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SCOPE

JCSM Journal of Clinical Sleep Medicine focuses on clinical sleep medicine. Its emphasis is publication of papers with direct applicability and/or relevance to the clinical practice of sleep medicine. This includes, clinical trials, clinical reviews, clinical commentary and debate, medical economic/practice perspectives, case series and novel/interesting case reports. In addition, the journal will publish proceedings from conferences, workshops and symposia sponsored by the American Academy of Sleep Medicine or other organizations related to improving the practice of sleep medicine.
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<td></td>
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Obstructive sleep apnea (OSA), the most common subtype of sleep breathing disorder, is characterized by sleep-related decreases (hypopneas) or pauses (apneas) in respiration.\textsuperscript{1} The prevalence of OSA increases with age and is higher among males than females. Among the population between 30 to 65 years of age, 24% of men and 9% of women have been demonstrated to suffer from OSA.\textsuperscript{2}

Depression is prevalent in people with OSA, ranging from 5% to 63% in clinical and community studies.\textsuperscript{3} In a large and retrospective review study, a significantly higher prevalence of depression was identified in people with OSA (21.8%) compared to those without OSA (9.43%).\textsuperscript{4} While this higher prevalence of depression among OSA points toward an underlying association, some OSA and depressive symptoms may overlap (e.g., fatigue, loss of interest, poor concentration),\textsuperscript{5} thus making it difficult to determine whether OSA contributes to the following occurrence of depression.

Although prior studies have addressed the link between OSA and depression, results in the literature are mixed. Some studies, including two large-scale studies,\textsuperscript{6,7} have reported no association between the disorders, while one longitudinal study reported an increased risk of subsequent depression that exhibited a dose-response relationship with OSA severity.\textsuperscript{8} Two retrospective studies also observed OSA to be linked with depression.\textsuperscript{9,10} Inconsistencies in previous findings may be attributable to inadequate control of confounders (e.g., obesity, hypertension, diabetes, alcohol consumption), biases (e.g., self-reported data), and other measurement issues (e.g., different study populations, questionnaires, and scales).\textsuperscript{11,13} Based upon the heterogeneity of these data and numerous confounding factors, follow-up
studies of patient populations have been suggested to better address the link between OSA and depression. In addition, while males are more frequently diagnosed with OSA, higher rates of depression have been found in female patients with OSA. Previous findings have rarely examined the modifying effects of gender, as most studies are unable to enroll sufficient numbers of both males and females to report sex-stratified risks of consequent depression. We hypothesized that risks of depressive disorder (DD) among female patients with OSA are higher than their male counterparts.

Thus, the objective of this nationwide population-based study was to assess the risk of DD in one year following a diagnosis of OSA. The association between OSA and DD was further be examined by sex.

**METHODS**

**Database**

We retrieved the data from the Longitudinal Health Insurance Database 2000 (LHID2000), which is derived from Taiwan’s Bureau of National Health Insurance (NHI) records and released by the Taiwan National Health Research Institute annually. The LHID2000 includes the registration files and medical claims data for the reimbursement of 1,000,000 beneficiaries under the NHI program. These 1,000,000 beneficiaries were randomly selected from the year 2000 Registry of Beneficiaries (n = 23.72 million) of the NHI by the Taiwan National Health Research Institute. Prior studies have validated the completeness and accuracy of the claims data of NHI research database. Hundreds of researchers have employed the data from the Taiwan NHI to perform and publish their studies in peer-reviewed journals. In particular, 3 recent studies have employed the LHID2000 to explore the relationships between OSA and DD.

The LHID2000 consists of de-identified secondary data released to the public for research purposes and was therefore exempted from full review, following consultation with the Taipei Medical University’s Institutional Review Board.

**Study Sample**

This retrospective cohort study included a study cohort and a comparison cohort. For the study cohort, we first identified individuals who had been diagnosed with OSA (ICD-9-CM codes 327.23, 780.51, 780.53, or 780.57) after receiving polysomnography during ambulatory care visits between January 1, 2002, and December 31, 2008 (n = 3,292). Since administrative datasets are often criticized for poor diagnostic validity, this study included only patients who had received OSA diagnoses following polysomnography to better ensure diagnostic validity. To include only newly diagnosed cases and to avoid the potential effects of chronicity, we excluded those individuals who had received a diagnosis of OSA prior to 2002 (n = 212). As OSA in children is distinct from OSA in adults, we further excluded individuals younger than 18 years (n = 103) to increase the homogeneity of our study sample. Finally, we assigned the date of their first ambulatory care visit in which they received a diagnosis of OSA following polysomnography as the index date. We excluded those individuals who had received a diagnosis of DD (ICD-9-CM codes 296.2, 296.3, 300.4, and 311) schizophrenia, or bipolar disorder prior to their index date (n = 159). As a result, a total of 2,818 individuals with OSA were included in the study cohort.

For the selection of the comparison cohort, we likewise extracted the individuals from the LHID2000. We first excluded all the individuals who had ever been diagnosed with OSA since the initiation of the NHI program (from 1995 to 2009) from our consideration. Then we randomly selected 14,090 beneficiaries (5 for each patient in the study cohort) matched with the study cohort in sex, age (18-34, 35-39, 40-44, 45-49, 50-54,55-59, 60-64, 65-69, and > 69), urbanization level (5 levels, with 1 referring to the most urbanized and 5 referring to the least), and year of index date, using the SAS program proc SurveySelect (SAS System for Windows, Version 8.2). For the study cohort, the index date was defined as the year in which the cases received their first diagnosis of OSA; index date for the comparison cohort was simply a matched year in which the comparison individuals had used medical services. For the comparison cohort, we assigned their first use of medical care occurring in the year of index as their index date. In addition, we matched the variable of urbanization level of the patient’s residence to help control for error variables, namely unmeasured neighborhood socioeconomic characteristics between the study cohort and comparison cohort. According to a prior study, all 359 cities/towns in Taiwan were stratified into 5 groups ranked by urbanization level. We further ensured that patients selected for the comparison cohort had never been diagnosed with DD, schizophrenia, or bipolar disorder prior to their index date.

We individually followed up each sampled individual (n = 16,998) for a one-year period starting from their index date to identify those individuals who subsequently received a diagnosis of DD (ICD-9-CM codes 296.2, 296.3, 300.4, and 311).

**Statistical Analysis**

The SAS statistical package (SAS System for Windows, Version 8.2, Cary NC, USA) was used to perform all statistical analyses in this study. We used \( \chi^2 \) tests to compare differences in monthly income, geographic region, and prevalence of hypertension, diabetes, coronary heart disease (CHD), hyperlipidemia, obesity, and alcohol abuse/alcohol dependency syndrome between the study cohort and comparison cohort. We calculated the one-year DD-free survival rates by the Kaplan-Meier method, with the log-rank test also being used to examine differences in DD-free survival rates between cohorts. Stratified Cox proportional hazards regressions (stratified on sex, age group, urbanization level, and index date) were performed to compute the risk for DD during the one-year follow-up period between the study cohort and the comparison cohort. In this study, we have also examined the proportional hazards assumption and found this assumption to be satisfied because the survival curves for both strata (individuals in the study cohort and comparison cohort) had hazard functions that were proportional over time. A two-sided p-value < 0.05 was considered statistically significant for this study.

