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Statement of Educational Purpose/Overall Education Objectives
JCSM is a peer-reviewed clinical journal addressing sleep, circadian rhythms, and the diagnosis and treatment of the broad spectrum of sleep disorders. Its mission and educational purpose is to promote the science and art of sleep medicine and sleep research. Sleep disorders medicine draws clinical and scientific applications from a wide variety of primary disciplines, including pulmonology, neurology, psychiatry, psychology, otolaryngology, and dentistry. Readers of JCSM should be able to: 1) appraise sleep research in basic science and clinical investigation; 2) interpret new information and updates on clinical diagnosis/treatment and apply those strategies to their practice; 3) analyze articles for the use of sound scientific and medical problems; and 4) recognize the inter-relatedness/dependence of sleep medicine with primary disciplines.

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Insomnia is common in the general population. From the review study of Ohayon, about one-third of the general population suffers symptoms of insomnia. The prevalence is between 9% and 15% when daytime consequences of insomnia are taken into account. A strong association between insomnia and anxiety/depression is also found in the community and in hospitals. Chronic insomnia may aggravate the severity of anxiety and depression. In addition, while insomnia or excessive sleepiness is a risk factor for depression in all individuals, it is a much greater risk factor in rotating or night shift workers.

Shift work disorder (SWD) is a circadian rhythm sleep disorder characterized by sleepiness or insomnia that can be attributable to the person’s work schedule. According to second edition of the International Classification of Sleep Disorders (ICSD-2), the major feature of circadian rhythm sleep disorder is “a misalignment between the patient’s sleep pattern and the sleep pattern that is desired or regarded as the societal norm.” People who work shifts have great difficulty adjusting their internal clocks and develop SWD due to a mismatch between the sleep/wake schedule required by their jobs and their own circadian sleep/wake cycles. It is estimated that around 20% of the US and 35% of the Taiwan labor force works night, evening, or rotating shifts, and that 10% of these individuals suffer from SWD. Circadian misalignment can be caused by shift work. The resulting circadian misalignment associated with shift work can produce significant morbidity associated with disturbed sleep and impaired alertness. The longitudinal study of Bara and Arber found that women’s mental health and anxiety/depression were more adversely affected by

Study Objectives: The present study investigated whether bright light exposure during the first half of the evening/night shift combined with light attenuation in the morning is effective in improving sleep problems in nurses undertaking rotating shift work who suffer from clinical insomnia.

Methods: This was a prospective, randomized control study. The Insomnia Severity Index (ISI) and the Hospital Anxiety Depression Scale (HADS) were used to evaluate insomnia and anxiety/depression severity, respectively. Female hospital nurses on rotating shifts during the evening or night shift with an ISI score > 14 were enrolled. Subjects in the treatment group (n = 46) were exposed to bright light at 7,000-10,000 lux for ≥ 30 minutes. Exposure was continued for at least 10 days during 2 weeks, and the subjects avoided daytime outdoor sun exposure after work by wearing dark sunglasses. Subjects in the control group (n = 46) were not exposed to bright light, but also wore sunglasses after work. Statistical analyses were performed to examine group differences and differences across treatments.

Results: After treatment, the treatment group showed significant improvements in the ISI score and the HADS total and subscale scores as compared with pre-treatment. The ISI, HADS, and subscales of the HADS scores were significantly improved across treatments in the treatment group as compared with the control group.

Conclusions: The design of this study is easy to put into practice in the real world. This is the first study to document that a higher intensity and briefer duration of bright light exposure during the first half of the evening/night shift with a daytime darkness procedure performed in rotating shift work female nurses suffering from clinical insomnia could improve their insomnia, anxiety, and depression severity.

Keywords: Bright light, circadian rhythm, shift work, rotating shift, insomnia, anxiety, depression, nurses

Commentary: A commentary on this article appears in this issue on page 647.

Citation: Huang LB; Tsai MC; Chen CY; Hsu SC. The effectiveness of light/dark exposure to treat insomnia in female nurses undertaking shift work during the evening/night shift. J Clin Sleep Med 2013;9(7):641-646.

BRIEF SUMMARY

Current Knowledge/Study Rationale: Bright light exposure during the first half of the night shift and daytime darkness have been shown to improve daytime sleep and nocturnal functioning in nurses working the night shift. We aimed to investigate the effectiveness of bright light exposure during the first half of the evening/night shift combined with light attenuation in the morning in nurses undertaking rotating shift work who suffer from clinical insomnia.

Study Impact: Bright light exposure with morning time darkness is effective to improve insomnia, anxiety, and depression severity in rotating shift work female nurses suffering from clinical insomnia. The design of this study is easy to put into practice in the real world.
varied shift patterns than by night work. Nurses are the largest working group in a hospital and most are on a rotating shift work schedule. Research has shown that shift work, in particular night work, can have negative effects on the health, safety, and well-being of nurses.\textsuperscript{16,17} The prevalence of depression is significantly higher in those who work rotating and night shifts than in day workers.\textsuperscript{7} Lin et al.\textsuperscript{18} also found that female nurses have a rotation shift work schedule tend to experience poor sleep quality and mental health in Taiwan.

Light is the dominant environmental time cue that entrains the human circadian clock to a 24-h day, and the timing of light exposure will determine whether the internal clock is phase delayed or advanced.\textsuperscript{19} Using this principle, bright light exposure during the first half of the night shift and daytime darkness have been shown to improve daytime sleep and nocturnal functioning in night shift workers.\textsuperscript{20,21}

However, no studies have investigated whether bright light exposure could improve sleep problems in nurses working rotating or night shifts with moderate to severe insomnia (clinical insomnia). The aim of the present study was to investigate whether bright light exposure during the first half of the evening/night shift combined with light attenuation in the morning would be effective in improving sleep problems in nurses working rotating shifts during the evening/night shift who suffer from clinical insomnia in a hospital setting. In addition, we also investigated the changes in the anxiety and depression scores after bright light intervention.

\section*{METHODS}

\subsection*{Study Design}

This was a randomized controlled study performed to assess the effectiveness of bright light exposure in treating insomnia, anxiety, and depression in female nurses working a 3-shift rotation during the evening/night shift. The project was approved by the Institutional Review Board of Chang Gung Memorial Hospital. The inclusion criteria were: (1) a score on the Chinese version of the Insomnia Severity Index (ISI)\textsuperscript{22} > 14; (2) rotating-shift female nurses working the evening/night shift; (3) 3-shift rotation including day, evening, and night shifts in the most recent 6 months; and (4) the same work schedule during treatment. The exclusion criteria were: (1) substance abuse or dependence according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV),\textsuperscript{23} including caffeine, alcohol, nicotine, and over-the-counter sleeping pills; and (2) unstable physical conditions. Participants were randomly divided into 2 groups, the treatment group and the control group. Randomization was performed using a random digit table. An even number was allocated to the treatment group and an odd number was allocated to the control group. All subjects completed the Chinese version of the Hospital Anxiety and Depression Scale (HADS)\textsuperscript{24} and the ISI during work before and after intervention. This study was performed in a real workplace. Subjects in the treatment group were exposed to artificial bright light of 7,000-10,000 lux for \( \geq 30 \) min; evening shift exposure took place between 19:30 and 20:30, while night shift exposure occurred between 23:00 and midnight. During exposure, the subjects undertook charting or reading. Light was delivered by an Apollo briteLITE 6. A light box was placed at a 45 degree angle from the face, just above eye level. Light exposure of 7,000-10,000 lux could be obtained at a distance of around 70 cm from the light box to the nurse. Light intensity was measured using a Lutron Electronic LX-1102 light meter. Ward illumination at night is maintained in the range of 100-400 lux in our hospital. Treatment was continued for \( \geq 10 \) days during 2 weeks, and daytime outdoor sun exposure after work and before sleep was avoided by the subjects by wearing dark sunglasses with UV protection, including on off-days. The subjects in the control group were not exposed to artificial bright light, but also wore sunglasses to avoid outdoor sun exposure after work and before sleep. Other aspects of lifestyle were not changed, including off-days, in either group. Subjects who used sleep medications did not change the pattern of use across the treatment duration. All participants were reminded of the study procedure by a telephone call before and after work to enhance protocol adherence.

\subsection*{Subject Enrollment}

This study was conducted at a medical center in northern Taiwan from May 1, 2009, to March 31, 2010. Around 2,500 three-shift rotating nurses in the most recent 6 months received information regarding the study by e-mail and during nursing meetings in the hospital in May 2009. Using \( t \)-tests and a one-sided type I error of 5\%, we estimated that 50 participants in each group would be necessary to achieve a power of 80\% to detect the effect size at 0.5. One hundred two nurses agreed to join this study. Ten participants were excluded because their pre-treatment ISI score was <15. A total of 92 rotating-shift female hospital nurses working the evening shift (4 pm to midnight) or night shift (midnight to 8 am) with an ISI score >14 were recruited. Written informed consent was obtained from all participants before study enrollment. Forty-six subjects were in the treatment group, and the remainder were in the control group. All subjects completed the study procedure reported by themselves.

\subsection*{Instruments}

\textbf{Insomnia Severity Index (ISI)}

The ISI, developed by Morin, is a 7-item self-rated scale designed to assess subjective perception of the severity of insomnia.\textsuperscript{22} The scale contains items including difficulty falling asleep, difficulty maintaining sleep, early morning awakening, satisfaction with sleep, concerns about insomnia, and the functional impact of insomnia. The total score, ranging from 0 to 28, can be used to categorize patients into different levels of insomnia severity (0-7, no clinically significant insomnia; 8-14, sub-threshold insomnia; 15-21, clinical insomnia, moderate severity; >21, clinical insomnia, severe severity).\textsuperscript{22} A total score >14 represents moderate to severe insomnia. The scale was found to have an adequate internal consistency (Cronbach \( \alpha = 0.74 \)).\textsuperscript{23} The Insomnia Severity Index-Chinese version also has a good internal consistency, with a Cronbach \( \alpha \) coefficient of 0.94.\textsuperscript{25} The Cronbach \( \alpha \) of the ISI before treatment in this study was 0.65.

\textbf{Hospital Anxiety and Depression Scale (HADS)}

The HADS\textsuperscript{25} is a 14-item self-rated scale designed to assess clinically relevant anxiety and depression. It is divided into an Anxiety subscale (HADS-A) and a Depression subscale (HADS-D), both containing 7 intermingled items. The original English version has been translated into and validated in many languages,
including Chinese. In most studies an optimal balance between sensitivity and specificity was achieved when caseness was defined by a score ≥ 8. The HADS, HADS-A, and HADS-D before treatment had good internal consistency in this study, with a Cronbach α coefficient ranging from 0.72 to 0.82.

Statistical Analysis
Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS 17.0) for Windows 7. The demographic data of the treatment group and the control group were compared using Student t-test, the χ² test, or Fisher test. The independent-samples t-test was used to compare the differences in the scores for insomnia, anxiety, and depression between the 2 groups before and after treatment. We used the paired-samples t test to assess the effectiveness of bright light exposure (change from pre-treatment to post-treatment in each group). All continuous variables were compared across both groups using an analysis of covariance model (ANCOVA) to assess the change from pre-treatment, with pre-treatment as the covariate. We also used ANCOVA to compare the changes in anxiety and depression severity in both groups, with the ISI change from pre-treatment to post-treatment as the covariate. The Pearson correlation was used to assess the correlations between the changes in the ISI, HADS-A, and HADS-D scores. All statistical tests were 2-sided, and a significance level of 0.05 was used for all comparisons.

RESULTS

During the study period, all subjects completed the study and did not use psychotropic medication other than sleep medications. All subjects reported that they did not change their lifestyle, such as mealtimes, exercise periods, sleep/wake schedule, and pattern of alcohol/substance/medication use, including off-days, during the study. Although none of the participants met the diagnosis of substance dependence or abuse, 19 nurses (20.7%) use one cup of caffeinated drink per day habitually. Ten subjects were in the treatment group; the remainder were in the control group. There was no significant difference between the two groups. Most subjects (93.6%) did not use sleep medications; 6 participants used sleep medications (zolpidem or lorazepam) prescribed by physicians. Table 1 shows the demographic data of both groups of participants. All demographic data were comparable between groups, including previous work schedule and sleep medications use.

Differences in ISI, HADS, HADS-A, and HADS-D between Treatment and Control Groups before and after Treatment
There were no significant differences in the ISI, HADS, HADS-A, and HADS-D scores between the groups before treatment. The treatment group had significantly lower scores on the insomnia, anxiety, and depression scales than the control group after treatment (Table 2).

Differences across Treatment in ISI, HADS, HADS-A, and HADS-D between Treatment and Control Groups
After treatment, the treatment group exhibited significantly improved ISI, HADS, HADS-A, and HADS-D scores as compared with pre-treatment (paired-samples t test, all p < 0.001). Depression became worse after treatment, as measured by the HADS and HADS-D, in the control group (paired-samples t test, p < 0.001). The mean changes in the scores of the ISI, HADS, HADS-A, and HADS-D from pre-treatment in the treatment group were -12.2 ± 5.1, -6.6 ± 5.1, -3.8 ± 2.8, and -2.8 ± 3.4, respectively; while those in the control group were -0.2 ± 1.7, 1.5 ± 2.5, 0.2 ± 1.3, and 1.3 ± 1.8, respectively. For subjects in the glassess-only group, the pre-treatment depression score was categorized as either a HADS-D score < 8 or ≥ 8. The mean changes in the scores of depression across treatment in the HADS-D < 8 group and ≥ 8 group were 1.9 ± 1.8 and 0.3 ± 1.0, respectively. The depression score became worse only in the group with a HADS-D < 8 (paired-samples t test, p < 0.001). Relative to the control group, the scores of the ISI, HADS, HADS-A, and HADS-D significantly improved across treatment in the treatment group according to ANCOVA (all p < 0.001; Figure 1). After treatment, in the treatment group 37 nurses (80.4%) met the criterion for no insomnia (ISI < 8). Meanwhile, no nurse met the criterion for no insomnia in the control group.

Differences across Treatment in the ISI, HADS, HADS-A, and HADS-D between Evening and Night Shift Nurses in Treatment and Control Groups
The scales of the ISI, HADS, HADS-A, and HADS-D were not significantly different between nurses undertaking the evening and night shifts in either group. We analyzed whether the

Table 1—Demographic data of the treatment and control groups

<table>
<thead>
<tr>
<th>Variables</th>
<th>Treatment (n = 46)</th>
<th>Control (n = 46)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), M ± SD</td>
<td>30.2 ± 4.5</td>
<td>30.3 ± 4.7</td>
</tr>
<tr>
<td>Employment (years), M ± SD</td>
<td>5.1 ± 4.7</td>
<td>5.3 ± 4.8</td>
</tr>
<tr>
<td>Education, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14 years</td>
<td>14 (30.4)</td>
<td>16 (32.6)</td>
</tr>
<tr>
<td>16 years</td>
<td>32 (69.6)</td>
<td>30 (67.4)</td>
</tr>
<tr>
<td>Marital Status, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single/divorced/separated</td>
<td>39 (84.8)</td>
<td>36 (78.3)</td>
</tr>
<tr>
<td>Married</td>
<td>7 (15.2)</td>
<td>10 (21.7)</td>
</tr>
<tr>
<td>Department, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>21 (45.7)</td>
<td>21 (45.7)</td>
</tr>
<tr>
<td>Internal Medicine</td>
<td>20 (43.5)</td>
<td>21 (45.7)</td>
</tr>
<tr>
<td>Psychiatry</td>
<td>5 (10.9)</td>
<td>4 (8.7)</td>
</tr>
<tr>
<td>Character of ward, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute ward</td>
<td>42 (91.3)</td>
<td>46 (100)</td>
</tr>
<tr>
<td>Intensive care unit</td>
<td>4 (8.7)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Three-shift rotation: Work schedule last month, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day shift</td>
<td>16 (34.8)</td>
<td>19 (41.3)</td>
</tr>
<tr>
<td>Evening shift</td>
<td>17 (37.0)</td>
<td>16 (34.8)</td>
</tr>
<tr>
<td>Night shift</td>
<td>13 (28.3)</td>
<td>11 (23.9)</td>
</tr>
<tr>
<td>Three-shift rotation: Current work schedule, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Evening shift</td>
<td>32 (69.6)</td>
<td>30 (65.2)</td>
</tr>
<tr>
<td>Night Shift</td>
<td>14 (30.4)</td>
<td>16 (34.8)</td>
</tr>
<tr>
<td>Prescription sleep medications use, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1 (2.2)</td>
<td>5 (10.8)</td>
</tr>
<tr>
<td>No</td>
<td>45 (97.8)</td>
<td>41 (89.1)</td>
</tr>
</tbody>
</table>

All variables p > 0.05. M ± SD, mean ± standard deviation.
Changes in the scores for insomnia and mood might differ between evening and night shift workers in the treatment group. The mean changes in the scores of the ISI, HADS, HADS-A, and HADS-D from pre-treatment in the evening shift workers were -11.3 ± 5.5, -6.4 ± 5.1, -3.8 ± 2.8, and -2.7 ± 3.2, respectively; while those in the night shift workers were -14.1 ± 3.5, -7.1 ± 5.2, -4.0 ± 2.9, and -3.1 ± 3.8, respectively. There were no significant differences in the insomnia/mood scores across treatment between the evening and night shift workers in either groups.

Changes in HADS, HADS-A, and HADS-D scores between Groups after Controlling for Severity of Insomnia

We analyzed whether the changes in anxiety and depression directed the change in insomnia severity. After treatment, the correlations between the changes in the severity of insomnia, anxiety, and depression were high (Pearson correlation between 0.515 and 0.693, p < 0.001). The treatment group nevertheless had significantly decreased scores on the HADS, HADS-A, and HADS-D after treatment as compared with the control group, even when the factor of ISI change was controlled (all p < 0.001).

DISCUSSION

To the best of our knowledge, this was the first randomized control study to investigate the effectiveness of bright light exposure at night with attenuation of morning light in female nurses undertaking rotating shift work suffering from clinical insomnia during the evening/night shift. Our study found that bright light therapy of 7,000-10,000 lux for at least 30 minutes at night for at least 10 days during 2 weeks significantly improved the sleep problems of nurses working the evening or night shift. Studies have found that bright light exposure improves daytime sleep and nocturnal alertness\[21,29\] in nurses working the night shift. However, the subjects in these studies did not necessarily have insomnia. The study of Yoon et al.\[21\] also found that these improvements could be maximized by attenuation of morning light on the way home. Light attenuation in the morning only was found to be ineffective in improving insomnia in our study.

There is no consistent design of bright light therapy for evening/night shift workers, including schedule, intensity, and duration. Various light intensities, from 1,200 to 10,000 lux, with durations of exposure ranging from 3 to 6 hours, have been used successfully to realign circadian rhythms and improve performance and sleep during the night shift.\[20,21\] Previous studies\[30,31\] have recommended that either intermittent or continuous light exposure begins early in the shift and terminates approximately 2 hours before the end of shift, with the wearing of sunglasses outdoor in the morning was efficacious for phase delay. Importantly, a delayed circadian phase was found to be positively correlated with improved sleep, even in the control group, in subjects during the night shift.\[31,32\] The design of our treatment procedure is easy to put into practice in the real world. Higher intensity and shorter bright light exposure once before work or

<table>
<thead>
<tr>
<th>Variables</th>
<th>Treatment group</th>
<th>Control group</th>
<th>95% CI</th>
<th>Statisticsa</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-treatment</td>
<td>17.9 ± 2.5</td>
<td>17.1 ± 2.3</td>
<td>-0.22, 1.78</td>
<td>p = 0.123</td>
</tr>
<tr>
<td>Post-treatment</td>
<td>5.7 ± 5.0</td>
<td>16.9 ± 3.2</td>
<td>-12.91, -9.44</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>HADS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-treatment</td>
<td>16.2 ± 5.5</td>
<td>15.1 ± 6.3</td>
<td>-1.33, 3.60</td>
<td>p = 0.364</td>
</tr>
<tr>
<td>Post-treatment</td>
<td>9.6 ± 3.9</td>
<td>16.6 ± 5.9</td>
<td>-9.09, -4.95</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>HADS-A</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-treatment</td>
<td>9.1 ± 3.3</td>
<td>8.8 ± 3.7</td>
<td>-3.43, 2.56</td>
<td>p = 0.133</td>
</tr>
<tr>
<td>Post-treatment</td>
<td>6.1 ± 2.7</td>
<td>9.0 ± 3.5</td>
<td>-4.21, -1.62</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>HADS-D</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-treatment</td>
<td>6.3 ± 0.6</td>
<td>6.3 ± 3.5</td>
<td>-1.45, 1.49</td>
<td>p = 0.977</td>
</tr>
<tr>
<td>Post-treatment</td>
<td>3.5 ± 1.9</td>
<td>7.6 ± 3.2</td>
<td>-5.21, -3.01</td>
<td>p &lt; 0.001</td>
</tr>
</tbody>
</table>

ISI, Chinese version of the Insomnia Severity Index; HADS, Chinese version of the Hospital Anxiety Depression Scale; HADS-A, anxiety subscale of the HADS; HADS-D, depression subscale of the HADS; CI, confidence interval. *Independent-samples t test.

Figure 1—Mean change in the ISI, HADS, HADS-A, and HADS-D scores after treatment in the treatment and control groups

All p < 0.001 between groups. Note: p-values reflect the results of the change from the pre-treatment analyses using ANCOVA. ISI, Chinese version of the Insomnia Severity Index; HADS, Chinese version of the Hospital Anxiety Depression Scale; HADS-A, anxiety subscale of the HADS; HADS-D, depression subscale of the HADS.
in a break during the first half of the evening/night shift and a daytime darkness procedure were implemented in our study. The study of Drake et al. 7 found that insomnia or daytime sleepiness is a risk factor for major depression, but it is a much greater risk factor for rotating or night shift workers. A systematic review by Even et al. 33 examined the efficacy of light therapy in nonseasonal depression. They found that bright light monotherapy is efficacious in treating seasonal depression, but its efficacy in treating nonseasonal depression is inconsistent. This is the first study to report that in female nurses working rotating shifts, anxiety and depression scores were significantly improved after bright light therapy, even when the change in insomnia severity was controlled. It must be noted that the mean HADS-D score as a group was not above the cutoff point (≥ 8) according to the criteria for depression either before or after intervention in our study, but the scores were high. Besides, the nurses were not diagnosed with depression, nor was the clinical severity of depression evaluated in this study. Some factors may contribute to these findings, such as (1) according to the general criteria of the International Classification of Sleep Disorders, 2nd ed. (ICSD-2) 8 for insomnia, depressive symptoms related to nighttime sleep difficulty are commonly reported by insomniacs; (2) treating insomnia in patients with major depressive episode improves mood problems other than insomnia. 34-36 It must be mentioned that light therapy is not the only choice of treatment for insomnia or depression. Subjects undertaking shift work can improve insomnia and mood problems through pharmacotherapy, behavioral therapy, or other therapy.

There were some primary limitations in our study. First, this study was not a double-blind study, and “placebo effects” should be considered. The subjects in both groups might work in the same unit, and the use of a sham light box (a light box of a much lower intensity or red light) in the control group would be able to be detected by the controls, who would discern the difference. Therefore, we considered that the “placebo effect” could not have been solved by the use of a sham light box. Second, as this study was performed in a real workplace, it was difficult to measure the differences in endogenous circadian rhythm change and the real intensity and duration of light exposure in groups. Aoki et al. 37 reported melatonin could be suppressed by light intensities of around 300 lux. However, compared to ordinary room light (< 250 lux), Martin and Eastman 38 found that medium- and high-intensity light, approximately 1,230 lux and 5,700 lux, respectively, for 3 hours, significantly increased the percentage of subjects who adapted to the night shift, as measured by temperature rhythm phase shifts. Larger phase shifts were correlated with more sleep and less fatigue. Third, we only used questionnaires to measure the severity of insomnia, anxiety, and depression in the nurses working shifts. We were not able to confirm the diagnosis of insomnia, because subjects might suffer from shift work disorder (SWD), primary insomnia, insomnia due to mental disorders, or other insomnia-related disorders. According to data from the Detroit tri-county population, 32.1% of night workers and 26.1% of rotating shift workers suffer from insomnia or excessive sleepiness. Thus, the “true prevalence” of SWD in the night- and rotating-worker samples was 14.1% and 8.1%, respectively. 7 In a study performed in Norway, 39 it was found that 44.3% of nurses working on a three-shift rotation met the criteria of SWD by asking shift work-related symptom questions. Fourth, although the study was a randomized control study, we did not assess the differences in rotation patterns, lifestyle during days off, and off-work periods in the groups. Circadian misalignment might be aggravated by these factors. Rotation patterns such as the number of shifts separated by less than 11 hours and the number of nights worked were found to be positively associated with SWD in the study of Norwegian nurses. 39 Lin et al. 38 also reported that rotation shift nurses who had at least two days off after their most recent night shift showed significantly improved sleep quality and mental health. Finally, 67.4% of the subjects in the present study were working the evening shift, and 32.6% were working the night shift. In this study, different timings of bright light exposure were employed in the evening and night shift groups. No significant differences were found in the change of insomnia/mood scales across treatment in treatment and control groups. However, since statistical power is reduced by dividing the subjects into smaller subgroups by shift schedule, further studies would be indicated to assess effectiveness under the two different situations.

In conclusion, the design of this study is easy to put into practice in the real world. Female nurses working the evening/night shift with insomnia can improve their sleep problems by higher intensity and shorter bright light exposure once before work or in a break during the first half of work combined with a daytime darkness procedure. In addition, anxiety and depression scores can be improved after intervention.

ACKNOWLEDGMENTS

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SUBMISSION & CORRESPONDENCE INFORMATION

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DISCLOSURE STATEMENT

This was not an industry supported study. The authors have indicated no financial conflicts of interest.
In this issue of Journal of Clinical Sleep Medicine, Huang and colleagues investigated the effectiveness of bright light exposure in shift working nurses on an evening or night shift schedule. Nurses working in a hospital were divided into two groups, where the treatment group received bright light of 7,000-10,000 lux for 30 minutes at about 8 pm (evening shift) or at about 11:30 pm (night shift), whereas the control group did not receive any light treatment. Both groups were instructed to wear dark sunglasses to avoid outdoor light after work and before sleep. The study period was 10-14 days. The outcome measures were well-validated self-report instruments: Insomnia Severity Index (ISI) and Hospital Anxiety and Depression scale (HADS). The results showed that the treatment group impressively improved sleep. Furthermore, the scores on the anxiety and depression scale decreased significantly. No effects were seen in the control group.

Many shift workers suffer from poor sleep and sleepiness. The most afflicted workers may be diagnosed with shift work disorder (SWD), a circadian rhythm sleep disorder, characterized by a complaint of insomnia or excessive sleepiness that is temporally associated with a recurring work schedule that overlaps the usual time for sleep over the course of at least one month. In nurses, the prevalence of SWD varies according to work schedule, but may be as high as 44% among nurses involved in night shifts. On the other hand, it may be surprising that the majority of shift workers, also those involved in night work, do not report insomnia or excessive sleepiness. In addition to poor sleep and sleepiness, some studies show that night workers are at increased risk of anxiety/depression.

Sleep is regulated by an interaction between homeostatic, circadian, and behavioral factors. Shift work, especially when night work is part of the schedule, results in a misalignment between the endogenous circadian timing system and the external 24-h environment. The treatment options for circadian rhythm sleep disorders comprise bright light treatment and exogenous melatonin administration. Both these chronobiotics need to be timed according to specific phase-response curves to have the wanted effect. For instance, bright light before the minimum (nadir) of the core body temperature will phase delay the circadian rhythm, whereas bright light after nadir produces a phase advance. This means that incorrectly timed bright light will likely worsen sleep and sleepiness complaints. Nadir is usually located about 1 to 2 hours before the habitual wake-up time. In the study by Huang and colleagues, the timing of treatment was appropriate, although even better results may have been expected if bright light had been timed according to the nurses’ individual circadian rhythms.

The findings presented in the study by Huang and coworkers were surprisingly strong, and more impressive than seen following bright light treatment in, for instance, night workers in the petroleum industry. One reason may be that all participants in the study by Huang et al. had moderate to severe insomnia before treatment, whereas other studies may include participants with fewer complaints. However, a reduction in ISI score from 17.9 to 5.7 following treatment, compared to no effect in the control group, is amazing. In fact, 80% of the nurses did not have insomnia following treatment, whereas all nurses in the control group still met the criteria for insomnia. Similarly, the HADS scores were clearly reduced in the treatment group. It was somewhat surprising that light attenuation following work and before sleep (control group) had no effect. Other studies have shown that such an approach could help night workers with circadian adaptation.

One of the major take-home messages from the Huang et al. study is that such a treatment approach is relatively easy to implement into clinical practice. Bright light exposure of 30 minutes duration seems feasible in the workplace. Furthermore, there were few inclusion/exclusion criteria, suggesting that the findings may generalize to large groups of nurses working evening and/or night shifts. The improvements in sleep and psychological health may also have large consequences in terms of higher productivity, reduced risk of accidents/errors at work, as well as reduced sickness absence.

**REFERENCES**


DISCLOSURE STATEMENT

Dr. Bjorvatn has participated in speaking engagements for GlaxoSmithKline, Nycomed, ResMed, Confex, and Medi3. Dr. Waage has indicated no financial conflicts of interest.
Serum Brain-Derived Neurotrophic Factor Levels Are Associated with Dyssomnia in Females, but not Males, among Japanese Workers

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Study Objectives: Brain-derived neurotrophic factor (BDNF) is a member of the neurotrophin family of growth factors that promote the growth and survival of neurons. Recent evidence suggests that BDNF is a sleep regulatory substance that contributes to sleep behavior. However, no studies have examined the association between the serum BDNF levels and dyssomnia. The present study was conducted to clarify the association between the serum BDNF levels and dyssomnia.

Methods: A total of 344 workers (age: 40.1 ± 10.5 years, male: 204, female: 140) were included in the study. The serum BDNF levels were categorized into tertiles according to sex.

Results: The prevalence of dyssomnia was 35.1% in males and 30.0% in females. In the females, the BDNF levels were found to be negatively associated with dyssomnia after adjusting for age, body mass index, hypertension, dyslipidemia, hyperglycemia, depression, smoking, alcohol intake, and regular exercise. Compared with the females in the high BDNF group, the multivariate odds ratio (95% CI) of dyssomnia was 2.08 (0.62-6.98) in females in the moderate BDNF group and 8.41 (2.05-27.14) in females in the low BDNF group. No such relationships were found in the males.

Conclusions: The serum BDNF levels are associated with dyssomnia in Japanese female, but not male, workers.

Keywords: Serum brain-derived neurotrophic factor, dyssomnia, sex, Japanese worker

Citation: Nishichi R; Nufuji Y; Washio M; Shuzo Kumagai S. Serum brain-derived neurotrophic factor levels are associated with dyssomnia in females, but not males, among Japanese workers. J Clin Sleep Med 2013;9(7):649-654.
from the study subjects were obtained from 08:00 to 10:00 after overnight fasting. In addition to performing these routine health check-up examinations, the serum BDNF levels were measured, and sleep quality and depressive symptoms were assessed with interviews by trained nurses.

Subjects
The subjects of this study were employees of the Creative Research Community (CRC) Company (Fukuoka, Japan), which provides services such as health check-up support, genetic testing, and clinical testing. A total of 400 workers, 20 years of age or older underwent an annual health check-up at their company in 2009. Among these workers, 30 did not agree to participate and 26 who did not complete the questionnaires or biochemical tests were excluded from the study. Ultimately, a total of 344 participants (204 males and 140 females) were included in this study. Two hundred eighty-two study subjects (82%) were day workers. All participants received oral and written information about the experimental procedures before giving their written informed consent. This study was approved by the Ethics Committee of St. Mary’s College and monitored by the institutional review committee.

Serum BDNF Levels
After the blood was centrifuged 2000 × g for 10 min at 4°C, the serum was stored at -80°C until the analyses were performed. The serum BDNF concentrations were measured using an enzyme-linked immunoassay (ELISA) kit (Promega, Madison, WI) following the manufacturer’s instructions. Briefly, 96 well plates were coated with anti-BDNF monoclonal antibodies and incubated at 4°C for 16 h. The plates were then incubated in a blocking buffer for 1 h. All of the incubation stages were conducted at room temperature. The serum samples were diluted to 1:200, and the plasma samples were diluted to 1:19 in Block & Sample 1 × Buffer. After adding the samples and the BDNF standard, the plates were incubated with shaking for 2 h, then washed in washing buffer. The plates were then incubated with anti-human BDNF polyclonal antibodies for 2 h. After being washed, the plates were incubated with anti-IgY HRP conjugate with shaking for 1 h and washed. Next, TMB One solution was added for 10 min, and the reaction was stopped with 1 M HCl. The absorbance at 450 nm was measured within 30 min after stopping the reaction.

Dyssomnia
Sleep quality was assessed according to the Pittsburgh Sleep Quality Index (PSQI). The PSQI is used worldwide as a tool for the assessment of sleep quality. The scores were obtained according to the PSQI-scoring method (0-1-2-3-4). The cutoff for the total score of the PSQI is 5.5 points, and scores above the cutoff are considered to indicate dyssomnia.

Other Variables
BMI was calculated as the weight in kilograms divided by the height in meters squared. Obesity was defined as BMI ≥ 25 kg/m². Antihypertensive medication use, antihyperlipidemic drug use, oral hypoglycemic intake or insulin administration, and current lifestyle factors, including smoking, alcohol intake, and regular exercise were determined by interviews with trained nurses. Hypertension was defined as blood pressure ≥ 140/90 mm Hg and/or current treatment with antihypertensive medications. Dyslipidemia was defined as LDL-cholesterol ≥ 140 mg/dL, triglyceride ≥ 150 mg/dL, HDL-cholesterol < 40 mg/dL and/or current treatment with antihyperlipidemic drugs. Hyperglycemia was defined as fasting plasma glucose concentrations ≥ 110 mg/dL and/or the use of antidiabetic medications. Depressive symptoms were evaluated using the Japanese version of the Center for Epidemiological Studies Depression Scale (CES-D). Depression was defined as a CES-D score ≥ 16 points.

Statistical Analyses
The serum BDNF levels were categorized into tertiles according to sex (males: < 10.91, 10.92 to 13.81, > 13.82 ng/mL; females: < 9.32, 9.33 to 12.12, > 12.13 ng/mL). The crude mean values and the frequencies of the variables were compared between the groups using the χ² test and one-way analysis of variance as appropriate. Dunnett test was employed for all post hoc tests. The odds ratios (OR) and 95% confidence intervals (95% CI) of dyssomnia for each BDNF tertile group were calculated by taking the highest tertile as the referent using the logistic regression models. A p-value less than 0.05 was considered to be statistically significant. All statistical analyses were performed using the SPSS software program (Statistical Package for Social Sciences, version 18.0, SPSS Inc., Chicago, IL, USA).

RESULTS
Characteristics of Participants
The prevalence of dyssomnia was 35.1% in the males and 30.0% in the females. The serum BDNF levels were significantly higher in the males (12.72 ± 4.08 ng/mL) than in the females (11.13 ± 3.28 ng/mL, p < 0.001).

Table 1 presents the characteristics of the male participants by tertile of the serum BDNF levels. There were no significant differences in PSQI scores or prevalence of dyssomnia among the 3 groups of males. The frequency of regular exercise was significantly higher in the low BDNF group than in the high BDNF group. There were no significant differences in any of the other parameters among the 3 groups of males. Table 2 presents the characteristics of the female participants by tertile of the serum BDNF levels. The mean PSQI scores in the low and moderate BDNF groups were significantly higher than that in the high BDNF group among females (p < 0.01, p = 0.02, respectively). Additionally, there were significant differences in the prevalence of dyssomnia among the 3 groups (p < 0.001). The prevalence of dyssomnia in the low BDNF group was significantly higher than that in the high BDNF group (p < 0.01). There were no significant differences in any of the other parameters among the 3 groups of females.

