM, arousal index, and sleep efficiency (Table 2). Higher PLMI was associated with more time in stage 2 sleep (p < 0.0001), less time in stage 3-4 sleep (p < 0.0001), less time in REM sleep (p = 0.005), lower sleep efficiency (p = 0.006), and higher ArI (p < 0.0001). Differences in sleep architecture indices were largest when comparing men in the highest PLMI quintile (≥ 65.1) to men with PLMI quintiles of 1 to 4. This comparison showed that those with a PLMI in the highest quintile spent a greater percentage of time in stage 2 sleep (unadjusted mean ± SD 64.7% ± 9.8% vs. 62.2% ± 9.6%), less time in stage 3-4 sleep (10.1% ± 8.7% vs. 11.5% ± 9.1%), and REM sleep (18.3% ± 6.9% vs. 19.4% ± 6.6%), and higher ArI (25.8 ± 13.1 vs. 23.1 ± 11.3), and lower sleep efficiency (74.4% ± 13.1% vs. 76.5% ± 11.7%) (all p < 0.004). These differences were statistically significant, but small in magnitude. There was no significant association between PLMI and stage 1 or ESS score.
Multivariable analyses were performed to determine if the unadjusted associations remained after adjustment for age, race, site, physical activity score, IADL impairment, GDS score, history of cardiovascular disease, history of hypertension, antidepressant medication use, and AHI (Table 3). Adjusted linear regression analyses showed that higher PLMI continued to be significantly associated with many sleep outcomes, including more time spent in stage 2 sleep (p-trend < 0.0001), decreased stage 3-4 sleep (p-trend < 0.0001), and higher ArI (p-trend < 0.0001). Multivariate analyses were repeated in the subset with AHI < 15 (n = 1,620) and confirmed these results. Comparison of the highest quintile of PLMI to quintiles 1-4 by multivariate analyses showed virtually the same results as the unadjusted analyses. Quintile comparison in the subset with AHI < 15 (n = 1,620) and confirmed these results. Comparison of the highest quintile of PLMI to quintiles 1-4 by multivariate analyses showed virtually the same results as the unadjusted analyses. Quintile comparison in the subset with AHI < 15 (n = 1,620) and confirmed these results. Comparison of the highest quintile of PLMI to quintiles 1-4 by multivariate analyses showed virtually the same results as the unadjusted analyses. Quintile comparison in the subset with AHI < 15 (n = 1,620) and confirmed these results.
AHI < 15, confirmed results for stages 2, 3-4, and ARI, and were also statistically significant for REM and sleep efficiency.

**Distribution of PLMA and Association with Sleep Measures**

Seven hundred eighty-eight participants (27.4%) had PLMA ≥ 5; 623 (21.7%) had PLMA 5 to < 15; and 165 (5.8%) had PLMA ≥ 15. Mean PLMA was 4.1 ± 5.7, with a median of 1.8 (interquartile range 0.3-5.5). The Spearman correlation between PLMI and PLMA was 0.86 (p < 0.0001). Characteristics of the participants by quintiles of PLMA are shown in Table 4. Men in the higher PLMA quintiles were older on average and more likely to be Caucasian than men in the lower quintiles (p < 0.0001). A higher percentage of the men with elevated PLMA reported cardiovascular disease (p = 0.01) and were more likely to be taking SSRI medication (p = 0.03), but there were no differences between the PLMA quintiles for other comorbidities, including history of renal disease.

### Table 3—Sleep architecture and arousal index by quintile of PLMI and PLMA*

<table>
<thead>
<tr>
<th>PLMI quintiles</th>
<th>% Stage 1</th>
<th>% Stage 2</th>
<th>% Stage 3-4</th>
<th>% REM</th>
<th>Arousal Index</th>
<th>Sleep Efficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (&lt; 1.7)</td>
<td>6.7 (6.3, 7.0)</td>
<td>61.6 (60.8, 62.3)</td>
<td>12.2 (11.5, 13.0)</td>
<td>19.5 (19.0, 20.0)</td>
<td>21.2 (20.4, 22.1)</td>
<td>75.8 (74.8, 76.7)</td>
</tr>
<tr>
<td>2 (1.7-14.7)</td>
<td>6.9 (6.6, 7.2)</td>
<td>61.8 (61.0, 62.6)</td>
<td>12.3 (11.6, 13.0)</td>
<td>19.0 (18.5, 19.5)</td>
<td>23.1 (22.3, 23.9)</td>
<td>76.7 (75.7, 77.6)</td>
</tr>
<tr>
<td>3 (14.7-73.5)</td>
<td>6.6 (6.3, 6.9)</td>
<td>62.7 (61.9, 63.4)</td>
<td>11.3 (10.6, 12.0)</td>
<td>19.4 (18.9, 19.9)</td>
<td>23.1 (22.3, 23.9)</td>
<td>77.2 (76.2, 78.1)</td>
</tr>
<tr>
<td>4 (35.3-66.1)</td>
<td>7.0 (6.7, 6.3)</td>
<td>62.9 (62.1, 63.7)</td>
<td>10.4 (9.7, 11.2)</td>
<td>19.7 (19.1, 20.2)</td>
<td>23.4 (22.6, 23.8)</td>
<td>76.1 (75.1, 77.0)</td>
</tr>
<tr>
<td>5 (≥ 66.1)</td>
<td>6.9 (6.6, 7.3)</td>
<td>64.6 (63.9, 65.4)</td>
<td>9.9 (9.2, 10.6)</td>
<td>18.5 (18.0, 19.0)</td>
<td>21.8 (21.2, 22.4)</td>
<td>74.8 (73.9, 75.8)</td>
</tr>
</tbody>
</table>

*Data are adjusted mean (95% CI). Means are adjusted for age, race, site, PASE score, IADL impairment, GDS score, history of cardiovascular disease, history of hypertension, antidepressant medication use, and apnea-hypopnea index. GDS, Geriatric Depression Scale; IADL, instrumental activities of daily living; PASE, Physical Activity Scale for the Elderly; PLMA, periodic leg movement causing EEG arousals index; PLMI, periodic leg movement index.

### Table 4—Characteristics by PLMA quintile

<table>
<thead>
<tr>
<th>PLMA quintiles</th>
<th>Overall (N = 2,872)</th>
<th>Quintile 1 (N = 573)</th>
<th>Quintile 2 (N = 575)</th>
<th>Quintile 3 (N = 574)</th>
<th>Quintile 4 (N = 575)</th>
<th>Quintile 5 (N = 575)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean ± SD</td>
<td>76.4 ± 5.5</td>
<td>75.8 ± 5.1</td>
<td>75.6 ± 5.4</td>
<td>76.2 ± 5.5</td>
<td>76.5 ± 5.6</td>
<td>77.8 ± 5.8</td>
</tr>
<tr>
<td>Caucasian, N (%)</td>
<td>2,604 (90.7)</td>
<td>493 (86.0)</td>
<td>500 (87.0)</td>
<td>521 (90.8)</td>
<td>539 (93.7)</td>
<td>551 (95.8)</td>
</tr>
<tr>
<td>Body mass index (kg/m²), mean ± SD</td>
<td>27.2 ± 3.8</td>
<td>27.0 ± 3.9</td>
<td>27.3 ± 3.9</td>
<td>27.1 ± 3.6</td>
<td>27.1 ± 3.8</td>
<td>27.3 ± 3.8</td>
</tr>
<tr>
<td>At least some college, N (%)</td>
<td>2,254 (78.5)</td>
<td>443 (77.3)</td>
<td>458 (80.0)</td>
<td>455 (79.3)</td>
<td>453 (78.8)</td>
<td>445 (77.4)</td>
</tr>
<tr>
<td>MMSE (range 0-100), mean ± SD</td>
<td>92.7 ± 6.2</td>
<td>93.0 ± 5.6</td>
<td>92.8 ± 6.3</td>
<td>92.7 ± 6.3</td>
<td>92.8 ± 5.7</td>
<td>92.4 ± 6.9</td>
</tr>
<tr>
<td>PASE score, mean ± SD</td>
<td>145.7 ± 7.1</td>
<td>146.7 ± 7.02</td>
<td>147.9 ± 7.74</td>
<td>142.4 ± 7.09</td>
<td>149.4 ± 7.00</td>
<td>142.0 ± 6.76</td>
</tr>
<tr>
<td>IADL impairment, N (%)</td>
<td>600 (20.9)</td>
<td>111 (19.4)</td>
<td>117 (20.4)</td>
<td>109 (19.0)</td>
<td>122 (21.2)</td>
<td>141 (24.5)</td>
</tr>
<tr>
<td>GDS score (range 0-15), mean ± SD</td>
<td>1.8 ± 2.2</td>
<td>1.7 ± 2.1</td>
<td>1.7 ± 2.2</td>
<td>1.8 ± 2.1</td>
<td>1.8 ± 2.3</td>
<td>1.8 ± 2.0</td>
</tr>
<tr>
<td>Alcohol use (drinks/week), mean ± SD</td>
<td>3.4 ± 4.2</td>
<td>3.4 ± 4.2</td>
<td>3.4 ± 4.1</td>
<td>3.3 ± 4.3</td>
<td>3.5 ± 4.2</td>
<td>3.5 ± 4.3</td>
</tr>
<tr>
<td>Use of antidepressant medication, N (%)</td>
<td>222 (7.7)</td>
<td>31 (5.4)</td>
<td>49 (8.5)</td>
<td>54 (9.4)</td>
<td>48 (8.4)</td>
<td>40 (7.0)</td>
</tr>
<tr>
<td>Use of SSRI, N (%)</td>
<td>123 (4.3)</td>
<td>12 (2.1)</td>
<td>32 (5.6)</td>
<td>29 (5.1)</td>
<td>28 (4.9)</td>
<td>22 (3.8)</td>
</tr>
<tr>
<td>Use of benzodiazepines, N (%)</td>
<td>130 (4.5)</td>
<td>24 (4.2)</td>
<td>34 (5.9)</td>
<td>27 (4.7)</td>
<td>28 (4.9)</td>
<td>17 (3.0)</td>
</tr>
<tr>
<td>History of cardiovascular disease, N (%)*</td>
<td>953 (33.3)</td>
<td>168 (29.4)</td>
<td>179 (31.2)</td>
<td>182 (31.8)</td>
<td>206 (35.8)</td>
<td>218 (38.0)</td>
</tr>
<tr>
<td>History of COPD, N (%)†</td>
<td>390 (13.6)</td>
<td>72 (12.6)</td>
<td>79 (13.7)</td>
<td>81 (14.1)</td>
<td>77 (13.4)</td>
<td>81 (14.1)</td>
</tr>
<tr>
<td>History of diabetes, N (%)</td>
<td>380 (13.2)</td>
<td>64 (11.2)</td>
<td>75 (13.0)</td>
<td>80 (13.9)</td>
<td>73 (12.7)</td>
<td>88 (15.3)</td>
</tr>
<tr>
<td>History of hypertension, N (%)</td>
<td>1,439 (50.1)</td>
<td>263 (46.0)</td>
<td>296 (51.5)</td>
<td>284 (49.5)</td>
<td>308 (53.6)</td>
<td>288 (50.1)</td>
</tr>
<tr>
<td>History of kidney disease, N (%)</td>
<td>30 (1.0)</td>
<td>8 (1.4)</td>
<td>8 (1.4)</td>
<td>6 (1.1)</td>
<td>5 (0.9)</td>
<td>3 (0.5)</td>
</tr>
</tbody>
</table>

PLMA quintile cutoff points were as follows: quintile 1, < 0.1; quintile 2, 0.1-1.0; quintile 3, 1.0-3.0; quintile 4, 3.0-6.8; quintile 5, ≥ 6.8. p values are from ANOVA for normally distributed continuous variables and Kruskal-Wallis for skewed continuous variables. p values for categorical data are from a χ² test from homogeneity. *Cardiovascular disease is defined as self-report of physician diagnosis of myocardial infarction, angina, or congestive heart failure, or self-report of coronary bypass surgery or angioplasty or pacemaker implant. †History of COPD is defined as self-report of physician diagnosis of chronic obstructive pulmonary disease, chronic bronchitis, asthma, or emphysema. COPD, chronic obstructive pulmonary disease; GDS, Geriatric Depression Scale; IADL, instrumental activities of daily living; MMSE, Mini-Mental State Examination; PASE, Physical Activity Scale for the Elderly; PLMA, periodic leg movement causing EEG arousals index; PLMI, periodic leg movement index.
In unadjusted analyses, participants with a higher PLMA had, on average, a shorter sleep duration, spent greater percentage time in stage 1 and stage 2 sleep and less percentage time in stage 3-4 and REM sleep, had a higher ArI, and had lower sleep efficiency (all $p < 0.0001$) (Table 5). Similar to the analysis of PLMI, these associations were driven by men with the highest PLMA quintile ($\geq 6.8$). Compared to men in quintiles 1-4 of PLMA, men in the highest quintile spent a greater percentage of time in Stage 1 sleep (unadjusted mean ± SD $7.7\% \pm 5.1\%$ vs. $6.6\% \pm 4.1\%$), more time in stage 2 sleep ($65.6\% \pm 9.5\%$ vs. $62.0\% \pm 9.6\%$), less time in stage 3-4 sleep ($9.1\% \pm 8.1\%$ vs. $11.8\% \pm 9.1\%$) and REM sleep ($17.6\% \pm 6.9\%$ vs. $19.6\% \pm 6.6\%$), had higher ArI ($33.8\% \pm 13.0\%$ vs. $21.1\% \pm 9.9\%$), and lower sleep efficiency ($72.5\% \pm 13.4\%$ vs. $77.0\% \pm 11.5\%$) (all $p < 0.0001$). Participants with a higher PLMA also had a higher AHI ($p = 0.003$). There was no significant association between PLMA and ESS score. The relationship between PLMA and sleep state distribution, the arousal index, and sleep efficiency remained significant after multivariate adjustment (all $p \leq 0.005$) (Table 3). Comparison of the highest quintile of PLMA to quintiles 1-4 by multivariate analyses showed virtually the same results as the unadjusted analysis. Multivariate analyses and quintile comparison were repeated in the cohort subset with AHI < 15 ($n = 1,620$) which confirmed both analyses.

<table>
<thead>
<tr>
<th>Table 5—Sleep characteristics by PLMA quintile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
</tr>
<tr>
<td>Epworth Sleepiness Scale Score (range 0-24), mean ± SD</td>
</tr>
<tr>
<td>ESS &gt; 10, N (%)</td>
</tr>
<tr>
<td>Time in bed (hours), mean ± SD</td>
</tr>
<tr>
<td>Total sleep time (hours), mean ± SD</td>
</tr>
<tr>
<td>Apnea-hypopnea index, mean ± SD</td>
</tr>
<tr>
<td>AH1 ≥ 5, N (%)</td>
</tr>
<tr>
<td>AH1 ≥ 15, N (%)</td>
</tr>
<tr>
<td>% time in stage 1 sleep, mean ± SD</td>
</tr>
<tr>
<td>% time in stage 2 sleep, mean ± SD</td>
</tr>
<tr>
<td>% time in stage 3-4 sleep, mean ± SD</td>
</tr>
<tr>
<td>% time in REM sleep, mean ± SD</td>
</tr>
<tr>
<td>Arousal index, mean ± SD</td>
</tr>
<tr>
<td>Sleep efficiency (%), mean ± SD</td>
</tr>
</tbody>
</table>

PLMA quintile cutoff points were as follows: quintile 1, < 0.1; quintile 2, 0.1-1.0; quintile 3, 1.0-3.0; quintile 4, 3.0-6.8; quintile 5, ≥ 6.8. p values are from ANOVA for normally distributed continuous variables and Kruskal-Wallis for skewed continuous variables. p values for categorical data are from a $\chi^2$ test from homogeneity. AHI, apnea-hypopnea index; ESS, Epworth Sleepiness Scale; PLMA, periodic leg movement causing EEG arousals index.

**DISCUSSION**

The results of this study in 2,872 subjects demonstrate that periodic limb movements in sleep are common in elderly men. Overall, we found a strikingly high prevalence of PLMS when using a PLMI threshold of 5 (71%) or 15 (60%). When using a PLMA threshold of 5 (27%) or 15 (6%) as a disease-defining metric, PLMS was common but less prevalent. Importantly, both metrics were associated with poorer sleep outcomes after multivariate adjustment for various possible confounders.

A higher PLMA was consistently associated with more frequent arousals, lower sleep efficiency, and a pattern of altered sleep stages suggesting lighter sleep (more stage 1 and 2 and less stage 3-4 and REM). Except for stage 1, REM and sleep efficiency, similar findings were consistently observed for PLMI. These results suggest that leg movements that do not cause arousals as well as those that do cause arousals are associated with perturbed sleep quality, although on average, these associations are modest in this sample with relatively low stage 3-4 sleep and a high arousal index. The highest quintile of PLMI (≥ 65.1) and PLMA (≥ 6.8) had the strongest association and showed the largest magnitude of effect on sleep outcomes, and PLMA had a larger magnitude effect across more sleep outcomes. Despite associations with PSG indices of sleep quality, neither PLMI nor PLMA was associated with daytime sleepiness, based on ESS score.

A significant association of sleep quality with PLMI differs from our prior report in the SOF (female) cohort. Potential explanations for why PLMI had a stronger effect on sleep outcomes in men could include the higher power of the larger MrOS study and ability to detect relatively small effects. Alternatively, sleep architecture in older women is generally better than in older men, and thus it is possible that the sleep of women is less sensitive to disturbances than in men.

The results of this study in older men and the SOF study in elderly women support the hypothesis that PLMS increase in elderly women support the hypothesis that PLMS increase in elderly women with age, as suggested by Coleman and Ancoli-Israel. However, studies to date including the current study have been cross-sectional, and the extent to which longitudinal changes in PLMS occur within aging subjects is unclear. The longitudinal data of Gehrman in a small subset of the San Diego community cohort did not show an increase at 18-year follow-up, emphasizing the need for further longitudinal assessments to better determine the extent to which PLMS represents age-dependent pathophysiology.
Subjective sleepiness, as defined by an ESS > 10, was present only in 13.1% of the cohort. The lack of an association of either the PLMI or PLMA with subjective sleepiness may be due to several factors, including the low prevalence of subjective sleepiness in the cohort, potential insensitivity of the ESS to daytime functional impairment in elderly populations, lack of tight correlation between subjective sleep (ESS) and objective sleep measures (PSG), or because of the relative modest association between PLMS and indices of sleep quality. Consistent with other studies, the clinical effect of PLMs on daytime sleepiness has not been established; the sleep stage changes in this study did not correlate with subjective sleepiness based on ESS score. Since both an elevated PLMI and elevated PLMA were previously shown in MrOS to predict cardiovascular disease, other serious health outcomes besides daytime sleepiness should be considered when evaluating PLMS.

In considering prevalence estimates for PLMS, it is important to note that the optimal criterion for diagnosing PLMS is unknown, as are the implications of using alternative sensors for quantifying frequency of leg movements. More specifically, PLMS has been defined using cutoff values of both PLMI ≥ 5 and PLMI ≥ 15. Since it is evident that leg movements increase with aging, it is likely that cutoff values may need to be modified to reflect the age distribution of the study sample. Although the PLMI and PLMA were highly correlated, the frequency of leg movements associated with arousals was much lower. Our data that the highest quintiles of PLMI (≥ 65.1) and PLMA (≥ 6.8) showed the largest associations with indices of sleep quality supports the position that alternative threshold values for identifying abnormality may need to be used that account for the underlying distributions of PLMS in each respective population, reflecting age and comorbidity as well as recording techniques.

Our study had a number of strengths including a large sample size with standard scoring of PSG-derived data. Our sample focused on an older male population in whom there has been only limited prior objective sleep data. Enrollment of these community-dwelling men was not determined on the basis of PLMS, so our results are generalizable to other community samples. The importance of understanding determinants and measurement issues related to sleep disturbances in older men is underscored by the high prevalence of subjective symptoms of sleep problems and the frequency of chronic comorbidities in this population. The sleep and leg movement data were objectively scored independently of one another by a group of highly trained scorers, providing reliable information that allowed various sleep indices to be independently compared. The sleep component of MrOS was added after the original recruitment, so there was less likelihood of recruitment bias for sleep symptoms. Further, the characteristics of the large percentage of participants with PLMS data in the study were similar to those for the small percentage of the MrOS cohort without PLMS data, supporting the generalizability of the findings to other community-based populations of older men.

Our cross-sectional study had a few limitations. Because our population consisted of older men, results cannot be generalized to other groups such as women, younger people, or certain ethnic groups not broadly represented in MrOS. Our scoring algorithm for leg movements explicitly excluded movement clusters that were exclusively associated with respiratory events; however, since we did not measure esophageal pressure, we could not exclude upper airway resistance events as a cause of PLMS. In addition, our questionnaire did not include validated restless leg questions or information about iron deficiency, which prevented analysis of the relationship between restless leg symptoms and objective polysomnographic outcomes. It is possible that the physiological impact of PLMS differs in subgroups with and without daytime symptoms of restless legs syndrome. Leg movements were measured by piezo sensors, which are commonly used clinically, rather than by EMG. The optimal method for quantifying leg movements is an area of active investigation. In preliminary unpublished work using both piezo sensors and EMG electrodes, we observed similar patterns of PLMS. Specifically, in a sample of 51 subjects studied at the Sleep Reading Center studied with both piezoelectric and leg EMG sensors, with leg movements assessed by the piezoelectrodes annotated using the rules applied to the MrOS sample and the EMG data analyzed using newly published leg movement scoring rules, a correlation coefficient of 0.81 was observed, indicating an excellent level of agreement. Finally, information regarding RLS symptoms and iron deficiency was not available, so whether or not these findings can be extrapolated to RLS is unclear. Although PLMS occur in approximately 80% of RLS sufferers, it occurs in several other conditions and often in the elderly without RLS symptoms.

A single measurement of PLMS at baseline does not account for night-to-night variability and changes in PLMS over time.

In summary, these PSG data indicate that PLMS are very common in older men. An elevated PLMI and an elevated PLMA were both associated with a consistent, albeit a modest, pattern of sleep disruption, suggesting that both PLMI and PLMA contribute to poor sleep quality. The highest quintiles for PLMA and PLMI showed the strongest effect on sleep outcomes, particularly PLMA. Similar to data reported in elderly women in SOF, neither the PLMI nor PLMA was associated with daytime sleepiness. As the population continues to age, these results highlight the need for further research to better determine if there is a threshold level of PLMA and PLMI that identifies older participants at increased risk for comorbidity or functional limitations.

**ABBREVIATIONS**

AASM, American Academy of Sleep Medicine
AH1, apnea-hypopnea index
ANOVA, analysis of variance
Arl, arousals index
BMI, body mass index
CI, confidence interval
COPD, chronic obstructive pulmonary disease
ECG, electrocardiogram
EEG, electroencephalogram
EMG, electromyogram
EOG, electrooculogram
ESS, Epworth Sleepiness Scale
GDS, Geriatric Depression Scale
IADL, instrumental activities of daily living
REFERENCES


ACKNOWLEDGMENTS

Investigators in the Outcomes of Sleep Disorders in Older Men study (MfOS Sleep)

Coordinating Center (California Pacific Medical Center Research Institute and University of California, San Francisco): K.L. Stone (Principal Investigator), D.C. Bauer (co-Investigator), S.R. Cummings (co-Investigator), N. Goldschlager (co-Investigator), R. Fullman (Project Director), R. Benard, T. Blackwell, L. Concepcion, J. Diehl, S. Ewing, C. Fox, M. Jaime-Chavez, E. Kwan, S. Litwack, W. Liu, L.Y. Liu, J. Schneider, R. Scott, D. Tanaka, J. Ziam; Administrative Center (Oregon Health & Sciences University): E. Own (Principal Investigator), K. Phipps (co-Investigator), L. Marshall (co-Investigator), J. Babich Blank (Project Director), L. Lambert, B. Chan, D. Neveil; University of Alabama, Birmingham: C.E. Lewis (Principal Investigator), J. Shankey (co-Investigator), P. Johnson (Project Director), C. Odem, S. House, N. Webb, K. Hardy, S. Felder, J. Wilkoff, J. King, T. Johnsone, M. Young, J. Smith, C. Sassaman, C. Collier, C. Atkins; University of Minnesota: K. Ensrud (Principal Investigator), H. Fink (co-Investigator), D. King (Program Manager), N. Michaels (Asst. Program Manager), N. Nelson (Clinic Coordinator), C. Bird, D. Blanks, F. Imker-Witte, K. Moen, M. Paule, M. Stinsaday; Stanford University: M. Stefanick (Principal Investigator), A. Hoffman (co-Investigator), K. Kant, B. Malig, S. Wong; University of Pittsburgh: J. Cauley (Principal Investigator), J. Zmuda (co-Investigator), M. Danielson (Study Administrator), L. Harper (Project Director), L. Buck (Clinic Coordinator), M. Nasim, D. Cusick, M. Gorecki, N. Watson, C. Bashada, C. Newman; University of California, San Diego: E. Barrett-Conner (Principal Investigator), S. Anciello (co-Investigator), T. Dart (co-Investigator), ML Carrion-Petersen (Project Director), P. Miller, N. Kamarlingue; Central Sleep Reading Center: S. Redline (Principal Investigator).
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Submitted for publication January, 2013
Submitted in final revised form July, 2013
Accepted for publication July, 2013
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DISCLOSURE STATEMENT
This was not an industry supported study. This work was performed at the San Francisco Coordinating Center, University of California, San Francisco, and Case Western Reserve University. The authors have indicated no financial conflicts of interest. There was no intervention. There was no off-label or investigational treatment. The Osteoporotic Fractures in Men (MrOS) Study is supported by National Institutes of Health funding. The following institutes provide support: the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), the National Institute on Aging (NIA), the National Center for Research Resources (NCRR), and NIH Roadmap for Medical Research under the following grant numbers: U01 AR45580, U01 AR45614, U01 AR45632, U01 AR45647, U01 AR45654, U01 AR45583, U01 AG18197, U01-AG027810, and UL1 RR024140. The National Heart, Lung, and Blood Institute (NHLBI) provides funding for the MrOS Sleep ancillary study "Outcomes of Sleep Disorders in Older Men" under the following grant numbers: R01 HL071194, R01 HL070848, R01 HL070847, R01 HL070842, R01 HL070841, R01 HL070837, R01 HL070838, and R01 HL070839.
Effects of Sleep Disorders on the Non-Motor Symptoms of Parkinson Disease

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Study Objectives: To evaluate the impact of sleep disorders on non-motor symptoms in patients with Parkinson disease (PD).

Design: This was a cross-sectional study. Patients with PD were evaluated for obstructive sleep apnea (OSA), restless legs syndrome (RLS), periodic limb movement syndrome (PLMS), and REM sleep behavior disorder (RBD). Cognition was assessed with the Montreal Cognitive Assessment and patients completed self-reported questionnaires assessing non-motor symptoms including depressive symptoms, fatigue, sleep complaints, daytime sleepiness, and quality of life.

Setting: Sleep laboratory.

Participants: 86 patients with PD (mean age = 67.4 ± 8.8 years; range: 47-89; 29 women).

Interventions: N/A.

Measurements and Results: Having sleep disorders was a predictor of overall non-motor symptoms in PD (R² = 0.33, p < 0.001) while controlling for age, PD severity, and dopaminergic therapy. These analyses revealed that RBD (p = 0.006) and RLS (p = 0.014) were significant predictors of increased non-motor symptoms, but OSA was not. More specifically, having a sleep disorder significantly predicted sleep complaints (ΔR² = 0.13, p = 0.006), depressive symptoms (ΔR² = 0.01, p = 0.03), fatigue (ΔR² = 0.12, p = 0.007), poor quality of life (ΔR² = 0.13, p = 0.002), and cognitive decline (ΔR² = 0.09, p = 0.036). Additionally, increasing number of sleep disorders (0, 1, or ≥ 2 sleep disorders) was a significant contributor to non-motor symptom impairment (R² = 0.28, p < 0.001).

Conclusion: In this study of PD patients, presence of comorbid sleep disorders predicted more non-motor symptoms including increased sleep complaints, more depressive symptoms, lower quality of life, poorer cognition, and more fatigue. RBD and RLS were factors of overall increased non-motor symptoms, but OSA was not.

Keywords: Parkinson disease, sleep disorders, non-motor symptoms, quality of life

Citation: Neikrug AB; Maglione JE; Liu L; Natarajan L; Avanzino JA; Corey-Bloom J; Palmer BW; Loredo JS; Ancoli-Israel S. Effects of sleep disorders on the non-motor symptoms of Parkinson disease. J Clin Sleep Med 2013;9(11):1119-1129.

BRIEF SUMMARY

Current Knowledge/Study Rationale: Parkinson disease (PD) is a progressive neurodegenerative disorder primarily characterized not only by motor symptoms but also by non-motor symptoms (NMS) such as sleep dysfunction, sleepiness, fatigue, pain, and depressive symptoms. This study evaluated the impact of sleep disorders on non-motor symptoms in patients with PD.

Study Impact: These findings indicate a significant relationship between sleep disorders and increased NMS impairment in patients with PD. More specifically, having sleep disorders predicted increased sleep complaints, lower quality of life, increased depressive symptoms, poorer cognition, and more fatigue. The finding of increased NMS in RBD adds further support to a growing body of literature that suggests that RBD is related to increased frequency and severity of non-motor impairment and subsequent poorer quality of life.

Sixty to 98% of patients with PD complain of sleep-related difficulties. In a community-based study of sleep disorders in PD, 32% complained of difficulty falling asleep, 39% reported frequent awakenings during the night, and 23% reported early morning awakenings. A longitudinal study of...
nocturnal sleeping problems in PD reported that 83% of the patients with PD reported sleep complaints at one or more visits during the 8-year study, and such complaints were related to disease duration and depression. Another study reported that sleep complaints significantly predicted poor health-related quality of life in PD.

Sleep disorders such as obstructive sleep apnea (OSA), restless legs syndrome (RLS), periodic limb movements syndrome (PLMS), and REM sleep behavior disorder (RBD) are commonly reported in patients with PD in rates similar or higher than in the general older adult population. Sleep disorders result in complaints about disturbed sleep, excessive daytime sleepiness, cognitive decline, and depression, all of which are also recognized as NMS of PD. Additionally, sleep disorders have been shown to substantially impact health-related quality of life in patients with PD.

Few studies have assessed possible relationships between any given sleep disorder and different NMS in PD population. Those studies that did question this relationship primarily assessed RBD, which has been demonstrated to be associated with hallucinations, cognitive impairment, psychiatric comorbidity, increased falls, poor emotional functioning, and lower quality of life. Studies looking at OSA in PD had conflicting results, with only one study reporting that OSA was the most important risk factor associated with EDS in PD, while another study reported no relationship with NMS (e.g., sleepiness, depression, and cognitive impairment). Finally, previous findings from our laboratory suggested a relationship between increased periodic leg movements during the night (not associated with arousals), sleep complaints, and poorer quality of life. However, to our knowledge, there have been no studies that simultaneously assessed multiple sleep disorders in patients with PD and the effect of having these sleep disorders on overall NMS impairment. We hypothesized that sleep disorders would be significant contributors to the overall NMS experienced and reported by patients with PD and that PD patients with more sleep disorders would experience more NMS impairment.

### METHODS

**Participants**

Participants were recruited for this study at talks given at PD support group meetings, by flyers, advertisements, or were referred by neurologists at either the University of California, San Diego (UCSD) or in the San Diego County community. A consort table is provided (Figure 1). Of the 183 patients with
PD that were contacted, 106 patients met inclusion/exclusion criteria (Table 1), agreed to participate, and consented for this study. The study was approved by UCSD Human Research Protection Program and San Diego Veterans Administration Healthcare System.

Procedures

All participants were screened by telephone. For those meeting inclusion criteria, a meeting was scheduled and the study was described in detail and signed informed consent was obtained. All enrolled participants were tested for cognitive performance by a research associate, were evaluated by a neurologist, and were assessed by a physician trained in sleep medicine for a detailed sleep history, assessment of possible sleep disorders, overall medical condition, and medication use. Additionally, all participants completed the self-administered questionnaire packet that included questionnaires assessing multiple symptoms of PD, and fatigue. All patients were admitted to the General Clinical Research Center (now Clinical and Translational Research Institute) Gillin Laboratory for Sleep and Chronobiology for an overnight video-enabled polysomnography (PSG).

PD Assessment

Participants were evaluated for PD by a neurologist using the Unified Parkinson’s Disease Rating Scale (UPDRS) to characterize the progression of PD. Additionally the Hoehn and Yahr Scale (H&Y) was utilized to assess PD severity. The H&Y grades patients from stage 0 (no signs of disease) to stage 5 (wheelchair bound or bedridden unless assisted).

Clinical Sleep Evaluation

All participants were evaluated by a physician trained in sleep medicine for RBD, RLS, medication use, and overall health. RBD was evaluated using the REM Behavior Disorder Sleep Questionnaire (RBDSQ). The RBDSQ was used to assess clinical history of dream enactment behavior. This screening tool for RBD is based on the clinical criteria of the International Classification of Sleep Disorders, second edition (ICSD-II). The RBDSQ was previously validated with a cutoff score of 5, exhibiting 96% sensitivity and 56% specificity. RLS was evaluated using a structured questionnaire according to the 4 criteria delineated in the International Restless Legs Syndrome Study Group criteria.

Exclusion Criteria

1. Bronchospastic and symptomatic chronic obstructive pulmonary disease as indicated by regular use of bronchodilators, steroids, history of carbon dioxide retention, waking hypoxemia, or use of supplemental oxygen
2. Current diagnosis of active seizure disorder; presence of any neurodegenerative disorder other than PD
3. Symptomatic coronary or cerebral vascular disease (history of myocardial infarction, angina, stroke, transient ischemic attacks), history of life-threatening arrhythmias, cardiomyopathy, or current alcohol or drug abuse
4. Receiving current treatment for obstructive sleep apnea
5. Receiving deep brain stimulation treatment for PD
6. Current alcohol and/or drug abuse/dependence
7. Any significant physiological (e.g., incontinence) or psychological impairments (i.e., bipolar depression) that would have limited their participation

Mood Evaluation

Beck Depression Inventory- 2nd edition (BDI-II) was used to evaluate symptoms of depression and was completed by the patients. The BDI-II is well validated and is the most frequently used scale for depression. Visser et al. evaluated the reliability and validity of the BDI-II in PD. A study that validated sub-threshold depression in PD concluded that a BDI-II score of 9-15 best differentiates sub-threshold depression in PD.

NMS Questionnaires

Multiple Symptoms Evaluation

The Non-motor Symptoms Questionnaire (NMSQuest) is a 30-item questionnaire that was completed by patients. The NMSQuest allows a brief yet comprehensive assessment of the non-motor features of PD, including neuropsychiatric, sleep, autonomic, gastrointestinal, sensory, and other disturbances. Number of symptoms endorsed is added up for a total score. This scale was shown to have good psychometric properties and to be valid as an instrument for detecting NMS in PD.

Medications

Medication use (i.e., type, dose, frequency, time of administration, reason for use, and duration of use) was assessed for all patients. As dopaminergic therapy regimen highly differs between patients with PD, and in order to allow comparisons among patients on different dopaminergic regimens, drug dosages were converted to levodopa dosage equivalents (LDE) according to the formula provided by Tomlinson et al.

Cognitive Evaluation

The Montreal Cognitive Assessment (MoCA) was used to assess cognition. The MoCA is a brief screening tool designed to identify mild cognitive impairment. The MoCA was administered by trained study staff during consent. The MoCA has been demonstrated to have good reliability and validity in PD and is more sensitive in detecting mild cognitive impairment than the Mini Mental State Exam. A cutoff of 26 is suggestive of mild cognitive impairment.

Table 1—Inclusion/exclusion criteria

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
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<tbody>
<tr>
<td>1. A clinical diagnosis of PD</td>
<td>1. Bronchospastic and symptomatic chronic obstructive pulmonary disease as indicated by regular use of bronchodilators, steroids, history of carbon dioxide retention, waking hypoxemia, or use of supplemental oxygen</td>
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<tr>
<td>2. MMSE ≥ 18</td>
<td>2. Current diagnosis of active seizure disorder; presence of any neurodegenerative disorder other than PD</td>
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<tr>
<td>3. Over the age of 50 years</td>
<td>3. Symptomatic coronary or cerebral vascular disease (history of myocardial infarction, angina, stroke, transient ischemic attacks), history of life-threatening arrhythmias, cardiomyopathy, or current alcohol or drug abuse</td>
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<tr>
<td>4. Stable health</td>
<td>4. Receiving current treatment for obstructive sleep apnea</td>
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<tr>
<td>5. Fluent English speaking</td>
<td>5. Receiving deep brain stimulation treatment for PD</td>
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<tr>
<td>6. Participants willing and able to remain stable on the same medication regimen for 2 months prior to enrollment in the study</td>
<td>6. Current alcohol and/or drug abuse/dependence</td>
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<tr>
<td>7. Any significant physiological (e.g., incontinence) or psychological impairments (i.e., bipolar depression) that would have limited their participation</td>
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Sleep Disorders and NMS of Parkinson Disease
this population. The use of the BDI-II in PD was championed by expert panels for monitoring severity of symptoms and for evaluation of therapeutic interventions.

Quality of Life Evaluation
Parkinson’s Disease Questionnaire (PDQ-39) was designed and validated specifically for evaluating quality of life in PD. The PDQ-39 has 39 items on mobility, emotional well-being, stigma, social support, cognitions, communication, and bodily discomfort. A higher score on this scale indicates poorer quality of life. In a review of different quality of life scales for patients with PD, Marinus et al. concluded that the PDQ-39 is the single most appropriate quality of life instrument for this population.

Daytime Sleepiness Evaluation
The Epworth Sleepiness Scale (ESS) is a self-administered questionnaire assessing daytime sleepiness. The ESS has been shown to reliably distinguish good sleeping from those with excessive daytime sleepiness disorders including obstructive sleep apnea, narcolepsy, and idiopathic hypersomnolence. A cutoff score ≥ 10 suggests clinically significant daytime sleepiness.

Fatigue Evaluation
The Short Form of the Multidimensional Fatigue Symptom Inventory (MFSI-SF) is a short questionnaire (30 questions) that provides a total fatigue score and 5 subscales: General, Physical, Emotional, Mental, and Vigor. A total score is computed based on subscales with higher scores indicating worse fatigue. Assessment of the MFSI-SF showed sound psychometric properties and a stable multidimensional factorial structure.

Sleep Complaints Evaluation
The Parkinson’s Disease Sleep Scale (PDSS) is a self-administered questionnaire that is designed to assess sleep complaints and nocturnal difficulties that are more pertinent in PD. Items address overall quality of sleep, sleep onset and sleep maintenance insomnia, nocturnal restlessness, nocturnal psychosis, nocturia, nocturnal motor symptoms, sleep refreshment, and daytime dozing. Scores for each of 15 items range from 0 (symptom severe and always present) to 10 (symptom free). The mean of the scales is computed, with lower scores suggesting more severe sleep disruption.

Overnight PSG and Diagnostic Criteria for Sleep Disorders
The first 4 patients were evaluated with the Embla (Planegg, Germany) while the remaining participants were evaluated with the video-enabled Compumedics Somté (Charlotte, NC). Electroencephalography (F4, C4, O1 or O2), electrooculography (left and right outer canthus), submental electromyography, respiratory effort (thoracic and abdominal piezoelectric bands), airflow (nasal pressure transducer), electrocardiogram, oximetry, and tibialis electromyography were recorded. In addition, technicians noted any visible arousals (e.g., restroom visits, taking medication), any environmental changes (e.g., noise), any vocalization during sleep (e.g., yelling/talking), and any movements (e.g., kicking/arms flailing), both on the PSG recording and in a journal.

All PSG records were staged according to accepted American Academy of Sleep Medicine criteria. Apnea-hypopnea index (AHI; the number of apneas + hypopneas/h of sleep), periodic leg movement index (PLMI; the number of leg kicks in a 5- to 90-sec period of ≥ 4 consecutive leg movements/h of sleep), and periodic leg movement arousal index (PLMArI; periodic leg movements associated with arousals/h of sleep) were computed.

To assess for RBD, submental electromyography was assessed for REM sleep without atonia using criteria nearly identical to the scoring method developed by Lapiere and Montplaisir and validated by Consens et al., including computation of tonic and phasic components as defined by the American Academy of Sleep Medicine guidelines. An electromyography score (EMG score) was calculated as the average of the percent of tonic REM sleep epochs and the percent of phasic REM sleep mini-epochs. The EMG score is similar to the RBD measure previously proposed by Consens et al., which established a cutoff score of 10% with a sensitivity of 89% and specificity of 57%.

Sleep Disorders Criteria
OSA definition was based on an AHI (yes-OSA [AHI ≥ 10] and no-OSA [AHI < 10]), PLMS definition was based on the PLMArI (yes-PLMS [PLMArI ≥ 5] and no-PLMS [PLMArI < 5]), and RLS diagnosis was based on the RLS criteria (yes-RLS [endorsed all 4 RLS questions] and no-RLS [endorsed < 4 RLS questions]). Finally, RBD diagnosis was based on the ICSD-II, which requires subjective clinical history with objective documentation of either REM sleep without atonia or dream enactment behavior during an overnight PSG. Patients were classified into 3 RBD groups based on subjective (RBDSQ) and objective (EMG-score and/or clear evidence of REM sleep without atonia as recorded during overnight PSG) measures; Group 1, Yes-RBD group (RBDSQ ≥ 5 and EMG score ≥ 10% or clear evidence of REM sleep without atonia as recorded during overnight PSG); Group 2, No-RBD group (RBDSQ < 5 and EMG score < 10); and Group 3, Probable-RBD group (either RBDSQ ≥ 5 or EMG-score ≥ 10%).

Analysis
Summary statistics (means, SDs, ranges, frequencies) were computed for all variables of interest. Of the 7 outcome measures, only the BDI-II and MoCA violated normality assumption and thus were appropriately transformed for subsequent analyses. Analyses were computed both with the transformed and untransformed data. Pearson correlations were used to assess the relationship between NMS measures.

Given that 7 NMS variables were under consideration (i.e., MoCA, NMSQuest, BDI-II, MFSI-SF, PDQ-39, PDSS, and ESS), and in order to avoid multiple comparisons, principal component analysis (PCA) was used to derive component/factor scores that best described the NMS of PD by distinguishing sets of variables with stronger relationships among multiple observed variables (e.g., mood, sleepiness, functional impairment, and quality of life).

A hierarchical linear regression correlation was used to assess the relationship between the NMS score (i.e., first principal
component of each principal component analysis) and the presence of sleep disorders while controlling for age, PD severity, and dopaminergic therapy (LDE). Using regression analysis allowed the assessment of the unique effects of each explanatory variable (unique sleep disorders) while statistically controlling (partialing) the effects of the other explanatory variables in a single model, thus minimizing the likelihood of a type I error."m

Age, PD severity (H&Y), and dopaminergic therapy (LDE) were included in block 1 and the sleep disorders were included in block 2 to assess if the inclusion of sleep disorders into the model resulted in significant increases of variance explained in the NMS score ($\Delta R^2$ and $\Delta F$ statistic). Additionally, a separate model assessed the impact of having 0, 1, or ≥ 2 sleep disorders on NMS score while controlling for age, disease severity, and dopaminergic therapy (LDE). All analyses were executed using SPSS (version 17.0, SPSS, Chicago, IL).

RESULTS

A total of 86 patients with PD (mean age = 67.4 ± 8.8 years; range: 47-89, 29f) were included in this study (Figure 1). The majority of the sample was Caucasian (91%), married (73%), and retired (66.3%). The patients had been diagnosed with PD for an average of 6.3 years. The majority of the patients were at H&Y stage I or II (79%), and no patients had stage IV or V. The specific dopaminergic therapy (i.e., levodopa, carbidopa, dopamine agonist) widely differed between patients, and only 6 participants were not receiving any dopaminergic therapy. Additionally, 28% of the patients reported taking an antidepressant.

Of the total sample, 55% (n = 47) were diagnosed with OSA, 42% (n = 36) with RBD, and 22% (n = 19) with RLS. PLMI for the sample was considerably high (PLMI = 21.0) however, these events were rarely associated with arousals and only 2 patients (2%) were diagnosed with PLMS (had a PLMArI ≥ 5). Due to this small number, PLMS was omitted from further analyses.

Finally, 10 (11.6%) of the patients had no sleep disorders, 52 (60.5%) had only 1 sleep disorder, and 24 (27.9%) patients had ≥ 2 sleep disorders.

Complete clinical and sleep characteristics for the entire sample and by sleep disorder is provided in Table 2. Descriptive measures resulted in a single component extracted (NMS eigenvalue = 3.75). Each of the remaining components had an eigenvalue < 1.0 and explained ≤ 14% of the variability in the measures.

Principal Component Analysis

Principal component analysis on the 7 NMS outcome measures resulted in a single component extracted (NMS score) that explained 53.5% of the variance (Eigenvalue = 3.75). Each of the remaining components had an Eigenvalue < 1.0 and explained ≤ 14% of the variability in the set of NMS variables. Examining the extracted weights for each variable revealed that most of the variable loaded heavily (> |0.8|) on this component with only subjective sleepiness (ESS = 0.48) and cognition (MoCA = -0.27) not heavily loading on this component.
independent variables was significant ($R^2 = 0.20, F = 6.93, p < 0.001$). In this model only age ($\beta = -0.24, p = 0.016$) and LDE ($\beta = 0.37, p = 0.004$) were significant predictors of the NMS score, while PD severity was not ($\beta = 0.16, p = 0.13$). Including sleep disorders (i.e., OSA, RBD, RLS) into this model significantly improved the model ($\Delta R^2 = 0.13, \Delta F = 5.01, p = 0.003$). The full model with the NMS score as the dependent variable and age, PD severity, LDE, OSA, RBD, and RLS, as independent variables was significant ($R^2 = 0.33, F = 9.97, p < 0.001$) with age ($\beta = -0.23, p = 0.014$), LDE ($\beta = 0.28, p = 0.004$), RBD ($\beta = 0.26, p = 0.006$), and RLS ($\beta = 0.24, p = 0.014$) as significant predictors of the NMS score. PD severity ($\beta = 0.15, p = 0.12$) and OSA ($\beta = 0.06, p = 0.52$) were not significant predictors of the NMS score. In summary, sleep disorders (specifically, RBD and RLS) were significant contributors and predictors of NMS score above and beyond which is explained by age, LDE, and PD severity. Sleep disorders alone accounted for 13% of the variance in the NMS score. Overall this model was significant and explained 33% of the variance in the NMS score.

Patients with RBD ($t = 2.51, p = 0.014$) and with RLS ($t = -2.57, p = 0.012$) had a significantly higher NMS score than those without RBD or RLS; there were no significant differences in patients with or without OSA.