**RESULTS**

The distribution of demographic characteristics and comorbidities between the study cohort and the comparison cohort were examined.
Table 1—Demographic characteristics for the sampled Taiwanese patients stratified by the presence/absence of obstructive sleep apnea, 2002-2008 (n = 16,908)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Patients with obstructive sleep apnea (n = 2,818)</th>
<th>Comparison patients (n = 14,090)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td>1.000</td>
</tr>
<tr>
<td>Male</td>
<td>1,879</td>
<td>9,395</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>939</td>
<td>4,695</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td>1.000</td>
</tr>
<tr>
<td>&lt; 35</td>
<td>396</td>
<td>1,980</td>
<td></td>
</tr>
<tr>
<td>35-39</td>
<td>319</td>
<td>1,595</td>
<td></td>
</tr>
<tr>
<td>40-44</td>
<td>329</td>
<td>1,645</td>
<td></td>
</tr>
<tr>
<td>45-49</td>
<td>356</td>
<td>1,780</td>
<td></td>
</tr>
<tr>
<td>50-54</td>
<td>357</td>
<td>1,785</td>
<td></td>
</tr>
<tr>
<td>55-59</td>
<td>249</td>
<td>1,245</td>
<td></td>
</tr>
<tr>
<td>60-64</td>
<td>161</td>
<td>805</td>
<td></td>
</tr>
<tr>
<td>65-69</td>
<td>111</td>
<td>555</td>
<td></td>
</tr>
<tr>
<td>≥ 70</td>
<td>540</td>
<td>2,700</td>
<td></td>
</tr>
<tr>
<td>Urbanization level</td>
<td></td>
<td></td>
<td>1.000</td>
</tr>
<tr>
<td>1 (most urbanized)</td>
<td>1,046</td>
<td>5,230</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>818</td>
<td>4,090</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>506</td>
<td>2,530</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>278</td>
<td>1,390</td>
<td></td>
</tr>
<tr>
<td>5 (least urbanized)</td>
<td>170</td>
<td>850</td>
<td></td>
</tr>
<tr>
<td>Monthly Income</td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>NT$1-15,840</td>
<td>1,098</td>
<td>6,063</td>
<td></td>
</tr>
<tr>
<td>NT$15,841-25,000</td>
<td>854</td>
<td>4,998</td>
<td></td>
</tr>
<tr>
<td>≥ NT$25,001</td>
<td>866</td>
<td>3,029</td>
<td></td>
</tr>
<tr>
<td>Geographic region</td>
<td></td>
<td></td>
<td>0.053</td>
</tr>
<tr>
<td>Northern</td>
<td>1,460</td>
<td>7,172</td>
<td></td>
</tr>
<tr>
<td>Central</td>
<td>711</td>
<td>3,480</td>
<td></td>
</tr>
<tr>
<td>Southern</td>
<td>613</td>
<td>3,170</td>
<td></td>
</tr>
<tr>
<td>Eastern</td>
<td>34</td>
<td>2,68</td>
<td></td>
</tr>
<tr>
<td>Obesity</td>
<td>110</td>
<td>96</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>802</td>
<td>2,233</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>427</td>
<td>1,534</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>994</td>
<td>3,176</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>457</td>
<td>1,338</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Alcohol abuse/alcohol dependence syndrome</td>
<td>9</td>
<td>61</td>
<td>0.391</td>
</tr>
<tr>
<td>Insomnia</td>
<td>449</td>
<td>1,179</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

cohort is shown in Table 1. Of the total of 16,908 individuals, the mean age was 46.4 years (SD 15.7 years); only one-third were females. It also shows that individuals with OSA had a higher prevalence of hypertension (p < 0.001), diabetes (p < 0.001), CHD (p < 0.001), hyperlipidemia (p < 0.001), obesity (p < 0.001), and insomnia (p < 0.001) than comparison individuals. However, no significant difference in the prevalence of alcohol abuse/alcohol dependency syndrome (p = 0.391) and restless legs syndrome (p = 0.527) was observed between the study cohort and the comparison cohort.

Table 2 presents the incidence of DD during the one-year follow-up period after the index date for the sampled individuals. The incidence of DD during the one-year follow-up period was 18.10 (95% CI = 13.62-23.61) and 8.23 (95% CI = 6.83-9.84) for individuals with and without OSA, respectively. The log-rank test revealed that individuals with OSA had significantly lower one-year DD-free survival rates than comparison individuals. Figure 1 compares the DD incidence rates between these 2 cohorts.

Table 2 also presents the hazard ratio (HR) of DD between the study and comparison cohort. After adjusting for monthly income, geographic region, hypertension, diabetes, CHD, hyperlipidemia, obesity, and alcohol abuse/alcohol dependency syndrome, stratified Cox proportional hazards regressions (stratified on sex, age group, urbanization level, and the year of index date) revealed that the HR for DD among individuals with OSA was 2.18 (95% CI = 1.55-3.08, p < 0.001) times that of comparison individuals.

As the interaction between OSA and sex reached a level of significance (p < 0.1) sufficient to suggest the inclusion of sex in the model, we further present the HR of DD stratified by sex in Table 3. We found that among females, the adjusted hazard of DD during the one-year follow-up period was 2.72 (95% CI = 1.68-4.40) for individuals with OSA when compared with the
However, among males, the adjusted HR of DD among OSA individuals was only 1.81 (95% CI = 1.09-3.01) times that of matched comparison individuals. Table 4 further presents the HR of DD stratified by age group. We found that among patients < 40 and 40-64 years old, the adjusted HR of DD during the one-year follow-up period was 2.64 (1.22-5.69) and 2.41 (95% CI = 1.52-3.82), respectively, for individuals with OSA when compared with the comparison cohort. However, among patients older than 64 years, there was no significant relationship between DD and OSA.

**DISCUSSION**

We found that during a one-year follow-up, the incidence of DD per thousand person-years was about twice as high among patients with OSA than those without OSA. Within one year following their diagnosis, patients with OSA were also independently associated with a 2.18 times increased risk of consequent DD, after taking confounders into consideration, including monthly income, geographic region, hypertension, diabetes, obesity, alcohol abuse/alcohol dependence syndrome, and insomnia.

**Table 2**—Hazard ratios of depressive disorder among the sample patients during the one-year follow-up periods (n = 16,908)

<table>
<thead>
<tr>
<th>Depressive disorder</th>
<th>Total (n = 16,908)</th>
<th>Patients with obstructive sleep apnea (n = 2,818)</th>
<th>Comparison patients (n = 14,090)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>167 (0.99)</td>
<td>51 (1.81)</td>
<td>116 (0.82)</td>
</tr>
<tr>
<td>Incidence rate per 1,000 person-years (95% CI)</td>
<td>9.88 (8.46-11.46)</td>
<td>18.10 (13.62-23.61)</td>
<td>8.23 (6.83-9.84)</td>
</tr>
<tr>
<td>Crude HR (95% CI)</td>
<td>–</td>
<td>2.22*** (1.59-3.10)</td>
<td>1.00</td>
</tr>
<tr>
<td>Adjusted HR (95% CI)α</td>
<td>–</td>
<td>2.18*** (1.55-3.08)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

HR, hazard ratio. HR was calculated by stratified Cox proportional hazard regressions (stratified by sex, age group, urbanization level, and the year of index date); ***p < 0.001. *Adjustments are made for patient’s monthly income, geographic region, hyperlipidemia, diabetes, hypertension, coronary heart disease, obesity, alcohol abuse/alcohol dependence syndrome, and insomnia.

**Table 3**—Hazard ratios of depressive disorder by gender among the sample patients during the one-year follow-up periods

<table>
<thead>
<tr>
<th>Depressive disorder</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>Patients with obstructive sleep apnea</td>
<td>Comparison patients</td>
</tr>
<tr>
<td>23 (1.22)</td>
<td>66 (0.71)</td>
<td></td>
</tr>
<tr>
<td>Incidence rate per 1,000 person-years (95% CI)</td>
<td>12.24 (7.95-18.08)</td>
<td>7.08 (5.52-8.95)</td>
</tr>
<tr>
<td>Crude HR (95% CI)</td>
<td>1.74* (1.08-2.80)</td>
<td>1.00</td>
</tr>
<tr>
<td>Adjusted HR (95% CI)α</td>
<td>1.81* (1.09-3.01)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

HR, hazard ratio. HR was calculated by stratified Cox proportional hazard regressions (stratified on sex, age group, urbanization level, and the year of index date); *p < 0.05, ***p < 0.001. *Adjustments are made for patient’s monthly income, geographic region, hyperlipidemia, diabetes, hypertension, coronary heart disease, obesity, alcohol abuse/alcohol dependence syndrome, and insomnia.
Table 4—Hazard ratios of depressive disorder by age among the sample patients during the one-year follow-up periods