Association between Serum BDNF Levels and Dyssomnia by Sex
Table 3 shows the association between the serum BDNF levels and dyssomnia. Compared with the females in the high BDNF group, the age-adjusted OR (95% CI) of dyssomnia was 2.04 (0.68-6.09) in females in the moderate BDNF group and 8.18 (2.89-23.13) in females in the low BDNF group. These associations remained statistically significant even after ad-
adjusting for age, BMI, dyslipidemia, diabetes mellitus, depression, regular exercise, and so on (moderate: OR 1.73, 95% CI 0.51-5.90; low: OR 8.77, 95% CI 2.71-28.38). In contrast, compared with the males in the high BDNF group, the males in the low BDNF group showed a decreased age-adjusted OR for dyssomnia (OR 0.47, 95% CI 0.23-0.97). However, this association disappeared after adjusting for confounding factors (OR 0.58, 95% CI 0.23-1.28).

**Association between Serum BDNF Levels and Patterns of Dyssomnia**

Table 4 shows the association between serum BDNF levels and the scores of 7 components of PSQIG. Serum BDNF levels in females were significantly inversely correlated with the score of sleep duration ($r = -0.191$, $p < 0.05$), sleep disturbance ($r = -0.179$, $p < 0.05$), daytime dysfunction ($r = -0.270$, $p < 0.01$), and global ($r = -0.295$, $p < 0.001$). No such correlations were found in males.

**DISCUSSION**

We found the serum BDNF levels to be negatively associated with dyssomnia in females. Because the serum BDNF levels have been reported to change according to age, BMI, body weight, depression, metabolic disorders, including diabetes mellitus, and regular exercise, we adjusted the model for these potential confounding factors. The association between the serum BDNF levels and dyssomnia remained statistically significant even after adjusting for these confounders. Among females, the multivariable-adjusted odds ratio of dyssomnia in the low BDNF group was eight times higher than that in the high BDNF group. However, these associations were not observed in the male subjects. To our knowledge, this is the first study to demonstrate an association between the serum BDNF levels and dyssomnia.

There are many kinds of dyssomnia, and it is an important issue to determine what types of dyssomnia correlate with the serum BDNF levels. Low level of serum BDNF is considered to associate with intrinsic circadian rhythm disorder, since the majority of study subjects were day workers. Therefore, the association between serum BDNF levels and extrinsic circadian rhythm disorder should be investigated in the future. The results of this study showed that serum BDNF levels were negatively associated with sleep duration, sleep disturbance, and daytime dysfunction in the female, although the degrees of these associations seem to be weak. Thus, further large-scale studies are recommended to confirm how serum the BDNF level correlates with the occurrence of dyssomnia.

An association between the serum BDNF levels and dyssomnia is biologically plausible. Since BDNF can cross the blood-barrier and brain, it may be involved in the pathophysiology of dyssomnia.

**Table 1—Characteristics of participants by tertile of serum BDNF levels in men (n = 204)**

<table>
<thead>
<tr>
<th>Serum BDNF level ng/mL</th>
<th>High (≥ 13.82)</th>
<th>Middle (10.92-13.81)</th>
<th>Low (≤ 10.91)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>69</td>
<td>69</td>
<td>69</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>43.1 ± 10.0</td>
<td>41.8 ± 10.9</td>
<td>42.6 ± 11.6</td>
<td>0.78</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.1 ± 4.0</td>
<td>23.0 ± 2.7</td>
<td>24.0 ± 3.2</td>
<td>0.11</td>
</tr>
<tr>
<td>Obesity</td>
<td>26 (37.7%)</td>
<td>16 (23.2%)</td>
<td>22 (33.2%)</td>
<td>0.17</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>135.2 ± 18.8</td>
<td>133.6 ± 16.9</td>
<td>136.4 ± 16.4</td>
<td>0.65</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>84.0 ± 16.6</td>
<td>82.8 ± 12.3</td>
<td>81.9 ± 12.4</td>
<td>0.69</td>
</tr>
<tr>
<td>Hypertension</td>
<td>29 (42.0%)</td>
<td>30 (43.5%)</td>
<td>30 (45.5%)</td>
<td>0.92</td>
</tr>
<tr>
<td>TC (mg/dL)</td>
<td>218.7 ± 33.4</td>
<td>216.7 ± 31.9</td>
<td>207.2 ± 33.4</td>
<td>0.10</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>59.2 ± 14.2</td>
<td>61.7 ± 15.3</td>
<td>60.4 ± 11.4</td>
<td>0.56</td>
</tr>
<tr>
<td>LDL-C (mg/dL)</td>
<td>126.5 ± 30.2</td>
<td>126.5 ± 28.9</td>
<td>120.7 ± 27.4</td>
<td>0.41</td>
</tr>
<tr>
<td>TG (mg/dL)</td>
<td>147.2 ± 110.6</td>
<td>123.4 ± 67.6</td>
<td>11.2 ± 62.7</td>
<td>0.05</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>33 (47.8%)</td>
<td>34 (49.3%)</td>
<td>26 (39.4%)</td>
<td>0.46</td>
</tr>
<tr>
<td>FBG (mg/dL)</td>
<td>102.9 ± 26.3</td>
<td>98.1 ± 15.5</td>
<td>101.4 ± 19.6</td>
<td>0.40</td>
</tr>
<tr>
<td>HbA1C (%)</td>
<td>5.0 ± 0.8</td>
<td>4.8 ± 0.5</td>
<td>4.9 ± 0.7</td>
<td>0.32</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>11 (15.9%)</td>
<td>6 (8.7%)</td>
<td>16 (24.2%)</td>
<td>0.05</td>
</tr>
<tr>
<td>PSQIG score</td>
<td>5.4 ± 2.4</td>
<td>4.8 ± 2.3</td>
<td>5.0 ± 2.4</td>
<td>0.32</td>
</tr>
<tr>
<td>Dyssomnia</td>
<td>29 (43.3%)</td>
<td>19 (27.5%)</td>
<td>23 (34.8%)</td>
<td>0.73</td>
</tr>
<tr>
<td>CESD score</td>
<td>12.0 ± 6.5</td>
<td>10.1 ± 6.3</td>
<td>11.1 ± 7.1</td>
<td>0.25</td>
</tr>
<tr>
<td>Depression</td>
<td>16 (23.5%)</td>
<td>11 (15.9%)</td>
<td>15 (22.7%)</td>
<td>0.49</td>
</tr>
<tr>
<td>Smoking</td>
<td>27 (39.7%)</td>
<td>30 (43.5%)</td>
<td>28 (42.4%)</td>
<td>0.90</td>
</tr>
<tr>
<td>Alcohol drinking</td>
<td>41 (60.2%)</td>
<td>43 (62.3%)</td>
<td>50 (75.7%)</td>
<td>0.12</td>
</tr>
<tr>
<td>Regular exercise</td>
<td>25 (36.8%)</td>
<td>22 (32.4%)</td>
<td>37 (55.4%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Service form</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day worker</td>
<td>52 (77.6%)</td>
<td>55 (80.9%)</td>
<td>55 (84.6%)</td>
<td>0.59</td>
</tr>
<tr>
<td>Two shift worker (the day and night)</td>
<td>15 (22.4%)</td>
<td>13 (19.1%)</td>
<td>10 (15.4%)</td>
<td></td>
</tr>
</tbody>
</table>

Data presented are number (row percentages) or mean value ± standard deviation. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; FBG, Fasting blood glucose; BDNF, brain-derived neurotrophic factor.
brain barrier in both directions and brain tissue is the main contributor to circulating BDNF, low serum BDNF levels may reflect decreased BDNF levels in the brain. An experimental animal study suggested that BDNF in the brain contributes to the regulation of sleep behavior and promotes NREM sleep. Hence, decreased levels of brain BDNF may be related to poor control of sleep behavior.

On the other hand, decreased serum BDNF levels may be caused by dyssomnia. Recent studies in humans suggest that acute or chronic sleep deprivation affects the hypothalamic-pituitary-adrenal (HPA) system and changes the secretion of cortisol. Vgontzas et al. demonstrated that 24-h mean cortisol secretion in chronic insomniacs is higher than that in normal controls. Intriguingly, glucocorticoids have been reported

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**Table 2**—Characteristics of participants by tertile of serum BDNF levels in women (n = 140)

<table>
<thead>
<tr>
<th>Seron BDNF level ng/mL</th>
<th>High (≥ 12.13)</th>
<th>Middle (9.33-12.12)</th>
<th>Low (≤ 9.32)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>47</td>
<td>47</td>
<td>46</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>37.1 ± 8.8</td>
<td>36.0 ± 8.5</td>
<td>36.6 ± 9.6</td>
<td>0.62</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>20.6 ± 2.8</td>
<td>20.9 ± 3.8</td>
<td>21.2 ± 2.5</td>
<td>0.69</td>
</tr>
<tr>
<td>Obesity</td>
<td>2 (4.3%)</td>
<td>4 (8.5%)</td>
<td>4 (8.7%)</td>
<td>0.64</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>122.3 ± 15.5</td>
<td>118.1 ± 11.4</td>
<td>118.1 ± 12.8</td>
<td>0.21</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>75.3 ± 11.1</td>
<td>74.8 ± 8.6</td>
<td>74.0 ± 9.1</td>
<td>0.74</td>
</tr>
<tr>
<td>Hypertension</td>
<td>7 (14.9%)</td>
<td>4 (8.5%)</td>
<td>6 (13.0%)</td>
<td>0.62</td>
</tr>
<tr>
<td>TC (mg/dL)</td>
<td>218.7 ± 33.8</td>
<td>206.2 ± 39.5</td>
<td>203.4 ± 26.0</td>
<td>0.49</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>75.4 ± 15.5</td>
<td>77.0 ± 14.8</td>
<td>75.1 ± 13.6</td>
<td>0.37</td>
</tr>
<tr>
<td>LDL-C (mg/dL)</td>
<td>114.3 ± 29.2</td>
<td>111.9 ± 26.8</td>
<td>110.3 ± 22.6</td>
<td>0.76</td>
</tr>
<tr>
<td>TG (mg/dL)</td>
<td>77.1 ± 50.0</td>
<td>64.0 ± 27.0</td>
<td>75.3 ± 44.9</td>
<td>0.26</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>10 (21.3%)</td>
<td>6 (13.0%)</td>
<td>11 (23.4%)</td>
<td>0.41</td>
</tr>
<tr>
<td>FBG (mg/dL)</td>
<td>93.1 ± 15.1</td>
<td>91.4 ± 14.4</td>
<td>90.2 ± 7.2</td>
<td>0.54</td>
</tr>
<tr>
<td>HbA1C (%)</td>
<td>4.7 ± 0.3</td>
<td>4.7 ± 0.6</td>
<td>4.6 ± 0.2</td>
<td>0.66</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>3 (6.4%)</td>
<td>4 (8.5%)</td>
<td>1 (2.2%)</td>
<td>0.41</td>
</tr>
<tr>
<td>PSQI score</td>
<td>4.3 ± 2.2</td>
<td>3.9 ± 2.2</td>
<td>5.6 ± 2.4</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Dyssomnia</td>
<td>6 (12.8%)</td>
<td>11 (23.4%)</td>
<td>25 (54.3%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>CESD score</td>
<td>9.7 ± 7.7</td>
<td>9.6 ± 7.2</td>
<td>11.5 ± 8.2</td>
<td>0.41</td>
</tr>
<tr>
<td>Depression</td>
<td>6 (12.8%)</td>
<td>10 (21.3%)</td>
<td>13 (28.3%)</td>
<td>0.18</td>
</tr>
<tr>
<td>Smoking</td>
<td>8 (17.0%)</td>
<td>6 (13.0%)</td>
<td>4 (8.7%)</td>
<td>0.49</td>
</tr>
<tr>
<td>Alcohol drinking</td>
<td>21 (44.7%)</td>
<td>22 (46.8%)</td>
<td>28 (60.9%)</td>
<td>0.24</td>
</tr>
<tr>
<td>Regular exercise</td>
<td>16 (34.0%)</td>
<td>15 (32.6%)</td>
<td>16 (36.4%)</td>
<td>0.93</td>
</tr>
<tr>
<td>Service form</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day worker</td>
<td>39 (83.0%)</td>
<td>42 (91.3%)</td>
<td>39 (84.8%)</td>
<td>0.47</td>
</tr>
<tr>
<td>Two shift worker (the day and night)</td>
<td>8 (17.0%)</td>
<td>4 (8.7%)</td>
<td>7 (15.2%)</td>
<td></td>
</tr>
</tbody>
</table>

Data presented are number (row percentages) or mean value ± standard deviation. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; FBG, Fasting blood glucose; BDNF, brain-derived neurotrophic factor.

**Table 3**—Distribution of Japanese workers with and without dyssomnia according to serum BDNF levels, with corresponding OR and 95% CI

<table>
<thead>
<tr>
<th>Serum BDNF level</th>
<th>Number of participants</th>
<th>Dyssomnia case</th>
<th>Age- and Sex-adjusted OR (95%CI)</th>
<th>p value</th>
<th>Multivariable-adjusted OR (95%CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>69</td>
<td>29</td>
<td>1</td>
<td>1</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Middle</td>
<td>69</td>
<td>19</td>
<td>0.67 (0.33-1.36)</td>
<td>0.32</td>
<td>0.51 (0.23-1.12)</td>
<td>0.09</td>
</tr>
<tr>
<td>Low</td>
<td>66</td>
<td>23</td>
<td>0.47 (0.23-0.97)</td>
<td>0.05</td>
<td>0.58 (0.23-1.28)</td>
<td>0.18</td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>47</td>
<td>6</td>
<td>1</td>
<td>1</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Middle</td>
<td>47</td>
<td>11</td>
<td>2.04 (0.68-6.09)</td>
<td>0.02</td>
<td>1.73 (0.51-5.90)</td>
<td>0.38</td>
</tr>
<tr>
<td>Low</td>
<td>46</td>
<td>25</td>
<td>8.18 (2.89-23.13)</td>
<td>&lt; 0.001</td>
<td>8.77 (2.71-28.38)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Multivariable-adjusted OR: The odds ratios (OR) and 95% confidence intervals (95% CI) of dyssomnia for each BDNF tertile group were calculated by taking the highest tertile as the referent using the logistic regression models, adjusted for age, BMI, dyslipidemia, hyperglycemia, depression, smoking, alcohol drinking, and regular exercise, service form.
to suppress the BDNF expression in the hippocampus. Additionally, a human study demonstrated a negative association between the cortisol levels and the BDNF levels in the blood. Therefore, dyssomnia may reduce the BDNF levels in the brain and the blood by altering the activity of the HPA system to increase the secretion of cortisol.

Many epidemiological studies have suggested gender differences are associated with dyssomnia. However, it remains unclear as to whether or not the sex differences in BDNF observed in the results of the present study are related to sex differences in dyssomnia.

Several limitations should be noted. First, the cross-sectional design of the study limits the interpretation of causality between the serum BDNF levels and dyssomnia. Second, since the sample size was relatively small and the subjects were workers, the subjects may not be representative of the entire Japanese population.

Third, we only obtained one serum sample at morning for measurement of serum BDNF level from study subjects. Therefore, we could not investigate the association between the circadian change of serum BDNF levels and dyssomnia in this study. This association should be investigated in future study, since the serum level of BDNF has been demonstrated to be influenced by several conditions, such as meal intake and level of activity. Finally, we did not measure any other hormones or mediators which were reported to correlate with dyssomnia. Thus, further study is needed to clarify how serum BDNF levels associate with those hormones and mediators, such as cortisol, growth hormone, sex hormones, and melatonin.

**CONCLUSION**

In this study, serum BDNF levels were associated with dyssomnia in females but not in males. The association observed in the female subjects remained statistically significant even after adjusting for possible confounding factors, including age, BMI, hypertension, dyslipidemia, diabetes mellitus, depression, smoking, drinking, and regular exercise. Our results support the emerging concept that BDNF is a sleep regulatory substance and may contribute to improving understanding of the pathogenic mechanisms of dyssomnia. Further longitudinal studies of large populations are required to elucidate the precise relationship between the serum BDNF levels and dyssomnia.


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Identification of Insomnia in a Sleep Center Population Using Electronic Health Data Sources and the Insomnia Severity Index

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Study Objectives: To assess the validity and efficacy of using electronic health data to identify a physician diagnosis of insomnia in a population of patients referred for testing at a tertiary sleep center.

Methods: Retrospective cohort study in a tertiary sleep center in Calgary, Alberta, Canada. Cohort consisted of 1,207 patients referred for sleep diagnostic testing and/or assessment by a sleep physician. Two sleep physicians independently assigned each patient a primary sleep diagnosis. Univariate logistic regression was used to identify variables that were predictive for insomnia from online questionnaire and diagnostic testing data. Diagnostic algorithms derived from these predictors and from the Insomnia Severity Index were evaluated against physician diagnosis as a reference standard.

Results: The combination of self-reported sleep latency > 20 minutes, total sleep time < 6.5 hours per night, the inability to fall asleep after waking, BMI < 27 kg/m², and Epworth Sleepiness Scale score < 9 had very high specificity (99.3%) for diagnosing insomnia; however, sensitivity was poor (11.8%). Other algorithms derived from these data had either high sensitivity or high specificity. No combination of variables yielded simultaneous high sensitivity and specificity. Likewise, the Insomnia Severity Index can be highly sensitive or highly specific at identifying insomnia, but not both.

Conclusions: Diagnostic algorithms derived from electronic data can provide high specificity or high sensitivity for identifying insomnia.

Keywords: Insomnia, clinical prediction, decision rule, diagnostic algorithm

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T he prevalence of chronic insomnia is as high as 30%, but estimates range considerably, depending on the criteria used to define insomnia and the sample population used.1-3 Insomnia has also been associated with high levels of healthcare utilization, and increased direct and indirect healthcare costs. For instance, Ozminkowski et al.4 estimated that the combined direct and indirect costs over a 6-month time-period for adults in the U.S. with insomnia were, per person, $1253.00 more than matched controls. Similarly, Morin et al.5 estimated the cumulative costs of insomnia in the Canadian province of Quebec (population approximately 8 million6) to exceed six billion dollars (Cdn) per annum.

A diagnosis of insomnia is typically established through assessment by an experienced clinician. Several efficacious treatments for insomnia, such as cognitive behavioral therapy (CBT), exist. Yet wait times and lack of access to insomnia specialists can be a barrier to diagnosis and treatment. Moreover, insomnia may occur independently, or may coexist with other sleep disorders, which can complicate diagnosis and treatment. Screening tools that can accurately and reliably identify primary insomnia could help from a triage standpoint, as they may direct newly referred patients to the appropriate specialists and/or diagnostic testing. In a research setting, an insomnia screening tool would be desirable for case finding. While a breadth of insomnia questionnaires and screening tools exist, most of these tools were developed for use in large epidemiologic studies and lack validation in a clinic setting. Moreover, very few have used a clinician defined reference standard for insomnia.7-9

The aim of this study was to assess the validity and efficacy of using electronic health data to identify a physician diagnosis of insomnia in a population of patients referred for testing at a tertiary sleep center.

METHODS

Patients

We identified all patients who completed an online questionnaire and underwent clinical assessment and/or sleep diagnostic testing at the Foothills Medical Center (FMC) Sleep Center between January...
Criteria were not employed for non-ICSD-2 diagnoses. Disease specific diagnostic ICSD-2 diagnosis a diagnosis was assigned based on the primary not be consistently extracted from the medical record, for non-
Given that validated criteria for many of these diagnoses could tigue, uncomplicated snoring, fibromyalgia, other, and normal.

**Determination of Primary Diagnosis**

**Insomnia**

Two American Academy of Sleep Medicine board-certified sleep physicians independently reviewed all patient charts and assigned a primary sleep diagnosis to each patient in the cohort. Insomnia was defined based on either: (a) primary clinical diagnosis by the treating clinician (if treating clinician was ABSM certified in Behavioral Sleep Medicine); (b) primary clinical diagnosis of insomnia by the treating physician AND a chart review of the patient history to determine if patient met International Classification of Sleep Disorders, 2nd edition (ICSD-2), criteria A-C (if the treating clinician was not an ABSM certified psychologist). Primary insomnia was determined to be present if there was consensus from both reviewing physicians on the diagnosis. If a diagnosis could not be agreed upon, the disagreement was noted and the patient was excluded from analysis.

**Other**

A total of 13 other diagnostic categories were selected prior to chart review. Eight diagnoses were developed based on the ICSD-2 criteria: central sleep apnea (CSA); central nervous system (CNS) hypersomnolence; insomnia; obstructive sleep apnea syndrome (OSAS); parasomnia; restless leg syndrome (RLS); OSA/hypopnoea; and upper airway resistance syndrome (UARS). Diagnoses were assigned based on a primary diagnosis by the treating physician AND chart review of the history and diagnostic testing (to ensure that ICSD-2 criteria were met).

Six non-ICSD-2 diagnoses were also assigned: depression, fatigue, uncomplicated snoring, fibromyalgia, other, and normal. Given that validated criteria for many of these diagnoses could not be consistently extracted from the medical record, for non-ICSD-2 diagnosis a diagnosis was assigned based on the primary impression of the treating physician. Disease specific diagnostic criteria were not employed for non-ICSD-2 diagnoses.

**Electronic Data Elements**

**Online Questionnaire**

The online questionnaire is composed of 108 questions, which provide a comprehensive overview of a patient’s demographics, anthropometrics, snoring history, daytime function, and medical history, as well as sleep schedule, behavior, and complaints. Three smaller, commonly used questionnaires are also administered within the online questionnaire: the Epworth Sleepiness Scale (ESS), Patient Health Questionnaire (PHQ), and the Insomnia Severity Index (ISI).

**Ambulatory Monitoring**

All patients undergo portable monitoring (level III sleep diagnostic testing) as part of the referral and triage process. The

**RESULTS**

**Patient Characteristics**

Figure 1 illustrates the flow of patients. We identified 1,426 patients who underwent clinical assessment with or without
sleep diagnostic testing; 202 did not provide written consent and were excluded. Of the remaining 1,223 patient charts, 16 were excluded from the analysis due to lack of consensus over the primary sleep diagnosis, leaving a final cohort size of 1,207.

Insomnia was the primary diagnosis in 339 patients (28%).

Tables 1 and 2 summarize the distribution of sleep diagnoses and baseline characteristics of the cohort. The mean age in the entire cohort was 45.4 ± 12.1 years, 56.8% were men, and mean body mass index (BMI) was 30.6 ± 7.6 kg/m². The mean ESS and ISI scores of all patients were 11.1 ± 5.7 and 3.0 ± 6.8, respectively. The mean self-reported sleep latency for all patients was 0.47 ± 0.72 hours.

Patients with insomnia were significantly younger and had lower BMI, weight, and ESS scores than patients without insomnia. Patients with insomnia reported taking longer to fall asleep and had higher ISI scores than patients without a diagnosis of insomnia.

Diagnostic Agreement

Physicians agreed on 98.69% of assigned diagnoses (1,207/1,223). The un-weighted κ statistic was 0.98 (± 0.016).

Univariate Predictors of Insomnia

Self-reported use of a sleep aid, sleep latency (measured in hours), and sedative/hypnotic use were predictive of a diagnosis of insomnia (Table 3). The Epworth score, BMI, average sleep time, and ability to return to sleep after waking during the night were predictive of a diagnosis other than insomnia. The following binary cutoffs for continuous predictive variables were selected from ROC curves and box plots: sleep latency (20 min), sleep time (6.5 h), BMI (27 kg/m²), and ESS (9/24).

Algorithm Performance

Diagnostic algorithm performance is summarized in Table 4. The combination of self-reporting a sleep latency > 20 min, sleep time < 6.5 h sleep/night, inability to fall asleep after waking, a BMI < 27, and ESS score < 9 had very high specificity (99.3%) for a diagnosis of insomnia; however, sensitivity was poor (11.8%). Similarly, a self-reported sleep time < 6.5 h with concomitant sedative/hypnotic use had a high specificity (96.7%) at the expense of sensitivity (18.6%). No combination of variables simultaneously had a high sensitivity and specificity. A model incorporating the use of a sedative/hypnotic or a reported sleep time < 6.5 h maximized diagnostic performance (sensitivity 71.4%, specificity 67.4%, positive predictive value 46.1%, negative predictive value 85.8%).

The combination of clinical and diagnostic test data did not improve diagnostic performance when compared to clinical data alone. For instance, using a self-reported sleep time < 6.5 h and an RDI < 5 yields moderate sensitivity (76.4%) and specificity (71.5%). The inability to fall asleep after waking and an RDI < 5 yields similar levels of sensitivity (70.2%) and specificity (68.1%).
The diagnostic performance of the Insomnia Severity Index (ISI) is also summarized in Table 3. In our clinic population, the ISI demonstrated either high sensitivity or specificity, but not both. An ISI score ≥ 8 demonstrates the highest sensitivity (92.7%) that could be achieved using ISI data alone; however, specificity was poor (16.5%). An ISI score ≥ 22 yields the maximum specificity that could be achieved with the ISI alone (86.7%), but at the expense of sensitivity (28.0%). No single ISI cutoff resulted in simultaneously high sensitivity and specificity.

Table 4—Performance of Diagnostic Algorithms

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sens</th>
<th>Spec</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep latency &gt; 20 min</td>
<td>11.8</td>
<td>99.3</td>
<td>87.0</td>
<td>74.2</td>
</tr>
<tr>
<td>Sleep time &lt; 6.5 hours</td>
<td>18.6</td>
<td>96.7</td>
<td>68.5</td>
<td>75.2</td>
</tr>
<tr>
<td>BMI &lt; 27</td>
<td>54.5</td>
<td>77.2</td>
<td>43.7</td>
<td>84.0</td>
</tr>
<tr>
<td>ESS score &lt; 9</td>
<td>71.4</td>
<td>67.4</td>
<td>46.1</td>
<td>85.8</td>
</tr>
<tr>
<td>Do not return to sleep after waking</td>
<td>76.4</td>
<td>71.5</td>
<td>41.2</td>
<td>86.2</td>
</tr>
<tr>
<td>Sleep time &lt; 6.5 hours</td>
<td>70.2</td>
<td>68.1</td>
<td>46.2</td>
<td>85.3</td>
</tr>
<tr>
<td>Use sedative/hypnotic</td>
<td>92.7</td>
<td>65.5</td>
<td>36.5</td>
<td>81.3</td>
</tr>
<tr>
<td>RDI &lt; 15</td>
<td>87.8</td>
<td>63.7</td>
<td>37.7</td>
<td>79.6</td>
</tr>
<tr>
<td>RDI &lt; 30</td>
<td>73.2</td>
<td>43.7</td>
<td>40.3</td>
<td>75.8</td>
</tr>
<tr>
<td>ISI ≥ 8</td>
<td>28.0</td>
<td>86.7</td>
<td>52.3</td>
<td>69.9</td>
</tr>
<tr>
<td>ISI ≥ 11</td>
<td>94.1</td>
<td>43.4</td>
<td>35.0</td>
<td>95.8</td>
</tr>
<tr>
<td>ISI ≥ 15</td>
<td>97.6</td>
<td>23.8</td>
<td>29.4</td>
<td>96.9</td>
</tr>
<tr>
<td>ISI ≥ 22</td>
<td>54.5</td>
<td>77.2</td>
<td>43.7</td>
<td>84.0</td>
</tr>
</tbody>
</table>

The ISI could identify patients with physician-diagnosed insomnia with high sensitivity and specificity: an ISI score ≥ 11 yielded a sensitivity of 79% and a specificity of 57%.13 The aim of the HSDQ is to assess the six different groups of sleep disorders as defined by ICSD-2 criteria (sleep-related breathing disorder, hypersomnia, circadian rhythm sleeping disorder, parasomnias, sleep related movement disorders, and insomnia). When administered to a population of 891 patients referred for testing to a sleep center in Holland, their 40-item questionnaire had an optimized sensitivity of 82% and optimized specificity of 69% at differentiating between insomnia and the other five classes of sleep disorders.14 While both of these questionnaires have moderate levels of combined sensitivity and specificity, neither measure is maximized.

The Insomnia Severity Index is a brief, well-validated questionnaire designed to assess insomnia severity and outcomes.14-18 Morin et al. examined the ability of the ISI to identify insomnia in a clinical population, demonstrating that the ISI could identify patients with physician-diagnosed insomnia with high sensitivity and specificity: an ISI score ≥ 11 yielded a sensitivity and specificity of 92.7% and 100%, respectively. However, in our clinic-based population, the ISI did not achieve simultaneously high sensitivity and specificity. The differences in ISI performance can likely be attributed to the different populations. Though both studies used similarly rigorous definitions of insomnia, Morin et al. looked at the ability of the ISI to identify patients with insomnia when comparing those patients to a cohort of healthy controls, whereas we examined the ability of the ISI to identify patients with insomnia in patients who were referred to a sleep center. Given the overlap in comorbidity and symptoms between different sleep disorders, it is not surprising that shared symptoms dilute the diagnostic accuracy of any screening instrument.

The GSAQ, HSDQ, and our data present similarly moderate measures of combined sensitivity and specificity. Additionally though, we present algorithms to maximize either measure on their own. This is important, as there are situations when a high sensitivity or specificity is desirable even if the reciprocal measure is lower. For instance, practice parameters suggest that polysomnography is not necessary for the routine assessment and diagnosis of insomnia.19 Highly specific algorithms that rule in a diagnosis of insomnia may reduce the need for polysomnography in patients positively identified by the algorithm. Given the cost of polysomnography, the identification of even a small subset of patients not needing PSG could lead to large healthcare and insurance savings. How-

DISCUSSION

To the best of our knowledge, this is the first study to validate diagnostic algorithms using electronic health data in a clinic-based population. Diagnostic algorithms using electronic health data from an online questionnaire can achieve high sensitivities or specificities for identifying insomnia, but not both. A high diagnostic specificity can be achieved using a self-reported sleep latency of greater than 20 minutes, estimated sleep time of less than 6.5 hours, inability to fall asleep after waking, BMI of less than 27 kg/m², and an ESS score of less than 9 (sensitivity 12%, specificity 99%). Similar results could be achieved with a combination of self-reported sleep time of less than 6.5 hours and sedative or hypnotic use (sensitivity 19%, specificity 97%). Although lacking simultaneously high sensitivities and specificities, these diagnostic algorithms provide a simple and highly accurate method of identifying at least a subset of patients with and without insomnia.

Only two published questionnaire-based tools have been developed to differentiate between insomnia and other sleep disorders in a sleep clinic population: the Global Sleep Assessment Questionnaire (GSAQ) and the Holland Sleep Disorders Questionnaire (HSDQ).13,14 When administered to a combination of primary care and sleep clinic patients, the 11-item GSAQ could discriminate between insomnia and other sleep disorders (as diagnosed by a sleep clinician) with a sensitivity of 79% and a specificity of 57%.13 The aim of the HSDQ is to assess the six different groups of sleep disorders as defined by ICSD-2 criteria (sleep-related breathing disorder, hypersomnia, circadian rhythm sleeping disorder, parasomnias, sleep related movement disorders, and insomnia). When administered to a population of 891 patients referred for testing to a sleep center in Holland, their 40-item questionnaire had an optimized sensitivity of 82% and optimized specificity of 69% at differentiating between insomnia and the other five classes of sleep disorders.14 While both of these questionnaires have moderate levels of combined sensitivity and specificity, neither measure is maximized.
ever, polysomnography would still be required in patients with persistent symptoms despite primary management or in some patients for whom sleep disordered breathing has not been ruled out. Conversely, highly sensitive algorithms allow us to confidently rule out a diagnosis, which could help us direct patients to the correct provider and thus improve clinic efficiency. Highly sensitive or specific algorithms are also important in a research setting as they are used in identifying cohorts, validating comorbidities and monitoring prevalence and incidence, for example.

The use of an online questionnaire or electronic health data is compelling both in terms of potential for scalability and resource demands for data acquisition and analysis. For instance, questionnaires can be disseminated to large numbers of patients or study cohorts simply by providing a link or web address. Furthermore, the collection and storage of responses in a structured and computable manner facilitates linkage to existing clinical databases. Electronic algorithms can also be easily integrated with well-structured electronic databases, allowing for several potential uses. In a triage setting, for example, such algorithms could be implemented to automatically classify patients and alert triage nurses to this identification. From a research perspective, diagnostic algorithms can be used to rapidly query massive datasets to find large samples for study inclusion. As an example, case finding algorithms to identify outbreaks of influenza have been previously reported and show the potential use of electronic health data sources for this purpose.20

We suggest that using highly sensitive or specific algorithms has the potential to improve clinical efficiency by identifying subsets of patients and directing them to the correct provider or clinical test. However, the ability of electronic algorithms to improve clinical efficiency is largely unexamined in the literature. A recent study by Stein et al.21 used brief self-reported electronic questionnaires delivered via a computer kiosk to help assess and treat women presenting to the emergency department for urinary tract infections. These investigators found that patients randomized to use this system had shorter lengths of stay in the emergency department than patients who continued via regular clinical pathways. Though not implementing a diagnostic algorithm electronically, the results of Stein et al. suggest that implementation of electronic questionnaires have potential to improve clinical efficiency. Further research is necessary to assess and quantify how electronic algorithms may improve efficiency and patient flow in a clinical setting.

Our results should be interpreted within the context of the strengths and limitations of our study. Firstly, our cohort was selected from referrals to a single academic sleep center. There are only a few other referral choices for sleep medicine in our catchment area, and there is no incentive for referring physicians to choose one center over the other. This fact, coupled with our large sample size, low exclusion rate, and the consistency of our cohort’s demographic characteristics with those of other referral populations, suggest that selection bias due to a single center is not a concern.

Secondly, it should be noted that a clinical interview was not part of the diagnosis process. However, to ensure the integrity of our reference standard, diagnoses were assigned through independent chart review and required consensus by two board-certified sleep physicians. The strength of our reference standard is reflected in the high κ score and percent agreement between the two raters (0.98 (± 0.016) and 98.69%, respectively).

Finally, although all patients underwent level III sleep diagnostic testing, polysomnography was at the discretion of the treating physician. Given the use of ambulatory monitoring, it is unlikely that sleep disordered breathing would be missed. However, non-respiratory ICSD-2 polysomnographically based diagnoses could be missed, if not initially suspected by the treating clinician. Moreover, non-ICSD-2 diagnoses were assigned based on the impression of the treating clinician and may not necessarily be valid.

CONCLUSION

Diagnostic algorithms derived from electronic data can provide high specificity or high sensitivity for identifying insomnia. While it is not feasible to simultaneously achieve both high sensitivity and specificity using these data, it is possible to simply and accurately identify a subset of patients with and without insomnia using only a few simple questions extracted from online and/or electronic sources. When used to direct patients to the correct provider, or to preclude the need for polysomnography, this could have significant impact on centralized triage processes, clinician decision support, and healthcare costs. Furthermore, these algorithms can be used in a research capacity to identify cohorts and monitor prevalence and incidence, among other uses. Towards these ends, the ability of these algorithms to improve clinic efficiency and decision support, and their uses in a research setting warrant further study and validation.