Assessment of the impact of having multiple sleep disorders (0, 1, or ≥ 2 sleep disorders) on the NMS score and including this variable in the model while controlling for age, PD severity, and LDE, revealed that the model significantly improved ($\Delta R^2 = 0.07, AF = 8.33, p = 0.005$). The full model with the NMS score as the dependent variable and age, PD severity, dopaminergic therapy, and number of sleep disorders per patient as independent variables was significant ($R^2 = 0.28, F = 7.75, p < 0.001$) with age ($\beta = -0.25, p = 0.01$), LDE ($\beta = 0.3, p = 0.002$), and number of sleep disorders ($\beta = 0.27, p = 0.005$) being significant predictors of the NMS score.

There were no differences in NMS score between those with no sleep disorders and those with only 1 sleep disorder. However, compared to those with ≥ 2 sleep disorders, those with no sleep disorders ($t = 2.1, p = 0.04$) and those with only one sleep disorder ($t = 2.32, p = 0.023$) had significantly lower NMS scores.

### Individual NMS Domain Assessment

As summarized in Table 5, after controlling for age, PD severity, and dopaminergic therapy, sleep disorders were significant predictors of sleep complaints evaluation (i.e., PDSS) ($\Delta R^2 = 0.13, \Delta F = 4.54, p = 0.006$), mood evaluation ($\Delta R^2 = 0.01, \Delta F = 3.17, p = 0.03$), quality of life evaluation ($\Delta R^2 = 0.13, \Delta F = 5.63, p = 0.002$), fatigue evaluation ($\Delta R^2 = 0.12, \Delta F = 4.29, p = 0.007$), and cognition evaluation ($\Delta R^2 = 0.09, \Delta F = 3.0, p = 0.036$).

### Sleep Complaints

After controlling for age, PD severity, and LDE, only RBD ($\beta = -0.3, p = 0.003$) was a significant predictor of the subjective sleep evaluation, while OSA ($\beta = 0.08, p = 0.42$) and RLS ($\beta = -0.17, p = 0.078$) were not. Sleep disorders alone accounted for 14% of the variance in this measure. Overall this model was significant ($F = 4.85, p < 0.001$) and explained 27% of the variance in the subjective sleep evaluation.
ders significantly improved the models of multiple symptoms. Dopaminergic therapy revealed that number of sleep disorders (0, 1, or ≥ 2 sleep disorders) on the individual NMS domains while controlling for age, PD severity, and dopaminergic therapy accounted for 12% of the variance in this measure. Overall this model was significant (β = 0.23, p = 0.023) were significant predators of fatigue, while OSA (β = 0.05, p = 0.61) was not. Sleep disorders alone accounted for 13% of the variance in this measure. Overall this model was significant (F = 9.02, p < 0.001) and explained 43% of the variance in the quality of life evaluation.

**Fatigue**

Of the sleep disorders, RBD (β = 0.26, p = 0.01) and RLS (β = 0.23, p = 0.023) were significant predators of fatigue, while OSA (β = 0.05, p = 0.61) was not. Sleep disorders alone accounted for 12% of the variance in this measure. Overall this model was significant (F = 4.88, p < 0.001) and explained 27% of the variance in the fatigue evaluation.

**Cognition**

Only OSA (β = -0.28, p = 0.01) was a significant predator of cognition, while RBD (β = -0.11, p = 0.31) and RLS (β = -0.07, p = 0.51) were not. Sleep disorders alone accounted for 9% of the variance in this measure. Overall this model was significant (F = 4.06, p = 0.001) and explained 25% of the variance in the cognition evaluation.

**Multiple Sleep Disorders**

When assessing the impact of having multiple sleep disorders (0, 1, or ≥ 2 sleep disorders) on the on the individual NMS domains while controlling for age, PD severity, and dopaminergic therapy revealed that number of sleep disorders significantly improved the models of multiple symptoms evaluation (ΔR² = 0.06, ΔF = 6.01, p = 0.017), quality of life evaluation (ΔR² = 0.07, ΔF = 7.95, p = 0.006), fatigue evaluation (ΔR² = 0.05, ΔF = 4.92, p = 0.03), and mood evaluation (ΔR² = 0.06, ΔF = 5.31, p = 0.024). In summary, increased number of sleep disorders significantly predicted more NMS symptoms, poorer quality of life, increased fatigue, and more severe mood symptoms (Figure 2).

**DISCUSSION**

This study assessed the relationship between sleep disorders and NMS in PD. Using dimension reduction techniques to derive a single factor score representing overall NMS for each individual, the analyses revealed that sleep disorders...
were independent and significant contributors to the non-motor impairment experienced in PD. Specifically, the data revealed that having a sleep disorder predicted more NMS impairment (i.e., higher scores on the NMS score) with a moderate effect size \( R^2 \) = 0.33) after controlling for age, PD severity, and dopaminergic therapy (LDE). This relationship between sleep disorders and overall NMS score held true when omitting the sleep related measures (i.e., ESS, MFSI-SF, and PDSS) from the derived factor, which indicated that sleep symptoms per se did not bias the finding that having sleep disorders increase overall NMS endorsement by patients with PD (data not shown). The multivariate results revealed that sleep disorders were significant predictors of increased sleep complaints, depressive symptoms, lower quality of life, increased fatigue, and poorer cognition.

Furthermore, these results revealed a relationship between the number of sleep disorders per patient and reports of NMS. More specifically, patients with at least two sleep disorders reported significantly more overall NMS than those having no sleep disorders or only one sleep disorder. Additionally, increased number of sleep disorders predicted higher scores on the individual measures of multiple symptoms, quality of life, fatigue, and mood.

Our results showed that RBD was associated with increased NMS in PD. Such findings align with previous research which has shown that patients with PD with RBD have unique clinical characteristics and experience increased NMS (e.g., more visual hallucinations, falls, more cognitive impairment). It is important to point out that many of these studies report conflicting findings which are likely due to the different methodology employed and different RBD definitions used. Diagnosis of RBD is challenging and includes subjective and objective assessments which are costly and time consuming. Additionally, in many of these studies NMS domains were assessed with a single question, and most studies assessed a derived factor, which indicated that sleep symptoms per se did not bias the finding that having sleep disorders increase overall NMS endorsement by patients with PD (data not shown).

In our study, only two patients met criteria for PLMS. Periodic leg kicks are thought to be more frequent in diseases with impaired dopaminergic transmission, like PD and multi-system atrophy. A previous study in our laboratory concurred with these reports and showed high prevalence in periodic kicks during the night in PD and an association with lower quality of life. However, these studies assessed periodic leg kicks which were independent of arousals. In general, a diagnosis of PLMS is made when leg kicks result in arousals.

Sleep disruption in PD is likely due to a multitude of factors including the neurodegenerative process of the disease itself. PD is marked by dopamine dysfunction and degeneration of the dopaminergic neurons. Dopamine circuitry is also thought to be implicated in several major sleep disorders common in PD such as insomnia, circadian rhythm disruption, and daytime sleepiness. In addition, brain stem deterioration is reported in PD and is also implicated in the REM sleep processes such as muscle atonia during REM. Other factors may also be responsible for disturbed sleep in PD, including the medications used to treat the PD, motor symptoms, pain, nocturia, and other sleep disorders common in this age group. Nonetheless, our results suggest that even when controlling for disease (dopaminergic treatment and PD severity) and age, sleep disorders had a negative impact on NMS in PD.

These findings that sleep disorders are unique predictors of increased NMS and subsequently poorer quality of life is important for considering disease management approaches. Additional studies are now required to determine whether the treatment of sleep disorders in PD may offer significant benefit in terms of overall NMS and quality of life. A recent pilot study that provided behavioral treatment for sleep in a small sample of patients with PD suggested that improving nighttime sleep in these patients improved quality of life both for the patients and their caregivers. While treating sleep disorders will likely not affect PD progression, it has the potential for improving NMS and may potentially reduce overall disability and thereby improve the lives of PD patients and their caregivers.

The major strengths of this study include the systematic and objective assessment of sleep disorders in this sample of patients with PD. The availability of overnight PSG data allowed for reliably diagnosing OSA, RBD, and PLMS in PD. Additionally, this study utilized multiple previously validated measures of NMS and the employed advanced statistics to assess different NMS in a cohesive manner and avoiding multiple comparisons. Nonetheless, this study also had several limitations. Video recordings during PSG were available for less than half of the sample for diagnosing RBD. However, detailed clinical notes
were maintained by the technician and these notes were available for all patients. Additionally, the scorer of EMG activity was not blind to technician’s notes as notes were made on the PSG records. In our study, only one-night PSG recording was conducted and while this more closely resembles clinical findings, single-night recordings may miss RBD occurrences due to high night-to-night variability. However, while we may have underestimated RBD in our sample, our RBD occurrence rate was similar to other studies using similar methodology. In our sample, 28% were using antidepressants, which may result in increased muscle tone during REM sleep. However, EMG score was not significantly different between those taking vs. not taking antidepressants in the entire sample or in any of the RBD groups. Our study was also limited to a subjective assessment of self-reported symptoms (excluding cognition which was evaluated with a single objective measure) and future studies should include objective measures and/or clinical interviews to further support such findings. Also, due to inclusion/exclusion criteria, our sample may not be generalizable to the overall PD population or to patients with more severe PD. Although our models revealed that sleep disorders significantly predicted higher NMS scores and contributed to the variance explained above and beyond age, PD severity, and dopaminergic therapy, this study modeled associations among variables and thus no inferences of causality can be made. Future research will have to assess rather treating sleep disorders in this population will result in decreased non-motor symptomology to better understand this observed association.

In summary, this study showed that in patients with PD, the presence of comorbid sleep disorders predicts more NMS symptoms in general. More specifically, having sleep disorders predicted increased sleep complaints, lower quality of life, increased depressive symptoms, poorer cognition, and more fatigue. Of the sleep disorders assessed in this study, RBD and RLS were indicators of overall increased NMS but OSA was not. The findings of increased NMS in RBD adds further support to a growing body of literature that suggests RBD is related to increased frequency and severity of non-motor impairment and subsequent poorer quality of life. This is the first study to systematically assess the effect of RLS on NMS in PD and further research is needed to corroborate these findings.

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Sleep-related disturbances, including insomnia and excessive daytime sleepiness, are some of the most common complaints of patients with Parkinson disease (PD). As many as 60% to 76% of PD patients experience insomnia.1,2 Nocturnal hypokinesia, nocturnal and early morning dystonia, and impaired bed mobility are thought to be common causes.2,3 In practice, attention often focuses on motor symptoms of PD, and these are probably considered first as possible causes of sleep disturbance. Although non-motor symptoms, such as depressed mood, anxiety, pain, or frequent nocturia tend to receive less clinical consideration, such symptoms could have substantial impact on sleep.4 In particular, depression is the most common psychiatric problem in PD, with an estimated prevalence of 17% to 50%,4,5 depending on the rating scales or structured clinical diagnosis used to identify the problem. Several studies have examined the relationship between depressed mood and sleep disturbance in PD patients.7 The relative contributions, however, of motor and non-motor features to sleep disturbance remains unclear, despite the important impact that sleep disturbance can have on quality of life in patients with PD. Furthermore, the potential value of objective sleep laboratory data, in understanding sleep-related disturbances, including insomnia and excessive daytime sleepiness, are some of the most common complaints of patients with Parkinson disease (PD). As many as 60% to 76% of PD patients experience insomnia.1,2 Nocturnal hypokinesia, nocturnal and early morning dystonia, and impaired bed mobility are thought to be common causes.2,3 In practice, attention often focuses on motor symptoms of PD, and these are probably considered first as possible causes of sleep disturbance. Although non-motor symptoms, such as depressed mood, anxiety, pain, or frequent nocturia tend to receive less clinical consideration, such symptoms could have substantial impact on sleep.4 In particular, depression is the most common psychiatric problem in PD, with an estimated prevalence of 17% to 50%,4,5 depending on the rating scales or structured clinical diagnosis used to identify the problem. Several studies have examined the relationship between depressed mood and sleep disturbance in PD patients.7 The relative contributions, however, of motor and non-motor features to sleep disturbance remains unclear, despite the important impact that sleep disturbance can have on quality of life in patients with PD. Furthermore, the potential value of objective sleep laboratory data, in understanding sleep-related symptoms, fatigue, and autonomic symptoms, are associated with subjective insomnia, whereas fatigue and dopaminergic medication dose are associated with subjective daytime sleepiness. Objective sleep laboratory data provided little insight into complaints of insomnia and sleepiness, though obstructive sleep apnea predicted worsened sleepiness when measured objectively. 

Keywords: Parkinson disease, insomnia, daytime sleepiness, depression, non-motor symptoms

Citation: Chung S; Bohnen NI; Albin RL; Frey KA; Müller MLTM; Chervin RD. Insomnia and sleepiness in Parkinson disease: associations with symptoms and comorbidities. J Clin Sleep Med 2013;9(11):1131-1137.

BRIEF SUMMARY

Current Knowledge/Study Rationale: Sleep disturbance and daytime somnolence are common complaints in patients with Parkinson disease (PD), but the main causes remain unclear. This study was done to explore associations between sleep-related complaints and potential contributors, including both motor and non-motor PD symptoms.

Study Impact: Non-motor features of PD, such as mild depressive symptoms, fatigue, and autonomic symptoms, are associated with subjective insomnia, whereas fatigue and dopaminergic medication dose are associated with subjective daytime sleepiness. In evaluation of PD patients who complain of insomnia or sleepiness, clinicians should explore other non-motor symptoms, in particular, as possible causes or co-morbidities.

complaints in PD, remains unclear. The main objective of this study was to examine associations of both motor and non-motor PD symptoms with reported sleep problems. We hypothesized that non-motor and motor symptoms of PD patients would each show independent association with subjective insomnia or daytime sleepiness. In a subset of patients, we also assessed the extent to which polysomnography and the multiple sleep latency test (MSLT) may help to understand sleep complaints in PD.
Subjects
A total of 128 subjects, including 96 men and 32 women, were recruited from the Movement Disorders Clinics at the University of Michigan and the Veteran Affairs Ann Arbor Health System. Inclusion criteria included PD according to the UK Parkinson Disease Society Brain Bank Research Center clinical diagnostic criteria. Subjects’ PD severity ranged, from modified Hoehn and Yahr stages 1 to 4, and brain imaging showed a typical pattern of nigrostriatal dopaminergic denervation on [11C]dihydrotetrazenazine (DTBZ)-positron emission tomography (PET). Subjects were not selected on the basis of any specific sleep complaints. Among the 128 subjects, 38 (30%) volunteered to undergo nocturnal polysomnography and MSLTs. Some data from subjects who underwent sleep studies have been described previously in a report about [11C]-3-amino-4-(2-dimethylaminomethyl-phenylsulfanyl)benzonitrile (DASB) positron emission tomography (PET) imaging. We recorded information on demographics, motor symptoms, medications, and comorbidities. Of the 128 subjects, 67 (52%) took carbidopa/levodopa, 11 (8%) took dopamine agonist, 42 (33%) took a combination of carbidopa/levodopa and a dopamine agonist, and 8 (6%) subjects did not take any medication. For ≥2 months prior to study entry, no subjects received neuroleptics, psychostimulants, antimuscarinics, or acetylcholinesterase inhibitors. Among the 38 subjects who underwent nocturnal polysomnography, none were taking trazodone, modafinil, St. John’s Wort, or bupropion. None of the subjects who underwent nocturnal polysomnography were taking anti-inflammatories, which could have interfered with tracer binding during [11C]DASB PET imaging required for the parent protocol. During the 2 weeks prior to sleep studies, no subjects received activating or sedating medications, including benzodiazipines and antihistamines. In contrast, 19 (21%) of the 90 subjects who did not have a nocturnal polysomnogram were taking an antidepressant.

Clinical Assessment
All patients were clinically evaluated by a movement disorder neurologist. A family member or caregiver provided additional information. Each subject signed a written informed consent, approved by the University of Michigan Medical School Institutional Review Board (IRBME). Clinical information collected included assessment of disease severity with the Movement Disorder Society-sponsored revision of the Unified Parkinson Disease Rating Scale (MDS-UPDRS). This instrument has 4 sections: Part I - non-motor experiences of daily living, Part II - motor experiences of daily living, Part III - motor examination, and Part IV - motor complications of medication. We included only parts I–III as primary independent variables in statistical analyses. Subjective measures of sleep disturbance and daytime sleepiness were assessed with the well-validated Insomnia Severity Index (ISI) and Epworth Sleepiness Scale (ESS). Secondary exploratory variables included the Montreal Cognitive Assessment, Beck Depression Inventory, trait portion of the State-Trait Anxiety Inventory, Fatigue Severity Scale, Survey of Autonomic Symptoms, and the 39-item Parkinson Disease Questionnaire (as a quality of life rating scale for Parkinson disease patients).

Sleep Evaluation
Polysomnograms included 6 electroencephalography (EEG) channels, 2 electrocorticography (EOG) channels, chin and bilateral anterior tibialis surface electromyelography (EMG), 2 electrocardiography (EKG) leads, nasal and oral airflow (thermocouples), nasal pressure monitoring, thoracic and abdominal excursion (uncalibrated inductance plethysmography), snoring, and finger oximetry, all in accordance with American Academy of Sleep Medicine 2007 recommendations. Scoring was performed according to standard guidelines by a single, experienced registered technologist masked to results of patients’ clinical assessments and measurements. A board-certified sleep specialist (R.D.C.), masked to patients’ clinical data, reviewed scoring and interpreted each sleep study. The apnea-hypopnea index ([AHI] events per hour of sleep), was used to identify absence of significant obstructive sleep apnea (<5, no OSA), mild OSA (5 to <15), moderate OSA (15 to <30), and severe OSA (≥30). Subjects underwent polysomnography after taking their normal schedule of dopamine replacement medications. On the day following polysomnography, MSLTs were performed using only the EEG, chin EMG, EKG, and EOG channels. The test consisted of 5 nap opportunities of 20 min every 2 hours throughout the day, and followed standard guidelines.

Statistical Analysis
Statistical analyses were performed with SPSS Ver. 19.0 for Windows (IBM software). Data are summarized as means ± SD. The level of significance was defined as p < 0.05 in 2-tailed tests for all analyses. We analyzed our data in 2 ways. First, we performed logistic regression analysis with subjective insomnia (ISI) or daytime sleepiness (ESS) as the dependent variables and parts I–III of MDS-UPDRS as the primary independent variables to test our hypothesis that non-motor and motor symptoms of PD patients show independent association with subjective insomnia and daytime sleepiness. Second, we followed a 2-step analysis approach to examine the influence of secondary measures. We performed a data reduction step by exploring which variables correlated with the subjective sleep measures using the nonparametric Spearman correlation coefficient rho. Significant variables were then entered into stepwise logistic regression models with subjective insomnia (ISI) or sleepiness (ESS) as the dependent variables.

RESULTS
The mean age of the 128 participants was 65.7 ± 7.6 years old (range: 50-84); 96 (75%) were men; and the mean duration of illness was 5.9 ± 4.3 years (range: 0.5-20). The mean Hoehn and Yahr stage was 2.4 ± 0.5 (range: 1-4). Mean score on the Montreal Cognitive Assessment was 25.9 ± 2.5, and 70 (61%) of the subjects showed normal cognitive function as defined by a score ≥ 26. The mean levodopa equivalent dosage of medications taken for PD was 689.2 ± 521.7 mg/day. Male and female patients showed no significant difference in age, duration of illness, Hoehn and Yahr stages, cognitive function, subjective insomnia severity, subjective daytime sleepiness, depressed
mood, anxiety, fatigue, and Parkinson disease-related quality of life, though scores on the Survey of Autonomic Symptoms did differ (male 4.2 ± 4.1, female 6.1 ± 4.6, p = 0.03). The distributions of ISI and ESS scores are presented in Figure 1.

Associations of Insomnia and Subjective Sleepiness with Motor and Non-Motor PD Symptoms

Multivariate logistic regression models showed that part I of MDS-UPDRS (non-motor symptoms) rather than parts II (motor symptoms) or III (motor examination findings) mainly contributed to subjective insomnia assessed using the ISI (Table 1). However, none of the MDS-UPDRS parts were significantly associated with subjective daytime sleepiness assessed using the ESS.

Associations of Insomnia and Subjective Sleepiness with Specific PD Features and Comorbidities

For the 128 subjects, insomnia severity as reflected by ISI score correlated significantly with age, levodopa equivalent dose, Beck Depression Inventory, Trait Anxiety Score, Fatigue Severity Scale, Survey of Autonomic Symptoms, 39-item Parkinson Disease Questionnaire, and parts I and II subcategories of the MDS-UPDRS (Table 2). Daytime sleepiness as assessed by the ESS was significantly correlated with Hoehn and Yahr stage, duration of illness, levodopa equivalent dose, Beck Depression Inventory, trait score of State Trait Anxiety Inventory, Fatigue Severity Scale, Survey of Autonomic Symptoms, 39-item Parkinson Disease Questionnaire, and each of the 3 assessed components of the MDS-UPDRS. Subjects who were taking dopamine agonists alone (n = 11) and those who took levodopa alone (n = 67) showed no significant differences in ESS scores. The ISI and ESS scores were moderately correlated with each other.

A multivariable stepwise logistic regression model showed that Beck Depression Inventory, Survey of Autonomic Symptoms, Fatigue Severity Scale, and age each contributed statistically in an independent manner to insomnia (Table 3). The levodopa equivalent dose and Fatigue Severity Scale showed the closest independent associations with sleepiness.

Insomnia, Subjective Sleepiness, and Sleep Laboratory Findings

The 38 participants who volunteered to have polysomnography and MSLTs had a mean age of 64.3 ± 6.2 years; mean disease duration was 4.9 ± 3.6 years. Mean Hoehn and Yahr stage was 2.3 ± 0.4, and 31 (81.6%) of these patients were male. There were no significant differences in these clinical characteristics or the rating scale scores (ISI, ESS, Montreal Cognitive Assessment, Beck Depression Inventory, State Trait Anxiety Inventory, Fatigue Severity Scale, Survey of Autonomic Symptoms, 39-item Parkinson Disease Questionnaire, and part I–III of

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**Table 1**—Results of multivariate logistic regression analysis (n = 128)

<table>
<thead>
<tr>
<th>Outcome variables</th>
<th>Overall model F</th>
<th>Explanatory variables*</th>
<th>B</th>
<th>S.E.</th>
<th>Odds ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insomnia Severity Index ≥ 8</td>
<td>F = 21.46</td>
<td>MDS-UPDRS part I#</td>
<td>0.95</td>
<td>0.26</td>
<td>2.58</td>
<td>1.54-4.33</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MDS-UPDRS part II</td>
<td>0.10</td>
<td>0.26</td>
<td>1.10</td>
<td>0.66-1.85</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MDS-UPDRS part III</td>
<td>-0.20</td>
<td>0.23</td>
<td>0.82</td>
<td>0.52-1.29</td>
</tr>
</tbody>
</table>

| Epworth Sleepiness Scale ≥ 10 | F = 4.93 | MDS-UPDRS part I# | 0.21 | 0.22 | 1.24 | 0.80-1.90 |
| | | MDS-UPDRS part II | 0.10 | 0.24 | 1.10 | 0.68-1.77 |
| | | MDS-UPDRS part III | 0.20 | 0.21 | 1.22 | 0.81-1.86 |

S.E., standard error; CI, confidence interval; MDS-UPDRS, Movement Disorder Society version of the Unified Parkinson Disease Rating Scale. *Items that ask directly about sleep problems (1.7) and daytime sleepiness (1.8) were excluded. *Explanatory variables were normalized ((x-mean)/SD), so that the associated odds ratio reflects the effect of 1 SD increase in the explanatory variable.

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**Figure 1**—Frequency distribution of insomnia severity index (A) and Epworth sleepiness scale (B) scores in patients with Parkinson disease

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Table 4 shows the results of nocturnal polysomnography for the 38 subjects. Subjects with insomnia and without it showed no significant difference in several polysomnographic variables (Table 4). Similarly, subjects with and without subjective daytime sleepiness showed no significant difference on polysomnography. Objective measure of daytime sleepiness (mean sleep latency ≤ 8 min on MSLT) was significantly associated with only short nocturnal sleep latency among polysomnographic variables.

Among the 38 subjects who had polysomnography, sleep latency correlated with autonomic symptoms as assessed by the Survey of Autonomic Symptoms and part I of the MDS-UPDRS (Table 2). Sleep efficiency correlated with Survey of Autonomic Symptoms. Sleep efficiency was not correlated with PLM index or PLM arousal index. In addition, the mean sleep latency on the MSLT was not significantly correlated with demographic variables of subjects and various rating scales scores.

The AHI was not significantly correlated with rating scale scores or demographic variables except for body mass index (BMI, rho = 0.50, p = 0.002). Obstructive sleep apnea (AHI ≥ 5 events per hour of sleep) was found in 28 (74%) of the subjects. The AHI suggested no OSA in 10 subjects, mild OSA in 5, moderate OSA in 12, and severe OSA in 11. No significant difference emerged in total sleep time, sleep latency, and sleep efficiency among these 4 groups. However, the AHI correlated with objective daytime sleepiness, as reflected by shorter mean sleep latency on the MSLT (rho = -0.47, p = 0.003). Urinary problems (on the MDS-UPDRS part-I) and OSA (AHI, RDI, or mean O₂ saturation) showed no significant correlation.

**DISCUSSION**

This study of 128 patients with PD demonstrates that non-motor symptoms, including fatigue, depressed mood, and autonomic problems, rather than motor symptoms, are most closely

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**Table 2**—Correlation of subjective sleep questionnaire (n = 128) and objective polysomnographic findings (n = 38) with age and measures of Parkinson disease or related symptom severity

<table>
<thead>
<tr>
<th>Sleep questionnaires (n = 128)</th>
<th>Polysomnography (n = 38)</th>
<th>MSLT (n = 38)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISI (rho)</td>
<td>ESS (rho)</td>
<td>Sleep latency (rho)</td>
</tr>
<tr>
<td>Age</td>
<td>-0.25**</td>
<td>-0.05</td>
</tr>
<tr>
<td>Hoehn &amp; Yahr stage</td>
<td>0.04</td>
<td>0.28**</td>
</tr>
<tr>
<td>Duration of illness</td>
<td>0.16</td>
<td>0.23**</td>
</tr>
<tr>
<td>Levodopa equivalent dose of PD medications</td>
<td>0.20*</td>
<td>0.32**</td>
</tr>
<tr>
<td>Insomnia Severity Index</td>
<td>-</td>
<td>0.37**</td>
</tr>
<tr>
<td>Epworth Sleepiness Scale</td>
<td>0.37**</td>
<td>-</td>
</tr>
<tr>
<td>Montreal Cognitive Assessment</td>
<td>0.06</td>
<td>-0.03</td>
</tr>
<tr>
<td>Beck Depression Inventory</td>
<td>0.49**</td>
<td>0.31**</td>
</tr>
<tr>
<td>State-Trait Anxiety Inventory (trait score)</td>
<td>0.28**</td>
<td>0.19*</td>
</tr>
<tr>
<td>Fatigue Severity Scale</td>
<td>0.45**</td>
<td>0.37**</td>
</tr>
<tr>
<td>Survey of Autonomic Symptoms</td>
<td>0.39**</td>
<td>0.22*</td>
</tr>
<tr>
<td>Parkinson Disease Questionnaire-39</td>
<td>0.41**</td>
<td>0.39**</td>
</tr>
<tr>
<td>MDS-UPDRS Part I*</td>
<td>0.40**</td>
<td>0.29**</td>
</tr>
<tr>
<td>MDS-UPDRS Part II</td>
<td>0.22*</td>
<td>0.29**</td>
</tr>
<tr>
<td>MDS-UPDRS Part III</td>
<td>0.1</td>
<td>0.26**</td>
</tr>
</tbody>
</table>

ISI, insomnia severity index; ESS, Epworth sleepiness scale; MSLT, multiple sleep latency test; PD, Parkinson disease; MDS-UPDRS, Movement Disorder Society version of the Unified Parkinson Disease Rating Scale. *p < 0.05; **p < 0.01 for Spearman correlation coefficient. #Items that ask directly about sleep problems (1.7) and daytime sleepiness (1.8) were excluded.

Table 3—Results of multivariate stepwise logistic regression of insomnia symptoms or sleepiness on specific Parkinson disease features and comorbidities (n = 128)

<table>
<thead>
<tr>
<th>Outcome variables</th>
<th>Overall model F</th>
<th>Explanatory variables*</th>
<th>B</th>
<th>S.E.</th>
<th>Odds ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insomnia Severity Index ≥ 8</td>
<td>F = 45.66</td>
<td>Beck Depression Inventory</td>
<td>0.58</td>
<td>0.29</td>
<td>1.79</td>
<td>1.01-3.19</td>
</tr>
<tr>
<td>Age</td>
<td>-0.49</td>
<td>0.23</td>
<td>0.61</td>
<td>0.39-0.96</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epworth Sleepiness Scale ≥ 10</td>
<td>F = 17.09</td>
<td>Levodopa equivalent dosage of medication</td>
<td>0.55</td>
<td>0.24</td>
<td>1.74</td>
<td>1.08-2.80</td>
</tr>
<tr>
<td>Fatigue Severity Scale</td>
<td>0.13</td>
<td>0.06</td>
<td>1.14</td>
<td>1.02-2.12</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

S.E., Standard error; CI, confidence interval. *Explanatory variables were normalized ((x-mean)/SD), so that the associated odds ratio reflects the effect of 1 SD increase in the explanatory variable.
Insomnia and Sleepiness in Parkinson Disease

Table 4—Results of nocturnal polysomnography among subjects with and without significant insomnia or daytime sleepiness (n = 38)

<table>
<thead>
<tr>
<th></th>
<th>Mean ± SD (n = 38)</th>
<th>Range</th>
<th>ISI ≥ 8 (n = 22)</th>
<th>ISI &lt; 8* (n = 16)</th>
<th>ESS ≥ 10 (n = 16)</th>
<th>ESS &lt; 10* (n = 22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total sleep time (min)</td>
<td>359.3 ± 80.9</td>
<td>72.0-478.0</td>
<td>352.2 ± 79.2</td>
<td>347.7 ± 85.6</td>
<td>372.8 ± 58.4</td>
<td>334.0 ± 91.8</td>
</tr>
<tr>
<td>Sleep latency (min)</td>
<td>17.9 ± 17.8</td>
<td>1.5-80.0</td>
<td>16.8 ± 16.8</td>
<td>19.4 ± 19.8</td>
<td>15.5 ± 20.1</td>
<td>19.6 ± 16.2</td>
</tr>
<tr>
<td>Wake after sleep onset (min)</td>
<td>103.8 ± 48.4</td>
<td>30.0-405.5</td>
<td>114.8 ± 78.3</td>
<td>107.4 ± 54.1</td>
<td>101.5 ± 49.3</td>
<td>119.1 ± 79.8</td>
</tr>
<tr>
<td>Sleep efficiency (%)</td>
<td>75.0 ± 10.7</td>
<td>15.0-93.4</td>
<td>72.8 ± 16.1</td>
<td>74.2 ± 12.0</td>
<td>76.0 ± 11.1</td>
<td>71.5 ± 16.4</td>
</tr>
</tbody>
</table>

Sleep stages

- N1 (%) 22.1 ± 19.7 1.8-81.6 21.4 ± 17.8 24.8 ± 23.0 25.2 ± 21.3 21.1 ± 19.2
- N2 (%) 55.6 ± 15.9 17.2-87.8 54.6 ± 14.7 55.3 ± 18.7 55.8 ± 17.7 54.3 ± 15.5
- N3 (%) 6.7 ± 9.2 0.0-44.8 7.7 ± 7.8 6.2 ± 11.5 5.3 ± 5.6 8.4 ± 11.3
- REM (%) 15.6 ± 7.9 0.0-29.4 16.3 ± 7.9 13.7 ± 8.6 13.8 ± 8.6 16.2 ± 7.9

Apnea-hypopnea index (h) 21.7 ± 20.6 0.4-88.5 20.1 ± 16.0 24.3 ± 25.5 22.4 ± 18.2 21.5 ± 22.1

Mean O₂ saturation (%) 93.9 ± 1.7 90.0-97.0 93.7 ± 1.9 94.0 ± 1.5 93.9 ± 2.0 93.7 ± 1.6

Periodic limb movements index (events/h) 20.9 ± 31.5 0.0-98.5 22.4 ± 32.2 17.6 ± 30.7 9.6 ± 22.2 28.3 ± 34.9

Periodic limb movements related arousal index (events/h) 1.69 ± 3.4 0.0-16.3 2.1 ± 4.1 1.1 ± 2.0 0.7 ± 1.6 2.4 ± 4.1

Mean sleep latency in MSLTs (min) 8.4 ± 5.1 1.5-18.6 8.3 ± 5.4 8.6 ± 4.9 7.1 ± 5.0 9.4 ± 5.1

MSLTs, multiple sleep latency tests; ISI, insomnia severity index; ESS, Epworth sleepiness scale; SD standard deviation. *No differences between low and high ISI and ESS groups reached significance (T-test p-value all > 0.05).

and independently associated with reported insomnia. Younger age was also correlated with insomnia. Levodopa equivalent dose and fatigue severity showed the strongest independent associations with subjective daytime sleepiness. Surprisingly, we also found in a subsample of 38 subjects that gold-standard, sleep laboratory-based nocturnal polysomnography and MSLTs did not discriminate PD patients with subjective insomnia or daytime sleepiness from PD patients who did not report these problems.

In general, depressed mood is one of the leading causes of insomnia, and insomnia is one of core symptoms of depression. Delayed sleep onset, disrupted sleep continuity, decreased slow wave sleep, and alterations in REM sleep are often reported in patients diagnosed as having depression. Insomnia is reported as a risk factor for the progression of depression, suicidal ideation, and recurrence of depression. Depressed mood in PD may be associated with dopaminergic dysfunction, as dopamine agonist medication can improve depressive symptoms, and depressed mood can occur after discontinuation of these agents in PD patients. However, depressed mood in PD patients is usually under-recognized, perhaps because relevant symptoms may be confused with other conditions. Depressive symptoms in PD patients should be managed as effectively as possible, only in part because this may enhance control of sleep disturbances and improve quality of life.

Autonomic dysfunction can influence the severity of insomnia in PD patients. Autonomic dysfunction such as urinary problems and gastrointestinal symptoms could give rise to sleep complaints. Nocturia, particularly in elderly people, is often overlooked as a cause of sleep disturbance. In the current study, the ISI score was significantly correlated with urinary problems and constipation (individual items within part I of the MDS-UPDRS, data not shown). Some authors have speculated that the anatomical proximity and concomitant degeneration of sleep and autonomic regulatory centers in the brain stem may explain this correlation.

We also found that the ISI score shows an independent, inverse association with age. In contrast, outside the context of PD, the prevalence of insomnia increases with age. However, previous studies have suggested that the severity of insomnia is less affected by age than by anxiety, depression, fatigue, dysfunctional belief toward sleep, and personality. Parkinson symptom severity could conceivably contribute to the inverse association we identified, but in fact age correlated directly with Hoehn and Yahr stages (rho = 0.32, p < 0.0001), part II (rho = 0.29, p = 0.001) and part III (rho = 0.21, p = 0.02) of the MDS-UPDRS. Among individual symptom items of MDS-UPDRS, there was no item except sleep problems (rho = -0.27, p = 0.004) that improved with age (data not shown).

We observed that fatigue is associated with subjective insomnia in PD patients. Fatigue is a common condition in chronically ill PD patients, and the reported prevalence of fatigue in PD ranges from 33% to ~58%, depending on its definition. Fatigue itself can decrease physical activity during the daytime in PD patients, and therefore could significantly influence the frequency and severity of insomnia. In addition, fatigue is usually associated with depressed mood, although fatigue is a symptom that should be distinguished from depressed mood. However, our cross-sectional analysis does not allow us to exclude the likely possibility that for some patients, poor nocturnal sleep augments fatigue, or that a third variable fosters both fatigue and insomnia.

In our data, fatigue was also associated with daytime sleepiness. In PD patients, daytime sleepiness and fatigue are often considered to arise from sleep disturbance, disease progression, depressive symptoms, or the presence of other comorbid illness. In particular, medications have been suspected to contribute to insomnia or daytime sleepiness in PD patients.
as dopaminergic agents can have daytime sleepiness or sudden-onset sleep attacks as an adverse effect. We observed that high doses of medications were associated with daytime sleepiness in accordance with other previous studies.32,33 Although daytime sleepiness followed by nocturnal sleep disturbance has a large impact on quality of life in PD, control of medication-related daytime sleepiness may not be simple because high doses of antiparkinsonian medication may be necessary to reduce severe motor symptoms.

Among our 38 PD patients who underwent nocturnal polysomnography, longer sleep latency was associated with increased autonomic symptoms and the part I subcategory of the UPDRS. We previously found, among a larger set of PD subjects (including those who had polysomnography in the current study), that the total UPDRS score correlated with sleep efficiency rather than sleep latency,10 and we believe that the difference in the sample as well as the current focus on separate UPDRS parts is likely to explain this difference. Decreased sleep efficiency was associated only with increased autonomic symptoms. In contrast, previous investigators found something that we could not confirm with objective measures, namely that subjective sleep efficiency was associated only with increased autonomic symptoms and the part I subcategory of polysomnography, longer sleep latency was associated with increased autonomic symptoms, and daytime MSLTs did not reflect subjective daytime sleepiness as measured by the ESS. Previous studies also have documented little or no correlation between subjective sleepiness and MSLT results,36 even among PD patients.37

Obstructive sleep apnea was frequently observed in our PD patients. A previous study found OSA in 43% of 49 PD patients and implicated OSA as a cause of daytime sleepiness and tiredness.38 The OSA may arise in part from upper airway muscle dysfunction caused by nocturnal akinesia or dyskinesia. However, a recent report suggested that the frequency of OSA in PD is not different from that seen in the general population.19 Our previous study also showed that neither serotonergic nor dopaminergic neuron degeneration play a key role in OSA among our PD patients.20 In the current study, the variables that predicted the apnea-hypopnea index in PD patients were BMI and objective daytime sleepiness, rather than motor or non-motor symptoms of PD. Our findings support the lack of direct association between OSA and disease status or progression in PD patients.

Several limitations in this study should be considered. First, objective sleep measures including nocturnal polysomnography and daytime MSLTs were obtained for only 30% of the subjects, though those who volunteered for these studies did not differ from remaining subjects on key PD or sleep measures. Second, Hoehn and Yahr scores of the subjects in this study suggested early to moderate PD, when motor symptoms may not yet have made a large contribution to insomnia or daytime sleepiness. Third, our data on depression and ability to discern its association with sleep problems may have been limited by use of antidepressants among 19 (21%) of the 90 subjects who did not have sleep studies. However, Beck Depression Inventory scores were higher (not lower) among patients who took anti-depressants than among those who did not (p = 0.03, data not shown). Fourth, the MDS-UPDRS part II does not capture all motor issues related to sleep. For example, nocturnal and early morning dystonia are not addressed, though limitations to turning in bed and getting out of bed are addressed. Perhaps most importantly, our study was cross-sectional, and results cannot be used to confirm cause-and-effect relationships.

We did observe that non-motor features such as mild depressive symptoms, fatigue, and autonomic symptoms are associated with insomnia ratings among PD patients, whereas fatigue and dopaminergic medication dose are associated with subjective sleepiness. Our findings suggest that clinicians should pay particular attention to uncontrolled non-motor features as potential causes or results of insomnia or daytime sleepiness among patients diagnosed with Parkinson disease. Subjective rating scales may be useful to assess routinely for insomnia and daytime sleepiness in PD patients, and laboratory-based sleep studies may be informative when evaluation for OSA and associated, objective daytime sleepiness is desired.

REFERENCES

Insomnia and Sleepiness in Parkinson Disease

The authors thank C. Minderovic for expert assistance with execution of this protocol.

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Submitted for publication April, 2013
Submitted in final revised form June, 2013
Accepted for publication July, 2013
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DISCLOSURE STATEMENT

This was not an industry supported study. Dr. Chung is supported by University of Ulsan College of Medicine and Asan Medical Center in South Korea. Dr. Bohnen has received funding from the NIH, Department of Veterans Affairs, and the Michael J. Fox Foundation. Dr. Aldrich receives research support from the NIH, Department of Veterans Affairs, and the Cure Huntington Disease Initiative. He served on DSMBs for the HORIZON and QE3 trials. He receives reimbursement for medical-legal consulting. Dr. Frey has received support from the NIH and General Electric (GE Healthcare). He is a consultant to AVID Radiopharmaceuticals (a subsidiary of Eli Lilly & Co), Bayer-Scherling pharmaceuticals and MIM Software. He holds common stock in Bristol-Myers Squibb, General Electric, Johnson & Johnson and Novo Nordisk. Dr. Müller has received support from the NIH and Department of Veterans Affairs. Dr. Chervin has received support from the NIH, the University of Michigan Health System, Respironics, and Fisher Paykel. He receives honoraria from the American Academy of Sleep Medicine and UpToDate.
Is there a First Night Effect on Sleep Bruxism? A Sleep Laboratory Study

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Study Objectives: Sleep bruxism (SB) is reported to vary in frequency over time. The aim of this study was to assess the first night effect on SB.

Methods: A retrospective polysomnographic (PSG) analysis was performed of data from a sample of SB patients (12 females, 4 males; age range: 17-39 years) recorded in a sleep laboratory over 2 consecutive nights. Sleep parameters and jaw muscle activity variables (i.e., rhythmic masticatory muscle activity [RMMA]) for SB were quantified and compared between the 2 nights. Subjects were classified into groups according to severity of RMMA frequency, such as low frequency (2-4 episodes/h and/or < 25 bursts/h) and moderate-high frequency (≥ 4 episodes/h and ≥ 25 bursts/h).

Results: Overall, no first night effects were found for most sleep variables. However, total sleep time, sleep efficiency, and stage transitions showed significant time and group interactions (repeated measures ANOVAs, p ≤ 0.05). The RMMA episode index did not differ between the 2 nights, whereas the second night showed significantly higher burst index, bruxism time index, and mean burst duration (repeated measure ANOVAs, p ≤ 0.05). Five patients of 8 in the low frequency group were classified into the moderate-high frequency group on the second night, whereas only one patient in the moderate-high frequency group moved to the low frequency group.

Conclusions: The results showed no overall first night effect on severity of RMMA frequency in young and healthy patients with SB. In clinical practice, one-night sleep recording may be sufficient for moderate-high frequency SB patients. However, low RMMA frequency in the first night could be confirmed by a second night based on the patient’s medical and dental history.

Keywords: Sleep bruxism, rhythmic masticatory muscle activity, first night effect, polysomnography, sleep laboratory

Citation: Hasegawa Y; Lavigne G; Rompré P; Kato T; Urade M; Huynh N. Is there a first night effect on sleep bruxism? A sleep laboratory study. J Clin Sleep Med 2013;9(11):1139-1145.

BRIEF SUMMARY
Current Knowledge/Study Rationale: The first night effects on sleep parameters and the frequency of rhythmic masticatory muscle activity (RMMA) were assessed based on two-night polysomnographic recordings in sleep bruxism (SB) patients.

Study Impact: Overall, no first night effects were found for sleep variables and RMMA frequency. However, since RMMA frequency might be underestimated in some patients for the first night, low frequency of RMMA can be confirmed by a second night based on the patient’s medical and dental history in clinical practice.

---

Sleep bruxism (SB), a sleep-related movement disorder, is characterized by repetitive jaw muscle activity associated with tooth grinding or clenching of teeth.1-4 SB can be associated with orofacial pain, masticatory muscular hypertrophy, temporomandibular joint disorders, headaches, sleep apnea, and insomnia.2,3 SB is subjectively reported by patients who are aware of jaw clenching upon awakening or who have been told by their parents or sleep partner that they grind their teeth. SB diagnosis is based on subjective reports and clinical signs and symptoms (e.g., tooth wear), and its current presence can be confirmed by electromyographic (EMG) recordings of the masseter and/or temporalis muscles.1 The SB-related EMG jaw muscle activity recorded are rhythmic masticatory muscle activity (RMMA) episodes and bursts, which are scored as sleep traces and quantified in number.2 RMMA can be observed in 60% of controls, but shows a higher frequency in bruxers (≥ 2 episodes/h).2 However, a previous study showed that SB patients may be categorized into heterogeneous frequency groups in terms of RMMA episode index, such as low frequency (2-4 episodes/h and/or < 25 bursts/h) and moderate-high frequency (≥ 4 episodes/h and ≥ 25 bursts/h) groups.3 In support of this categorization, the two groups differed in terms of certain clinical features (history of more frequent grinding reports and less jaw pain in the moderate-high than low frequency group).4 To our knowledge, with the exception of a few studies using home ambulatory recordings with one to three EMG channels on masticatory muscles, the influence of the first night effect on jaw muscle activity related to SB has not been assessed.5,7 The first night effect in the sleep laboratory is reported to affect many recorded sleep variables, and thus, in clinical research settings, polysomnography (PSG) recordings obtained during the first night of a study are generally excluded from the analysis to avoid the first night effect. The main characteristics of the first night effect are short total sleep time and REM sleep,
lower sleep efficiency, longer REM sleep latency, and decreased slow wave sleep.6,9

Jaw muscle activity related to SB can be recorded in a sleep laboratory or at home using ambulatory recording systems. Home sleep recordings offer a stronger likelihood of capturing environmental influences on jaw muscles activity related to SB.10,11 However, in the absence of video control to distinguish RMMA from other orofacial activity (e.g., coughing, swallowing, or somniloquy), RMMA is overestimated by about 20%.12 In addition to these limitations of sleep recording, SB related EMG recording can be very challenging due to night-to-night variability. RMMA frequency has been reported to fluctuate over time for both sleep laboratory and ambulatory home sleep recordings.6,13 In a sleep laboratory setting, night-to-night variability, from second night recordings and above, was reported to be 25.3% for RMMA episodes per hour and 30.4% for burst number per hour.13 The variability of RMMA episodes over time is critical in studies assessing the benefit of management approaches, such as cognitive behavioral therapies, medication, or oral appliances or devices known to alter jaw muscle activity.14-17

The aim of this study was to assess the first night effect on categorization according to severity of RMMA frequency and in relation to sleep macro-structure, while controlling for first night to second night variability. We also assessed the first night effect on psychosocial variables (e.g., anxiety, stress, fatigue) in relation to consecutive nights at the sleep laboratory.