<table>
<thead>
<tr>
<th>Depressive disorder</th>
<th>Patients with obstructive sleep apnea</th>
<th>Comparison patients</th>
<th>Patients with obstructive sleep apnea</th>
<th>Comparison patients</th>
<th>Patients with obstructive sleep apnea</th>
<th>Comparison patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>10 (1.40)</td>
<td>20 (0.56)</td>
<td>29 (2.00)</td>
<td>64 (0.68)</td>
<td>12 (1.64)</td>
<td>32 (0.97)</td>
</tr>
<tr>
<td>Incidence rate per 1,000 person-years (95% CI)</td>
<td>13.99 (7.10-24.93)</td>
<td>5.61 (3.52-8.51)</td>
<td>19.97 (13.63-28.31)</td>
<td>8.84 (6.83-11.21)</td>
<td>18.43 (9.99-31.54)</td>
<td>9.74 (6.79-13.59)</td>
</tr>
<tr>
<td>Crude HR (95% CI)</td>
<td>2.51* (1.17-5.39)</td>
<td>1.00</td>
<td>2.29*** (1.47-3.56)</td>
<td>1.00</td>
<td>1.91 (0.98-3.73)</td>
<td>1.00</td>
</tr>
<tr>
<td>Adjusted HR (95% CI)</td>
<td>2.64* (1.22-5.69)</td>
<td>1.00</td>
<td>2.41*** (1.52-3.82)</td>
<td>1.00</td>
<td>1.72 (0.84-3.52)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

HR, hazard ratio. HR was calculated by stratified Cox proportional hazard regressions (stratified on sex, age group, urbanization level, and the year of index date); *p < 0.05, ***p < 0.001. Adjustments are made for patient’s monthly income, geographic region, hyperlipidemia, diabetes, hypertension, coronary heart disease, obesity, alcohol abuse/alcohol dependence syndrome, and insomnia.

those without OSA, the odds of developing depression during a 4-year interval were increased by 1.6-, 2.0-, and 2.6-fold for participants with minimal, mild, and moderate or worse OSA, respectively. Nevertheless, a null association between OSA and DD was observed in two retrospective studies. Methodological variation (e.g., different populations, study designs, disease definitions, and assessment instruments) or limitations (e.g., inappropriate consideration of confounding effects) may render comparison between investigations difficult. After considering confounding factors, we confirmed a prospective link between OSA and subsequent DD within the first year following OSA diagnosis in this nationwide population-based study.

Regarding the modifying effects of gender, Enright et al. examined 5,201 community adults aged 65 years and older and observed apneas to be associated with depression in women but not in men. Consistent with previous findings, our large-scale study identified women as having higher risks of subsequent DD within the first year following OSA diagnosis. This might reflect a more general finding that depression is more prevalent in women than in men.

The underlying mechanisms explaining the association between OSA and DD are not clearly delineated. Yet, a biological plausibility exists. First, sleep fragmentation or oxygen desaturation during sleep in OSA patients may impact the presentation of mood symptoms, although the results regarding this possibility are mixed. In a randomized controlled trial, hypoxia in OSA was shown to potentially associate with depression, as a significant reduction of depressive symptoms was observed for patients with OSA receiving oxygen therapy. Recent preliminary imaging data also suggested that hypoxemia linked with OSA might play a part in affecting mood. On the other hand, sleep fragmentation, mainly causing excessive daytime sleepiness in OSA was proposed to contribute to the depressive symptomatology of OSA. Nevertheless, depression was also not found to be associated with either sleep fragmentation or hypoxia in OSA. This issue will need to be further clarified in the future with studies utilizing larger sample sizes and the appropriate consideration of confounders (e.g., body mass index, hypertension).

Second, it is possible that there is a shared signaling pathway possibly involving proinflammatory markers, neurotransmitters, or undisclosed underlying factors between the two conditions. While OSA was associated with increased levels of IL-6 and tumor necrosis factor, an immune response implicating proinflammatory cytokines IL-1, IL-6, and interferons was observed among patients with DD. Several excitatory and inhibitory neurotransmitters, such as serotonin, norepinephrine, and γ-aminobutyric acid (GABA), may also be involved in both the sleep/wake cycle and mood regulation. Shared common risk factors (e.g., obesity, cardiovascular disease, metabolic syndrome) are another plausible explanation. Finally, as depression was prevalently observed in patients with chronic medical diseases, OSA may decrease patients’ quality of life, further leading to other chronic diseases including depression.

Our study contributes to the emerging findings regarding the association between OSA and DD. As comorbid DD was found to exacerbate OSA and to have a negative impact on self-management and treatment adherence of chronic medical illness such as OSA, it is possible that prompt detection and appropriate treatment of DD can aid in the management of OSA. We suggest that clinicians should be more aware of the frequently observed link between OSA and DD. Since patients with OSA might not voluntarily voice mood symptoms in the context of a sleep evaluation, regular screening and monitoring of psychiatric condition among patients with OSA are needed, especially among women. Proper and timely referral for assessment and treatment of mood symptoms, not just the treatment of OSA itself, might assist in promoting patients’ well-being and reducing the detrimental health consequences that might follow.

Our study has several strengths. Important confounders were carefully addressed. Both OSA and DD have independently been reported to associate with metabolic syndrome and cardiovascular disease. Potential confounding factors (e.g., obesity, hypertension, diabetes) that may impact the connection between OSA and DD were taken into consideration in our analysis. In addition, as consideration of the modifying effects of gender was felt to be of great importance in elucidating the prospective link between OSA and depression, we used a nationwide population-based dataset with ample sample size to clarify this issue. Finally, established clinical diagnostic criteria were used for the identification of depression.
DD and OSA, with the diagnosis of the latter stipulating the confirmatory results of polysomnography to ensure for diagnostic validity. Furthermore, in Taiwan a diagnosis of DD can only be made by psychiatrists. However, four limitations merit attention. First, the LHID2000 database represents patients who had sought treatment for OSA and DD. OSA is a highly prevalent but underdiagnosed illness. While the diagnosis of DD is based on DSM-IV criteria, certain factors, such as socioeconomic status and social stigma might lead some psychiatric patients to decline healthcare services. Moreover, the symptoms of these illnesses are often overlooked, potentially leading to underappreciation, underdiagnosis, and undertreatment. Secondly, although our study only included newly diagnosed cases to avoid potential effects of chronicity, it should be kept in mind that some of them may not be newly developed OSA cases. Patients might have had undetected OSA for years before being diagnosed. Thirdly, the subsequent risk of depression could not be analyzed or compared between patients with treated and untreated OSA in our study. As treatment for OSA is not covered under the National Health Insurance Program, this information is unavailable in our claims dataset. However, to the best of our knowledge most OSA patients are left untreated. Currently, the most effective treatments for OSA are devices (e.g., continuous positive airway pressure [CPAP]) that may be uncomfortable to use. Therefore, because of out-of-pocket costs and difficulties becoming accustomed to using these devices, most patients are left untreated. Finally, referral bias should be of concern for studies investigating clinical populations. It is possible that the frequent medical consultation of patients with OSA might prompt referrals and boost the detection of DD. Meanwhile, due to the overlap of symptoms in OSA and DD, we are not able to rule out the possibility that symptoms of DD might be attributed to a prior diagnosis of OSA and work to reduce further identification of DD.

A prospective link between OSA and subsequent DD within the first year following OSA diagnosis was confirmed in our study. However, four limitations merit attention. First, the LHID2000 database represents patients who had sought treatment for OSA and DD. OSA is a highly prevalent but underdiagnosed illness. While the diagnosis of DD is based on DSM-IV criteria, certain factors, such as socioeconomic status and social stigma might lead some psychiatric patients to decline healthcare services. Moreover, the symptoms of these illnesses are often overlooked, potentially leading to underappreciation, underdiagnosis, and undertreatment. Secondly, although our study only included newly diagnosed cases to avoid potential effects of chronicity, it should be kept in mind that some of them may not be newly developed OSA cases. Patients might have had undetected OSA for years before being diagnosed. Thirdly, the subsequent risk of depression could not be analyzed or compared between patients with treated and untreated OSA in our study. As treatment for OSA is not covered under the National Health Insurance Program, this information is unavailable in our claims dataset. However, to the best of our knowledge most OSA patients are left untreated. Currently, the most effective treatments for OSA are devices (e.g., continuous positive airway pressure [CPAP]) that may be uncomfortable to use. Therefore, because of out-of-pocket costs and difficulties becoming accustomed to using these devices, most patients are left untreated. Finally, referral bias should be of concern for studies investigating clinical populations. It is possible that the frequent medical consultation of patients with OSA might prompt referrals and boost the detection of DD. Meanwhile, due to the overlap of symptoms in OSA and DD, we are not able to rule out the possibility that symptoms of DD might be attributed to a prior diagnosis of OSA and work to reduce further identification of DD.