REFERENCES


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Middle-of-the-Night Hypnotic Use in a Large National Health Plan

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Study Objectives: Although difficulty maintaining sleep (DMS) is the most common nighttime insomnia symptom among US adults, many FDA-approved hypnotics have indications only for sleep onset, stipulating bedtime administration to offset residual sedation. Given the well-known self-medication tendencies of insomniacs, concern arises that maintenance insomniacs might be prone to self-administer their prescribed hypnotics middle-of-the-night (MOTN) after nocturnal awakenings, despite little efficacy-safety data supporting such use. However, no US data characterize the actual population prevalence or correlates of MOTN hypnotic use.

Methods: Telephone interviews assessed patterns of prescription hypnotic use in a national sample of 1,927 commercial health plan members (ages 18-64) receiving prescription hypnotics within 12 months of study. The Brief Insomnia Questionnaire assessed insomnia symptoms.

Results: 20.2% of respondents reported MOTN hypnotic use, including 9.0% who sometimes used twice-per-night (once at bedtime plus once MOTN) and another 11.2% who sometimes used MOTN, but never twice-per-night. The remaining 79.8% used MOTN exclusively at bedtime. Among exclusive MOTN users, only 14.0% used MOTN on the advice of their physician (52.6% of those seen by sleep medicine specialists and 42.6% by psychiatrists vs. 5.2% to 13.6% seen by other physicians). MOTN use predictors included DMS being the most bothersome sleep problem, long duration of hypnotic use, and low frequency of DMS.

Conclusions: One-fifth of patients with prescription hypnotics used MOTN, only a minority on advice from their physicians. Since significant next-day cognitive and psychomotor impairment is documented with off-label MOTN hypnotic use, prescribing physicians should question patients about unsupervised MOTN dosing.

Keywords: Insomnia, sleep maintenance, hypnotics, middle-of-the-night, dosing, medication adherence, prevalence

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Insomnia is the most common nighttime sleep problem, and sleep maintenance insomnia the most common insomnia symptom both in the general population1 and among adults with clinical insomnia.2 An estimated one-fourth of all non-institutionalized US civilians and two-thirds of US insomniacs report frequent sleep maintenance problems involving nocturnal awakenings and/or prolonged wake time after nocturnal awakenings.2 Although insomnia symptoms are highly variable from night to night and frequently co-occur, DMS presents alone in roughly 20% of transiently or moderately symptomatic adults and 17% of insomniacs.2 DMS persists in more than 90% of population-based cases for at least 6 months2 and upwards of 70% for at least one year.4 Sleep maintenance insomnia is associated with a variety of impairments, including: daytime sleepiness5; disruptions in cognition, motor coordination, and mood5; decrements in perceived health2; and increased healthcare utilization.5 Sleep maintenance insomnia accounts for more daytime sleepiness6 and poor perceived health5 than any other nighttime insomnia symptom.

Despite the high prevalence of sleep maintenance insomnia, the indications of many widely used hypnotics currently approved by the US Food and Drug Administration specify efficacy only for sleep onset.7,8 Furthermore, among those hypnotics that are approved for nocturnal awakenings and/or prolonged wake time after nocturnal awakenings, all but one stipulate bedtime administration with middle-of-the-night use being explicitly disapproved to minimize risk of residual sedation. In other words, such bedtime hypnotics are designed to be preventative treatments for possible nocturnal awakenings rather than active treatments administered after nocturnal awakenings occur. The single hypnotic accepted by the FDA for as-needed MOTN...
use after nocturnal awakenings to date was approved only very recently (http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm281013.htm. Published November 23, 2011. Accessed November 23, 2011).

Given that 40% to 80% of insomniacs with prominent sleep maintenance problems do not experience symptoms every night,9 and many are only symptomatic 3-4 nights a week,3 one potentially important difference between nightly bedtime hypnotic use to prevent nocturnal awakening and as-needed MOTN use only after nocturnal awakenings occur is a dramatic reduction in the frequency of hypnotic use with MOTN dosing. Although it is difficult to know if this reduced frequency of hypnotic use would have beneficial health effects, as documenting adverse effects of prolonged hypnotic use is problematic given the well-known physical and psychological vulnerabilities of long-term hypnotic users. It is noteworthy, though, within the context of that limitation that prolonged hypnotic use has been linked with multiple subsequent adverse health outcomes.10

Hypnotics approved for bedtime use to prevent nocturnal awakenings have demonstrated inconsistent effects on sleep maintenance parameters during controlled treatment trials.8 In light of these inconsistent efficacy profiles, experimental studies have begun exploring efficacy-safety of MOTN dosing of FDA-approved (for bedtime use) hypnotics8,11-13 and investigational agents.14,15 Although these studies have found MOTN dosing of these medications associated with improvements in sleep maintenance, trials involving off-label use of approved hypnotics have also found next-day compromises in psychomotor and cognitive functioning,13,16-18 especially at higher dosages. Concerns have been raised that the tight controls in these studies may underestimate real-life adverse effects of MOTN use owing to patient non-compliance regarding hypnotic dosages and timing of doses.17,18 For instance, studies of blood levels among drivers stopped for driving under the influence (DUI) in the United States,19 Norway,20 and Sweden21 have found higher-than-expected blood levels of various hypnotic drugs, suggesting that hypnotic misuse involving escalated dosages and/or improper timing of doses may be associated with impaired driving.22 This is consistent with other evidence that high proportions of insomniacs self-medicate.23

Since many of the most widely used hypnotics approved by the FDA have indications that specify efficacy only for sleep onset symptoms, concern arises that maintenance insomniacs might be prone to self-administer their prescribed hypnotics after nocturnal awakenings despite little efficacy-safety data supporting off-label MOTN use. Given possible adverse short-term impacts of off-label MOTN dosing on cognitive and psychomotor functioning, possible long-term impacts of prolonged hypnotic use on health, and the very high prevalence of DMS, it is important to establish the extent of unsupervised MOTN hypnotic use in the population. However, we are aware of no community-based epidemiological data regarding the actual magnitude or correlates of MOTN dosing. We conducted a survey to provide basic data of this sort in a sample of insured employees of a large national health plan receiving hypnotic prescriptions during the 12 months before study. As restrictive conditions on recruitment imposed by the Health Plan resulted in a low survey response rate, caution must be used interpreting results. Nonetheless, the findings are useful given absence of other data on this issue.

METHODS

The Sample

The sample consisted of adult (ages 18-64 years) members of a large (over 34 million members) national US commercial health plan who received prescriptions for one or more FDA-approved hypnotics at some time in the 12 months before the survey. The sample was restricted to fully insured members enrolled in the Health Plan for at least 12 months in order to allow claims data to be used in substantive analyses. Sample eligibility was also limited to members who provided the Plan with a telephone number, spoke English, and had no impairment that precluded their ability to be interviewed by telephone. The sample was selected with stratification to match the health plan distribution on the cross-classification of age (18-34, 35-49, 50-64) and sex. In an effort to limit sample burden, attempts to contact respondent households were limited by the Health Plan to 2 contacts, except for a 25% subsample of households, in which up to 9 calls were permitted in order to obtain at least some information about hard-to-reach respondents. The data were weighted to adjust for this under-sampling of hard-to-reach respondents.

Recruitment and Consent

Survey recruitment began with an advance letter sent to a probability sample of Plan members meeting eligibility requirements explaining that the survey was designed “to better understand how sleep problems affect the daily lives of people,” that respondents were randomly selected, that responses were confidential, that participation was voluntary and would not affect health care benefits, and that a $20 incentive was offered for participation among eligible respondents. A toll-free number was included for respondents who wanted to ask questions or opt out. Following initial phone contact, verbal informed consent was obtained before beginning interviews. The Human Subjects Committee of the New England IRB (www.neirb.com) approved these recruitment, consent, and field procedures.

Measures

The survey consisted of two parts. All respondents were administered Part I, which asked them to specify when during the course of the evening or night they used their sleep medication(s) in the past 12 months. Part II of the survey was then administered only to (i) all Part I respondents who acknowledged using FDA-approved hypnotics after nighttime waking in order to resume sleep, but who never used hypnotics twice in one night (i.e., both at bedtime to get to sleep and also after waking at night to resume sleep), whom we refer to throughout this paper as one-per-night MOTN users, and (ii) a random 20% subsample of Part I respondents who reported using sleep medications exclusively at bedtime, whom we refer to as exclusive bed-time users. We excluded from Part II all those who ever used both at bedtime to get to sleep and also after waking at night to resume sleep, whom we refer to as twice-per-night MOTN users. The Part II data were weighted so that the exclusive bedtime users received a weight of
5 (i.e., the reciprocal of 20%) to adjust for their under-sampling into Part II, making the weighted Part II sample representative of all once-per-night MOTN users or exclusive bedtime users.

In addition to assessing patterns of hypnotic use, the Part II survey examined insomnia symptoms using the Brief Insomnia Questionnaire (BIQ),\(^2\) a self-report measure of insomnia symptoms without diagnostic hierarchy rules or organic exclusion rules that has been validated for use in telephone surveys. As respondents were by definition treated insomniacs, BIQ questions asked how frequently they would have each of 4 nighttime sleep problems if they were unable to use sleep medications: difficulty initiating sleep (DIS), difficulty maintaining sleep (DMS), early morning awakening (EMA), and non-restoreative sleep (NRS). This was done by prefacing the questions with the following instruction: Imagine that you were unable to take your sleep medicine at all. We then asked respondents to estimate about how many nights out of 7 in a typical week they would have problems falling asleep, have problems remaining asleep throughout the night, wake up before you wanted to, and wake up still feeling tired or unrested if they were unable to take sleep medicine. Follow-up questions to positive responses then probed for information about typical duration (e.g., how many minutes or hours it would typically take them to fall asleep). Respondents reporting more than one of these sleep problems were asked which one was most bothersome. Respondents were also asked about the duration and frequency of their hypnotic use. MOTN users were additionally asked about frequency of this use. Finally, all Part II respondents were administered a battery of standard sociodemographic questions. The complete text of the interview is posted at http://www.hcp.med.harvard.edu/wmh/AIS_Study.php.

**Analysis Methods**

Given the low response rate, analysis began by comparing respondents to non-respondents on key characteristics available from health plan records. This was done with simple cross-tabulations. A post-stratification weight using the regression-based propensity score method\(^25\) was then used to correct for significant differences between respondents and non-respondents on these variables prior to carrying out substantive analyses. Cross-tabulations with these weighted data were then used to estimate the prevalence of MOTN use in the Part I sample (all of whom, as noted above, received prescriptions for ≥ 1 FDA-approved hypnotic(s) in the past 12 months), while means were calculated to estimate the proportion of all instances of hypnotic use that occurred at bedtime versus MOTN. Cross-tabulations and multiple logistic regression analysis were then used in the weighted Part II sample (which, as noted above, included once-per-night MOTN users and exclusive bedtime users, but excluded twice-per-night MOTN users) to study the correlates of once-per-night MOTN use versus exclusive bedtime use. Logistic regression coefficients and their standard errors were exponentiated for ease of interpretation and are reported as odds ratios (ORs) with 95% confidence intervals. As survey data are weighted, the design-based Taylor series linearization method\(^26\) implemented in the SAS 9.2 software system\(^27\) was used to estimate standard errors of coefficients and to calculate F tests and Wald \(\chi^2\) tests. Standard errors of prevalence estimates are reported in parentheses in the text to the right of the prevalence estimates. Statistical significance was consistently evaluated using 0.05-level two-sided tests.

**RESULTS**

### The Survey Cooperation Rate

The survey cooperation rate among resolved cases (i.e., the rate of survey completion among target respondents with known working telephone numbers who were reached and whose status was resolved as either completers or refusers, excluding respondents who were never reached and those who were reached but remained unresolved when data collection ended) was 40.7% (Table 1). This is comparable to the cooperation rates found in major government telephone surveys. For example, the 2009 CDC Behavioral Risk Factor Surveillance Survey\(^28\) had a cooperation rate, calculated in the same way as here, of 43.1% (ftp://ftp.cdc.gov/pub/Data/Brfss/2009_Summary_Data_Quality_Report.pdf; Accessed September 28, 2011).

It should be noted, though, that the Health Plan imposed rather restrictive conditions on the recruitment process, as any potential respondent household that was reached twice without obtaining a resolution (an interview, a refusal, or a confirmation of ineligibility) could not be contacted a third time. Unresolved cases included those in which the target respondent was not at home or said it was an inconvenient time to be interviewed. Since Plan restrictions on number of phone contacts prevented follow-up with many unresolved cases, the survey response rate (i.e., the proportion of all households we attempted to contact that yielded an interview exclusive of those known not to be eligible) was only 11.6%. This is much lower than response rates
obtained in surveys in which no such limitations on number of contact attempts are imposed.

Comparisons between Respondents and Non-Respondents

The 1,927 respondents who completed the Part I survey (including both the subsample administered the Part II survey and the subsample administered only the Part I survey) were compared to non-respondents on key characteristics available from Health Plan records, including sociodemographics (age, sex), geographic information obtained by matching the zip code of household residence with Census data (region of the country, urbanicity, and median household income in the Block Group of residence), and global illness severity in the 12 months before interview as assessed by the Deyo-Charlson score. Respondents were somewhat older than non-respondents, somewhat more likely to be female and to live either in the Midwest or South, and less likely to live in the West or in major metropolitan areas. Respondents also lived in zip code areas with lower incomes than non-respondents. (Detailed results are available on request.) Finally, respondents had higher global illness severity than non-respondents. As noted in the section on analysis methods, a weight was imposed on the respondent data to adjust for these differences between respondents and non-respondents.

Prevalence of MOTN Hypnotic Use

While 79.8% (1.1) of Part I respondents, representing all hypnotic users, reported that they were exclusive bedtime users, the other 20.2% (1.1) reported being MOTN users (Table 2). The latter include 11.2% (0.8) once-per-night MOTN users (2.1% [0.4] exclusively MOTN and 9.1% [0.8] sometimes at bedtime and other times MOTN) and 9.0% (0.8) twice-per-night MOTN users. As noted above in the section on analysis methods, the parenthetical entries to the right of the prevalence estimates are the standard errors of these estimates.

The health plan from which we selected the survey sample reported that 2.6% of members in the 18- to 64-year age range had a prescription sleep medication at some time in the 12 months before the survey. If we assume provisionally that this rate applies to the total US population in the age range of the sample and that the sample estimate that 20.2% of prescription hypnotic users use MOTN applies equally to other hypnotic users in the US population, then the total of such MOTN users in the population ages 18-64 would be approximately 1 million Americans (95% CI: 800,000-1,200,000), with once-per-night MOTN users representing approximately 550,000 (95% CI: 450,000-650,000) Americans in the same age range.

Comparison of Once-per-Night MOTN Users with Exclusive Bedtime Users

MOTN users in the Part I sample did not differ significantly from exclusive bedtime users in average age ($F_{1,1924} = 2.0$, $p = 0.13$), percent females ($F_{1,1924} = 4.9$, $p = 0.08$), or the specialty of the physician who most recently prescribed their sleep medication ($F_{1,1924} = 0.2-1.4$, $p = 0.49-0.91$; Table 3). However, mean number of years of hypnotic use was significantly longer for MOTN users (5.5 years for once-per-night MOTN users and 6.2 years for twice-per-night MOTN users) than for exclusive bedtime users (4.3 years; $F_{1,1924} = 9.8$, $p < 0.001$). MOTN users also differed significantly from exclusive bedtime users in frequency of hypnotic use. Frequency of use was significantly lower among once-per-night MOTN users (means of 9.2 nights in the past month and 105.6 in the past 12 months) than exclusive bedtime users (means of 12.4 nights in the past month, $F_{1,1924} = 14.4$, $p < 0.001$; and 155.0 in the past 12 months, $F_{1,1924} = 28.1$, $p < 0.001$), but significantly higher among twice-per-night MOTN users than exclusive bedtime users (means of 18.1 nights in the past month and 228.6 in the past 12 months, $F_{1,1924} = 22.1-28.1$, $p < 0.001$; Table 3).

In the Part II sample, once-per-night MOTN users were asked how many times they used MOTN in the past month (30 nights). The mean was 2.8 (0.4) compared to the 9.2 mean for overall monthly use. This means that the majority (70%) of use among once-per-night MOTN users is at bedtime rather than MOTN.

Doctor Recommendations and Personal Rules for Once-per-Night MOTN Use

Only a small minority of once-per-night MOTN users (14.0% [2.9]) reported that the doctor who prescribed their sleep medicine advised them to use it in the middle of the night to resume sleep. However, the proportion of patients reporting such directions for use varies significantly by type of provider ($\chi^2 = 20.5$, $p < 0.001$), due to much higher proportions of reported doctor advice to use MOTN among once-per-night MOTN users treated by a sleep medicine specialist (52.6% [35.3]) or psychiatrist (42.6% [13.3]) than by a primary care doctor (9.6% [2.9]), pain specialist (13.6% [7.5]), or other doctor (5.2% [5.2]).

The vast majority of once-per-night MOTN users (86.0% [2.6]) reported having a personal rule for MOTN use. By far the most common rules either involved amount of time left in bed, such as not using MOTN unless it was possible to sleep in the next morning (73.2% [3.5]); Presence vs. absence of a rule for use was not significantly related to whether or not MOTN use was based on doctors’ advice ($t = 1.8$, $p = 0.071$). Nor was presence vs. absence of a rule significantly related either to frequency of MOTN use ($t = 0.7$, $p = 0.48$) or to the mean individual-level proportion of overall hypnotic use that was MOTN (44.4% [3.4] with a rule vs. 48.6% [10.3] without a rule; $t = 0.4$, $p = 0.70$).
Middle-of-the-Night Hypnotic Use

Nighttime Sleep Problems among Exclusive Bedtime versus Once-per-Night MOTN Users

Types of sleep problems were assessed only in the Part II sample. NRS was the most commonly reported nighttime sleep problem (reported by 63.8% of Part II respondents), followed by DMS (59.4%), DIS (53.7%), and EMA (47.3%; Table 4). The sum of these 4 percentages is greater than 100%, which means that the typical respondent with sleep problems had more than one symptom. However, only 81.2% of respondents reported any of these 4 symptoms, the remaining 18.8% reporting that feeling tired during the day was their only sleep problem. DIS was reported as the most bothersome sleep problem by the largest proportion of respondents (46.1%) followed by DMS (30.1%), NRS (17.4%), and EMA (5.3%). The proportion of respondents in Part II of the sample who are once-per-night MOTN users is 12.3%. (This is higher than the 11.2% in Table 2 because twice-per-night MOTN users were included in the Table 1 calculation but are excluded in Part II of the sample.) This proportion is higher among respondents in the Part II sample who reported EMA (14.3%) than other nighttime sleep problems (10.1% to 11.8%; Table 4). The situation is somewhat different in the subsamples of respondents who reported specific sleep problems as their most bothersome, where the highest proportions with once-per-night MOTN use are among those whose most bothersome problems are either EMA (20.6%) or DMS (15.4%). The proportions of once-per-night MOTN use are much lower among those whose most bothersome problems are DIS (8.6%) or NRS (8.4%).

Predictors of MOTN Use

A logistic regression analysis was carried out among Part II respondents to examine significant predictors of once-per-night MOTN use from among the variables considered previously. Respondents who reported that DMS was their most bothersome sleep problem had a significantly elevated OR (95% CI) of 1.9 [1.2-3.1], indicating that those for whom DMS was most bothersome were nearly twice as likely as others to use once-per-night MOTN rather than exclusively at bedtime (Table 5). Number of years since starting hypnotic use also had a significantly elevated
**Table 5—Predictors of once-per-night MOTN medication user versus exclusive bedtime use in the Part II sample**

<table>
<thead>
<tr>
<th>Predictor</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of nights with DMS in a typical week in the absence of medication</td>
<td>0.8 (0.7-0.9)^1</td>
</tr>
<tr>
<td>Number of minutes awake on a typical DMS night</td>
<td>1.0 (0.9-1.1)</td>
</tr>
<tr>
<td>Number of awakenings/night on a typical DMS night</td>
<td>0.9 (0.8-1.0)</td>
</tr>
<tr>
<td>Number of nights with EMA in a typical week in the absence of medication</td>
<td>1.1 (1.0-1.2)</td>
</tr>
<tr>
<td>Number of years since first starter to take hypnotics</td>
<td>1.1 (1.0-1.1)^1</td>
</tr>
<tr>
<td>DMS reported as most bothersome sleep problem</td>
<td>1.9 (1.2-3.1)^1</td>
</tr>
</tbody>
</table>

*Based on a multivariate logistic regression equation comparing n = 207 once-per-night MOTN users with n = 303 exclusive bedtime users.*

**Significant at the 0.05 level, two-sided test.**

OR (95% CI) with once-per-night MOTN use (1.1 [1.0-1.1], p = 0.014). Number of nights per week respondents typically experienced nighttime awakenings in the absence of medication, in comparison, was inversely related to once-per-night MOTN use (0.8 [0.7-0.9], p = 0.002). The other predictors considered in the analysis (number of nights per week with early morning waking, number of nighttime awakenings on nights when they occur, mean overall time awake at night) were all insignificant ($\chi^2 = 0.1-2.5$, p = 0.11-0.69).

**DISCUSSION**

No previous research exists on the epidemiology of MOTN use in the general population. Such research is warranted, though, given the high prevalence and persistence of sleep maintenance insomnia and the suspicion that off-label MOTN use is common. The current results are the first systematic large-scale survey data to estimate the prevalence of MOTN hypnotic use in any detail. Although the external validity of findings is limited by a low response rate and the fact that the sample was restricted to insured people in the age range 18-64, results nonetheless provide a preliminary view of real-world MOTN hypnotic use patterns in the community.

Within the context of these sample constraints, the results suggest that approximately one-fifth of hypnotic users in the age range of 18 to 64 years use hypnotics off-label in the middle of the night to resume sleep. Nearly half of these MOTN users take hypnotics twice in the same night. The data also suggest that once-per-night and twice-per-night MOTN users are quite different, in that the former use hypnotics significantly less frequently than exclusive bedtime users while the latter use hypnotics significantly more frequently than exclusive bedtime users. We were unable to make more detailed comparisons of once-per-night versus twice-per-night MOTN users because the latter were excluded from Part II of the survey, but we were able to compare once-per-night MOTN users with exclusive bedtime users. The fact that once-per-night MOTN users take hypnotics at bedtime less often than exclusive bedtime users (averages of 6.4 nights/month vs. 12.4 nights/month, respectively) is indirectly consistent with the suggestion in the introduction that PRN dosing options could lead to a reduction in nightly hypnotic use among patients with a primary concern about DMS. However, the fact that once per month MOTN users have a longer duration of use than exclusive bedtime users might indicate an opposite long-term effect. Causal interpretations of these naturalistic associations are inappropriate, though, and can only be confirmed by controlled studies.

That twice-per-night MOTN users had much higher numbers of uses (an average of 18.1 nights/month compared to 12.4 nights/month among exclusive bedtime users) might be due to them having more complex insomnia (e.g., high rates of both DIS and DMS). Alternatively, one might speculate that twice-per-night MOTN users take hypnotics at bedtime with the intent of being able to sleep through the night, and when they awaken, despite having taken the medication at bedtime, they re-medicate. This possibility is consistent with our finding that twice-per-night MOTN users have been taking hypnotics for a longer duration than exclusive bedtime users. Although laboratory studies suggest that tolerance and dose escalation is not a significant issue with hypnotics, it may be that long-term users habituate to the sedative effects of prescription hypnotics and experience “breakthrough” sleep maintenance symptoms, which then need a second medication dosing for adequate coverage. Such speculations, however, extend beyond the data available here.

We found that the vast majority of once-per-night MOTN users switch between bedtime use and MOTN use, with MOTN use occurring much less often than bedtime use (on average of 2.8 MOTN uses/month compared to an average of 6.4 bedtime uses/month). Frequency of MOTN use among patients who use twice a night was not determined, as they were not included in Part II of the survey. However, as twice-per-night MOTN dosing occurs much more frequently than once-per-night MOTN dosing (an average of 18.1 in the past 30 days among twice-per-night MOTN users compared to 9.2 among once-per-night MOTN users) and are almost as numerous as once-per-night MOTN users (9.0% vs. 11.2% of all hypnotic users), it is not implausible that the rate of overall MOTN use among twice-per-night MOTN users in the age range of the sample might accumulate to twice that of once-per-night MOTN users. This would put the total annual number of MOTN uses in this age range in the country as a whole at well over 50 million if we assumed that sample estimates apply to the total population and that the proportion of the population using prescription hypnotics is consistent with previous national estimates.

This high estimated rate of off-label MOTN use is perhaps explainable in light of broader evidence that insomniacs frequently use alcohol, over-the-counter medications, and a variety of prescription medications other than hypnotics to self-medicate their sleep problems, along with evidence that sleep maintenance insomniacs are particularly prone to self-medication. We found that only a small proportion of once-per-night MOTN users (14.0%) reported that their MOTN use was on the advice of a physician, although this physician advice was reported by patients to be much more common among once-per-night MOTN users treated by a sleep medicine specialist or psychiatrist than by other practitioners. Being mindful that this result is based on patient self-report, it is possible that specialists in sleep medicine and psychiatry are more sophisticated.
than other practitioners regarding sleep psychopharmacology, more familiar with newer short-acting hypnotic agents, and more comfortable prescribing them for MOTN use. However, such speculations are beyond the scope of the current data. One thing is clear, though, regarding the implications of the overall low rate of physician recommendation in light of the potential adverse effects of off-label MOTN hypnotic use: that prescribing physicians should routinely ask patients with hypnotic prescriptions about possible MOTN use and caution them against off-label MOTN use. Although we are aware of no controlled studies on the effects of such an intervention, experimental studies of the basic psychological processes underlying treatment adherence suggest that physician efforts to help patients understand the rationale for discouraging off-label hypnotic use could lead to substantial reductions.

Comparison of once-per-night MOTN users with exclusive bedtime users found only three significant correlates: DMS as a most bothersome sleep problem, long duration of hypnotic use, and low weekly frequency of DMS. The first two of these three associations are easily interpreted, as we might expect patients to be more aggressive in self-medicating problems they consider most bothersome and as they become more familiar with medication effects over time. It is somewhat more difficult to understand the finding that frequency of DMS is lower among MOTN users than other hypnotic users, perhaps due to the intermittent character of symptoms. Evidence consistent with the possibility of lower symptom tolerance has been reported in a study of predictors of sham self-medication,34 consistent with the possibility of lower symptom tolerance has been reported in a study of predictors of sham self-medication,34 but future research is needed to determine the extent to which this accounts for the association of MOTN use with low DMS frequency. Future research is also needed to examine other predictors of off-label MOTN use, such as the presence and severity of comorbid physical and mental disorders.

REFERENCES


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**DISCLOSURE STATEMENT**

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Cognitive impairment and dementia are disabling conditions expected to rise in prevalence with the rapidly aging population.1,2 The identification of modifiable risk factors for cognitive impairment can provide important prevention strategies with significant public health implications. The impact of inadequate sleep on cognition can be profound. Besides producing sleepiness, which has detrimental effects on mood, job performance, and accident risk, poor sleep is associated with adverse health outcomes.3,4 This is particularly relevant to the aging population as sleep-wake patterns and sleep quality may change throughout the lifetime, with 50% of the elderly reporting sleep disturbances, and up to one-third reporting either short sleep or long sleep duration.5,6 Abnormal sleep duration may impair attention/vigilance and cause executive dysfunction,7,8 but it is unclear if these relationships persist after accounting for the risk of sleep disordered breathing (SDB). SDB is highly prevalent in the elderly, seen in up to 62% of those older than 65 years of age and is associated with poor cognitive function.8,9,10 Determining the relationship between sleep duration and cognition could lead to novel strategies to improve health as sleep duration is potentially modifiable.11

The aim of this analysis is to evaluate the association between self-reported sleep hours and short and long sleep duration with worse global cognitive function in an elderly racially/ethnically diverse population-based cohort.

METHODS

Study Population

The Northern Manhattan Study (NOMAS) enrolled 3,298 stroke-free participants randomly sampled from the Northern Manhattan Study cohort. We conducted nonparametric and logistic regression to examine associations between continuous, short (< 6 h) and long (≥ 9 h) sleep hours with performance on the Mini Mental State Examination (MMSE). There were 927 stroke-free participants with data on self-reported sleep hours and MMSE scores (mean age 75 ± 9 years, 61% women, 68% Hispanics). The median (interquartile range) MMSE was 28 (10-30). Sleep hours (centered at 7 h) was associated with worse MMSE (β = -0.01; SE [0.03], p = 0.012), while reporting short sleep was not significantly associated with MMSE performance. Long sleep duration was also associated with low MMSE score when dichotomized (adjusted OR: 2.4, 95% CI: 1.1-5.0).

Conclusion: In this cross-sectional analysis among an elderly community cohort, long sleep duration was associated with worse MMSE performance.

Keywords: Sleep duration, cognition, short sleep, long sleep, cognitive impairment, mini mental score

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Manhattan population between 1993 and 2001 using the following criteria: (1) resident of Northern Manhattan ≥ 3 months; (2) from a household with a telephone; (3) age ≥ 40 years at the time of first in-person assessment; and (4) no history of stroke. For the purpose of this analysis, we included participants with self-reported sleep hours obtained during annual telephone follow-up evaluation in 2006 and Mini-Mental Examination (MMSE) scores within one year of reported sleep hours. From the parent cohort, a total of 2,266 subjects were available for follow up in 2006. Of the available sample, a total of 927 participants had reports of sleep hours and MMSE within one year of each assessment. The sample of 927 participants had a similar proportion of women (61%), but a greater proportion of Hispanics (68%) compared to the overall baseline cohort (53%). NOMAS was approved by the Columbia University Medical Center and University of Miami, Miller School of Medicine IRBs, and all participants provided written informed consent.

Cognitive Assessment

Cognitive status was assessed in person by bilingual (English or Spanish) trained research assistants using MMSE. The MMSE is a brief 30-point questionnaire test used to evaluate cognitive function. The MMSE measures various domains of cognitive functioning including memory, orientation to place and time, naming, reading, visuospatial orientation/construction ability, writing, and the ability to follow a 3-stage command. It has good sensitivity (71% to 92%) and specificity (56% to 96%) to screen for cognitive impairment and dementia.

We used the total score of the MMSE as the outcome. Lower educational levels (≤ 8th grade) can adversely affect the MMSE scores. We defined low MMSE scores as a dichotomous outcome by adjusting for age and educational level based on established MMSE cutoffs. A cutoff of MMSE < 24 was used for those with > 8 years education and MMSE < 20 for those with ≤ 8 years of education.

Sleep Hours

We collected self-reported sleep duration as an estimate of hours of nightly sleep in the four weeks prior to the annual telephone follow-up interview in 2006, using the following question: “During the past 4 weeks, how many hours, on average, did you sleep each night?” Respondents reported in 30-min increments of each hour. The responses ranged from 3 to 12 h of sleep with a median of 7 hours.

High Risk for Sleep Disordered Breathing

High risk for SDB was estimated by constructing the Berlin questionnaire, based on reports of frequent snoring and daytime sleepiness along with objective information on hypertension and obesity in our sample. Sleep symptoms were derived from a sleep questionnaire during follow-up examination in 2004-2005. The questionnaires were administered in English or Spanish. Habitual snoring was defined as self-report of snoring ≥ 3 times per week, based on prior definitions of habitual snoring. The Epworth Sleepiness Scale was used and adapted for relevance to characteristics of people living in northern Manhattan. Daytime sleepiness was categorized as sum score ≥ 10 based on the established definition for daytime sleepiness from the Epworth Sleepiness Scale. The presence of 2 of the 3 following items was used to classify participants into high risk for SDB: (1) frequent snoring (snoring > 3 times per week), (2) daytime sleepiness (sum score ≥ 10), and (3) presence of hypertension or obesity (BMI > 30 kg/m²).

Risk Factor Assessments

Data were collected through interviews by trained bilingual research assistants using standardized data collection instruments described elsewhere. Race and ethnicity were defined by self-identification based on questions modeled after the US census. Race/ethnicity were categorized into mutually exclusive groups as non-Hispanic Black, non-Hispanic White, and Hispanic. Depressive symptoms were evaluated with the Center for Epidemiological Studies Depression scale (CES-D). The CES-D is a 20-item scale documenting 4 factors: depressive affect, somatic complaints, positive affect, and interpersonal relations. Scores on the CES-D range from 0 to 60, with higher scores indicating more symptoms of depression. Depressive symptoms were categorized as present if the sum of the scores was ≥ 16 or if the participant was taking an antidepressant medication. Hypertension was defined as a systolic blood pressure > 140 mm Hg or a diastolic blood pressure > 90 mm Hg or a patient’s self-report of a history of hypertension or use of antihypertensive medications. Diabetes mellitus was defined as fasting blood glucose ≥ 126 mg/dL or the patient’s self-report of diabetes or use of insulin or hypoglycemic medications. Cardiac disease included history of angina, MI, coronary artery disease, atrial fibrillation, congestive heart failure, or valvular heart disease.

We obtained self-reported medication use at baseline. We created a dichotomous variable (yes vs. no) based on the use of the following medications: antidepressant, antiepileptic, pain, and antipsychotic, that could affect sleep duration and cognitive function.

Statistical Analysis

Results are presented as mean ± standard deviation or median (interquartile range) for continuous variables according to the variable distribution, and proportion for categorical variables. The χ² test was used to compare proportions, while ANOVA, or the Kruskal-Wallis test if data were not normally distributed, was used to compare mean or median for continuous variables. We examined self-reported sleep hours in categories of short sleep (< 6 h) and long sleep (≥ 9 h), with 6 to 8.9 h of nightly sleep as the reference. We performed nonparametric regression to test for the association between sleep hours centered at 7 h of sleep continuously and comparing categories of < 6 h and ≥ 9 h versus the reference with the non-normally distributed MMSE using SAS procedure COUNTRIG. Sequential models were done to evaluate the unadjusted association between sleep hours (centered at 7 h) and MMSE. We then adjusted for demographic factors: age, sex, education, race/ethnicity, and insurance status (Model 2); alcohol consumption, hypertension, diabetes, depression, medications, and risk for SDB (Model 3). Logistic regression was performed with the categories for low MMSE score as the outcome. As a sensitivity analysis, we also evaluated the relation between sleep hours and memory performance on the MMSE, given that verbal 3-word recall on the MMSE has been reported as an acceptable estimate of episodic memory in epidemiologic studies.
to register 3 initial words, impaired verbal recall was defined by a score of 0 or 1 obtained on the subsequent 3-word recall task of the MMSE.\textsuperscript{24} Additionally, we evaluated the interactions between sleep hours and the covariates. All analyses were performed using SAS software version 9.3 (SAS Institute Inc, Cary, NC).

**RESULTS**

The mean age was $75 \pm 9$ years, with 61% women, 68% Hispanics, and 41% with less than a high school education. Table 1 presents the characteristics of the overall sample and across categories of sleep duration. Self-reports $< 6$ h were seen in 24% of the sample, and $\geq 9$ h were reported by 9% ($n = 87$). Participants reporting $\geq 9$ h of sleep were older, had greater frequencies of hypertension, diabetes, and lower MMSE scores than the reference ($p < 0.0001$). There was no statistical difference in the frequencies of sex, education, race-ethnicity, Medicaid or no insurance status, BMI, depression, cardiac disease, or risk of SDB among the groups.