MATERIALS AND METHODS

Study Population and Screening

In this retrospective study, data were drawn from 16 SB patients (12 females; mean age ± standard error = 25.2 ± 1.5 years) who underwent ≥ 2 consecutive overnight PSG recordings in a sleep laboratory at the Hôpital du Sacré-Cœur de Montréal. Initial inclusion criteria were age from 18 to 45 years with a reported history of teeth grinding ≥ 3 times per week. Subjects were then screened for orofacial and general health problems using: (1) questionnaires addressing general health, SB, SB and pain, headaches, daytime sleepiness, and sleep quality; (2) a clinical examination by a dentist to detect SB signs, including a physical assessment of the jaw, neck, and mouth; and (3) a panoramic dental X-ray to assess dental health and the temporomandibular joint. The sleep study was performed to confirm the SB diagnosis according to the Research Diagnostic Criteria for SB12 and to rule out additional sleep disorders (i.e., periodic limb movement syndrome, obstructive sleep apnea). All patients were nonsmokers and were not taking any medication. They were instructed to refrain from consuming caffeine and alcohol on the day before sleep recording. The sleep recording protocol was approved by the hospital’s ethics committee, and all study participants read and signed a written consent form.

Data Recording

Polysomnographic recordings (≥ 7 h) were performed for each participant on 2 consecutive nights. Surface electrodes included 2 electroencephalograms (EEG: C3A2 and O2A1), bilateral electrooculograms (EOGs), an electrocardiogram (ECG), and 7 EMGs on the chin/suprahyoid, bilateral masseter, temporalis, and anterior tibialis muscles. All masseter and temporalis EMG channels were used to score RMMA. A detailed description of the method is provided elsewhere.18 To assess respiratory function and exclude sleep breathing disorders, nasal airflow was measured with a thermistor sensor (Thermocouple; Protech, Woodinville, WA, USA). Respiratory efforts were assessed with thoracic and abdominal effort belts. Oximetry was continuously monitored with a finger pulse oximeter (Datex-Ohmeda; Louisville, CO). All signals were recorded using acquisition and analysis software (Harmonie Software; Stellate Systems; Montreal, QC, Canada). Simultaneous audio-video recordings were made for visual scoring of sleep motor activities, other body movements, and oropharyngeal sounds.

An independent sleep technologist scored sleep stages based on polygraphic traces according to the standard method developed by Rechtschaffen and Kales,19 using 20-sec instead of 30-sec epochs. Cortical arousals (microarousals) were scored for both nights (Night 1 and Night 2) according to the American Academy of Sleep Medicine criteria.20 PSG sleep data were first scored by a trained sleep technician working at the sleep research center. EMG muscle activity was scored by another trained research technician and calibrated by one of the investigators (GL). Masseter and temporal EMG bursts with durations > 0.25 sec were selected for sleep motor activity scoring, which was conducted according to published criteria.5,18 The presence of RMMA is recognized by contraction patterns for both the masseter and temporal muscles: phasic (≥ 3 rhythmic EMG bursts lasting from 0.25 to 2.0 sec) and tonic (sustained EMG burst lasting > 2.0 sec) bursts.21-23 RMMA bursts are grouped into RMMA episodes (with ≥ 3-s interval between RMMA episodes): phasic (≥ 3 phasic bursts), tonic (≥ 1 sustained EMG tonic burst), and mixed episode (phasic and tonic bursts).21-23

Orofacial activity was defined as all types of motor activity (activity of the bilateral masseter or temporalis muscles), not including the above-mentioned RMMA characteristics.23 Audio and video recordings were carried out simultaneously to distinguish RMMA from nonspecific orofacial activities, and to document any body movements that co-occurred with orofacial movements.23 Based on the scoring, the following variables were calculated: episode index (number of RMMA episodes per hour of sleep), burst index (number of RMMA bursts per hour of sleep), orofacial index (number of orofacial episodes per hour of sleep), and bruxism time index. These indices include all types of bursts (phasic and tonic) for calculated bursts index and bruxism time index.23 The calculated episode index includes all types of episodes (phasic, tonic, and mixed), even though only 0.5% of episodes were tonic in this study.

Subjects were categorized into 2 groups according to the frequency of RMMA episodes, represented by the calculated RMMA episode index, in order to determine night-to-night variability.5,18 The low frequency group included patients who showed a low frequency of RMMA (2-4 episode index and/or < 25 burst index) in ≥ 1 of the 2 consecutive nights. The moderate-high frequency group included patients who showed a moderate to high frequency of RMMA (≥ 4 episode index and ≥ 25 burst index) in the 2 consecutive nights.

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Comparing the low frequency and moderate-high frequency time and stage transitions, \( p = 0.07 \) for sleep efficiency). When compared to Night 1 (paired \( t \)-test, \( p < 0.05 \) for total sleep group showed higher values for these three variables in Night 25.6 years (17-37) for the moderate-high frequency group. 26.1 years (17-39, min-max) for the low frequency group and consisted of 8 subjects each (6 female; 2 male). Mean age was

### Statistical Analysis

The population sample size was estimated using a preliminary analysis of the data, with a conventional \( \alpha \) of 0.05 and a power level of 0.80 to avoid incorrect inferences in the results interpretation.

The normality of the data distribution was verified using the Shapiro–Wilk test. When data were non-normally distributed, square root or logarithmic transformations were performed. To compare data between Night 1 and Night 2 or between the low and moderate-high frequency groups, repeated measures analysis of variance (ANOVA) were performed with time (Night 1, Night 2) as a repeated measure and group (low frequency and moderate-high frequency) as the between-group factor. Paired \( t \)-tests or two-sample \( t \)-tests were performed when the interaction between time and group was significant. Correlations between Night 1 and Night 2 were assessed as either Pearson correlation coefficient (normal distributions) or Spearman correlation coefficient (non-normal distributions). Changes in self-reported psychosocial variables (anxiety, stress, fatigue) were assessed using McNemar test. Night-to-night variability was estimated with the coefficient of variation. A \( p \) value \( \leq 0.05 \) was considered statistically significant. No \( p \) value adjustment for multiple tests was done, since the tests were in accordance with the aim of the study. All statistical analyses were performed using a commercially available software package (IBM SPSS Statistics, Version 20.0.0 for Windows; SPSS, Chicago, IL).

### RESULTS

Both the low frequency and moderate-high frequency groups consisted of 8 subjects each (6 female; 2 male). Mean age was 26.1 years (17-39, min-max) for the low frequency group and 25.6 years (17-37) for the moderate-high frequency group.

### Sleep Variables

Table 1 presents the sleep characteristics and the RMMA distribution over Night 1 and Night 2. Total sleep time, sleep efficiency, and stage transitions showed significant time and group interactions (repeated measures ANOVA, \( p \leq 0.05 \)). For these variables, no significant differences were found between Night 1 and Night 2 in the low frequency group (paired \( t \)-test, \( p \geq 0.32 \)). On the other hand, the moderate-high frequency group showed higher values for these three variables in Night 2 compared to Night 1 (paired \( t \)-test, \( p < 0.05 \) for total sleep time and stage transitions, \( p = 0.07 \) for sleep efficiency). When comparing the low frequency and moderate-high frequency groups for both nights, no significant differences were found for these 3 variables (two-sample \( t \)-test), with the exception of

### Questionnaires

Participants answered 5-point questions concerning anxiety, stress, fatigue, and nervousness at 4 different times in relation to sleep recordings: in the evening just before PSG recording and in the morning just after PSG recording for both nights. Items of the evening and morning questionnaires were as follows: “At this moment, do you feel anxious? (Anxiety); stressed? (Stress); nervous? (Nervousness); fatigue? (Fatigue); depressed?” (Depression). The results of the 5-point questions were classified as 1 = “No” or 2-5 = “Yes.”

### Rhythmic Masticatory Muscle Activity

For all jaw muscle activity variables, no significant time and group interactions were found (repeated measure ANOVA; Table 1). For the RMMA burst index, bruxism time index, mean burst duration, and orofacial index, a significant difference was observed between Night 1 and Night 2 (repeated measure ANOVA, \( p \leq 0.05 \)). For the low frequency and moderate-high frequency groups, the burst index was 1.6 and 1.4 times lower and EMG activity was 2.2 and 1.4 times shorter (e.g., bruxism time index), respectively, in Night 1 compared to Night 2 (\( p \leq 0.05 \), Table 1 and Figure 1). The orofacial index for Night 1 was 1.5 and 1.6 times lower than that for Night 2 for the low and moderate-high frequency groups (Table 1, \( p = 0.03 \)). The other variables showed no significant differences between Night 1 and Night 2.

For the 2 groups, the RMMA episode index increased from Night 1 to Night 2 in 10 of 16 subjects (6 subjects in the low frequency group, 4 in the moderate-high frequency group). The RMMA burst index increased from Night 1 to Night 2 in 12 of 16 subjects (6 subjects in the low frequency group, 6 in the moderate-high frequency group). In other words, 63% of subjects showed an increase in the RMMA episode index in Night 2, and 75% of subjects showed an increase in the RMMA burst index in Night 2 (Figure 1). When the severity of RMMA frequency was assessed, 5 low frequency SB patients in Night 1 fell into the moderate-high frequency group in Night 2 based on the RMMA episode index, whereas using the RMMA burst index, 3 low frequency SB patients in Night 1 fell into the moderate-high frequency group in Night 2. However, only one patient with moderate-high frequency RMMA group in Night 1 changed to the low frequency group in Night 2 based on the RMMA episode index. Overall, 6 of 16 patients (37.5%) changed category from Night 1 to Night 2 based on the RMMA episode index.

The correlation coefficients for the RMMA episode index were -0.01 and 0.74 for the low frequency and moderate-high frequency group, respectively. The correlation coefficients for the RMMA burst index were 0.19 and 0.43 for the 2 groups, respectively. The correlation coefficients for the bruxism time index were 0.43 and 0.72 in the low frequency and moderate-high frequency groups, respectively. Thus, for these variables, the low frequency group showed weak correlation between Night 1 and Night 2, whereas the moderate-high frequency group showed strong correlation.

### Questionnaires

Fourteen of the 16 subjects answered the 5-point questions concerning anxiety, stress, fatigue, and nervousness (Table 3). No significant differences were observed between Night 1 and
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In this study, we assessed the first night effect on the frequency of RMMA and jaw muscle activity in a sleep laboratory. The results showed no first night effect on the sleep of young healthy subjects with SB. The RMMA episode index did not differ between the first and second nights, although the burst variables (e.g., burst duration) significantly changed between the two nights. However, RMMA showed first night effects in less than 40% of a low frequency group, where some patients had a low frequency of RMMA in Night 1 which increased to a moderate-high frequency in Night 2.

**First Night Effect of Sleep Variables**

In PSG studies, the first night effect is common: it lasts from one night up to several nights before normalizing. The main characteristics include decreased total sleep time, lower sleep efficiency, more intermittent wake time, decrease in slow wave sleep and REM, and longer REM latency. The origin of the first night effect is multifactorial and can include the following factors: (1) discomfort caused by electrodes, (2) restricted movement due to gauges and cables, (3) potential psychological consequences of being under scrutiny, and (4) changes in the environment. Therefore, in sleep mechanism studies and randomized controlled trials, the first night is usually used for adaptation to sleep laboratory conditions: data drawn from the first night are used mainly to exclude sleep disorders. On the other hand, several characteristics related to the variability in sleep parameters of the first night effect (e.g., sleep efficiency, total sleep time, microarousal) were not observed in some

**DISCUSSION**

**Table 1—Sleep and jaw muscle activity variables**

<table>
<thead>
<tr>
<th></th>
<th>Low</th>
<th>Moderate-high</th>
<th>ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Night 1</td>
<td>Night 2</td>
<td>Interaction</td>
</tr>
<tr>
<td>Total sleep time (min)</td>
<td>450.7 (424-484)</td>
<td>452.7 (386-502.7)</td>
<td>0.01</td>
</tr>
<tr>
<td>Sleep onset latency (min)</td>
<td>13.3 (7.3-40.7)</td>
<td>18.5 (4-39)</td>
<td>0.34</td>
</tr>
<tr>
<td>Number of awakenings</td>
<td>27.4 ± 5.8</td>
<td>28.0 ± 2.5</td>
<td>0.71</td>
</tr>
<tr>
<td>Microarousal index (no./h)</td>
<td>10.3 ± 2.2</td>
<td>11.7 ± 1.9</td>
<td>0.62</td>
</tr>
<tr>
<td>Sleep efficiency (%)</td>
<td>96.3 (92.6-98.8)</td>
<td>95.5 (91-97.7)</td>
<td>0.03</td>
</tr>
<tr>
<td>Stage 1 (%)</td>
<td>4.9 (2.7-8.1)</td>
<td>4.8 (4.2-9.1)</td>
<td>0.60</td>
</tr>
<tr>
<td>Stage 2 (%)</td>
<td>51.8 ± 2.6</td>
<td>48.3 ± 3.1</td>
<td>0.28</td>
</tr>
<tr>
<td>Stage 3 (%)</td>
<td>21.8 ± 2.5</td>
<td>22.8 ± 3.1</td>
<td>0.70</td>
</tr>
<tr>
<td>Stage REM (%)</td>
<td>21.1 ± 1.0</td>
<td>23.5 ± 1.7</td>
<td>0.28</td>
</tr>
<tr>
<td>Stage transitions (no.)</td>
<td>212.5 (158-267)</td>
<td>187.0 (171-338)</td>
<td>0.05</td>
</tr>
<tr>
<td>Episode index (no./h)</td>
<td>3.0 (1.6-4.5)</td>
<td>4.2 (1.1-9)</td>
<td>0.46</td>
</tr>
<tr>
<td>Burst index (no./h)</td>
<td>15.0 (6.6-26)</td>
<td>24.3 (5.2-52.8)</td>
<td>0.57</td>
</tr>
<tr>
<td>Bruxism time index</td>
<td>0.19 ± 0.04</td>
<td>0.42 ± 0.11</td>
<td>0.92</td>
</tr>
<tr>
<td>Episode associated with wake (no.)</td>
<td>2.5 ± 0.7</td>
<td>4.1 ± 1.4</td>
<td>0.33</td>
</tr>
<tr>
<td>Mean episode duration (sec)</td>
<td>4.9 ± 0.6</td>
<td>5.3 ± 0.6</td>
<td>0.94</td>
</tr>
<tr>
<td>Mean burst duration (sec)</td>
<td>0.4 ± 0.03</td>
<td>0.5 ± 0.03</td>
<td>0.91</td>
</tr>
<tr>
<td>Orofacial index (no./h)</td>
<td>8.0 ± 1.4</td>
<td>12.5 ± 3.3</td>
<td>0.61</td>
</tr>
</tbody>
</table>

Mean ± standard error for variables with normal distribution, median (min-max) for variables with non-normal distribution. *P*-value of the interaction between groups and time with repeated measures ANOVA. **P**-value between Night 1 and Night 2 with repeated measures ANOVA. ***P**-value between the low frequency group and moderate-high frequency groups with repeated measures ANOVA. Bruxism time index, percentage of total sleep time spent bruxing. Low, low frequency group; Moderate-high, moderate-high frequency group.

**Table 2—Correlation coefficients for Night 1 and Night 2**

<table>
<thead>
<tr>
<th></th>
<th>Low</th>
<th>Moderate-high</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R</td>
<td>P-value</td>
<td>R</td>
</tr>
<tr>
<td>Total sleep time (min)</td>
<td>0.76</td>
<td>0.03</td>
<td>0.67</td>
</tr>
<tr>
<td>Sleep onset latency (min)</td>
<td>0.83</td>
<td>0.01</td>
<td>0.67</td>
</tr>
<tr>
<td>Number of awakenings</td>
<td>0.89</td>
<td>0.003</td>
<td>0.22</td>
</tr>
<tr>
<td>Microarousal index (no./h)</td>
<td>0.78</td>
<td>0.02</td>
<td>0.80</td>
</tr>
<tr>
<td>Sleep efficiency (%)</td>
<td>0.71</td>
<td>0.05</td>
<td>0.86</td>
</tr>
<tr>
<td>Stage 1 (%)</td>
<td>0.50</td>
<td>0.21</td>
<td>0.88</td>
</tr>
<tr>
<td>Stage 2 (%)</td>
<td>0.94</td>
<td>0.001</td>
<td>0.91</td>
</tr>
<tr>
<td>Stage 3/4 (%)</td>
<td>0.95</td>
<td>&lt;0.001</td>
<td>0.90</td>
</tr>
<tr>
<td>Stage REM (%)</td>
<td>0.72</td>
<td>0.04</td>
<td>0.92</td>
</tr>
<tr>
<td>Stage transitions (no.)</td>
<td>0.29</td>
<td>0.49</td>
<td>0.86</td>
</tr>
<tr>
<td>Episode index (no./h)</td>
<td>-0.01</td>
<td>0.98</td>
<td>0.74</td>
</tr>
<tr>
<td>Burst index (no./h)</td>
<td>0.19</td>
<td>0.65</td>
<td>0.43</td>
</tr>
<tr>
<td>Bruxism time indexa</td>
<td>0.43</td>
<td>0.29</td>
<td>0.72</td>
</tr>
<tr>
<td>Episode associated to wake (no.)</td>
<td>0.02</td>
<td>0.96</td>
<td>0.46</td>
</tr>
<tr>
<td>Mean episode duration (sec)</td>
<td>0.69</td>
<td>0.06</td>
<td>0.81</td>
</tr>
<tr>
<td>Mean burst duration (sec)</td>
<td>0.12</td>
<td>0.81</td>
<td>0.14</td>
</tr>
<tr>
<td>Orofacial Index (no./h)</td>
<td>0.56</td>
<td>0.15</td>
<td>0.92</td>
</tr>
</tbody>
</table>

R, correlation coefficient for either Pearson (normal distributions) or Spearman (non-normal distributions); P-value, from the correlation coefficient; Low, low frequency group; Moderate-high, moderate-high frequency group. Bruxism time index, percentage of total sleep time spent bruxing.

Night 2. However, the p-value for fatigue approached significance (p = 0.07), suggesting that these subjects felt slightly more fatigued in Night 1 than in Night 2.
previous investigations\textsuperscript{30,31} of healthy young adults. In this study in healthy young subjects, no first night effect on sleep variables was observed, with the exception of slightly longer stage 2 sleep. The results of this study are similar to those of previous studies. Edinger et al.\textsuperscript{32} and Suetugi et al.\textsuperscript{33} demonstrated longer stage 2 sleep in Night 1 than in Night 2 in healthy young adults. Similar to our results, some studies\textsuperscript{30,31} have demonstrated no change in sleep variables from Night 1 to Night 2. It is possible that the first night effect could be diminished by better quality recording environment and improved comfort for subjects.

Interestingly, only the moderate-high frequency group showed shorter sleep and more stage transitions, in addition to a trend towards lower sleep efficiency. A bruxer has higher stress sensitivity (and panic symptoms) than a non-bruxer.\textsuperscript{34} Therefore, patients with moderate-high RMMA frequency might have greater difficulty adapting to the sleep laboratory environment.

**First Night Effect of RMMA**

The results showed no overall first night effect on severity of RMMA frequency in young and healthy patients with SB. Although the RMMA episode index did not change overall, a higher RMMA burst index, burst duration, and bruxism time index on the second night was observed. In other words, only the burst modality within each episode differed between Night 1 and Night 2. Thus, no effects were observed on the severity of RMMA frequency (i.e., low and moderate-high frequency). The following hypotheses might explain the low impact on the classification according to the severity of RMMA frequency. First, the number of stage transitions was significantly higher in Night 2 than in Night 1 for the moderate-high frequency group. The majority of RMMA episodes occur during NREM sleep,\textsuperscript{14,18,34} most often during the unstable sleep time immediately before transition into REM sleep.\textsuperscript{34} This explains the slight increase in the RMMA burst index during Night 2 despite the lack of difference in the RMMA episode index. Second, the results showed a substantial night-to-night fluctuation in these variables. According to previous studies, the coefficient of variation for night-to-night variation in the RMMA episode index was about 25\% over 37 nights in 9 SB patients with moderate-high RMMA frequency,\textsuperscript{13} 22\% over 30 nights in a subject who underwent sleep laboratory PSG recordings,\textsuperscript{35} and 37\% over 4 nights per subject (n = 6 with SB) using ambulatory PSG recording.\textsuperscript{6} Compared with these data, the night-to-night variation in the RMMA episode index in this study was slightly higher (at 30\%) using sleep laboratory PSG recordings.

Furthermore, our results suggest that if night-to-night variability is taken into account, the first night effect on RMMA occurrence is weak. For the second night, 63\% of subjects showed an increased RMMA episode index, and 75\% showed

**Table 3—Self-reports of psychosocial variables between Night 1 and Night 2**

<table>
<thead>
<tr>
<th></th>
<th>Evening (%)</th>
<th>Morning (%)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Night 1</td>
<td>Night 2</td>
<td>P-value \textsuperscript{a}</td>
<td>Night 1</td>
</tr>
<tr>
<td>Anxiety</td>
<td>7.1</td>
<td>21.4</td>
<td>1.00</td>
<td>7.1</td>
</tr>
<tr>
<td>Stress</td>
<td>21.4</td>
<td>21.4</td>
<td>1.00</td>
<td>7.1</td>
</tr>
<tr>
<td>Nervousness</td>
<td>14.3</td>
<td>28.6</td>
<td>0.63</td>
<td>7.1</td>
</tr>
<tr>
<td>Fatigue</td>
<td>42.9</td>
<td>85.7</td>
<td>0.07</td>
<td>57.1</td>
</tr>
<tr>
<td>Depression</td>
<td>0</td>
<td>7.1</td>
<td>–</td>
<td>0</td>
</tr>
</tbody>
</table>

The percentage of subjects in the sample who answered yes to these psychosocial variables (N = 14). \textsuperscript{a}Comparison between evening of Night 1 and evening of Night 2 using McNemar test. \textsuperscript{b}Comparison between morning of Night 1 and morning of Night 2 using McNemar test.
an increased RMMA burst index. Under natural conditions, 50% of subjects would be expected to show an increase and 50% a decrease due to random variability. However, in our study, the percentage of subjects who showed an increase in the second night is slightly above what would be expected for random night-to-night variability.

The results of the questionnaires indicated no first night effects on anxiety, stress, fatigue, or nervousness, either before or after sleep. Additionally, no group differences were found in the results on any question items. Consequently, we could not conclude an association between psychological factors and bruxism, in accordance with previous studies. This might be explained by the absence of differences for the sleep variables and the fact that all subjects were young and healthy.

Sleep Bruxism Recordings

SB is a disorder related to sleep instability and arousal, and is primarily associated with RMMA. A clinical diagnosis of SB is usually based on reports of grinding sounds by sleep partners, tooth attrition, tooth mobility, tooth fracture, and damage to tooth restorations and prostheses. Because the RMMA incidence readily changes over time, it is difficult to diagnose current SB activity. Clinically useful diagnostic criteria for SB have been established by the American Academy of Sleep Medicine. Various assessment tools are now used for clinical and research purposes. Methods are also available for assessing SB, including the use of oral appliances and muscle activity recorders. However, these methods are limited in their clinical application due to insufficient standardization of numerical criteria for jaw muscle activity and the lack of evidence-based justifications such as reliability, accuracy, and reproducibility. In 1996, Lavigne et al. proposed PSG cutoff criteria for SB diagnosis to be used in combination with an overall patient assessment. The discriminative power of these criteria was recently reconfirmed. However, the fluctuating nature of RMMA will inevitably be reflected in fluctuations in PSG recording results. According to these criteria, despite the inter-individual variability of first night effects on the RMMA occurrence, an SB diagnosis in patients with moderate-high RMMA frequency, determined in the first night (e.g., ≥ 4 episode index and ≥ 25 burst index) remains stable, as suggested by the previous study. However, the severity of SB activity frequency would be underestimated on the first night when patients show low RMMA frequency.

Study Limitations

Several limitations of this study should be considered when interpreting the results. First, the sample size is small, and the subjects were young and healthy. Second, in order to focus on first night effects on SB, SB patients with no orodontal or sleep problems were investigated. However, SB can occur concomitantly with other common sleep disorders such as obstructive sleep apnea and periodic leg movements in sleep. Unlike SB, these sleep disorders are more prevalent in the elderly than in young adults. Third, we did not consider sleep position, which can influence RMMA frequency as well as respiratory functions. Finally, it remains to be clarified how RMMA frequency is influenced by other proposed risk factors for SB (e.g., caffeine, alcohol). The potential influence of the above-mentioned factors on the first night effects of SB would therefore constitute a clinically relevant direction for future studies.

In conclusion, in young and healthy patients with SB, first night effects were absent for sleep macrostructure and on severity of RMMA frequency. In clinical practice, one-night sleep recording may be sufficient for SB patients with moderate-high frequency of RMMA. However, low RMMA frequency in the first night could be confirmed by a second night based on the patient’s medical and dental history.

REFERENCES

Is there a First Night Effect on Sleep Bruxism?

Sleep problems are very common during childhood and constitute a source for major concern to parents and professionals.1-3 These problems tend to be persistent4-6 and associated with daytime behavior problems and parental distress.2,3,7,8 Seeking professional help is usually based on parental perception that their child has a sleep problem.9 In most clinical settings, the child’s sleep assessment is solely based on parental reports.1,10 Parental reports may rely on realistic perceptions of the child’s sleep characteristics; however, their accuracy may be compromised by situational and subjective factors.1,11,11a Previous studies have suggested that parental perceptions and reports on their child’s sleep may be influenced by factors such as unrealistic expectations and interpretations, lack of developmental knowledge, socioeconomic status, demographic factors, and broader cultural norms, beliefs, and attitudes.9,12-15 A major limitation is that parents become aware of many events during the night (e.g., night wakings) only if the child signals and requires attention11,11a; therefore, their knowledge may be significantly influenced by the child’s tendency to signal. Recently, Gregory et al.1 concluded that assessing sleep using exclusively the sleep items of the Child Behavior Checklist, which is one of the most popular parental reports on children’s behavior problems, is insufficient for assessing sleep and should be combined with other sleep assessment methods.

The limitations of parental reports on children’s sleep becomes more prominent in preschool children, who develop increased capacity for independent falling asleep and resuming sleep following night wakings.2,10 In comparison to infants and toddlers, preschool children are, therefore, less likely to signal and require help, and their parents are less likely to be aware of these events during the nights. However, this picture may be different in preschool children with special clinical presentation who are more likely to signal. For instance, preschool children are very vulnerable to nighttime fears and nightmares.17,20 Furthermore, it has been recently demonstrated that preschool children with nighttime fears are more likely than controls to wake up at night and signal and require parental assistance to resume sleep.21

The purpose of the present study was to assess the accuracy of parental reports on a brief questionnaire assessing sleep patterns in preschool children and to examine to what extent this accuracy is related to the presence of a clinical sleep-related issue (nighttime fears). The comparison of reported sleep was made against actigraphy-based sleep measures. To the best of
our knowledge, this is the first study assessing the correspondence between objective and subjective sleep assessment tools comparing clinical and healthy control groups of preschool children. We hypothesized that the reports of parents of children with nighttime fears would be more accurate than reports of parents of control children because children with nighttime fears require increased parental involvement during the night.

**METHODS**

**Participants**

Children and their parents were recruited from the local kindergarten system by informing them about a service for children with nighttime fears (NTF) and inviting parents of children with no fears to volunteer as well. The clinical group of children with severe NTF consisted of 109 preschool children (64 boys and 45 girls between the ages 4 and 6 years, mean age 58.91 months; SD 8.32). Inclusion criteria for the clinical group were: (a) NTF ≥ 2 months; (b) NTF exerted significant adverse impact on the child and family; (c) NTF requiring parental intervention ≥ 2 nights per week to comfort the child. NTF was determined solely by parent reports during the screening and intake interviews.²¹

The control group included 30 healthy children from the same age group who did not meet criteria for NTF (16 boys and 14 girls, mean age 58.93 months, SD 7.62 months). There were no group differences on any of the demographic variables.²¹ Exclusion criteria for both samples were: (a) major health or neurological-developmental problems; (b) concurrent psychiatric treatment; (c) concurrent psychotherapy or similar interventions. Additional information on the participants is available in earlier publications.²¹,²²

**Measures**

**Brief Child Sleep Questionnaire (BCSQ)**

The BCSQ provides information on children’s sleep habits and problems. The questionnaire’s items were derived from the Brief Infant Sleep Questionnaire (BISQ)²³ and from the Sleep Habits Questionnaire (SHQ).²⁴ The BISQ was developed and validated as a brief infant sleep screening tool for clinical and research purposes.²³ Measures of internal consistency (Cronbach α) for the SHQ scales range between 0.72 and 0.82.²⁴ The parents were instructed to refer to their child’s sleep during the past week. The items assessed sleep time, total sleep duration during the night, number of night wakings, and total time awake during the night.

**Actigraphy**

Actigraphy is based on a small device that resembles a wristwatch that can be worn by the child for a substantial period of time and monitor sleep-wake patterns in the child’s natural sleep environment.²⁵-²⁷ The parents were instructed to attach the device (Mini Motionlogger, Ambulatory Monitoring Inc.) to their child’s non-dominant wrist for a period of one week, during the evening before bedtime and to remove it in the morning after rise time. The actigraph collected data in 1-minute epochs. Sleep measures were derived from the raw data using the validated Sadeh algorithm.²⁸ Because of compliance problems and technical issues, actigraphy data were available for ≥ 4 nights in 88% percent of the children. For the rest of the sample, actigraphy data were available in 4.5%, 3%, and 4.5% for 1, 2, or 3 nights, respectively.

Actigraphic measures included: (1) sleep onset time; (2) sleep period—total sleep period from sleep onset to morning rise time; (3) number of night wakings (lasting ≥ 5 min); (4) wake time after sleep onset (WASO)—total time of wakefulness during the night.

**Family Background Information Questionnaire**

This questionnaire includes 25 questions covering demographic and developmental data. This questionnaire has been extensively used in previous studies.¹⁰,²¹,²⁴

**Procedures**

The study was approved by the departmental ethical committee and the Chief Scientist of the Israeli Ministry of Education. After signing the informed consent, parents completed the questionnaires. Parents were interviewed about nighttime fears. Parents were instructed to attach the actigraph to children’s non-dominant wrist every evening before bedtime for a period of one week.

**Data Analysis**

Data analysis included the following components: (a) between-groups comparison of the actigraphy versus reported sleep discrepancies; (b) within-group correlations between actigraphy and reported sleep measures and comparison of the correlations between the groups using Fisher r to z transformations; and (c) discriminant analysis to assess the ability of actigraphic and reported sleep measures in predicting the clinical status (clinical versus control group) of the children. Because not all measures met normal distribution criteria, we used nonparametric methods, including Spearman correlations, univariate sign test for paired comparisons, and Wilcoxon rank sum test.³⁰

**RESULTS**

Statistically significant and strong correlations were found between actigraphic and reported sleep schedule measures (sleep period and sleep onset time) in both groups (Table 1). The correlation for sleep period was significantly higher in the control group. In both groups, significant strong correlations between actigraphic and reported sleep measures were found for sleep onset time and sleep period. In both groups the correlations for night wakings and WASO were low and insignificant.

In considering the discrepancies between actigraphic and reported sleep measures (Table 2), it was clear that parents in both groups underestimated sleep onset time and overestimated sleep period. In the control group, parents also significantly underestimated the number of night wakings and WASO. With the exception of WASO, the discrepancies in the control group were significantly larger in the control group than the clinical group.

To assess whether parental nighttime fear-management strategies (e.g., cosleeping vs. limited presence near their child) affected the correspondence between actigraphy and reported...
sleep in the clinical sample, a new variable was composed based on a method used in a previous study.33 Children were divided into 2 groups: cosleeping (i.e., children who, upon waking at night, fell asleep again in their parents’ room and stayed there either throughout the night or for a limited time) and limited presence (i.e., children who, upon waking at night, fell asleep again with limited parental presence near their own bed). However, the results revealed that the fear-management strategies had no effect on the correspondence between actigraphy and reported sleep.

Discriminant analysis was conducted separately for each group to examine how well equivalent reported and actigraphic sleep measures predicted group classification. Actigraphic sleep measures explained 11.6% of the variability and provided 60.8% correct group classifications. The reported sleep measures explained 31.8% of the variability and provided 81.2% correct group classifications.

**DISCUSSION**

To the best of our knowledge, this is the first study assessing the correspondence of sleep measures between actigraphy and parental sleep questionnaire, comparing a clinical group of preschool children with severe nighttime fears to healthy controls. The results of our study suggest that: (a) there are general discrepancies between reported and actigraphic sleep measures; and (b) the presence of a clinical sleep-related problem may have significant impact on the correspondence between reported and objective measures of sleep.

With regard to the sleep schedule measures, correlations between actigraphic and reported measures were relatively high and significant (range: 0.54-0.89). However, significant discrepancies existed between actigraphic and reported sleep measures in both groups. For instance, actigraphy estimated sleep onset time to be, on average, 50 or 75 minutes later than reported in the clinical and control groups, respectively. The discrepancies between actigraphic and reported sleep measures were significantly higher in the control group, suggesting that parents of children with nighttime fears are more accurate because of their higher involvement with the child around bedtime and during the night.33

When sleep quality measures are considered, poor correlations between actigraphic and reported measures were found for the number of night wakings and WASO in both groups.

<table>
<thead>
<tr>
<th>Measure</th>
<th>Clinical</th>
<th>Control</th>
<th>Fisher’s r to z comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep onset time</td>
<td>0.56**</td>
<td>0.76**</td>
<td>1.6</td>
</tr>
<tr>
<td>Sleep period</td>
<td>0.54**</td>
<td>0.85**</td>
<td>3.6*</td>
</tr>
<tr>
<td>Night wakings</td>
<td>0.15</td>
<td>0.13</td>
<td>0.1</td>
</tr>
<tr>
<td>WASO</td>
<td>-0.02</td>
<td>-0.11</td>
<td>0.3</td>
</tr>
</tbody>
</table>

*p < 0.005, **p < 0.0001.

Table 1—Spearman correlations between actigraphic and reported (BCSQ) sleep measures in each group and Z score for the comparison of correlations between groups using Fisher’s r to z transformation

When sleep quality measures are considered, poor correlations between actigraphic and reported measures were found for the number of night wakings and WASO in both groups.

### Table 2—Differences between actigraphic and reported sleep measures within each group and comparison of the discrepancies between groups

<table>
<thead>
<tr>
<th>Measure</th>
<th>Clinical</th>
<th>Control</th>
<th>Wilcoxon Rank Sum Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep onset time</td>
<td>41.87***</td>
<td>73.38***</td>
<td>2.89**</td>
</tr>
<tr>
<td>Sleep period</td>
<td>-13.25*</td>
<td>-33.20***</td>
<td>-2.42*</td>
</tr>
<tr>
<td>Night wakings</td>
<td>0.20</td>
<td>1.33***</td>
<td>3.58***</td>
</tr>
<tr>
<td>WASO</td>
<td>39.25***</td>
<td>33.40***</td>
<td>-0.54</td>
</tr>
</tbody>
</table>

The significance levels within each group indicate which discrepancy (actigraphy versus reports) within each group is statistically significant (univariate sign test for paired comparisons). The Wilcoxon rank sum test was used to assess group differences in these discrepancies. *p < 0.01, **p < 0.005, ***p < 0.0005.

These findings further support the hypothesis that at this age group, parents have very limited knowledge about their children’s sleep disruptions and time spent in wakefulness during the night.10,11,12,13 However, it should be noted that the correlation between actigraphic and reported number of night wakings was statistically significant only in the clinical group, and the discrepancies were significantly smaller for this measure in the clinical group, suggesting that higher involvement required by the parents of children with nighttime fears leads to more accurate reporting about night wakings in this group.

Our results are in line with previous studies demonstrating the discrepancies between sleep measures obtained using different sleep assessment methods among clinical populations. Previous studies have revealed discrepancies in sleep measures based on actigraphy versus parental reports. For example a previous study assessed the quantity and quality of sleep in children with autism, developmental delay without autism, and typically developing children using actigraphy and parental reports.33 Across all subjects, parent diaries and actigraphy data mean values differed. Parental reports underreported sleep onset latency times and wakefulness after sleep onset compared to actigraphy. Reports on sleep start times, morning rise time, and the number and duration of daytime naps were more similar to the objective measures. Another study compared sleep behaviors of children with autism spectrum disorders with sleep behaviors of typically developing children using the Children’s Sleep Habits Questionnaire (CSHQ) and actigraphy.34 According to parental reports 62.5% of children with autism, 76.2% of children with PDD-NOS, and 58.3% of children with Asperger disorder had sleep problems. However, 75%, 52.4%, 75% of the children, respectively, had disturbed sleep according to actigraphic data.

Additional studies revealed discrepancies on various sleep measures comparing actigraphy and PSG. For example, a large-scale study compared total sleep time derived from actigraphy and PSG in adolescents with and without sleep-disturbed breathing.35 The results revealed that overall, actigraphy underestimated sleep time in comparison to PSG. Another study compared actigraphy and PSG in children with intellectual deficits and motor handicaps, sleep-disordered children without motor handicaps, and healthy controls.36 In healthy children
without sleep disorders, there was good correspondence in sleep time assessment; however, in the sleep disturbed and the handicapped children, significant discrepancies existed between measures derived from PSG and actigraphy. The discriminant analysis revealed that the reported sleep measures were better predictors of group classification (clinical versus control) in comparison to the equivalent actigraphic measures. This is not surprising considering the fact that parents decide to seek clinical help on the basis of their own perceptions regarding their child’s sleep, regardless of how biased these perceptions may be.  

The results of our study highlight the limitations of studying sleep in young children with exclusive reliance on parental reports. Parental knowledge about sleep quality is very limited, and the accuracy of this knowledge is significantly influenced by the clinical context. In other words: the differences between the actual sleep quality of clinical versus control children may not be as large as manifested by parental reports. The parents of children with nighttime fears are much more likely to be involved with their child during the night (e.g., in different forms of cosleeping), and are therefore more likely to report more accurately on sleep-related events. Our findings suggest that conclusions based on parental reports on children’s sleep can be biased or misleading. However, parental reports are very informative in providing valuable information on behavioral consequences of sleep-wake patterns and the presentation of clinically relevant manifestations such as nighttime fears and their management. Actigraphy can play a substantial complementary role in providing a more objective picture that is not affected by the clinical context and perceptual biases. Therefore, it is recommended that both methods be used as complementary sources in the evaluation of sleep in clinical and research settings.

REFERENCES


ACKNOWLEDGMENT

The authors are thankful to Orit Arbel for coordinating and managing the study and to the participating families.

SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication February, 2013
Submitted in final revised form May, 2013
Accepted for publication June, 2013
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DISCLOSURE STATEMENT

This was not an industry supported study. The authors have indicated no financial conflicts of interest. The research was supported by the Israel Science Foundation (Grant # 1047/08 to Avi Sadeh).
Adequate sleep is an important aspect of healthy development. Evidence for this conclusion comes from a large body of research documenting associations between inadequate or disrupted sleep and decrements in cognitive functioning, school adjustment, emotional regulation, and behaviors during the preschool and school-age years. Persistent early sleep disturbances also forecast the later development of psychopathology and substance use. Understanding of factors that promote and/or contribute to inadequate or disrupted sleep patterns early in life therefore has implications for both research and clinical practice.

Bedtime resistance, nighttime fears, and middle of the night awakenings are common in preschoolers, affecting up to 35% of typically developing children. Although a range of child-level variables including neurodevelopmental and temperamental factors contribute to sleep-based individual differences, research has similarly established the influence of parenting behaviors as significant determinants of children’s sleep patterns and behaviors. For example, one particularly important aspect of parenting is the establishment of and adherence to a consistent and appropriate bedtime. A regular bedtime, which helps facilitate transition from wakefulness to sleep, is independently associated with better sleep and adjustment in children. In preschool-aged children, later and irregular bedtimes are associated with longer periods required to initiate sleep, less overall sleep, and poorer sleep quality. Conversely, consistent bedtime routines have been...
linked with better sleep and daytime behaviors including fewer tantrums.  

Along with regular bedtimes and presleep routines, a range of other parenting practices and parent-child interactions likely serve to encourage or interfere with a child’s capacity for sleep regulation. Surprisingly little research has focused on these relationships during the preschool years (i.e., 3-5 years). This empirical gap is particularly remarkable in light of normative developmental changes that occur during this period. As children transition from a crib to a bed, give up daytime naps, and learn to dress and care for themselves, parental involvement in sleep routines declines. Consistent with these changes, negative relationships between certain nighttime parenting behaviors and the quality and duration of child sleep have been reported. For instance, parental presence at sleep onset or after a nighttime awakenings is associated with greater sleep-related problems in young children. \(^\text{10,14}\)

The preschool years may therefore be a critical period for understanding the influence of specific parenting behaviors on children’s sleep. 

Importantly, the decisions that parents make with regard to their children’s sleep reflect not only individual differences but also ethnically/culturally based beliefs and traditions. For example, whereas White preschool-aged children in the U.S. most commonly sleep in their own beds, a majority of Black and Hispanic children sleep with their parents. \(^\text{15}\) Black children also give up daytime naps at later ages than do White children. \(^\text{26}\) Such differences are similarly evident with regard to sleep schedules and routines. Among a large U.S. sample, Hale and colleagues\(^\text{13}\) found that Black and Hispanic families were significantly less likely to provide young children with regular bedtimes and bedtime routines even after accounting for a range of other relevant factors. Milan and colleagues\(^\text{15}\) also found significant racial/ethnic differences in specific presleep activities (e.g., White parents commonly read to their children at bedtime, while Black parents more often include bathing in bedtime routines). Although the precise nature of these differences is not well understood, there is a clear need to consider the role of culture as part of scale development related to children’s sleep.

Several brief validated questionnaires for assessing children’s sleep-wake patterns have emerged in recent years. \(^\text{21}\) Most measures screen for a range of potential sleep problems and disorders (e.g., insomnia, sleep disordered breathing, parasomnias) by assessing the occurrence/frequency of these problems. Measures for evaluating parenting behaviors and interactions surrounding sleep are comparatively lacking. Such assessment differs from sleep-wake assessment but is no less important to the construct of sleep since it provides necessary understanding of factors that may give rise to and/or exacerbate sleep problems.\(^\text{21}\) Indeed, the effectiveness of behavioral interventions may hinge upon such information. At least one validated questionnaire designed to assess parenting behaviors in relation to infants’ sleep is available (e.g., the Parental Interactive Bedtime Behavior Scale),\(^\text{22}\) but no such measure exists for use in preschool-aged children.

The primary goals of the present study were to determine the factor structure of a new instrument for assessing sleep-related parent behaviors and interactions among preschool-aged children—the Parent-Child Sleep Interactions Scale (PSIS)—and to determine the instrument’s psychometric properties. Thus, using exploratory factor analysis, we examined relationships between PSIS scores and child sleep problems based on a parent-report measure and a structured clinical interview. Associations between PSIS scores and parent-reported sleep problems during the first year of life also were explored. In addition, based on established relationships between nighttime sleep and daytime behavior problems,\(^\text{1,4}\) associations with internalizing and externalizing behaviors were investigated. Finally, we examined differences in PSIS scores based on race/ethnicity.

**METHODS**

**Participants**

The parents of 209 preschool-aged children (ages 3 to 5 years; \(M = 3.79\) years, \(SD = 0.78\); 47.4% female) comprised the current sample. Families were recruited from the local community in 2 diverse metropolitan areas: Washington, DC, and Houston, TX. Families from the Washington, DC, area (\(n = 155; M = 3.75\) years, \(SD = 0.76\); 51.6% female) were recruited for a study on neuroendocrine function and risk for depression. Potential families were identified using advertisements/flyers sent to local schools, daycares, and health care providers. A proportion of flyers specifically targeted parents with a history of depression. Families with a child between 3 and 5 years of age who lived with an English-speaking biological parent, and who did not have significant medical conditions or developmental disabilities were eligible for the study. Participation included 2 laboratory visits that included observational assessments of child emotionality and behavior and parent-child interactions, and child and parent clinical assessments. The mean ages of mothers and fathers were 34.87 years (\(SD = 6.31\)) and 37.19 years (\(SD = 6.84\)), respectively. Participating families were White (41.9%), Black (31.0%), Hispanic (12.3%), Asian (1.9%), multiracial (9.0%), or other race/ethnicity (12.3%). Most children lived with 2 parents (72.9%) and had at least one parent with a 4-year college degree (69.7%).

Families in the Houston, TX, area (\(n = 54; M = 3.94\) years, \(SD = 0.83\); 35.2% female) were recruited for a study examining daytime and nighttime behavior in preschool-aged children using community flyers and advertisements. Families with a child between 3 and 5 years of age were invited to complete an online anonymous survey. None of the children had significant medical conditions or developmental disabilities. The mean ages of mothers and fathers were 34.10 years (\(SD = 5.71\)) and 36.48 years (\(SD = 6.36\)), respectively. Participating families were White (68.5%), Black (7.4%), Hispanic (14.8%), Asian (1.9%), multiracial (5.6%), or other race/ethnicity (1.9%). Like the Washington, DC, sample, most children lived with both biological parents (74.1%) and had at least one parent with a 4-year college degree (82.4%). Comparisons between the 2 subsamples did not reveal any significant site differences in child age, child gender, maternal age, paternal age, race/ethnicity, parental marital status, and parental education (all \(p > 0.07\)). Similarly, the samples did not significantly differ
in terms of any sleep or behavior measure. Therefore, data from both sites were combined in subsequent analyses. Demographic characteristics of the study sample are presented in Table 1. Both studies were approved by the institutional review boards at the University of Maryland and University of Houston.

Measures

**Demographics/Child Development Questionnaire**

All parents completed a questionnaire pertaining to the demographic characteristics of the family (race/ethnicity, marital status, and parental education, etc.) as well as the child’s medical and developmental history. The questionnaire included a dichotomously scored item assessing whether the child had problems sleeping during the first year of life.

**Parent-Child Sleep Interaction Scale**

Parents completed the Parent-Child Sleep Interaction Scale (PSIS), a parent report measure developed to measure a wide range of bedtime behaviors and interactions among parents and their preschool-aged child. Thus, rather than specific bedtimes or other quantitative sleep indices, the PSIS was developed to assess sleep-related behaviors and parent-child interactions related to sleep that may give rise to and/or maintain problematic sleep patterns/disorders in young children, such as parental involvement in sleep routines, non-independent sleep patterns, and reinforcement of good sleep behaviors.

The PSIS was constructed based upon recommended procedures outlined by Spruyt and Gozal, including: (1) initial generation of items based on clinical and empirical evidence; (2) solicitation of input from experts; (3) administration of the questionnaire to a community sample; (4) item reduction procedures; (5) exploratory factor analysis (EFA); and (6) examination of internal consistency and convergent validity. Specifically, an initial list of items was generated by the first author and sent to 3 pediatric sleep experts (including a psychologist, a psychiatrist, and a developmental pediatrician) for review based on the items’ relevance in assessing child sleep/bedtime routines. Expert feedback and recommendation resulted in an initial 35-item version of the measure. A Likert-type response format was created requiring parents to indicate how frequently each behavior/interaction occurred during the past month: 0 = never; 1 = rarely; 2 = sometimes; 3 = frequently; 4 = always/almost always.