A prospective link between OSA and subsequent DD within the first year following OSA diagnosis was confirmed in our study. Further studies should seek to elucidate the underlying pathophysiological mechanisms for this link. Studies on the effect of appropriate management of OSA on the subsequent risk of DD might help yield strategies for more effective prevention and intervention programs.

ACKNOWLEDGMENTS

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DISCLOSURE STATEMENT

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The study by Chen and colleagues\(^1\) represents a significant step in documenting a link between obstructive sleep apnea (OSA) and depression. Because the analyses were conducted on a dataset of patients in Taiwan, a place where most OSA patients are left untreated due to lack of insurance, this study is able to offer a unique examination of the impact of newly diagnosed and untreated OSA on depression one year later. Previous research suggests much lower rates of depression in Taiwan than the U.S., potentially due to stigma and other cultural differences in symptom reporting. Depression was measured by psychiatric diagnosis in this report. Therefore, the results showing a temporal link between OSA and MDD may actually be conservative.

Overall, these findings challenge us to question how well our sleep medicine and mental health systems interface in the detection and treatment of depression. Depression is a serious and insidious disorder. In 2002, depression was ranked as the fourth leading cause of disability throughout the world, and it is projected to be the second leading cause in the coming decades.\(^2\) Depression is associated with increased all-cause mortality, and individuals with depressive disorders have significantly shortened life expectancy (for depressed males 11 years; for depressed females 7 years).\(^3\)

In addition to OSA, depression is often comorbid with other sleep disorders, such as insomnia\(^4\) and narcolepsy.\(^5,6\) As such, sleep physicians are likely to treat a high number of individuals with depression. Unfortunately, depression often remains undetected or undertreated. A systematic review of 36 studies found that non-psychiatric physicians miss the diagnosis of depression in more than half of patients seen.\(^7\) In my experience, depression has the tendency to fall through the cracks with physicians who are struggling to manage a host of medical and sleep-related concerns in 15-30 minute appointments.

Given these data, I am disheartened by trends in our field leading to separate clinical practice by sleep psychologists and sleep physicians. Referrals between practices can be costly, often requiring excessive clinic staff time for insurance pre-authorization. Depressed patients often lack the motivation to seek care or follow through on referrals. Referrals are not the long-term answer for this population.

We should pay attention to the findings presented by Chen and colleagues, along with results linking depression and other sleep disorders. Mental health providers are uniquely trained and positioned to assess and treat depression. Successful clinical systems like Kaiser Permanente and Veteran’s Health Affairs have increasingly recognized financial and health care benefits of integrative care by including psychologists as integral members of interdisciplinary pain and primary care teams. Mental health collaboration has the added benefits of improving medical outcomes. Mental health providers can administer motivational interviewing and cognitive behavior therapy to facilitate PAP machine adherence, OSA prevention (weight loss, smoking cessation), and CBT for insomnia. We should learn from the top sleep centers in the nation that are successfully incorporating mental health providers as equal members of integrative sleep medicine teams.

Depression and OSA have many similarities. They both share symptoms like fatigue, loss of concentration, and insomnia. Both may present subtly and are easily ignored by patients for some time. Both disorders can lead to early mortality—whether it occur due to car crash, suicide, or poor health-related behaviors. It is unclear which disorder should be prioritized in treatment. Is it solid clinical practice to prioritize sleep in a depressed patient if the patient is presenting in a sleep center? And conversely, do we prioritize depression, if an untreated OSA patient is presenting to a mental health clinic?

I feel fortunate that in my career working in a significant number of mental health outpatient clinics with depressed, anxious, and impulsive individuals, I have had only one patient successfully commit suicide. I did not see that 28-year-old single mother with depression in a mental health clinic. I saw her in my sleep clinic. It’s time to start bridging mental health and sleep medicine so that sleep centers are truly interdisciplinary and integrative. An excellent place to start may be a higher level of classification by the American Academy of Sleep Medicine (AASM) for those accredited sleep centers that include the presence of mental health or behavioral sleep medicine providers on staff. The findings by Chen and colleagues provide further support for this recommendation.
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Obstructive sleep apnea (OSA) is a commonly unrecognized condition with an especially high prevalence among morbidly obese subjects. OSA is characterized by apneas and hypopneas due to the collapse of upper airways and is defined by ≥ 5 apneas or hypopneas per hour during sleep, as measured by the apnea-hypopnea index (AHI). Mild OSA is defined as 5-15 episodes of apneas or hypopneas per hour, moderate OSA 15-30, and severe OSA ≥ 30. A meta-analysis from 2009 concluded that continuous positive airway pressure (CPAP) is a cost-effective treatment of OSA among morbidly obese subjects. OSA is characterized by surgical and conservative weight loss strategies on obstructive sleep apnea (OSA). We hypothesized that Roux-en-Y gastric bypass (RYGB) would be more effective than intensive lifestyle intervention (ILI) at reducing the prevalence and severity of OSA (apnea-hypopnea-index [AHI] ≥ 5 events/hour).

Methods: A total of 133 morbidly obese subjects (93 females) were treated with either a 1-year ILI-program (n = 59) or RYGB (n = 74) and underwent repeated sleep recordings with a portable somnograph (Embletta).

Results: Participants had a mean (SD) age of 44.7(10.8) years, BMI 45.1(5.7) kg/m², and AHI 17.1(21.4) events/hour. Eighty-four patients (63%) had OSA. The average weight loss was 8% in the ILI-group and 30% in the RYGB-group (p < 0.001). The mean (95%CI) AHI reduced in both treatment groups, although significantly more in the RYGB-group (AHI change -6.0 [ILI] vs -13.1 [RYGB]), between group difference 7.2 (1.3, 13.0), p = 0.017. Twenty-nine RYGB-patients (66%) had remission of OSA, compared to 16 ILI-patients (40%), p = 0.028. At follow-up, after adjusting for age, gender, and baseline AHI, the RYGB-patients had significantly lower adjusted odds for OSA than the ILI-patients—OR (95% CI) 0.33 (0.14, 0.81), p = 0.015. After further adjustment for BMI change, treatment group difference was no longer statistically significant—OR (95% CI) 1.31 (0.32, 5.35), p = 0.709.

Conclusion: Our study demonstrates that RYGB was more effective than ILI at reducing the prevalence and severity of OSA. However, our analysis also suggests that weight loss, rather than the surgical procedure per se, explains the beneficial effects.

Keywords: General, bariatric surgery, obstructive sleep apnea, weight loss

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The prevalence of OSA in the Wisconsin Sleep Cohort study was 9% among women and 24% among men. Recently, we demonstrated a much higher prevalence of OSA among the morbidly obese: 55% in women and 80% in men. Despite the close relationship between OSA and obesity, only a few recently published randomized controlled trials have assessed the effect of weight loss on obstructive sleep apnea. Tuomilehto et al. examined the effect of a very low calorie diet followed by lifestyle counseling for one year in overweight and
obese patients with mild OSA. The intervention group had significantly lower odds of having OSA at follow-up than the control group: OR 0.24 (95% CI 0.08, 0.72). Isolated physical activity without weight loss may also have a positive effect on OSA. Exercise leads to more muscles and less fat; the lower pharyngeal pressure from diminished fat deposits might decrease the severity of OSA.

In the Sleep AHEAD study, intensive lifestyle changes in overweight and obese patients with type 2 diabetes and mild to severe OSA were associated with a significant improvement in AHI. Finally, Johansson et al. reported that in obese men with moderate to severe OSA, a very low energy 9-week diet improved OSA, particularly severe OSA, compared to a control group who adhered to their usual diet. A recent meta-analysis of 12 surgical studies including 342 patients argued that patients undergoing bariatric surgery should not expect to be cured of OSA after surgically induced weight loss. Accordingly, some surgically treated patients will still be in need of continued CPAP treatment. In another meta-analysis the authors were unable to conclude whether surgically induced weight loss was associated with greater improvements in OSA than conservative treatment. Further, it remains unknown whether RYGB may influence the severity of OSA through a mechanism other than weight loss. To summarize, weight reduction reduces the severity of OSA, but the relative efficacy of lifestyle modifications versus bariatric surgery in terms of reducing AHI remains to be established.