The covariates that were associated with the lower MMSE scores were increased age ($\beta = -0.004$; $p < 0.0001$), $\leq 8$th grade education ($\beta = -0.14$; $p < 0.0001$), having Medicaid or no insurance ($\beta = -0.14$; $p < 0.0001$), Hispanic race/ethnicity ($\beta = -0.09$, $p < 0.001$) compared to non-Hispanic white, depression ($\beta = -0.05$, $p = 0.0029$), diabetes ($\beta = -0.05$, $p = 0.012$), hypertension ($\beta = -0.05$, $p = 0.0007$), and medications ($\beta = -0.08$, $p < 0.0001$). Male sex ($\beta = 0.04$; $p = 0.0065$) and moderate alcohol consumption alcohol ($\beta = 0.04$, $p = 0.009$) were positively associated with the MMSE. The BMI ($\beta = 0.0005$, $p = 0.74$), non-Hispanic black ($\beta = 0.006$, $p = 0.71$) compared to non-Hispanic white race/ethnicity, current smoking ($\beta = 0.001$, $p = 0.94$), cardiac disease ($\beta = 0.006$, $p = 0.71$), and risk for SDB ($\beta = -0.02$, $p = 0.11$) were not associated to the MMSE.

Self-reported sleep hours (continuous) was associated with worse MMSE scores in sequential models (Table 2). In addition, categorical analysis showed that self-reports of $\geq 9$ h (long sleep duration), compared to 6-8.9 h of sleep were associated with worse MMSE scores in fully adjusted models (Table 2). When evaluating cognitive scores as a binary outcome, we

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**Table 1**—Demographic and vascular risk factors and cognitive scores across categories of sleep hours

<table>
<thead>
<tr>
<th>Mean ± SD or N (%) or as indicated</th>
<th>Total (N = 927)</th>
<th>&lt; 6 h (n = 224, 24%)</th>
<th>6-8.9 h (n = 616, 66%)</th>
<th>≥ 9 h (n = 87, 9%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>75 ± 9</td>
<td>74 ± 8</td>
<td>74 ± 9</td>
<td>77 ± 9*</td>
</tr>
<tr>
<td>Women</td>
<td>567 (61)</td>
<td>144 (64)</td>
<td>371 (60)</td>
<td>52 (60)</td>
</tr>
<tr>
<td>≤ 8th grade education</td>
<td>381 (41)</td>
<td>100 (45)</td>
<td>241 (38)</td>
<td>40 (46)</td>
</tr>
<tr>
<td>Medicaid or no insurance</td>
<td>302 (33)</td>
<td>68 (30)</td>
<td>199 (32)</td>
<td>35 (40)</td>
</tr>
<tr>
<td>Race-Ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic White</td>
<td>127 (14)</td>
<td>25 (11)</td>
<td>93 (15)</td>
<td>9 (11)</td>
</tr>
<tr>
<td>Non-Hispanic Black</td>
<td>163 (18)</td>
<td>42 (19)</td>
<td>104 (17)</td>
<td>17 (20)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>615 (68)</td>
<td>152 (69)</td>
<td>405 (67)</td>
<td>58 (69)</td>
</tr>
<tr>
<td><strong>Risk Factors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28.2 ± 4.7</td>
<td>28.4 ± 5.0</td>
<td>28.1 ± 4.7</td>
<td>27.5 ± 4.7</td>
</tr>
<tr>
<td>Moderate alcohol</td>
<td>363 (39)</td>
<td>69 (31)</td>
<td>259 (42)</td>
<td>35 (41)*</td>
</tr>
<tr>
<td>Current smoking</td>
<td>155 (17)</td>
<td>32 (14)</td>
<td>104 (17)</td>
<td>19 (22)</td>
</tr>
<tr>
<td>Depression</td>
<td>185 (20)</td>
<td>53 (24)</td>
<td>111 (18)</td>
<td>21 (24)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>634 (68)</td>
<td>140 (63)</td>
<td>429 (70)</td>
<td>65 (75)*</td>
</tr>
<tr>
<td>Diabetes</td>
<td>131 (14)</td>
<td>34 (15)</td>
<td>75 (12)</td>
<td>22 (25)**</td>
</tr>
<tr>
<td>Cardiac disease</td>
<td>163 (18)</td>
<td>37 (17)</td>
<td>105 (17)</td>
<td>21 (24)</td>
</tr>
<tr>
<td>Medication\textsuperscript{2}</td>
<td>216 (23)</td>
<td>63 (28)</td>
<td>131 (21)</td>
<td>22 (25)</td>
</tr>
<tr>
<td>High risk SDB</td>
<td>245 (26)</td>
<td>54 (24)</td>
<td>166 (27)</td>
<td>23 (29)</td>
</tr>
<tr>
<td><strong>Mini-Mental Score (MMSE)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMSE, median (interquartile range)</td>
<td>28 (10-30)</td>
<td>28 (3)</td>
<td>28 (4)</td>
<td>26 (6)**</td>
</tr>
<tr>
<td>Low MMSE score (Based on age/education cutoff)</td>
<td>93 (10)</td>
<td>18 (6)</td>
<td>59 (10)</td>
<td>16 (18)*</td>
</tr>
</tbody>
</table>

SDB, sleep disordered breathing. *$p < 0.05$, **$p < 0.001$, ***$p < 0.0001$. \textsuperscript{2}Antidepressant, antiepileptic, pain, and/or antipsychotic medication.

**Table 2**—Association between sleep hours and Mini-Mental Score Examination

<table>
<thead>
<tr>
<th>Sleep hours</th>
<th>β (SE) per hour</th>
<th>p</th>
<th>β (SE) per hour</th>
<th>P</th>
<th>β (SE) per hour</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Centered at 7 h</td>
<td>-0.01 (0.004)</td>
<td>0.0180</td>
<td>-0.009 (0.004)</td>
<td>0.0393</td>
<td>-0.01 (0.004)</td>
<td>0.0113</td>
</tr>
<tr>
<td>Categorical</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 6 h</td>
<td>0.005 (0.02)</td>
<td>0.74</td>
<td>0.01 (0.02)</td>
<td>0.46</td>
<td>0.01 (0.02)</td>
<td>0.39</td>
</tr>
<tr>
<td>6-8.9 h</td>
<td>Reference</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>≥ 9 h</td>
<td>-0.07 (0.02)</td>
<td>0.0012</td>
<td>-0.05 (0.02)</td>
<td>0.0187</td>
<td>-0.06 (0.03)</td>
<td>0.0120</td>
</tr>
</tbody>
</table>

Model 1: univariate. Model 2: adjusted for age, sex, race-ethnicity, education, and Medicaid or no insurance status. Model 3: adjusted for covariates in model 2 and reported alcohol consumption, depression, diabetes mellitus, hypertension, high risk for SDB, and medications. SE, standard error.
found that long sleep duration (≥ 9 h) was associated with increased odds of low MMSE scores (Table 3). There was no association between sleep hours and delayed verbal memory and no interactions between sleep hours and demographic, vascular risk factors, medications, and risk for SDB.

**DISCUSSION**

In this cross-sectional study, we found that self-reported long sleep duration was associated with worse global cognitive function in the elderly, racially/ethnically diverse NOMAS sample, after adjusting for vascular risk factors, depression, and risk for SDB.

Self-reported long sleep duration is linked to greater mortality, and an increased risk of stroke and cardiovascular disease. While very few NOMAS participants had dementia and our results most likely reflect subtle cognitive differences, our findings are in agreement with prospective data from an elderly (≥ 65 years) population-based cohort showing a positive association between long sleep duration (≥ 9 h) and incident dementia. A cross-sectional analysis of the Osteoporotic Fractures in Men Study (MrOS) also demonstrated an association between long sleep (≥ 8 h) by actigraphy and worse global cognitive scores. Population-based studies have reported associations between long sleep duration and worse cognitive performance by measures of global cognition (MMSE), as well as verbal fluency, delayed recall, and psychomotor speed.

Most studies on sleep hours and cognitive function have examined homogenous populations, with a paucity of data from racially/ethnically diverse communities. Studies comparing self-reported sleep duration in Hispanics and non-Hispanic blacks have provided inconsistent results, suggesting that habitual sleep duration is possibly dependent on factors other than race-ethnicity. We previously described greater long sleep duration in Hispanics compared to non-Hispanic whites and observed an inverse relation between Hispanic race/ethnicity and MMSE scores. In NOMAS, a greater proportion of Hispanics have less than eight years of formal education as well as Medicaid or no insurance, both surrogate markers of lower SES. Lower SES is associated with a number of comorbidities that could result in long sleep duration.

Self-reports of long sleep duration have been associated with older age, low socioeconomic status (SES), diabetes, and vascular disease, but we observed an association between long sleep duration and MMSE after controlling for these factors. Additionally, long sleep duration was associated with worse MMSE score after controlling for depressive symptoms, medications (e.g., antidepressants, antiepileptics) and risk for SDB, factors that may worsen cognitive function. Our findings suggest that in the elderly, long sleep duration (≥ 9 h) could be an independent predictor of worse cognitive function.

It is suggested that the relation between long sleep and adverse health outcomes could be confounded by SDB. In our study, there was no difference in risk for SDB among the sleep duration groups, and high risk for SDB did not modify the relation between self-reported long sleep and worse MMSE scores. Our findings are in accordance with an analysis of the Osteoporotic Fractures in Men study that characterized differences in demographic, sleep, and vascular risk factors among elderly participants (mean age 76.4 years) with long sleep duration compared to average sleepers. In this study there were no differences in the apnea-hypopnea index between long sleep compared to 7-8 hours of sleep. In addition, self-reported long sleep duration was positively associated with increased time in bed and sleep time by actigraphy that was not explained by sleep disorders, such as SDB or vascular risk factors.

Our findings could be explained by sleep fragmentation. Fragmented sleep has been linked to long sleep duration. Fragmented sleep measured by actigraphy was associated with worse global cognitive function, independent of sleep duration, in a cross-sectional analysis of the Rush Memory and Aging Project. Sleep fragmentation is directly related to time in bed, and perhaps long sleep duration could be a surrogate or a compensatory response to fragmented sleep in those with worse cognitive function. Sleep-wake disturbances could also exacerbate cognitive dysfunction and cause further sleep disturbances, such as advancement of circadian phase with subsequent prolongation of sleep.

In our study, self-reported short sleep duration was not associated with MMSE. Short sleep duration has been associated with worse global cognitive function, memory impairment, and psychomotor speed, but stronger associations have been described for long sleep duration. Our findings are in accordance with population based studies where short sleep duration was not associated, either by self-report or actigraphy, with MMSE. Short sleep duration can cause deficits in attention and vigilance through excessive sleepiness, but the mechanisms by which long sleep duration could affect cognitive function are not fully understood.

Several limitations should be noted. The current study is cross-sectional and does not allow assessment of causality between self-reported sleep hours and cognition. Sleep duration was obtained by subjective reports from a sleep questionnaire. In particular, it could be that those with cognitive impairment tend to report longer sleep duration. Also, we were not able to capture night to night variability of sleep duration, daytime napping, or objective measures of sleep. However, other observational studies of sleep duration and adverse health outcomes are similarly based on subjective reports from sleep questionnaires. Self-reports of long sleep duration might represent a greater sleep time or just more time in bed, which cannot be determined from the current data. There might be unmeasured confounders (e.g., autoimmune disorders) that could cause fatigue and sleepiness and in part explain the results of our study. In spite of these limitations, our findings suggest that long sleep duration could be associated with worse cognitive function in the elderly.
of these limitations there are several strengths to our study. We evaluated a relatively large, racially/ethnically diverse, community-based cohort with a high burden of vascular risk factors, risk of SDB, depression, and systematically applied measures of cognition with the MMSE.

In conclusion, we found a cross-sectional association between self-reported long sleep duration, and greater odds of worse cognitive scores that were not explained by high risk of SDB. Prospective studies in racially/ethnically diverse samples are needed to confirm our findings and determine if long sleep duration is in the causal pathway and a harbinger of cognitive decline.

REFERENCES

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SUBMISSION & CORRESPONDENCE INFORMATION

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Characterization of REM Sleep without Atonia in Patients with Narcolepsy and Idiopathic Hypersomnia using AASM Scoring Manual Criteria

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Introduction: The AASM Manual for the Scoring of Sleep and Associated Events (Manual) has provided standardized definitions for tonic and phasic REM sleep without atonia (RSWA). This study used Manual criteria to characterize REM sleep in patients with narcolepsy and idiopathic hypersomnia (IH).

Methods: A retrospective review of PSG data from ICSD-2 defined patients with narcolepsy or IH, performed by two board certified sleep medicine physicians. Data compiled included REM sleep epochs and the presence in REM sleep of epochs scored as sustained muscle activity (tonic), and excessive transient muscle activity (phasic) as defined by Manual criteria.

Results: PSG data from 8 narcolepsy patients (mean age: 27.5 years; age range: 11-55) showed mean ± standard deviation values for: total REM sleep epochs 205 ± 46.1; RSWA/phasic epochs 56.1 ± 25.4; and RSWA/tonic epochs 15.0 ± 10.7. PSG data from 8 IH patients (mean age: 33.1 years; age range: 20-57) showed mean ± standard deviation values of total REM sleep epochs 163.8 ± 67.9; RSWA/phasic epochs 6.2 ± 3.5; and RSWA/tonic epochs 0.2 ± 0.4. Comparison revealed intergroup differences in phasic REM sleep (p < 0.01) and tonic REM sleep (p < 0.01) were significantly increased in narcoleptics compared to IH.

Conclusion: Our retrospective analysis showed that RSWA phasic activity and RSWA tonic activity are significantly increased in patients meeting ICSD-2 criteria for narcolepsy compared to patients meeting ICSD-2 criteria for IH. This robust difference, with further validation, could be useful as electrophysiological criteria differentiating the two disorders and understanding the physiological differences.

Keywords: Narcolepsy, idiopathic hypersomnia, rapid eye movement sleep, REM sleep without atonia, phasic, tonic


The International Classification of Sleep Disorders-second edition (ICSD-2) classifies narcolepsy and idiopathic hypersomnia (IH) under hypersomnias of central origin. The diagnostic criteria for both conditions include at least three months of subjective excessive daytime sleepiness (EDS) occurring almost daily and a mean sleep latency of less than eight minutes in the multiple sleep latency test (MSLT). These two conditions are electrophysiologically differentiated based on the number of sleep onset REM periods (SOREMS) in the MSLT: two or more for narcolepsy and less than two for IH. The ICSD-2 further subdivides narcolepsy into narcolepsy with cataplexy (N+C) and narcolepsy without cataplexy (N-C). For both narcolepsy and IH, medical, mental, neurological, or pharmacological causes must also be excluded. The conditions must also not be accounted for by another sleep disorder or drug use.

Several earlier reports have presented evidence of REM dysfunction in patients with narcolepsy including: different patterns in REM sleep distribution/REM density across the night, REM sleep phasic activity, and early onset REM sleep periods. REM behavior disorder (RBD) has been reported in up to 36% of patients with narcolepsy, with higher prevalence in N+C. On rare occasions, RBD has been the presenting complaint in patients with undiagnosed narcolepsy. However, the motor manifestations of RBD in narcolepsy have been found to be both less frequent and less severe than in idiopathic RBD. REM sleep without atonia (RSWA) has been previously reported in narcoleptics who do not meet criteria for RBD.

Different methods have been used to assess motor dysregulation in patients with narcolepsy. Automated computerized scoring has demonstrated increased EMG activity in the chin during sleep, while video monitoring studies have shown “mild” motor behaviors in narcolepsy as opposed to full-blown violent/aggressive RBD. IH closely resembles narcolepsy both clinically and in polysomnography (PSG) features. Furthermore, REM related symptoms, such as hypnagogic hallucinations and sleep paralysis,
sis, have been found to be higher in a subgroup of patients with IH than in the general population.9

The goal of this study was to analyze PSG data scored in accordance with the American Academy of Sleep Medicine (AASM) Manual for the Scoring of Sleep and Associated Events (Manual) in narcolepsy and IH to evaluate electrophysiologic differences between these two conditions, with special attention to whether RSWA differs in these two conditions.10 No prior studies of RSWA in narcolepsy have explicitly utilized the Manual criteria.

**METHODS**

**Selection Criteria**

Over a 2-year period (03.01.2010 to 03.01.2012), all patients with a new diagnosis of narcolepsy or IH were identified from patient records at the Sleep Disorders Center of the Louisiana State University Health Sciences Center in Shreveport, Louisiana. The diagnosis of IH, N-C, and N+C was made by a board certified

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**Figure 1**—Examples of typical rapid eye movement sleep without atonia (RSWA) epochs

(A) RSWA - phasic activity. (B) RSWA - tonic activity.
sleep medicine physician based on history, clinical symptoms, and nocturnal PSG and MSLT according to ICSD-2 criteria. To these narcolepsy and IH patient records we applied the following exclusion criteria: presence of obstructive sleep apnea defined by total sleep time (TST) apnea hypopnea index > 5, circadian disorder, insufficient sleep syndrome based on sleep diaries, positive drug screen performed with MSLT, REM sleep altering/cataplexy suppressing medications (e.g., tricyclic antidepressants, selective serotonin and/or norepinephrine reuptake inhibitors, sodium oxybate), PSG/MSLT done at another facility, psychiatric or neurological comorbidity, and PSG/MSLT recording obscured by significant artifact. The remaining patients used for the study consisted of 8 patients with IH, 4 patients with N+C, and 4 patients with N-C.

**Data Acquisition**

All patients had a nocturnal PSG followed by an MSLT. The PSG recordings were acquired using the Alice 5 system (Respironics, Inc., Murrysville, PA, USA) and included 6 electroencephalogram channels (F3/A2, F4/A1, C3/A2, C4/A1, O1/A2, O2/A1), vertical and horizontal electrooculograms, chin and bilateral tibialis anterior muscle electromyogram, 1-channel electrocardiogram, and respiratory monitors (nasal pressure transducer, thermistor, thoracic and abdominal plethysmograp-
phy belts, microphone and pulse oximetry). PSG scoring was in accordance with the Manual.

Quantification of RSWA

Each PSG was scored in agreement by 2 board certified sleep medicine physicians (LD, RH) in accordance with the Manual. RSWA was scored using section 7: movement rules; Number 6: Scoring PSG features of REM sleep behavior disorder.10 Figures 1A and 1B show sample epochs with RSWA.

Calculation of RSWA Index (RSWAI)

RSWAI, the total number of RSWA epochs per hour of REM sleep, was calculated using the formula below:

\[ \text{RSWAI (RSWA 30 sec epochs per hour of REM sleep)} = \frac{120}{\text{total number of RSWA epochs/total REM sleep epochs}} \]

The total number of RSWA epochs is the sum of the total number of epochs meeting criteria for RSWA by phasic and by tonic criteria.

Statistical Analysis

Analysis of variance for non-parametric samples was performed using the Mann-Whitney U calculation. P-values less than 0.05 were considered statistically significant.

RESULTS

Demographics

Demographic data of the 3 patient groups is presented in Table 1. Mean age for the 8 narcolepsy patients was 27.5 years (range: 11-55); 4 patients were women. Four patients had N+C; 4 patients had N-C. Mean age for the 8 IH patients was 33.12 years (range: 20-57); 7 patients were women. Age, body mass index, and Epworth Sleepiness Scale score were not significantly different between the narcoleptic and IH groups. Two patients with narcolepsy had questionnaire reports of dream-enacting behavior consisting of non-injurious nocturnal arm and leg movements. No patients reported injurious parasomnias or had a primary complaint of parasomnias. Three patients with narcolepsy (all N+C) and 3 with IH reported daily ingestion of caffeinated beverages. As the PSG and MSLT studies were to establish a hypersomnia related diagnosis, all patients were off stimulants and sleep/wake or REM sleep altering medications for > 2 weeks.

PSG Data

PSG data is summarized in Table 2. Total REM sleep in minutes was not significantly different between narcoleptics (206.75 min) and IH (163.88 min), but REM sleep % was significantly different between narcoleptics (24.76%) and IH (17.91%). The use of MSLT to support a diagnosis of narcolepsy requires TST > 6 h on the prior night.1 Patients from both groups exceeded this amount considerably. TST was significantly different between narcoleptics and IH. The mean TST in narcoleptics was 419.56 min; it was 461.31 min in IH. The narcoleptics TST ranged from 382.5 min to 517 min. The IH TST ranged from 428 min to 532 min. Wake after sleep onset (WASO), sleep efficiency, N1 percentage, N2 percentage, N3 percentage, and periodic limb movement indices (PLMI) were not significantly different between narcoleptics and IH. Neither the narcoleptics nor the IH patients exhibited abnormal REM sleep behaviors during the video PSG recording.

Significant intergroup variances were found between IH, N+C, and N-C in total tonic REM sleep epochs, total phasic REM sleep epochs, RSWAI, and REM sleep latency at p < 0.01; and in sleep latency at p < 0.05. When comparing narcolepsy to IH, N+C to IH, and N-C to IH: significant Mann-Whitney statistical differences at p < 0.01 were found in total tonic epochs, total phasic epochs, and RSWAI. When comparing N+C to IH: significant statistical difference at p < 0.01 was found in sleep latency. RSWAI comparisons are shown in Figure 2A. The range of RSWAI values in narcoleptics and IH do not overlap with one another and seem to have distinct ranges (Figures 2A and 2B).

No significant statistical difference was found in sleep latency when comparing narcolepsy to IH or when comparing N-C to IH. Significant statistical difference (p < 0.05) in sleep latency and WASO was found between N+C and N-C.

Mean REM sleep onset was 21.13 min in all narcoleptics, 4.63 min in N+C, 37.63 min in N-C, and 119.88 min in IH. Statistically significant differences in REM sleep onset at p < 0.01 were seen when comparing narcolepsy to IH, and when com-
paring N+C to IH. Statistically significant differences in REM sleep onset at p < 0.05 were seen when comparing N-C to IH. Despite the difference in mean REM sleep onset between N+C and N-C, this difference was not statistically significant.

Epoch distribution of REM sleep across the night and REM sleep onset in narcolepsy and IH are shown in Figures 3A and 3B, respectively. A more even distribution of REM sleep across the night with more REM sleep earlier in the sleep period was seen in narcolepsy than in IH. IH showed REM sleep predominance later in the sleep period.

Phasic RSWA and tonic RSWA are much more prominent in narcolepsy compared to IH (Figure 4). In both narcolepsy and IH: phasic RSWA was more prominent than tonic RSWA; phasic RSWA was most prominent in the third quarter of night and decreases in the final quarter of the night; and tonic RSWA was more prominent in the first half of the night and decreased in the second half of the night.

**DISCUSSION**

In assessing PSG differences between narcolepsy and IH, this study revealed a statistically significant difference in overnight REM sleep distribution between groups. This finding is consistent with a previous study of the overnight distribution of motor episodes in patients with narcolepsy with cataplexy, which demonstrated that RBD episodes in these patients are less predictable than in patients with idiopathic RBD and independent of time of night or REM sleep period length. The differences in sleep latency and REM sleep onset between narcolepsy and IH shown in our study are consistent with prior investigations.

Our study demonstrates a robust electrophysiologic difference in both tonic and phasic RSWA between IH and narcolepsy, independent of cataplexy status. Recent studies in vivo suggest that the mechanism of REM sleep atonia is dependent on glutamatergic neurons from the sublaterodorsal (SLD) nucleus projecting to glycinergic neurons on the ventromedial medulla (VMM) and/or spinal cord. Muscle atonia is also maintained by simultaneous withdrawal of histaminergic, serotonergic, and noradrenergic input. The areas implicated in muscle atonia during REM sleep include the magnocellular reticular formation, locus ceruleus, subceruleus, pedunculopontine tegmentum, and laterodorsal tegmentum. The presence and complexity of REM sleep motor behavior exhibited in RBD may depend on the neuroanatomical site affected. For example, a case of narcolepsy with RBD has been reported in association with an isolated pontine tegmental lesion.
Hypocretin containing neurons, localized in the hypothalamus with widespread projections throughout the CNS, not only stabilize the sleep/wake cycle but also play a role in modulating muscle atonia during REM sleep by regulating the activity of lumbar motor neurons through both pre-synaptic and postsynaptic mechanisms in a sleep/wake stage dependent manner. N+C patients have been found to have over 90% deficiency in hypocretin neurons, while N-C patients have been found to have a 30% deficiency in hypocretin neurons. RBD in narcolepsy has been associated with hypocretin deficiency, independent of cataplexy status.

Limitations of our study include: retrospective rather than prospective analysis, small patient sample, evaluation of single night PSG data from each patient, patient recruitment from a single institution, and lack of blinded comparisons. These issues may be addressed in future larger multicenter studies. The purpose of this study was to compare RSWA in hypersomnias of central origin, but future studies may also include comparisons to patients who meet ICSD-2 criteria for idiopathic RBD. Our study may support a common putative pathology for RSWA in both narcolepsy groups that differ from IH. This finding may add an extra electrophysiologic measure, RSWA, which can potentially be used as an extra marker in aiding in the differentiation between these two central hypersomnias. If confirmed by larger numbers of patients and other investigators, a RSWAI cutoff value obtained from a diagnostic PSG using Manual criteria may be established to help support the differential diagnosis between narcolepsy or IH.

REFERENCES

Targeted Case Finding for OSA within the Primary Care Setting

Keith R. Burgess, Ph.D.; Adrian Havryk, Ph.D.; Stephen Newton, M.B.A.; Willis H. Tsai, M.D., F.A.A.S.M.; William A. Whitelaw, M.D., Ph.D.

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Objectives: The aim was to determine the feasibility of using an unattended 2-channel device to screen for obstructive sleep apnea in a population of high-risk patients using a targeted, case-finding strategy. The case finding was based on the presence of risk factors not symptoms in the studied population.

Methods: The study took place from June 2007 to May 2008 in rural and metropolitan Queensland and New South Wales. Family doctors were asked to identify patients with any of the following: BMI > 30, type 2 diabetes, treated hypertension, ischemic heart disease. Participants applied the ApneaLink+O2 at home for a single night. The device recorded nasal flow and pulse oximetry. Data were analyzed by proprietary software, then checked and reported by either of two sleep physicians.

Results: 1,157 patients were recruited; mean age 53 ± 14.6, M/F% = 62/38, mean BMI = 31.8, obesity = 35%, diabetes = 16%, hypertension = 39%, IHD = 5%, Mean Epworth Sleepiness Scale score (ESS) = 8.3. The prevalence of unrecognized OSA was very high: 71% had an AHI > 5/h, 33% had an AHI > 15/h, and 16% had an AHI > 30/h. The ApneaLink+O2 device yielded technically adequate studies in 93% of cases.

Conclusion: The study shows that a "real world" simple low cost case finding and management program, based on unattended home monitoring for OSA, can work well in a population with risk factors and comorbidities associated with OSA, independent of the presence of symptoms. The prevalence of unrecognized OSA was very high.

Keywords: Obstructive sleep apnea, ApneaLink, unattended sleep study

Citation: Burgess KR; Havryk A; Newton S; Tsai WH; Whitelaw WA. Targeted case finding for OSA within the primary care setting. J Clin Sleep Med 2013;9(7):681-686.

BRIEF SUMMARY

Current Knowledge/Study Rationale: It is important to find and treat patients with OSA, but screening of whole populations would have a relatively low yield. We wished to assess the feasibility and the yield of a targeted case finding program to screen high risk patients for unrecognized OSA regardless of whether they had typical symptoms.

Study Impact: The study shows that a simple low cost case finding and management program, based on unattended home monitoring for OSA, focused on patients with obesity, hypertension and diabetes can work well in a population with risk factors and comorbidities associated with OSA. The prevalence of unrecognized OSA in this population was high, so these data support the testing for OSA in high risk groups whether they have the traditional symptoms of OSA or not.

METHODS

The study used data which was collected from June 2007 to May 2008 at sites in rural and metropolitan Queensland, (Bundaberg and Brisbane) and 4 regions across the state of
New South Wales (the Northern, Eastern and North Western Suburbs of Sydney and the rural Southern Highlands). It was done with the cooperation of general practitioners located across these regions and Healthy Sleep Solutions (HSS), a private company that specializes in facilitating home diagnostic studies and provision of CPAP therapy on behalf of Specialist Sleep Physicians. The geographic catchment area was approximately equally divided between urban and rural areas, (47% and 53% respectively), with a total population of approximately 560,000. The de-identified data were provided by HSS. Patients gave consent to HSS for the data collection. The data analysis was approved by an institutional review board (IRB); the Northern Sydney Central Coast Human Research Ethics Committee [1101-032M(QA)]. The results of the testing and reporting physician recommendations were conveyed to the patients by the referring family physicians. Subsequent treatment decisions and implementation were then the result of doctor and patient decisions, which were beyond the control of the authors.

**Recruitment**

Doctors were approached for participation in the study initially by mail and then by office visits from a specially trained clinical coordinator representing Healthy Sleep Solutions or a cooperating representative of a pharmaceutical company. General practitioners were asked to identify from among their patients those with a body mass index (BMI) > 30, type 2 diabetes, treated hypertension, ischemic heart disease, or with the traditional risk factors of snoring, sleepiness, and witnessed apneas.5 Prior to the study, the consenting subjects were interviewed by one of the HSS clinical coordinators to record clinical data, including height, weight, blood pressure, and details of their history and medications. Subjects also completed an Epworth Sleepiness Scale.15

Hypertension was considered present according to self-report or use of antihypertensive medication. Type 2 diabetes was defined by an abnormal fasting plasma glucose, or use of oral hypoglycemic medications. Ischemic heart disease was defined by self-report, or use of cardiac medications.

Each patient was then instructed in the use of the ApneaLink+O₂, took a device home, and applied it for a single night of recording. Data were extracted and analyzed by proprietary software (ResMed) and were then reviewed and reported by 2 respiratory physicians experienced in sleep medicine, and approved by the Health Insurance Commission to report laboratory polysomnograms.

**ApneaLink+O₂**

ApneaLink+O₂ is a proprietary monitor based on analysis of nasal pressure and oxygen saturation signals. An earlier version, employing only a nasal pressure signal, has been tested against simultaneously recorded laboratory polysomnography in a study of 59 subjects, and found to have sensitivity 0.91 and specificity 0.84 for OSA;19 comparable to other similar monitors that have been validated against polysomnography.17,18 Very recently, the 2-channel device used in this study has been validated in a study of 143 subjects against home polysomnography (PSG) in a Chinese population.19 Those authors found very high sensitivity and specificity for the diagnosis of OSA compared to in home PSG; the areas under the reader operator curves (ROC) were both 0.933. The new version continues to base its calculation of AHI on the nasal pressure tracing, but a second channel recording oxygen saturation allows it to count the number of dips per hour > 4%, which was used as a substitute for AHI if the nasal pressure probe was lost, and has the potential to reduce the study failure rate. (This approach is supported by the similar high sensitivities and specificities of both the oximetry and nasal flow signals [-85%]²⁰). The ApneaLink+O₂ displays tracings of nasal pressure, oxygen saturation, and pulse rate. The pulse oximeter was a Nonin Xpod 3012 with a Nonin 7000A finger probe and a sampling rate of 1 Hz. Flow was sampled at 100 Hz. Tracings were reviewed initially at 5 cm/min, but expanded as necessary. The device provides statistics, including an apnea-hypopnea index derived from the flow tracing plus minimum saturation, the number per hour of desaturations of 4%, oxygen desaturation index (ODI), and mean pulse rate.

To be considered technically “good,” a study must have lasted ≥ 4 h and must have recorded data from both flow and oxygen saturation channels ≥ 90% of the time. A second category was considered “acceptable,” which meant that either the oximetry or the flow signal was missing, or of poor quality for > 10% of the recording, but the study could still be interpreted with confidence on data from the remaining channel.

One of two accredited sleep physicians reviewed each tracing, assessed their quality, noted the Epworth score, (score ≥ 11 being considered excessive sleepiness), medications, medical history, and daytime oxygen saturation and issued a report and recommendation based on an algorithm (Figure 1). AHI was used as the primary criterion of severity, but on the few occasions when the oxygen desaturation index was higher than the AHI because of a problem with the flow signal for part of the recording, the higher number was used. If the initial test was inadequate, a repeat test was requested.

Recommendations were based on a modification of published algorithm.²⁰ Because of previous uncertainty as to the accuracy of the ApneaLink device when AHI is between 10 and 30, and because of the recognized lack of certainty about benefits of treatment in that range, we recommended that these patients be referred to a respiratory/sleep physician for assessment, (probably including polysomnography), and management. We recommended that all patients with AHI > 30/h undergo a trial of treatment with continuous positive airway pressure (CPAP), because this degree of OSA is considered likely to be detrimental to a patient’s health, even if no symptoms are reported. In addition, however, we recommended trials of treatment with CPAP for patients with an AHI > 20/h who had comorbidities that can be worsened by the presence of untreated OSA, e.g. type 2 diabetes, hypertension, and ischemic heart disease. These constituted 40% of patients for whom CPAP was recommended. Referral to a sleep physician was recommended for patients who had excessive daytime sleepiness and AHI < 10/h. If snoring was an important complaint and AHI < 10/h, a mandibular advancement device was recommended.

**Statistics**

Patients were described using mean and 95% confidence intervals. A χ² test for linear trend was used to determine if the prevalence of comorbidity had a dose dependent relationship with OSA severity. Patient characteristics were treated as con-

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continuous variables, but where appropriate, (e.g., Sleepy [ESS > 10], and Obese [BMI > 30]), were also analyzed as categorical variables. Comorbidities were treated as categorical variables. The prevalence of OSA was identified in selected populations. Predictors of OSA (at varying levels of severity) were identified using multiple logistic regression.

**RESULTS**

Of patients who agreed and underwent the initial clinical assessment, 95% attended for overnight testing and 92% completed testing. A total of 1,157 patients were referred to the study, had an initial workup, and underwent a night of monitoring. Characteristics of the population are listed in Table 1. Comments about technical adequacy were provided by the reporting physicians for 1,098, or 95% of the 1,157 studies performed (Table 1). Of those, 79% were technically good and an additional 13% were acceptable. Only 7% were technically unsatisfactory, for whom repeat studies were requested. Review of the studies for which the physicians had not made a comment at the time, shows that they were similar with respect to distribution of AHI. All but 7 of the patients eventually had a technically satisfactory test. The most common reason for technical inadequacy was complete or partial absence of data, from both the flow channel and the oximetry channel. The second most common reason was a study of short duration, (defined as < 4 h). In most cases, short studies were not due to equipment failures, but the patient’s decision to abandon the test, or remove the oximeter probe, or the nasal cannulae, because of discomfort or difficulty sleeping.

**Prevalence of Unrecognized OSA**

Prevalence of OSA at different levels of severity is shown in Table 1. Mean AHI for the population was 15.8 ± 14.6 and mean lowest oxygen saturation was 83% ± 7%. Table 1 also shows the percentage prevalences within the whole group and various subgroups, (by severity of AHI) of key clinical features: diabetes, hypertension, obesity, coronary artery disease, and sleepiness (Epworth score > 10). As OSA severity increased, there were highly significant increases in prevalence of diabetes (p < 0.001), hypertension (p < 0.001), coronary artery disease (p = 0.005), and sleepiness (p < 0.001), but not obesity (p = 0.08). Some subjects were not included in the subgroup analysis because of missing data as shown below Table 1 (Dropped patients: No BMI: 12, Unacceptable tests: 12, No ESS: 14, No diabetes/HTN recorded: 10).
that had been previously done by others,16,19 The study was intended to validate the device against home or laboratory PSG, because subjects defined by comorbidity or risk factors, (obesity, diabetes, hypertension, coronary artery disease and sleepiness). The prevalence of OSA remained high even when cases were identified by a single risk factor. 

**DISCUSSION**

**Prevalence of OSA**

The prevalence of unrecognized OSA was very high: 71% had an AHI > 5/h; 33% had an AHI > 15/h; and 16% had an AHI > 30/h. **Table 2** shows the prevalence of OSA, divided into the 3 usual grades of severity by AHI (AHI > 5/h, > 15/h, > 30/h) for the whole study population and for subgroups of subjects defined by comorbidity or risk factors, (obesity, diabetes, hypertension, coronary artery disease and sleepiness). The prevalence of OSA remained high even when cases were identified by a single risk factor.