**Child Behavior Checklist for Ages 1½-5 (CBCL)**

All parents completed the CBCL, a 113-item parent-report scale assessing a broad range of behavioral problems, and social and academic functioning. The CBCL is one of the most extensively tested rating scales available and possesses excellent psychometrics. The measure yields a Total Problem Behavior score, 2 broad-band Internalizing and Externalizing scores, and 8 subscale scores. For the purpose of this study, the Internalizing, Externalizing and Sleep Problems Subscales were examined. The Sleep Problems Scale is composed of 7 items including: doesn’t want to sleep alone, has trouble getting to sleep, nightmares, resists going to bed at night, sleeps less than most kids during day and/or night, talks or cries out in sleep, and wakes up often at night. As with other items on the CBCL, parents were asked to describe their child now or within the past 6 months (0 = not true, 1 = somewhat or sometimes true, 2 = frequently; 4 = always/almost always). Internal consistency (Cronbach’s α) for the Sleep Problems scale in the current study was 0.77.

**Preschool Age Psychiatric Assessment (PAPA)**

Parents of preschoolers from the Washington, DC, sample (n = 155) were interviewed in person using the Preschool Age Psychiatric Assessment (PAPA), which uses a structured-format and interviewer-based approach to assess psychopathology in preschool-aged children, 2 to 6 years. Interviews

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**Table 1—Demographic characteristics of the study sample by site (N = 209)**

<table>
<thead>
<tr>
<th>Demographic Variable</th>
<th>Total Sample</th>
<th>Site 1</th>
<th>Site 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child mean age: years (SD)</td>
<td>3.79 (0.78)</td>
<td>3.75 (0.76)</td>
<td>3.94 (0.83)</td>
</tr>
<tr>
<td>Mother mean age: years (SD)</td>
<td>34.68 (6.16)</td>
<td>34.87 (6.31)</td>
<td>34.10 (5.71)</td>
</tr>
<tr>
<td>Father mean age: years (SD)</td>
<td>37.01 (6.72)</td>
<td>37.19 (6.84)</td>
<td>36.48 (6.36)</td>
</tr>
<tr>
<td>Child sex: female % (n)</td>
<td>47.4 (99)</td>
<td>51.6 (80)</td>
<td>35.2 (19)</td>
</tr>
<tr>
<td>Child race/ethnicity: % (n)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White/non-Hispanic</td>
<td>48.8 (102)</td>
<td>41.9 (65)</td>
<td>68.5 (37)</td>
</tr>
<tr>
<td>Black</td>
<td>24.9 (52)</td>
<td>31.0 (48)</td>
<td>7.4 (4)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>12.9 (27)</td>
<td>12.3 (19)</td>
<td>14.8 (8)</td>
</tr>
<tr>
<td>Asian</td>
<td>1.9 (4)</td>
<td>1.9 (3)</td>
<td>1.9 (1)</td>
</tr>
<tr>
<td>Multiracial</td>
<td>8.1 (17)</td>
<td>9.0 (14)</td>
<td>5.6 (3)</td>
</tr>
<tr>
<td>Other</td>
<td>3.3 (7)</td>
<td>12.3 (19)</td>
<td>1.9 (1)</td>
</tr>
<tr>
<td>Parents’ marital status: % (n)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>71.8 (150)</td>
<td>69.0 (107)</td>
<td>79.6 (43)</td>
</tr>
<tr>
<td>Divorced, separated, or widowed</td>
<td>8.6 (18)</td>
<td>7.1 (11)</td>
<td>13.0 (7)</td>
</tr>
<tr>
<td>Never married</td>
<td>8.6 (18)</td>
<td>23.9 (37)</td>
<td>7.4 (4)</td>
</tr>
<tr>
<td>≥ 1 parent college graduate</td>
<td>72.8 (150)</td>
<td>108 (69.7)</td>
<td>82.4 (42)</td>
</tr>
</tbody>
</table>

*p < 0.10; *p < 0.05; **p < 0.01; ***p < 0.001. Site 1 is University of Maryland, College Park; Site 2 is University of Houston.
were conducted by advanced graduate students in clinical psychology supervised by a Ph.D. level, licensed psychologist with extensive experience and training in the PAPA. Fourteen dichotomously scored items from the PAPA assessing sleep problems were examined. Given the range of item content, an EFA was conducted using principle axis extraction and oblique rotation to identify an underlying factor structure. Items were removed if they failed to load onto any primary factor (i.e., loading < 0.40). Based on the eigenvalue > 1.0 rule and inspection of the scree plot, 3 factors were extracted consisting of a total of 9 items. Items from each factor were summed to yield 3 sleep scales: Inadequate Sleep (restless sleep, inadequately rested by sleep, morning irritability), Sleep Assistance (sleeps with family members, reluctance to sleep alone, night waking, rises to check on family members), and Daytime Sleepiness (seems sleepy during day, easily tired). In addition, all 9 items were summed to create a Total PAPA Sleep Problems scale. Interrater ICCs were acceptable for all scales: Inadequate Sleep (1.00); Sleep Assistance (0.98); Daytime Sleepiness (1.00), and PAPA Total Sleep Problems (0.99).

Data Analysis

Initial item reduction procedures were based on examination of item endorsement, content, and item-total correlations. An EFA using principal axis extraction and oblique rotation (oblimin) was used, as associations between sleep behaviors and interactions tend to be interrelated. Since little work has been conducted on presleep behaviors and parent-child interaction among preschoolers, we did not attempt to group the initial list of items within conceptually based factors. The critical eigenvalue was set at 1.0. Items were removed if they failed to load on any factor (loading < 0.50) or had high secondary loadings (> 0.30), and the analysis was re-run with the remaining items. The EFA continued in this manner until all remaining items had a primary factor loading > 0.50 and secondary loadings < 0.30. The psychometric properties of the fully scale and subscales were then assessed. Internal consistency was assessed by calculating Cronbach’s α for PSIS total and all subscale scores.

Differences in PSIS scores based on demographic characteristics (e.g., child sex, parental education, and household income) were examined using t-tests, univariate analyses of variance (ANOVAs), and Pearson correlation coefficients. In order to assess convergent validity, correlations were calculated to determine associations between PSIS total and subscale scores, CBCL Sleep Problems Scores, and Sleep Problems reported during the PAPA. Correlations between PSIS scores, CBCL Internalizing and Externalizing subscales, and parent-endorsed sleep problems during the first year of life were also examined.

To increase statistical power for analyses, racial/ethnic groups were collapsed into 4 categories: White, Black, Hispanic, and Other. The “Other” group (n = 28) included children identified as multiracial, Asian, or other. Analyses using these 4 categories as compared to 6 racial/ethnic groups (i.e., White, Black, Hispanic, Asian, multiracial, and other) revealed similar results. All subsequent analyses therefore used the more parsimonious solution of 4 groups. To examine differences in PSIS scores across racial/ethnic groups, a series of univariate ANOVAs were conducted with race/ethnicity as the between-subject factor. Significant main effects were followed with post-hoc comparisons using Tukey’s honestly significant difference (HSD) tests.

RESULTS

PSIS Item Reduction

We first examined response distributions for the 35 PSIS items to identify items with low variability (i.e., low sensitivity to individual differences). Six of the 35 items evidenced significantly unbalanced distributions (all skew and kurtosis p’s < 0.01) and were therefore removed from the item pool. Next, using the criterion of 0.30 as an acceptable item-total correlation value, we examined item–total correlations among the remaining PSIS items. Eleven of the remaining 29 items failed to meet this criterion and were removed. One additional item was removed based on redundancy with another item (i.e., “My child sleeps in my bed all night” versus “My child sleeps in my room all night”). This resulted in a final list of 17 items used for factor analysis. The Kaiser-Meyer Olkin (KMO) statistic (0.784) and Bartlett’s test of sphericity ($\chi^2 = 1151.65$) were both significant ($p < 0.001$) indicating suitability of these items for factor analysis.

Factor Structure of the PSIS

An EFA using principal axis extraction and oblimin rotation was conducted to identify the structure of the PSIS. Two of the 17 items did not load onto any individual factor and were removed from the dataset. The scree plot of eigenvalues for the remaining 15 items indicated that a 4-factor solution could be interpreted. The fourth factor (eigenvalue = 1.10) accounted for 7.3% of the variance in PSIS scores. However, the three items comprising this factor showed limited content/conceptual overlap and similarly low internal consistency (Cronbach’s α = 0.53). These items were therefore removed and the EFA was re-run revealing a 3-factor solution (Table 2). Items loading on the first factor indicated this to be a measure of parental reassurance/reinforcement of child sleep behaviors. This factor was named Sleep Reinforcement and accounted for 33.1% of the variance in PSIS scores. The second factor, which accounted for 14.5% of the total variance, was named Sleep Conflict based on item loadings related to conflict and child noncompliance surrounding sleep. Item loadings on the third factor were indicative of problems with independent sleep. The third factor was named Sleep Dependence and accounted for 12.6% of the variance in PSIS scores. The 12-item PSIS scale showed good internal consistency (Cronbach’s α = 0.82). Means, standard deviations, and internal consistency for the PSIS subscales also were acceptable and are presented in Table 3.

Associations between PSIS Scores and Demographic Variables

Table 4 summarizes the extent to which the PSIS scales were significantly associated with demographic variables. Child age was significantly negatively associated with Sleep Conflict scores; marital status was significantly associated with PSIS Total, Sleep
Reinforcement, and Sleep Dependence scores, whereby married parents reported lower scores than children of parents who were divorced, separated, widowed, and/or never married; and parental education was significantly negatively associated with PSIS Total and Sleep Dependence scores. No significant associations were observed for maternal age or child gender.

**Associations between PSIS Scales and CBCL Sleep Problems**

As shown in Table 5, PSIS Total scores as well as all 3 subscale scores were significantly positively correlated with CBCL Sleep Problems.

**Associations between PSIS Scales and CBCL Behavior Problems**

CBCL Externalizing scores correlated significantly with PSIS Total scores ($r = 0.30, p < 0.01$), Sleep Conflict ($r = 0.37, p < 0.01$), and Sleep Dependence ($r = 0.25, p < 0.01$) scores. CBCL Internalizing scores were significantly correlated with PSIS Total ($r = 0.24, p < 0.01$) and Sleep Conflict ($r = 0.31, p < 0.01$) scores.

**Associations between PSIS Scales and PAPA Sleep Problems**

Correlation coefficients for the PSIS scales and PAPA Sleep scales are presented in Table 5.

**Inadequate Sleep**

PSIS Total scores, Sleep Reinforcement, and Sleep Conflict scores were significantly positively associated with PAPA Inadequate Sleep scores. Sleep Dependence was positively associated with PAPA Inadequate Sleep at a trend-level of significance.

**Sleep Assistance**

PSIS Total scores, Sleep Reinforcement, Sleep Conflict and Sleep Dependence scores were significantly positively associated with PAPA Sleep Assistance.

---

**Table 2—Rotated factor loadings from an exploratory factor analysis of items from the Parent-Child Sleep Interactions Scale**

<table>
<thead>
<tr>
<th>Parent-Child Sleep Interactions Scale Item</th>
<th>Mean (SD)</th>
<th>Item-Total Correlation</th>
<th>Sleep Reinforcement</th>
<th>Sleep Conflict</th>
<th>Sleep Dependence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. My child sleeps someplace other than his/her own bed.</td>
<td>1.2 (1.3)</td>
<td>0.472</td>
<td>0.031</td>
<td>-0.046</td>
<td>0.810</td>
</tr>
<tr>
<td>2. My child sleeps in my room all night.</td>
<td>0.81 (1.3)</td>
<td>0.367</td>
<td>0.125</td>
<td>-0.031</td>
<td>0.814</td>
</tr>
<tr>
<td>3. My child comes to my room at bedtime.</td>
<td>1.3 (1.4)</td>
<td>0.530</td>
<td>0.013</td>
<td>0.156</td>
<td>0.727</td>
</tr>
<tr>
<td>4. At bedtime, I remind/tell my child several times to go to sleep.</td>
<td>1.9 (1.2)</td>
<td>0.541</td>
<td>0.088</td>
<td>0.601</td>
<td>0.253</td>
</tr>
<tr>
<td>5. I reassure my child that he/she is safe at night.</td>
<td>2.0 (1.5)</td>
<td>0.487</td>
<td>0.772</td>
<td>-0.087</td>
<td>0.105</td>
</tr>
<tr>
<td>6. I reassure my child about his/her ability to fall/stay asleep.</td>
<td>1.6 (1.4)</td>
<td>0.577</td>
<td>0.775</td>
<td>0.054</td>
<td>0.078</td>
</tr>
<tr>
<td>7. I praise my child for good sleep behaviors.</td>
<td>2.3 (1.4)</td>
<td>0.458</td>
<td>0.853</td>
<td>-0.085</td>
<td>-0.026</td>
</tr>
<tr>
<td>8. I provide privileges or rewards for good sleep behaviors.</td>
<td>0.79 (1.2)</td>
<td>0.410</td>
<td>0.659</td>
<td>0.147</td>
<td>-0.115</td>
</tr>
<tr>
<td>9. I read to my child if my child cannot sleep.</td>
<td>1.2 (1.2)</td>
<td>0.483</td>
<td>0.238</td>
<td>0.035</td>
<td>0.535</td>
</tr>
<tr>
<td>10. My child &amp; I argue about bedtimes/sleep schedules.</td>
<td>0.87 (1.0)</td>
<td>0.433</td>
<td>-0.042</td>
<td>0.879</td>
<td>-0.018</td>
</tr>
<tr>
<td>11. I physically take my child to his/her room because of bedtime/sleep non-compliance.</td>
<td>0.69 (0.93)</td>
<td>0.363</td>
<td>0.043</td>
<td>0.705</td>
<td>-0.054</td>
</tr>
<tr>
<td>12. My child has a tantrum/screams/cries if he/she is made to go to sleep.</td>
<td>0.66 (0.91)</td>
<td>0.423</td>
<td>-0.046</td>
<td>0.833</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Item loadings on representative scales are in bold.

---

**Table 3—Means, standard deviations, and internal reliability coefficients for the PSIS scales**

<table>
<thead>
<tr>
<th>PSIS Scale</th>
<th>Mean</th>
<th>SD</th>
<th>Internal Reliability Coefficients</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSIS Sleep Reinforcement</td>
<td>6.77</td>
<td>4.32</td>
<td>0.78</td>
</tr>
<tr>
<td>PSIS Sleep Conflict</td>
<td>4.15</td>
<td>3.15</td>
<td>0.76</td>
</tr>
<tr>
<td>PSIS Sleep Dependence</td>
<td>4.59</td>
<td>3.95</td>
<td>0.74</td>
</tr>
<tr>
<td>PSIS Total Score</td>
<td>15.35</td>
<td>8.62</td>
<td>0.82</td>
</tr>
</tbody>
</table>

PSIS, Parent-Child Sleep Interactions Scale.

**Daytime Sleepiness**

No significant associations were observed between any of the PSIS scales and the PAPA Daytime Sleepiness scale.

**PAPA Total Sleep Problems**

PSIS Total scores, Sleep Reinforcement, Sleep Conflict, and Sleep Dependence scales were significantly positively associated with PAPA Total Sleep Problems.

**Associations between PSIS Scores and Sleep Problems During Infancy**

Child sleep problems during the first year of life were modestly but significantly associated with PSIS Sleep Conflict scores ($r = 0.15, p < 0.05$) as well as PSIS Total scores ($r = 0.19, p < 0.01$).

**Racial/Ethnic Differences in PSIS Total and Subscale Scores**

Univariate analysis of PSIS Total scores revealed a significant main effect for race/ethnicity, $F_{3, 191} = 9.23, p < 0.001$. Post hoc tests revealed that Black ($M = 20.66, SD = 9.26$), Hispanic ($M = 23.20, SD = 9.20$), and children of other race/ethnicities ($M = 25.93, SD = 9.20$) had significantly higher PSIS Total scores than White children ($M = 16.29, SD = 9.59$), $p < 0.05$, $p = 0.01$, and $p < 0.001$, respectively.
PSIS Sleep Reinforcement

A significant main effect of race/ethnicity was found for Sleep Reinforcement scores, $F_{3, 203} = 6.20, p < 0.001$. Post hoc tests indicated that Hispanic participants had significantly higher scores (M = 9.26, SD = 4.49) than White children (M = 5.69, SD = 4.09), $p = 0.001$.

PSIS Sleep Conflict

Analysis of Sleep Conflict scores revealed a significant main effect for race/ethnicity, $F_{3, 205} = 3.48, p = 0.02$. Tukey HSD post hoc tests revealed children in the Other race/ethnicity group to have significantly higher Sleep Conflict scores (M = 5.32, SD = 3.07) than White children (M = 3.57, SD = 3.05), $p = 0.04$.

PSIS Sleep Dependence

A significant main effect for race/ethnicity also emerged based on Sleep Dependence scores, $F_{3, 197} = 12.09, p < 0.001$. Post hoc tests revealed Black children to have significantly higher scores (M = 5.79, SD = 3.78) compared to White children (M = 3.18, SD = 3.64), $p < 0.001$. Children in the Other race/ethnicity group had the highest scores (M = 7.39, SD = 4.03), $p = 0.0001$.
race/ethnicity group demonstrated significantly higher Sleep Dependence scores (M = 7.39, SD = 4.30) than White children (M = 3.18, SD = 3.64) and Hispanic children (M = 4.31, SD = 2.59), p < 0.001, and p < 0.01, respectively.

Results based on racial/ethnic group differences were similar when other demographic variables significantly associated with PSIS scores (i.e., child age, paternal age, parental marital status, parental education) were included in analyses.

**DISCUSSION**

Parent-child interactions are theorized to serve a regulating function on child sleep patterns since they act as external regulators of biological rhythms and capacity for self-regulation. As compared to measures that screen for specific sleep problems and disorders, validated instruments for assessing parent behaviors and parent-child interactions related to sleep are lacking. The factor structure and initial psychometric properties of the Parent-Child Sleep Interactions Scale (PSIS) were therefore evaluated in a large sample of preschool-aged children. Three discrete factors with substantial face validity emerged including Sleep Reinforcement, Sleep Conflict, and Sleep Dependence. These subscales explained 60% of the variance in Total PSIS scores. Internal consistency (i.e., reliability) for all subscales in addition to the total scale was good.

Associations between PSIS total and subscale scores and independent measures of child sleep problems (CBCL and PAPA sleep scales) provide evidence of satisfactory convergent validity. As would be expected, associations between the PSIS and sleep problems scales were positive and in the moderate range, with the exception of the PAPA Daytime Sleepiness scale for which nonsignificant associations were found. The latter result is somewhat surprising in light of significant relationships between PSIS scores and inadequate sleep scores on the PAPA but may relate to how sleepiness is exhibited during this developmental period (i.e., young children who are overly tired often become hyperactive). Significant associations also were identified between PSIS scores and CBCL Internalizing and Externalizing scores, corroborating findings from a wealth of research documenting associations between children’s sleep at night and their emotional/behavioral functioning during the day.

PSIS total and subscale scores also demonstrated expected associations with demographic variables. Consistent with normative declines in parental involvement related to sleep, we found a negative relationship between Sleep Conflict and child age. Children of married parents had lower Sleep Reinforcement and Sleep Dependence scores than children of parents who were divorced, separated, widowed, and/or never married. Also, lower levels of parental education were associated with higher PSIS total and Sleep Dependence scores. Overall, these findings are consistent with previous research demonstrating lower SES to be associated with more problematic sleep in children.

Findings with regard to racial/ethnic differences are somewhat consistent with results from previous research and underscore the role of cultural differences in understanding child sleep habits and parent-child sleep interactions. White children in our sample had significantly lower PSIS total scores than all other racial/ethnic groups. Based on examinations of specific subscales, Black children had higher Sleep Dependence scores than White children, a finding consistent with those reported by Milan and colleagues. Children in the “Other” race/ethnicity category also scored higher on Sleep Dependence than both White and Hispanic children and had higher Sleep Conflict scores than White children. Finally, Hispanic children scored higher on Sleep Reinforcement than Caucasian children. To some extent, these results corroborate findings from previous studies indicating Black and Hispanic children are less likely to have consistent bedtimes and bedtime routines than White children.

Although we were able to examine potential differences among Black, Hispanic, and White children, the diverse composition of the “Other” racial/ethnic group renders these findings difficult to interpret. Indeed, this catch-all category necessarily included children of Asian, mixed, and other races/ethnicities due to the overall small number of children falling into these groups. Larger multicultural samples are therefore an important direction for future research. It is similarly necessary to emphasize the importance of not assuming that ethnorracial differences in child sleep behaviors/patterns translate to child sleep problems or impairment. As an example, Milan and colleagues found that despite differences in bedtime routines and sleeping arrangements, no differences in sleep onset or daytime tiredness were found among Black, Hispanic, and White children. Overall, the growing diversity of families in the U.S. creates need for research focused on understanding relationships between culturally based sleep practices and children’s sleep.

A number of other limitations are noteworthy. Due to the cross-sectional design of our study it is not possible to determine the directionality of identified relationships. For example, although some research suggests that greater parental involvement in bedtime and sleep routines interferes with a child’s ability to regulate their sleep independently, it is equally possible that young children who experience problems sleeping require greater parental attention/interaction at night to help them settle to sleep. Follow-up studies based on prospective rather than retrospective reports are needed to clarify these relationships. Our study did not include an independent, validated measure of sleep problems in this age group but instead relied on two other validated but broad instruments for assessing behavior problems in young children. In conjunction with validated sleep instruments, future research including clinical populations (e.g., children with behavioral or sleep disorders) is needed to determine whether the PSIS can discriminate among subgroups of preschoolers. Finally, the fact that parents completed measures concerning sleep interactions/behaviors as well as child sleep problems creates the possibility of shared reporter variance. Convergent validity of the PSIS based on other types of sleep assessments (e.g., actigraphy, video of bedtime routines) remains to be established.

In summary, the PSIS is a brief, easy to administer measure of parent-child interactions and behaviors related to sleep in preschool-aged children. We envision the PSIS to have both clinical and empirical utility in identifying behaviors/interactions that may lead to and/or maintain sleep-related problems in young children. The PSIS may also have utility as a measure of...
effectiveness of behavioral sleep interventions. For example, an elevated Sleep Dependence score might signal a need for graduated extinction procedures in helping children to learn to sleep independently, whereas an elevated Sleep Conflict score might inform a focus on positive bedtime routines as part of treatment. In research settings, the PSIS may assist in delineating specific environmental mechanisms of early childhood insomnia. The PSIS items and scoring are included in Table 2 and we invite further use of this measure among clinicians and researchers.
Acoustic Pharyngometry Measurement of Minimal Cross-Sectional Airway Area Is a Significant Independent Predictor of Moderate-To-Severe Obstructive Sleep Apnea

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1Division of Pulmonary and Critical Care, University of California San Diego, San Diego CA; 2Division of Sleep Medicine, Brigham and Women’s Hospital & Harvard Medical School, Boston, MA

Study Objectives: The current gold-standard method of diagnosing obstructive sleep apnea (OSA) is polysomnography, which can be inefficient. We therefore sought to determine a method to triage patients at risk of OSA, without using subjective data, which are prone to mis-reporting. We hypothesized that acoustic pharyngometry in combination with age, gender, and neck circumference would predict the presence of moderate-to-severe OSA.

Methods: Untreated subjects with suspected OSA were recruited from a local sleep clinic and underwent polysomnography. We also included a control group to verify differences. While seated in an upright position and breathing through the mouth, an acoustic pharyngometer was used to measure the minimal cross-sectional area (MCA) of the upper airway at end-exhalation.

Results: Sixty subjects were recruited (35 males, mean age 42 years, range 21-81 years; apnea-hypopnea index (AHI) 33 ± 30 events/h (mean ± standard deviation), Epworth Sleepiness Scale score 11 ± 6, body mass index (BMI) 27 ± 8 kg/m²). In univariate logistic regression, MCA was a significant predictor of mild-no OSA (AHI < 15). A multivariate logistic regression model including MCA, age, gender, and neck circumference significantly predicted AHI < 15, explaining approximately one-third of the total variance ($\chi^2(4) = 37$, $p < 0.01$), with only MCA being a significant independent predictor (adjusted odds ratio 54, standard error 130; $p < 0.01$).

Conclusions: These data suggest that independent of age, gender, and neck size, objective anatomical assessment can significantly differentiate those with mild versus moderate-to-severe OSA in a clinical setting, and may have utility as a component in stratifying risk of OSA.

Keywords: Acoustic pharyngometry, obstructive sleep apnea, lung, sleep, airway

Citation: DeYoung PN; Bakker JP; Sands SA; Batool-Anwar S; Connolly JG; Butler JP; Malhotra A. Acoustic pharyngometry measurement of minimal cross-sectional airway area is a significant independent predictor of moderate-to-severe obstructive sleep apnea. J Clin Sleep Med 2013;9(11):1161-1164.
Figure 1—Example tracing of the recording from pharyngometry showing cross-sectional area as a function of distance from the incisors

In this example, the minimal cross-sectional airway area is 0.95 cm².

METHODS

Adults (≥ 18 years) with suspected OSA were recruited from a local sleep clinic (N = 51) as well as a control group from the community (N = 9). Exclusion criteria were use of stimulants (for example amphetamines, modafinil), known head injury, dementia or retardation, alcohol or drug abuse, and pregnancy. All subjects gave informed written consent. The study was approved by Partners’ Institutional Review Board.

Data Collection

The subjects recruited from the sleep clinic underwent a standard overnight laboratory polysomnography (PSG) (electroencephalogram, electrooculogram, chin and anterior tibial electromyogram, electrocardiogram, airflow using nasal pressure and oronasal thermistor, respiratory excursions using inductance plethysmography, and pulse oximetry). Those recruited from the community underwent a home sleep test level II (electroencephalogram, airflow using nasal pressure, respiratory excursions using inductance plethysmography, and pulse oximetry). All study data were manually scored by a blinded certified scorer using American Academy of Sleep Medicine alternative criteria (hypopneas defined as 50% decrease in airflow associated with 3% desaturation and/or arousal).14 We defined the presence of moderate/severe OSA as AHI ≥ 15 events/h. Clinical characteristics including body mass index (BMI) and neck circumference were measured by an experienced medical assistance naive to research study objectives during the daytime clinic visit.

Acoustic Pharyngometry

Pharyngometry data were collected as previously described15 between the hours of 08:30 and 14:30. Briefly, while seated in an upright position on a straight-back chair, subjects breathed orally through a pharyngometer (Eccovision Acoustic Pharyngometry Sleep Group Solutions, Miami FL) with the aid of a nose clip. A disposable mouthpiece was used to stabilize the tongue and provide a reproducible bite position. At normal resting lung volume (functional residual capacity), subjects were instructed to pause breathing at end-exhalation while maintaining a relaxed airway, during which acoustic measurement of upper airway cross-sectional area was made (≥ 10 pressure pulses). Measurements were repeated 3 times (see Figure 1). During a fourth measurement, subjects were asked to close their airway; subjects were coached until this occurred at the level of the glottis as observed on the pharyngogram.5 Data were plotted as cross-sectional area versus distance from the incisors. This pharyngogram was inspected and the minimal cross-sectional area (MCA) was measured between the oropharyngeal junction (OPJ) up to but excluding the glottis (7-18 cm from the incisors). The first 3 individual MCA measurements were pooled to obtain the mean. The purpose of the fourth measurement was to determine the location of the glottis. These 4 measurements took less than 15 min per subject.

Statistical Analysis

Statistical analysis was performed using SPSS (Version 20, IBM, NY USA). Between-group differences in continuous data were assessed using t-tests or Mann-Whitney tests as appropriate for parametric and nonparametric data, respectively. Between-group differences in categorical data were assessed using χ² tests. Univariate and multivariate logistic regression forced-entry models were used to assess the ability of hypothesized variables to predict AHI < 15. Based on our sample size, 3 predictor variables in addition to MCA were prespecified for inclusion.16 Predictors were chosen to encompass potential independent covariates or confounders of the relationship between MCA and AHI. Potential multicollinearity was investigated by assessing variance inflation factors and simple correlations. Statistical tests were considered significant when p < 0.05. A receiver operating characteristic (ROC) curve was created, and positive/negative predictive values were calculated.

RESULTS

Among the 60 subjects studied, 30 patients had moderate/severe OSA defined as AHI ≥ 15 (Table 1). The OSA (AHI ≥ 15) and mild/no-OSA (AHI < 15) groups were significantly different in terms of measures of apnea severity, BMI, age, and neck circumference. The median MCA of the OSA group was 1.66 (IQR 0.42) compared with 2.22 (IQR 0.44) in the control group (p ≤ 0.01).

Results of the univariate and multivariate logistic regression models are shown in Table 2. Age, neck circumference, and MCA were all significant univariate predictors of AHI < 15, with age and MCA remaining as significant independent predictors of AHI < 15 after controlling for gender and neck circumference. Overall, the model had a pseudo-R² of 0.46 ($\chi^2$(4) = 36.79, overall p < 0.01). The area under the ROC curve for MCA predicting AHI < 15 was 0.85. The optimum MCA cutoff point for detecting an AHI < 15 was 1.86 cm² (95% CI 0.69 to 0.96); at this point, the positive predictive value was 0.87 and the negative predictive value was 0.87 (true positive: AHI < 15 and MCA < 1.86 cm²).
DISCUSSION

The current study demonstrates that MCA, determined by acoustic pharyngometry, can significantly differentiate between those with mild/no-OSA versus moderate-to-severe OSA. When analyzed alongside other variables such as gender, age, and neck circumference, acoustic pharyngometry was the only independent predictor of detecting the absence of moderate-to-severe OSA. This easily obtained measurement thus has potential utility as a component in a diagnostic algorithm for OSA.

With healthcare reform, sleep testing may become less readily available, making decisions to prioritize testing in certain patients important.

Acoustic pharyngometry may also be a useful objective tool in occupational health clinics. The population in certain environments may minimize subjective symptoms in sleep questionnaires, leading to the need for simple and cost-effective tools for objective assessments. In conjunction with basic anthropometric characteristics, pharyngometry can help objectively determine those at high risk for OSA.

Other anatomical assessments have been used in the literature, although each has limitations. Neck circumference is easy to measure but underestimates OSA in lean individuals, and did not perform as well as pharyngometry in the present study. Computed axial tomography involves ionizing radiation exposure and is not readily available in many sleep clinics or other offsite centers; moreover, it is time consuming and costly. Similarly, cephalometrics require radiation and only have modest predictive value for OSA. Magnetic resonance imaging (MRI) avoids ionizing radiation and provides excellent definition of parapharyngeal soft tissues, but is also expensive, and thus unlikely to replace PSG as a method of choice for initial risk assessments of OSA. However, MRI does have theoretical advantages over pharyngometry when tissue definition and specific identification of certain tissue structures are needed, for example in preoperative assessment to determine preferred surgical procedure.

Some of the prior literature with acoustic pharyngometry has focused primarily on the OPJ, rather than the MCA per se. We chose to focus on the MCA for a number of reasons. We could reliably identify the MCA in all patients, whereas in some patients the OPJ was either difficult to identify or unclear based on review by multiple experts. We also aimed to identify a strategy which was easily implementable by clinicians in practice and thus did not rely on measurements that required expertise or experience to obtain. In addition, there are significant variabilities in anatomical factors compromising the pharyngeal airway in OSA and thus we did not want to limit our observations to the OPJ.

Despite the study’s strengths, we acknowledge a number of limitations. First, we had a limited sample size, in large part due to the move towards home sleep testing, currently very strong in Massachusetts, and few patients without complications are undergoing clinical in-laboratory polysomnography. This trend toward home testing was a major motivation underlying the present study. Second, pharyngometry does not provide insights as to the mechanisms underlying airway obstruction. For reproducibility reasons, acoustic pharyngometry is best used while awake and seated. We would also note that although supine sleep is clearly relevant to OSA pathogenesis, our assessments of

### Table 1—Characteristics of patients with moderate-severe OSA and mild/no OSA

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mild/no OSA (AHI &lt; 15)</th>
<th>Moderate-severe OSA (AHI ≥ 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 30</td>
<td>n = 30</td>
</tr>
<tr>
<td>Males (number, %)</td>
<td>17 (57%)</td>
<td>18 (60%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>33.5 (16.5)</td>
<td>44.5 (25.8)*</td>
</tr>
<tr>
<td>Sleep efficiency (%)</td>
<td>89.2 (13)</td>
<td>80.9 (19)</td>
</tr>
<tr>
<td>AHI (events/h)</td>
<td>3.4 (10.43)</td>
<td>40.6 (35.8)**</td>
</tr>
<tr>
<td>Supine AHI (events/h)</td>
<td>3.1 (9)</td>
<td>45.9 (57)**</td>
</tr>
<tr>
<td>Oxygen desaturation index (events/h, ≥ 4% desaturation)</td>
<td>1.7 (8)</td>
<td>24.9 (34)**</td>
</tr>
<tr>
<td>Minimum oxygen saturation (%)</td>
<td>89.0 (7)</td>
<td>79.5 (14)**</td>
</tr>
<tr>
<td>Epworth Sleepiness Scale score (/24)</td>
<td>8.0 ± 4.4</td>
<td>12.0 ± 5.8**</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>27.5 (10.3)</td>
<td>33.4 (13.3)**</td>
</tr>
<tr>
<td>Neck circumference (cm)</td>
<td>35.6 (5.7)</td>
<td>41.3 (4.5)**</td>
</tr>
</tbody>
</table>

AHI, apnea-hypopnea index. Data are presented as mean ± standard deviation, or median (interquartile range) as appropriate. *p < 0.05; **p < 0.01.

### Table 2—Univariate and multivariate logistic regression models with outcome AHI < 15 events/h

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Univariate</th>
<th>Multivariate*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds ratio (SE) p-value</td>
<td>Odds ratio (SE) p-value</td>
</tr>
<tr>
<td>Age (years)</td>
<td>0.96 (0.02) 0.02</td>
<td>0.94 (0.02) 0.02</td>
</tr>
<tr>
<td>Gender (1 = male)</td>
<td>1.15 (0.71) 0.79</td>
<td>4.82 (7.43) 0.09</td>
</tr>
<tr>
<td>Neck circumference (cm)</td>
<td>0.85 (0.05) &lt; 0.01</td>
<td>0.87 (0.07) 0.09</td>
</tr>
<tr>
<td>Minimal cross-sectional airway area (cm²)</td>
<td>18.63 (21.73) &lt; 0.01</td>
<td>54.21 (130.02) &lt; 0.01</td>
</tr>
</tbody>
</table>

*Including all univariate predictors (i.e. age, gender, neck circumference and minimal cross-sectional area). Overall pseudo-R² = 0.46, χ²(4) = 36.79, p < 0.01.
patients during upright wakefulness still provided good predictive value in distinguishing OSA patients from controls. Thus, our data do not speak to the mechanism of decreased MCA, but do describe the phenomenon adequately. We encourage further efforts into anatomical assessment of the upper airway to determine the role of tongue anatomy, fat deposition, and mandibular structure. Third, multiple mechanisms underlie OSA, including but not limited to upper airway dilator muscle activity, end-expiratory lung volume, and ventilatory control instability. Thus, we would not expect anatomical assessments to account for all of the variance underlying OSA.24 This concept suggests the need for further efforts into apnea phenotyping,23 such that the mechanisms underlying apnea can be determined by clinicians caring for afflicted patients. Despite these limitations, we believe our findings are robust and worthy of further testing.

In conclusion, we have demonstrated that acoustic pharyngometry provides an objective and simple test with strong independent predictive value for the presence or absence of moderate-to-severe OSA. Further efforts will be required to validate these findings in an occupational setting, where self-report is often unreliable, and may contribute to the identification of mechanisms underlying apnea and promoting individualized therapy for OSA in the future.

ABBREVIATIONS

AHI, apnea-hypopnea index
BMI, body mass index
MCA, minimal cross-sectional area
MRI, magnetic resonance imaging
OPJ, oro-pharyngeal junction
OSA, obstructive sleep apnea
PSG, polysomnography
ROC, receiver operating characteristic
SE, standard error

REFERENCES


ACKNOWLEDGMENTS

The authors thank the staff at Brigham and Women’s Hospital Sleep Disorders Research Program for being amazing.

SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication July, 2012
Submitted in final revised form June, 2013
Accepted for publication June, 2013

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DISCLOSURE STATEMENT

Pharyngometry equipment and support of its use was provided by Sleep Group Solutions; no other financial support was obtained for this project. Dr. Sands is supported by an American Heart Association Postdoctoral Fellowship. Dr. Malhotra was a consultant for Philips Respironics, SHC, SGS, Apnicure, Apnex, and Pfizer, but has relinquished all outside personal income from May 2012. The other authors have indicated no financial conflicts of interest.
Obstructive Sleep Apnea Severity Is Associated with Left Ventricular Mass Independent of Other Cardiovascular Risk Factors in Morbid Obesity

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Objective: To evaluate the relation between obstructive sleep apnea (OSA) and left ventricular mass (LVM) in morbid obesity and the influence of gender, menopausal status, anthropometry, body composition, hypertension, and other cardiovascular risk factors in this relationship.

Design: Cross-sectional descriptive study.

Methods: Polysomnographic and echocardiographic studies were performed in a cohort of 242 patients (86 men, 100 premenopausal (PreM) and 56 postmenopausal (PostM) women), with grade II obesity and above (BMI: 43.7 ± 0.4 kg/m²) to investigate OSA and LVM respectively. Anthropometry, body composition, glucose tolerance, and blood pressure were also recorded.

Results: OSA to different degrees was diagnosed in 76.2% of the patients (n: 166), its prevalence being 90.9% (n: 70) for men, and 76% (n: 38) and 63.8% (n: 58) for PostM and PreM women, respectively (p < 0.01). LVM excess was greatest for PostM women (90.2%), followed by men (81.9%) and PreM females (69.6%) (p < 0.01). LVM values increased in accordance to OSA severity (absence, 193.7 ± 6.9 g; mild, 192.6 ± 7.8 g; moderate, 240.5 ± 12.5 g; severe, 273.6 ± 14.6 g; p < 0.01). LVM magnitude correlated with the menopausal state, age, central adiposity, hypertension (HT), type 2 diabetes (DM), desaturation index (DI), and apnea-hypopnea index (AHI) (r = 0.41; p < 0.01). The relationship between LVM and AHI persisted in the multivariate analysis (β = 0.25; p < 0.05) after adjusting for age, gender, menopausal state, BMI, waist circumference, neck circumference, DI, fasting plasma glucose, DM, and HT. But if tobacco habits are included, the statistical difference disappears (β = 0.22; p = 0.06).

Conclusions: Morbid obesity is frequently associated with abnormal LVM, particularly in patients with OSA; this association is independent of HT, BMI, body composition, and other clinical factors, supporting a direct role of OSA on LVM in morbid obesity. This suggests that OSA and LVM might be taken as predictors of the cardiovascular risk in these patients.

Keywords: Sleep apnea, left ventricular mass, morbid obesity, apnea-hypopnea index

Citation: Pujante P; Abreu C; Moreno J; Barrero EA; Azcarate P; Campo A; Urrestarazu E; Silva C; Maria JG; Tebar J; Frühbeck G; Salvador J. Obstructive sleep apnea severity is associated with left ventricular mass independent of other cardiovascular risk factors in morbid obesity. J Clin Sleep Med 2013;9(11):1165-1171.

Obstructive sleep apnea (OSA) is characterized by intermittent and repeated occlusion of the upper airways during sleep, leading to partial (hypopnea) or total (apnea) interruptions of the airflow. As a result, sustained variations in oxygen saturation and frequent wake-up episodes take place, which may impair respiratory, cardiac, metabolic, and cognitive functions. OSA prevalence in the general population has been shown to be around 2% to 5% in women and 3% to 6% in men, although these values are probably underestimated due to difficulties in confirming the diagnosis and to the low relationship between the clinical manifestations and the number of apneas and hypopneas per hour (apnea-hypopnea index, AHI).

Development of OSA depends on several factors such as age, menopause, alcohol consumption, smoking, and administration of drugs that induce muscle relaxation, thus favoring respiratory airflow obstruction. However, obesity may represent the most determining factor. In the context of the present

BRIEF SUMMARY

Current Knowledge/Study Rationale: This work was designed to explore the possible relationship between obstructive sleep apnea (OSA) and alterations of the left ventricular mass (LVM) in patients with morbid obesity. The influence of gender, menopausal status, body composition, and cardiovascular risk factors were also taken into consideration. The results show a high prevalence of sleep apnea and LVM alterations in this population, especially for men and PostM women. Interestingly, the apnea-hypopnea index related to LVM independently of age, gender, menopausal status, and other cardiovascular risk factors, including hypertension. These results support a direct effect of OSA on LVM, and suggest that LVM should be assessed in all patients with morbid obesity and OSA, particularly men and postmenopausal women.

Study Impact: Morbid obesity is frequently associated to left ventricular mass alterations and obstructive sleep apnea. In this study we aimed to assess a possible direct relation between both cardiovascular risk factors and the influence played by complications such as hypertension and type 2 diabetes, often associated with obesity.
The obesity epidemic, the prevalence of subjects with BMI higher than 35 kg/m² is increasing significantly, reaching 15.5% of the population in the USA. Obese patients frequently display an altered breathing pattern due, at least in part, to neck fat accumulation, which provokes airway collapse during sleep. It is estimated that obesity multiplies the risk of OSA by ten, waist circumference being the anthropometric factor that best correlates with its occurrence. This high OSA prevalence in morbidly obese patients contributes to increasing their cardiometabolic morbidity by different mechanisms such as the increase of the extracellular volume and sodium retention, changes in the endothoracic pressure, and increase in sympathetic nervous system tone and reninangiotensin system activity. Furthermore, OSA is becoming a recognized cause of resistant hypertension (HT), as deduced by the relation found between high AHI values and its development. The same may be true for the association between obesity and HT, which represent well-established factors of left ventricular mass (LVM) increase and cardiovascular risk (CVR). But OSA might increase the risk of developing cardiovascular disease itself. It is known that OSA patients display alterations in myocardial function or structure. However, it is unclear whether these changes are due to OSA, obesity, or other frequently associated comorbidities, such as type 2 diabetes mellitus (DM) or HT. Given that an integral therapeutic approach should be programmed for most patients with OSA, it is important to know whether this condition is directly associated with myocardial disturbance, independent of the presence of other potentially related factors, such as fat mass excess, HT, or DM, since in that case the interest in detecting and treating OSA for cardiovascular prevention should be reinforced.

This study was designed to explore the relationship between OSA and the changes observed in LVM in morbidly obese patients, as well as to assess whether this relation is influenced by gender, age, menopausal state, body mass index (BMI), body composition, and HT.

**METHODS**

**Patients**

We examined 242 Spanish patients with morbid obesity, BMI ≥ 35 kg/m² (BMI: 43.7 ± 0.4 kg/m²), of whom 156 were women (56 postmenopausal [PostM] and 100 premenopausal [PreM]) and 86 men. The mean age was 43.2 ± 0.8 years (range 1,871 years). Patients with a history of coronary heart disease, heart failure, or established diagnosis of cardiac abnormalities were excluded. They were recruited in the Endocrinology Department; the cause of consultation was obesity in all cases. The response rate was 88% (n = 215).

**Anthropometry and Body Composition**

All the patients were subjected to routine anthropometric examinations including body weight, height, and waist and neck circumference measurements. Body composition studies were carried out by air displacement plethysmography (BodPod; Life Measurements, Concord, CA, USA), which is a validated bicompartimental method to determine the percentage of fat mass and fat-free mass.

**Cardiovascular Risk Factors Studied**

**Smoking**

Three groups were defined: non-smokers (those that never smoked), ex-smokers (who had given up smoking ≥ 6 months prior to the study), and active smokers.

**Hypertension**

Mean values of two measurements of blood pressure were considered. Patients undergoing antihypertensive treatment or those with systolic pressure > 140 mm Hg and/or diastolic pressure > 90 mm Hg were considered as hypertensive.

**Diabetes Mellitus**

An oral glucose tolerance test (OGTT) was performed in all patients with no previous history of DM. The patients were diagnosed as diabetic if the syndrome had been diagnosed previously, were being treated, or the condition was shown by OGTT according to ADA criteria.

**Biochemical Measurements**

Fasting plasma glucose was measured by spectrometry using an enzymatic-colorimetric method. Fasting plasma insulin was determined by immunoassay (Immulite 2500. Siemens). As an indicator of insulin resistance, the HOMA index (insulin [μU/mL] x glucose [mmol] / 22.5) was calculated in all cases.

**Polysomnographic Study**

All patients underwent a full night polysomnographic study. Nocturnal sleep was recorded with a Harmonic 5.2 system (Stellate, Montreal, QC, Canada) using Lamont 32-Sleep amplifiers (Lamont Medical, Madison, WI, USA). The recordings included 7 electroencephalogram channels referenced to balanced mastoids, right and left electrooculogram, oxygen saturation, airflow thoracic-abdominal bands, body position sensor and electrocardiogram. In accordance with established criteria, apnea was defined as the cessation of nasal or oral airflow > 10 seconds. Hypopnea was defined as ≥ 30% decrease in the airflow channel > 10 sec, accompanied by ≥ 4% oxygen desaturation in ≥ 90% of the events. The AHI and DI were automatically calculated as functions of the mean number of apneic and hypopneic desaturation events per hour of sleep, respectively. The frequency and severity of oxygen desaturations were also measured. The hypnogram was visually analyzed off-line following standard criteria. The severity of OSA was classified according to the number of apnea events per hour following established criteria: absent (< 5), mild (5-15), moderate (15-30), and severe (> 30).

**Echocardiographic Study**

Doppler echocardiography was carried out the day before the polysomnographic study. All determinations were performed by the same echocardiography specialist using a Sonos 7500 (Philips, Eindhoven, The Netherlands). Morphological measurements were taken in M mode with respect to a parasternal long axis view.

The left ejection fraction was measured as a systolic function parameter (EF = (TDV − TSV) / TDV), where TDV and
TSV are the telediastolic and telesystolic volumes, respectively. EF alterations were classified into 4 categories: reference, ≥ 55%; mild alteration, 45% to 54%; moderate, 30% to 44%; severe, < 30%.

The left ventricular mass (LVM) was calculated according to the formula: \(0.8 \times (\text{TDD} + \text{PPD} + \text{SD})^3 - (\text{TDD})^3 + 0.6 \text{ g}^{16}\), where TDD is the telediastolic diameter, PPD the diameter of the posterior wall and SD the septal diameter. The values were adjusted according to sex into the following categories of abnormality\(^{15}\): women: reference, 66-150 g; mild alteration, 151-171 g; moderate, 172-182 g; severe, > 183 g; men: reference, 96-200 g; mild alteration, 201-227 g; moderate, 228-254 g; severe, > 255 g.