Our main hypothesis was that Roux-en-Y gastric bypass (RYGB) would be more effective than intensive lifestyle intervention (ILI) at reducing the prevalence and severity of OSA. To address this issue, we performed sleep recordings both before the start of each intervention type and one year after.

METHODS

Study Design

This study is part of a non-randomized, controlled clinical trial; the MOBIL-study (Morbid Obesity treatment, Bariatric surgery versus Intensive Lifestyle intervention Study) (ClinicalTrials.gov number NCT00273104). The design and setting of the study has previously been described in detail. A brief summary of materials and methods is given below.

Setting

The study was conducted at the Morbid Obesity Centre (MOC) under the auspices of Vestfold Hospital Trust, a regional tertiary care center in Health Region South East, Norway. The intensive lifestyle intervention programme was carried out at Evjelesklinnen, a center specializing in obesity treatment.

All eligible patients underwent a thorough (up to 6 month) assessment by a multidisciplinary team consisting of an internist, a dietitian, a physiotherapist, and a trained “obesity” nurse. During the first visit, the internist established a detailed medical history, checked previous diagnostic workups, performed a physical examination, and briefly informed the patients of further investigations and treatment alternatives. At the second visit the doctor reiterated this message, providing complete information about the possible risks and benefits of an operation and also encouraged the patients to incorporate their own values and preferences in the decision-making process. If no contraindication against surgery existed, the patient and the physician together agreed upon the most appropriate choice of therapy, either surgical or conservative.

Participants

The patients were recruited from the MOC and the study approved by the Regional Ethics Committee (ClinicalTrials.gov registry trial number NCT00273104). All patients provided written informed consent. All patients were morbidly obese, i.e., BMI ≥ 40 kg/m² or BMI ≥ 35 kg/m² with at least one obesity related comorbidity.

A total of 139 patients completed the MOBIL study—63 in the ILI-group and 76 in the RYGB-group. After the exclusion of 6 patients with missing sleep registrations, (4 in the ILI-group and 2 in the RYGB group), 133 patients (93 females), 59 in the ILI group and 74 in the RYGB group were eligible for inclusion.

Intervention

The patients in the ILI-group underwent a 1-year lifestyle program at a rehabilitation center (Evjelesklinnen, Norway). This program comprised 4 intermittent stays, one lasting 2 weeks and 3 lasting 1 week each (total, 7 weeks). The program included organized physical activity (3-4 h), psychosocially oriented interventions, and individual consultations with a medical doctor, nutritionist, physiotherapist, and trained nurse. Those leading the counseling interviews were trained in motivational interviewing, a client-centered counseling style that aims to invoke behavioral changes. The patients also took part in group sessions focusing on the emotional aspects of sedentary behavior and classroom lessons on topics related to nutrition, physical activity, and comorbidities. Patients were encouraged to follow the guidelines of the Norwegian National Council of Nutrition, which recommend that the daily intake of protein, fat, and carbohydrate, should account for 10% to 20%, < 30%, and 50% to 60% of energy consumed, respectively. When at home, patients were encouraged to self-monitor their lifestyle habits (e.g., by keeping a physical activity diary and a food diary) and visit their general practitioner for weight monitoring. They were contacted by telephone every 2 weeks. The treatment aim was ≥ 10% weight loss. Vitamin supplements were not prescribed.

Roux-en-Y gastric bypass was performed laparoscopically with a gastric pouch of about 25 mL. In order to reduce liver size, surgical patients consumed a low-calorie diet (900 kcal) for 3 weeks preoperatively.

Variables

An apnea event was defined as ≥ 90% reduction in baseline nasal air flow lasting ≥ 10 seconds. Hypopnea events were defined as a 50% to 90% decrease in pre-event nasal air flow lasting ≥ 10 sec accompanied by ≥ 3% drop in oxygen saturation and/or signs of awakening or increased stress. Both supine and non-supine values of AHI were recorded, given that these might have clinical implications. Oxygen desaturation index (ODI) was defined as the number of episodes with ≥ 3% drop in oxygen saturation per hour. Oxygen saturation (SpO₂), both mean and lowest value through the night, was measured by a finger pulse oximeter.
The primary outcome variables were changes in the prevalence and severity of OSA in both treatment groups. OSA was addressed as both a continuous (AHI) and categorical variable (OSA; yes/no, if yes: mild, moderate, severe). Other outcome variables were resolution of OSA (AHI cutoff 5) and improvement of moderate or severe OSA (AHI ≥ 15) to mild or no OSA. OSA was categorized as mild (AHI 5-14), moderate (AHI 15-29), or severe (AHI ≥ 30). Scoring rules were in accordance with the 2007 American Academy of Sleep Medicine (AASM) manual for the scoring of sleep.17

The main explanatory variable was treatment group. Other possible explanatory or confounding variables were age, gender, anthropometric measures (BMI, weight, and neck circumference), and baseline AHI.

**Data Sources/Measurement**

Portable monitors were used for somnography such that each patient could be monitored in their natural sleeping habitat with their everyday pre-bed rituals. Portable sleep diagnostic systems like the Embletta have a high sensitivity and are considered reliable in the diagnosis of OSA, as there are few false positive results compared to polysomnography.18,19

For the sleep registrations, we used Embletta, a portable multi-channel recorder consisting of a nasal cannula, 2 piezoelectric belts, a finger pulse oximeter, and a body position detector. To monitor respiratory movements, 2 piezoelectric belts were placed around the thorax and abdomen. To avoid interrater variation, Embletta recordings were manually scored by the same person (JMF).

Patients received both written and oral instructions regarding equipment usage. Patients equipped themselves, and registrations were manually scored the following day. Treatment was provided according to current guidelines.4 Patients already using CPAP had a one-week washout period prior to the sleep registration where they did not use the machine. A case report form (CRF) was completed for all patients.

**Statistical Methods**

Data are given as either mean (SD) or proportions (%) unless stated otherwise. All patients (n = 133) were included in the analysis of the change in prevalence of OSA, while only patients with OSA at baseline (n = 84) were included in the analysis of changes in the severity of OSA. Skewed data were transformed using natural logarithms. Between-group comparisons at baseline were analyzed using independent samples t-test for continuous variables and Fisher exact test for categorical variables. Within-group comparisons were performed using paired samples t-test for continuous variables and McNemar test for dichotomized variables. Between-group differences in outcome variables were assessed using t-test, Fisher exact test, and multiple logistic regression analyses with predefined explanatory variables.

In the first logistic regression model, the effect of treatment choice on the prevalence of OSA was adjusted for established confounding factors; baseline AHI, age, and gender. In a second analysis we further adjusted for BMI change. In supplementary analyses, BMI change was replaced with either weight change or neck circumference. AHI cutoffs at both 5 and 15 events/h were used in the regression analyses.

**RESULTS**

**Baseline Characteristics**

Baseline demographic and anthropometric characteristics of the 133 morbidly obese patients are listed in Table 1. A total of 84 patients (63%) had OSA (32% mild, 13% moderate, and 18% severe). The prevalence of mild, moderate, and severe OSA did not differ significantly between groups (p = 0.159). The mean AHI, ODI, SpO2, and lowest SpO2 did not differ significantly between the 2 intervention groups at baseline (all p > 0.16). The RYGB patients were significantly heavier and younger than the ILI patients.14

**Effect of the Interventions**

Compared with baseline, the prevalence of OSA was significantly lower after treatment in both the ILI-group (46% vs 68%) and the RYGB-group (20% vs 60%) (Figure 1). In addition, a significant number of patients changed from an AHI ≥ 15 events/h (requiring CPAP) at baseline to AHI < 15 (not requiring CPAP) at follow-up: 19 subjects (73%) in the RYGB group and 8 subjects (53%) in the ILI group, within-group difference, p < 0.001 and 0.039, respectively, between-group difference p = 0.306 (Figure 1).