**Table 2** shows the analysis of results by selected risk factors for OSA. “Sleepiness” indicates an Epworth Sleepiness Scale score > 10. Total: n = 1,109. *χ² test for linear trend. (Dropped patients: No BMI: 12, Unacceptable tests: 12, No ESS: 14, No diabetes/HTN recorded: 10). †Epworth Sleepiness Scale score > 10. Total: n = 1,109.

**Table 3**—Management recommendations

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>N = 1,157</th>
</tr>
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<tbody>
<tr>
<td>Referral to sleep physician†</td>
<td>388 (33.5%)</td>
</tr>
<tr>
<td>CPAP therapy‡</td>
<td>260 (22.5%)</td>
</tr>
<tr>
<td>MAD‡</td>
<td>182 (15.7%)</td>
</tr>
<tr>
<td>Repeat study‡</td>
<td>71 (6.1%)</td>
</tr>
<tr>
<td>Current care§</td>
<td>197 (17.0%)</td>
</tr>
<tr>
<td>Missing</td>
<td>59 (5%)</td>
</tr>
</tbody>
</table>

†For patients with 10/h ≤ AHI ≤ 30/h or ESS > 10 not obviously explained by AHI. ‡For AHI (or desaturation index) ≥ 30 or AHI (or desaturation index) ≥ 20 plus hypertension and/or type 2 diabetes. §For patients with AHI < 10/h plus moderate or worse snoring. For technically inadequate studies. **Current care** patients, with an AHI < 10/h, were generally referred back to their general practitioner with a recommendation for weight loss in cases of obesity and for consideration of a dental device if snoring was more than “moderate” and was a clinical issue.

In keeping with the previous literature, we found, incidentally, that the prevalence of OSA was higher than for the rest of the population, in patients with diabetes who are sleepy (ESS > 10), but not in patients with diabetes who were not sleepy.21 Also, as expected, there was a dose-dependent relationship between OSA severity and hypertension or coronary artery disease.

The implications for the management of patients with a high risk of having OSA, such as the population that we have chosen...
Hillman’s data\(^1\) showed that untreated OSA patients consume more health related dollars than those who are treated or do not have OSA, and Sivertsen et al. have shown increased work disability.\(^2\) It can be expected, therefore, that a plan to identify and treat cases early, would reduce health care costs and thus be of interest to both the community at large and to funding organizations.

The most widely quoted prevalence data for OSA comes from the Wisconsin Cohort Study, which took place over two decades ago.\(^1\) Recent survey data from the National Sleep Foundation, suggests that the prevalence may be higher, most likely because of the rising prevalence of obesity. Using the Berlin Questionnaire in 1,506 respondents, Hiestand et al. in 2006 estimated a prevalence of OSA of up to 25%.\(^3\)

In a population survey in Spain, Duran et al.\(^4\) found the overall prevalence of AHI > 10/h in men aged 30 to 70 to be 19%, in women 15%. Prevalence increased considerably with age, from 8% in the 30-40 decade to 32% in the 60-70 decade in men, and from 2% to 26% in women. That population had a mean BMI in men of 26.2 and in women of 25.1. Bixler at al\(^5\) conducted a telephone survey of 4,364 men and chose from them a stratified random sample, taking progressively higher percentages of subjects, according to how many of four risk factors for OSA (snoring, daytime sleepiness, obesity, and hypertension) they had. They found the prevalence of AHI > 15/h increased from 2% in those with no risk factors to 34% for those with 4 risk factors, (but including only 2 of our risk factors—obesity and hypertension). Their prevalence of AHI > 15/h increased from 3% in those aged 20-44, to 13% in those over 65, confirming aging as a separate risk factor for obstructive sleep apnea syndrome (OSAS).

Critique of the Methods

The prevalence found in a program like this would depend on criteria for selection. The nature of the recruiting process, where family physicians were invited to refer patients, made it impossible to define rigorously the criteria for selection. Although the primary criterion was intended to be the presence of type 2 diabetes, obesity, or hypertension, a small number of patients were selected by the family physicians primarily because of symptoms that suggested OSA. (The study itself raised awareness of sleep apnea by participating physicians). The rate of discovery of previously unsuspected cases will depend on awareness on the part of both patients and physicians and on local resources for assessment and treatment.

Portable monitors, similar to the ApneaLink+O\(_2\) used unattended at home, have been assessed by many authors over recent years.\(^6\)\(^-\)\(^8\) Most have been found to reliably identify patients with severe OSA and those with minimal OSA as determined by PSG. In general, agreement with PSG for classifying mild and moderate OSA (AHI 5-15/h range) is not as good. Although the very recent study by Gantner et al.\(^9\) found good correlation between ApneaLink+O\(_2\) and home PSG for both OSA and oxygen desaturation index (ODI) in the normal to mild OSA range, they found underestimation of severity by the ApneaLink+O\(_2\) in the severe range. Despite that, they reported a high level of diagnostic accuracy in the moderate to severe range of OSA.\(^9\)

The clinical importance of finding an exact AHI, or of the differences in results between polysomnography and unattended portable monitors used at home, however, is questionable. Unattended portable monitors have been compared in randomized controlled trials with laboratory polysomnography, as decision making tools for the investigation and management of patients with OSA.\(^10\)\(^11\) These showed no difference in treatment outcome between patients tested by portable monitors at home and those tested by polysomnography in the laboratory.\(^12\)

The statistics presented here assume that all cases of sleep apnea that were found were OSA, rather than central sleep apnea (CSA). The analysis software calculated a central sleep apnea index for each study based on a proprietary algorithm (Resmed Pty Ltd, Sydney, Australia). This was available to the reviewing physicians, but they placed more emphasis on their interpretation of the raw data tracings than the CSA index, when deciding whether events were central or obstructive. Although tracings from ApneaLink can give strong indications, such as round rather than flat topped inspiratory flow curves, lack of snoring, and constant cycle length, which favor a diagnosis of CSA, polysomnography is usually considered essential to verify that. The number of cases of CSA in the study population is therefore not known. It is likely very small, however, since only two cases were being treated for congestive heart failure, and only three were known to have cerebrovascular disease.

Although the technical inadequacy rate for laboratory polysomnography is lower than that for the portable monitor in this study, it has been reported as 3%.\(^3\) A rate of 7% for a portable monitor should therefore be very acceptable for most purposes, given the low unit cost of the test.

We did not evaluate the effect of targeted screening on outcome measures such as CPAP adherence or quality of life. The goal of the study was to determine the feasibility of a targeted case finding strategy in high-risk patients using simple criteria likely to be found in the primary care chart. We also wished to determine whether there was a sufficiently high prevalence of patients with unrecognized OSA to justify case finding in the first place. Given the results of this study, further research is necessary to determine if targeted case finding results in effective treatment of the identified cases.

CONCLUSIONS

The study shows that a simple low cost case finding and management program, based on unattended home monitoring for OSA, focused on patients with obesity, hypertension, and diabetes, can work well in a population with risk factors and comorbidities associated with OSA. The prevalence of unrecognized OSA in this population was high, and many patients stand to benefit from the discovery and treatment of their disease. These data support the testing for OSA in high-risk groups, whether they have traditional symptoms of OSAS or not.

REFERENCES

Obstructive Sleep Apnea in Patients with End-Stage Lung Disease

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S

leep disordered breathing (SDB) describes a group of disorders of respiratory pattern or ventilation during sleep. Obstructive sleep apnea (OSA) is the most common subtype. Prevalence estimates of OSA vary widely, depending upon definition and population studied. In the general population, prevalence estimates range from 5% to 22%. Several reports have assessed the epidemiologic relationship between chronic obstructive pulmonary disease (COPD) and OSA. Most data suggest that the prevalence of OSA in patients with COPD is similar to that of the general population, but previously studied cohorts include very few subjects with advanced lung disease. Patients undergoing evaluation for lung transplantation constitute a cohort of well-characterized subjects with advanced lung disease. Few studies have looked at the case rate of OSA in patients with ESLD being evaluated for lung transplantation. In one study of 50 patients with ILD, there was a high prevalence of OSA (88%). Both end-stage lung disease (ESLD) and OSA have been associated with decreased health-related quality of life (HRQOL) and important comorbidities. If the rate of OSA in ESLD patients is substantial, some of the associated changes in HRQOL and comorbidities could be due to the presence of concomitant OSA. In view of the scarcity of data on the case rate of OSA in patients with ESLD and a possible association between OSA and multiple comorbidities as well as poor HRQOL, we performed a retrospective review of patients with ESLD referred to our lung transplant service for evaluation. We hypothesized that OSA is common in this patient group. We also compared the frequency of OSA between patients with COPD and those with restrictive lung disease due to interstitial lung disease (ILD).

METHODS

Study Design and Sample

In this study, we retrospectively reviewed the archived data of 60 subjects with ESLD referred for initial lung transplantation evaluation to the lung transplant clinic of the University of Maryland. As part of the clinic protocol, patients being evaluated for lung transplant underwent polysomnography (PSG) in...
the sleep disorders center of the University of Maryland, regardless of preexisting risk factors for OSA. Patients also underwent pulmonary function testing (PFT) as well as extensive clinical evaluation. Demographic, polysomnographic, spirometric characteristics, comorbidities, and medication utilization data were extracted from patient records. Patients with Epworth Sleepiness Scale (ESS) scores ≥ 10 were considered to have excessive daytime sleepiness. Comorbidities presented are those present in ≥ 20% of the cohort. The University of Maryland School of Medicine Institutional Review Board approved this protocol.

Measurements

**Pulmonary Function Testing**

Spirometry (FEV₁, FVC, FEV₁/FVC ratio), measurement of static lung volumes (total lung capacity [TLC] by body box plethysmography) and measurement of diffusion capacity of the lung for carbon monoxide (DLCO% predicted) by the single-breath technique were performed (Vmax22, SensorMedics, Yorba Linda, CA, USA), with the patient in the seated position according to approved standards. Subjects with a ventilatory defect (defined as FEV₁ < 70% predicted) were included. Subjects were categorized into obstructive (FEV₁/FVC ratio < 70%, TLC > 80% predicted) or restrictive (FEV₁/FVC > 70% and TLC < 80% predicted) disease.

**Polysomnography**

All PSGs included ≥ 6 h of overnight sleep in an American Academy of Sleep Medicine accredited sleep laboratory. The PSGs were performed according to commonly accepted clinical standards. The montage included encephalogram leads O1A2, O2A1, C1A2, C2A1, F1A2, F2A1; electromyogram leads for left eye, right eye, submentalis, and leg (left and right separately), electrocardiogram, and respiratory status measures by nasal airflow (nasal air pressure) and oronasal airflow (thermistor, used for backup), rib cage and abdominal respiratory effort (respiratory impedance plethysmographs), and pulse oximetry. Sleep scoring was done in 30-sec epochs according to the system of Rechtschaffen and Kales, as modified by the 2007 AASM scoring manual. Respiratory events were scored according to the 2007 AASM scoring manual. Obstructive apneas were scored where there was a decrease in nasal airflow to < 10% of baseline for ≥ 10 s with continued respiratory effort. Obstructive hypopneas were scored as a decrease in nasal airflow by 50% to 90% of baseline accompanied by oxygen desaturation > 4% for 10 s with continued respiratory effort. Respiratory event-related arousals (RERAs) were scored as a decrease in airflow by 30% to 90% accompanied by ≥ 3% decrease in oxygen saturation and/or a terminal arousal. Severity of SDB was quantified in two ways. First, we calculated the respiratory disturbance index (RDI), equal to the sum of apneas, hypopneas, and RERAs per hour of sleep. Second, we calculated the apnea-hypopnea index (AHI, equal to the sum of apneas and hypopneas per hour of sleep). For primary clinical purposes, the severity of OSA was defined as follows: “mild” = RDI 5-14.9, “moderate” RDI 15-29.9, and “severe” = RDI ≥ 30. Other PSG diagnoses were scored according to the AASM manual. Patients used oxygen during their PSG testing if ordered by their referring physician.

Data Analysis

Categorical variables are reported as counts and percentages, and were analyzed by using the Fisher exact test. For continuous variables, Gaussian distribution was evaluated by the Kolmogorov-Smirnov normality test. Normally distributed variables are presented as mean (standard deviation), and non-normally distributed variables are presented as median (interquartile range). Between-group comparisons employed non-paired t-tests for normally distributed variables and a Mann-Whitney rank sum test for skewed variables. The association between medication use and SDB was assessed with univariate logistic regression. Bivariate linear regression analyses were used to assess the association between clinical correlates with SDB. The following independent variables were tested: body mass index (BMI), DLCO%, and PSG measures of sleep architecture and indices of oxygen saturation. In addition, backward stepwise multivariate regression analyses were conducted while treating AHI/RDI as a dependent variable. Independent variables were chosen if the bivariate associations were significant. For all comparisons, a two-tailed p < 0.05 was considered significant. SigmaPlot 12.0 (Systat Software Inc., San Jose, CA) was used for all analyses and graph production.

RESULTS

Subject characteristics are summarized in Table 1. Sixty subjects meeting inclusion criteria were identified. Comparison based on their primary ventilatory defect (obstructive versus restrictive) showed similar demographic indices (age, gender distribution, BMI, ESS, and supplemental oxygen use) and major comorbid conditions (Tables 1, 2). The combined patient group was characterized by a median age of 58.5 years, BMI of 32.3, equally balanced gender distribution (52% male), and a median ESS of 9. Half the subjects were on home supplemental oxygen treatment, and 40% used supplemental oxygen during their overnight polysomnography.

No difference was noted in DLCO% predicted between the obstructive and restrictive subgroups. Both groups included mostly patients with severely diminished pulmonary function as indicated by a low FEV₁ < 50% predicted and/or DLCO% < 40% predicted. The use of antihypertensive medications and systemic steroid use was equally distributed between both obstructive and restrictive patient groups (Table 1). Inhaled medication use was significantly more common in the obstructive group.

PSG data are summarized in Table 3. None of the variables differed between the obstructive and restrictive groups. Hence, for further analysis, we have pooled the data for the entire cohort. Median sleep efficiency was reduced, with half the patients demonstrating sleep efficiency < 77.3%. Slow wave and REM sleep were also severely reduced. Sleep onset latency was slightly increased. The median AHI (9.7) and RDI (12.7) were in the mild range. Forty of 60 subjects (67%) had OSA, as defined by an RDI > 5/h (Figure 1). Fourteen (23%) had mild OSA and 26 (43%) had moderate-to-severe OSA (RDI > 15/h). Periodic leg movement index (PLMI) was elevated (> 15/h) in 13 patients (21.7%), with no differences between obstructive and restrictive patients. Time with oxygen saturation below 90% (T90%) was 17.7% ± 22.6% of total sleep time, with a median minimal saturation of 84%.

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Table 1—Demographic, medication, and pulmonary function testing (PFT) characteristics according to underlying breathing abnormality

<table>
<thead>
<tr>
<th>Variables</th>
<th>Total (n = 60)</th>
<th>Obstructive (n = 31)</th>
<th>Restrictive (n = 29)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, year</td>
<td>58.5 (49.5 to 63)</td>
<td>58 (49 to 63)</td>
<td>59 (53 to 62.25)</td>
<td>ns</td>
</tr>
<tr>
<td>Male/Female</td>
<td>31/29</td>
<td>19/12</td>
<td>12/17</td>
<td>ns</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>32.3 (25.4 to 38.7)</td>
<td>32.1 (25.3 to 35.9)</td>
<td>32.3 (25.6 to 39.4)</td>
<td>ns</td>
</tr>
<tr>
<td>Supplemental home O₂</td>
<td>30 (50%)</td>
<td>16 (52%)</td>
<td>14 (48%)</td>
<td>ns</td>
</tr>
<tr>
<td>PSG on supplemental O₂</td>
<td>24 (40%)</td>
<td>13 (42%)</td>
<td>11 (38%)</td>
<td>ns</td>
</tr>
<tr>
<td>ESS</td>
<td>9 (6 to 11.5)</td>
<td>8 (4, 10)</td>
<td>10 (7 to 12)</td>
<td>ns</td>
</tr>
<tr>
<td>Medications</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE-I, %</td>
<td>19 (32%)</td>
<td>12 (39%)</td>
<td>7 (24%)</td>
<td>ns</td>
</tr>
<tr>
<td>ARB</td>
<td>8 (13%)</td>
<td>2 (6%)</td>
<td>6 (21%)</td>
<td>ns</td>
</tr>
<tr>
<td>Diuretic</td>
<td>24 (40%)</td>
<td>10 (32%)</td>
<td>14 (48%)</td>
<td>ns</td>
</tr>
<tr>
<td>β-blocker</td>
<td>14 (23%)</td>
<td>6 (19%)</td>
<td>8 (28%)</td>
<td>ns</td>
</tr>
<tr>
<td>Calcium channel blocker</td>
<td>16 (27%)</td>
<td>10 (32%)</td>
<td>6 (21%)</td>
<td>ns</td>
</tr>
<tr>
<td>β-agonist inhaler</td>
<td>36 (60%)</td>
<td>25 (80%)</td>
<td>11 (38%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Anticholinergic blocker</td>
<td>30 (50%)</td>
<td>23 (74%)</td>
<td>7 (24%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>ICS</td>
<td>29 (48%)</td>
<td>21 (68%)</td>
<td>8 (28%)</td>
<td>0.007</td>
</tr>
<tr>
<td>Systemic steroids</td>
<td>21 (35%)</td>
<td>9 (29%)</td>
<td>12 (41%)</td>
<td>ns</td>
</tr>
<tr>
<td>PFT results</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV₁, %</td>
<td>45.2 ± 17.9</td>
<td>37.5 ± 14.9</td>
<td>53.1 ± 17.6</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>FVC, %</td>
<td>53.1 ± 14.5</td>
<td>57.1 ± 13.9</td>
<td>48.7 ± 14.1</td>
<td>0.025</td>
</tr>
<tr>
<td>FEV₁/FVC</td>
<td>63.7 ± 20.1</td>
<td>47.5 ± 13.3</td>
<td>80.5 ± 9</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>TLC, %</td>
<td>78.7 ± 33.5</td>
<td>102.3 ± 30.6</td>
<td>54.3 ± 11.7</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>DLCO, %</td>
<td>38.9 ± 17.1</td>
<td>42.1 ± 18.7</td>
<td>35.3 ± 14.6</td>
<td>ns</td>
</tr>
</tbody>
</table>

Results are presented as number (%), mean ± SD or median (interquartile range) as appropriate. BMI, body mass index; PSG, polysomnography; ESS, Epworth Sleepiness Score; ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; ICS, inhaled corticosteroids; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; TLC, total lung capacity; DLCO, diffusion capacity of the lung for carbon monoxide; ns, nonsignificant.

Table 2—Major comorbid conditions grouped by ventilator defect and RDI

<table>
<thead>
<tr>
<th>Hypertension</th>
<th>Diabetes Mellitus</th>
<th>IHD</th>
<th>Hyperlipidemia</th>
<th>GERD</th>
<th>Sinusitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Total (n = 60)</td>
<td>68</td>
<td>25</td>
<td>20</td>
<td>38</td>
<td>25</td>
</tr>
<tr>
<td>% Obstructive (n = 31)</td>
<td>77</td>
<td>19</td>
<td>23</td>
<td>39</td>
<td>19</td>
</tr>
<tr>
<td>% Restrictive (n = 29)</td>
<td>59</td>
<td>31</td>
<td>17</td>
<td>38</td>
<td>31</td>
</tr>
<tr>
<td>% RDI &lt; 5 (n = 20)</td>
<td>60</td>
<td>10</td>
<td>25</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>% RDI ≥ 5 (n = 40)</td>
<td>73</td>
<td>33</td>
<td>18</td>
<td>43</td>
<td>23</td>
</tr>
</tbody>
</table>

Observed differences between restrictive versus obstructive and RDI < 5 versus RDI ≥ 5 were all nonsignificant (χ² and Fisher exact test as appropriate). RDI, respiratory disturbance index; IHD, ischemic heart disease; GERD, gastroesophageal reflux disease.

Table 3 summarizes the observed correlations to RDI and AHI. RDI and AHI correlated positively to both predicted FEV₁% and predicted DLCO% values (p < 0.05 and p < 0.01, respectively). RDI and AHI were inversely correlated with the minimal oxygen saturation value (p < 0.01) and the percentage of time spent in slow wave sleep (p < 0.01). Subgroup analysis of subjects who had PSG done with and without supplemental oxygen showed persistence of these associations. Neither the Epworth score nor any of the other spirometric values correlated with the RDI or AHI. None of the major comorbid conditions was associated with an RDI ≥ 5/h (Table 2). No association could be found between the PLMI and the AHI, RDI, or ESS.

Multivariable modeling included a backward stepwise regression using significant predictors from Table 3 was performed. Only DLCO% and minimum O₂ saturation were found to be significant predictors (p = 0.013 and p = 0.023, respectively) of RDI (Figures 2 and 3, respectively) and AHI (p = 0.034 and p = 0.023, respectively). A multi-linear regression model incorporating the above predictors generated the following equations:

RDI = 66.606 + (0.497 × DLCO %) − (0.792 × minimum nocturnal oxygen saturation)

AHI = 67.223 + (0.421 × DLCO %) − (0.791 × minimum nocturnal oxygen saturation)

The use of ACE inhibitors was strongly associated with the occurrence of moderate-to-severe OSA (odd ratio of 4.67 CI 1.45-15.03; p = 0.017). This association was not evident for any other antihypertensive medications, including angiotensin receptor blockers. Only patients with hypertension received ACE inhibitors. Also, the association between ACE inhibitors and the occurrence of moderate-to-severe OSA was independent of comorbid conditions and BMI.
DISCUSSION

In this study of patients with ESLD, we demonstrated a high rate of sleep fragmentation, OSA, and PLM disorder. Factors such as BMI and ESS failed to predict OSA in patients with ESLD. Conversely, higher DLCO% and lower saturation during sleep correlated to higher RDI and AHI. In the ensuing discussion we consider these findings in the light of the currently available literature.

Few studies on sleep disorders have been directed at patients with ESLD. The majority (67%) of the patients had obstructive sleep apnea (OSA) as defined by an RDI ≥ 5 events/h, with 23 of 40 (57.5%) subjects diagnosed with moderate-to-severe OSA (RDI ≥ 15/h). No difference in the case rate of OSA was noted between the “obstructive” group and the “restrictive” group, despite the inherent differences in the underlying respiratory mechanical abnormalities. These facts underscore the complexity and yet poorly understood etiology of OSA among subjects with lung diseases.

We note that the median BMI among our patients was high. Patients with higher BMIs are known to have an increased incidence of OSA. Since we did not have a control group matched for BMI, we cannot say that the rate of OSA was higher than what would be expected on the basis of BMI alone. The effect of age on polysomnographic respiratory abnormalities in healthy individuals was previously reported by Pavlova et al., who showed a positive correlation between age and RDI with an average RDI of 12.8/h in the 50-65 year age range. Thus, it is possible that part of the high prevalence of sleep disordered breathing reported here is related to the age of the patients we evaluated. Prior reports of lung disease patients including COPD, idiopathic pulmonary fibrosis (IPF), and patients on the waiting list for lung transplantation reported different frequencies of OSA. Some of these are reviewed in Table 5. Depending on the definition of sleep disordered breathing and differences in population base, rates of 14% to 88% have been reported in patients with ESLD. The reasons for differences between reported prevalence estimates between studies are likely attributable to differences in patient
The potential to predict the occurrence of OSA in patients with advanced lung disease would facilitate more effective and efficient screening of this growing patient population. In our study, associations were found between OSA (as indicated by higher AHI/RDI scores) and multiple physiological parameters, including higher DLCO%, lower oxygen saturations during sleep, and percent of total sleep time spent in slow wave sleep. Though all of the above parameters have been found to correlate with OSA in previous studies, only DLCO% and minimal oxygen saturation remained independent predictors in the multivariate analyses. High rates of nocturnal oxygen desaturation have been described extensively in both COPD and ILD patients, being further deranged among those with superimposed OSA. The concept of predicting OSA by overnight pulse oximetry to monitor severity of nocturnal oxygen desaturation was thoroughly reviewed by Netzer et al. Those authors concluded that overnight pulse oximetry is a useful tool for the screening for OSA, although they did not specifically consider patients with ESLD. Our study is consistent with the notion that OSA and ESLD have additive negative effects on oxygenation, and that indices of oxygenation could be useful for prescreening patients with OSA being considered for lung transplant. Interestingly, the association between minimum saturation and RDI was also present in those patients receiving oxygen at night.

The reasons for the direct correlation between DLCO% and OSA are not clear. This could be explained by a number of factors. Keens et al. have shown that adding external resistance during inspiration leads to an increase in DLCO in normal subjects. Therefore, increased inspiratory airflow resistance, typical of OSA patients, could have resulted in improved DLCO. It is possible that increased inspiratory effort associated with increased upper airways resistance leads to increased pulmonary capillary volume, both related to increases in venous return and increased afterloading of the left ventricle, hence leading to improved DLCO with worse OSA. Elevated DLCO has been reported in adults with increased BMI, although these findings are not universal. It is also possible that in ESLD capillary destruction (lower DLCO), results in a greater degree of intermittent hypoxemia, which in turn could lead to increased respiratory drive (peripheral chemoreceptors), including the abductors of the upper airway—thus providing some protection from OSA. Hence, with worsening DLCO the severity of OSA might have been mitigated, as we observed (Figure 2).

Excessive sleepiness as assessed by the ESS did not correlate with severity or the occurrence of OSA. The reasons for the dissociation between excessive sleepiness and severity of OSA are not clear. Others have also demonstrated that the ESS is a poor predictor of the severity of sleep disorders and that the ESS may not reflect sleepiness measured objectively. It is possible that the ESS is a poor predictor of the severity of sleep disorders and that the ESS may not reflect sleepiness measured objectively.

### Table 4—Univariate coefficients of correlation between sleep disordered breathing indices and demographic, spirometric, and polysomnographic variables

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>AHI Pearson correlation (β)</th>
<th>p value</th>
<th>RDI Pearson correlation (β)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.130 ns</td>
<td></td>
<td>0.143 ns</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>0.255 ns</td>
<td></td>
<td>0.255 ns</td>
<td></td>
</tr>
<tr>
<td>ESS</td>
<td>0.073 ns</td>
<td></td>
<td>0.065 ns</td>
<td></td>
</tr>
<tr>
<td>FEV1, %</td>
<td>0.262 &lt; 0.05</td>
<td></td>
<td>0.274 &lt; 0.05</td>
<td></td>
</tr>
<tr>
<td>DLCO, %</td>
<td>0.367 &lt; 0.01</td>
<td></td>
<td>0.410 &lt; 0.01</td>
<td></td>
</tr>
<tr>
<td>SWS%</td>
<td>-0.290 &lt; 0.05</td>
<td></td>
<td>-0.334 &lt; 0.01</td>
<td></td>
</tr>
<tr>
<td>Minimal Saturation, %</td>
<td>-0.343 &lt; 0.01</td>
<td></td>
<td>-0.341 &lt; 0.01</td>
<td></td>
</tr>
<tr>
<td>T &lt; 90%</td>
<td>0.069 ns</td>
<td></td>
<td>0.057 ns</td>
<td></td>
</tr>
</tbody>
</table>

BMI, body mass index; ESS, Epworth Sleepiness score; FEV1, forced expiratory volume in 1 second; DLCO, diffusion capacity of the lung for carbon monoxide; SWS%, slow wave sleep percentage of total sleep time; T < 90%, time with oxygen saturation below 90%; ns, nonsignificant.

### Figure 2—Bivariate correlation between RDI and CO diffusion capacity (DCO)

For linear regression: $RDI = -3.653 + (0.626 \times DCO\%)$; $r = 0.410$; $p = 0.002$.

### Figure 3—Bivariate correlation between RDI and minimal $O_2$ saturation during polysomnography

For linear regression: $RDI = 89.934 − (0.850 \times minsat)$; $r = -0.341$; $p = 0.008$. 
that sympathetic hyperstimulation, or anxiety could induce a “hyperalert” state, thereby diminishing the extent of perceived sleepiness. In their study of sleep quality in patients with COPD, Scharf et al.34 found that in spite of a high incidence of self-reported poor sleep quality and insufficient sleep, few patients had excessive sleepiness as measured by ESS. These authors speculated that these patients also had a “hyperalert” state.

Intriguingly, we found a significant and substantial positive association between moderate-severe OSA and the use of an angiotensin-converting enzyme inhibitor (odds ratio 4.67). This association did not exist for other antihypertensive medication categories. While possibly due to chance, these findings are in agreement with those of Cicolin et al.35 who, in a small case series, showed that withdrawal of ACE inhibitors can lead to a significant decrease in AHI. These findings led the authors to suggest that through inhibition of degradation of bradykinin, ACE inhibitors induced vasodilatation and plasma extravasation in the upper airway in turn increasing the propensity for OSA.

We failed to find that the presence of any particular RDI cutoff was predictive of the occurrence of self-reported hypertension. The association between OSA and hypertension is well established.36 In our cohort, it is possible that confounding factors such as obesity and the presence of lung disease may have weakened the association between hypertension and OSA, so that it was not detected in our small cohort.

Finally, the finding of the high prevalence of sleep disordered breathing in patients with end-stage lung disease might appear surprising. The association between lung disease and OSA could be related to the release of proinflammatory cytokines due to the underlying lung inflammation with subsequent edema and swelling of the upper airway, which would increase the likelihood for OSA. Alternatively, during OSA there is release of cytokines and oxidant stress, which could have accelerated the progression of the underlying lung.37

Our study has several limitations. It is limited by its relatively small size and its retrospective nature. Furthermore, clinical necessity mandated the use of supplemental oxygen during the overnight sleep study in a large portion of our study population, potentially masking hypoxic episodes and leading to underestimation of the true prevalence of nocturnal oxygen desaturation—a critical determinant of hypopnea definition.

In summary, we observed a high case rate of OSA among a group of patients with advanced lung disease, irrespective of underlying etiology or subjective symptoms of excessive sleepiness. Diagnosis of OSA could well lead to improved quality of life, better perioperative management, and possibly improved course of the underlying disease.38 Additional studies will be necessary to further understand the true prevalence of OSA in advanced lung disease and its consequences, as well as the effects of treatment of OSA. There is a large disease burden borne by patients with ESLD. Addressing a common and underdiagnosed comorbidity such as OSA would appear to be an important component of their evaluation. Our study suggests that OSA is common in patients with ESLD, and therefore these patients might benefit from OSA screening with overnight polysomnography.

### Table 5—Previously reported prevalences of OSA in lung disease patients (polysomnographic recordings)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Definition SDB</th>
<th>OSA Moderate-severe OSA</th>
<th>Hypopnea</th>
<th>Prevalence SDB</th>
<th>N</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mermigkis et al.20</td>
<td></td>
<td>AHI &gt; 5</td>
<td>Both AASM 2007 hypopnea rules</td>
<td>59%</td>
<td>34</td>
<td>Idiopathic pulmonary fibrosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AHI ≥ 15</td>
<td>VII.4.A/VII.4.B only</td>
<td>15%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lancaster et al.5</td>
<td></td>
<td>AHI &gt; 5</td>
<td>AASM 2007 hypopnea rule VII.4.B only</td>
<td>88%</td>
<td>50</td>
<td>Idiopathic pulmonary fibrosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AHI &gt; 15</td>
<td></td>
<td>68%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pascual et al.21</td>
<td></td>
<td>AHI ≥ 10</td>
<td>Reduction of airflow ≥ 50% +</td>
<td>n/a*</td>
<td>31</td>
<td>Patients on the lung transplantation waiting list (17) + control (14)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>oxygen desaturation ≥ 4% ±</td>
<td>mean AHI:</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>arousal</td>
<td>patients 6.1 ± 6</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>control 4.3 ± 4.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malouf et al.32</td>
<td></td>
<td>RDI ≥ 10 or TST ≥ 10%</td>
<td>with oxygen saturation ≤ 90% in</td>
<td>36%</td>
<td>117†</td>
<td>Awaiting lung transplantation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>the presence of awake oxygen</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>saturation ≥ 90%</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Sanders et al.5</td>
<td></td>
<td>RDI &gt; 10</td>
<td></td>
<td>22%</td>
<td>1,132</td>
<td>Age &gt; 40, FEV1/FVC &lt; 70</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RDI &gt; 15</td>
<td></td>
<td>14%</td>
<td></td>
<td>Unattended home PSG</td>
</tr>
</tbody>
</table>

*OSA prevalence not reported. †Emphysema, n = 27; cystic fibrosis, n = 44; ILD (interstitial lung disease), n = 25; bronchiectasis, n = 7; other, n = 14.

### REFERENCES

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Inter-Observer Reliability of Candidate Predictive Morphometric Measurements for Women with Suspected Obstructive Sleep Apnea


Division of Respiratory, Critical Care and Sleep Medicine, and Department of Medicine, University of Saskatchewan, Saskatoon, Saskatchewan, Canada

Objective: Obstructive sleep apnea (OSA) is increasingly recognized as a public health concern. Definitive diagnosis is by overnight polysomnographic (PSG) examination. Identification of clinical predictors would be beneficial in helping prioritize high-risk patients for assessment. Practical application of morphometric predictive variables would require a high level of reproducibility in a clinical setting. In this study, our objective was to evaluate reliability between observers in measurements of candidate morphometric parameters in women.

Design and Methods: This was a prospective study of 71 women who had been referred for PSG with suspected OSA. Selected morphometric parameters were measured independently in the sleep laboratory by two trained sleep physicians.

Results: Neck circumference and truncal measurements for lower costal, midabdominal, and hip circumferences had higher reliability coefficients (intraclass correlation coefficients [ICC] of 0.78, 0.95, 0.95, and 0.81) than the smaller dimension measurements, including cricomental distance or retrognathia (ICC of 0.04 and 0.17). Of the women participating in this study, 50 of 71 had apnea-hypopnea indexes (AHI) ≥ 5. Body mass index (BMI), neck circumference, lower costal girth, midabdominal girth, and hip girth were all significantly higher (p < 0.001-0.004) in women with AHI ≥ 5.

Conclusions: There was wide variation in inter-observer reliability for different physical dimensions. We propose that any clinical morphologic measurement employed in predictive modeling should be reliably reproducible in clinical setting conditions. Our findings support the use of several truncal measures, BMI, and neck circumference as predictive measures in women undergoing evaluation for OSA.

Keywords: Women, sleep, body measures

Citation: Gjevre JA; Taylor-Gjevre RM; Reid JK; Skomro R; Cotton D. Inter-observer reliability of candidate predictive morphometric measurements for women with suspected obstructive sleep apnea. J Clin Sleep Med 2013;9(7):695-699.

BRIEF SUMMARY

There have been efforts made to identify specific morphometric measurements, which could be employed as clinical predictors for OSA, either alone or in conjunction with other parameters.1,12

In order for such dimensions to be employed as practical screening tools, it is crucial to understand the reliability of measurements in a clinical environment. A physical dimension measurement that in a particular range is predictive for OSA may prove to be misleading should the measurement itself be subject to substantial variation between physicians. In
this study, we address this concern by examination of interobserver agreement in candidate predictive morphometric measures in women who are undergoing polysomnography for suspected OSA.

METHODS

Consecutive women scheduled for routine PSG testing for evaluation of clinically suspected OSA were invited to participate in this study. Informed consent was obtained. This study was approved by the institutional research ethics board and is in accordance with the Helsinki Declaration.

Inclusion criteria included age ≥ 21 years and ability to provide informed consent. Exclusion criteria were: referring sleep physician’s strong suspicion of another primary sleep disorder (primary insomnia, narcolepsy, restless legs syndrome, parasomnia, or nocturnal seizures) as indicated on the patient’s referral form.