There is not a specific value adjusted for obesity, for this reason we adopted the most commonly used: LVM adjusted according to height (LVM/height\(^2\))\(^{17}\) and to the body surface [(BS \(m^2\)]. In the first case a cutoff point of 51 g/m\(^2\) was taken as indicative of alteration,\(^{18,19}\) while in the second the formula \(\sqrt{\text{height} (\text{cm}) \times \text{weight} (\text{kg}) / 3600}\) was used to calculate the left ventricular mass index (LVMI), defined as LVM/BS. As reference values 115 g/m\(^2\) in men and 95 g/m\(^2\) in women were taken.\(^{19}\) The geometry of the left ventricular mass of the patients was calculated as a function of their relative wall thickness (WRT, mm) and LVMI (g/m\(^2\)) and classified into 4 groups:\(^{15}\): normal: WRT ≤ 0.42 and LVMI ≤ 95 and ≤ 115 for women and men respectively; concentric remodelling: WRT > 0.42 and LVMI ≤ 95 (women) / ≤ 115 (men); concentric hypertrophy WRT > 0.42 and LVMI > 95 (women) / > 115 (men); eccentric hypertrophy WRT ≤ 0.42 and LVMI > 95 (women) / > 115 (men).

Informed consent was obtained from each patient after full explanation of the purpose and nature of all procedures used.

**Statistical Analysis**

The values are expressed as mean ± standard error for quantitative variables and as percentages for categorical variables. Means were compared for groups by one-way ANOVA with Bonferroni post hoc test and contingency tables to calculate \(\chi^2\) when comparing categorical variables. The correlation analyses were assessed with the Pearson correlation coefficient and with multivariate linear and logistic regression studies. All the analyses were carried out with the statistical package SPSS v.15.0 (SPSS, Inc., Chicago, IL).

**RESULTS**

**General Characteristics of the Patients and Influence of Gender and Menopause**

In Table 1 the information on the variables under study is recorded. It comprises the age of the patients, their anthropometric characteristics, smoking habits, prevalence of HT and DM and the echocardiographic and polysomnographic data as a function of sex and menopausal state. The mean age was roughly equivalent between men and women and, as expected, PreM women were younger than their PostM counterpart. All patients displayed an obesity degree ≥ 2, and no significant differences were observed in their respective BMIs. The body composition analysis showed a higher percentage of fat mass in women (p < 0.01) with no differences between the PreM and PostM subgroups. Men presented a more intense central fat distribution than women, as deduced from their respective waist circumference measurements (p < 0.01). Similarly, neck circumference was higher in men than in women, being similar in the PreM and PostM clusters. No differences were observed in smoking habits. Hypertension was diagnosed in 55.4% of the patients, with men and PostM subgroups displaying a higher HT prevalence than PreM women. Diabetes was found in 25.6% of the patients, with no statistical difference between men and women as a whole; however, DM was significantly more prevalent in the PostM than in the PreM consortia. HOMA index calculations showed that men were more insulin resistant, with no differences between PreM and PostM women.

The prevalence of OSA in the whole group of patients was found to be 76.2%. However, the frequency among men rose up to 90.9%, while in women it accounted for 68.1%, the difference being statistically significant, as was that of the PreM (63.8%) and PostM (76%) clusters.

Similar echocardiographic values of the ejection fraction were found for men and PreM and PostM women, all of them being within the normal range. Significant differences (p < 0.01) were found in the LVM values of men and women and, within the latter, between the PreM and PostM subgroups. However, when LVM was adjusted for height and body surface, the differences between women and men became less (p < 0.05) and nonsignificant, respectively, although they remained as such in the case of the PreM and PostM clusters. No difference was found in the WRT of the three cohorts under study. Finally, concentric and eccentric hypertrophies were similar for both sexes taken as a whole; nevertheless, the condition affected a significantly higher proportion of PostM than PreM women (p < 0.01).

**Influence of Patient Characteristics on OSA Occurrence**

In Table 2 the characteristics of the group of patients are related to the severity of OSA. A clear tendency towards its association with increasing age, weight, BMI, body fat, waist and neck circumference, and the HOMA index was observed (p < 0.01 in all cases). Similarly, the more severe the degree of OSA, the greater the likelihood of associated comorbidities, especially HT and DM. In contrast, the systolic function, as assessed by the LV ejection fraction, was similar irrespective of the degree of OSA severity.

A gradual increase in LVM was observed concomitant with OSA severity (p < 0.01) which was clearly enhanced by HT, as can be observed in Figure 1. Similarly, a gradual increment of LVM, when adjusted with respect to height, was seen as a function of the presence and intensity of OSA (p < 0.01). However, OSA severity did not correlate to heart hypertrophy or gender.

Univariate correlation of the data showed that LVM significantly correlated with age (r = 0.24; p < 0.01), gender (r = 0.44; p < 0.01), menopausal state (r = 0.33; p < 0.01), BMI (r = 0.16; p < 0.01), percentage of fat mass (r = 0.21; p < 0.01), waist circumference (r = 0.42; p < 0.01), neck circumference (r = 0.44; p < 0.01), HT (r = 0.30; p < 0.01), DM (r = 0.35; p < 0.01), smoking habits (r = 0.15; p < 0.01), fasting plasma glucose (r = 0.19; p < 0.01), DI (r = 0.28; p < 0.01), and AHI (r = 0.41; p < 0.01).
p < 0.01). No correlations were found with the HOMA index or with fasting plasma insulin.

The correlation between LVM and AHI persisted in the multivariate regression analysis (β = 0.25; p < 0.05) after adjusting for age, gender, menopausal state, BMI, waist circumference, neck circumference, DI, fasting plasma glucose, DM, and HT. But if tobacco habits are included the statistical difference disappears (β = 0.22; p = 0.06).

Similarly, the data on LVM adjusted for height were positively associated with age (r = 0.36; p < 0.01), gender (r = 0.16; p < 0.05), menopausal state (r = 0.34; p < 0.01), BMI (r = 0.18; p < 0.05), waist circumference (r = 0.29; p < 0.01), neck circumference (r = 0.19; p < 0.05), HT (r = 0.31; p < 0.01), DM (r = 0.41; p < 0.01), fasting plasma glucose (r = 0.21; p < 0.01) DI (r = 0.22; p < 0.01), and AHI (r = 0.41, p < 0.01). However, no relationship was found with the HOMA index, fasting plasma insulin, or fat mass. The correlation between LVM/height$^{2.7}$ and AHI persisted in the multivariate regression analysis (β = 0.15; p < 0.05) after adjusting for age, gender, menopausal state, BMI, waist circumference, and HT.

**Influence of Anthropometrical and Metabolic Parameters on the OSA–LVH Association**

The univariate analysis of the left ventricular hypertrophy data with those on the severity of OSA indicates that a clear relation between them exists (Table 3). Since OSA is dependent on several other factors, such as age, gender, menopausal state, and smoking habits, a multivariate analysis that took these variables into consideration was undertaken. The data obtained indicate that these factors significantly contributed to the outcome especially for patients that suffered moderate and severe OSA.

| Table 1—Patient anthropometric characteristics, risk factors and echocardiographic study as a function of gender and menopausal state |
|---|---|---|---|---|---|---|
| | Total (n = 242) | Men (n = 86) | Women (n = 156) | p | PreM women (n = 100) | PostM women (n = 56) | p |
| Age (y) | 43.2 ± 0.7 | 42.4 ± 1.1 | 43.6 ± 1.0 | NS | 36.2 ± 0.9 | 56.6 ± 0.7 | ** |
| Weight (kg) | 120.7 ± 1.5 | 132.8 ± 2.3 | 113.9 ± 1.7 | ** | 116.5 ± 1.9 | 109.3 ± 3.1 | * |
| BMI (kg/m$^2$) | 43.7 ± 0.4 | 43.4 ± 0.6 | 43.9 ± 0.5 | NS | 44.4 ± 0.7 | 43.0 ± 0.9 | NS |
| Body fat (%) | 49.9 ± 0.5 | 43.5 ± 0.7 | 53.2 ± 0.4 | ** | 53.1 ± 0.5 | 53.4 ± 0.7 | NS |
| Neck circumference (cm) | 41.3 ± 0.4 | 46.1 ± 0.7 | 39.1 ± 0.3 | ** | 38.7 ± 0.4 | 39.7 ± 0.6 | NS |
| Waist circumference (cm) | 122.7 ± 0.9 | 128.9 ± 1.3 | 119.3 ± 1.1 | ** | 118.3 ± 1.3 | 121.1 ± 1.9 | NS |
| Tobacco (%) | Non-smoker 57.9 | 51.2 | 61.5 | NS | 57.0 | 69.6 | NS |
| | Ex-smoker 10.3 | 10.5 | 10.3 | NS | 10.0 | 10.7 | NS |
| | Smoker 31.8 | 38.4 | 28.2 | NS | 33.0 | 19.6 | NS |
| HT (%) | 55.4 | 67.4 | 48.7 | ** | 32.0 | 78.6 | ** |
| DM (%) | 25.6 | 31.4 | 22.4 | NS | 14.0 | 37.5 | ** |
| HOMA | 5.1 ± 0.2 | 5.9 ± 0.4 | 4.5 ± 0.3 | ** | 4.4 ± 0.3 | 4.8 ± 0.4 | NS |
| OSA (%) | Absent 23.8 | 9.1 | 31.9 | ** | 36.2 | 24.0 | ** |
| | Mild 27.1 | 16.9 | 32.6 | ** | 37.4 | 24.0 | ** |
| | Moderate 20.2 | 18.2 | 21.3 | ** | 12.1 | 38.0 | ** |
| | Severe 28.9 | 55.8 | 14.2 | ** | 14.3 | 14.0 | ** |
| EF (%) | 59.9 ± 0.3 | 59.2 ± 0.6 | 60.4 ± 0.4 | NS | 60.4 ± 0.6 | 60.4 ± 0.8 | NS |
| AHI | 24.6 ± 1.8 | 41.1 ± 3.8 | 15.6 ± 1.6 | ** | 14.2 ± 2.0 | 18.1 ± 2.6 | NS |
| DI | 18.0 ± 1.8 | 28.1 ± 3.3 | 12.9 ± 2.0 | ** | 11.1 ± 2.6 | 16.0 ± 3.0 | NS |
| LVM (g) | 223.4 ± 5.7 | 275.2 ± 11.1 | 197.3 ± 5.4 | ** | 181.1 ± 5.7 | 226.3 ± 9.8 | ** |
| Altered LVM (%) | 78.6 | 81.9 | 76.9 | * | 69.6 | 90.2 | ** |
| LVM/height$^{2.7}$ (g/m$^2$) | 56.8 ± 1.3 | 61.4 ± 2.5 | 54.5 ± 1.5 | * | 49.8 ± 1.6 | 63.0 ± 2.8 | * |
| Altered LVM/height$^{2.7}$ (%) | 49.2 | 53.5 | 46.8 | NS | 36.0 | 66.1 | ** |
| LVM/BS (g/m$^2$) | 98.9 ± 4.9 | 108.8 ± 4.3 | 93.9 ± 7.0 | NS | 79.5 ± 2.4 | 120.0 ± 18.7 | ** |
| Altered LVM/BS (g/m$^2$) | 40.9 % | 41.9 % | 40.4 % | NS | 27.0 % | 64.3 % | ** |
| WRT (mm) | 0.42 ± 0.01 | 0.42 ± 0.01 | 0.42 ± 0.01 | NS | 0.42 ± 0.01 | 0.42 ± 0.01 | NS |
| Altered WRT (%) | 47.1 | 48.8 | 46.2 | NS | 44.0 | 48.8 | NS |
| Hypertrophy (%) | Eccentric 20.7 | 22.1 | 19.9 | NS | 14.0 | 30.4 | ** |
| | Concentric 20.2 | 19.8 | 20.5 | NS | 13.0 | 33.9 | ** |

NS, non-statistically significant difference; *p < 0.05; **p < 0.01.
The inclusion of the BMI and fat mass data had a minor influence on the data recovered. Conversely, fat distribution played an important role, especially when neck perimeter was taken into consideration, thus confirming that blockage of the pulmonary airway is an important predisposing factor for OSA. Finally, while HT appeared to positively influence OSA severity, this relation was not noted with carbohydrate metabolism alterations, such as DM.

**DISCUSSION**

The correlation between OSA and alteration of myocardial function is a controversial issue. While some studies have suggested a relation between LVH, AHI and the duration of oxygen saturation periods, research carried out on obese patients with or without OSA found no differences in their LVM. Furthermore, the association observed between the increase in LVM and OSA was not maintained after adjusting for BMI or other associated covariates, thus suggesting that other clinical factors might influence the link between OSA and the changes in myocardial morphology. However, the results of the Sleep Heart Health Study showed that increases in LVM

| Table 2—Comparison of the patient cohort anthropometric values, risk factors and echocardiographic data with their OSA severity |
|-----------------|----------------|----------------|----------------|----------------|----------------|
|                  | Absent         | Mild           | Moderate       | Severe         | p              |
| Age (y)          | 39.4 ± 1.6     | 40.8 ± 1.7     | 47.8 ± 1.9     | 45.0 ± 1.2     | **             |
| Weight (kg)      | 112.5 ± 2.3    | 117.1 ± 2.4    | 119.1 ± 4.7    | 132.8 ± 2.8    | **             |
| BMI (kg/m²)      | 41.9 ± 0.7     | 43.5 ± 0.8     | 44.1 ± 1.1     | 45.6 ± 0.8     | *              |
| Body fat (%)     | 50.6 ± 1.0     | 50.9 ± 0.9     | 50.9 ± 1.1     | 47.7 ± 0.9     | *              |
| Neck circumference (cm) | 38.6 ± 0.6 | 39.9 ± 0.5     | 42.5 ± 1.0     | 44.7 ± 0.9     | **             |
| Waist circumference (cm) | 116.8 ± 1.5 | 118.7 ± 1.7     | 125.3 ± 2.2     | 130.3 ± 1.5     | **             |
| Tobacco (%)      | Non-smoker     | 57.7           | 64.4           | 63.6           | 42.9           | NS             |
|                  | Ex-smoker      | 7.7            | 10.2           | 4.5            | 15.9           | NS             |
|                  | Smoker         | 34.6           | 25.4           | 31.8           | 41.3           | NS             |
| HT (%)           | 38.5           | 40.7           | 75.0           | 65.1           | **             |
| DM (%)           | 11.5           | 18.6           | 34.1           | 35.0           | **             |
| HOMA             | 3.7 ± 0.3      | 4.8 ± 0.5      | 5.6 ± 0.6      | 6.1 ± 0.5      | **             |
| EF (%)           | 59.7 ± 0.6     | 58.9 ± 0.7     | 60.5 ± 1.0     | 60.2 ± 0.7     | NS             |
| AHI              | 2.3 ± 0.2      | 8.6 ± 0.3      | 20.6 ± 0.6     | 60.8 ± 3.3     | **             |
| DI               | 3.4 ± 0.7      | 7.1 ± 1.8      | 14.8 ± 1.7     | 45.1 ± 4.7     | **             |
| LVM (g)          | 193.7 ± 6.9    | 192.6 ± 7.8    | 240.5 ± 12.2   | 273.6 ± 14.6   | **             |
| Altered LVM (%)  | 79.2           | 62.7           | 79.6           | 73.0           | NS             |
| LVM/height² (g/m²) | 51.6 ± 1.9    | 51.0 ± 2.0     | 62.6 ± 3.5     | 64.4 ± 3.1     | **             |
| Altered LVM/height² (%) | 46.2       | 40.7           | 56.8           | 58.7           | NS             |
| LVM/BS (g/m²)    | 86.3 ± 2.8     | 83.6 ± 3.2     | 126.0 ± 23.8   | 108.8 ± 5.3    | *              |
| Altered LVM/BS (%) | 38.5         | 32.2           | 43.2           | 47.6           | NS             |
| WRT (mm)         | 0.42 ± 0.01    | 0.41 ± 0.01    | 0.43 ± 0.01    | 0.43 ± 0.01    | NS             |
| Altered WRT (%)  | 46.2           | 40.7           | 54.4           | 52.4           | NS             |
| Hypertrophy (%)  | Eccentric     | 17.3           | 18.6           | 11.4           | 25.4           | NS             |
|                  | Concentric    | 21.2           | 13.6           | 31.8           | 22.2           | NS             |

NS, non statistically significant difference; *p < 0.05; **p < 0.01.
and in LVH prevalence were related to AHI, independent of age, sex, ethnicity, BMI, smoking, alcohol consumption, DM, and previous acute myocardial infarction.24

In the present study, we have addressed the relation of OSA severity with LVM increase in obese patients with BMIs over 35 kg/m², to determine whether there was a cause/effect between both or if other cardiovascular risk factors, usually present in these patients, played a role as well. This might, in addition, promote the realization of prospective studies aiming to provide information on the possible effects of weight loss or gain on the OSA and LVM relationship.

The results obtained indicate that a high prevalence of OSA occurs in patients with morbid obesity, reaching 76.2% of the cases. A high prevalence of LVM alterations in morbidly obese patients that were affected by OSA (up to 78.6%) was observed, a result that agrees with that of a previous report where a high prevalence of LVM alterations in morbidly obese patients was observed, reaching 76.2% of the cohort. This relationship might be indirectly influenced by fat distribution, HT, and DM, all of which are conditions that probably influence the association between severe OSA and LVH. Furthermore, the changes in LVM were observed in both non- and hypertensive patients. However, HT induces more pronounced changes in the LVM of patients with OSA, suggesting a synergistic effect of both conditions. These data agree with those of recently published reports21,29 indicating that severe OSA impairs left ventricular function independent of age, insulin resistance or blood pressure,30 although these conditions may worsen it. LVH also represents an established cardiovascular risk factor31 particularly relevant in patients with severe OSA that exhibit an LVH prevalence of over 50% in our cohort. This relationship might be indirectly influenced by fat distribution, HT, and DM, all of which are conditions that probably influence the association between severe OSA and LVH.

It is known that insulin resistance promotes the increment of LVM and LVH through raising the extracellular volume and sodium retention32 and through hyperactivation of the renin-aldosterone system.33 A direct relationship was found between HOMA and LVM alterations, which were independent of the age and other confounding factors such as HT.34 However, we could not find an association between fasting plasma insulin or HOMA index and LVM, suggesting that additional factors may be involved in the pathophysiology of LVM in patients with morbid obesity. On the other hand, the relation of fat distribution with both the degree of OSA severity and insulin resistance suggests that the latter may be considered as an important anthropometric clue when OSA is suspected and therefore, may represent an indirect marker for detecting LVM alterations in obese patients.

Table 3—Cox proportional hazard ratios (95% CI) for the association between OSA and left ventricular hypertrophy

<table>
<thead>
<tr>
<th>Cases</th>
<th>Absent</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Univariate</td>
<td>52</td>
<td>59</td>
<td>44</td>
<td>63</td>
</tr>
<tr>
<td>Multivariate*</td>
<td>1</td>
<td>0.76 (0.35-1.66)</td>
<td>1.22 (0.54-2.75)</td>
<td>1.45 (0.69-3.11)</td>
</tr>
<tr>
<td>+ BMI</td>
<td>1</td>
<td>0.71 (0.31-1.63)</td>
<td>0.80 (0.32-1.96)</td>
<td>1.24 (0.52-3.00)</td>
</tr>
<tr>
<td>+ FAT%</td>
<td>1</td>
<td>0.67 (0.29-1.60)</td>
<td>0.74 (0.29-1.83)</td>
<td>1.09 (0.44-2.70)</td>
</tr>
<tr>
<td>+ circumference perimeter</td>
<td>1</td>
<td>0.58 (0.24-1.40)</td>
<td>0.72 (0.28-1.84)</td>
<td>0.95 (0.36-2.45)</td>
</tr>
<tr>
<td>+ neck perimeter</td>
<td>1</td>
<td>0.62 (0.25-1.51)</td>
<td>0.68 (0.26-1.78)</td>
<td>0.83 (0.32-2.23)</td>
</tr>
<tr>
<td>Multivariate*</td>
<td>1</td>
<td>0.46 (0.15-1.43)</td>
<td>0.63 (0.18-2.45)</td>
<td>0.47 (0.12-1.84)</td>
</tr>
<tr>
<td>+ HC alteration</td>
<td>1</td>
<td>0.71 (0.31-1.63)</td>
<td>0.80 (0.32-1.96)</td>
<td>1.24 (0.52-3.00)</td>
</tr>
<tr>
<td>+ HT</td>
<td>1</td>
<td>0.77 (0.33-1.80)</td>
<td>0.82 (0.33-2.03)</td>
<td>1.23 (0.51-3.00)</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>0.76 (0.32-1.83)</td>
<td>0.63 (0.25-1.62)</td>
<td>1.04 (0.41-2.60)</td>
</tr>
</tbody>
</table>

FAT%, percentage of fat mass; HC, carbohydrate metabolism; HT, hypertension. *Multivariate: model adjusted by age, gender, menopausal state, and smoking habits.
In contrast with a previous report,\textsuperscript{14} our study showed no differences in the ejection fraction of patients included in any of the four categories of OSA severity, suggesting that OSA was not inducing changes in their systolic function. These discrepancies may be due to the fact that patients with established cardiac disturbances were excluded from the previous report and to the age heterogeneity of our sample.

In summary, this study establishes that OSA is highly prevalent among morbidly obese patients, being especially frequent in men and PostM women. LVM alterations and LVH are also very common in these patients, and their occurrence is associated with OSA independent of other classic cardiovascular risk factors, including HT. These data suggest that OSA should be investigated and an echocardiographic study performed in all patients with morbid obesity, independent of their HT status, and especially in men and PostM women. The improvement obtained in myocardial performance following treatment with CPAP in patients with OSA,\textsuperscript{11} supports the interest of this diagnostic strategy in the prevention or treatment of myocardial dysfunction and cardiovascular risk in this group of patients.

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**ACKNOWLEDGMENTS**

Work for this study was performed in Clínica Universidad de Navarra.

**SUBMISSION & CORRESPONDENCE INFORMATION**

Submitted for publication November, 2012
Submitted in final revised form May, 2013
Accepted for publication June, 2013
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**DISCLOSURE STATEMENT**

This was not an industry supported study. The authors have indicated no financial conflicts of interest.
Prevalence and Symptoms of Occult Sleep Disordered Breathing among Older Veterans with Insomnia

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1Geriatric Research, Education and Clinical Center (GRECC): Veterans Administration Greater Los Angeles Healthcare System, Los Angeles, CA; 2David Geffen School of Medicine at the University of California, Los Angeles, Los Angeles, CA; 3Western University of Health Sciences

Study Objectives: To determine the prevalence of occult sleep disordered breathing (SDB) and describe the relationship between classic SDB symptoms (e.g., loud snoring) and occult SDB in older veterans with insomnia.

Methods: We analyzed baseline survey and in-home sleep study data for 435 veterans (mean age = 72.0 years [SD 8.0]) who had no known history of SDB, met International Classification of Sleep Disorders 2nd Edition criteria for insomnia, and were enrolled in a behavioral intervention trial for insomnia. Variables of interest included apnea-hypopnea index (AHI) ≥ 15, age, race/ethnicity, marital status, body mass index (BMI), insomnia subtype (i.e., onset, maintenance, or terminal), self-reported excessive daytime sleepiness, snoring, and witnessed breathing pause items from the Berlin Questionnaire. We computed the frequency of AHI ≥ 15 and assessed whether each classic SDB symptom was associated with an AHI ≥ 15 in 4 separate multivariate logistic regression models.

Results: Prevalence of AHI ≥ 15 was 46.7%. Excessive daytime sleepiness (adjusted odds ratio 1.63, 95% CI 1.02, 2.60, p = 0.04), but not snoring loudness, snoring frequency, or witnessed breathing pauses was associated with occult SDB (AHI ≥ 15). Insomnia subtypes were not significantly associated with occult SDB (p > 0.38).

Conclusions: In our sample of older veterans with insomnia, nearly half had occult SDB, which was characterized by reported excessive daytime sleepiness, but not loud or frequent snoring or witnessed breathing pauses. Insomnia subtype was unrelated to the presence of occult SDB.

Keywords: Sleep disordered breathing, prevalence, risk factors, older adults, comorbid insomnia

Citation: Fung CH; Martin JL; Dzierzewski JM; Jouldjian S; Josephson K; Park M; Alessi C. Prevalence and symptoms of occult sleep disordered breathing among older veterans with insomnia. J Clin Sleep Med 2013;9(11):1173-1178.

BRIEF SUMMARY

Current Knowledge/Study Rationale: Although older veterans are at high risk for both occult sleep disordered breathing (SDB) and insomnia, the prevalence of occult SDB among older veterans with insomnia has not been reported. Furthermore, the strength of association between classic SDB symptoms and occult SDB has not been examined in older veterans with insomnia.

Study Impact: We found that nearly half of participants had occult SDB, and although the presence of excessive daytime sleepiness was associated with occult SDB, snoring frequency, snoring loudness, and witnessed breathing pauses were not associated with occult SDB. Researchers and clinicians should account for the high prevalence of occult SDB among older veterans when planning research studies and initiating therapies for insomnia.
Recognizing that sleep disturbance is due to both SDB and insomnia may affect treatment, because interactions between these conditions are a concern. For example, patients with untreated SDB resulting in excessive daytime sleepiness could have difficulty adhering to sleep restriction.

Symptoms of SDB in the general population have been examined in numerous studies, but fewer studies have focused on symptoms of SDB among patients with insomnia. In one study of older adults, classic SDB symptoms such as loud snoring were associated with increased odds of SDB among older adults with insomnia, whereas excessive daytime sleepiness was not significantly associated with SDB (AHI ≥ 15). In contrast, a study of older adults with insomnia and occult SDB found that self-reported snoring did not differ between participants with and without occult SDB. In theory, the symptom pattern of occult SDB in the context of insomnia could differ from formally diagnosed SDB because symptoms that are bothersome to bed partners such as frequent snoring might prompt patients to seek medical attention for possible SDB. Interestingly, however, a study that examined this question among non-veterans found the same pattern of symptoms exhibited by clinic patients formally diagnosed with SDB as community-dwelling individuals identified with occult SDB. To our knowledge, the strength of association between classic SDB symptoms (loud snoring, frequent snoring, witnessed breathing pauses, and excessive daytime sleepiness) and occult SDB has not been examined in older veterans with insomnia.

We sought to compute the prevalence of occult SDB among older veterans meeting International Classification of Sleep Disorders 2nd Edition (ICSD-2) diagnostic criteria for insomnia and to describe the relationship between each classic SDB symptom (i.e., snoring loudness, snoring frequency, witnessed breathing pauses, and excessive daytime sleepiness) and occult SDB in older veterans with insomnia. We tested whether SDB symptoms that are bothersome to bed partners (e.g., frequent snoring, loud snoring) are less likely to be associated with occult SDB in models adjusting for demographic data (age, race/ethnicity, marital status), BMI, and insomnia subtype (i.e., onset, maintenance, or terminal), and whether other classic SDB symptoms (e.g., witnessed breathing pauses and excessive daytime sleepiness) are more likely to be associated with occult SDB among older veterans with insomnia in adjusted models.

METHODS

Study Design, Sample, and Data Collection

We analyzed baseline screening data for individuals who were considered for a randomized controlled trial testing a behavioral treatment for insomnia targeting older veterans (see study flow diagram in Figure 1). Between May 2010 and December 2011, we sent a postal questionnaire to all veterans in the Los Angeles area aged ≥ 60 years who had at least one healthcare provider visit within the past 24 months at a Veterans Administration (VA) outpatient clinic, had a valid Los Angeles or Ventura County address, and lived within 25 miles of our study site, as determined by a review of VA administrative data. The postal questionnaire collected information needed to determine if the respondent met basic diagnostic criteria for an insomnia disorder using the ICSD-2. Older veterans with sleep disturbance accompanied by daytime consequences (i.e., met ICSD-2 criteria for insomnia) lasting ≥ 3 months based upon their postal questionnaire responses and who agreed to be contacted (i.e., did not check an “opt out” box) underwent a telephone interview with research staff to further determine eligibility for the controlled trial. Individuals were excluded if they were homeless or had an atypical sleeping arrangement (e.g., homeless, slept on a floor), were

---

Figure 1—Study flow chart

Veterans were mailed survey N = 9,080

Returned survey N = 4,751

Met insomnia diagnostic criteria based upon postal survey responses N = 2,461

Indicated willingness on postal survey to be contacted N = 1,947

Underwent telephone interview N = 1,753

Enrolled in study and did not report history of SDB N = 496

Reported history of SDB N = 377a

Excluded for other reasons (described in text) N = 561

Eligible but refused N = 336

Excluded due to MMSE < 24 N = 12

Withdrawn before completing baseline assessment N = 14

Baseline assessment incomplete N = 35

*Includes participants who answered “yes” to a question asking whether a doctor had told him or her that she or he has sleep apnea (includes participants who reported that they no longer have sleep apnea due to surgery, weight loss, or other interventions).
unavailable to travel to 5 weekly sessions, or reported self-assessed “significant health or emotional problems” that would preclude participation in the study.

Individuals were considered eligible for face-to-face baseline assessment if they met the eligibility criteria above and denied a history of sleep apnea or a prior prescription for positive airway pressure (PAP) therapy. All individuals meeting these criteria were invited to complete a face-to-face interview with our research staff, where baseline health data were collected, and a single-night unattended in-home sleep study was conducted (described below).

The full study methods were approved by the institutional review board of the VA Greater Los Angeles Healthcare System.

Measures

We collected information on patients’ race/ethnicity and marital status in the postal questionnaire. Age was calculated based upon date of birth obtained from an administrative database from the VA’s Austin Automation Center, which also provided the patients’ gender. We abstracted each patient’s most recent height and weight from the patient’s electronic health record and calculated their BMI.

Sleep Measures

Presence of Occult SDB

We performed a single-night, unattended in-home sleep study (WatchPAT, WP100, Itamar Medical) that includes an actigraphy channel for differentiating between periods of sleep and wake. After visual inspection of the recording, AHI was calculated using the manufacturer’s automated, validated scoring algorithms.23 We employed ICSD-2 obstructive sleep apnea (OSA) (adult) criteria, selecting AHI ≥ 15 as the threshold for categorizing a participant with occult SDB. The WatchPAT device has high sensitivity (93.3%) and specificity (73.3%) for diagnosis of OSA at an AHI ≥ 15 threshold.24

Snoring Frequency, Snoring Loudness, and Witnessed Breathing Pauses

During the face-to-face interview, participants completed an adapted version of the Berlin questionnaire,25 which included items that assessed snoring loudness, snoring frequency, and presence/absence of witnessed breathing pauses. We defined “habitual snoring” to be ≥ 3 times per week and “moderately frequent snoring” to be ≥ 1 time per week but ≤ 2 times per month. We defined “extremely loud snoring” to be “very loud—can hear in the next room” and “moderately loud snoring” to be “as loud as talking or louder than talking.”25

Excessive Daytime Sleepiness

During a face-to-face interview, participants indicated whether or not they “take a nap or doze off during the daytime” (yes/no) because they “did not sleep well at night.”

Insomnia Subtypes

During the face-to-face interview, participants indicated whether they have “trouble falling asleep” (yes/no), “trouble staying asleep all night” (yes/no), and “wake up earlier than you wanted” (yes/no).

Data Analysis

Participants with insomnia who denied a history of SDB and who completed both the face-to-face interview and the in-home sleep study formed the sample for these analyses. Descriptive statistics were calculated for each participant characteristic. The prevalence of SDB was defined as AHI ≥ 15. Finally, 4 multivariate logistic regression models were constructed using the presence or absence of SDB as the dependent variable, to assess the independent association of four classic SDB symptoms (loud snoring, frequent snoring, witnessed breathing pauses, and excessive daytime sleepiness) with SDB, above and beyond the influence of demographics (age, race/ethnicity, marital status, and BMI). Variables for the models were selected based upon risk factors for SDB identified in the literature.11,14,18,25-28 Two-sided testing was performed, and α was set at 0.05. Statistical analyses were performed using Stata/SE 11.2 (StataCorp LP, College Station, Texas).

RESULTS

Descriptive Statistics

Four hundred thirty-five participants completed both a face-to-face interview and an in-home sleep study. Table 1 summarizes participant characteristics for this sample. The prevalence of AHI ≥ 15 was 46.7%.

Table 2 summarizes the multivariate logistic regression results. The presence of self-reported excessive daytime sleepiness was associated with a 1.62 fold increased odds of AHI ≥ 15. Snoring frequency (habitual or moderately frequent snoring), snoring loudness (extremely loud or moderately loud snoring), and witnessed breathing pauses were not associated with an increased odds of AHI ≥ 15 (p > 0.22). In all 4 models, BMI was associated with a 1.16- to 1.17-fold increased odds of AHI ≥ 15 (p < 0.001), whereas insomnia subtypes were not significant predictors of AHI ≥ 15 (p > 0.38). Age (p > 0.06), ethnicity (p > 0.15), and marital status (p > 0.80) were not significant predictors of AHI ≥ 15.

DISCUSSION

In our study of older veterans with insomnia, nearly half of participants had SDB (AHI ≥ 15) that had not been previously diagnosed. This high prevalence is concerning, since all of the older adults in our study had at least one healthcare provider visit within 24 months of receiving our postal questionnaire and because our medical center is home to a comprehensive sleep disorders center. Our findings suggest that occult SDB is very common among older veterans with insomnia. When we examined which classic SDB symptoms are associated with occult SDB, only the presence of excessive daytime sleepiness was significant, whereas snoring frequency and loudness and witnessed breathing pauses were not associated with occult SDB in the context of insomnia. We also found that the insomnia type was not associated with occult SDB.

Our finding of a high prevalence of occult SDB among older adults with insomnia is similar to other studies that have measured prevalence of SDB in the context of insomnia.11,14,29

In comparison to some studies conducted in non-veteran
in some situations.32,33 Given the widespread use of sedative-hypnotics, and these medications may worsen OSA rate may be that these two studies excluded patients who used older veterans. One explanation for our higher prevalence of ≥ 15; our prevalence rate would have been much higher if in our methods section, we chose a conservative AHI threshold

The study's prevalence rate is slightly lower. As described in our methods section, we chose a conservative AHI threshold of ≥ 15; our prevalence rate would have been much higher if we had selected an AHI ≥ 5. Compared to two other studies in non-veteran populations that employed the same AHI threshold used in our study,11,14 we found a higher prevalence rate among older veterans. One explanation for our higher prevalence rate may be that these two studies excluded patients who used sedative-hypnotics, and these medications may worsen OSA in some situations.32,33 Given the widespread use of sedative-hypnotics among older adults,34 our study's findings may be more representative of the true prevalence rate of abnormal

### Table 1—Participant characteristics (N = 435)

<table>
<thead>
<tr>
<th>Continuous Variables</th>
<th>Mean (SD)</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>72.0 (8.0)</td>
<td>435</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>28.39 (4.7)</td>
<td>427</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Categorical Variables</th>
<th>Frequency (%)</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>425 (97.7)</td>
<td>435</td>
</tr>
<tr>
<td>Female</td>
<td>10 (2.3)</td>
<td></td>
</tr>
<tr>
<td>Race/Ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>29 (6.8)</td>
<td>426</td>
</tr>
<tr>
<td>Asian</td>
<td>8 (1.9)</td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic White</td>
<td>345 (81.0)</td>
<td></td>
</tr>
<tr>
<td>Native Hawaiian</td>
<td>1 (0.2)</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>33 (7.7)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>10 (2.3)</td>
<td></td>
</tr>
<tr>
<td>Marital status</td>
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<td></td>
</tr>
<tr>
<td>Married</td>
<td>243 (55.9)</td>
<td>435</td>
</tr>
<tr>
<td>Other</td>
<td>192 (44.1)</td>
<td></td>
</tr>
<tr>
<td>Snores</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Don't know</td>
<td>5 (1.1)</td>
<td>435</td>
</tr>
<tr>
<td>No</td>
<td>134 (31.1)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>296 (68.8)</td>
<td></td>
</tr>
<tr>
<td>Snoring loudness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slightly louder</td>
<td>47 (10.8)</td>
<td>298</td>
</tr>
<tr>
<td>As loud as talking</td>
<td>104 (23.9)</td>
<td></td>
</tr>
<tr>
<td>Louder than talking</td>
<td>55 (12.6)</td>
<td></td>
</tr>
<tr>
<td>Very loud—can be heard</td>
<td>55 (12.6)</td>
<td></td>
</tr>
<tr>
<td>Don't know</td>
<td>37 (8.5)</td>
<td></td>
</tr>
<tr>
<td>Snoring frequency</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nearly every day</td>
<td>97 (22.3)</td>
<td>284</td>
</tr>
<tr>
<td>3-4 times/week</td>
<td>54 (12.4)</td>
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</tr>
<tr>
<td>1-2 times/week</td>
<td>52 (12.0)</td>
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</tr>
<tr>
<td>1-2 times/month</td>
<td>31 (7.1)</td>
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<tr>
<td>Never or nearly never</td>
<td>50 (11.5)</td>
<td></td>
</tr>
<tr>
<td>Witnessed breathing pauses during sleep</td>
<td></td>
<td>435</td>
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<tr>
<td>No</td>
<td>371 (85.3)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>60 (13.8)</td>
<td></td>
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<tr>
<td>Don't know</td>
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<tr>
<td>Excessive daytime sleepiness</td>
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<td>No</td>
<td>114 (26.2)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>321 (73.8)</td>
<td></td>
</tr>
</tbody>
</table>

Two participants responded to item assessing snoring frequency despite a report of not snoring.

Our study has several limitations. First, because our study population was recruited from patients with a recent VA clinical visit and most of our participants were male and Caucasian, our results may not be generalizable to non-Veteran, female, and ethnically diverse populations. Second, we were not able to perform gold-standard attended polysomnography to verify the AHI for participants, but unattended in-home sleep studies are commonly used to diagnose SDB in patients with sleep...
disturbances, particularly among individuals with a high index of suspicion. Third, we relied on participants’ self-report of a prior diagnosis of SDB rather than a medical chart review to determine the presence/absence of previously diagnosed SDB. Some of our cases of “occult” SDB may have actually been recognized cases; however, because the first-line therapy for SDB for moderate to severe SDB is PAP therapy—a therapy that entails a lot of patient involvement—we believe it is unlikely that participants would have forgotten a diagnosis of SDB. Finally, our data were derived from participants who had some level of interest in participating in a clinical trial for insomnia. As a result they may differ from a cross-section of clinical insomnia patients. A major strength of our study is our sampling strategy, in which all potentially appropriate individuals who had received healthcare at our facility within 24 months were included in our sampling frame. This strategy increases the generalizability of our findings within the older veteran population.

In conclusion, we found a high prevalence of occult SDB among older veterans with insomnia who were screened for eligibility for a clinical trial on behavioral treatment of insomnia. When planning insomnia trials involving older veterans, researchers should account for the high prevalence of comorbid SDB among prospective study participants and recognize that some classic SDB symptoms may not be associated with the presence of occult SDB. Clinicians caring for older veterans with insomnia should also consider the high prevalence of occult SDB when initiating therapies for insomnia, particularly if pharmacological treatments that may affect SDB severity are being considered or if increased sleepiness during the early weeks of CBT-I is a concern. Additional studies are needed to understand why SDB among older veterans is so commonly underdiagnosed and how best to address this very common disorder in the context of existing healthcare systems.

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CH Fung, JL Martin, JM Dzierzewski et al


DISCLOSURE STATEMENT

Funded by the Department of Veterans Affairs Advanced Geriatrics Fellowship Program (Fung, Dzierzewski), Veterans Administration Health Services Research and Development (Alessi IIR 08-295), the American Sleep Medicine Foundation Psychi- cian Scientist Training Award (Fung), Veterans Administration Greater Los Angeles Geriatric Research, Education and Clinical Center, American Federation for Aging Research (Fung), Medical Student Training in Aging Research Program, National Institute on Aging (Park T35AG026736), the John A. Hartford Foundation (Fung, Park), the MeLife Foundation (Park), and the Lillian R. Gleitsman Foundation (Park). The authors have indicated no financial conflicts of interest. All work was completed at VA Greater Los Angeles Healthcare System. This study did not involve any off-label or investigational use.
Palatal Sensory Threshold Reflects Nocturnal Hypoxemia and Airway Occlusion in Snorers and Obstructive Sleep Apnea Patients

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Study Objectives: Upper airway sensory deficit has been reported to be associated with snoring or obstructive sleep apnea. There are limited data on the correlation between disease severity and upper airway sensation. In this study, we investigated the relationship between clinical parameters and standardized palatal sensory threshold (SPST) using Semmes Weinstein monofilaments.

Methods: We recruited 40 snorers and 19 control subjects. Palatal sensory threshold was measured in all study subjects, using Semmes Weinstein monofilaments. Standardized palatal sensory threshold was determined by subtraction of hard palate sensation from uvular sensation. All subjects with snoring underwent a modified Muller maneuver during wakefulness before polysomnography.

Results: SPST was higher in snorers than in control subjects, but did not differ according to the severity of obstructive sleep apnea. Patients with higher SPST (≥ 0.45 g/mm²) were older and had more severe hypoxemia indices: lower nadir oxyhemoglobin saturation (SpO₂) and higher percentage of sleep time at < 90% SpO₂. Adjusted for age, sex, neck circumference, and body mass index, SPST was correlated with the apnea-hypopnea index and hypoxemia indices. With a cutoff value ≥ 0.45 g/mm², the sensitivity of SPST for nocturnal hypoxemia (nadir SpO₂ < 80%) was 81.3%. Patients with higher SPST (≥ 0.45 g/mm²) showed more airway occlusion in modified Muller maneuver, than those with lower values.

Conclusions: The SPST measured using Semmes Weinstein monofilaments reflects nocturnal hypoxemia and airway occlusion. This test provides a potential tissue marker of the severity of hypoxemia in patients who snore.

Keywords: Hypopnea, apnea, hypoxemia, sensation, threshold

Citation: Kim SW; Park HW; Won SJ; Jeon SY; Jin HR; Lee SJ; Chang DY; Kim DW. Palatal sensory threshold reflects nocturnal hypoxemia and airway occlusion in snorers and obstructive sleep apnea patients. J Clin Sleep Med 2013;9(11):1179-1186.

Obstructive sleep apnea hypopnea syndrome (OSAS) is characterized by recurrent episodes of upper airway obstruction during sleep leading to nocturnal hypoxemia or brief arousals, which result in sleep fragmentation and changes in sleep architecture. The underlying pathophysiology of OSAS is complex and not fully understood. However, it is generally accepted that an overall imbalance of upper airway luminal pressure and muscular activity during sleep induces airway collapsibility. Among several pathomechanisms, defective upper airway reflexes, primarily sensory impairment, may be an abnormality in OSAS and make the balance difficult. Sensory dysfunction in the upper airway of patients with sleep disordered breathing has been documented and reported to be associated with the severity of disease in a few studies. Additionally, topical oropharyngeal anesthesia, leading to impaired airway reflex, can increase pharyngeal airflow resistance during wakefulness and sleep in normal subjects and in patients with obstructive sleep apnea. There are limited data on the clinical significance of pharyngeal sensory tests. Furthermore, sensory tests introduced previously may not be practical because they were developed for specific studies and may be difficult to use generally in the clinical setting.

To check palatal sensory threshold (PST), we used the Semmes Weinstein monofilament examination, which is a noninvasive, inexpensive, and easy-to-apply test for diabetic peripheral sensory neuropathy, and for sensory threshold determination in various clinical settings. We also standardized the PST by subtracting the sensory threshold examined in
the non-collapsible hard palate area from the threshold in the uvula, the most collapsible area. The aim of this study was to investigate the relationship between clinical parameters and standardized palatal sensory threshold (SPST).

MATERIALS AND METHODS

Subjects

All snorers (n = 40) underwent full overnight polysomnography, including airflow, respiratory movements, body position, snoring, and pulse oximetry (Somte; Compumedics, Melbourne, Australia). Apnea was defined as a drop in peak thermal sensor excursion by ≥ 90% of baseline for ≥ 10 s; hypopnea was defined as a drop in nasal pressure signal excursion by ≥ 30% of baseline for ≥ 10 s with ≥ 4% desaturation, according to the 2007 recommendations of the American Academy for Sleep Medicine. The proportion of snoring was expressed as the number of epochs with > 50% snoring signal/total number of epochs. Thirty snorers with OSAS (15 mild apnea patients, with an apnea-hypopnea index [AHI] between 5 and 20 events/h; 15 moderate-to-severe apnea patients with AHI ≥ 20 events/h), 10 simple snorers (AHI < 5 events/h), and 19 non-snorers were included. Snorers with suspicion of OSAS were recruited consecutively from our sleep apnea clinic. Among the patients who visited our rhinology clinic, non-snorer volunteers (n = 19) with no symptoms compatible with OSAS, including habitual snoring, daytime sleepiness, and morning headache, as confirmed by their bed partners, were enrolled for control data on PST. A medical history and clinical data, including tonsil size and body mass index (BMI), were obtained from all subjects. Tonsil size was graded on a 5-point scale: 0 = absent, 1+ = small within the tonsillar fossa, 2+ = extends beyond the tonsillar pillar, 3+ = hypertrophic but not touching in the midline, 4+ = hypertrophic and touching in the midline.

Exclusion criteria were as follows: neurological illness or medical disease, including diabetes mellitus capable of causing peripheral neuropathy; previous soft palate surgery; previous treatment for OSAS; recent upper airway infection or inflammation; exaggerated gag reflex that prevented pharyngeal examination; and no visible soft palate. This study was approved by the Institutional Review Board of Gyeongsang National University Hospital.

Palatal Sensory Threshold

One investigator (WSJ), who was blinded to the study groups, used Semmes Weinstein monofilaments to examine the PST in patients and control subjects at 3 sites: the center of the uvula, and the right and left lateral walls of the hard palate, 2 mm from the border between the hard and soft palates (Figure 1A, 1B). One set of the test consists of 20 monofilaments ranging from the lightest (0.008 g/mm²) to the heaviest (300 g/mm²). The monofilaments were applied perpendicularly to the 3 sites in random order until they bent for 1 s. Starting with the lightest monofilm, the value of the monofilament that caused the patient to feel the sensation for the first time was determined as the PST. The uvular sensory threshold was defined as the lightest monofilm value recognized at the uvula, and the reference sensory threshold was the average value of the lightest monofilaments recognized at the lateral walls of the hard palate. We calculated SPST by subtracting the reference sensory threshold from the uvular sensory threshold, to minimize individual sensitivity.
Airway occlusion were counted and compared between groups. To be significant airway occlusion. The number of sites showing representative photos. Grade 3 or 4 redundancy was considered consensus was reached by our research team by reviewing obstruction. Before polysomnographic data were obtained, 2 = ~50% obstruction, 3 = ~75% obstruction, and 4 = complete obstruction. On a 5-point scale: 0 = no obstruction, 1 = ~25% obstruction, 2 = ~50% obstruction, 3 = ~75% obstruction, and 4 = complete obstruction. Because topical anesthesia can influence the results of polysomnography, a modified Muller maneuver was conducted to snorers at the first visit to the sleep apnea clinic. The procedure was performed with the patient in the supine position after application of topical nasal anesthesia (4% lidocaine plus 0.5% ephedrine spray). A flexible nasopharyngoscope was inserted through anesthetized nasal cavity. Redundancy of the soft palate, lateral pharyngeal wall, and tongue base was evaluated during a maximal inspiratory effort against a closed mouth and sealed nose. Redundancy was graded by examiners potential bias, therefore, the PST test was conducted by an independent investigator blinded to the design and goal of the study.