Among the 84 patients with OSA at baseline OSA severity reduced in both groups, although significantly more in the
RYGB group than in the ILI group (Table 2). AHI reduced significantly more in the RYGB than in the ILI group, mean between-group difference (95% CI) 7.2 (-5.4, -2.9) events/h, p = 0.003. BMI-change correlated significantly with the change in AHI, r = 0.273, p = 0.001. Mean SpO2 improved in both treatment groups, but was significantly better in the RYGB group. Snoring improved in both groups, but there was no significant difference between groups.

At follow-up, remission of OSA (AHI < 5 events/h) was registered in 29 of 44 (66%) RYGB patients and 16 of 40 (40%) ILI patients, between group difference p = 0.028. Another 5 (13%) ILI patients and 7 (16%) RYGB patients improved to a less severe level of OSA at follow-up (Figure 2).

A total of 3 patients in the ILI group and one in the RYGB group deteriorated from no OSA to mild OSA. One RYGB patient and two ILI patients with mild OSA deteriorated to moderate OSA, and one patient in the ILI group deteriorated from moderate to severe OSA. AHI was reduced, with 0.93 events/h per kg weight reduction in the ILI group and 0.52 in the RYGB group, mean between-group difference (95% CI) 0.41 (-0.6, 1.4), p = 0.405.

Predictors of OSA at One Year
Treatment choice was an independent predictor of the presence of OSA (AHI ≥ 5 events/h) at one year after adjusting for age, gender, and baseline AHI. The surgical patients had a 67%
lower odds of OSA at one year (OR [95% CI] 0.33 [0.14, 0.81], p = 0.015). After adding BMI change to this model treatment group assignment was no longer significant: OR (95% CI) 1.31 (0.32, 5.35), p = 0.709. There was no significant interaction between gender and treatment group in a multivariate logistic regression model (data not shown).

DISCUSSION

Our findings suggest that gastric bypass surgery is more effective than intensive lifestyle intervention at reducing the prevalence and severity of OSA in morbidly obese patients.

Although the proportion of patients with remission of OSA was higher in the RYGB group than in the ILI group, it should be noted that 2 of 5 patients in the ILI group had remission of OSA (compared to 2 of 3 in the RYGB group). The beneficial effect of ILI on remission of OSA should not therefore be underestimated.

To the best of our knowledge, no prospective clinical trial has compared the effects of bariatric surgery and intensive lifestyle intervention on the severity or resolution of OSA. Our findings are, however, in accordance with previous observational studies addressing the effect of bariatric surgery and lifestyle intervention.4,9 In accordance with our findings, a recent meta-analysis of 12 studies focusing on the effects of bariatric surgery reported an average 71% reduction in AHI events.12 The ILI patients reduced their weight by approximately 10% and their AHI by approximately 40%. This also corresponds well with the findings of a study that found a 50% reduction in AHI when patients reduced their body weight by 10% to 15%.23

Although the beneficial effect on OSA was more pronounced in the RYGB group, multivariate analyses indicated that this effect seemed to be mediated by weight loss rather than treatment choice. It is widely accepted that weight loss leads to improvements in OSA;5 comparing different methods of weight reduction and their effects on OSA might therefore be useful in the determination of appropriate treatment options. Body composition and the distribution of muscles and fat deposits also play a role in the pathogenesis of OSA, not only body weight.

We have previously published data demonstrating a greater increase in the physical activity levels of the lifestyle group than the surgery group.14 We cannot exclude the possibility of an independent effect of physical activity on sleep apnea, but, unfortunately, our study was not powered to address this hypothesis. The majority of patients with absolute indication for CPAP (AHI ≥ 15) at baseline improved to mild/no OSA at follow-up—73% in the RYGB group and 53% in the ILI group. The apparent lack of significant difference between groups might be explained by the relatively low number of patients (type II error). Nonetheless, CPAP is an effective treatment option, but many patients struggle with the use of the machine. Compliance is at best moderate, and prescription of the device is considered by some patients to be stigmatizing. Even though CPAP use helps improve quality of life,25 one should not disregard the many reservations patients might have. The positive effects of CPAP cessation, often overlooked, ought to be further investigated. Our results indicate that both RYGB and ILI may reduce the need for CPAP-treatment in morbidly obese patients.

The strengths of the present study include the prospective design and the relatively high number of patients in two comparable groups. Although the RYGB subjects were slightly heavier and younger, the two treatment groups were not significantly different in terms of baseline AHI and gender. This study has a number of limitations. Firstly, it suffers from a lack of randomization, which was after ethical and legal consultations considered unethical.14 Our center is a public health care provider; according to national guidelines patients should be offered either conservative or surgical therapy in an obesity clinic based on the multidisciplinary team model.15 Randomization to surgery would therefore be obsolete if the patient both wanted and qualified for a lifestyle intervention program, and vice versa. Second, as the intensive lifestyle intervention was delivered in the form of a residential program this could limit the generalizability of the results. Further, compliance with respect to physical activity and CPAP usage was not registered. Intakes of alcohol and sedative drugs were not addressed.

The subjects were mainly Caucasians, limiting the generalizability of our findings to other ethnicities. We used a portable sleep recorder, which is the most widely used device in Scandinavia. Consequently, we could not score sleep stages and had to rely on a sleep diary and time in bed to define when patients slept.

CONCLUSION

Gastric bypass surgery was more effective than intensive lifestyle intervention at reducing the prevalence and severity of OSA in a population of treatment seeking morbidly obese patients. The beneficial effect of surgical treatment seemed to be mediated by weight loss rather than RYGB per se. Intensive lifestyle intervention was also associated with significant improvements in OSA.

REFERENCES


Obstructive sleep apnea (OSA) is characterized by repetitive upper airway collapse during sleep, causing hypoxemia and sleep fragmentation that lead to daytime sleepiness and increased risk of cardiovascular incidents, motor vehicle, and occupational accidents. The gold standard for the treatment of OSA is continuous positive airway pressure (CPAP). It has been demonstrated that successful CPAP treatment improves systemic hypertension and prolongs survival. However, the clinical effectiveness of CPAP is often limited by low patient acceptance, poor tolerance, and suboptimal compliance. Therefore, non-CPAP alternatives for the treatment of sleep disordered breathing, such as oral appliance therapy with custom-made titratable mandibular advancement devices, surgery, or upper airway stimulation (UAS) has gained growing interest. UAS therapy, which uses electrical stimulation of the hypoglossal nerve, has been previously reported to be safe and efficacious in a select group of OSA patients who cannot or will not use CPAP as primary treatment. In non-selected OSA patients undergoing UAS therapy, a large interindividual difference in response to stimulation is observed. A recent study by Van de Heyning et al. examined a set of factors predictive for therapy response to UAS.

Evaluation of Drug-Induced Sleep Endoscopy as a Patient Selection Tool for Implanted Upper Airway Stimulation for Obstructive Sleep Apnea

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Keywords: Electrical stimulation, hypoglossal nerve, neuromodulation, obstructive sleep apnea hypopnea syndrome, prediction, sleep disordered breathing, snoring

Study Objectives: To study the possible predictive value of drug-induced sleep endoscopy (DISE) in assessing therapeutic response to implanted upper airway stimulation (UAS) for obstructive sleep apnea (OSA).

Methods: During DISE, artificial sleep is induced by midazolam and/or propofol, and the pharyngeal collapse patterns are visualized using a flexible fiberoptic nasopharyngoscope. The level (palate, oropharynx, tongue base, hypopharynx/epiglottis), the direction (anteroposterior, concentric, lateral), and the degree of collapse (none, partial, or complete) were scored in a standard fashion.

Results: We report on the correlation between DISE results and therapy response in 21 OSA patients (apnea-hypopnea index [AHI] 38.5 ± 11.8/h; body mass index [BMI] 28 ± 2 kg/m², age 55 ± 11 y, 20 male/1 female) who underwent DISE before implantation of a UAS system. Statistical analysis revealed a significantly better outcome with UAS in patients (n = 16) without palatal complete concentric collapse (CCC), reducing AHI from 37.6 ± 11.4/h at baseline to 11.1 ± 12.0/h with UAS (p < 0.001). No statistical difference was noted in AHI or BMI at baseline between the patients with and without palatal CCC. In addition, no predictive value was found for the other DISE collapse patterns documented.

Conclusions: The absence of palatal CCC during DISE may predict therapeutic success with implanted UAS therapy. DISE can be recommended as a patient selection tool for implanted UAS to treat OSA.