Morphometric variables were assessed by standardized, focused upper airway examination and general examination. For each participant, this was performed by 2 independent sleep physician observers to assess inter-observer reliability. Measurements included: neck circumference, lower costal or chest circumference (lower margin of the antero-lateral ribs, while standing at functional residual capacity [FRC]), umbilical abdominal (mid-abdominal) circumference (peri-umbilical circumference of the abdomen with abdominal muscles relaxed at FRC while standing), hip circumference (widest circumference of the buttocks while standing), lateral pharyngeal space narrowing (grading by Tsai et al.11), vertical pharyngeal space narrowing (modified Mallampati score),12 cricoidal space (in mm), maxillary over jet (in mm), and retrognathia (in mm). The presence or absence of tongue ridging, macroglossia, and tonsillar enlargement were also recorded.11,13

The pharyngeal grading system described by Tsai included a 4-class categorization, with class I designated when the palatopharyngeal arch intersects at the edge of the tongue, class II when the palatopharyngeal arch intersects at ≥ 25% of the tongue diameter, class III when the palatopharyngeal arch intersects at ≥ 50% of the tongue diameter, and class IV when the palatopharyngeal arch intersects at ≥ 75% of the tongue diameter.11

All 5 sleep physicians assessing patients for this study participated in a standardized training session on morphometric measurement techniques prior to study initiation.

Patients were studied overnight in the sleep lab using the standard 15-channel PSG (Sandman Elite version 8.0 sleep diagnostic software, Ottawa, Canada). Established protocols were used for all PSG studies.14 This included electroencephalogram (EEG, 3-channel), electrooculogram (2-channel), electromyogram (chin and leg), electrocardiogram, heart rate, snoring, thermistor airflow, nasal pressure airflow, oxygen saturation, chest wall motion, and abdominal motion.

Statistical Analysis

SPSS v.17.0 was employed for data entry and analysis. Means and standard deviations were calculated for continuous data. Proportions were calculated for categorical data. Between group comparisons of continuous data were evaluated with independent 2-tailed t-tests. Between group comparisons of categorical data were evaluated with χ2 testing and Fisher exact test when the cell size was < 5. Measures of agreement between observers were calculated for morphometric measurements, κ coefficients for categorical data, and intraclass correlation coefficients for continuous data.15,16

For this reliability study using intraclass correlations, we used conventional values for α of 0.05 and β of 0.20. As each patient underwent separate measurements by 2 different observers, using a minimum acceptable level of agreement of κ = 0.4, and an expected level of agreement of κ = 0.9, then approximately 7 subjects would be the estimated sample required per reliability assessment.17

For 2 group comparisons based on an apnea hypopnea index (AHI) cutoff of 5, mean morphometric values derived from the 2 observers were utilized. Receiver operator characteristic (ROC) curves were plotted for the predictive relationships between abnormal range AHI (≥ 5) and morphometric parameters.

RESULTS

Of 95 consecutive female patients who attended the sleep lab during the study period, 71 consented to participate. The means and standard deviations of morphometric measurements by 2 physicians and the measures of agreement are detailed in Table 1. A greater degree of inter-observer agreement, as represented by the intra-class correlation coefficients and κ coefficients,15,16 was observed for some measurements compared to others. The greatest agreement was observed for the truncal measures of lower costal girth, midabdominal girth, and hip circumferences. The lowest degree of agreement was evident for the smaller dimension measurements for cricoidal distance and retrognathia. Subjective dichotomous observations for the presence or absence of tongue enlargement, tongue ridging, or tonsillar enlargement also had lower measures of agreement between observers.

Of the 71 participants, 50 had AHI ≥ 5. Comparisons of morphometric continuous measurements between the 2 groups are detailed in Table 2. Mean measurement scores derived from the 2 observers were employed for this 2-group comparison. There were no significant differences in proportions of participants designated to have tongue ridging, macroglossia, or tonsillar abnormalities between those with elevated AHI and those with normal AHI values. Predictive relationships for abnormal AHI (≥ 5) with morphometric measures are described in Figures 1 and 2 and Table 3.

DISCUSSION

Although obesity has been linked to OSA and there are comparable frequencies of obesity between genders, the prevalence of OSA in women has been lower than in men.1 In men, increased BMI and increased neck circumference are predictive of OSA.6 It is less clear that these variables are predictive in women with OSA.5-10,18 Whittle et al. have demonstrated in magnetic resonance imaging (MRI) studies of men and women that there are differences in neck fat deposition distribution between the genders and greater overall soft tissue volume around the airway in men. They speculate that these or other anatomic factors may contribute to the
Table 1—Comparison of morphometric measurements between observers

<table>
<thead>
<tr>
<th>Measure</th>
<th>Observer 1, mean (SD)</th>
<th>Observer 2, mean (SD)</th>
<th>Measure of Agreement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neck circumference (cm)</td>
<td>38.33 (4.76)</td>
<td>38.16 (4.49)</td>
<td>0.780</td>
</tr>
<tr>
<td>Lower costal girth (cm)</td>
<td>100.91 (14.53)</td>
<td>100.25 (15.77)</td>
<td>0.952</td>
</tr>
<tr>
<td>Midabdominal girth (cm)</td>
<td>104.85 (18.98)</td>
<td>105.23 (19.84)</td>
<td>0.949</td>
</tr>
<tr>
<td>Hip girth (cm)</td>
<td>121.47 (19.22)</td>
<td>120.89 (18.61)</td>
<td>0.810</td>
</tr>
<tr>
<td>Retrognathia (mm)</td>
<td>5.72 (4.56)</td>
<td>5.00 (5.83)</td>
<td>0.174</td>
</tr>
<tr>
<td>Cricomental distance (mm)</td>
<td>5.45 (5.84)</td>
<td>5.06 (7.05)</td>
<td>0.044</td>
</tr>
<tr>
<td>Maxillary overjet (mm)</td>
<td>2.50 (2.01)</td>
<td>2.38 (1.78)</td>
<td>0.579</td>
</tr>
<tr>
<td>Lateral pharynx (mm)</td>
<td>2.54 (0.92)</td>
<td>2.61 (0.80)</td>
<td>0.327</td>
</tr>
<tr>
<td>Vertical pharynx (mm)</td>
<td>2.32 (0.96)</td>
<td>2.35 (0.95)</td>
<td>0.246</td>
</tr>
<tr>
<td>% Tongue ridging</td>
<td>63.4%</td>
<td>76.1%</td>
<td>0.329*</td>
</tr>
<tr>
<td>% Tongue enlarged</td>
<td>40.8%</td>
<td>42.3%</td>
<td>0.488*</td>
</tr>
<tr>
<td>% Tonsils abnormal</td>
<td>9.9%</td>
<td>9.9%</td>
<td>0.363*</td>
</tr>
</tbody>
</table>

SD, standard deviation; cm, centimeter; mm, millimeter. *κ coefficient for categorical variables, intraclass correlation coefficient for continuous variables.

Table 2—Comparison of morphometric measures between groups based on AHI

<table>
<thead>
<tr>
<th>Measure</th>
<th>AHI ≥ 5, mean (SD)</th>
<th>AHI &lt; 5, mean (SD)</th>
<th>Significance</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body mass index (kg/m²)</td>
<td>39.37 (10.50)</td>
<td>30.33 (5.14)</td>
<td>&lt; 0.001</td>
<td>4.230, 13.845</td>
</tr>
<tr>
<td>Neck circumference (cm)</td>
<td>39.39 (4.55)</td>
<td>35.54 (2.24)</td>
<td>&lt; 0.001</td>
<td>1.766, 5.935</td>
</tr>
<tr>
<td>Lower costal girth (cm)</td>
<td>104.65 (15.18)</td>
<td>90.89 (8.96)</td>
<td>&lt; 0.001</td>
<td>6.664, 20.850</td>
</tr>
<tr>
<td>Midabdominal girth (cm)</td>
<td>110.58 (18.67)</td>
<td>91.86 (13.14)</td>
<td>&lt; 0.001</td>
<td>9.772, 27.672</td>
</tr>
<tr>
<td>Hip girth (cm)</td>
<td>125.07 (18.06)</td>
<td>111.93 (14.38)</td>
<td>0.004</td>
<td>4.277, 21.996</td>
</tr>
<tr>
<td>Retrognathia (mm)</td>
<td>4.95 (3.61)</td>
<td>6.33 (4.80)</td>
<td>0.186</td>
<td>-3.453, 0.684</td>
</tr>
<tr>
<td>Cricomental distance (mm)</td>
<td>4.22 (4.25)</td>
<td>7.73 (4.80)</td>
<td>0.003</td>
<td>-5.799, -1.213</td>
</tr>
<tr>
<td>Maxillary overjet (mm)</td>
<td>2.30 (1.73)</td>
<td>2.88 (1.56)</td>
<td>0.200</td>
<td>-1.479, 0.315</td>
</tr>
<tr>
<td>Lateral pharynx (mm)</td>
<td>2.59 (0.76)</td>
<td>2.57 (0.56)</td>
<td>0.934</td>
<td>-0.354, 0.384</td>
</tr>
<tr>
<td>Vertical pharynx (mm)</td>
<td>2.41 (0.77)</td>
<td>2.14 (0.71)</td>
<td>0.175</td>
<td>-0.122, 0.656</td>
</tr>
</tbody>
</table>

SD, standard deviation; cm, centimeter; mm, millimeter; kg, kilogram; m, meter; CI, confidence interval.

Figure 1—ROC curve for prediction of AHI ≥ 5 from truncal measures

Figure 2—ROC curve for prediction of AHI ≥ 5 from upper airway/mandibular measures
gender disparity in OSA prevalence. Identification of clinical predictors for OSA in women would help prioritize PSG evaluation. Morphometric measures have been examined for identification of candidate variables to aid in the screening process. In this group of female patients who had been referred for polysomnography we found significantly different mean values for a number of measures (BMI, neck circumference, lower costal girth, midabdominal girth, hip girth, and the cricomental distance) between groups based on AHI category. However, of these potentially predictive measurements, the cricomental distance has a quite low measure of inter-observer agreement.

As illustrated by Figure 1 and 2 ROC curves, there is substantial overlap in the predictive relationship between truncal measures for an abnormal AHI, whereas the upper airway/mandibular measures have a lesser area under the curve and are observed to be clustered about the reference line, which implies lack of predictive contribution. The truncal parameters each provide a statistically significant predictive measure, with BMI and neck circumferences having the highest area under the curve. It is possible that greater predictive capacity may be achieved by an additive combination of physical measures, or alternatively by ratio (through adjustment for height as an example). However, identification of such predictive models was outside the scope of this study.

The extent of inter-observer reproducibility would be expected to influence utilization of any predictive morphometric parameter. In this study evaluating measure of agreement between observers in a variety of morphometric assessments, we observe the greatest degree of agreement for truncal dimensions and neck circumference, and the lowest agreement for smaller upper airway/mandibular dimensions, such as cricomental distance. We propose that any clinical morphologic measurement employed in a predictive capacity would need to be one reliably reproduced in clinical settings in order to be of practical value. Our findings support the use of truncal measures, BMI, and neck circumference as predictive measures in women undergoing evaluation for OSA.

Table 3—Area under the curve (AUC) for prediction of abnormal AHI

<table>
<thead>
<tr>
<th>Measure</th>
<th>AUC</th>
<th>Significance</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body mass index</td>
<td>0.785</td>
<td>&lt; 0.001</td>
<td>0.679, 0.890</td>
</tr>
<tr>
<td>Neck circumference</td>
<td>0.785</td>
<td>&lt; 0.001</td>
<td>0.679, 0.891</td>
</tr>
<tr>
<td>Lower costal girth</td>
<td>0.782</td>
<td>&lt; 0.001</td>
<td>0.672, 0.893</td>
</tr>
<tr>
<td>Midabdominal girth</td>
<td>0.778</td>
<td>&lt; 0.001</td>
<td>0.668, 0.888</td>
</tr>
<tr>
<td>Hip girth</td>
<td>0.715</td>
<td>&lt; 0.004</td>
<td>0.586, 0.844</td>
</tr>
<tr>
<td>Retroglossa</td>
<td>0.410</td>
<td>0.247</td>
<td>0.263, 0.557</td>
</tr>
<tr>
<td>Cricomental distance</td>
<td>0.313</td>
<td>0.16</td>
<td>0.176, 0.449</td>
</tr>
<tr>
<td>Maxillary overjet</td>
<td>0.396</td>
<td>0.183</td>
<td>0.255, 0.537</td>
</tr>
<tr>
<td>Lateral pharynx</td>
<td>0.500</td>
<td>1.00</td>
<td>0.356, 0.644</td>
</tr>
<tr>
<td>Vertical pharynx</td>
<td>0.603</td>
<td>0.187</td>
<td>0.456, 0.750</td>
</tr>
</tbody>
</table>

CI, confidence interval.

REFERENCES

ACKNOWLEDGMENTS

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Sleep is considered to be of paramount importance for brain development during the first two years of life. In fact, children spend over half of their first two years of life sleeping, with daily sleep duration decreasing from 14.5 to about 13 hours between 6 months and 2 years of age. In the preschool years, daily sleep needs remain high, decreasing from 13 hours at 2 years to about 11 hours at 5 years. During infancy and childhood, frequent night awakenings or difficulty falling asleep are among the most frequent developmental complaints. Studies estimate that from 10% to 75% of parents report that their children have sleep problems. Importantly, sleep problems tend to persist during childhood and are associated with several adverse consequences for behavioral, cognitive, and emotional health. For example, it has been shown that sleep problems are associated with behavioral and emotional self-regulation problems. In fact, results suggest that when the sleep of preschoolers is insufficient or fragmented by wakefulness, they show more difficulty inhibiting emotional responses and more frequent impulsive and aggressive behavior. Poor sleep quality also seems associated with obesity in preschool children. Studies further suggest that sleep problems, whether occurring in infancy or at school age, are associated with lower cognitive performance. In light of the prevalence and the serious consequences of pediatric sleep problems, it is essential to accurately measure sleep quality in young children.

Studies and clinicians use different methods to assess children’s sleep, each presenting strengths and weaknesses. For example, parental retrospective child sleep questionnaires and prospective sleep diaries are often criticized because parents can notice that their children awaken only when the children signal it. These measures are also influenced by the reporter’s perception (usually the mother). Videosomnography and direct behavioral observations are often used in home settings, but they may interfere with family routines and privacy. Although polysomnography (PSG) is the gold standard for measuring sleep, it requires considerable equipment and technical resources. Furthermore, this invasive method may interfere with sleep, and therefore mask habitual sleep quality.

Actigraphy, which uses a watch-size movement sensor to determine sleep and wake episodes, provides a useful alternative: the device is small and inexpensive, and it allows for

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**Study Objectives:** The algorithms used to derive sleep variables from actigraphy were developed with adults. Because children change position during sleep more often than adults, algorithms may detect wakefulness when the child is actually sleeping (false negative). This study compares the validity of three algorithms for detecting sleep with actigraphy by comparing them to PSG in preschoolers. The putative influence of device location (wrist or ankle) is also examined.

**Methods:** Twelve children aged 2 to 5 years simultaneously wore an actigraph on an ankle and a wrist (Actiwatch-L, Mini-Mitter/Respironics) during a night of PSG recording at home. Three algorithms were tested: one recommended for adults and two designed to decrease false negative detection of sleep in children.

**Results:** Actigraphy generally showed good sensitivity (> 95%; PSG sleep detection) but low specificity (± 50%; PSG wake detection). Intraclass correlations between PSG and actigraphy variables were strong (> 0.80) for sleep latency, sleep duration, and sleep efficiency, but weak for number of awakenings (< 0.40). The two algorithms designed for children enhanced the validity of actigraphy in preschoolers and increased the proportion of actigraphy-scored wake epochs scored that were also PSG-identified as wake. Sleep variables derived from the ankle and wrist were not statistically different.

**Conclusion:** Despite the weak detection of wakefulness, Actiwatch-L appears to be a useful instrument for assessing sleep in preschoolers when used with an adapted algorithm.

**Keywords:** Actigraphy, polysomnography, validation, children

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**BRIEF SUMMARY**

Current Knowledge/Study Rationale: The algorithms used to derive sleep variables from actigraphy were developed with adults. Because children change position during sleep more often than adults, algorithms may detect wakefulness when the child is actually sleeping (false negative). This study compares the validity of three algorithms for detecting sleep with actigraphy by comparing them to PSG in preschoolers.

Study Impact: Despite the weak detection of wakefulness, Actiwatch-L appears to be a useful instrument for assessing sleep in preschoolers when used with an adapted algorithm. However, further studies are needed to validate its ability to detect wakefulness in pediatric populations with sleep disturbances.
Figure 1—Linear regression between activity counts at the wrist and ankle

\[ Y = 0.513x \]

\[ R^2 = 0.9955 \]

Equation and percentage of fit are also illustrated.

METHODS

Subjects

Twelve children (4 boys, 8 girls) aged from 2 to 5 years (\(M = 3.1, SD = 1.0\)) participated in this study. None had sleep problems, according to their parents. The project was approved by the institutional review board of the investigators’ university. The parents of all participants signed a consent form that informed them on the nature and risks of participating, and they received financial compensation for the study.

Procedures

Children simultaneously wore an actigraph (Actiwatch-L, Mini Mitter Co., Inc., Respironics, Inc., Bend, OR). Actigraphy data were collected in 30-s epochs. Two Actiwatch-L activity monitors were used. The same monitor was used on the wrist or the ankle for all children. To calibrate the 2 monitors, they were fixed to a piece of wood (\(3/4\)” \(\times\) 3” \(\times\) 12”) that rotated on a vertical axis at 15 different intensities. Estimated activity counts differed between the 2 actigraphs even if induced movements at the 15 intensities. Estimated activity counts were then visually inspected to detect any temporal gaps between the 2 measures. Once the child was asleep, the technician and the research assistant left the home. The research assistant returned in the morning to remove the electrodes and bring the equipment back to the laboratory.

Measures

Actigraphy

Non-dominant wrist and ankle activity were recorded using an Actiwatch-L (Mini Mitter Co., Inc., Respironics, Inc., Bend, OR). Actigraphy data were collected in 30-s epochs. Two Actiwatch-L activity monitors were used. The same monitor was used on the wrist or the ankle for all children. To calibrate the 2 monitors, they were fixed to a piece of wood (\(3/4\)” \(\times\) 3” \(\times\) 12”) that rotated on a vertical axis at 15 different intensities. Estimated activity counts differed between the 2 actigraphs even if induced movements at the 15 intensities were identical for the 2 actigraphs (see Figure 1). Consequently, a regression was used to adjust the monitor with higher activity counts (ankle) to activity counts of the other (wrist; \(y = 0.513x\)). Both raw and adjusted data are presented in this paper.

PSG Recordings

A digital ambulatory sleep recording system (Vitaport-3 System; TEMEC Instruments, Kerkrade, The Netherlands) was used to record sleep at home. Electroencephalograph (EEG) electrodes (Cz, Oz) were placed according to the international 10-20 system, using a referential montage with linked ears, right and left electrooculogram (EOG), and chin electromyogram (EMG). EEG signals were filtered at 70 Hz (low pass) with 1-s time constant and digitized at a sampling rate of 256 Hz. Sleep stages were scored visually on-screen with 30-s epochs (Stellate System, Montreal) according to the AASM cri-
criteria, but using only the C4 derivation. The 30-s epochs were chosen to match the 30-s actigraphy epochs.

Data Analysis

Two sets of analyses were performed to determine PSG and actigraphy agreement: an epoch-by-epoch agreement analysis and a sleep variables concordance analysis. The epoch-by-epoch agreement analysis provided sensitivity, specificity, accuracy, and negative predictive value (NPV) parameters. Sensitivity was defined as the proportion of all epochs scored as sleep by PSG that were also scored as sleep by actigraphy. Specificity was the proportion of all epochs scored as wake by PSG that were also scored as wake by actigraphy. Accuracy was the proportion of all epochs correctly identified by actigraphy. NPV was the proportion of epochs scored as wake by actigraphy that were also scored as wake by PSG. The second set of analyses involved comparisons between sleep variables estimated with PSG and with actigraphy.

Three methods of scoring the actigraphy-derived sleep/wake activity counts were applied. The first 2 were threshold-based method algorithms included in the ActiWatch-L software (Mini Mitter Inc. Respironics, Inc. Bend, OR). Actiware uses a weighting algorithm with 3 different thresholds: low (20), medium (40), and high (80), which were validated on sleep disordered patients. They score original activity counts by a weighting scheme that reflects the temporal distance relative to the scored epoch. Each 30-s epoch is rescored as follows:

\[ A = 0.04E_1 + 0.04E_2 + 0.2E_3 + 2E_4 + 0.2E_5 + 0.04E_6 + 0.04E_7 \]

where \( A \) = the sum of activity counts for the 30-s scored epoch and the surrounding epochs; and \( E_n \) = the activity counts for the previous, successive, and scored epoch. If the summed activity count exceeds the defined threshold, the epoch is scored as wake; otherwise it is scored as sleep. The 40 (ACT40) and 80 (ACT80) activity count thresholds were used in the present study because the ACT40 is widely used with adult populations, whereas the ACT80 requires more movement to score an epoch as wake (and thus could presumably be more appropriate for children, who move more frequently than adults when asleep).

The third actigraphy scoring method (AlgoSmooth) used in the current study is described in a paper by Sitnick and colleagues and has never been validated with PSG. These authors rescored or secondarily “smoothed” actigraphy data derived from the ACT40 sensitivity threshold to reduce the number of awakenings per night to a range more consistent with parent diaries and video recordings. More precisely, this method requires a minimum 2-min awakening period following sleep onset (WASO) to score an awakening. The scoring criteria are:

1. When \( \geq 2 \) consecutive minutes with activity counts \( > 100 \) were immediately preceded by any activity count above 0, that epoch was considered the start of the awakening;
2. The end of a wake period, or a return to sleep, was scored at the first of 3 consecutive Os (no activity).

This third method was automated using an Excel (Microsoft, Redmond, WA) spreadsheet.

Four sleep variables were calculated, with the same definitions for PSG and the 3 actigraphy scoring algorithms. The sleep variables derived from PSG, from the 2 threshold-based method algorithms (ACT40 and ACT80) and from the smoothed algorithm (AlgoSmooth), were calculated using an in-house visual C++ program. Sleep latency was defined as the number of minutes from the time of lights off to the first 10 successive sleep epochs (the default criterion for the Actiware program). Total sleep time (TST) was the number of minutes scored as sleep from lights off to lights on. The number of awakenings was equal to the number of wake periods. Sleep efficiency (SE) was TST/total recording time * 100.

Statistical Analyses

Two-way repeated measures ANOVAs with activity type (ankle, raw wrist, and adjusted wrist) and algorithm (ACT40, ACT80, and AlgoSmooth) as factors were performed on sensitivity (ability to detect PSG sleep), specificity (ability to detect PSG wake), accuracy (PSG sleep and PSG wake), and NPV (percentage of wake detected by actigraphy that is PSG wake). Similarly, 2-way repeated measures ANOVAs with activity type (ankle, raw wrist, and adjusted wrist) and scoring method (PSG, ACT40, ACT80, and AlgoSmooth) as factors were performed on sleep variables. Simple effect analyses were performed when significant activity type by algorithm interactions were found. The post hoc Tukey HSD test was used for multiple comparisons of means on significant main effects. Since repeated measures had more than 2 levels, the Huynh-Feldt correction for sphericity was applied, but epsilon values and original degrees of freedom are reported. The Dunnett post hoc test was also used to determine whether the results derived from the actigraphy algorithms differed significantly from the PSG-derived results. Finally, to assess PSG and actigraphy agreement, intraclass correlations were computed on the 4 sleep variables. Statistical analyses were conducted using SPSS version 17 (SPSS Inc., Chicago, IL). Significance level was set at 0.05.

RESULTS

Epoch-by-Epoch Agreement

Sensitivity, specificity, accuracy, and NPV values (means and SD) derived from epoch-by-epoch comparisons between each actigraphy scoring algorithm and PSG for the 3 activity types are presented in Table 1. Overall, sensitivity was higher than 88%, whereas specificity was lower (from 57% to 81%).

A 2-way repeated measures ANOVA performed on sensitivity revealed an interaction between algorithm and activity type, \( F_{4,44} = 13.02, p < 0.001; \ varepsilon = 0.63 \). AlgoSmooth showed the highest sensitivity and ACT40 the lowest, with ACT80 in between, but these differences were more pronounced for adjusted wrist data. A significant interaction between algorithm and activity type was also found for specificity, \( F_{4,44} = 4.08, p = 0.045, \ varepsilon = 0.38 \). ACT40 showed the highest specificity and AlgoSmooth showed the lowest, with ACT80 in between, for both adjusted wrist and ankle data. For raw wrist data, ACT40 also showed the highest specificity, but specificity did not differ between ACT80 and AlgoSmooth activity type. The 2-way repeated measures ANOVA performed on accuracy revealed an
interaction between algorithm and activity type, $F_{4,44} = 5.92$, $p = 0.003$; $\varepsilon = 0.70$. AlgoSmooth showed the highest accuracy and ACT40 the lowest, with ACT80 in between, but these differences were more pronounced for adjusted wrist data. A 2-way repeated measures ANOVA performed on NPV showed an algorithm effect only, $F_{2,22} = 33.0$, $p < 0.001$, $\varepsilon = 0.52$. Post hoc mean comparisons showed significant differences ($p < 0.05$) among the 3 algorithms, with AlgoSmooth showing the highest NPV (AlgoSmooth: 76.6%; ACT80: 52.7%; and ACT40: 42.8%).

### Sleep Variable Concordance

Sleep variables calculated from PSG and estimated with the 3 actigraphy scoring algorithms for the 3 activity types are presented in Table 2. Sleep latency derived from the 3 algorithms did not differ significantly from PSG. A significant interaction between algorithm and activity type was found for TST ($F_{6,66} = 10.81$, $p < 0.01$; $\varepsilon = 0.62$) and for SE ($F_{6,66} = 13.42$, $p < 0.001$; $\varepsilon = 0.78$). Dunnett post hoc results showed that the ACT40 algorithm underestimated TST by > 25 min and SE by > 4% ($p < 0.001$) compared to PSG for the 3 activity types (ankle, raw wrist, and adjusted wrist). TST and SE derived from ACT80 and AlgoSmooth did not differ significantly from PSG when using ankle or raw wrist data. However, when using adjusted wrist data, ACT80 underestimated TST by 21 min and SE by 3.5% ($p < 0.001$), whereas AlgoSmooth overestimated TST by 6 min and SE by 1% ($p < 0.001$). Finally, a 2-way repeated measures ANOVA performed on number of awakenings showed no significant differences among the algorithms.

### Table 1—Means (± SD) for sleep sensitivity, specificity, accuracy, and NPV of epoch-by-epoch comparisons with PSG of the three actigraphy scoring algorithms with the three activity types

<table>
<thead>
<tr>
<th>Statistical parameter</th>
<th>Activity type</th>
<th>Scoring algorithms</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ankle</td>
<td>ACT40</td>
</tr>
<tr>
<td>Sensitivity (%)</td>
<td></td>
<td>90.5 (2.8)</td>
</tr>
<tr>
<td></td>
<td>Raw wrist</td>
<td>92.7 (2.7)</td>
</tr>
<tr>
<td></td>
<td>Adjusted wrist</td>
<td>87.9 (2.7)</td>
</tr>
<tr>
<td>Specificity (%)</td>
<td></td>
<td>75.1 (19.2)</td>
</tr>
<tr>
<td></td>
<td>Raw wrist</td>
<td>69.9 (16.4)</td>
</tr>
<tr>
<td></td>
<td>Adjusted wrist</td>
<td>81.0 (14.8)</td>
</tr>
<tr>
<td>Accuracy (%)</td>
<td></td>
<td>89.3 (3.5)</td>
</tr>
<tr>
<td></td>
<td>Raw wrist</td>
<td>90.7 (3.0)</td>
</tr>
<tr>
<td></td>
<td>Adjusted wrist</td>
<td>87.5 (2.8)</td>
</tr>
<tr>
<td>NPV (%)</td>
<td></td>
<td>41.7 (13.7)</td>
</tr>
<tr>
<td></td>
<td>Raw wrist</td>
<td>47.4 (15.8)</td>
</tr>
<tr>
<td></td>
<td>Adjusted wrist</td>
<td>39.4 (13.3)</td>
</tr>
</tbody>
</table>

ACT40, Actiware medium threshold algorithm; ACT80, Actiware high threshold algorithm; AlgoSmooth, Sitnick et al.’s smoothing algorithm; NPV, negative predictive value.

### Table 2—Sleep parameters (mean ± SD) scored with PSG and estimated by the three actigraphy scoring algorithms with the three activity types

| Sleep parameters       | Activity type   | PSG*                  | Scoring algorithms |
|------------------------|-----------------|-----------------------|
|                        | Ankle           | ACT40  | ACT80  | AlgoSmooth |
| Sleep latency (min)    |                 | 34.5 (20.2) | 31.9 (22.3) | 39.2 (21.8) |
| Total sleep time (min) |                 | 558.8 (49.2) | 518.7 (49.0)** | 543.8 (49.5)** |
| Sleep efficiency (%)   |                 | 90.9 (3.5) | 84.4 (4.9)** | 86.8 (3.9)** |
| Number of awakenings   |                 | 23.0 (9.8) | 59.0 (9.5)** | 60.0 (13.5)** |

*Activity type does not apply to PSG. ACT40, Actiware medium threshold algorithm; ACT80, Actiware high threshold algorithm; AlgoSmooth, Sitnick et al.’s smoothing algorithm. Asterisks denote a significant difference (*$p \leq 0.05$ and **$p \leq 0.01$) between the sleep parameters derived from PSG and from actigraphy algorithms.
ings showed an algorithm effect only, \( F_{0.06} = 139.93, p < 0.001 \), \( \varepsilon = 0.62 \), with ACT40 and ACT80 yielding a significantly higher number of awakenings and AlgoSmooth a lower number of awakenings than PSG (p < 0.001).

Table 3 shows the intraclass correlations between sleep parameters derived from PSG and estimated from the 3 actigraphy scoring algorithms for the 3 activity types. In general, the correlation coefficients were high for all algorithms and activity types regarding sleep latency (ICC > 0.75), TST (ICC > 0.91), and SE (ICC > 0.70). In contrast, the correlations were low for all algorithms and activity types regarding number of awakenings (ICC < 0.42).

**DISCUSSION**

We evaluated the ability of the Activwatch-L device to detect sleep/wake in preschool children using three algorithms. Results clearly showed that the Activwatch-L is better able to detect sleep than to detect wake. Importantly, ACT80 and AlgoSmooth enhanced the ability of actigraphy to detect sleep in preschool children compared to ACT40. However, ACT80 and AlgoSmooth decreased the ability of actigraphy to detect wakefulness compared to ACT40. The low specificity (about 60% of PSG wakefulness is scored as wakefulness by actigraphy) observed in our data is similar to that found in previous studies that compared different brands of actigraphy with PSG in infants\(^{11,20}\) and children,\(^{1,22}\) highlighting the difficulty of correctly identifying wake with actigraphy. Nevertheless, when the actigraphs scored wake, AlgoSmooth showed higher agreement with PSG (NPV = 76.6%) than the other two algorithms (42.8% and 52.7%), suggesting that AlgoSmooth is better suited for this purpose. Importantly, the general accuracy of actigraphy to detect sleep and wake remained high, despite the low specificity, probably because most of the assessed intervals consisted of sleep.

Statistical comparisons between sleep variables derived from actigraphy and PSG as well as intraclass correlations suggest that ACT80 and AlgoSmooth performed better overall than ACT40 in preschoolers. Except for number of awakenings, ACT80 and AlgoSmooth showed no substantial differences from PSG, and intraclass correlations were high. Consequently, the results suggest that ACT80 and particularly AlgoSmooth should be used with populations of preschoolers. The two Actiware algorithms (ACT40 and ACT80) clearly overestimated the number of awakenings, whereas AlgoSmooth underestimated them. These results indicate that number of awakenings is not a valid indicator of sleep quality when assessed with actigraphy in preschoolers. For this reason, we attempted to adapt the smoothing algorithm (AlgoSmooth) described by Sitnick and colleagues\(^{19}\) to increase the number of awakenings detected. The adapted criteria were: (1) when there was 1 or more consecutive minute(s) with activity counts greater than 100, that epoch was considered to be the start of the awakening; (2) the end of a wake period, or a return to sleep, was scored at the first of 3 consecutive 0s (no activity). This method was automated using a Matlab function and was applied to the wrist data. The number of awakenings estimated by this adapted algorithm did not significantly differ from the number of awakenings derived from PSG (M = 22.6, SD = 6.0 for the adapted algorithm vs M = 23.0, SD = 9.8 for PSG, \( t_{11} = -0.20, p = 0.85 \)). Unfortunately this was at the expense of sensitivity and accuracy; these were significantly lower with AlgoSmooth, which had higher values (sensitivity: M = 88.4; SD = 4.2, \( t_{11} = -5.83, p < 0.001 \); accuracy: M = 87.8; SD = 3.6, \( t_{11} = -7.11, p < 0.001 \)). Hence compared to PSG, the adapted algorithm showed lower sleep efficiency (M = 80.6; SD = 6.2 vs M = 90.9, SD = 3.5; \( t_{11} = -9.85, p < 0.001 \)) and reduced sleep duration (M = 495.5; SD = 56.3 vs M = 558.8; SD = 49.2; \( t_{11} = -10.07, p < 0.001 \)), and was therefore discarded. These results further suggest that actigraphy-derived number of awakenings is not a valid indicator of sleep quality with preschoolers.

To our knowledge, most laboratories use actigraphy without calibration. In this study, when similar movements were
induced, estimated activity counts differed between the two actigraphs. The criteria for most algorithms to determine wake and sleep require absolute activity counts. Thus, for similar movements, actigraphs with higher activity counts will detect more wakefulness than those with lower activity counts. This is reflected in our data by lower sleep efficiency with adjusted than raw wrist data. Importantly however, when using ACT80 or AlgoSmooth, sleep variables derived from ankle, raw wrist, and adjusted wrist data were comparable.

Overall, the Activwatch-L appears to be an effective instrument for assessing sleep in preschoolers. However, further studies are needed to validate its ability to detect wakefulness in pediatric populations with sleep disturbances.

REFERENCES


ACKNOWLEDGMENTS

This study was supported by funding from the Fonds de Recherche en Santé du Québec (FRSQ) and the Natural Sciences and Engineering Research Council of Canada (NSERC). We thank Sonia Frenette (project coordinator), Manon Robert (research assistant), Nicolas Pellerin, and Jonathan Godbout (computer programmers) for help with data collection and analysis.