### Results

Subject characteristics are summarized in Table 1. Briefly, subjects with moderate-to-severe OSA had wider neck circumference than other subjects. The severity of OSA was well correlated with some polysomnography parameters related to oxygen saturation, including lowest oxygen saturation and oxygen desaturation index ([ODI] \( p < 0.05 \)). Control subjects showed significantly lower BMI than other subjects, which might result in the distinct appearance of patients among groups. To avoid potential bias, therefore, the PST test was conducted by an independent investigator blinded to the design and goal of the study.

### Test-Retest Reliability of the PST Test

At all 3 test sites, the PST test was fairly reproducible. The ICC (95% CI) was 0.95 (0.88-0.98), 0.97 (0.93-0.99), and 0.98 (0.94-0.99) at the right and left reference areas and uvula, respectively. Because the PST test showed high test-retest reliability for non-snorer volunteers, it was not performed on snorers or sleep apneic patients.

### Palatal Sensory Threshold Values in Each Group

In control subjects, the uvular sensory threshold was 0.25 ± 0.31 g/mm², the reference sensory threshold was 0.24 ± 0.26 g/mm², and SPST was 0.00 ± 0.14 g/mm². Although there were individual differences, the standard deviation of the mean decreased from 0.31 g/mm² to 0.14 g/mm² after standardization.

### Differences in Palatal Sensory Threshold by OSAS Severity

In simple snorers, the uvular sensory threshold was 2.06 ± 2.69 g/mm², the reference sensory threshold was 0.96 ± 0.10 g/mm², and the SPST was

| Table 1—Demographic data and clinical characteristics of the study population |
|-----------------|-----------------|-----------------|-----------------|-----------------|
|                 | Non-snorer  (N = 19) | Simple snorer  (N = 10) | Mild apneic patient  (N = 15) | Moderate to severe apneic patient  (N = 15) |
| Age, years      | 41.5 (13.3) | 39.8 (13.4) | 47.5 (13.9) | 44.7 (12.9) |
| Male/Female     | 13/6 | 9/1 | 10/5 | 15/0 |
| Neck circumference, cm | 37.8 (2.6) | 38.6 (1.8) | 37.5 (2.8) | 39.8 (3.8) * |
| Tongue size, grade | 2.2 (0.3) | 2.2 (0.4) | 2.4 (0.5) | 2.0 (0.6) |
| BMI, kg/m²      | 23.3 (2.2) * | 25.4 (3.3) | 24.6 (3.2) | 27.2 (5.4) |
| PSG             |          |          |          |          |
| AHI, events/h   | NA | 2.8 (0.9) | 11.9 (4.8) | 42.7 (15.2) † |
| Mean awake SpO₂, % | NA | 95.1 (1.8) | 95.6 (1.6) | 95.1 (1.9) |
| Nadir SpO₂, %   | NA | 89.2 (5.0) | 82.7 (4.8) | 66.6 (12.9) † |
| ODI (> 4%), events/h | NA | 3.0 (2.6) | 11.9 (8.4) | 42.8 (16.7) † |
| Percentage of time spent below 90% of SpO₂, % | NA | 0.8 (1.0) | 5.2 (10.3) | 28.6 (25.5) † |
| Proportion of snoring, % | NA | 23.9 (17.3) | 22.5 (12.8) | 43.2 (13.4) * |

HT, hypertension; BMI, body mass index; PSG, polysomnography; SpO₂, oxygen saturation; AHI, apnea-hypopnea index; ODI, oxygen desaturation index; NA, not applicable. Proportion of snoring is expressed as the ratio of the number of epochs including > 50% snoring signal/total number of epochs. Analysis of variance (Kruskal-Wallis test or post hoc pair-wise Mann-Whitney U test) between the control and three patient groups, or only among the three patient groups when control data were not available. Values represent mean (SD). Parameters with symbols (*, †) differed significantly from those in other groups.

### Statistical Analyses

The results are expressed as means ± SD. Test-retest reliability of the PST testing was assessed by the intraclass correlation coefficients (ICC). Group analysis was performed using the Mann-Whitney U test or Kruskal-Wallis test. Correlations between clinical parameters and polysomnographic data were evaluated with Pearson correlation coefficient or partial correlation coefficient adjusted for confounding factors. Fisher exact test was used to compare qualitative data. All data were analyzed with SPSS software (ver. 13.0; SPSS, Inc., Chicago, IL, USA). Statistical significance was set at \( p < 0.05 \).
Mild apneic patients had a uvular sensory threshold of 2.42 ± 2.69 g/mm², reference sensory threshold of 1.29 ± 1.32 g/mm², and SPST of 1.13 ± 1.59 g/mm². Snorers had higher uvular and reference sensory thresholds than control subjects. Subjects with moderate-to-severe apnea had higher uvular sensory threshold than simple snorers. After standardization, additionally, the differences between simple snorers and control subjects were more significant (*p < 0.05, **p < 0.001).

Sensitivity of SPST for Nocturnal Hypoxemia Screening

The SPST results of snorers with nocturnal hypoxic events are shown in Figure 3. Snorers with severe hypoxemia (nadir SpO₂ < 80%) had higher SPST than those with mild hypoxemia (nadir SpO₂ ≥ 80%; p = 0.008), and the difference tended to be greater in the elderly. With a cutoff level of 0.45 g/mm², the sensitivity of the SPST test for screening nocturnal hypoxemia (nadir SpO₂ < 80%) was 81.3% (Figure 4). The area under the receiver operating characteristic curve was 0.719 (95% CI 0.540-0.898; p = 0.023).

Differences in Clinical Characteristics by SPST

When snorers were divided into 2 groups in terms of SPST, the higher threshold group (≥ 0.45 g/mm²) were older (p = 0.005) and had a lower nadir SpO₂ (p = 0.009) and higher percentage of time spent < 90% SpO₂ (p = 0.023). There was no difference in any other polysomnographic parameter between the 2 groups (Table 2). However, a correlation analysis showed an association between SPST and additional clinical parameters such as AHI, BMI, neck circumference, and ODI, as well as percentage of time spent below 90% SpO₂ and nadir SpO₂. Furthermore, when adjusted for confounding factors such as age, neck circumference, and BMI, SPST showed a significant correlation with AHI and 3 hypoxemia indices (Table 3).
Although there was no difference in tonsil size between groups according to SPST or OSAS severity (Tables 1, 2), the percentage of cases with ≥ 2 airway occlusion sites by the Muller maneuver was significantly higher for the higher SPST group (≥ 0.45 g/mm²) compared with the lower SPST group (< 0.45 g/mm²; 76% vs. 31%, respectively; p = 0.015). In contrast, there was no difference between groups by OSAS severity (Figure 5).

**DISCUSSION**

To sum up our results, the PST test using Semmes Weinstein monofilament was a reliable method. Standardized PST values by subtracting the sensory threshold value at the hard palatal reference point from uvular sensory threshold were significantly different between control subjects and snorers/OSA patients. The level of SPST was closely related to the severity of nocturnal hypoxemia, and the SPST of ≥ 0.45 g/mm² indicated the occurrence of nadir SpO₂ < 80% with a sensitivity of 81.3%. Additionally, higher SPST level was associated with airway occlusion at multiple sites.

**Methodological Issues**

To our knowledge, no reported study has attempted to standardize sensory threshold values because the control sites used, i.e., the lip, tongue, and hand, are innervated differently compared with the palatal mucosa. In this study, a non-collapsible area innervated by the lesser palatine nerve, which also innervates the uvula, was used as a control site. Standardized palatal sensory threshold was calculated by subtracting the

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**Table 2**—Comparison of clinical characteristics according to standardized palatal sensory threshold in snorers with and without obstructive sleep apnea

<table>
<thead>
<tr>
<th>Standardize palatal sensory threshold</th>
<th>&lt; 0.45 g/mm² (N = 19)</th>
<th>≥ 0.45 g/mm² (N = 21)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>39.53 (12.50)</td>
<td>49.15 (12.78)</td>
<td>0.005*</td>
</tr>
<tr>
<td>Male/Female</td>
<td>15/4</td>
<td>19/2</td>
<td>0.398*</td>
</tr>
<tr>
<td>Polysomnography</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean awake SpO₂, %</td>
<td>95.29 (1.40)</td>
<td>95.13 (1.80)</td>
<td>0.897*</td>
</tr>
<tr>
<td>AHI, events/h</td>
<td>14.90 (14.35)</td>
<td>27.63 (22.68)</td>
<td>0.095*</td>
</tr>
<tr>
<td>Nadir SpO₂, %</td>
<td>82.58 (7.62)</td>
<td>72.16 (14.67)</td>
<td>0.009*</td>
</tr>
<tr>
<td>ODI (&gt; 4%), events/h</td>
<td>11.89 (12.56)</td>
<td>28.23 (24.69)</td>
<td>0.252*</td>
</tr>
<tr>
<td>Percentage of time spent below 90% of SpO₂, %</td>
<td>4.89 (8.88)</td>
<td>20.77 (25.76)</td>
<td>0.023*</td>
</tr>
<tr>
<td>Proportion of snoring, %</td>
<td>29.12 (16.66)</td>
<td>31.02 (17.57)</td>
<td>0.622*</td>
</tr>
</tbody>
</table>

BMI, body mass index; SpO₂, oxygen saturation; AHI, apnea-hypopnea index; ODI, oxygen desaturation index. Proportion of snoring is expressed as the ratio of the number of epochs including > 50% snoring signal/total number of epochs. †Fisher exact test to compare qualitative data. *Mann-Whitney U test to compare between groups. Bold type, p < 0.05.

**Table 3**—Correlation between palatal sensory threshold and clinical parameters in snorers with and without obstructive sleep apnea

<table>
<thead>
<tr>
<th>Age</th>
<th>AHI</th>
<th>NC</th>
<th>BMI</th>
<th>Nadir SpO₂</th>
<th>SpO₂ &lt; 90%</th>
<th>ODI</th>
<th>Snoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sense (U)</td>
<td>0.449**</td>
<td>0.387*</td>
<td>0.278</td>
<td>0.283</td>
<td>-0.482*</td>
<td>0.415*</td>
<td>0.435*</td>
</tr>
<tr>
<td>Sense (R)</td>
<td>0.366*</td>
<td>0.130</td>
<td>-0.167</td>
<td>-0.167</td>
<td>-0.141</td>
<td>0.184</td>
<td>0.158</td>
</tr>
<tr>
<td>Sense (S)</td>
<td>0.380*</td>
<td>0.393*</td>
<td>0.375*</td>
<td>0.371*</td>
<td>-0.528*</td>
<td>0.405*</td>
<td>0.440*</td>
</tr>
</tbody>
</table>

Partial correlation coefficient adjusted by age, gender, neck circumference, and BMI

| Sense (U) | NA | 0.431* | NA | NA | -0.413* | 0.429* | 0.489** | 0.212 |
| Sense (R) | NA | 0.268 | NA | NA | -0.190 | 0.234 | 0.291 | 0.169 |
| Sense (S) | NA | 0.407* | NA | NA | -0.431* | 0.438* | 0.465** | 0.173 |

AHI, apnea-hypopnea index; NC, neck circumference; BMI, body mass index; Min. SpO₂, minimal oxygen saturation; SpO₂ < 90%, percentage of time spent below 90% SpO₂; ODI, oxygen desaturation index; Sense (U), uvular sensory threshold; Sense (R), sensory threshold in the reference area; Sense (S), standardized sensory threshold [Sense (U) – Sense (R)]; NA, not applicable. Values are expressed as Pearson’s correlation coefficients or partial correlation coefficients. *p < 0.05, **p < 0.01. Bold type, p < 0.05.
sensory threshold in this non-collapsible area from that in the center of the uvula. Control subjects had nearly the same sensory threshold in the uvula and hard palate; SPST = 0.00 ± 0.14 g/mm². Less variability in the standard deviation of SPST, compared with that of the uvular sensory thresholds, indicates that this method may compensate for individual differences in factors such as age, gender, and race. Thus, SPST may reflect OSAS-specific sensory dysfunction more precisely than other sensory threshold tests previously reported.

The center of the uvula was chosen as the test site in this study because it had been reported to show histopathological findings such as disorganization of epithelial and connective tissues and decreased number of nerves in OSAS.16-19 The Semmes Weinstein monofilaments we used are an excellent tool for targeting the center of the uvula. As mentioned above, this method has been validated for checking sensory thresholds in many clinical studies.11-13

Airway collapsibility can be estimated by assessing electromyographic activity in response to negative pressure20 or changes in esophageal pressure during sleep.8 Airway collapsibility is influenced by not only deficits in respiratory neuro-muscular control but also redundant anatomical structures such as palatine tonsils and edema of pharyngeal tissues.21 Several previous studies have documented that snoring-induced chronic inflammation can cause upper airway mucosal thickening22,23 and peripheral nerve injury,24,25 which represent anatomical redundancy and deficits in neuromuscular reflexes, respectively. The modified Muller maneuver could not reflect true collapsibility of the upper airway observed during natural sleep because, of course, it was conducted in awake patients. Given previous findings, however, redundancy identified by the modified Muller maneuver was presumed to mirror airway collapsibility to some extent. In the present study, subjects with higher SPST showed multilevel airway obstructions more frequently than those with lower SPST (Figure 5), indicating that higher sensory deficit is associated with broader redundancy in the soft tissues of the upper airways. As no significant difference in tonsil size was found between subjects with higher and lower SPSTs (Table 2), it was assumed that redundancy of the upper airway may be due to the sensory deficits and anatomical factors other than palatine tonsils (i.e., mucosal thickening). Despite these results, further methods such as drug-induced sleep endoscopy are needed to confirm an association between airway collapsibility and sensory deficits in the upper airway.

Pathomechanism of Sensory Dysfunction

Obstructive sleep apnea is characterized by repetitive upper airway collapse, causing nocturnal hypoxemia and sleep fragmentation. Obstructive sleep apnea or snoring is well known to be associated with sensory deficits.26 A few studies have demonstrated that the severity of OSAS is correlated with the degree of sensory deficit in the upper airway.2 Our study is consistent with these studies. Standardized palatal sensory threshold showed a positive association with AHI when adjusted for age, BMI, and neck circumference (Table 3). However, no difference in the severity of snoring was found between subjects with higher and lower SPST values (Table 2). This may be because the percentage of epochs having > 50% snoring signal was used as a snoring parameter without considering the total number of years for which subjects had snored. Obtaining reliable data on a snoring period is difficult because total snoring years are not remembered correctly by most patients. As a marker for the severity of snoring, in addition, the intensity may be a better one compared to the proportion of snoring time. In our polysomnography system, however, the intensity of snoring could not be evaluated because snoring was measured by nasal pressure transducer, not by microphone or sound level meter, which is a limitation of this study.

Several pathomechanisms that could lead to nerve or sensory receptor injury in the upper airway have been suggested. Airway edematous inflammation, presumably related to repetitive snoring-induced vibration and forceful suction collapse of the upper airway during sleep, could potentially damage the nerve endings in the upper airway mucosa.16,18 Another possible explanation is that nocturnal hypoxemia in OSAS patients may induce peripheral neuropathy. Chronic hypoxemia, like chronic obstructive pulmonary disease and diabetes mellitus, is well known to induce peripheral neuropathy.26 Although there is no confirmatory evidence of peripheral neuropathy caused by intermittent hypoxemic condition occurring at night in OSA patients, some studies have provided evidence of peripheral neuropathy in OSA patients.27,28 In a previous case-control study, median nerve conduction was examined in OSA and control subjects. Preischemic sensory and mixed nerve potential amplitudes and sensory conduction velocity were lower in OSA patients than in control subjects, and the severity of peripheral nerve dysfunction was partly related to the level of nocturnal hypoxemia.27 Similarly, in another case-control study, OSA patients had significantly more clinical signs of polyneuropathy than control subjects. Furthermore, the severity of nerve damage was correlated with the percentage of the night time with oxygen
saturation below 90%. Our study also showed a close relationship between nocturnal hypoxemia and the SPST, indicating that chronic intermittent hypoxemia may play a role in aggravating sensory defects. In addition to differences in the sensory threshold at the uvula, there were also differences in the sensory threshold at a non-collapsible reference area between snorers/apneic patients and control subjects (Figure 2). These findings could be evidence of hypoxemia-induced neuropathy in OSAS, although further study is required to exclude the possibility that chronic inflammation due to snoring-induced trauma, and not hypoxemia, influenced the non-collapsible area.

The consistent association between SPST and hypoxemia parameters (Table 2) prompted us to try to simplify the diagnosis of nocturnal hypoxemia. According to the dissociation curve of oxyhemoglobin, when blood is 70% to 80% saturated, the partial pressure of oxygen is 40 mm Hg, which is the normal case at capillaries in resting tissues. This indicates that oxygen is not efficiently released from hemoglobin and is delivered to the tissues at under 70% to 80% SpO2, which is associated with hypoxic tissue injury. Thus, we chose a nadir SpO2 < 80% as the criterion for nocturnal hypoxemia in the receiver operating characteristic curve analysis. Consequently, the severity of nocturnal hypoxemia was associated with the level of SPST (Figure 3), and a cutoff level of 0.45 g/mm² was useful for predicting the existence of nocturnal hypoxemia (nadir SpO2 < 80%) with a sensitivity of 81.3% (Figure 4).

One limitation of this study is that control subjects did not undergo polysomnography. Although no control subjects reported history of witnessed snoring or apnea, some of them might have had undiagnosed snoring or apnea. Additionally, our study design does not provide information whether the sensory dysfunction in the upper airway region is primary or acquired. A longitudinal cohort study on OSA patients with no sensory dysfunction will be needed to prove it. If the sensory dysfunction is acquired, it can possibly be reversible by long-term treatment with nasal continuous positive airway pressure therapy.

In conclusion, SPST using Semmes Weinstein monofilaments reflected nocturnal hypoxemia and airway occlusion assessed using the modified Muller maneuver. This noninvasive and easy-to-use test may provide a potential tissue marker of the severity of hypoxemia in snorers/OSA patients.

ABBREVIATIONS

AHI, apnea-hypopnea index
BMI, body mass index
ODI, oxygen desaturation index
OSAS, obstructive sleep apnea/hypopnea syndrome
PST, palatal sensory threshold
SPST, standardized palatal sensory threshold

REFERENCES

ACKNOWLEDGMENTS

Sang-Wook Kim and Hyun Woo Park contributed equally to this article.

SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication January, 2013
Submitted in final revised form June, 2013
Accepted for publication June, 2013

DISCLOSURE STATEMENT

This was not an industry supported study. The authors have indicated no financial conflicts of interest.
Air Leak during CPAP Titration as a Risk Factor for Central Apnea

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Objectives: Emergence of central sleep apnea has been described in the setting of continuous positive airway pressure (CPAP) initiation. The underlying mechanism is unclear; however, we postulate that air leak washing out anatomical dead space is a contributing factor.

Design: Data were obtained from 310 patients with obstructive sleep apnea (OSA) who underwent either split-night or full-night CPAP titration during January to July of 2009. The majority of patients (n = 245) underwent titration with a nasal mask. Average total leak and maximum total leak were measured at therapeutic CPAP level. Unintentional leak was calculated by subtracting manufacturer-defined intentional leak from maximum leak.

Results: Subjects were divided into two groups: central apnea index (CAI) during titration < 5/hour and ≥ 5/hour. The groups were similar in terms of gender, age, BMI, and AHI. The CAI < 5 group had a median average leak of 45.5 L/min (IQR 20.8 L/min) versus 51.0 L/min (IQR 21.0 L/min) with CAI ≥ 5 (p = 0.056). Maximum leak was 59.5 L/min (IQR 27.0 L/min) with CAI < 5 and 75.0 L/min (IQR 27.8 L/min) with CAI ≥ 5 (p = 0.003). In the subset of subjects titrated using a nasal mask, median average leak was 42.0 L/min (IQR 17.0) in the CAI < 5 group and 50.0 L/min (IQR 16.8) in the CAI ≥ 5 group (p = 0.001). In the CAI < 5 group, median maximum leak was 57.0 L/min (IQR 23.0) versus 74.5 L/min (IQR 24.3) in the CAI ≥ 5 group (p < 0.001).

Conclusions: Leak during CPAP titration is associated with the development of acute central apnea; these data may have mechanistic and therapeutic implications for complex apnea.

Keywords: Sleep apnea, air leak, central apnea

Commentary: A commentary on this article appears in this issue on page 1193.

Citation: Montesi SB; Bakker JP; Macdonald M; Hueser L; Pittman S; White DP; Malhotra A. Air leak during CPAP titration as a risk factor for central apnea. J Clin Sleep Med 2013;9(11):1187-1191.

Obstructive sleep apnea (OSA) is a common yet underdiagnosed and underappreciated disorder.1 Once diagnosed, continuous positive airway pressure (CPAP) therapy is the treatment of choice. CPAP has been shown to be effective at reducing obstructive apnea when adequate pressure is applied. However, in a proportion of patients, initiation of CPAP treatment has been associated with the development of central apneas.2,3 Traditionally, central apnea has been observed in the setting of congestive heart failure,4,6 cerebrovascular disease,7,8 and high altitude.9 More recently, the recognition of CPAP-induced central apnea has led to considerable discussion.3,10,11 The terms “complex sleep apnea” and “treatment-emergent central apnea” have been used to describe the development of central apnea upon exposure to CPAP.3,10 From retrospective data of over 1200 patients with OSA initiated on CPAP, 6.5% were found to have treatment-emergent acute central apnea, with persistence after 8 weeks in only 1.5% of titrations.12 Prior observational studies have also supported that for the majority of patients, the central apneas resolve with time.13 Patients who have a poor initial experience with CPAP may be reluctant to use CPAP in the long term; therefore, stabilization of breathing acutely may have benefits. On the other hand, expensive newer devices may be unnecessary if the breathing pattern is likely to stabilize spontaneously without any impact on clinical outcome.

Several possible mechanisms are theorized to explain the development of central apneas with the initiation of CPAP therapy.14,15 First, pulmonary stretch receptors may inhibit ventilatory motor output, such that central apneas would be predicted to occur with high CPAP levels due to lung stretch.15 Second, CPAP serves to stabilize the upper airway, which would be predicted to increase controller gain in these patients.15,16 Chemoresponsiveness, defined as the body’s ventilatory response to CO2 plus the ability to respond to chemical stimuli (an open airway), would increase with CPAP-induced patency of the upper airway.17 Thus, central apnea may occur due to CPAP-induced hypocapnia.18 Third, and of particular importance in the current study, CPAP may reduce PaCO2 by reducing the amount of dead space, particularly in patients who develop leak while on therapy.15 The CPAP mask and the upper airway are both sources of re-breathing, and the delivery of fresh gas from the CPAP machine may serve to wash out...
these sources of re-breathing, therefore lowering PaCO₂ for any given minute ventilation. For example, in nasal CPAP treated patients with mouth leak, there may be a lowering of PaCO₂ due to washout of anatomical dead space in the upper airway. Thus, a number of potential mechanisms exist which could explain why these central apneas occur upon CPAP initiation. Deciphering the underlying mechanisms has clinical importance as it may help inform the optimal intervention to reduce these events.

Based on the above logic, we sought to determine whether air leak was associated with the development of central apnea among patients undergoing CPAP titration. We performed a consecutive case series of patients with predominantly obstructive events undergoing CPAP titration to test the hypothesis that leak would be higher in those developing central apnea.

**METHODS**

**Protocol**

Data were obtained from adult patients with OSA undergoing either full-night diagnostic polysomnography followed by a separate attended titration, or split-night diagnostic/titration studies, at Sleep HeathCenters affiliated with Brigham and Women’s Hospital in Boston, MA, during the time period of January to July of 2009. Patients were excluded if they were known to have one of the following medical conditions: lung disease including home oxygen use, congestive heart failure, valvular heart disease or cardiomyopathy, atrial fibrillation, implanted cardiac defibrillator or pacemaker. Use of oxygen during the sleep study and a total < 15 minutes of sleep time at optimal CPAP level were also grounds for exclusion.

Protocol approval was obtained through the Allendale Institutional Review Board (MR-0821-RFLW-BOS).

**Sleep Studies**

PSG consisted of electroencephalogram (C4-A1, C3-A2, O2-A1, O1-A2), bilateral electro-oculogram, bilateral chin and tibial electromyogram, electrocardiogram, airflow using thermistor and nasal pressure sensors, abdominal and thoracic respiratory excursion measured by piezo bands, pulse oximetry, and body position. Sleep studies were performed and scored by registered polysomnographic technologists according to published guidelines (blinded and naive to the goals of our study). Subjects were titrated using either oro-nasal cushion, or nasal pillow masks as determined by technologist and subject preference.

An OmniLab multi-mode titration device (Respironics, Murrysville, PA, USA) was used for both the split and full-night CPAP titrations, which recorded a continuous estimation of total leak. The average total leak and the maximum total leak were measured at optimal CPAP level. Maximum leak was defined by non-transient maximal elevation with duration > 3 seconds. Any periods of time during which the CPAP mask was removed were excluded from data analysis. Intentional leak was for each type of mask used was defined according to manufacturer specifications. The amount of excess leak was determined by subtracting intentional leak from total leak.

**Additional Measured Variables**

Variables obtained for each subject included gender, age, body mass index (BMI), and Epworth Sleepiness Scale (ESS) score. The presence or absence of known hypertension, diabetes mellitus, or ischemic heart disease was recorded.

**Data Analysis**

Statistical analysis was performed using SigmaStat Version 11 (Systat Software Inc., IL USA). Continuous data were analyzed for normality of distribution and homogeneity of variance; all outcome data were not normally distributed; therefore, between-group comparisons were made using Mann-Whitney tests. Categorical data were compared using \( \chi^2 \) tests. All \( p \)-values are 2-sided, and were considered statistically significant at \( \leq 0.05 \).

**RESULTS**

**Subjects**

Data from 310 subjects with predominantly obstructive events during the diagnostic period were obtained. Of these, 240 titrations were performed with nasal CPAP masks (either cushion or pillow designs). Subjects were divided into 2 groups: those that had a central apnea index < 5 (n = 280) and ≥ 5/h (n = 30) during the titration period (at optimal CPAP level). The 2 groups were not significantly different in terms of age, BMI, ESS, gender, or the presence of hypertension, diabetes mellitus, or ischemic heart disease as detailed in Table 1. The groups were similar in terms of diagnostic AHI, sleep efficiency, and the % of REM sleep. The groups diverged when comparing the diagnostic CAI, the titration AHI, and titration sleep efficiency (see Table 1).

**Leak Measurements and Analysis**

When performing leak analysis for all 310 subjects, trends towards differences were found between the 2 groups with regards to the amount of average and peak leak measured (see Table 2). Subjects in the CAI < 5 group had an average leak of 45.5 L/min with an average unintentional leak of 19.0 L/min, whereas subjects in the CAI ≥ 5 group had an average leak of 51.0 L/min with an average unintentional leak of 24.5 L/min (\( p = 0.056 \) for average leak and \( p = 0.057 \) for average unintentional leak). Differences were also seen in peak leak amounts between the 2 groups with a peak and peak excess leak of 59.5 L/min and 34.0 L/min, respectively, with CAI < 5 and a peak and peak excess leak of 75.0 L/min and 52.5 L/min, respectively with CAI ≥ 5 with \( p \)-values of 0.003 and 0.001 (peak and excess peak, respectively).

For the 240 subjects undergoing nasal CPAP titrations only, significant differences were found between the 2 groups in both average leak and peak leak measurements (Table 3). Average leak was 42.0 L/min with an average excess leak of 18.0 L/min in the CAI < 5 group and 50.0 L/min with an average excess leak of 25.5 L/min in the CAI ≥ 5 group (\( p = 0.001 \) and \( p = 0.005 \) for average leak and average excess leak, respectively). In the
CAI < 5 group, peak leak and peak excess leak were 57.0 L/min and 33.0 L/min versus 74.5 L/min and 53.0 L/min in the CAI ≥ 5 group (p < 0.001 and p < 0.001, respectively).

**DISCUSSION**

During this study, we observed that both average and maximum leak were associated with the development of central apnea during CPAP titration, particularly in subjects using a nasal mask. These findings were independent of the applied CPAP level and comorbidities which were balanced between groups, which may have confounded prior reports of complex apnea. We believe that nasal masks may be particularly problematic in predisposing to central apneas since the fresh gas can easily wash out the anatomical dead space when exiting through the mouth. However, oro-nasal masks may worsen pharyngeal mechanics by forcing the mandible posteriorly. Thus, treatment decisions may need to be individualized at least for certain patients.

The development of central apnea while on CPAP has a number of important physiological implications. The evolutionary advantage of anatomical dead space has often been questioned, since the “wasting” of 25% to 30% of each breath would seem inefficient upon initial consideration. Some have suggested that the development of speech may have required anatomical dead space rather than a respiratory apparatus with no ability to control airflow. However, one interpretation of our findings, albeit speculative, might be that the anatomical dead space provides stabilization of breathing. That is, without anatomical dead space, the propensity for breathing instability would be high in response to perturbations (for example, ascent to altitude, exercise, cardiac disease). Assuming typical minute ventilation and CO₂ production, one would calculate that a 28 mL change in dead space would yield a 3 mm Hg fall in PaCO₂. Depending on the prevailing CO₂ apnea threshold, even a small change in dead space may produce central apnea in susceptible individuals. Although one might predict a lowering of minute ventilation to occur in the face of hypo-capnia, such a response is clearly not observed to an adequate extent among those patients who develop central apnea. Thus, mechanoreceptive and chemoreceptive homeostatic
mechanisms are clearly inadequate to eliminate central apnea acutely. However, based on our study design we have no way of proving that leak caused central apneas or instead was a marker of overtitration (or other factors) that yielded central apnea by other mechanisms (for example, pulmonary stretch or upper airway dilation). The fact that not all CPAP-treated patients develop central apnea may speak to the importance of raising end-expiratory lung volume such that larger lung volumes, and therefore greater gas stores, may improve breathing stability on CPAP. Moreover, the fact that oral appliance-induced central apnea is extremely rarely reported suggests that mechanisms beyond upper airway opening are important in yielding central apnea.

Classic literature by Fowler et al. has reported marked reductions in dead space through expiratory breathhold. The authors surmised that mixing would occur in the distal airways, such that a pause in breathing would facilitate CO₂ excretion as they observed with experimental measurements. The authors described a moving of the peripheral boundary of pure inspired gas up the bronchial tree during breathhold. In theory, a central apnea may produce similar physiology such that CO₂ may be cleared from the distal airways via diffusion and potentially cardioballistic mixing. Thus, the development of central apnea may further increase the propensity for PaCO₂ lowering by mechanisms described by Fowler in the 1940s. The combination of CO₂ elimination from the proximal airways by CPAP (via leak) plus the Fowler mechanisms during breathhold may work together to perpetuate central apnea. The fact that treatment-emergent central apnea generally resolves over time suggests that either resolution of leak or alteration of the chemical apnea threshold is occurring over time.

Despite its strengths, our study has a number of limitations which we acknowledge. First, we did not measure PetCO₂ or minute ventilation using gold standard pneumotachometers via a sealed nasal mask. Our goal was to perform a clinical study whereby patients were receiving usual care rather than being heavily instrumented, as normally is performed in our physiology laboratory. Some authors have suggested that treatment-emergent central apneas may be a function of poor sleep quality (i.e., state transition apneas), and thus our goal was to give standard instrumentation for clinical polysomnography rather than for an invasive physiological study. Moreover, a tightly sealed nasal mask to assess airflow would have defeated the purpose of our study from the standpoint of leak assessment. Second, we did not quantify changes in chest wall movement (lung volume), which may have been helpful to test the hypothesis that pulmonary stretch was having an important effect on ventilatory motor output. However, again, our goal was to perform a clinical real-world study rather than a physiological investigation. Chest wall movement is difficult to quantify in obese patients, and some increase in chest wall excursion would be expected while on CPAP. Thus, magnetometer or calibrated impedance bands would have been of interest but would not have yielded definitive data. Third, we did not systematically track adherence to CPAP among our participants in the long term. We have data on patients who received their PAP equipment from our sleep laboratory (although others receive equipment through a variety of home care companies) but did not receive ethics approval to track the patients who left our sleep laboratory for PAP treatment. Among those patients who received CPAP from our sleep laboratory, adherence was, if anything, slightly better among those patients who developed central apneas (5.1 h/night) as compared to those who did not develop central apneas (4.1 h/night). However, we would emphasize that these data represent only 212 of the total of 310 participants and may not be representative since the source of equipment may be affected by insurance coverage, socioeconomic status, etc. Thus, we cannot draw any definitive conclusions about how complex apnea may influence long-term CPAP adherence from our data. Despite these limitations, we believe that our results are interesting and that our findings are robust given the constraints of a clinical study.

In conclusion, air leak has an important association with the development of treatment-emergent central apnea, independent of applied CPAP level and common comorbidities associated with central apnea. The underlying mechanism is not clear, but we speculate that proximal airway CO₂ elimination in the setting of leak as well as breathhold mechanisms described by Fowler et al. are important contributors. It is likely that with time either the leak resolves and/or the apnea threshold is reset resulting in cessation of central apneas. Whether efforts to eliminate mask leak will lead to abrupt resolution of central apneas will require further study. While further investigation is needed, our results add to the growing body of information on treatment-emergent central apneas and may speak to some evolutionary advantage for anatomical dead space which has been previously regarded as “wasted ventilation.”

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ACKNOWLEDGMENTS

Data collection was performed at Sleep HealthCenters affiliated with Brigham and Women’s Hospital. Abstract format of results was presented at SLEEP 2010, the 24th Annual Meeting of the Associated Professional Sleep Societies, LLC.

SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication March, 2013
Submitted in final revised form July, 2013
Accepted for publication July, 2013
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DISCLOSURE STATEMENT

This was not an industry supported study. Ms. Macdonald, Ms. Hueser, Mr. Pittman, and Dr. White are employees of Philips Respironics. Dr. Malhotra has received consulting and/or research income from NIH, AHA, Philips, SGS, SHC, Apnex, Apnicure, and Pfizer but has relinquished all outside personal income since May 2012. Drs. Montesi and Bakker have indicated no financial conflicts of interest.
The Complexities of Complex Sleep Apnea

Commentary on Montesi et al. Air leak during CPAP titration as a risk factor for central apnea.


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The discussion regarding the pathophysiology of complex sleep apnea (CompSAS, CPAP-emergent sleep apnea) has been taking place for about a decade, since the original description of this syndrome by Gilmartin et al.1 Several mechanisms, including elevated chemoreceptor sensitivity, decreased arousal threshold, prolonged circulation time, and use of opioid medications have been suggested to induce central apneas in patients with obstructive sleep apnea (OSA) treated with continuous positive airway pressure (CPAP) and other methods. These diverse processes likely all have some merit as contributors to the pathophysiology of CompSAS, leading to the striking heterogeneity of phenotypes in this disorder.2

The work of Montesi et al.3 introduces another piece to this puzzle. In a subset of patients with OSA and without significant cardiac disease, the authors observed an association between the appearance of central apneas at CPAP pressure controlling the airway obstruction and the mask leak at that pressure. Having divided their group of patients with OSA into patients displaying central apneas with central apnea index (CAI) of more than 5 (consistent with CompSAS) and less than 5, they reported significantly higher mask leaks in patients with higher CAIs. The authors speculate that improving mask leakage over time might be the factor responsible for known decline in central apneas with continued CPAP therapy in some patients.

Unfortunately, as the authors themselves admit, the design of the study does not allow making any conclusions as to the causal relationships between mask leak and central apneas, nor does it allow answering what about the leaking mask might make the central apneas appear. They propose that the higher CAIs observed in patients with leaking masks were due to an increased washout of the CO₂ in the upper airway dead space leading to a drop in pCO₂ closer to the apneic threshold, thus making the central apneas appear. While this is possible, the paucity of presented data (lack of polysomnographic variables such as arousal indices during the PAP titration, noninvasive measurements of pCO₂ at night, or blood gas pCO₂ following the treatment) does not support making any such firm conclusions. Taking another perspective, one might equally plausibly explain the association between leaks and CAI by increased arousals in patients with CompSAS; such arousals might then lead to frequent oscillations between sleep and wakefulness, with a known “sleep-onset central apnea” phenomenon. In this regard, lower sleep efficiency in patients with high CAI that Montesi et al. reported would also be consistent with findings of prior studies on CompSAS. Additionally, mask leakage could potentially be a phenomenon secondary to more fragmented sleep in patients developing central apneas for another reason.

Recognizing these methodological shortcomings of the study by Montesi et al., there remains an interesting point that warrants further exploration. The issue of decreasing of pCO₂ by PAP, either through breath holding and thus lowering physiological dead space (through the mechanism proposed by Fowler, a precious reference that the authors cite),4 or via mask leakage causing dead space washout is still crucial in developing central apneas, and has practical applications. There is a growing body of evidence that increasing pCO₂ either by increasing dead space or timed supplementation with external CO₂ helps resolve central apneas in heart failure.5 Going forward, analyzing the whole population of patients with CompSAS, (including those with heart failure excluded from the current study), measuring this drop in pCO₂, timing of central apneas to the arousals and periods of maximal mask leak, and longitudinal studies on mask leak and central apneas might give us more insight into the pathophysiology of CompSAS. Another area of untapped knowledge in this regard is the data contained in the CPAP compliance data, which typically report such leaks.

In the background of this research, there is another, more practical issue. There is an ongoing discussion about the most appropriate treatment for patients with CompSAS. While adaptive servomventilation offers better and faster control of obstructive and central apneas, it is also more costly than CPAP. Proponents of CPAP argue that, due to dynamic factors in a new CPAP user stabilizing sleep, such as decreasing chemoresponsiveness (and as Montesi et al. propose, improving mask leak), starting CPAP and “waiting and seeing” might be the best therapeutic option in patients with CompSAS. I do not think the data they present can just support this approach, both due to methodological shortcomings of the study and because many “real life” patients with CompSAS have comorbidities that would have excluded them from their study. Therefore, from the practical standpoint, the take home message to me is that one needs to pay close attention to the mask interface and its leakage during the PAP titration study, when trying to resolve the complexities of complex sleep apnea.
CITATION

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ACKNOWLEDGMENTS
Dr. Kuźniar thanks Dr. Timothy Morgenthaler for his helpful remarks.

SUBMISSION & CORRESPONDENCE INFORMATION
Submitted for publication October, 2013
Accepted for publication October, 2013
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DISCLOSURE STATEMENT
Dr. Kuźniar has received support for his participation in a clinical trial sponsored by ResMed.
Caffeine Effects on Sleep Taken 0, 3, or 6 Hours before Going to Bed

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Study Objective: Sleep hygiene recommendations are widely disseminated despite the fact that few systematic studies have investigated the empirical bases of sleep hygiene in the home environment. For example, studies have yet to investigate the relative effects of a given dose of caffeine administered at different times of day on subsequent sleep.

Methods: This study compared the potential sleep disruptive effects of a fixed dose of caffeine (400 mg) administered at 0, 3, and 6 hours prior to habitual bedtime relative to a placebo on self-reported sleep in the home. Sleep disturbance was also monitored objectively using a validated portable sleep monitor.

Results: Results demonstrated a moderate dose of caffeine at bedtime, 3 hours prior to bedtime, or 6 hours prior to bedtime each have significant effects on sleep disturbance relative to placebo (p < 0.05 for all).

Conclusion: The magnitude of reduction in total sleep time suggests that caffeine taken 6 hours before bedtime has important disruptive effects on sleep and provides empirical support for sleep hygiene recommendations to refrain from substantial caffeine use for a minimum of 6 hours prior to bedtime.

Keywords: Caffeine, sleep hygiene, insomnia, sleep habits, stimulant

Caffeine in doses ranging from 200-400 mg have been shown to be effective and are often utilized to sustain performance in the context of sleep deprivation, sedation, and sleep restriction.1-7 Up to 500 mg of caffeine can be found in commercially available 16-oz servings of brewed coffee.8 The use of similarly high doses of caffeine-containing beverages, including energy drinks has led to a doubling of caffeine-related emergency department visits from 2007-2011.9 The increase in ED visits in association with cardiovascular and other adverse events has been labeled a “rising public health problem in the US” and has led the Food and Drug Administration to investigate the cardiovascular safety of high caffeine content beverages.10 Importantly, the adverse effects of caffeine intake are not limited to the cardiovascular system but also produce significant sleep disruptive effects, particularly when taken later in the day or when multiple doses are utilized.11 One recent population-based study of 18- to 58-year-olds (mean age = 28.5 years of age) estimated that 90% of individuals consume caffeine in the afternoon (12:00-18:00) and 68.5% of people consume caffeine in the evening (18:00-00:00).12

Caffeine content in beverages and foods is increasing in terms of dose and availability, with recent estimates of total daily caffeine consumption suggesting that the average person consumes 319.32 ± 180.94 mg of caffeine per day.12 Information on the sleep-disrupting effects of high doses of caffeine taken in the afternoon and early evening is important, given the increasingly popular use of caffeinated energy drinks and the high caffeine content of premium coffee.13 Such investigations are also critical due to increased caffeine use in younger age groups, where chronic sleep restriction is also increasingly common.14,15 Indeed, recent data show that in younger samples, 37% report first use of caffeine during the day at 17:00 or later.16

The sleep disruptive effects of caffeine administration at bedtime are well documented.17 Indeed, caffeine administration has been used as a model of insomnia.18 Dose-response studies demonstrate that increasing doses of caffeine administered at or near bedtime are associated with significant sleep disturbance.19-21 One of the most common recommendations for appropriate sleep hygiene practices is to avoid caffeine close to bedtime. However, evidence is less clear regarding the consumption of caffeine at earlier time points in the day. Due to the high variability in the elimination half-life of caffeine administered to healthy adults,22,23 specific recommendations on what time of day to discontinue caffeine use vary widely from 4 to 11 hours prior to bedtime.24-26 One limiting factor for such recommendations is that few studies have compared the sleep disruptive effects of
caffeine given at different times before bed. Thus, it remains unclear to what degree caffeine taken in the afternoon disrupts nocturnal sleep relative to doses consumed closer to bedtime.

One study examining the sleep effects of 400 mg caffeine administered 30 minutes before bedtime demonstrated both severe sleep disruption as well as important cardiovascular effects during sleep likely related to increased sympathetic activity. In one of the few studies that evaluated caffeine administered in the evening, a 200 mg dose was used with 100 mg 3 h before bed and an additional 100 mg 1 h before bed. The caffeine condition reduced sleep efficiency by 5%, prolonged sleep latency by 12-16 min, and reduced total sleep time by 25-30 min relative to placebo. However, as this study investigated the combined effects of the 2 doses, the comparative effects of time of administration could not be determined. A study that administered caffeine (200 mg) 16 h prior to bedtime produced minimal effects on standard sleep parameters compared to a dose near bedtime, likely due to low blood levels of caffeine at bedtime and the relatively low dose utilized. Nonetheless, even at such small doses with a large intervening time before bed, the effects of caffeine were detectable on sleep parameters.

To our knowledge, no studies have systematically determined the disruptive effects of a fixed dose of caffeine administered at different times prior to sleep. The present study aimed to determine the magnitude of caffeine effects on sleep when administered in the home environment at 0, 3, and 6 hours prior to habitual bedtime.

METHODS

Subjects
Participants were recruited from the Detroit tri-county area through local advertisements. The study group comprised 12 healthy normal sleepers, as determined by a physical examination and clinical interview. The exclusion of insomnia was based on systematic clinical evaluations by a sleep specialist that included no history of difficulty falling asleep, staying asleep or non-restorative sleep for a month or more. Subjects were confirmed to be free of insomnia and sleepiness based on the Insomnia Severity Index (2.3 ± 1.5) (mean ± standard deviation) and the Epworth Sleepiness Scale (3.9 ± 1.5). As polysomnography was not performed, sleep apnea was screened out during the clinical evaluation using the Berlin Questionnaire. Habitual sleep data were determined by self-report with a 1-week sleep diary the week prior to participation. Only individuals with habitual total sleep times between 6.5 and 9 h, with a sleep onset < 30 min were included. All subjects reported good health based on both medical history and physical examination. Any individuals with reported current or previous history of any psychiatric illness or current medical disorder were excluded from participation. Individuals currently using oral contraceptives, hypnotics, or any central nervous system acting medications were also excluded. Habitual caffeine consumption was based on self-report. Habitual caffeine consumption was calculated from the question “How much caffeine do you consume in an average day, including coffee, pop, tea, chocolate, or energy drinks? Please specify type and amount.” Daily and weekly servings (100 mg) of caffeine were then estimated based on type and amount indicated. The amount of caffeine in specific beverages/sources was determined based on information provided at the brand website and published literature. If home-brewed coffee was indicated, an 8-oz cup was calculated to be equal to 100 mg of caffeine (1 serving). Subjects were selected if they met either of the following criteria: (1) ≥ 3 servings of caffeine in any single day or (2) ≥ 5 caffeinated servings per week. Subjects who consumed > 5 caffeinated beverages per day were excluded from participation. There were no inclusion or exclusion criteria as to time of caffeine consumption. All subjects were screened for current depression using the Hamilton Depression Rating Scale (HDRS), and only individuals with < 10 on the HDRS participated. The mean body mass index (BMI) of the sample was 25.1 ± 4.9.

A total of 16 healthy day workers met initial screening criteria; data were not used from 4 subjects due to violation of the study protocol before the study blind was broken. This included 2 subjects who took caffeine on 4 consecutive nights without the required 1 night washout, one subject who did not go to bed at the scheduled times 3 of 4 nights, and one subject who did not comply with 8-h time in bed on study nights. Thus, 12 subjects completed the full protocol (6F, 6M; aged 19-48; mean age 29.3 ± 7.6). The mean baseline caffeine intake for the sample was 115 ± 169 mg/day of caffeine. All study procedures were approved by the institutional review board and informed consent was obtained from all participants. Individuals were compensated for their participation.