Study Impact: In this study, the predictive value of drug-induced sleep endoscopy (DISE) was assessed towards UAS treatment success in 21 OSA patients. The results demonstrate a strong correlation between the absence of a complete circular collapse at the level of the palate as documented during DISE and a successful treatment outcome with UAS; based on these results, DISE can be recommended as a patient selection tool for implanted upper airway stimulation for obstructive sleep apnea. J Clin Sleep Med 2013;9(5):433-438.
Drug-induced sleep endoscopy (DISE) is increasingly being performed, offering the possibility of dynamic upper airway evaluation during artificial sleep as a promising technique for selecting the proper non-CPAP treatment for OSA patients.\textsuperscript{18,19}

The aim of this study was to perform a detailed assessment of the possible predictive value of DISE in the evaluation of therapeutic response to implanted UAS therapy for OSA. Some of the results of this study have been previously reported in the form of an abstract.\textsuperscript{20}

**METHODS**

We report on OSA patients who underwent a DISE before UAS system implantation.\textsuperscript{15} Patients with moderate to severe OSA (apnea-hypopnea index [AHI] ≥ 15/h sleep) and BMI < 35 kg/m\textsuperscript{2} were selected for UAS system implantation if they failed or were intolerant of CPAP treatment. Exclusion criteria included chronic obstructive pulmonary disease, New York Heart Association class III or IV congestive heart failure, neuromuscular diseases, or prior upper airway surgeries not related to OSA. The trial was approved by the institutional review boards or ethics committees at all participating centers, and informed consent was obtained from all study subjects.

**Polysomnography**

An 18-channel in-laboratory polysomnography examination was conducted according to the American Academy of Sleep Medicine (AASM) guidelines.\textsuperscript{21} Hypopneas were scored according to the AASM 2007 Rule 4a: a nasal pressure drop ≥ 30% of baseline, duration > 10 sec, ≥ 4% desaturation from baseline, and ≥ 90% of the event duration must meet the amplitude reduction criteria for hypopnea.

**Drug-Induced Sleep Endoscopy (DISE)**

The DISE procedure was performed by an ENT surgeon in a semi-dark and silent operating room with the patient in supine position.\textsuperscript{22,23} Continuous monitoring of cardiac rhythms and oxygen saturation was provided.\textsuperscript{22} Unconscious sedation was induced by intravenous administration of midazolam with a bolus injection of 1.5 mg and/or with propofol using a target-controlled infusion system at a target of 2.0 to 3.0 mcg/mL. During DISE, the level (palate, oropharynx, tongue base, hypopharynx/epiglottis), the direction (anteroposterior [AP], lateral), and degree of upper airway collapse (none, partial, or complete) were scored in a standard fashion, with an average age of 55 ± 11 years, a baseline AHI of 38.5 ± 11.8/h, and a BMI of 28 ± 1 kg/m\textsuperscript{2} (Table 1).

**Upper Airway Stimulation (UAS) System**

The UAS system consists of a respiration sensor, a programmable implanted pulse generator, and stimulating electrodes (Inspire Upper Airway Stimulation therapy, Inspire Medical Systems, Minneapolis, MN, USA). The Inspire II Upper Airway Stimulation (UAS) system (Inspire Medical Systems, Maple Grove, MN) consisted of a respiration sensor, programmable implanted pulse generator (IPG), and stimulating electrodes. The sensor detected respiratory efforts from the chest that were analyzed by the IPG. From the sensor signal, the IPG predicted the onset of inspiration, delivering stimulation pulses between the end of expiration and the beginning of the next expiratory phase of each respiratory cycle. The electrical pulses were applied to the hypoglossal nerve through platinum/iridium electrodes. The patient was given a programming device capable of initiating and terminating the UAS therapy. The operative technique of the implantation of the UAS system used in this study has been described in detail previously.\textsuperscript{13,27}

**Definition of Treatment Success**

The present study used the criteria established by Sher et al. to define treatment success as AHI < 20/h after treatment and an AHI reduction ≥ 50% as compared to baseline.\textsuperscript{28} Additionally, success rates were assessed for a success definition of AHI < 15/h sleep. To assess daytime sleepiness, patients filled out the Epworth Sleepiness Scale (ESS).\textsuperscript{29}

**Statistical Analysis**

The pre-implantation AHI was compared to AHI 6 months after implantation. Statistical analysis was performed using MATLAB (The Mathworks, Natick, MA, USA) and Excel (Microsoft Corp, Redmond, WA, USA). A Wilcoxon signed-rank test was used to compare the pre-implantation AHI to the post-implantation AHI. Differences were considered statistically significant if the p-value was less than 0.05. Results were presented as means and standard deviations.

**RESULTS**

**Subjects**

DISE videos were recorded for 21 patients with an established diagnosis of moderate to severe OSA before the implantation of the UAS system. Patients were predominantly male, with an average age of 55 ± 11 years, a baseline AHI of 38.5 ± 11.8/h, and a BMI of 28 ± 2 kg/m\textsuperscript{2} (Table 1).

**DISE Analysis**

An overview of the distribution of the levels of upper airway collapse for all patients included in this study based on DISE scoring is provided in Figure 1 and Table 2. The majority of patients (91%) had multilevel collapse, predominantly at the palatal and tongue base levels and rarely at the oropharyngeal and hypopharynx/epiglottis levels (Figure 1). The most common upper airway collapse patterns noted in this study were AP collapse at the levels of the palate (76.2%) and the tongue base (71.4%) (Table 2).

Sixteen patients were categorized as having predominant AP palatal collapse, and 5 were categorized as having complete
concentric collapse (CCC) at the palatal level (Figure 2). There was no significant difference in baseline AHI, BMI, or age between patients with and without palatal CCC (Table 1).

In this patient group, 19 of 21 patients had multilevel collapse. All patients had at least a collapse at the level of the palate (Figure 1), whereas tongue base, hypopharynx/epiglottis, and oropharynx collapse were noted in 80.9%, 33.4%, and 23.9% of patients, respectively (Figure 1). Conversely, no patients had tongue base collapse without palatal collapse (Figure 1).

The most common combination of multilevel collapse was the combination of AP palatal and AP tongue base collapse without epiglottis collapse, which occurred in 33% of the patients.

UAS Effect on Various Collapse Types

Patients with palatal CCC did not have a significant change in AHI with UAS 6 months after implantation, as baseline AHI was 41.5 ± 13.8/h and AHI with UAS was 48.1 ± 18.7/h, (p = 0.44; Figure 2). The patients without palatal CCC had a significant improvement in AHI with UAS despite multilevel collapse at the palate and tongue base. For this subset of patients, AHI went from 37.6 ± 11.4/h at baseline to 11.6 ± 11.7/h with UAS (p < 0.001; Figure 2). Thirteen patients with both palatal AP and tongue base AP collapse had a significant improvement in the AHI, decreasing from 38.0 ± 10.3 at baseline to 13.6 ± 12.1 with UAS (p < 0.001).

Treatment Success Analysis

The overall UAS treatment success rate for all 21 patients included in this study using Sher’s criteria was 62% (13/21). Treatment success in the subset of patients without CCC collapse at the level of the palate was 81% (13/16), while treatment success could not be achieved in any patient with CCC collapse at the level of the palate in this study (0/5). When assessing the success rates specifically for AHI < 15, overall success would be achieved in 11/21 (52.4%) patients. In patients without palatal CCC success would be achieved in 11/16 patients (68.8%); in patients with palatal CCC this would be 0/5 (0%). There was no significant difference in BMI between baseline and 6 months in either group. Overall, ESS improved significantly from baseline 8.2 ± 5.0 to 6.4 ± 4.3 (p = 0.02; n = 18).