DISCLOSURE STATEMENT

This was not an industry supported study. The authors have indicated no financial conflicts of interest.
Migraine attacks are frequently preceded by premonitory signs and/or symptoms suggesting the involvement of the autonomic nervous system. In particular, symptoms of the prodromic phase (irritability, increased sensitivity to sounds, light, and smells) and symptoms and signs of attacks (nausea, vomiting, cutaneous vasoconstriction or vasodilatation, piloerection, sweating) have an autonomic basis. Several previous clinical studies investigated a possible dysfunction of the autonomic nervous system in migraineurs, but a large variety of measures have been used to assess autonomic function, and the results are consequently controversial. Sympathetic hypofunction, sympathetic instability or hyperfunction, and/or parasympathetic dysfunction have been described or suggested in migraine. Other authors reported mild sympathetic hyperactivity in migraineurs, without evidence for an impairment of the autonomic cardiovascular control. These contradictory results were probably caused by many factors that can bias autonomic function tests: age, weight, gender, test selection, test criteria, conditions of testing, and patient selection. At present, more than 30 years after the first description, the most widely used method for assessing the status of the cardiovascular sympatho-vagal balance is represented by spectral analysis of heart rate variability (HRV), which has the advantage of being noninvasive. This analysis, through the quantification of low-frequency oscillatory components (LF) and high-frequency oscillatory components (HF, synchronous with the respiratory rate, marker of vagal modulation) is used to estimate the respective role, and the balance, of the orthosympathetic and the parasympathetic components of the autonomic nervous system. Migraine has a close relationship with sleep. It is well known that the onset of migraine attacks can occur during sleep; conversely, in some patients, sleep may relieve the symptoms of migraine. On the basis of the time of onset of the attacks, some authors have defined a “sleep-related migraine,” in which the onset of attacks has a close correlation with sleep, that is, more than 75% of the attacks occur during sleep.
International Classification of Sleep disorders (ICSD 2nd edition) sleep-related migraine can be classified among the sleep-related headaches (Appendix A: sleep disorders associated with conditions classifiable elsewhere). Nevertheless, this form of migraine, defined on the basis of relation between sleep and the onset of attacks, is not coded in the International Classification of Headache Disorders - II.

Sleep induces deep modifications in the autonomic output, with a peculiar pattern of circadian and ultradian oscillations. In fact, patterns of autonomic activity undergo significant modifications through wake and sleep, through NREM and REM, and in each specific stage of sleep. These findings were confirmed in quantitative EEG and HRV studies during sleep. For these reasons, it could be hypothesized that peculiar modifications of autonomic nervous system activity, occurring during sleep, might facilitate the onset of attacks of migraine in predisposed subjects.

The aim of the present study was to investigate the modifications in the autonomic activity during sleep stages in a selected group of subjects with a very close relation between migraine attacks and sleep; this condition, in accordance with some previous reports, was called sleep-related migraine. We hypothesized that, in these patients, autonomic modification occurring during sleep stages could predispose to migraine attacks. In order to clinically define sleep-related migraine, we analyzed the sleep diaries and selected patients in whom more than 75% of the migraine attacks occurred during sleep and caused an awakening. Part of this group of patients was the object of a previous study, with the exception of triptans or non-steroidal anti-inflammatory drugs (NSAIDs) administered for the acute treatment of attacks. Exclusion criteria were heart disease, arrhythmias, or intake of cardiovascular active drugs; diabetes; uncontrolled hypertension; smoking; obesity; chronic respiratory disease; thyroid disease; psychiatric disorders; severe head trauma; and previous history of sleep disorders of any type or of other neurological diseases. The main clinical data concerning the patients’ group are summarized in Table 1.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Gender</th>
<th>Attacks per month</th>
<th>Duration of Illness</th>
<th>Comorbidity</th>
<th>Prophylaxis</th>
<th>Symptomatic</th>
<th>AHI (events/h)</th>
<th>BMI (kg/m²)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>62</td>
<td>F</td>
<td>8</td>
<td>&gt; 15 years</td>
<td>None</td>
<td>No</td>
<td>Triptans</td>
<td>3.1</td>
<td>23.7</td>
</tr>
<tr>
<td>2</td>
<td>47</td>
<td>F</td>
<td>10</td>
<td>10 years</td>
<td>None</td>
<td>No</td>
<td>Indomethacin</td>
<td>2.0</td>
<td>22.1</td>
</tr>
<tr>
<td>3</td>
<td>46</td>
<td>F</td>
<td>10</td>
<td>7 years</td>
<td>None</td>
<td>No</td>
<td>Triptans</td>
<td>1.7</td>
<td>19.8</td>
</tr>
<tr>
<td>4</td>
<td>49</td>
<td>M</td>
<td>10</td>
<td>6 months</td>
<td>None</td>
<td>No</td>
<td>NSAIDs</td>
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<td>23.2</td>
</tr>
<tr>
<td>5</td>
<td>46</td>
<td>F</td>
<td>6</td>
<td>3 years</td>
<td>None</td>
<td>No</td>
<td>Triptans</td>
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<td>22.6</td>
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<tr>
<td>6</td>
<td>48</td>
<td>F</td>
<td>8</td>
<td>1 year</td>
<td>Moebius syndrome</td>
<td>No</td>
<td>Triptans</td>
<td>3.2</td>
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<td>8</td>
<td>5 years</td>
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<td>24.8</td>
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<tr>
<td>8</td>
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<td>8 years</td>
<td>None</td>
<td>No</td>
<td>Acetaminophen</td>
<td>2.1</td>
<td>24.2</td>
</tr>
</tbody>
</table>

AHI, apnea-hypopnea index; BMI, body mass index; SD, standard deviation.

Methods

Patients

We enrolled in the study 8 consecutive patients of both genders (6 women and 2 men), aged between 30 and 62 years (mean 48.1 ± 9.3 years), fulfilling the criteria of the International Classification of Headache disorders 2nd edition for migraine without aura as well as the criteria of the ICSD for sleep-related headache. Patients were recruited from the Headache Center of the Catholic University in Rome over a period of 12 months. All outpatients, after the first evaluation, were asked to fill in a diary of headache episodes for a period of 4 weeks; this constitutes a standard procedure before defining a diagnosis and starting a prophylactic treatment. All the patients underwent a full medical and neurological evaluation, and were asked to complete a migraine diary for 2 weeks before and 2 weeks after the PSG recording.

Inclusion criteria were: (1) high frequency of attacks (≥ 5 per month) and (2) more than 75% of their attacks during sleep, causing an awakening. Episodes in which the patients presented headache on morning awakening but were not directly awakened by the pain were excluded. Other inclusion criteria were: the absence of prophylactic treatment during the study (no patient received drugs of any kind, chronically, in order to prevent the onset of migraine attacks) or in the previous 3 months; absence of pharmacological treatment of any kind in the month prior to the sleep study, with the exception of triptans or non-steroidal anti-inflammatory drugs (NSAIDs) administered for the acute treatment of attacks. Exclusion criteria were heart disease, arrhythmias, or intake of cardiovascular active drugs; diabetes; uncontrolled hypertension; smoking; obesity; chronic respiratory disease; thyroid disease; psychiatric disorders; severe head trauma; and previous history of sleep disorders of any type or of other neurological diseases. The main clinical data concerning the patients’ group are summarized in Table 1.

Controls

Heart rate variability and polysomnographic data obtained in patients were compared with data recorded in a control group of 55 healthy subjects (23 men and 32 women, mean age 54.2 ± 13.0); this population of healthy volunteers was previously enrolled to act as controls in previous sleep studies. The same exclusion criteria applied to the patients’ group were also applied to the controls. Moreover, as requested in the review process, a further comparison was performed between the patients and an age- and gender-matched control group composed of 8 subjects.
(6 women and 2 men, mean age 46.7 ± 10.7 years). All patients and controls gave written informed consent to participate. The study was performed in agreement with the Declaration of Helsinki and was approved by Ethics Committee of the Catholic University in Rome.

**Polysomnography**

Patients and controls underwent a full-night, attended, laboratory-based nocturnal video-polysomnography. In order to avoid any influence of acoustic stimuli on sleep, patients and controls slept in a partially soundproof room. Polysomnography were recorded by a Micromed System (Micromed, Mogliano Veneto, Treviso, Italy) 98 digital polygraph. Montages included 8 EEG leads applied to the following locations: Fp1, Fp2, C3, C4, T3, T4, O1, O2; reference electrodes applied to the left (A1) or right (A2) mastoids; 2 electrooculographic electrodes applied to the canthus of each eye, surface electromyography of submental and intercostal muscles, airflow measured by oronasal thermocouple, thoracic and abdominal effort, EKG (V2 modified derivation), and peripheral hemoglobin saturation. Impedances were kept below 5kΩ before starting the recording, and checked again at the end of the recording. Sampling frequency was 256 Hz. A/D conversion was made at 16 bit. Pre-amplifier amplitude range was ± 3,200 μV, and pre-filters were set at 0.15 Hz. Sleep monitoring lasted from 23:00 to 07:00 the next morning. A technician was present for data acquisition, and video monitoring was performed throughout the registration.

**Sleep Analysis**

Sleep stages were visually classified by an expert physician according to the criteria of American Academy of Sleep Medicine. The analysis of sleep-related respiratory events was made visually by an expert scorer, according to the criteria established by the AASM. Cyclic alternating pattern analysis was performed according to the standardized criteria.

**Heart Rate Variability Analysis**

Heart rate variability analysis is the measure of the variations of the interval between consecutive heart beats. It is widely accepted that heart rate variability represents a quantitative marker of autonomic activity. The variations in heart rate may be evaluated by time domain methods and frequency domain methods.

The time domain methods are based on the detection of the QRS in a normal EKG and on the determination of normal-to-normal (NN) intervals, which are all the intervals between adjacent QRS sinus complex. Time domain variables are: mean heart rate, heart rate standard deviation, the square root of the mean squared differences of successive NN interval (RMSSD), and the number of interval differences of successive NN intervals > 50 ms (NN50).

The frequency domain methods consist in the calculation of the power spectral density analysis of a plot of consecutive NN intervals, called tachogram. This power spectral density can be calculated with nonparametric and parametric methods. The parametric methods, as the autoregressive method used in this study, allow an accurate estimation of power spectral density even on a small number of samples on which the signal is supposed to maintain stationarity. Three major spectral components can be computed: very-low frequency (VLF), low-frequency (LF), and high-frequency (HF). The HF component of the spectrum is widely recognized as a measure of vagal activity, whereas the significance of LF component is more debated, and it seems to reflect at the same time both vagal and sympathetic activity. Overall, the LF/HF ratio may provide a quantitative esteem of the balance of the 2 branches of the ANS (sympatho-vagal balance). For a detailed description of the heart rate variability analysis, see: Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology.

In the present study, HRV analysis was performed during quiet wake before sleep and in the following sleep stages: N2-1C (stage N2, first sleep cycle), N2-LC (stage N2, last sleep cycle), N3, REM. For each sleep and wake stage, we selected a single time interval lasting 5 min during which no stage shift occurred. During these intervals the EKG trace was analyzed. For the analysis, we selected 5-min periods chosen with the following criteria: (1) 5 consecutive min of quiet wakefulness (W) before sleep onset, (2) first 5 consecutive min of stage 2 of NREM sleep in the first sleep cycle (N2-1C), (3) first 5 consecutive min of stage 2 of NREM sleep in the last sleep cycle (N2-CL), (4) first 5 consecutive min of stage 3 of NREM (N3), (5) 5 consecutive min of REM sleep (REM). Stage 1 NREM (N1) was excluded from the analysis because this state is considered, by definition, a stage of transition, and it is very unlikely to observe 5 consecutive min of stable N1 in polysomnographic recordings. We analyzed separately 2 intervals of N2 because this sleep stage may have deep differences when it occurs in proximity of SWS or REM sleep. In particular, it has been described as a progressive decrease in HRV sympathetic indexes during the transition toward SWS, contrasting with high and stable levels during N2 that evolves toward REM. Periods of EKG recording containing awakenings, arousals, extrasystoles, or movement artifacts were excluded from the analysis. We decided to analyze intervals of 5 min because we needed to select consecutive epochs of homogeneous recording for each sleep stage, not interrupted by stage shifts, micro-awakenings, fast-frequency EEG arousals, body movements, extrasystoles, or artifacts. Longer intervals of stable EEG and EKG recordings can hardly be observed, in particular during stages N3 and REM. Moreover, 5 min is the minimal length of EKG recording during which the signal is supposed to be stationary, thus allowing an accurate estimate of the spectral components with the autoregressive method.

Artifact rejection was performed visually. Dedicated software (Rembrandt SleepView-Medcare) calculated the RR intervals (tachogram). Another software program was used for automatic evaluation of heart rate variability parameters (HRV Analysis Software, Biomedical Signal analysis Group, Dept of Applied Physics, University of Kuopio, Finland).  HRV analysis was performed both in the time domain and in the frequency domain. In the time domain, the parameters calculated were: RMSSD and NN50; geometric measures: the NN triangular index, determined from the histogram of RR intervals, in which NN stands for normal-to-normal intervals (i.e., intervals between consecutive QRS complexes resulting from sinus node depolarization), SD1 (standard deviation of the instantaneous beat-to-beat RR interval variability, minor axis of...
the Poincaré plot), and SD2 (standard deviation of the long term RR interval variability major axis of the Poincaré plot).

In the frequency domain, HRV was analyzed using the autoregressive model (AR, model 16). The frequency bands considered were low frequency (LF, 0.04-0.15 Hz) and high frequency (HF: 0.15-0.4 Hz). The physiological explanation of the very low-frequency component (VLF, 0-0.04 Hz) is poorly defined; moreover, the very low-frequency assessed from short-term recordings is a dubious measure; for this reason the very low-frequency component was excluded from the analysis. The frequency domain parameters analyzed were therefore: the power of the LF and HF bands expressed in absolute values, normalized units, and the LF/HF ratio.

Statistical Analysis
Statistical comparisons were performed between migraineurs and controls (n = 55), as well as between migraineurs and the restricted group of matched controls (n = 8). Since HRV parameters show a skewed distribution in the general population, a nonparametric Mann-Whitney U-test was used for comparison. The test was used to compare sleep parameters between migraineurs and controls. The comparisons for categorical variables were performed by means of Fisher exact test. In case of multiples comparison, in order to avoid family-wise type I errors, a formal Bonferroni correction was applied to each family of comparisons, by dividing the limit of significance by the number of comparisons (for HRV parameters, 5 comparisons were made, in the conditions Wake, N2-1C, N2-LC, N3, REM; therefore the threshold level for significance was p = 0.05/5 = 0.01). Statistics were performed using the SYSTAT 12 software, version 12.02.00 for Windows (SYSTAT Software).

RESULTS
The diaries of migraine attacks collected by the patients in the weeks before and after the sleep study showed that all patients had ≥ 5 migraine attacks during this interval (Table 1). No patient presented migraine attacks in the 48 h before or after the sleep study. Migraineurs and controls did not differ for age (migraineurs = 48.1 ± 9.3, controls = 54.2 ± 13.0; U-test: 284.5, p = 0.183), gender (χ² = 0.572, p = 0.364) and body mass index (BMI migraineurs = 22.6 ± 1.8 kg/m²; controls = 22.6 ± 1.8 kg/m²; p = 0.465; matched controls = 20.9 ± 2.6 kg/m²; p = 0.753). No patient presented polysomnographic evidence of sleep disordered breathing (AHI migraineurs = 1.8 ± 1.0 events/h; AHI controls = 2.4 ± 1.3 events/h; AHI matched controls = 2.1 ± 0.8 events/h).

Sleep Structure
All patients had a normal night’s sleep; no patient had a migraine attack in the night of the sleep study. Patients and controls did not show snoring or other sleep-related breathing abnormalities. On average, the patients included in this study slept for 428.4 ± 43.4 min; their sleep efficiency index (total sleep time/time in bed) was 92.9% ± 3.0%; the number of awakenings > 1 min was 5.4 ± 4.0. No significant differences in sleep parameters and sleep stage composition was observed between patients and controls; only a trend towards decrease in N1 percentage was observed in patients (migraineurs = 5.5% ± 1.6%, controls = 10.8% ± 8.3%; U-test: 325, p = 0.030). As compared to controls (n = 55), migraineurs showed lower cyclic alternating pattern (CAP) rate (migraineurs = 22.8% ± 2.5%, controls = 30.1% ± 6.5%; U-test: 414, p < 0.001) and CAP time (migraineurs = 78.8 ± 8.0 min, controls = 118.3 ± 36.9 min; U-test: 354, p = 0.006). No significant differences were observed in the indexes of EEG arousals (number of arousals per hour of sleep, per hour of NREM, and per hour of REM). Mean values ± standard deviation of sleep macrostructure and microstructure parameters in patients and controls, and results of the statistical comparison, are reported in Table 2. When compared with the matched controls (n = 8), migraineurs showed no significant differences in macrostructural parameters, but they showed lower CAP rate (migraineurs = 22.8% ± 2.5%, matched controls = 47.01 ± 11.2%; U-test: 8.0, p = 0.004).

HRV: Time Domain Analysis
The most relevant difference observed in time domain concerned mean heart rate. In the migraineurs group, when compared with control group, there was a higher mean heart rate during wake (migraineurs = 69.6 ± 3.0, controls = 59.0 ± 3.3 beats/min; U-test: 7.0, p = 0.006), stage N2-1C (migraineurs = 69.3 ± 2.6, controls = 49.0 ± 2.1 beats/min; U-test: 39.0, p < 0.001), and stage N2-LC (migraineurs = 63.5 ± 7.2, controls = 53.5 ± 10.3 beats/min; U-test: 37.0, p = 0.003). Notably, no differences were observed in N3 and in REM sleep. The results of the HRV analysis in the time domain in migraineurs and control groups, with results of U-test and levels of significance, are reported in Table 3. Similar results were observed in the comparison between migraineurs and the matched control group (n = 8) (Table 4).

HRV: Frequency Domain Analysis
No significant differences in the measured parameters (LF, HF, LF/HF) were observed between migraineurs and controls in wake. In sleep stage N2, in the migraineurs group there was a statistically significant reduction of LF/HF ratio as compared to control group (migraineurs = 0.09 ± 0.01; controls = 1.49 ± 2.26; U-test: 42.5, p < 0.001); this occurred without significant modifications of the HF and LF spectral powers. The same result was observed in deep slow wave sleep N3 (migraineurs = 0.09 ± 0.02; controls = 0.78 ± 1.01; U-test: 64, p = 0.001). No significant differences were observed, between the 2 groups in REM sleep. Detailed results of the statistical comparison between migraineurs and controls are shown in Table 3; a plot of the LF/HF values in each sleep stage is shown in Figure 1. Similar results were observed in the comparison between migraineurs and the matched control group (n = 8) (Table 4).

DISCUSSION
The main result of this study is the reduction of LF/HF ratio during N2 and N3 sleep stages in migraineurs when compared with controls. As concerns sleep structure, no significant differences between migraineurs and controls were observed in sleep macrostructure; migraineurs had a lower degree of NREM sleep instability measured by CAP time and CAP rate. These latter findings have been described and discussed in a previous paper.19
General agreement exists on the functional meaning of spectral component of heart rate variability; nevertheless some matters of debate still exist. The HF component is universally considered as a marker of parasympathetic activity; whereas some doubt exist of the functional meaning of the LF component, which could be an expression of sympathetic tone or a mixture of sympathetic and parasympathetic activation.17,35 Most authors agree that the LF/HF ratio provides an esteem of the sympatho-vagal balance and its oscillations17,24,35; although this point of view has been critically reviewed and questioned by Eckberg.39 More recently, Burr demonstrated that LF and HF, expressed in normalized units, are predictable from each other, and that there is only one degree of freedom inherent in these two measures.40 With these limitations, we used the LF/HF ratio as an indicator of fluctuations of the sympatho-vagal balance during sleep.40

### Table 2—Results of the PSG study in migraineurs, controls, and matched controls, and results of statistical comparison

<table>
<thead>
<tr>
<th>PSG Parameters</th>
<th>Migraineurs (n = 8)</th>
<th>Controls (n = 55)</th>
<th>Mann-Whitney</th>
<th>Matched Controls (n = 8)</th>
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<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
<td>U-test</td>
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<td>Macrostructure</td>
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<td></td>
<td></td>
<td></td>
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<td>31.3 23.7</td>
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<td>Total sleep time, min</td>
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<td>Sleep period time, min</td>
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<td>Sleep efficiency index, %</td>
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<td>92.0 5.3</td>
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<td>91.3 5.3</td>
<td>41.0 0.345</td>
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<td>Sleep stages, %</td>
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<tr>
<td>REM</td>
<td>19.3 5.8</td>
<td>17.3 7.8</td>
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<td>N3</td>
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<td>294.5 0.124</td>
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<td>5.5 3.5</td>
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<td>14.4 6.1</td>
<td>19.0 0.172</td>
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<td>Arousal Index REM, n</td>
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<td>13.0 4.8</td>
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<td>CAP time, min</td>
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<td>118.3 36.9</td>
<td>354.0 0.006*</td>
<td>156.5 36.8</td>
<td>16.0 0.093</td>
</tr>
</tbody>
</table>

*Statistically significant differences. WASO, wake after sleep onset; CAP, cyclic alternating pattern; SD, standard deviation.

### Table 3—Results of the HRV analysis in migraineurs and controls, and results of the statistical comparison

<table>
<thead>
<tr>
<th>Time Domain</th>
<th>Migraineurs (n = 8)</th>
<th>Controls (n = 55)</th>
<th>Mann-Whitney</th>
<th>Matched Controls (n = 8)</th>
<th>Mann-Whitney</th>
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<td>SD</td>
<td>Mean</td>
<td>SD</td>
<td>U-test</td>
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<tr>
<td>Mean HR, bpm</td>
<td>69.6 69.3</td>
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<td>68.8 0.834</td>
<td>68.1 0.834</td>
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<tr>
<td>SD, bpm</td>
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<td>3.0 2.2</td>
<td>3.6 0.984</td>
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<td>RMSSD, ms</td>
<td>24.6 28.6</td>
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<td>29.1 0.834</td>
<td>29.1 0.834</td>
<td></td>
</tr>
<tr>
<td>NN50, count</td>
<td>21.8 30.4</td>
<td>52.1 43.0</td>
<td>33.1 0.834</td>
<td>33.1 0.834</td>
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</tr>
<tr>
<td>NNTI</td>
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<td>0.1 0.0</td>
<td>0.1 0.0</td>
<td>0.1 0.0</td>
<td></td>
</tr>
<tr>
<td>SD1, ms</td>
<td>17.6 20.2</td>
<td>26.9 21.0</td>
<td>20.6 0.834</td>
<td>20.6 0.834</td>
<td></td>
</tr>
<tr>
<td>SD2, ms</td>
<td>47.9 43.3</td>
<td>57.4 35.7</td>
<td>62.5 0.834</td>
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</tr>
<tr>
<td>Frequency Domain</td>
<td>W N2-1C N2-LC N3 REM</td>
<td>W N2-1C N2-LC N3 REM</td>
<td>W N2-1C N2-LC N3 REM</td>
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<tr>
<td>Abs. Power LF, ms²</td>
<td>69.8 156.2</td>
<td>149.0 93.0</td>
<td>105.4 0.834</td>
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<td>Abs. Power HF, ms²</td>
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<td>198.7 208.8</td>
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<td>HF, n.u.</td>
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<tr>
<td>LF/HF</td>
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<td>1.1 0.1</td>
<td>4.2 0.834</td>
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</tbody>
</table>

*Statistically significant differences. HR, heart rate; SD, standard deviation; RMSSD, root mean square of the differences between consecutive RR intervals; NN50, number of consecutive RR intervals differing by more than 50 ms; NNTI, NN triangular index (determined from the histogram of RR intervals, in which NN stands for normal-to-normal intervals [i.e., intervals between consecutive QRS complexes resulting from sinus node depolarization]); SD1, standard deviation of the instantaneous beat-to-beat RR interval variability, minor axis of the Poincaré plot; SD2, standard deviation of the long-term RR interval variability major axis of the Poincaré plot; Abs. Power, absolute power; LF, low frequency; HF, high frequency. N2-1C, sleep stage N2, first cycle; N2-LC, sleep stage N2, last cycle; bpm, beats per minute; n.u., normalized units.
The pattern of autonomic oscillations observed in the migraines was similar, but it was characterized by a much deeper reduction of LF/HF in NREM sleep; no difference between N2 and N3; and a greater, though not significant, rise in REM.

The functional meaning of these autonomic modifications during sleep in subjects with sleep-related migraine is not defined. It has been reported that during headache-free periods, migraineurs have a reduction in sympathetic function compared to controls, and that migraine is a disorder characterized by chronic sympathetic dysfunction.42 Seen in this view, sleep-related migraine could be a peculiar condition in which the sympathetic impairment occurs selectively during sleep, hypothesistically due to modifications of central nervous system arousability.19

Migraine attacks during sleep could be facilitated by this autonomic imbalance, and in particular by the relative prevalence of parasympathetic activity in NREM. In this case, most of the attacks should be emergent from NREM sleep stages. Alternatively, the trigger could be rapid shift from parasympathetic to sympathetic predominance which occurs at the NREM-to-REM transition. In this case, attacks should be more frequent in proximity to REM. Literature data suggest that migraine attacks can occur both in deep NREM sleep stages and in REM.43,44 No attacks were recorded in our patients.

Whatever the mechanism, these data are in accordance with our previous observation, concerning a group of patients who largely overlapped with this present sample.19 In that study we observed that migraineurs, compared to controls, had a significant reduction of NREM sleep instability (measured with cyclic alternating pattern) without modifications of the fast-frequency EEG arousals.19 It is known that CAP reflects a different arousal mechanism than that measured by fast-frequency EEG arousal.45 Essentially, slow-frequency microarousal (CAP phases type A1) and fast-frequency microarousal (fast EEG arousal and CAP phases types A2 and A3) represent state-specific

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**Table 4—Results of the HRV analysis in migraneurs and matched controls and results of the statistical comparison**

<table>
<thead>
<tr>
<th></th>
<th>Patients (n = 8)</th>
<th>Matched Controls (n = 8)</th>
<th>Mann-Whitney U-test (p)</th>
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<td>W N2-1C N2-LC N3 REM</td>
<td>W N2-1C N2-LC N3 REM</td>
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<td>69.3</td>
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<td>SD, bpm</td>
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<tr>
<td>RMSSD, ms</td>
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<td>28.6</td>
<td>37.9</td>
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<td>Abs. Power LF, ms²</td>
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<td>W N2-1C N2-LC N3 REM</td>
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<td>35.7</td>
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*pStatistically significant differences. HR, heart rate; SD, standard deviation; RMSSD, root mean square of the differences between consecutive RR intervals; N50, number of consecutive RR intervals differing by more than 50 ms; NNTI, NN triangular index (determined from the histogram of RR intervals, in which NN stands for normal-to-normal intervals [i.e., intervals between consecutive QRS complexes resulting from sinus node depolarization]); SD1, standard deviation of the instantaneous beat-to-beat RR interval variability, minor axis of the Poincaré plot; SD2, standard deviation of the long-term RR interval variability major axis of the Poincaré plot; Abs. Power, absolute power; LF, low frequency; HF, high frequency; N2-1C, sleep stage N2, first cycle; N2-LC, sleep stage N2, last cycle; bpm, beats per minute; n.u., normalized units

**Figure 1**—Plot of the mean values of LF/HF ratio in migraneurs and controls

![Graph](attachment:image_url)

n.s., not significant.
arousal responses, differently distributed along the NREM/REM cycles. Moreover, they differ in the power of autonomic effect which is associated: hierarchically, an increasing magnitude of vegetative activation is observed from the weaker slow-frequency microarousals (coupled with mild autonomic activation) to the stronger fast-frequency microarousal (coupled with a vigorous autonomic activation). Our sleep-related migraine patients seem to differ from controls essentially in the amount of slow-frequency microarousal, and this in accordance with the reduced amount of autonomic activation during NREM sleep. Taken together, these data suggest that a close correlation exists between the activity of arousal systems during sleep and the activity of the autonomic nervous system; and that in sleep-related migraine, a peculiar modification of both these systems can be observed.

It could be speculated that the hypothalamus might play a crucial role in the pathogenesis of sleep-related migraine. First, hypothalamus has a major role in regulation of autonomic activity. Second, neuroimaging studies have demonstrated that hypothalamic dysfunction may cause migraine attacks. Finally, the hypothalamus is a part of the arousal system. Experimental evidence indicates that regulation of autonomic functions and nociceptive processing are closely coupled in the hypothalamus and by means of the orexigenic transmission. Thus, the orexigenic system in the posterior hypothalamus is modulated by the biological clock and the cortex, and is involved in the modulation of dural nociceptive transmission. Moreover, it is well known that the posterior hypothalamus, as well as the orexigenic pathways, are involved in the regulation of wake, sleep, and arousal. Therefore, we are proposing that a hypothalamic dysfunction, probably involving the orexigenic system, is responsible for the link between the pain of primary neurovascular headaches, the autonomic dysfunction, and the reduced arousability.

In conclusion, in the present study we observed concurrent modifications of NREM sleep instability (CAP) and autonomic modulation during sleep in patients with sleep-related migraine. This is in accordance with a bulk of observations which consider the hypothalamus, where arousal-related and autonomic relays are located, a crucial structure in the pathogenesis of migraine attacks. This is analogous to what happens in another primary neurovascular headache, the autonomic dysfunction, and the reduced arousability.

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Cataplexy is a symptom of narcolepsy triggered by strong emotion that causes sudden muscle atonia with preserved consciousness. It may represent intrusion of REM sleep phenomena into wakefulness. A refractory period of up to several hours typically follows a cataplexy attack. Persistent cataplexy, known as status cataplecticus, is a rare, often misdiagnosed manifestation of cataplexy. Failure to recognize this condition can lead to unnecessary diagnostic testing that delays appropriate therapy.

Tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), and serotonin-norepinephrine reuptake inhibitors (SNRIs) prevent cataplexy by inhibiting “REM-on” neurons in the lateral dorsal tegmentum (LDT) and pedunculopontine tegmentum (PPT). The precipitous decrease in noradrenergic and serotonergic activity may reduce cataplexy by disinhibiting “REM-on” neurons. Interestingly, discontinuation of sodium oxybate, another anti-cataplexy medication that may exert its effect via GABAB receptors, has not been associated with status cataplecticus.

REPORT OF CASE

A 76-year-old female was evaluated 20 years ago for hypersomnolence and “irresistible sleep attacks” that began during adolescence. She experienced sleep paralysis but denied hypnagogic or hypnopompic hallucinations. Strong emotion such as anger, happiness, or excitement often precipitated slurring of speech, flattening of facial expression, and leg weakness. She cannot recall whether cataplexy appeared concurrently or after onset of somnolence. Medical history was significant for hypertension treated with lisinopril. Polysomnography demonstrated a normal apnea-hypopnea index. Multiple sleep latency testing revealed a mean sleep onset latency of 3 minutes with 3 sleep-onset REM periods. She was HLA-DQB1*0602 positive. CSF hypocretin levels were not obtained. The diagnosis of narcolepsy with cataplexy was made at age 56, nearly 40 years after symptom onset.

Status cataplecticus is a rare manifestation of narcolepsy with cataplexy episodes recurring for hours or days, without a refractory period, in the absence of emotional triggers. This case highlights a narcoleptic patient who developed status cataplecticus after abrupt withdrawal of venlafaxine.

Initial treatment consisted of imipramine and methylphenidate. Persistent cataplexy and hypersomnolence prompted a change to sodium oxybate and modafinil with almost complete resolution of symptoms. Sodium oxybate (9 grams nightly) was continued for seven years until she reported somnambulism and nocturnal sleep eating with multiple falls. As these were likely NREM parasomnias associated with sodium oxybate, anti-cataplexy therapy was changed to venlafaxine ER 75 mg/day. Cataplexy persisted, but further increase in venlafaxine was precluded by worsening hypertension, an adverse effect of venlafaxine. Fluoxetine 20 mg was suggested. The following day, she developed gastroenteritis; while she continued venlafaxine, she reported emesis shortly after taking medication. The next day, emotional upset triggered cataplexy, consisting of slurred speech and weakness in all extremities; this was witnessed by her family. Unlike her usual cataplexy episodes which rapidly resolve, she experienced continuous cataplectic attacks over the next 4 h, despite absence of further emotional triggers. She maintained consciousness throughout but recalled vivid hallucinations. Fluoxetine was ineffective; upon resuming venlafaxine, cataplexy resolved within several hours. Neurologic examination was not performed during status cataplecticus but was normal the following day after resolution of cataplexy.

DISCUSSION

Our patient experienced status cataplecticus within 48 hours of abrupt withdrawal of venlafaxine, due to diminished absorption from gastroenteritis. The resultant rapid decrease in noradrenergic and serotonergic tone may have precipitated status cataplecticus. Status cataplecticus has been reported in narcoleptic patients after abrupt withdrawal of clomipramine, a serotonergic reuptake inhibitor that augments adrenergic tone via its metabolite, desmethylclomipramine. Protracted episodes of cataplexy have also been reported after gradual withdrawal of TCAs and SSRIs, peaking 40 to 60 days after discontinuation. Status cataplecticus may also occur with administration of prazosin, an α-adrenergic antagonist.

While the neurophysiologic basis of cataplexy remains unclear, decreased hypocretinergic activity with reduced noradren-
ergic tone, possibly from decreased activity of locus coeruleus neurons, may contribute to decreased motoneuron excitation during cataplexy. Dysfunction of other neurotransmitters, including dopaminergic systems, may also contribute to cataplexy.6

Status cataplecticus is a rare complication in narcolepsy resulting from abrupt discontinuation of noradrenergic and serotonicergic medications. Behavioral management restricting social interaction to minimize cataplexy triggers, and limiting ambulation, may be helpful during status cataplecticus. Anti-cataplexy medications, with individualized risk-benefit analysis regarding adverse effects, such as parasomnias and fluid retention from sodium oxybate, hypertension from venlafaxine, and anticholinergic effects from clomipramine are necessary. First line therapy for cataplexy is sodium oxybate; however in this case, risk of falls from somnambulism in an elderly woman outweighed benefits. Venlafaxine ER was reinitiated and gradually increased to 150 mg/day with resolution of cataplexy; escalation of antihypertensive therapy controlled blood pressure.

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Numerous medical disorders, including obstructive sleep apnea, may cause nocturnal diaphoresis. Previous work has associated severe obstructive sleep apnea with nocturnal diaphoresis. This case report is of import as our patient with severe nocturnal diaphoresis manifested only mild sleep apnea, and, for years, his nocturnal diaphoresis was ascribed to other causes, i.e., first prostate cancer and then follicular B-cell lymphoma. Additionally, it was the nocturnal diaphoresis and not more common symptoms of obstructive sleep apnea, such as snoring, that led to the definitive diagnosis of his sleep apnea and then to treatment with a gratifying resolution of his onerous symptom.

**Keywords:** Diaphoresis, sleep apnea

**Citation:** Vorona RD; Szklo-Coxe M; Fleming M; Ware JC. Nocturnal diaphoresis secondary to mild obstructive sleep apnea in a patient with a history of two malignancies. *J Clin Sleep Med* 2013;9(7):717-719.

Diverse medical disorders including malignancies, infections, and endocrine abnormalities have been associated with nocturnal diaphoresis. Nocturnal diaphoresis may occur in obstructive sleep apnea syndrome (OSAS). Nevertheless, research has been limited and findings mixed. One study found night sweats to be associated with snoring and sleepiness but not apnea-hypopnea index (AHI). Excessive nocturnal diaphoresis occurred in 34% of patients with severe OSAS ([AHI] = 52). Our case is instructive as our patient’s severe nocturnal diaphoresis occurred with mild OSAS and was not clearly connected to his two malignancies.

**REPORT OF CASE**

A 67-year-old male first manifested diaphoresis in 2002 following a radical prostatectomy for T2N0MX prostate cancer. His clinicians reassured him that diaphoresis, common after surgery, should resolve.

It worsened; the patient often soaked through clothing and slept on a towel. Endocrine evaluation was negative. A negative QFT Gold Test for tuberculosis, negative HIV test, normal erythrocyte sedimentation rate test (1), and normal testosterone level (444) were obtained in 2010. However, follicular B-cell lymphoma was diagnosed (1/2011) and thought the likely cause of profuse, almost nightly sweats. The Rituximab treatment for lymphoma (3/2011) did not improve his diaphoresis. The patient’s oncologist recommended sleep medicine consultation.