Procedures
The protocol was a randomized, double-blind, double dummy, placebo-controlled, balanced Latin Square treatment sequence design. For the experimental period, participants were instructed to maintain their normal sleep schedules, including a bedtime between 21:00 and 01:00, wake times between 06:00 and 09:00, time in bed of 6.5-9 h, and no habitual napping. Study protocol began following one week of baseline sleep diaries. Each subject completed 4 conditions/nights which consisted of 400 mg of caffeine taken in pill form at either 6, 3, or 0 hours prior to scheduled bedtime, with identical placebo given at each of the other times. Thus, subjects were instructed to take 3 pills each study day with one of the pills being caffeine and the other 2 placebo. On one of the days, all 3 pills were placebo. Conditions were presented in a Latin Square Design. Each caffeine condition was preceded by a 1 washout night where subjects did not wear any sensors and did not take study drug. Thus, experimental nights occurred every other night during the protocol. However, sleep diary data were collected in the morning for all nights (experimental and washout). Subjects were given caffeine pills in an alarm activated pill case. Participants were required to maintain a fixed bedtime and wake time schedule based on sleep diaries throughout the protocol. Subjects were also given a sleep diary to complete each morning throughout the study. The pill case alarms were set according to the subjects’ habitual bedtime, and the alarm was designed to sound until the subject manually turned it off. In order to avoid any potential caffeine withdrawal effects subjects were allowed to use caffeine during the study. However, subjects...
were instructed to refrain from consuming any alcohol or caffeine after 16:00 on study days.

The aim of the present study was to determine if caffeine administered at different times before bed in the home environment impacts measures of sleep disturbance compared to placebo. It was important to measure reported sleep disturbance in response to home caffeine administration because disturbed sleep (e.g., sleep quality, difficulty falling asleep) is, at least in part, determined by self-report, insomnia is a symptom-based diagnosis, and because adherence to sleep hygiene rules is likely to be dependent upon perceived sleep quality effects. Thus, the impact of different caffeine administration times on sleep was measured using a standard sleep diary with items similar to those used for the consensus sleep diary. 35

Sleep disturbance was also measured objectively using a widely available and previously validated in-home sleep monitor. 36 The monitor was comprised of a headband unit containing dry fabric sensors that wirelessly transmitted a single-channel EEG signal obtained from the forehead to a bedside device for processing. Sleep parameters were computed in real-time by the device shown to have concordance with the current gold standard, polysonmography (PSG), as well as with actigraphy. 36 The intraclass correlation coefficients between the monitor and PSG were > 0.90 for total sleep time (TST) and sleep efficiency (SE), and > 0.81 for latency to persistent sleep (LPS) and wake time during sleep (WTDS), the duration and continuity measures that are of primary interest regarding the sleep disrupting effects of caffeine. The device also showed high concordance with actigraphy measures of sleep in the validation study. 36 While a more recent validation study showed moderate overall agreement between the headband device and PSG scoring, the portable device may significantly underestimate the number of wake epochs. 37 A separate study also found similarly moderate to high agreement between the device and PSG, but with underestimation of wake epochs. 38 Finally, the sensitivity of the ambulatory monitoring device to sleep extension in the home environment has also been documented. 39

Sleep variables measured included TST, LPS (first epoch of 10 min of consecutive sleep), WTDS, and SE. Although these were the primary measures of interest, we also examined exploratory measures of combined stage 1 and 2 sleep, slow wave sleep, and REM sleep. As previously reported, an important limitation regarding sleep architecture is that the device does not provide separate measures for stage 1 and stage 2 sleep; therefore, only a combined measure of these 2 sleep stages was available.

Subjects were instructed to put on the wireless system headband immediately upon going to bed with the intent to go to sleep, and to keep the headband on all night long and place it back on its bedside device upon rising from bed in the morning. Adherence with the timing of the 3 daily pill administrations was done through the use of 3 timed pill alarm cases, which contained study drug for each night. Study drug intake was monitored by having subjects call in to a time stamped answering machine to verify that the study drug was taken at each predetermined time period (6 h prior, 3 h prior, and at bedtime).

Data were analyzed using repeated-measures ANOVA with planned comparisons testing for differences between each caffeine administration time and placebo night. Data transformations were performed where appropriate when deviations from normality occurred. Significant omnibus results were followed by post hoc analyses to identify pairwise differences. A two-tailed α level of 0.05 was used for all statistical tests. A nonparametric Friedman two-way analysis of variance by ranks was used for variables which deviated from normality.

### RESULTS

Both subject report and objective measures of time in bed, bedtime, and wake time indicated the subjects maintained their normal sleep schedule throughout the study period as instructed. Data for the 7-day sleep diary taken during baseline as well as other self-report sleep-wake related measures are shown in Table 1. There were no differences in these parameters across the study conditions (p > 0.05). There were no differences in non-study related caffeine intake between any of the 4 conditions: 0 h = 126.1 ± 164.9 mg, 3h = 139.1 ± 199.2 mg, 6h = 154.1 ± 199.2 mg, placebo = 139.4 mg ± 189.6 (p > 0.05 for all pairwise comparisons). During the study protocol, time-stamped telephone verification indicated that all subjects took the required doses on each night at the instructed times.

Means and standard deviations of diary measures of sleep including latency to sleep, total sleep time, and WTDS during each condition are shown in Table 2. Caffeine had the most consistent effects on reducing total sleep time relative to placebo, with both administration at bedtime and 3 h prior to bedtime reaching statistical significance. Caffeine administered 6 h prior to bedtime reduced total sleep time by 41 min, which approached significance (p = 0.08). Significant effects were observed for sleep latency with caffeine taken 3 h before bed having the greatest effect relative to placebo. Although caffeine taken 6 h before bedtime more than doubled the reported time take to fall asleep, this effect did not reach statistical significance (p = 0.06). No significant effects were observed for WTDS, SE, or sleep quality. There were no significant differences between caffeine conditions for any of the sleep diary measures (Table 2).

Means and standard deviations of objective measures of sleep (i.e., latency to sleep, total sleep time, and WTDS)
are shown in Table 3. Evidence for the disruptive effects of caffeine was demonstrated for each of the sleep duration and continuity parameters. The different caffeine administration times (0, 3, or 6 h before bed) did not produce differential sleep disruption among the 3 active caffeine conditions. For TST, reductions in duration relative to placebo were significant at each of the caffeine administration time points, reducing TST between 1.1 to 1.2 hours. The 3-h condition significantly prolonged latency to persistent sleep (+17.2 min) relative to placebo. Latency to persistent sleep was similarly prolonged in the 0 and 6 h condition (+22.4 and +24.1 min, respectively), but neither reached statistical significance compared to placebo. The amount of wake time during sleep was also increased with all 3 caffeine administration times, reaching statistical significance for the 6 h (+8 min) and 3 h (+27.6 min) conditions. Sleep efficiency was reduced for each condition relative to placebo.

Sleep Architecture

Although the study aim was to detect the effects of caffeine on measures of sleep disturbance, the effects of caffeine on sleep stages was also explored. Caffeine administration at each of the 3 time points significantly reduced minutes of stage 1 and 2 sleep combined relative to placebo (Table 3). In each case, reduction in stage 1 and 2 sleep (combined measure) from placebo was similar, ranging from -40.6 min for caffeine administered at bedtime to -44.1 min for caffeine administered 6 h before bedtime, with no differences between the time of administration of caffeine. Reductions in the duration of slow wave sleep were observed for all 3 caffeine conditions, but reached significance only for administration at bedtime and 6 h before bedtime. As expected, caffeine had no effect on REM sleep for any time of administration. There were no significant differences in percentage of sleep stage distributions between caffeine conditions.

Table 2—Means ± SD of sleep diary-based measures for each condition

<table>
<thead>
<tr>
<th>Sleep Measure</th>
<th>Placebo</th>
<th>Caffeine at bedtime</th>
<th>Caffeine 3 hours before bed</th>
<th>Caffeine 6 hours before bed</th>
<th>F (3,33)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Latency to sleep (min)</td>
<td>21.00 ± 8.99</td>
<td>56.67 ± 74.23</td>
<td>62.50 ± 66.18*</td>
<td>44.17 ± 44.56*</td>
<td>3.06</td>
<td>0.04</td>
</tr>
<tr>
<td>Total sleep time (h)</td>
<td>7.82 ± 0.54</td>
<td>6.92 ± 1.10*</td>
<td>6.77 ± 0.95*</td>
<td>7.13 ± 0.93*</td>
<td>4.14</td>
<td>0.01</td>
</tr>
<tr>
<td>Wake time during sleep (min)</td>
<td>11.00 ± 11.24</td>
<td>9.18 ± 9.41</td>
<td>17.67 ± 33.99</td>
<td>9.27 ± 14.01</td>
<td>0.71</td>
<td>0.55</td>
</tr>
<tr>
<td>Sleep efficiency %</td>
<td>93.60 ± 3.47</td>
<td>86.43 ± 13.87</td>
<td>83.98 ± 12.68</td>
<td>89.05 ± 9.22</td>
<td>2.65</td>
<td>0.07</td>
</tr>
<tr>
<td>Sleep quality</td>
<td>6.20 ± 2.04</td>
<td>5.83 ± 2.33</td>
<td>5.17 ± 1.53</td>
<td>5.67 ± 2.19</td>
<td>0.63</td>
<td>0.60</td>
</tr>
</tbody>
</table>

Follow-up pairwise comparisons, where omnibus F-values are significant: *p < 0.05 vs. placebo; #p < 0.10.

Table 3—Objective sleep measures for each condition (mean ± SD)

<table>
<thead>
<tr>
<th>Sleep Measure</th>
<th>Placebo</th>
<th>Caffeine at bedtime</th>
<th>Caffeine 3 hours before bed</th>
<th>Caffeine 6 hours before bed</th>
<th>F (3,33)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Latency to persistent sleep (min)</td>
<td>20.59 ± 9.79</td>
<td>43.0 ± 38.93</td>
<td>37.82 ± 29.91</td>
<td>44.68 ± 54.60</td>
<td>2.05</td>
<td>0.13</td>
</tr>
<tr>
<td>Total sleep time (h)</td>
<td>7.68 ± 0.85</td>
<td>6.60 ± 1.10*</td>
<td>6.54 ± 1.36*</td>
<td>6.50 ± 1.32*</td>
<td>3.43</td>
<td>0.03</td>
</tr>
<tr>
<td>Wake time during sleep (min)</td>
<td>9.55 ± 14.73</td>
<td>27.04 ± 40.06</td>
<td>37.18 ± 43.0*</td>
<td>17.59 ± 22.28*</td>
<td>3.29</td>
<td>0.03</td>
</tr>
<tr>
<td>Sleep efficiency %</td>
<td>91 ± 5.71</td>
<td>83.1 ± 12.11*</td>
<td>82.51 ± 12.73*</td>
<td>82.33 ± 12.15*</td>
<td>7.50</td>
<td>0.058#</td>
</tr>
<tr>
<td>Stage 1 &amp; 2 (min)</td>
<td>266.77 ± 40.15</td>
<td>226.17 ± 57.75*</td>
<td>222.68 ± 62.24*</td>
<td>222.82 ± 48.83*</td>
<td>3.66</td>
<td>0.02</td>
</tr>
<tr>
<td>Stage 1 &amp; 2 (%)</td>
<td>58.02 ± 7.37</td>
<td>56.47 ± 7.77</td>
<td>56.77 ± 10.48</td>
<td>57.28 ± 6.26</td>
<td>0.22</td>
<td>0.88</td>
</tr>
<tr>
<td>Slow wave sleep (min)</td>
<td>71.45 ± 26.48</td>
<td>56.67 ± 21.48*</td>
<td>57.0 ± 16.78</td>
<td>48.91 ± 15.61*</td>
<td>4.26</td>
<td>0.01</td>
</tr>
<tr>
<td>Slow wave sleep (%)</td>
<td>15.47 ± 5.28</td>
<td>14.47 ± 4.85</td>
<td>14.84 ± 3.87</td>
<td>12.71 ± 3.88</td>
<td>1.22</td>
<td>0.28</td>
</tr>
<tr>
<td>REM (min)</td>
<td>123.27 ± 33.89</td>
<td>114.36 ± 28.53</td>
<td>112.5 ± 46.57</td>
<td>118.73 ± 39.75</td>
<td>0.30</td>
<td>0.83</td>
</tr>
<tr>
<td>REM (%)</td>
<td>26.62 ± 6.35</td>
<td>29.21 ± 7.19</td>
<td>28.39 ± 11.25</td>
<td>29.99 ± 6.54</td>
<td>0.88</td>
<td>0.46</td>
</tr>
</tbody>
</table>

*p < 0.05 pairwise comparisons vs. placebo; *p < 0.10. Nonparametric related samples test of Friedman two-way analysis of variance by ranks was performed as data was not normally disturbed following transformation.

DISCUSSION

The results of this study suggest that 400 mg of caffeine taken 0, 3, or even 6 hours prior to bedtime significantly disrupts sleep. Even at 6 hours, caffeine reduced sleep by more than 1 hour. This degree of sleep loss, if experienced over multiple nights, may have detrimental effects on daytime function. Thus, the present results suggest the common practice of afternoon consumption of caffeine should at a minimum be restricted to before 17:00, particularly with regard to the moderate-large doses of caffeine commonly found in increasingly popular premium coffees and energy drinks. Future research is needed to determine the sleep disruptive effects of afternoon caffeine in insomniacs relative to normal sleepers.

Caffeine-induced sleep disturbance was detected by both the self-report diary and objective sleep measures when taken at bedtime and 3 hours prior to bedtime, whereas only the objective measure detected differences when caffeine was taken 6 hours prior to bedtime. The discrepancy in subjective-objective measures is particularly evident in cases where awakenings may be relatively short lived as in the case of sleep fragmentation. Sleep fragmentation is a characteristic of nocturnal caffeine administration, and therefore may explain some of the subjective-objective discrepancy observed in the present study.
We believe this discrepancy (i.e., lack of subjective awareness of caffeine-induced sleep disturbance) is an important finding of the present study and suggests one potential reason for non-adherence to sleep hygiene recommendations regarding caffeine intake close to bedtime. The lack of perceived sleep disruption during early evening administration combined with the objective findings of the present study argue for continued education regarding the sleep disruptive effects of caffeine.

Disturbed sleep due to caffeine administered in divided doses within 3 hours of bedtime, including reduced total sleep time and stage 1-2 sleep, have previously been reported.28 The finding that sleep was disrupted even 6 hours prior to bedtime adds to our current knowledge of caffeine effects on sleep and suggests that larger doses will have an important impact even during daytime hours. Importantly, future studies should monitor blood levels of caffeine to determine if individual differences in absorption and or elimination during afternoon administration are directly related to the degree of nocturnal sleep disruption.

The study has several limitations. As plasma concentrations were not obtained, we were unable to determine the extent to which such variations influenced the disruptive sleep effects observed. However, this possibility was offset by the repeated measures design limiting the effects of intersubject variability related to caffeine sensitivity, absorption, and bioavailability and individual differences in habitual sleep patterns.44 Another limitation was the small number of subjects assessed in the present study, which may have contributed to reduced power to detect caffeine effects on sleep disturbance using self-report. Intermittent exposure to caffeine used in the present design precludes us from making any conclusions regarding possible tolerance to the effects observed. Habitual caffeine use by participants may have added to total caffeine exposure and increased the effects on sleep disturbance, although the crossover design minimizes the possibility of the influence of individual differences in habitual caffeine consumption. As the device used to assess sleep stages has only recently been validated against polysomnographic measures of sleep the effects of caffeine on sleep architecture found in the present study should be considered preliminary, particularly the effects on stage 2. Finally, the use of young/middle-age participants with moderate habitual caffeine use limits the generalizability of the findings. Future studies are required to determine if the effects would be elevated in samples of older subjects where nocturnal sleep disruption is more common or in naïve caffeine users.

Tolerance to the alertness enhancing effects of caffeine develops quickly,45 and the practice of using high doses of caffeine to improve alertness is becoming increasingly common among both adults and adolescents.46,47 However, the risks of caffeine use in terms of sleep disturbance are underestimated by both the general population and physicians.17 The present results show that high doses of caffeine will have an important negative impact upon sleep duration in the home environment even when used in the early evening hours.

REFERENCES


**ACKNOWLEDGMENTS**

The authors acknowledge Cathy Jefferson, Ashley Kick, and Heather Mengel for assistance with data collection and editorial comments on the manuscript.

**SUBMISSION & CORRESPONDENCE INFORMATION**

Submitted for publication March, 2013
Submitted in final revised form June, 2013
Accepted for publication July, 2013
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**DISCLOSURE STATEMENT**

The study was funded by an investigator initiated grant from Zeo Inc to Dr. Drake and performed at the Henry Ford Hospital Sleep Disorders & Research Center, Detroit, MI. Dr. Drake has received funding from Merck, Teva, and Zo. He has consulted for Teva. He has been a speaker for Teva, Purdue, and Jazz. Dr. Roehrs has been a speaker for Pfizer and has consulted for Sanofi Aventis. Mr. Shambroom has been a coauthor of publications appearing in the journal Sleep, supported by Zeo, Inc. He manages his own consulting business, Shambroom Associates, LLC, Framingham, MA. He has been in consulting relationships with Atentiv, Inc., Brainscope, Inc., SafeOp Surgical, Inc., and Cephalogics, Inc. He has been the VP Scientific Affairs for Zeo, Inc., from April 2007-April 2010. He no longer has financial interest in Zeo. Dr. Roth has served as a consultant for Abbott, Accadia, AstraZeneca, Aventis, AVER, Bayer, BMS, Cypress, Ferris, Glaxo Smith Kline, Impax, Intec, Jazz, Johnson and Johnson, Merck, Neurocine. He has received research support from Cephalon, Merck, Transcript and has participated in speaking engagements for Purdue.
Patient Safety Incidents During Overnight Polysomnography: A Five-Year Observational Cohort Study

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¹Center for Sleep Medicine and ²Pulmonary and Critical Care Medicine, Mayo Clinic, Rochester, MN

Introduction: Attended polysomnography (PSG) is a common procedure and is regarded as relatively safe. There have been few systematic evaluations of adverse events occurring during PSG. An understanding of the frequency and type of the adverse events during PSG should inform risk mitigation plans and the development of guidelines for sleep center accreditation. We aimed to identify, tabulate, and classify all adverse events that occurred during overnight PSG conducted at an accredited sleep center over a five-year period.

Methods: All adverse events occurring from Jan 1, 2005, to Dec 31, 2010, at the Center for Sleep Medicine, Mayo Clinic, were identified. Information was collated from calls made to emergency responders, to the adverse event reporting system, and events forwarded to the medical director.

Results: A total of 36,141 PSGs were performed over the study duration. Fifty-eight adverse events occurred during the study period (1 event/623 PSGs). Most adverse events were cardiac in nature (17/58; 29.3%), a majority involving acute chest pain. Falls were the next most common (20.6%), followed by neurologic (8.6%), pulmonary (3.4%), and psychiatric (3.4%) events. The rest were classified as miscellaneous.

Conclusion: Adverse events during a PSG were relatively uncommon. Previous emphasis on cardiac arrhythmias may be overstated, as chest pain and patient falls were commonest and resulted in hospitalization more often.

Keywords: Polysomnography, adverse events

Citation: Kolla BP; Lam E; Olson E; Morgenthaler T. Patient safety incidents during overnight polysomnography: a five-year observational cohort study. J Clin Sleep Med 2013;9(11):1201-1205.

BRIEF SUMMARY

Current Knowledge/Study Rationale: Although polysomnography is a common medical procedure performed in various settings across the United States, there is very little known about the breadth of patient safety issues encountered during polysomnography. This study sought to catalogue the variety of patient safety incidents encountered during over 36,000 consecutive attended polysomnography tests at a single integrated academic medical center.

Study Impact: We found that patient safety incident occurred in 1 of every 623 polysomnograms, and that chest pain, falls, and acute neurological events were the most common. These findings suggest that future emphasis on improving patient safety be oriented towards fall reduction, ensuring access to timely evaluation of acute medical problems, and thorough medical evaluation prior to PSG.

An influential report issued by the Institute of Medicine in 1999, “To Err is Human,” launched an era of unprecedented activity to improve safety in the American hospital.¹ Only more recently has attention been turned to a more keen understanding of outpatient safety.² Given that there are more than 300 outpatients for every one inpatient encounter, the almost exclusive focus on the inpatient environment for improving patient safety may be likened to looking for keys lost in the dark part of the parking lot under the streetlamp on account of the improved lighting conditions.³

Polysomnography (PSG) is a method of recording and analyzing physiologic measures associated with sleep and breathing in patients with sleep diseases. In clinical practice, it entails attended monitoring of sleeping patients, often with purely diagnostic intent, but since approximately 85% of tested patients are suspected of having sleep-related breathing disorders, PSG oftentimes is performed during the introduction of positive airway pressure (PAP) or other treatment modalities. In many ways, this monitoring, measuring, and interpreting physiologic signals is an activity that resembles those performed in “observation” areas used by some emergency centers or inpatient settings, with a few seminal differences intended. First, sleep centers generally intend to evaluate patients who are considered medically stable other than their sleep diseases, rather than those who have presented with chiefly acute medical illnesses. Secondly, sleep studies are attended by sleep technologists or respiratory therapists, not registered nurses or physicians, as one finds in the acute care setting. Finally, and importantly, PSG is not uniformly provided in settings equipped for ill or infirm patients. Instead, polysomnography may be performed in facilities inside a hospital, those that are adjacent to an acute care facility, or those operated as independent testing facilities, not attached to any other medical care facility. Less than half of such facilities (2,415 centers as of 2011) are accredited by the American Academy of Sleep Medicine (AASM), and only a few hundred are accredited by The Joint Commission (TJC). The rest are without known accreditation, and are therefore without any known safety standard requisites.

The number of PSGs performed in the United States was estimated to be around 1.17 million in 2001, and more recent
estimates indicate the number may have quadrupled concurrently with an increase in annual Medicare payments for PSG from $62 million to $235 million from 2001 to 2009.3,4 Thus, it is surprising that with almost certainly more than 4 million PSGs performed in varied settings annually, we have scant information about the safety of sleep studies and sleep centers. Thus far, a single multicenter study sought to quantify the frequency of predominantly cardiac events during polysomnography,5 but to our knowledge, there are no published studies tabulating the wide range of patient safety incidents that may occur. We sought to examine and classify all identifiable patient safety incidents occurring during overnight stays at our accredited sleep center over a five-year period.

METHODS

We identified all reported safety incidents occurring at the Center for Sleep Medicine, Mayo Clinic, Rochester, MN, between Jan 1, 2005, and Dec 31, 2010. Safety incidents were defined as any patient safety concern that was reported to the medical director, the institutional safety “event line,” or events that resulted in summoning emergency medical personnel or that resulted in the patient being transferred to the emergency department.

Over the study period, safety incidents were recorded in several different databases: emergency call logs, safety event database, and the medical director’s concern log. First, we searched the log of all calls made to emergency responders during the study duration. During the initial portion of the study, the sleep center was located inside the hospital facility, and critical care physicians who were on call from the critical care unit provided emergency coverage. Calls for assistance to these physicians were recorded in the health record, but not in a separately indexed database. However, in 2008 the sleep center moved to an outpatient setting, and emergency coverage was provided by emergency medical technicians summoned using standard emergency medical services (EMS). All calls made to the emergency medical technicians were recorded at a central repository, and this was accessed to obtain information regarding adverse events occurring during this study period. For patients who were hospitalized, information regarding their hospital course was obtained.

At our institution, during overnight PSG, when sleep technologists encounter cardiopulmonary arrest CPR is commenced, the code team alerted and the medical director is notified. In cases where tachy/bradyarrhythmias with clinical symptoms of chest pain/pressure, dyspnea, syncope/pre-syncope are encountered, the emergency medical response team and the medical director are notified. With sinus arrest > 3 seconds or ventricular tachycardia coinciding with oxyhemoglobin desaturation, nasal CPAP is commenced and the medical director notified.

In addition, in accordance with our institutional policy, patient safety events such as medication errors or falls were reported via an “event line” phone call and stored in a central adverse event database. Finally, consistent with policy and accreditation standards, PSG technologists reported all complications to the lead technologists in the morning following the study, and adverse events were then forwarded to the Medical Director of the Center for Sleep Medicine, Mayo Clinic.

All of the databases were queried to identify safety incidents. Only incidents occurring during the overnight stay in the sleep center were included. For the study purposes, this included events occurring from the time patients presented to the sleep lab reception area at night until they were discharged the following morning. Once identified, the medical records were then reviewed to obtain further information regarding any emergency care including whether they were transferred to the emergency department (ED), care received in the ED, if patients required hospitalization, and any pertinent details from their inpatient course if admitted.

The safety incidents were classified into cardiovascular, neurological, pulmonary, psychiatric, falls, and other miscellaneous events. For patients suffering a fall, information regarding hypnotic administration during the PSG and whether fall precautions were in place was obtained. Any injuries resulting from the fall were clarified upon review of the medical record. The study was approved by the Mayo Clinic Institutional Review Board (IRB 12-000494).

RESULTS

During the study period, a total of 36,141 PSGs were performed at the Center for Sleep Medicine, Mayo Clinic, Rochester, MN. During this time period, a total of 111 calls were made to the emergency medical services. Thirty-nine adverse events were reported to the safety event line, and 27 events were reported to the medical director of the sleep lab (Figure 1).

After excluding duplicates and events that did not occur during the overnight stay in the sleep center, there were a total of 58 adverse events during the study period. Eighty-five events that occurred during the day while the patients were being evaluated in the sleep clinic (not during PSG) were excluded from evaluation. The rate of adverse events was 1 event per 623 PSGs. Of the adverse events reported, the majority (17/58; 29.3%) were cardiovascular in nature. Falls were the next most frequent adverse event reported (12/58; 20.7%), followed by neurological (5/58; 8.6%), psychiatric (2/58; 3.4%), and
pulmonary events (2/58; 3.4%). The rest of events were classified as miscellaneous (20/58; 31.6%; Table 1).

Of the cardiac events, the majority involved chest pain (12/17). Arrhythmias accounted for 4/17, and the remaining patient suffered cardiac syncope. The majority of patients who experienced a cardiac event were transferred to the ED (15/17). Seven of these patients were admitted to an inpatient service. None of the patients who developed chest pains were found to have suffered a myocardial infarction. The arrhythmias noted were sinus tachycardia (1 patient), bradycardia with Mobitz II block (1 patient), and atrial fibrillation (2 patients). Atrial fibrillation was complicated by the development of rapid ventricular rate in one patient and a variable AV conduction block in another.

A substantial number of patients who sustained a fall during their overnight PSG received zolpidem, which was prescribed by the sleep provider, during the sleep study (41.6%). Seven of the patients who sustained a fall were on fall precautions (58.3%) as requested by the physician ordering the sleep study. Apart from two instances of minor skin bruising and knee discomfort that did not require further attention, the rest of the patients did not sustain serious injury following the fall. Two patients who sustained a fall were transported to the ED; neither was admitted.

The neurological events consisted of 2 instances of syncope, one of a seizure, and another patient who suffered a transient ischemic attack (TIA). There was also one instance of a patient with a severe headache who was found to have meningitis. The patient who developed a seizure during the PSG had a prior history of seizures. Four of the 5 patients with neurological events were transported to the ED; 2 of these patients were admitted. The patient with meningitis required ICU care.

Two patients experienced pulmonary adverse events during the study period. One developed dyspnea and another had hemoptysis. Both were transported to the ED and the patient with dyspnea was found to have pneumonia and was admitted to an inpatient bed.

Among patients who experienced psychiatric adverse events, one had a psychogenic seizure-like spell and another had an episode where they refused to open their eyes or respond to gentle stimulation. This was later characterized as psychogenic coma (DSM IV TR diagnosis of dissociative disorder NOS). This patient was transported to the ED and was admitted to an inpatient psychiatric service. The patient had no prior psychiatric history and was being evaluated for spells at the time of the PSG.

There were two instances of hyperglycemia occurring in patients who had a previous diagnosis of diabetes mellitus. Both these patients required an ED evaluation and an inpatient admission. One of these patients had undergone an ENT surgery 2 weeks prior to PSG, and PAP was not applied during the sleep study. In both instances the patients required ED evaluation where nasal packing was applied; neither patient was admitted.

There were two instances of hyperglycemia occurring in patients who had a previous diagnosis of diabetes mellitus. Both these patients required an ED evaluation and an inpatient admission. One of these patients was admitted to an ICU as they developed diabetic ketoacidosis. There were also two instances of parentally delivered physical child abuse recorded during the study period. As all PSGs at our center have video monitoring, these instances were captured on video and documentary evidence was present for these episodes.

Among the other adverse events, one patient developed sepsis. This patient had undergone a PSG that revealed complex obstructive sleep apnea. The patient was admitted to the ICU and the sleep study was terminated.

### Table 1—All patient related safety events occurring during the study period

<table>
<thead>
<tr>
<th>Event Class</th>
<th>Number of Events (% of total)</th>
<th>ER Visits (% of total ER Visits)</th>
<th>Number Hospitalized (% of total hospitalized)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chest Pain (12)</td>
<td>17 (29.3)</td>
<td>15 (40.5)</td>
<td>7 (46.7)</td>
</tr>
<tr>
<td>Arrhythmia (4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiogenic Syncope (1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Falls</td>
<td>12 (20.6)</td>
<td>2 (5.4)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Neurological</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seizures (1)</td>
<td>5 (8.6)</td>
<td>3 (8.1)</td>
<td>1 (6.7)</td>
</tr>
<tr>
<td>Syncope (2)</td>
<td></td>
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<td></td>
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<tr>
<td>Transient ischemic attack (1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meningitis (1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychiatry</td>
<td>2 (3.4)</td>
<td>1 (2.7)</td>
<td>1 (6.7)</td>
</tr>
<tr>
<td>Spell (1)</td>
<td></td>
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<tr>
<td>Psychogenic coma (1)</td>
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<tr>
<td>Pulmonary</td>
<td>2 (3.4)</td>
<td>2 (5.4)</td>
<td>1 (6.7)</td>
</tr>
<tr>
<td>Cough (1)</td>
<td></td>
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<tr>
<td>Dyspnea (1)</td>
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<tr>
<td>Miscellaneous</td>
<td>20 (34.5)</td>
<td>14 (37.8)</td>
<td>5 (33.3)</td>
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<tr>
<td>Epistaxis (2)</td>
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<td></td>
</tr>
<tr>
<td>Child Abuse (2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperglycemia (2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Others (14)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Total | 58 | 37 | 15
sleep apnea and was asked to return for a repeat overnight PAP titration. The patient in the interim underwent a bone marrow biopsy on the day of the titration study. The patient was found to have tachycardia and altered mental status at the sleep center and was transferred to the ED and required an admission to an ICU bed. Another patient who had a recent urethral stent placement developed significant hematuria requiring an inpatient admission and blood transfusion.

A patient developed significant dehydration resulting from a medication error; the patient’s son administered the wrong dosage of medication resulting in aggressive diuresis. This patient required inpatient admission to correct an electrolyte imbalance. Other miscellaneous adverse events included a foot laceration following an injury sustained by a patient who cut himself on a piece of broken glass in the shower after his PSG was completed. The other adverse events included an instance of a broken Hickman catheter, severe nausea, vaginal bleeding and one instance where the PSG had to be canceled in a pediatric patient as no guardian was willing to stay overnight with the patient.

DISCUSSION

In our five-year retrospective review of sleep center overnight stays, adverse events were infrequent, occurring at a rate of at one event for every 623 PSGs. The majority of adverse events were cardiac in nature, followed by falls. The majority of the patients experiencing an adverse event were transported to the ED, and 41% of the patients transported to the ED were admitted to an inpatient setting. There were no deaths at the sleep center during overnight PSG.

Prior research into the adverse effects associated with undergoing a PSG is extremely limited. The only previous study examined reports from multiple sleep centers in 4 states, and defined adverse events as “those requiring immediate medical attention (physician call or emergency room evaluation)” or arrhythmias found by re-scoring teams. In that study of 16,084 PSGs, there was one fatality from sudden cardiac death that was preceded by polymorphic ventricular tachycardia and subsequently ventricular fibrillation, 1 case of dyspnea with chest pain, 27 cases of arrhythmias prompting the PSG technologist to request immediate medical attention, and 28 cases of complex ventricular arrhythmias discerned on subsequent review of the PSG, apparently without symptoms. In their study, the event rate was 0.35% and there was 1 death. In our study, we found an overall event rate of 0.16% and no deaths. We also found comparatively fewer arrhythmias. There are several reasons we may have differing rates of adverse events. The nature of their definition might make low harm level events less likely to have been reported in their study in comparison to ours. In Mehra et al., the technologists were sensitized by the sudden death that occurred early in the study period, and were instructed to be particularly vigilant in arrhythmia reporting. In addition, because the enrolled patients were part of a multicenter study, all PSGs were later reviewed independently, likely resulting in complete ascertainment of all cardiac rhythm abnormalities. Their results may therefore exhibit some degree of observer-expectancy effect. In contrast, at our center more stable arrhythmias such as the development of atrial fibrillation or non-sustained ventricular tachycardia would have been noted by the sleep specialist, but not necessarily reported as patient safety incidents. Therefore, our data underreport the frequency of cardiac arrhythmias during PSG. However, the main focus of our study was to learn about the range of patient safety incidents incurred during an overnight stay in the sleep center; stable arrhythmias, many of which are occurring most nights of the patient’s life, may not be of primary interest.

In our retrospective review, falls were the second most common adverse event. Twenty-five percent of patients who sustained a fall required an ED evaluation, fortunately not leading to serious injury, but resulting in increased healthcare expenditure. This represents an opportunity for improvement. The literature reports that 60% of falls happen in homes, 30% in the community, and only 10% in institutions. Nonetheless, in hospitals, patient falls are a leading cause of death for those over 65 years of age, and are among the commonest adverse events reported. Total fall injury costs for those over 65 years old have been estimated at $27.3 billion, and some estimate that by 2020 cost of fall injuries may exceed $43.8 billion. National efforts are focusing on the reduction of injurious patient falls to reduce morbidity, mortality, and healthcare costs. Our sleep center long ago instituted on the PSG order sheet an opportunity for the sleep specialists to request “fall precautions.” Though the majority of patients who fell were placed on fall precautions by the ordering physicians these precautions did not appear to prevent these patients from falling. Patients on fall precautions are routinely assisted with ambulation down the hall and to the toilet, and are often provided with bedside urinals. However, our sleep technologists have not received the same fall mitigation education that our inpatient nurses receive, nor are patients and their families routinely educated in the sleep center regarding potential fall risks. In addition, 5 of the 12 patients who fell received zolpidem, which was prescribed by their sleep provider to ensure adequate amount of sleep was obtained on the night of the PSG. As most patients were instructed to continue on their home medication regimen, other patients might have self-administered hypnotic agents, but information regarding this was not available. Zolpidem has been shown to be associated with an increased fall risk in hospitalized patients, and as patients undergoing PSG might have significant medical comorbidity this prescription practice might need further evaluation to ascertain whether it might result in an increased number of falls in sleep centers as well.

Three of our patients required hospitalization to an ICU setting. These included a patient who developed serious headache and had developed meningitis, a patient who developed sepsis, and another patient with a prior diagnosis of diabetes who developed ketoacidosis. While the patient who developed ketoacidosis was seen in evaluation on the day of the PSG, there was a lag of a few days between the evaluation and night of PSG in the other two patients. An evaluation by a medical provider closer to the date of the PSG might have resulted in these conditions being picked up earlier, avoiding the necessity of a transfer to the ED and an ICU admission.
Patients who were evaluated at the Center for Sleep Medicine and were thought to have a high probability of having seizures were referred to the Epilepsy Monitoring Unit for further evaluation, likely resulting in the low number of adverse events related to seizures in our sample.

In our series, we discovered two instances of physical child abuse, which were captured on video. Sleep labs provide a unique opportunity and environment in which interactions between parents and children and also between caregivers and vulnerable adults can be assessed. Most sleep labs also use videography during the PSG, which provides objective evidence of these interactions. Sleep laboratories will need to consider policies regarding how the staff would ensure patient safety, clear guidelines for intervention during the study in case of concern about abuse, and their role in reporting these events to local protection services. The two cases in our series were reported to child protection services and video evidence was cited in the reporting.

Sleep center accreditation strives to improve quality and safety of patient care. Considering the prominence of cardiodrelated events, the recognition and response to cardiac arrhythmias in real time requires adequately trained and attentive personnel and appropriate monitoring equipment. The AASM center accreditation standards specify sleep technologist training and job descriptions along with ongoing tests of signal recognition as well as some minimum patient-to-technologist ratios to enhance monitoring. Additionally, the AASM accreditation is quite specific regarding quality of monitoring equipment. The Joint Commission accreditation is somewhat less specific regarding qualifications for sleep technologists, does not specify a staffing level, and does not specify type or quality of monitoring equipment. Both sets of standards address the physical plant of the sleep center, though the AASM standards are far more prescriptive. However, neither accreditation designates fall risk mitigation standards. Other important patient safety concerns, not reported in our series (and not specifically addressed in the AASM accreditation) regards infection control efforts, medication safety (specifically medication control), and patient security. There is room for improvement in current accreditation standards.

In recent times, home sleep testing is being used increasingly, especially in patients with a high pretest probability of having sleep apnea and those without major comorbidities. In relation to the adverse safety events associated with PSGs, home sleep testing might result in a decrease in falls and other injuries occurring at the sleep center. However, other events such as cardiac arrhythmias and seizures might be missed.

We tried to capture all the safety incidents that occur during overnight PSG. We were able to collect information from multiple sources ensuring that all voluntarily reported safety incidents were identified. We also were able to access information regarding the outcome of the ED visit and the course of the inpatient stay. However, our study must be viewed in light of some of the limitations inherent to a retrospective review and voluntary reporting. We relied on voluntary reports, which are only one source of patient safety information. Some estimates suggest that such voluntary reporting systems account for less than 10% of all safety incidents that occur in the acute care setting. Learning about safety incidents via patient reports, via office of patient affairs, surveys, audits using “trigger tools” or random review, and automated review of electronic medical records are all tools that have been more fully developed in the inpatient safety programs, but not yet systematically applied in outpatient venues.

CONCLUSION

Our retrospective review of 36,141 PSGs revealed that adverse events during a PSG were relatively uncommon, and a minority of these requires hospitalization. Previous emphasis on cardiac arrhythmias may be overstated, as chest pain and patient falls were most common and resulted in ED evaluation/hospitalization more often. A small number of adverse events could have been anticipated and likely prevented if patients at risk were identified and medical personnel evaluated these patients prior to the PSG.

REFERENCES


SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication May, 2013
Submitted in final revised form June, 2013
Accepted for publication June, 2013
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DISCLOSURE STATEMENT

This was not an industry supported study. The authors have indicated no financial conflicts of interest. This manuscript does not discuss any off-label or investigational procedures.
Disconnection between Periodic Leg Movements and Cortical Arousals in Spinal Cord Injury

Objective: In this study we examine the temporal connection between periodic leg movements (PLMs) and cortical arousals, as well as the treatment effect of pramipexole, in a clinical case with spinal cord lesion.

Methods: A patient with complete cervical spinal cord injury and PLMs during sleep underwent two baseline sleep recordings, one recording with dopaminergic treatment, and one recording with adaptive servoventilation.

Results: The PLMs were temporally dissociated from cortical arousals as well as from respiratory or heart rate events. PLMs were suppressed by pramipexole and persisted after treatment of apnea.

Conclusion: The disconnection of PLMs from arousals supports a spinal generator or peripheral trigger mechanism for PLMs. The suppression of movements by a dopamine agonist suggests that its site of action is caudal to the cervical lesion and outside of the brain. Our observation provides significant new knowledge about the pathogenesis of PLMs and warrants studies in larger populations.

Keywords: Periodic leg movements, spinal cord injury, dopamine agonist, cortical arousal, sleep apnea, case report

Citation: Salminen AV; Manconi M; Rimpilä V; Luoto TM; Koskinen E; Ferri R; Öhman J; Polo O. Disconnection between periodic leg movements and cortical arousals in spinal cord injury. J Clin Sleep Med 2013;9(11):1207-1209.

There is no common agreement on the origin of periodic leg movements (PLMs) during sleep. PLMs are suppressed by dopaminergic therapy, which has led to a hypothesis of dopaminergic dysfunction in the brain in or in the hypothalamo-spinal inhibitory pathways. PLMs are accompanied by simultaneous heart rate elevations and cortical arousals. However, the suppression of PLMs does not affect cortical arousals, and pharmacological reduction of cortical arousals does not affect PLMs. This may imply that PLMs and EEG arousals are simply synchronized with each other without a necessary causal relationship.

PLMs have also been described in spinal cord injury (SCI). These findings do not support the hypothesis of cerebral origin of PLMs. The movements in this subgroup of patients have not been analyzed in detail. In this study, we describe a clinical case with complete SCI in whom dopaminergic-responding PLMs are not synchronized with cortical and autonomic arousals.

REPORT OF CASE

A 35-year-old male, with a cervical SCI sustained in a car accident 17 years prior to the study, underwent 4 polysomnographic studies. The initial polysomnogram was a part of a larger project focusing on neuroimaging and respiratory functions in patients with cervical SCI. Magnetic resonance imaging confirmed the complete cervical spinal lesion between vertebrae C3 and C5. The patient had no motor or sensory function below the C5 level. The patient was treated with tizanidine (12 mg daily) and baclofen (30 mg daily) for muscle spasticity. The patient did not suffer from RLS or daytime sleepiness.

Two baseline recordings revealed excessive PLMs (PLM index 138/h and 36/h). Severe obstructive sleep apnea (apnea-hypopnea index 45.5/h and 74.5/h) was also discovered. The analysis of interval distributions of PLMs revealed a leptokurtic peak at 20-30 seconds in baseline recordings (Figure 1).

Cortical arousals, heart rate elevations, and respiratory events were synchronized but consistently temporally dissociated from PLMs (supplemental Figure S1). Increases in the heart rate were associated with the respiratory events, but were absent after PLMs (Figure 1). Resumption of respiration with cortical and autonomic arousals at the termination of apnea was not accompanied by PLMs.

To assess the response of the leg movements to dopamine agonists, a single test dose (0.25 mg) of pramipexole, a D3 preferential dopamine receptor agonist, was administered before a third recording. Pramipexole abolished PLMs completely. The sleep apnea was treated with adaptive servoventilation during a fourth night. The treatment resolved the sleep apnea, but PLMs persisted (PLM index 69.9/h).

The study was approved by the local ethics committee. Written informed consent was obtained from the patient.
DISCUSSION

Our case study indicates that PLMs may occur despite a complete lesion of the motor and sensory pathways at the level of the cervical spinal cord. However, they are not accompanied by the usual synchronous cortical events or heart rate responses. Our study also demonstrates that pramipexole is able to suppress PLMs even in the absence of a brain connection. These findings support the existence of a spinal generator or a peripheral trigger of PLMs. Suppression of PLMs by pramipexole suggests that the cerebral effects of dopamine agonists are not critical for achieving the therapeutic response.

Movements in our subject fulfill the standard criteria for PLMs. Their distribution of inter-movement intervals was typical for PLMs, and they were suppressed by pramipexole. Therefore they cannot be classified as other motor disorders frequently associated with myelopathies, such as spasticity or myoclonus.

Appearance of PLMs without synchronous cortical events in a patient with an impaired upper motor neuron suggests that the origin of the movements is outside the brain. Therefore, a spinal pacemaker or a peripheral trigger of PLMs is likely. This is supported by the absence of cardiac responses to PLMs in our subject. The findings are in line with the A11 theory of the origin of PLMs. Lack of supraspinal dopaminergic inhibition could result in activation of a pacemaker in the spinal cord to generate PLMs. Alternatively, a peripheral afferent stimulus triggering PLMs as a spinal reflex would also be supported by our findings.

The suppression of PLMs by pramipexole suggests that also the site of action of dopamine agonists in the suppression of PLMs is located outside of the brain. Spinal cord is one candidate for the site of action, but dopamine receptors are also present outside the nervous system.

In conclusion, PLMs may be generated independently from the brain, appear in disconnection from cortical events and from autonomic activations, and can be suppressed by a dopamine agonist without connection to the brain. These findings shed new light on the pathophysiology of PLMs, suggesting a spinal generator, with or without the concurrence of peripheral triggers. SCI is an interesting model for studying the mechanism of PLMs, also allowing systematic investigations in larger populations to confirm these results.

REFERENCES


**DISCLOSURE STATEMENT**

This was not an industry supported study. The authors have indicated no financial conflicts of interest. The work was performed at Tampere University Hospital and Unesta Research Centre, Tampere, Finland. The study was supported by the Tuberculosis Foundation of Tampere, Finland.

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**SUBMISSION & CORRESPONDENCE INFORMATION**

Submitted for publication May, 2013
Submitted in final revised form June, 2013
Accepted for publication June, 2013
Kleine-Levin Syndrome (KLS) is a rare sleep disorder of unknown cause characterized by repetitive, intermittent cycles of extreme sleepiness, and cognitive/behavioral disturbances including confusion, feelings of unreality, aggressiveness, and hypersexuality. Effective treatment is challenging. Stimulants marginally address sleepiness, but may increase irritability and do not improve cognitive and behavioral disturbances. Modafinil may shorten the symptomatic period but not the recurrence rate. Lithium and carbamazepine are beneficial in some cases, possibly related to similarities between KLS and affective disorders. Currently, no single medication is consistently successful in treating the syndrome. Here we report the short-term effect of clarithromycin in a patient with KLS.

**Keywords:** Kleine-Levin, hypersomnia, clarithromycin


**DISCUSSION**

We report a case of KLS with an initial clinical response to clarithromycin, a macrolide antibiotic best known for inhibiting bacterial protein synthesis, but also functioning as a GABA receptor antagonist. This latter functionality led us to use this treatment in our KLS patient.

Excitatory monoamines are either increased or within normal limits in the CSF of KLS patients, explaining the limited effectiveness of stimulants, which increase CSF monoamines, in treating this syndrome. This lack of monoaminergic involvement suggests a pathogenesis rooted in naturally occurring excess GABAergic signaling. Recent work suggests the presence of as yet undefined positive allosteric modulators of the GABA<sub>A</sub> receptor in hypersomnia patients, potentiating the effect of GABA on the receptor and enhancing GABAergic signaling.

We observed a short-term beneficial effect of clarithromycin that dissipated over time. The time-limited effect of this medication has a number of potential explanations. Clarithromycin penetrates extra-cerebral tissue well, but reaches sufficient CSF concentration only in the presence of meningeal inflammation due to high molecular mass and affinity for P-glycoprotein. Viral and autoimmune causative factors have been suggested.
in KLS, based on the frequent report of flu-like meningeal symptoms such as headache, photophobia, confusion, altered consciousness, irritability, and drowsiness during episodes, and a significant association with DQB1*02.\textsuperscript{7,8} Meningeal inflammation that fades over time could influence CSF penetration of clarithromycin and dissipate its effectiveness. This notion supports the hypothesis of viral or post-infectious autoimmune meningoencephalitis as a cause of KLS.\textsuperscript{7}  This dissipation effect may also explain why CSF is typically non-inflammatory in KLS,\textsuperscript{8}  as this would be dependent on CSF sampling in relation to disease course. Another potential explanation is that undefined KLS-related CSF somnogens may act at sites in addition to the GABA\textsubscript{A} receptor.