The patient presented 6/2011 to sleep medicine with a chief complaint of “severe night sweats that have gotten progressively worse over the last 12 months.” Sweating was most apparent 02:30 until 04:00. His registered nurse wife noted infrequent snoring and pauses in respiration. He denied restless sleep. Epworth Sleepiness Scale score was normal (5), though he felt tired upon arising after 7-8 hours in bed. He used minimal alcohol and no caffeine. He ceased smoking cigarettes in 1975 and reported a comfortable bedroom temperature.

Past medical history: Prostate cancer history (treated first with surgery, then with radiation therapy in 2006 for micro-metastatic disease), follicular B-cell lymphoma, radiation cystitis, coronary heart disease, supraventricular and ventricular dysrhythmias (dronedronerone previously stopped given concerns it contributed to diaphoresis), pacemaker implantation, adenomatous colon polyps with dysplasia, pneumonia, previous left upper extremity thrombophlebitis, gastroesophageal reflux disease (GERD), Barrett’s esophagus, and distant tonsillectomy history.

Medications (at time of initial sleep center visit) included clopidogrel, niacin, atorvastatin, aspirin, flecainide, pantoprazole, lubiprostone, glucosamine/chondroitin, and fish oil.

Review of systems demonstrated no recent change in weight, no history of diabetes mellitus or thyroid disease, and some difficulties with memory and concentration.

Exam demonstrated a tall, slender male with normal respiratory rate and pulse. Upper airway exam revealed no frank anterior septal deviation. He had a large tongue, borderline class III malocclusion, Mallampati IV, retrognathia, and 15-inch neck circumference. Neck exam revealed normal thyroid, and no cervical, supraclavicular, or axillary adenopathy. Cardiopulmonary exam: normal lung sounds and heart tones, and a pacemaker. There was no cyanosis, clubbing, or edema.

The patient’s diagnostic and continuous positive airway pressure (CPAP) polysomnographic data are presented in Table 1. By numeric indices, the patient’s diagnostic study manifested mild apnea that was more pronounced in stage R sleep. Pre and post blood pressures were normal at 109/67 and 104/64, respectively. Esophageal pressure monitoring and ambulatory blood pressure monitoring were not done as part of the patient’s clinical evaluation.
The CPAP titration study revealed control of the patient’s apnea and improved oxygen nadir. Blood pressures pre and post study, respectively, were again normal at 101/63 and 99/57. In neither study was there evidence for other sleep pathology such as periodic limb movements of sleep.

The patient began CPAP at 9 cwp. At 1-month follow-up, he noted near-disappearance of nocturnal diaphoresis. Diaphoresis had taken a few days after CPAP initiation to dissipate. Medications including niacin remained unchanged. A CPAP download revealed that during the first month (7/12/11-8/10/11), the patient used the machine 5 h 45 min per night, with 87% of the time ≥ 4 h and with an AHI of 2.9 on 9 cwp. His daily records for the preceding month indicated no night sweats save for “moist” neck area and armpits on 3 nights.

Endocrinology work up (8/2011), requested by the patient’s oncologist, revealed normal renal, hepatic, and glucose levels. The overall thyroid panel suggested “borderline low” thyroid function, yet TSH was normal (2.94).

His last visit (8/2012) revealed continued control of his diaphoresis with CPAP therapy. He noted some diaphoresis and snoring with CPAP interface slippage.

A CPAP download from 7/8/11-8/1/12 revealed that the patient used his CPAP machine an average of 5 h 8 min per night, with 77% of the time ≥ 4 h and with an AHI of 1.6 on 9 cwp.

At one and a half years post CPAP initiation, on phone communication, the patient believed his diaphoresis was still dramatically improved. The patient stated that if he stopped CPAP that the first night he would sweat only modestly. With CPAP discontinuation for a few days, he noted that increasingly severe diaphoresis ensued.

### DISCUSSION

Firstly, this report illustrates the importance of not excluding OSAS from the differential diagnosis of nocturnal diaphoresis, despite other more obvious potential etiologies. Secondly, this case indicates that even mild OSAS may result in severe diaphoresis, extending findings regarding its presence in severe OSAS. Thirdly, CPAP both treated mild OSAS and resolved the troubling night sweats. This case emphasizes the onerous nature of diaphoresis in OSAS, even when unaccompanied by more typical symptoms, such as prolific snoring and sleepiness. In this case, severe nocturnal diaphoresis was our primary clue to the presence of OSAS.

It is possible that the AHI underestimated the patient’s degree of respiratory instability and that the patient may have had concomitant respiratory event related arousals (RERAs). However, a careful review of the raw data did not reveal evidence for RERAs. For example, the patient’s breathing was usually in-phase, and the intercostal electromyogram signals were almost exclusively quiet. We did not see subtle out-of-phase breathing terminating in arousals. The normal arousal index also argued against our missing subtle upper airway events.

Sleep stages have been associated with different predispositions to diaphoresis. For that reason, we looked for changes in stage N3 sleep (the stage with greatest diaphoresis) and stage R sleep (the stage ostensibly with the least) that might have explained his diaphoresis and response to therapy. We found no explanation in our review of the sleep architecture (please see minutes of stage R for each study in Table 1. The patient had no stage N3 on either study).

We did not analyze heart rate variability (HRV), a measure of autonomic function. With only one night in each condition, selecting samples for analysis while controlling for proximity of apnea events, proximity of arousals, sleep stage, and time of night was beyond our capability.

The severe night sweats in this patient with mild OSAS were noteworthy. Few studies have investigated diaphoresis in OSAS. Electrodermal activity has also been utilized to probe this relationship in patients with severe apnea (AHI = 45.3). These findings, however, may not be generalizable to our patient, who had much milder apnea. Future studies aimed at assessing the prevalence of diaphoresis in mild OSAS and clarifying its pathophysiological basis may be warranted. Perhaps this severe diaphoresis reflects individual variability, just as some patients with mild OSAS by numeric indices may have severe sleepiness. The patient’s sympathetic nervous system may have been more sensitive to the impact of OSAS, and the sweating may have reflected heightened autonomic activity. The association of autonomic dysfunction with mild OSAS was previously reported in 2004, and in 2008, systolic non-dipping of blood pressure was reported to be associated with sleep apnea, even mild apnea.

Finally, this patient had a history of GERD. GERD has itself been reported to cause nocturnal sweats, to be comorbid with OSAS, and improved by CPAP. While the improvement of diaphoresis by CPAP may have been due to GERD reduction, the patient presented to the sleep center with diaphoresis notwithstanding use of a proton pump inhibitor. Thus, CPAP treatment of OSAS was likely primarily responsible for the gratifying response described herein.

### REFERENCES


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**Table 1—Summary of polysomnographic data**

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aHypopneas defined as: ≥ 30% decline in tidal volume for ≥ 10 seconds associated with ≥ 4% oxygen desaturation. bThe AHI on the CPAP titration study of 6/22/11 is averaged over all CPAP pressures.

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Defending Sleepwalkers with Science and an Illustrative Case

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Objective: To test whether laboratory-based research differentiating sleepwalkers (SW) from controls (C) can be applied in an uncontrolled forensic case as evidence the alleged crime was committed during an arousal from sleep in which the mind is not fully conscious due to a SW disorder.

Methods: A PSG study recorded 8 months after the defendant was charged was analyzed independently by spectral analysis. Slow wave activity (SWA) and cyclic alternating pattern (CAP) rates were computed. Clinical interviews and police records were reviewed for data re: the defendant’s sleep prior to the event and use of drugs, alcohol, and stimulants.

Results: The SWA distribution was abnormally low and flat, significantly lower than published controls; in the first NREM cycle, CAP rate 55 was above normal. Two weeks of prior sleep deprivation was confirmed from interviews and defendant’s observed daytime sleepiness. Caffeine intake the day before the event was calculated at 826 mg over 14 hours. Snoring and a mild breathing disorder were present in the PSG.

Conclusion: Testimony based on spectral analysis of PSG recorded following an alleged criminal event supported a SW explanation for the non-rational behaviors charged. The defendant was acquitted of all charges and has been successfully treated.

Keywords: Sleepwalking, spectral analysis, slow wave activity, sleep deprivation, caffeine

Citation: Cartwright RD; Guilleminault C. Defending sleepwalkers with science and an illustrative case. J Clin Sleep Med 2013;9(7):721-726.

INTRODUCTION: BACKGROUND PRIOR TO 2000

In 1987 and 1997, two highly publicized cases of first degree murder occurred in which there was no doubt the accused was the one who committed the crime.1,2 Nonetheless, a question was raised: were they guilty under the law? The question of guilt is based on the principle of mens rea; was the person’s mind conscious at the time? In both cases, the aggression took place following an arousal from sleep and was followed by profound amnesia and regret for what had happened. In both cases, the defense argued the accused was in a non-conscious state due to a sleepwalking (SW) disorder. One case was acquitted the other convicted. Since then, both prosecuting and defending lawyers have sought the advice of Sleep Medicine specialists for their opinion asking: is this a case of non-conscious behavior due to a sleep disorder? This has prompted a strong push-back from some in the Sleep Medicine community, denying there is a valid basis in sleep science for an opinion in such cases.3,5

Sleep Medicine was then relatively new as a clinical profession. The research supporting a diagnosis of several major sleep disorders was strong enough that experienced clinicians, supported by data from the polysomnogram (PSG) revealing the presence of specific sleep abnormalities, could make a diagnosis and recommend a treatment with confidence. An exception was a group of disorders that, although common in young children, were rarely sustained into adulthood, and so escaped systematic attention. These are the non-rapid eye movement (NREM) parasomnias. A landmark study by Broughton11 identified a number of their common features. Primary is that these arousals occur early in the major sleep period, prior to REM, when the PSG shows sleep to be in slow wave sleep (SWS), (also called delta sleep or stages 3 and 4 sleep). It is one of this class, SW, that has been the focus of concern about Sleep Medicine clinicians testifying in legal cases of adults. The basic issue is that SW is episodic; therefore, there can be no certainty that an individual, even one genetically vulnerable to such events,5,9 was sleepwalking at the time of the offence.

In fact, prior to 2000, the PSG was of limited value in differentiating an adult SW from a normal sleeper. Although SW have more frequent arousals from SWS than normal sleepers,9 this sleep instability had been observed in patients with other diagnoses such as obstructive sleep apnea (OSA).10 Therefore, once the many other possible diagnoses that might account for an alleged non-conscious episode of a defendant had been ruled out,11 sleep experts pre-2000 had to decide for themselves in this case likely to be one of sleepwalking or not. Most often the cases that came to trial were those involving aggressive behaviors inflicted on another person. More recently, persons charged with non-consensual sexual behavior (sexsomnia)12 have also become court cases, as have others in which the charge was unlawful entry with intent to commit robbery or rape.13 Other activities common during a SW such as sleep eating, protecting others, and exploring are unlikely to result in a criminal charge.

Without a clear diagnostic sign in the PSG, sleep experts acting for the defense were likely to base their testimony on their judgment of the accused’s truthfulness during a pre-trial interview, a history of prior witnessed SW, and the similarity of their behaviors before, during, and following the event to those in published case studies. Some of these characteristics were based on formal research, such as early SWS arousal with long lasting confusion and amnesia following,6 while others were extracted...
from a review of published case reports, showing non-rational behavior during the episode, amnesia, perplexity, and regret afterward.14 These became the basis of the formal clinical diagnosis of SW for the American Academy of Sleep Medicine15 and of the American Psychiatric Association.16

Sleep experts who acted for the prosecution were more likely to base their testimony on their judgment that the accused’s actions were premeditated; motivated by a prior negative relationship with the person attacked; or, in the case of sexual behaviors, that the accused took advantage of an opportunity that presented itself. In some cases the prosecution’s sleep expert argued the act was not sleep-related but planned during wakefulness and carried out while the accused was fully conscious.17 If the accused had been drinking alcohol prior to the event, the prosecution’s expert held that this was a voluntary behavior and therefore the accused was legally responsible for any aggressive or sexual acts that took place subsequently, even if these followed an arousal from SWS.18

SLEEP SCIENCE POST 2000

This difficulty concerning proof of SW changed in 2000 with the publication of two independent studies reporting new PSG findings in sleepwalkers not found in age- and gender-matched controls.19,20 A third study reporting the same major findings followed in 2001.21 These studies were carried out by independent investigators in different laboratories, in different countries. All three reported the same two significant differences.

SW demonstrated more disrupted sleep, whether reported as microarousals, wake after sleep onset (WASO), arousals, awakenings, or an abnormal amount of cyclic alternating pattern (CAP A2 and A3).22 This sleep fragmentation was significantly higher in the SWS of the SW than in the C groups. Figure 1 shows CAP episodes preceding a SW event recorded in the Stanford laboratory. Difficulty maintaining sleep in the first third of the night could now be considered a characteristic of a NREM parasomnia, as it was observed in all three studies to be significantly higher in SW than in C subjects only in the first third of the night, when most SW events occur. Those who arouse from REM sleep, REM behavior disorder (RBD), may also be aggressive but differ in demographics and PSG characteristics from NREM SW, and none have to date become published forensic cases.

The second finding is a difference in the amount of SWA. This is lower throughout the night in SW than in matched controls and is significantly lower in the first NREM cycle. The analysis of the PSG responsible for this finding is not the Rechtschaffen and Kales (R&K)23 delta percent but the more precise spectral analysis scoring (fast Fourier transform [FFT]) yielding the count of SWA in each NREM cycle.

These new findings did not, however, settle the concern expressed about sleep experts testifying in court, as stated in a recent publication, “…there is absolutely no after-the-fact poly-

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**Figure 1**—Example of CAP incidents prior to a sleepwalking event.

![CAP incidents prior to a sleepwalking event](Courtesy of C. Guilleminault).
somnographic finding that could possibly have any relevance as to whether the accused was sleepwalking at the time of the event in question.”24 This overlooks the extensive literature that spectral analysis scoring shows high reliability within individuals to reproduce their profile of the frequency of the various EEG wave forms across non-consecutive nights, including the delta power, under normal and sleep deprivation conditions.25-28 The objective of this study is to test the SWA in a forensic case to determine if it was significantly low in the first NREM cycle and if that indicated the presence of a predisposing condition and possibly a sleep problem which could be treated.

**AN ILLUSTRATIVE CASE**

In 2007 a patient, CD, on advice of his lawyer, presented to a sleep laboratory for an evaluation of SW. He was turned down as a patient because his SW was the issue in a pending legal case. The patient then applied to the Sleep Disorder Service at Rush University Medical Center where he was seen by two senior clinicians, both boarded in Sleep Medicine, a neurologist and a psychologist. The patient’s wife (LD) also attended the intake interview.

The initial exam showed CD to be a 39-year-old Caucasian male, height 70 inches, weight 187 pounds, with body mass index (BMI) = 26.8, married for 10 years and father of 3 children. He gave a childhood history of frequent episodes of SW, as did his elder brother. These were witnessed by both parents and by each other (as they shared a bedroom). The patient reported his SW persisted into his adult years, with frequent episodes witnessed by his wife and by her parents. Another witness, a physician, observed CD during a SW episode when they shared a hotel room during a trip to attend an athletic event. Although the episode was benign, CD walked about muttering to himself in a confused manner during a trip to attend an athletic event. Although the episode was benign, CD walked about muttering to himself in a confused state, the physician reported that episode to their local police as a safety precaution. LD reported her husband rarely walked outside prior to the episode for which he was now charged. No violence was involved in any of his episodes. His usual behavior was described as patrolling the house after having been aroused by a noise not heard by others. He sometimes moved objects in a non-rational manner. For example- before the expected third child was born, CD placed a clock into an empty cradle in a non-rational manner. For example- before the expected birth of third child. The baby arrived during that visit.

The family stayed on another week; then CD, whose work required his presence, returned home alone. This was Thanksgiving weekend; neighbors on either side of his house were away and had asked him to check on their homes as he usually did during their absence turning on lights to discourage intruders. CD performed this task the evening following work. Because he was responsible for a special program from 6 to 9 PM, he did this later than usual. CD rarely drank alcohol and had none that day but did drink many caffeinated beverages. He explained his unusually high caffeine intake by his need to stay alert at work following his considerable sleep loss the week before and the week following the birth, when he took over responsibility for the nighttime care of his 3- and 5-year-old children. The 5-year-old had multiple medical problems and difficulty sleeping requiring nighttime attention and medication.

On the Rush Sleep Center intake forms, CD listed he consumed ten large caffeinated drinks the day of the alleged SW event: two mugs of coffee at breakfast, two additional coffees between 9 AM and 11 AM, and two Diet Cokes in the afternoon; and during the evening program he drank “large tumblers” of Diet Pepsi. The total caffeine consumption was estimated to be 826 mg over a 14-h period.29 Studies of the effect of 600 mg of slow-release caffeine show it promotes wakefulness following sleep deprivation and improves vigilance.30 As caffeine blocks adenosine receptors, it inhibits sleep onset and sleep maintenance and reduces the amount of slow wave sleep and SWA in the first sleep cycle.31,32 High caffeine intake has been implicated in SW with violence.2,31

**The (Alleged) Sleepwalking Event**

A reconstruction of the event presented at the trial was based on the detectives’ interviews of CD, the complainant, the daughter (EF) of the family living opposite him and her boyfriend. CD recalled having difficulty sleeping that night. He remembers arising at about 3 AM and again later on hearing a noise. On looking out a window, believed he saw lights on in the house facing him and the front door standing partly ajar. He felt duty-bound to investigate. He crossed the street and entered through the unlocked front door. He then wandered from room to room checking for intruders. He believes he turned off the kitchen light then looked into the master bedroom. The room was very dark, but he heard EF whisper and then shout to the sleeping boyfriend to turn on the light. When the light came on CD ducked down at the foot of the bed but then arose and identified himself as her neighbor. She told him to get out. He left but wandered into the kitchen. She then got up, guided him to the door, watched while he crossed the street and entered his house. He stated he then went back to sleep, woke in the morning with no memory of the incident, and went to work. EF reported that she awoke feeling someone stroking her abdomen under the covers. She confirmed that he wandered into the kitchen, and she then led him out via the front door and went back to sleep. She did not call 911, did not tell her boyfriend about the “touching,” and was not afraid of CD when guiding him out. When her mother returned next morning, EF told her about the intruder. She described the touching as a tickling sensation, then as soft stroking under her pajamas but not under her panties. Her mother phoned the police who contacted CD to get his statement. He was surprised to hear that he was reported to have made a sexual attack, which he repeatedly denied. He waived his Miranda rights and told the police that he was not near her when the light came on. The boyfriend reported his impression of someone feeling his bedcovers. CD explained that he was being a Good Samaritan, wanted to apologize for the intrusion, and about his history of sleepwalking. The police had the physician’s report of CD’s previous event. CD believed that would be the end of it. Instead he was charged with criminal trespassing, criminal sexual abuse, and a felonious attempt to commit rape. His lawyer advised a sleep study.
The PSG Performed at Rush Sleep Center

Two nights of recording were ordered; the first a standard clinical night to rule out obstructive sleep apnea (OSA), as CD had a history of loud snoring. That study, performed on 8/16/2007, was scored according to the criteria of Rechtschaffen and Kales, and the arousals by the American Sleep Disorders Association Atlas (Figure 2). The scoring was approved by the attending neurologist. His report in summary read: “The study and clinical history is consistent with mild positional obstructive sleep apnea syndrome.” The sleep efficiency was low (60%) and sleep latency long (31 minutes); SWS% was low (3.6%), and arousals per hour moderately high (18.1). The oxyhemoglobin desaturation nadir was normal at 93%, and apnea+ hypopnea index 4.1 occurred only when supine. No periodic limb movements were recorded. The second night was to have CD undergo 25 hours of sleep deprivation while matching his reported excessive caffeine followed by 7 hours of recovery sleep. This would mimic the conditions the night of his intrusion event and maximize the possibility he would exhibit a SW episode in the laboratory. However, this plan required approval of the University Research Committee, and CD and his wife could not wait for this approval as the trial date was imminent.

The defense attorney requested the senior author, who had previous experience at SW trials, to act as a sleep expert for the defense. In the absence of further data, she reviewed the data in hand against the criteria for sleepwalking. The one central to the diagnosis—that the arousal typically occurs from SWS within the first or second REM cycle—could not be confirmed. CD had no episode during his diagnostic night and was not able to state conclusively his bedtime on the night of his event. His best guess was that this was later than usual as he had worked late and checked both neighboring houses before entering his home. He thought this was probably sometime close to or after midnight. Given the amount of caffeine he reported drinking that day, it was not possible to estimate the time to sleep onset nor the amount or depth of sleep he achieved before his behavioral arousal. CD’s wife was not able to report definitively whether his SW episodes typically took place early in the night or later, as she frequently slept separately due to his loud snoring. The best evidence of the time the intrusion occurred was given by the complainant, EF, who checked the clock when she awoke feeling she was being touched. It was between 4:30 and 5 AM.

The report confirmed CD had abnormally low SWS in the first NREM cycle. Esper et al. hypothesized that a low SWA results in an overt SW arousal if two further conditions are met: (1) there is pressure for more SWS (as follows sleep deprivation), and (2) there is a concurrent stimulus for increased arousal from SWS. This may be from a medication or substance such as excessive caffeine, from an untreated breathing disor-

Figure 2—Hypnogram and distribution of arousals in PSG of CD

The Independent Blind Scoring of SWA

A disk of the digitized sleep study was sent to Stanford where it was scored by three physicians; first by the second author, then by a visiting assistant professor of neurology and by a visiting research fellow who scored the record for the CAP frequency. Their final report received on 3/03/08 read: “Here are the data from the patient you can use as the official report. The delta power was calculated to determine the total per sleep cycle. The FFT was performed on the C3/A2 signal with a Hamming window applied. Two second windows were averaged over 30 epochs. Artifacts were first rejected. The results are clearly abnormal in distribution and with low delta power during the first sleep cycle. This is similar to what has been described by Gaudreau et al. and what we ourselves found in sleepwalkers (Guilleminault et al.).” Attached were the data in graphic form (Figure 3). These data points were plotted against those reported in the Gaudreau study (Figure 4). Additional findings were “The CAP rate was abnormally high at 55. The rate for normals in our lab is 32-35 for those of similar age.”

The report confirmed CD had abnormally low SWS in the first NREM cycle. Esper et al. hypothesized that a low SWA results in an overt SW arousal if two further conditions are met: (1) there is pressure for more SWS (as follows sleep deprivation), and (2) there is a concurrent stimulus for increased arousal from SWS. This may be from a medication or substance such as excessive caffeine, from an untreated breathing disor-
The jury listened attentively. The prosecuting attorney cross-examined to clarify whether CD was fully conscious when he responded to the light being turned on by first hiding then identifying himself. These points were addressed, citing CD’s continued mental confusion and failure to recall the event on waking. The jury returned a verdict of not guilty on all counts.

DISCUSSION

Laboratory-based research identifying SWA as differentiating SW from normal sleep using spectral analysis was replicated in a forensic case. The additional history of snoring and mild breathing disorder validated in the PSG may be a contributing cause of his low SWA, high CAP rate, and arousal into non-conscious acts when sleep deprived and over-caffeinated.

The jury returned a verdict of not guilty on all counts.

These data constituted the basis for the opinion that the defendant was likely in a non-rational state due to SW at the time of the events charged, even though the PSG was conducted eight months after the event. Those who have warned sleep medicine clinicians not to testify in forensic cases, stating this would be tantamount to practicing “junk science,” may not have been aware of the research establishing the reliability of the sleeping brain wave profile using spectral analysis. The application of relevant science, including spectral analysis scoring of PSG, should become integrated into the guidelines recommended for those serving as sleep experts. An unfortunate aim of the critical literature has been to discourage research given the description of these efforts as “attempts to ‘stimulate’ sleepwalking in the laboratory (by sleep deprivation, medication administration, or alcohol ingestion) are completely worthless and totally inappropriate.”

There is, for example, a strong need for research involving larger samples to clarify disparate findings between studies with small samples.

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ACKNOWLEDGMENTS

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DISCLOSURE STATEMENT

This was not an industry supported study. The authors have indicated no financial conflicts of interest. The senior author acted for the defense pro bono.
A 30-year-old man with past medical history of asthma presented for evaluation of nocturnal shortness of breath and daytime fatigue. His medications included an albuterol inhaler used as needed, fluticasone-salmeterol discus inhaler used daily, and cetirizine used daily. He smoked half a pack of cigarettes each day. Physical exam revealed an obese man with a body mass index of 33. Cardiac and respiratory exam were unremarkable.

A split-night polysomnogram (PSG) was performed. During the diagnostic portion of the PSG, total sleep time (TST) was 173 min, sleep onset was 3 min, sleep efficiency was 90%, wake after sleep onset was 16 min, TST apnea hypopnea index (AHI) was 5.9, and REM AHI was 85.7. During the titration portion of the PSG, sleep disordered breathing resolved at continuous positive airway pressure of 11 cm.

PSG review revealed an electrocardiogram (ECG) finding shown in Figure 1A, with an enlarged view of the relevant ECG shown in Figure 1B.

**QUESTION:**
What is the significance of this ECG finding?

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(A) Electrocardiogram (ECG) finding on polysomnogram (PSG). (B) Enlarged view of the ECG2 channel from the PSG.
DISCUSSION

Cardiac arrhythmias are the most common severe adverse effect encountered on nocturnal PSG. The severity of the cardiac arrhythmia noted on PSG may correlate with the apnea severity, especially in men, and may be seen more frequently in those with comorbid cardiac disease. It is critical for sleep technologists to recognize these events and take appropriate action.

The American Academy of Sleep Medicine (AASM) Manual for Scoring of Sleep and Associated Events (Scoring Manual) recommends the use of a modified Lead II (ECG2) for cardiac evaluation with two ECG electrodes: one on the right upper chest and another on the left lower chest. In our sleep laboratory, we apply three ECG electrodes: on the right upper chest, the left upper chest, and the left lower chest. The software in our PSG system (Alice 5, Respironics, Inc., Murrysville, PA, USA) allows the display of six ECG channels—three bipolar channels and three augmented channels (Figure 3). The three bipolar channels are Lead I (ECG1) consisting of both upper chest electrodes; Lead II (ECG2) consisting of the right upper chest and the left lower chest electrodes; and Lead III (ECG3) consisting of the left upper chest and left lower chest electrodes. The augmented leads are calculated post-acquisition and do not require the use of additional electrodes (Table 1). The use of multiple ECG channels allows the sleep physician the opportunity to more fully evaluate ECG rhythms and avoid electrodes contaminated by artifact.

Pseudo-ventricular tachycardia (VT) associated with tremor like movements has been previously reported. Three signs are useful in the identifying tremor/movement induced pseudo-VT on ECG: the sinus sign, the spike sign, and the notch sign.

The sinus sign in pseudo-VT is the presence of a normal sinus rhythm with normal P, QRS, and T waves in either a bipolar lead or an augmented lead during an apparent episode of VT. This is due to the fact that one of the upper limb electrodes is free of movement artifact.

The spike sign in pseudo-VT is the presence of regular or irregular spikes among the wide-complex QRS artifact that represents the superimposition of a normal sinus rhythm QRS complex during the vent.

The notch sign in pseudo-VT is the presence of a superimposed notch on the wide-complex QRS artifact that also represents the superimposition of a normal sinus rhythm QRS complex during the event.

In Figure 3 we can see the spike sign interspersed among the pseudo-VT wide-complex QRS artifact. In PSG interpretation, prompt evaluation of both the video recording and the patient’s status is also recommended. Our patient was medically stable throughout the course of the recording.
CLINICAL PEARLS

1. Scratching can produce a pseudo-ventricular tachycardia artifact on electrocardiography (ECG) monitoring.
2. The sinus sign, the spike sign, and the notch sign are useful in the identification of movement induced pseudo-ventricular tachycardia.
3. Evaluation of the PSG video recording for movement and assessment of patient clinical status are also recommended.
4. The use of an extended ECG montage composed of three bipolar channels and three augmented channels may allow more extensive visualization of ECG abnormalities when compared to single ECG channel.

REFERENCES


CITATION

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DISCLOSURE STATEMENT
This work was performed at the Louisiana State University School of Medicine in Shreveport, LA. The authors have no conflicts of interest, financial support, or off-label/investigational uses to disclose.
There is growing interest in the use of continuous positive airway pressure (CPAP) in the perioperative setting with untreated obstructive sleep apnea (OSA).1 Guralnick et al. describe CPAP adherence in patients with newly diagnosed OSA prior to elective surgery.2 The major findings were that African American race, male gender and depressive symptoms were associated with reduced CPAP adherence. However, we consider that some aspects of this study need clarification in order to extrapolate the findings into clinical practice.

First, we believe that the overall results could be separated according to the OSA severity categories of moderate or severe. This separation into two different groups could clarify the overall message of the study, since the literature suggests that more severe OSA is associated with greater CPAP adherence compared to milder severities.3 Moreover, previous studies have shown that a higher baseline apnea-hypopnea index (AHI) was the only significant independent predictor of better CPAP compliance.4

Secondly, the finding of male gender being a risk factor for poor CPAP adherence warrants further consideration.2 We suggest that male gender may be a surrogate for risk factors or comorbidities such as smoking, obesity, or anthropometric parameters such as neck circumference.

Thirdly, depressive symptomatology has been reported to be an independent predictor of reduced CPAP adherence.5 This aspect may have a dual interpretation in the population tested in this study and is not clearly in the same direction of previous studies.

Fourth, there is lack information about some relevant practical aspects that was not examined: (a) type of surgery and extent of postoperative pain; (b) the auto-set CPAP settings were atypical, with a pressure range of only 5 around the optimal pressure derived from polysomnography (PSG); (c) they do not report on the efficacy of CPAP from the machine download; (d) 50% of patient who scored highly on the questionnaire refused PSG—were their postoperative outcomes different to those who were treated with CPAP?

We propose to include a more accurate assessment of possible psychological disorders that may interfere with patient adherence to CPAP and hospital education program before surgery.

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CITATION

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DISCLOSURE STATEMENT
The authors have indicated no financial conflicts of interest.
We thank Drs. Esquinas and Cistulli for their thoughtful comments and careful review of our recent study in the Journal of Clinical Sleep Medicine.1 We believe the most important finding of our study was that the majority of patients referred from the Anesthesia Perioperative Medicine Clinic and subsequently diagnosed with obstructive sleep apnea (OSA) were poorly adherent to auto-PAP therapy during the perioperative period (median adherence of 2.5 h per night). As we pointed out in our discussion, the overall adherence was significantly lower than what we have reported in our clinical practice as well as what has been widely reported in the literature.2-5 In multivariate linear regression modeling, OSA severity was not a predictor of CPAP adherence. Esquinas and Cistulli note that increasing OSA severity is associated with better CPAP adherence. However, there are conflicting data on the association of OSA severity and the presence of daytime sleepiness with adherence to CPAP therapy. Although disease severity is frequently identified as influential on CPAP adherence, the relationships are relatively weak, and when other factors are included, disease severity and sleepiness are less contributory to CPAP adherence.6,7 In another independent cohort of 403 non-presurgical patients seen at our institution, we also found that the severity of OSA and the Epworth Sleepiness Scale were not predictive of CPAP adherence.2 In fact, the only predictors of reduced CPAP adherence in that cohort were African American race and non-sleep specialists ordering polysomnograms and CPAP therapy. We agree that male gender may simply be a marker of other important predictors of CPAP adherence, but unfortunately, our data do not allow us to better delineate it. Our regression model shows that a score above 16 on the validated Center for Epidemiologic Studies Depression Scale was independently associated with 65 minutes lower mean CPAP adherence per night during the first 30 days of therapy. Esquinas and Cistulli contend that this association has “dual interpretation in the population tested in this study and is not clearly in the same direction of previous studies.” Although we acknowledge that validated measures of depressive symptoms are not routinely measured or reported in the context of CPAP adherence, two prior studies have reported an association between lower psychological well-being and reduced CPAP adherence.7,8 As we discussed in the limitations, the findings in our inner-city urban cohort may not be applicable to other populations, and as such, further studies are needed to confirm our findings. We agree that our study was limited by lacking information on the extent of postoperative pain and sedative-narcotic use. However, the types of surgery are described in the first paragraph of the results.

Our entire cohort was directly referred from the Anesthesia Perioperative Medicine Clinic to the sleep laboratory for a diagnostic polysomnogram. On average, the patients underwent in-laboratory split-night polysomnograms just 4 days before the scheduled date of surgery. Given the time constraints and the inability of the sleep clinicians to fully evaluate the patients prior to surgery, we implemented a program in which the patients would receive an auto-PAP device upon awakening in the sleep laboratory. In regards to the pressure settings of the auto-PAP devices, we believe that providing a very wide range of pressures (e.g., 4-20 cm H2O) was not necessary since our patients had all been manually titrated during the polysomnogram. We set the upper limit of the auto-pap pressure just a few cm of H2O above the optimal pressure with the rationale that in the immediate postoperative period, the patients may need a higher pressure due to the effect of sedatives and narcotics on the upper airway collapsibility. We agree that having additional information on residual AHI and mask leak as estimated by the CPAP units would have been of interest, but unfortunately not all CPAP units had the capability of reporting these variables. We also agree that having postoperative outcomes would have strengthened our study, but as we pointed out in our limitations, given that overall serious postoperative complications due to OSA are rare, our study was neither powered nor designed to ascertain rates of postoperative complications.

Of interest, in a recent randomized controlled trial of patients undergoing elective hip/knee arthroplasty, patients suspected of having moderate or severe OSA were randomized to auto-PAP therapy during the perioperative period. Only 47% of patients were adherent, and the nightly adherence was 2.8 h per night. Our entire cohort was directly referred from the Anesthesia Perioperative Medicine Clinic to the sleep laboratory for a diagnostic polysomnogram. On average, the patients underwent in-laboratory split-night polysomnograms just 4 days before the scheduled date of surgery. Given the time constraints and the inability of the sleep clinicians to fully evaluate the patients prior to surgery, we implemented a program in which the patients would receive an auto-PAP device upon awakening in the sleep laboratory. In regards to the pressure settings of the auto-PAP devices, we believe that providing a very wide range of pressures (e.g., 4-20 cm H2O) was not necessary since our patients had all been manually titrated during the polysomnogram. We set the upper limit of the auto-pap pressure just a few cm of H2O above the optimal pressure with the rationale that in the immediate postoperative period, the patients may need a higher pressure due to the effect of sedatives and narcotics on the upper airway collapsibility. We agree that having additional information on residual AHI and mask leak as estimated by the CPAP units would have been of interest, but unfortunately not all CPAP units had the capability of reporting these variables. We also agree that having postoperative outcomes would have strengthened our study, but as we pointed out in our limitations, given that overall serious postoperative complications due to OSA are rare, our study was neither powered nor designed to ascertain rates of postoperative complications.

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postoperative period vs. standard of care. Even in this rigorous clinical trial, the median postoperative daily auto-PAP usage was suboptimal at 184.5 minutes per night. Moreover, empiric auto-PAP therapy led to a 1 day increase in median length of stay in those that were adherent to therapy. This study raises new questions about the role for empiric postoperative auto-PAP therapy. Therefore, we wholeheartedly agree with Esquinas and Cistulli that further research is needed to identify barriers to CPAP adherence in this patient population, or efforts directed towards diagnosis are likely to be wasted. Given the large volume of elective surgeries performed globally, implementation of systematic screening and empiric auto-PAP therapy in patients at risk for OSA would impose a significant cost burden. This underlines the need for further clinical research to determine the most efficient methods to identify presurgical patients that would benefit from CPAP therapy as well as the utility of education programs before surgery that aim to improve perioperative CPAP adherence and patient outcomes.

CITATION

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