In conclusion, this report shows a short-term beneficial effect of clarithromycin in KLS. The time-limited nature of the effect limits the practical usefulness of this medication, but it implies a role of the GABA\textsubscript{A} receptor in KLS pathophysiology. This finding suggests other medications that readily cross the blood brain barrier and act at this receptor, such as flumazenil,\textsuperscript{1}  may have utility in KLS. This case also suggests the possible presence of meningeal inflammation during syndromic episodes. Further research demonstrating meningeal inflammation or disease-related CSF somnogens is needed.

**REFERENCES**


**Table 1**—Subjective sleep hours and activities while treated with clarithromycin

<table>
<thead>
<tr>
<th>Day of Treatment</th>
<th>Clarithromycin Dose Timing</th>
<th>Total sleep time</th>
<th>Activities/Mood</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 0</td>
<td>N/A</td>
<td>16 hours</td>
<td>Tired and irritable</td>
</tr>
<tr>
<td>Day 1</td>
<td>12:00 PM, 12:00 AM</td>
<td>7 hours</td>
<td>Chills for the first 24 hours, bad nightmare, frightened</td>
</tr>
<tr>
<td>Day 2</td>
<td>11:00 AM, 11:00 PM</td>
<td>5 hours</td>
<td>Moderately irritable upon awakening. Energy level, concentration, and mood improved during the day. Stayed up past midnight. No more chills.</td>
</tr>
<tr>
<td>Day 3</td>
<td>10:00 AM, 10:00 PM</td>
<td>5 hours</td>
<td>Mood improved, less irritable. Worked on online studies. Patient felt like she was coming out of the dream like feeling.</td>
</tr>
<tr>
<td>Day 4</td>
<td>10:00 AM, 10:00 PM</td>
<td>6 hours</td>
<td>Continued to improve. Went for one hour walk. Studied.</td>
</tr>
<tr>
<td>Day 5-8</td>
<td>10:00 AM, 10:00 PM</td>
<td>6 hours</td>
<td>Walked for 1-1½ hour. Studied.</td>
</tr>
<tr>
<td>Day 9-10</td>
<td>10:00 AM, 10:00 PM</td>
<td>8 hours</td>
<td>Walked less than 1 hour. Studied.</td>
</tr>
<tr>
<td>Day 11-12</td>
<td>10:00 AM, 10:00 PM</td>
<td>10 hours</td>
<td>Tired. Walked less. Studied.</td>
</tr>
<tr>
<td>Day 13-28</td>
<td>10:00 AM, 10:00 PM</td>
<td>11-13 hours</td>
<td>Very tired. Not feeling good. Irritable. Didn’t go for walk.</td>
</tr>
<tr>
<td>Day 29</td>
<td>Stopped taking clarithromycin</td>
<td>13 hours</td>
<td>Very tired. Didn’t go for walk.</td>
</tr>
</tbody>
</table>

**SUBMISSION & CORRESPONDENCE INFORMATION**

Submitted for publication May, 2013
Submitted in final revised form July, 2013
Accepted for publication July, 2013
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**DISCLOSURE STATEMENT**

This was not an industry supported study. The authors have indicated no financial conflicts of interest.
The Relationship between Depressive Symptoms and Obstructive Sleep Apnea in Pediatric Populations: A Meta-Analysis

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Background: A higher incidence of depressive disorders and symptoms has been suggested among children suffering from obstructive sleep apnea (OSA). Yet, the extent to which OSA is related to increased depression is unclear.

Objectives: To evaluate (a) the relationship between depressive symptoms and OSA in pediatric populations, and (b) the efficacy of adenotonsillectomy (AT) for decreasing depressive symptoms among children with OSA.

Methods: A meta-analysis was conducted to assess the relationship between depressive symptoms and OSA, and the efficacy of AT for decreasing depressive symptoms. Studies reporting depressive symptoms of children with OSA through January 2013 were included.

Results: Eleven studies assessed depressive symptoms in both children diagnosed with OSA (n = 894) and a comparison group (n = 1,096). A medium relationship was found between depressive symptoms and OSA (Hedges’ g = 0.43, 95% CI: 0.22-0.64; p = 0.0005). Addressing the second question, 9 studies (n = 379 children) examined depressive symptoms pre- and post-AT. A medium improvement in depressive symptoms was found at follow-up (Hedge’s g = 0.41, 95% CI: 0.20-0.62; p ≤ 0.001).

Conclusion: Our findings suggest that depressive symptoms are higher among children with OSA. Therefore, patients with depressive symptomatology should receive screening for sleep disordered breathing. Treatment of OSA with AT might decrease clinical symptoms of depression, reduce pharmacotherapy, improve sleep patterns, and promote better health.

Keywords: Sleep disordered breathing, obstructive sleep apnea, depression, depressive symptoms, meta-analysis

and/or tonsils, the first line of treatment involves adenotonsillectomy (AT), which might lead to significant decreases in depressive symptoms for those with OSA.

Using meta-analysis, we sought to examine (a) the strength of the relationship between depressive symptoms and OSA in children and adolescents, and (b) the effectiveness of AT on reducing depressive symptoms for children and adolescents with OSA.

### METHODS

#### Study Selection

The PubMed/Medline, PsychInfo, Cochrane library, and Google Scholar data bases were searched using the terms “adenotonsillectomy,” “sleep disordered breathing,” “SDB,” “obstructive sleep apnea,” “OSA” and “depression,” “depressive symptoms,” “mood,” crossed by “child,” “children,” and “adolescents.” English-language studies through January 2013 were examined.

#### Inclusion and Exclusion Criteria

Selection of the articles was conducted by the first author (EY) and revised by the second (KS). Coded information included: sample size, age, gender, BMI, and study quality using the Newcastle-Ottawa scale. Studies of patients up to age 18 years were included in the meta-analysis (0-18 years old; no study was included if the oldest individual was older than 18).

Although there are several proposed methods to diagnose OSA, the gold standard diagnostic test remains polysomnography (PSG). Thus, in addressing our first question (i.e., the extent of a relationship between depressive symptoms and OSA), studies needed to include both PSG and a depression measure. In the first part, while pre- and post-adenotonsillectomy depressive symptom levels were compared in the second part of the study.

### Data Analysis

All statistics included mean values with their standard deviation (SD). Data were analyzed using the Comprehensive Meta-Analysis, version 2.0 (Biostat, Englewood, NJ) software program. ES was calculated using Hedges’ g and a random effects model, as is appropriate when there is heterogeneity in methodology among analyzed studies. Depressive symptom scores were compared between OSA and comparison groups in the first part, while pre- and post-adenotonsillectomy depressive symptom levels were compared in the second part of the study.

### RESULTS

In the first part of the study, 11 studies were included; a total of 894 children in the OSA group and 1,096 in the comparison group.

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### Table 1—Demographic information by group and the scale used

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Scale Used</th>
<th>Rater</th>
<th>Clinical Subjects</th>
<th>Comparison Subjects</th>
<th>Mean/SD Age Clinical Group (Age Range)</th>
<th>Mean/SD Age Control Group (Age Range)</th>
<th>BMI Clinical</th>
<th>BMI Comparison</th>
<th>Male % Clinical Group</th>
<th>Male % Comparison Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beebe et al., 2010</td>
<td>BASC</td>
<td>P&amp;T</td>
<td>100</td>
<td>37</td>
<td>13.74 ± 1.96</td>
<td>13.0 ± 2.0</td>
<td>39.02 ± 8.01</td>
<td>35.9 ± 6.5</td>
<td>47</td>
<td>18.9</td>
</tr>
<tr>
<td>Blunden et al., 2000*</td>
<td>CBCL (A&amp;D)</td>
<td>P only</td>
<td>16</td>
<td>16</td>
<td>7.2 ± 1.6</td>
<td>7.7 ± 1.6</td>
<td>(5.7-10.8)</td>
<td>(5.4-10.7)</td>
<td>43.75</td>
<td>43.75</td>
</tr>
<tr>
<td>Bourke et al., 2011</td>
<td>CBCL (A&amp;D)</td>
<td>P only</td>
<td>42</td>
<td>35</td>
<td>9.14 ± 1.40</td>
<td>9.5 ± 1.7</td>
<td>50.0</td>
<td>48.57</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carotenuto et al., 2012*</td>
<td>CDI</td>
<td>C-SR</td>
<td>94</td>
<td>107</td>
<td>10.15 ± 2.60</td>
<td>10.2 ± 2.44</td>
<td>18.93 ± 1.47</td>
<td>19.02 ± 1.33</td>
<td>52.13</td>
<td>40.19</td>
</tr>
<tr>
<td>Crabtree et al., 2004</td>
<td>CDI</td>
<td>C-SR</td>
<td>62</td>
<td>31</td>
<td>10.1 ± 1.45</td>
<td>9.56 ± 0.90</td>
<td>24.79 ± 4.67</td>
<td>17.50 ± 2.90</td>
<td>55.29</td>
<td>41.94</td>
</tr>
<tr>
<td>Huang et al., 2007</td>
<td>CBCL (A&amp;D)</td>
<td>P&amp;T</td>
<td>66</td>
<td>20</td>
<td>8.12 ± 4.31</td>
<td>8.85 ± 2.13</td>
<td>18.74 ± 2.83</td>
<td>18.84 ± 3.66</td>
<td>89.39</td>
<td>80</td>
</tr>
<tr>
<td>Kurnatowski et al, 2008</td>
<td>CDI</td>
<td>C-SR</td>
<td>121</td>
<td>104</td>
<td>(6-13)</td>
<td>(6-13)</td>
<td>63.27</td>
<td>40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Landau et al., 2012</td>
<td>CBCL &amp; C-TRF (A&amp;D)</td>
<td>P&amp;T</td>
<td>45</td>
<td>26</td>
<td>3.80 ± 0.77</td>
<td>4.05 ± 0.71</td>
<td>15.7 ± 2</td>
<td>16.4 ± 2</td>
<td>73.3</td>
<td>46.2</td>
</tr>
<tr>
<td>O’Brien et al., 2004*</td>
<td>CBCL (A&amp;D)</td>
<td>P only</td>
<td>35</td>
<td>35</td>
<td>6.7 ± 0.6</td>
<td>6.7 ± 0.5</td>
<td>19.8 ± 4.3</td>
<td>17.7 ± 3.5</td>
<td>49</td>
<td>49</td>
</tr>
<tr>
<td>Rosen et al., 2004*</td>
<td>CBCL (A&amp;D)</td>
<td>P only</td>
<td>162</td>
<td>667</td>
<td>9.3 ± 0.9</td>
<td>9.5 ± 0.8</td>
<td>19.0 ± 4.7</td>
<td>17.9 ± 3.5</td>
<td>42.5</td>
<td>50.2</td>
</tr>
<tr>
<td>Ting et al., 2011</td>
<td>CBCL (A&amp;D)</td>
<td>P&amp;T</td>
<td>128</td>
<td>10</td>
<td>10.2 ± 1.03</td>
<td>10.1 ± 0.9</td>
<td>18.39 ± 3.24</td>
<td>7.1 ± 0.8</td>
<td>63.27</td>
<td>40</td>
</tr>
</tbody>
</table>

*Sleep disordered breathing group was included (which is OSA with primary snoring) not only the obstructive sleep apnea group.*
comparison group. After excluding one study in each group that did not report gender data, the overall percentage of males was 57.83% (447/773) in the OSA group and 47.98% (476/992) in the comparison group. The mean unweighted age for the 10 studies in the OSA group was 8.85 ± 2.63 years, compared to 8.92 ± 2.38 for the comparison group.

**Question 1: Is there an elevated rate of depressive symptoms in children with OSA compared to those without?**

A significant relationship between depressive symptoms and OSA was found. Hedges’ g was 0.43 (95% CI = 0.22-0.64; p = 0.00005; see **Figure 1**), indicating a medium relationship. Testing for heterogeneity, the Q value with 10 d.f. was 20.46, signifying mild heterogeneity across studies, while I² was 51.13, p = 0.03, indicating moderate inconsistency among studies. When excluding one study that included children previously diagnosed with attention deficit hyperactivity disorder, the overall ES remained similar; 0.39 (95% CI = 0.18-0.60; p = 0.0002; see **Figure 1**). Testing for heterogeneity, the Q value with 9 d.f. was 17.39, again signifying mild heterogeneity across studies, while I² was 48.24, p = 0.04. In addition, Kendall’s tau = 0.05; this suggests that the standard errors of the means and the effect sizes were independent, indicating that there was not significant publication bias. To examine the ES of depressive symptoms separately in children with OSA versus those with primary snoring (PS), 4 studies were identified that included both OSA and primary snoring groups. While 3 of these studies used as criteria the presence of snoring and an AHI < 1 to diagnose PS, Crabtree and colleagues used a criteria of “mild OSA” for their snoring group. A nonsignificant ES was found in comparing children with OSA to those with PS (Hedges’ g = 0.04, p = 0.76, **Figure 2**), indicating that depressive symptoms are similarly elevated among children with PS as well as OSA. This was consistent after including only the 3 studies that satisfied the strict criteria of PS (Hedges’ g = 0.06, p = 0.73).

While the relatively small number of studies limited our ability to identify significant moderators of the relation between depressive symptoms and OSA, we did explore several potential moderators using the mean weighted ESs. Gender was found to be a significant moderator as studies having a higher percentage of males had higher ESs (beta = 0.66, p = 0.03). Thus, the relationship between depressive symptoms and OSA appears to be stronger for boys than for girls. None of the other potential moderators were significant: average group age

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### Table 1

<table>
<thead>
<tr>
<th>Study name</th>
<th>Group A</th>
<th>Group B</th>
<th>Hedges’ g and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beebe et al., 2010</td>
<td>-0.26</td>
<td>0.05</td>
<td>-0.69 0.17 0.23</td>
</tr>
<tr>
<td>Bourke et al., 2011</td>
<td>0.26</td>
<td>0.04</td>
<td>-0.14 0.65 0.21</td>
</tr>
<tr>
<td>Crabtree et al., 2004</td>
<td>-0.04</td>
<td>0.06</td>
<td>-0.53 0.46 0.89</td>
</tr>
<tr>
<td>Tripuraneni et al., 2012</td>
<td>0.20</td>
<td>0.08</td>
<td>-0.34 0.74 0.47</td>
</tr>
<tr>
<td>O’Brien et al., 2004*</td>
<td>0.04</td>
<td>0.02</td>
<td>-0.21 0.28 0.76</td>
</tr>
</tbody>
</table>

Group A represents the OSA group, while group B represents the depression group. *Groups having sleep disordered breathing (which is OSA with primary snoring) not only OSA. OSA, obstructive sleep apnea; LL, lower limit; UL, upper limit.

**Figure 1**—The relationship between OSA and depression

**Figure 2**—Difference in effect size between children with OSA and children with PS

OSA group are patients diagnosed with OSA, while PS group are children with primary snoring. OSA, obstructive sleep apnea; PS, primary snoring; LL, lower limit; UL, upper limit; Dep Sx, depressive symptoms.
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(beta = 0.07, p = 0.83), BMI (beta = -0.31, p = 0.43), or study quality (beta = 0.47; p = 0.13).

**Question 2: Do depressive symptoms decrease following adenotonsillectomy?**

In the second part of the study, 379 children across nine studies were assessed for depressive symptoms both pre- and post-surgery. Demographics of this group are presented in Table 2. The overall ES change between pre- versus post-surgery was 0.41 (95% CI = 0.20-0.62; p ≤ 0.001; see Figure 3), indicating a medium improvement occurred in depressive symptoms after AT. Testing for heterogeneity, the Q value with 8 d.f. was 16.11, again signifying mild heterogeneity across studies, while F was 50.34, p = 0.04, indicating moderate inconsistencies between studies. Of the 9 studies, 7 studies found ESs greater in the post-AT period compared to pre-surgery (ES = 0.54; p ≤ 0.001). One study found a negative effect size (ES = -0.94, 99% CI = -1.98-0.10; p = 0.08), while another found essentially no improvement following surgery (ES = -0.07; Figure 3). Of note, the largest ESs tended to be observed in studies that did not have a comparison group. Among the 3 studies that did have a comparison group, one showed mild improvement in the AT group compared to controls, the second showed no change, while the third showed worsening of symptoms after AT.

**DISCUSSION AND CONCLUSION**

This study found a medium relation between depressive symptoms in children with OSA, with an ES of 0.45. This relation was moderated by gender, as males showed a stronger relationship between depressive symptoms and OSA. In addition, children were found to exhibit fewer depressive symptoms after AT compared to pre-surgery, with an ES of 0.41. In the TuCASA study, 63 children suffering from RDI in the

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**Table 2—Demographic information of the clinical group undergoing adenotonsillectomy (AT) pre- and post-surgery**

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Scale Used</th>
<th>Rater</th>
<th># Clinical Subjects</th>
<th>AHI Before AT</th>
<th>Mean/SD Age Clinical Group</th>
<th>Male Percentage</th>
<th>BMI</th>
<th>AHI Cutoff</th>
<th>Post-AT Duration</th>
<th>Post-AT AHI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Galland et al., 2006</td>
<td>CBCL (D&amp;W)</td>
<td>P only</td>
<td>61</td>
<td>3.0 ± 2.60</td>
<td>7.0 ± 2.0 (4-11)</td>
<td>57.38 (35/61)</td>
<td>18.1 ± 4.0</td>
<td>1.5</td>
<td>3 months</td>
<td></td>
</tr>
<tr>
<td>Huang et al., 2007</td>
<td>CBCL</td>
<td>P&amp;T</td>
<td>25</td>
<td>3.32 ± 1.11</td>
<td>8.08 ± 1.28</td>
<td>92 (23/25)</td>
<td>18.51 ± 1.28</td>
<td>1.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lewin et al, 2002</td>
<td>CBCL (A&amp;D)</td>
<td>P only</td>
<td>28</td>
<td>9.51 ± 5.50</td>
<td>7.17</td>
<td>50 (14/28)</td>
<td>18.44 ± 4.8</td>
<td>0.5</td>
<td>6-18 months</td>
<td></td>
</tr>
<tr>
<td>Li et al., 2006</td>
<td>BASC (A&amp;D)</td>
<td>P only</td>
<td>40</td>
<td>10.6 ± 11.1</td>
<td>8.4 ± 1.6</td>
<td>90 (36/40)</td>
<td>18.6 ± 4.2</td>
<td>1</td>
<td>6 months</td>
<td>1.7 ± 2.1</td>
</tr>
<tr>
<td>Mitchell et al., 2005</td>
<td>BASC (D&amp;W)</td>
<td>P only</td>
<td>52</td>
<td>16.2 (5.0-88)</td>
<td>7.1 (2.5-14.9)</td>
<td>55.77 (29/52)</td>
<td>55</td>
<td>6 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mitchell et al., 2006</td>
<td>BASC (D)</td>
<td>P only</td>
<td>23</td>
<td>14.1 (5.2-88.0)</td>
<td>7.2 (2.5-14.8)</td>
<td>65 (15/23)</td>
<td>22.58</td>
<td>1</td>
<td>6 months</td>
<td></td>
</tr>
<tr>
<td>Mitchell et al., 2007</td>
<td>BASC (D)</td>
<td>P only</td>
<td>40</td>
<td>15.87 (1.7-48)</td>
<td>7.07 (3.1-14.9)</td>
<td>55 (22/40)</td>
<td>20.39</td>
<td>2</td>
<td>3-6 months</td>
<td>4.67</td>
</tr>
<tr>
<td>Mitchell et al., 2009</td>
<td>BASC (D)</td>
<td>P only</td>
<td>89</td>
<td>16.30 (3.0-88.0)</td>
<td>7.78</td>
<td>60.67 (54/89)</td>
<td>59.52</td>
<td>5</td>
<td>3 months</td>
<td></td>
</tr>
<tr>
<td>Tran et al., 2005</td>
<td>CBCL (A&amp;D&amp;W)</td>
<td>P only</td>
<td>42</td>
<td>5.8 ± 2.5 (2-11.5)</td>
<td>59.52 (25/42)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

All values are in standard deviation (SD) values; BASC, Behavior Assessment System for children; CBCL, Child Behavior Checklist; P, parent; P&T, parent and teacher; A&D, anxiety and depression subscale; D&W, depression and withdrawal; SD, standard deviation; BMI, body mass index; AHI, apnea-hypopnea index.

**Figure 3—Pre- and post-adenotonsillectomy depression/anxiety**

<table>
<thead>
<tr>
<th>Study name</th>
<th>Hedges’ g Variance</th>
<th>LL</th>
<th>UL</th>
<th>p-value</th>
<th>Sample size</th>
<th>Hedges’ g and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Galland et al., 2006</td>
<td>0.53</td>
<td>0.03</td>
<td>0.17</td>
<td>0.89</td>
<td>61</td>
<td>0.038</td>
</tr>
<tr>
<td>Huang et al., 2007</td>
<td>0.33</td>
<td>0.08</td>
<td>-0.22</td>
<td>0.88</td>
<td>25</td>
<td>0.2377</td>
</tr>
<tr>
<td>Lewin et al, 2002</td>
<td>-0.94</td>
<td>0.28</td>
<td>-1.98</td>
<td>0.10</td>
<td>7</td>
<td>0.0771</td>
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<tr>
<td>Li et al., 2006</td>
<td>0.62</td>
<td>0.05</td>
<td>0.17</td>
<td>1.06</td>
<td>40</td>
<td>0.0066</td>
</tr>
<tr>
<td>Mitchell et al., 2005</td>
<td>0.36</td>
<td>0.04</td>
<td>-0.03</td>
<td>0.74</td>
<td>52</td>
<td>0.0673</td>
</tr>
<tr>
<td>Mitchell et al., 2006</td>
<td>0.60</td>
<td>0.09</td>
<td>0.02</td>
<td>1.19</td>
<td>23</td>
<td>0.0415</td>
</tr>
<tr>
<td>Mitchell et al., 2007</td>
<td>0.67</td>
<td>0.05</td>
<td>0.22</td>
<td>1.12</td>
<td>40</td>
<td>0.0033</td>
</tr>
<tr>
<td>Mitchell et al., 2009</td>
<td>0.61</td>
<td>0.02</td>
<td>0.31</td>
<td>0.91</td>
<td>89</td>
<td>0.0001</td>
</tr>
<tr>
<td>Tran et al., 2005</td>
<td>-0.07</td>
<td>0.05</td>
<td>-0.50</td>
<td>0.35</td>
<td>42</td>
<td>0.7380</td>
</tr>
<tr>
<td>Mitchell et al., 2009</td>
<td>0.41</td>
<td>0.01</td>
<td>0.20</td>
<td>0.62</td>
<td>379</td>
<td>0.0002</td>
</tr>
</tbody>
</table>

LL, lower limit; UL, upper limit.

99% CI = -1.98-0.10; p = 0.08, while another found essentially no improvement following surgery (ES = -0.07; Figure 3). Of note, the largest ESs tended to be observed in studies that did not have a comparison group. Among the 3 studies that did have a comparison group, one showed mild improvement in the AT group compared to controls, the second showed no change, while the third showed worsening of symptoms after AT.
higher 15% were compared to 340 children suffering from the other 85% gradient. Higher anxious/depressed values were observed as assessed by CBCL in children suffering the severe form of OSA (55.3 ± 7.9 vs 54.4 ± 7.7), with an ES of 0.12 and variance = 0.02.

The underlying etiological mechanisms for the relationship between depressive symptoms and OSA remains poorly understood, although there are several possible explanations. OSA is associated with blood oxygen desaturation, which may cause micro-awakenings at night, decrease the slow wave stage, and cause restless sleep, thus leading to daytime fatigue and depressive symptoms. Hypoxia from desaturation might also lead to structural changes in the brain that in turn lead to depressive symptoms. In one study, lower blood oxygen desaturation gradients correlated with more profound depressive symptoms among patients with OSA. It is also possible that hormonal changes associated with OSA can lead to depressive symptoms. For example, among children with metabolic syndrome, those with OSA were found to exhibit higher leptin levels than those without OSA, suggesting leptin insensitivity in this population (i.e., with leptin insensitivity and relatively lower levels, this leads to increased appetite and weight gain). Given that leptin is involved in regulating food intake, leptin insensitivity may lead to obesity. Due to low self-esteem associated with body image and obesity, children and adolescents (especially females) might develop depression. Leptin levels normalized after 3 months of continuous positive airway pressure (CPAP).

Alternatively, obesity may contribute to both depressive symptoms and OSA. Obesity is a risk factor for both OSA and depression, although the effect of obesity on depression may be greater among adults. Obese children are often bullied and can have associated decreased mobility, thus, presenting with higher levels of internalizing symptoms secondary to their appearance (each of which can lead to the other). More severe OSA was found among obese children than normal-weight children with OSA and those with PS. Depressive symptoms were also significantly higher in the obese group than the other 2 groups. Likewise, obese patients can have fat deposition around the neck, hypotonia of airway muscles, and limited lung volumes leading to OSA, so it is possible that the associations between depressive symptoms and obesity with OSA may be caused by distinct mechanisms.

The effect of depression leading to obesity and worsening OSA has also been reported. Some depressed children have a higher tendency to overeat, have less energy leading to a sedentary lifestyle, and are socially isolated, possibly leading to weight gain and worsening of OSA. In addition, OSA has been linked to low serotonin levels, which is associated with depression, to sleep cycle irregularity, a known risk factor for depression, and to upper airway tone dyscontrol, also a risk factor for OSA.

We found the relation between depressive symptoms and OSA to be greatest in studies with a higher proportion of males. The incidence of both OSA and depression occur equally in preschool children. However a higher incidence of depression in females is observed in the post-pubertal period compared to males. OSA, on the other hand, occurs at a higher prevalence and more severe level in males than females after puberty, possibly suggesting a role of anthropometric face bony structure and female hormones as a protective factor to OSA. Usually males have coarse bony structures with possibly narrower airway. A dramatic increase in OSA risk occurs in postmenopausal women; this risk was decreased with hormone replacement therapy. Of note, some research has found obesity to be more strongly associated with depression in males than females during adolescence. This raises the possibility that while the BMI itself did not predict the ES between depressive symptoms and OSA in the current study, obesity and gender may interact such that obese boys with OSA are at greatest risk for increased depressive symptoms. Of note, however, most studies had similar proportions of males and females with the exception of Huang et al., who had a high proportion of males and a high ES. Thus, given that the significant moderator effect of gender on the relation between depressive symptoms and OSA was largely due to this one study, replication of this finding is needed.

Adenotonsillectomy, the main treatment for OSA in children, was associated with decreased depressive symptoms compared to pre-surgery levels. The effect size was fairly consistent across studies, with the exception of a large negative effect size found in one study of only 7 patients. Also of note, the ESs appeared to be lower among the 3 that had a comparison group, raising the possibility that some of the observed decrease in depressive symptoms could be related to regression to the mean or due to the effects of administering a measure of depressive symptoms over multiple time points, highlighting the need for future studies to include comparison groups of children who did not receive adenotonsillectomy. Although the exact mechanism for this improvement is unclear, improved oxygenation and nighttime sleep might explain children’s improvement in depressive symptoms. It is not clear if hormonal normalization (e.g., leptin) might contribute to long-term improvements in children’s depressive symptoms. However, weight gain is not an uncommon outcome post-AT surgery in the short term (i.e., within a 6-month period). Accordingly, it is possible that such weight gain (usually a change of more than 10%-15% of the baseline weight) would actually contribute to the worsening of OSA and depression in the post-surgery period. It remains unclear whether this weight gain would contribute to the worsening of OSA and relapse and/or worsening of the depressive symptoms later on. Of importance to note, although AT improves the severity of the OSA in most children, it might not cure it in many cases, necessitating reevaluation of possible residual OSA. Another treatment option in this population is continuous positive airway pressure (CPAP). Although there are limited studies relating CPAP to depressive symptoms in children, controversies exist in adults. In a study involving 51 patients with OSA treated with CPAP, depressive and anxiety symptoms decreased after 1 and 3 months of treatment. However, in a double-blind, placebo control study, CPAP treatment dramatically decreased AHI but had no effect on depressed mood. A limitation of these studies included small sample sizes and assessment of depression shortly after treatment duration possibly affecting the outcome.

Finally, OSA in children and in adults has been associated with poor concentration and negative effects on behavior and mood. A recent meta-analysis found a slightly greater
relation between sleep disordered breathing and attention deficit hyperactivity disorder symptoms (Hedges’ g = 0.57) than was found between OSA and depressive symptoms in the current meta-analysis, indicating that OSA may be related to a variety of psychiatric symptoms. As such, this highlights the importance of screening for emotional and behavioral adjustment among children with OSA.

Several limitations to this study exist. First, several studies included children with PS in the OSA group, possibly lowering the ES for the relationship between depressive symptoms and OSA. However, when the 4 studies including children with PS were compared to OSA children as measured by depressive symptoms, the ES was almost zero (Hedges’ g = 0.04, p = 0.76), indicating that the inclusion of children with PS likely did not lower the strength of relationship between OSA and depressive symptoms. This was maintained when incorporating only the 3 studies that used the strict criteria for PS. Second, all of the included studies used either the BASC or CBCL depression scales, which are not necessarily the most comprehensive measures of depressive symptoms in children. The CBCL “anxious/depressed” subscale, for example, includes anxiety as well as depressive symptoms. Moreover, studies of depressive symptoms and OSA have largely relied on parent ratings of depressive symptoms, but self-reports may be more valid for depressive symptom assessment, particularly among adolescents. Some depression scales might have better validity than those previously used in this literature. For example, the Center for Epidemiological Studies Depression Scale for Children (CES-DC) and the Beck Depression Inventory for adolescents might be preferred. On a related note, none of the included studies used a diagnostic interview, which would be the best measure of a diagnosis of depression. Inclusion of a diagnostic interview that included the assessment of other psychiatric problems (e.g., anxiety and disruptive behavior disorders) that may be comorbid to depression would be helpful to both assess the relation of OSA to clinical depression as well as the extent to which OSA is specific to depression versus other psychiatric problems. A recent meta-analysis, for example, found SDB to have a similar, medium relation to ADHD symptoms as the current meta-analysis found for depressive symptoms.

Third, the relatively modest number of studies included in the current meta-analysis limits our ability to identify moderators of the relationship between depressive symptoms and OSA. Finally, the definition of OSA varied across studies as some used 1/h as the cutoff, while others used 5/hour. This might suggest that children with milder forms of OSA (AHI between 1-5/h) have the strongest relationship to depressive symptoms. Thus, using a cutoff of AHI of 5/h or more might bias the relationship outcome.

Overall, the current study indicates that there is a medium relationship between depressive symptoms and OSA among children and adolescents. Treatment of depression includes primarily psychotherapy in mild to moderate cases, while psychopharmacological agents (e.g., antidepressant medications) can be used in more severe or therapy unresponsive cases. However, medication side effects, especially the debated risk of elevated rates of suicide in child populations, may limit the viability of medication as a treatment option. This meta-analysis suggests that depressive symptoms might improve in children having comorbid OSA, without the need for directly treating the depressive symptoms.

This meta-analysis also highlights the importance of screening for depressive symptoms in children presenting with OSA. Yet, well-controlled research is needed. Ideally, children from multiple clinics should be involved, with standardization of diagnostic criteria for OSA and exclusion of those with PS, given that the relationship with PS and depressive symptoms are not well delineated. Close monitoring of the AHI, as well as depressive symptoms before and after AT, and comparison of depressive symptoms in those with cured OSA versus those with residual symptoms will address more accurately whether a decrease in depressive symptoms directly coincides with a decrease in OSA. Despite the need for more research, this meta-analysis suggests that treating OSA may improve children’s depressive symptoms, possibly avoiding the need for psychopharmacological treatment.

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80. Sedky K, Bennett D, Carvalho K. The relationship between attention deficit hyperactivity disorder and sleep disordered breathing in pediatric populations: a meta-analysis. Sleep 2013;36(Abstract Supplement);A310.


ACKNOWLEDGMENTS
The authors would like to thank Dr. Ron Mitchell and his team for providing supplemental data from their published studies that were included in the meta-analysis.

SUBMISSION & CORRESPONDENCE INFORMATION
Submitted for publication June, 2013
Submitted in final revised form July, 2013
Accepted for publication July, 2013
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DISCLOSURE STATEMENT
This was not an industry supported study. The authors have indicated no financial conflicts of interest.
A 10-year-old girl with history of severe to profound bilateral sensorineural hearing loss and anxiety presented with daily tiredness, difficulty waking in the mornings, and requiring a parent in bed with her in order to fall asleep. History was obtained from her and her mother, who also has sensorineural hearing loss, via American Sign Language (ASL) interpreter.

The patient’s bedtime was 9 PM with sleep onset within 30 minutes. She endorsed anxiety about falling asleep and mother stayed in bed with her overnight. Occasional night wakings lasted 10-30 minutes. On school days, mother started waking the patient 45 minutes before she had to be out of bed. She often seemed grumpy in the morning but was not chronically tardy.

Mother was not aware of whether the patient snored during sleep. The patient sometimes mouth breathed. She had not had labored breathing, bruxism, night sweats, nocturnal enuresis, or morning headaches, and did not sleep with neck in hyperextension. She had had at least one episode thought to be sleepwalking.

Physical examination was notable for a thin child with prominent though non-erythematous tonsils and a receding chin.

QUESTION: What else should the clinician do in order to decide whether or not a polysomnogram is necessary?
DISCUSSION

Relatives of this patient with typical hearing reported her snoring within the past year. Subsequent overnight polysomnogram showed pediatric obstructive sleep apnea with an obstructive apnea-hypopnea index of 7.4 events per hour and sleep fragmentation (Figure 1). Oxygen nadir was 92%. Obstructive sleep apnea syndrome was diagnosed and the patient referred to otolaryngology.

Hearing loss or deafness affects more than 48.1 million individuals in the United States, with nearly 1 in 5 displaying unilateral or bilateral hearing loss as defined by World Health Organization criteria, and 14.9% of US children affected by hearing loss or deafness.1,2 The etiology is heterogeneous, with a variety of congenital and acquired conditions that can also lead to associated neurocognitive insult or increase potential risk for sleep problems. Genetic deafness (such as connexin 26 mutation, also referred to as gap junction beta-2 protein [GJB2]) represents one of the most common forms of congenital deafness and can lead to families with deaf parents and deaf children, as in the case above.

It is unknown at present if patients with hearing loss have a baseline increased risk for sleep disorders. However, sleep disorders are highly prevalent in the general population, and there is no reason to believe that they are less common among people who are deaf. For sleep medicine specialists, the case above highlights the risk of missing sleep disordered breathing in pediatric patients who are deaf or hard of hearing and raised by parents who are also deaf or hard of hearing. Among the elderly, where rates of age related hearing loss increase with each decade of life, an elderly bed partner with hearing loss may not endorse snoring. Integrating questions into clinical screenings that rely on visual signs or symptoms may improve detection of sleep disordered breathing in these patients, but ultimately snoring is an important sign of sleep disordered breathing. Involving other informants with typical hearing will increase detection of snoring in this population.

In families where the primary form of communication is ASL, there is often increased difficulty accessing health care, especially more specialized care, due to the shortage of providers trained and experienced in working with individuals who are deaf or hard of hearing. There is also a documented increased risk of difficulties communicating with health and mental health care providers due to the need for accommodations such as interpreters.3 Previous research has demonstrated deficits in health care knowledge in individuals who are deaf or hard of hearing compared with the general population. Providing health care information in written format does not always remedy this problem: the average reading level of students who are deaf or hard of hearing leaving high school is below a basic proficiency level in reading comprehension.4

ANSWER: Question family members who can hear about snoring.

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**Figure 1**—120 second epoch tracing of polysomnography recorded during N1 sleep reveals multiple obstructive apneic and hypopnic events accompanied by arousals and mild desaturations.

- EEG, electroencephalogram; F3-M2, C3-M2, and O1-M2, electroencephalogram leads; EOG, electrooculogram; E1-M2 and E2-M2, electrooculogram leads; ChinL, chin electromyelogram, left; SpO2, pulse oximetry; Thermistor, oronasal thermal flow; Flow_CU, nasal pressure; Thorax and Abdomen, ribcage and abdominal movements.
CLINICAL PEARLS

1. Increased suspicion of sleep disordered breathing in pediatric patients who are deaf or hard of hearing is required when caregivers are also deaf or hard of hearing and may not hear snoring.
2. Seek out collateral informants with typical hearing in elderly patients who present with other symptoms of sleep disordered breathing but have a bed partner with hearing loss.
3. Involvement and interview of hearing family members of the deaf child may be necessary in order to confirm auditory symptoms of sleep disordered breathing. Alternately, visual cues for sleep disordered breathing may be used when working with parents who are deaf or hard of hearing.

REFERENCES


CITATION


DISCLOSURE STATEMENT

This was not an industry supported study. The authors have indicated no financial conflicts of interest.
Adenotonsillectomy or Watchful Waiting in the Management of Childhood Obstructive Sleep Apnea


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ARTICLE SUMMARY

Question: Compared with watchful waiting, does the treatment of childhood obstructive sleep apnea (OSA) with adenotonsillectomy improve cognitive outcomes, symptoms, behavior, quality of life, and polysomnography findings?

Design: Multicenter, single-blind, randomized, controlled trial conducted at seven academic sleep centers; ClinicalTrials.gov number, NCT00560859.

Allocation: Children were randomly assigned to early adenotonsillectomy (EAT-surgery within 4 weeks after randomization) or a strategy of watchful waiting with supportive care (WWSC). Randomization was performed centrally using a web-based system that required confirmation of eligibility criteria prior to providing the treatment assignment.

Blinding: Single-blind; personnel involved in conducting psychometric evaluations and measuring other study outcomes, as well as study investigators (other than the surgeons), were blinded to randomization assignments, study participants and families were not blinded.

Follow-Up Period: 7 months.

Setting: The study recruited children with symptoms of obstructive sleep apnea syndrome (OSAS) from primary care, otolaryngology, and sleep clinics at 7 academic centers in the United States.

Subjects: 453 children, mean age 6.5 ± 1.4 years, 49% male, were randomized.

Inclusion Criteria: Age between 5 to 9 years, polysomnographic diagnosis of OSAS without prolonged oxyhemoglobin desaturation, and considered to be suitable candidates for adenotonsillectomy. OSAS was defined as an apnea–hypopnea index (AHI) score of 2 or more events per hour or an obstructive apnea index (OAI) score of 1 or more events per hour.

Exclusion Criteria: Children with an AHI score of more than 30 events per hour, an OAI score of more than 20 events per hour, or arterial oxyhemoglobin saturation of less than 90% for ≥ 2% of total sleep time, recurrent tonsillitis, a BMI z score of ≥ 3, and use of medication for attention deficit–hyperactivity disorder (ADHD).

Intervention: Participants meeting eligibility criteria were randomized to early adenotonsillectomy or a strategy of watchful waiting with supportive care (WWSC). Children completed in lab polysomnography at baseline and 7 month follow-up. At both time points, caregivers were asked to complete survey instruments evaluating behavior, intellectual functioning, quality of life, symptoms of sleepiness and sleep apnea; teachers were mailed behavioral assessments. Neuropsychological testing was performed during a morning visit, on a separate day from the polysomnogram, to avoid the influence of atypical sleep related to overnight monitoring. Tests were administered by psychometrists, blinded to the polysomnographic results.

Outcomes: The primary outcome was the change in the attention (A) and executive-function (E) score on the Developmental Neuropsychological Assessment (NEPSY).

Secondary outcome measures were: 1) caregiver and teacher ratings of behavior measured by Conners’ Rating Scale Revised: Long Version Global Index, comprising Restless–Impulsive and Emotional Lability factor sets and the Behavior Rating Inventory of Executive Function (BRIEF), comprising summary measures of behavioral regulation and metacognition; 2) symptoms of obstructive sleep apnea syndrome, as assessed by the Pediatric Sleep Questionnaire sleep-related breathing disorder scale (PSQ-SRBD); 3) sleepiness, assessed using the Epworth Sleepiness Scale modified for children; 4) global quality of life, evaluated by caregiver-rated total score from the Pediatric Quality of Life Inventory (PedsQL); 5) disease-specific quality of life measure based on the 18-item Obstructive Sleep Apnea assessment tool; 6) generalized intellectual functioning evaluated by the General Conceptual Ability score from the Differential Ability Scales-II (DAS); and 7) polysomnographic indexes.

A study sample size of 400 children, randomized 1:1 between the 2 study arms allowed for detection of an effect size, for the primary endpoint of the NEPSY A/E domain score, of ≥ 0.32 (an effect size estimated from one prior study) with 90% power.

Patient Follow-Up: 464 children were randomized between January 2008 and September 2011, 11 excluded due to lack of follow-up data, 35 were lost to follow-up, and 18 withdrew from the study. Follow-up visits were conducted for 400 children (86%), with 397 children having measurements of attention and executive function on the NEPSY (primary outcome) that could be evaluated. An intention to treat analysis was performed.

Main Results: The baseline attention and executive function score on the NEPSY (primary outcome) was close to the population mean of 100 in both groups. Average scores increased in both groups at 7 month follow-up, but there was no statistically significant difference between the groups in the primary outcome (7.1 ± 13.9 in the early-adenotonsillectomy group and 5.1 ± 13.4 in the watchful-waiting group, p = 0.16). The AHI score improved in both groups, but significantly more so in the early-adenotonsillectomy group (Effect size 0.57, p < 0.001). There were statistically significant improvements in behavioral, quality of life measures, and greater reduction in symptoms in the early adenotonsillectomy group than in the watchful-waiting group.

Neither obesity nor age significantly modified treatment responses for any of the outcomes reported. The relative improvements associated with
early-adenotonsillectomy were significantly lower for African American children compared to children of other ethnic/racial backgrounds for the caregiver completed behavioral questionnaires. There were 15 post-randomization serious adverse events, six of which occurred in children randomized to early adenotonsillectomy and nine in the control group. Eight of the events were associated with peri-operative complications (bleeding, dehydration, and pain). Nine treatment failures were also considered adverse events, occurring in the watchful waiting group; treatment failures were attributed to: increased problems with sleep quality or sleepiness, school behavioral problems, morning headaches, asthma exacerbation, hypertension, and bacterial infections. 

**Conclusion:** Among school age children with obstructive sleep apnea syndrome without prolonged oxygen desaturation, early adenotonsillectomy, as compared with a strategy of watchful waiting with supportive care, did not result in significantly greater improvement in scores on a formal test of attention and executive function after a period of 7 months. However, early adenotonsillectomy was associated with statistically significant improvements in polysomnographic findings, caregiver and teacher reported measures of behavior, quality of life, and sleep apnea symptoms. 

**Sources of Funding:** The study was supported by grants (HL083075, HL083129, UL1 RR024134, and UL1 RR024989) from the National Institutes of Health.

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**COMMENTARY**

This elegant study raises several questions for the treating clinician, including:

1. **Which children would benefit from watchful waiting,** since there was no significant difference in the primary outcome (attention and executive function) between early adenotonsillectomy and watchful waiting with supportive care after 7 months of treatment?
2. **Are the improved secondary outcomes sufficient to warrant adenotonsillectomy in children who have OSAS?**
3. **What are the implications of favoring surgery versus watchful waiting in children who have OSA?**

This was a well-designed and rigorously conducted study evaluating multiple outcomes in a large group of otherwise healthy children aged 5-9 years across several academic centers across the United States. Efforts were made to include children from primary care clinics. The methodology involved was impressively executed, with great efforts made towards appropriate screening, standardized testing and measurement, use of quality control measures, and ensuring surgery was also carried out in a standardized fashion among different centers. Factors that could exacerbate OSAS, including allergies and poorly controlled asthma, were assessed as part of the protocol, but did not affect randomization. The children were not tested formally for asthma and allergies, such that some children with either condition could have been randomized to the study, which could affect the severity of OSAS over time. Both groups were provided opportunity to improve sleep quality via good sleep structure and hygiene. However, medication was not included as an intervention or within the run-in period to determine how many children would benefit from medication alone.

Despite the rigorous methodology, there are several factors that must be considered for interpretation of these results. The children studied were those that were able to perform neurocognitive testing; however, OSAS in children starts at a much younger age and whether the timing of the surgery for younger children would result in different outcomes remains to be seen. In addition, for ethical reasons, the study group had very minimal intermittent hypoxemia (oxygen hemoglobin saturation less than 90% for ≥ 2% of the total sleep time). It is possible that the outcomes in children, who have more severe hypoxemia or more recurring desaturations, could have more noticeable changes in executive function to a certain extent; while those with very severe recurrent desaturations may not have any improvement, depending on the duration and severity of the disease. Furthermore, the primary outcome may be impacted by various factors including sleep deprivation, sleep apnea, sleep fragmentation, and genetic endowment to name a few, such that the lack of difference may be mitigated by other non-measurable factors. It is hoped that with randomization these non-measurable factors will also be equally distributed between the two groups. Nevertheless, this study did show significantly greater improvements in behavior, quality of life, and polysomnographic findings, as well as a reduction in symptoms in the children who underwent early adenotonsillectomy versus watchful waiting. A parent and the treating clinician may consider the secondary outcomes worthy enough to consider surgery, at least in some children. What is striking is that 46% of the children in the watchful waiting group did normalize their polysomnographic parameters, despite ongoing behavioral and quality of life impairment, which raises the question – which treatment outcomes should be considered of primary importance? Polysomnographic parameters may be evaluated within the context of clinical picture. In addition, it could be possible that the time at follow-up was too short to show differences in executive function and attention in those children that had watchful waiting versus surgery or that the subtle differences in function are not apparent in the neuropsychological testing. Finally, we eagerly await the data on physiological parameters that were measured within this study to determine if there are other criteria that would help decision making towards surgery versus watchful waiting.

Overall, not many children were treated medically prior to randomization and perhaps a period with medical treatment may also have been a viable option as some children with allergic rhinitis or poorly controlled asthma respond to treatment and the snoring may dissipate. This study suggests that children with OSAS warrant comprehensive evaluation to determine whether surgery is needed; ideally, after a trial of medical management. Additional large studies are needed to evaluate the role of medical management and surgery. If watchful waiting is chosen, the necessity for treatment should be considered after evaluation of neurocognitive and physical effects and potential impact to the child’s functioning and quality of life with follow-up. Future studies should also consider economic analyses of either management option. In summary, this study highlights that OSAS is a disease that results in end-organ dysfunction across various domains, such as physical and neurocognitive func-
The optimal timing and choice of intervention for children across the developmental trajectory is yet to be determined.

**CITATION**


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**DISCLOSURE STATEMENT**

The authors have indicated no financial conflicts of interest.