DISCUSSION

This study evaluates DISE as a patient selection tool for implanted UAS therapy to treat OSA. The results of this study indicate that the absence of CCC at the level of the palate as documented during DISE may predict therapeutic success for OSA patients with implanted UAS therapy. These findings are highly relevant to the field, as previous studies have indicated that the application of hypoglossal nerve stimula-
The role of DISE in non-selected OSA patients leads to high interindividual variation in therapeutic effectiveness. The actual effects of upper airway muscle activation on upper airway shape are dependent on both the upper airway region and cross-sectional area. Further research on DISE as a patient selection tool for implanted UAS may focus on upper airway behavior during UAS as assessed during DISE. In a recent study by Goding et al., cross-table fluoroscopic images were obtained during hypoglossal nerve stimulation in 26 subjects while two-dimensional changes in the AP dimensions of both the retropalatal and the retrolingual airway spaces were recorded. The results of this fluoroscopy study indicate that during hypoglossal nerve stimulation, an opening of the upper airway at the level of the palate occurs in a majority of cases, confirming the beneficial effect of hypoglossal nerve stimulation on the AP upper airway dimensions.

There is great interest in the prospective prediction of treatment outcome of non-CPAP options such as surgery and oral appliance therapy. DISE provides an alternative method of studying the upper airway in OSA patients while performing a fiberoptic endoscopy during sedation. The lack of uniformity in the methods used for sedation during DISE as well as the fact that a consensus on DISE scoring systems has not yet been established, are clear limitations to this study. Recent studies that address the test-retest and the intra- and interobserver variability in DISE scoring indicate that the reliability of both are moderate to fair, and that inter-observer agreement is higher in ENT surgeons who are experienced with DISE.

The limitations of this study also include the fact that DISE was performed only in the supine position, whereas upper airway collapse patterns should ideally be assessed in both the supine and non-supine position.

It is well known that the probability of a multilevel collapse is significantly associated with the severity of OSA, as higher AHI values are correlated with a higher percentage of multilevel collapse. This finding might explain the high prevalence of multilevel collapse in our study (91%) given the relatively high overall baseline AHI of 38.5 ± 11.8/h. Upper airway collapse at the level of the palate was the most common level of collapse in this study, with collapse at the level of the tongue base being the second most common (Figure 1). Again, these findings are in line with previous studies.

Two recent studies have shown a correlation between a patient’s BMI and the therapeutic response to UAS. In addition, a baseline AHI ≤ 50/h turned out to be a predictor of UAS therapy response.

Although the number of patients included in this study was relatively low, a clinically and statistically significant difference in AHI was detected between the two groups of OSA patients (those with versus those without palatal CCC; Figure 3). According to Sher’s criteria, treatment success in the patients without palatal CCC was 81%, while no patients with CCC at the level of the palate could be treated successfully with UAS. The correlation between the absence of CCC at the level of the palate and treatment success with UAS turned out to be independent from baseline AHI and the patient’s BMI (Table 1). Given that both parameters were previously described as predictors of therapeutic outcome with hypoglossal nerve stimulation for OSA, the fact that the absence of palatal CCC remains highly predictive independent from AHI and BMI certainly adds to the power of these findings.
In conclusion, based on the results of the reported study, DISE can be recommended as a patient selection tool for implanted UAS to treat OSA. Further analysis of the predictive value of DISE in assessing therapeutic response to UAS therapy needs to be performed in larger multicenter trials that are currently ongoing.

**ABBREVIATIONS**

AP, anteroposterior  
AHI, apnea-hypopnea index  
BMI, body mass index  
CCC, complete concentric collapse  
CPAP, continuous positive airway pressure  
DISE, drug-induced sleep endoscopy  
OSA, obstructive sleep apnea  
UAS, upper airway stimulation

**REFERENCES**

This study was supported by Inspire Medical Systems, Inc. Mr. Vanderveken is co-investigator for a study supported by Inspire Medical Systems Inc. Dr. Maurer is co-investigator for a study supported by Inspire Medical Systems Inc. He had paid speaking engagements with Inspire Medical Systems Inc. (USA), GlaxoSmithKline (Germany), Weinmann (Germany), Olympus (Germany), ResMed (Germany), Neuwirth (Germany), Medtronic (USA) and Heinen & Löwenstein (Germany). Dr. Maurer received paid speaking engagement and surgical cadaver training for beginners. Mr. Hohenhorst is investigator for Inspire Medical Systems Inc. Mr. Hamans is a consultant for Philips Healthcare. Mr. Lin has participated as a co-investigator in clinical trials sponsored by Inspire Medical Systems Inc. and has served as a consultant for Inspire Medical Systems Inc. Dr. Anders is co-investigator for a study supported by Inspire Medical Systems Inc. He had paid speaking engagements with Inspire Medical Systems Inc. (USA), GlaxoSmithKline (Germany), Weinmann (Germany), Olympus (Germany), ResMed (Germany), Neuwirth (Germany), Medtronic (USA) and Heinen & Löwenstein (Germany). He has also received paid speaking engagement and surgical cadaver training for beginners. Dr. de Vries is medical advisor for MSD, ReVENT, NightBalance; investigator for Inspire Medical Systems Inc.; consultant for Philips; and has stock options in ReVENT. Dr. Van de Heyning is an investigator for Inspire Medical Systems Inc. The other authors have indicated no financial conflicts of interest.
Obstructive sleep apnea (OSA), is a chronic disease that affects at least 2% to 4% of middle aged adults and is associated with significant morbidity and mortality. Among medical, surgical, and appliance options for treating OSA, continuous positive airway pressure (CPAP) is the treatment of choice for most patients. Increasing CPAP use is associated with dose-dependent improvements in several clinical outcomes. However, a significant number of patients struggle to consistently adhere to CPAP therapy.

Drake et al. reported that individuals whose sleep improved during the CPAP titration demonstrated two hours of increased nightly compliance, even after correcting for disease severity at initial polysomnography. Several investigators examined whether a short course of hypnotic therapy coincident with the start of CPAP therapy would improve compliance, but they found conflicting results. Bradshaw et al. reported that zolpidem immediately before CPAP titration improves 1-month CPAP adherence in subjects newly diagnosed with OSA.

CONCLUSION: A single dose of zaleplon at the start of a split-night CPAP titration does not result in superior CPAP adherence or improvement in symptoms at 1-month compared to placebo. Our data show that zaleplon is safe and is associated with shorter sleep latency during CPAP titration, but it does not translate into improved short-term CPAP adherence. Keywords: Continuous positive airway pressure, compliance, zaleplon, obstructive sleep apnea.

METHODS: After approval by our institutional review board, subjects referred to our multidisciplinary accredited sleep facility for obstructive sleep apnea...
suspected OSA between October 2004 and March 2006 were approached for enrollment. Inclusion and exclusion criteria are listed in Table 1. All subjects underwent an evaluation by a board-certified sleep specialist, were thought to likely have OSA, and were tested via a laboratory-based, technologist-attended polysomnogram (PSG). Prior to PSG, each subject viewed an educational video describing OSA, PSG, and CPAP, followed by a personalized CPAP interface sizing session with a polysomnographic technologist. Subjects were allowed to try on different interfaces with CPAP at 5 cm H2O. Participants completed the Functional Outcomes of Sleep Questionnaire (FOSQ), a 30-item questionnaire designed to assess 5 areas of functional outcomes affected by sleep disorders: general productivity, social outcomes, activity level, vigilance, and in- 
timate relationships.

PSGs were performed using a digital polygraph (NCI Lamont Medical, Inc., Madison, WI, or Bio-Logic Systems Corp., Mundelein, IL). The following parameters were recorded: electroencephalography (Fz-Cz; Cz-Oz; C4-M1 or C3-M2); electrooculography (right outer canthus-Fpz; Left outer canthus-Fpz); submental and anterior tibialis electromyography; snoring by laryngeal microphone; electrocardiography; pulse oximetry; and respiratory effort (thoracic, abdominal, and summed inductive plethysmography). Airflow was analyzed by nasal pressure transducer (standard at the time of this study). Obstructive apnea was defined as cessation of airflow ≥ 10 sec despite respiratory effort. Hypopnea was defined by ≥ 30% reduction in airflow ≥ 10 sec accompanied by ≥ 4% drop in oxyhemoglobin saturation. Sleep stages and arousals were manually scored by registered polysomnographic technologists using contemporary standards at the time of the study. Apnea-hypopnea index ≥ 5 noted at the time of randomization (i.e., after the diagnostic portion of the split-night polysomnogram) or New diagnosis of restless leg syndrome requiring treatment or Known pregnancy or breast feeding mothers

Table 1—Inclusion and exclusion criteria for study participants

<table>
<thead>
<tr>
<th>Inclusion criteria:</th>
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<tbody>
<tr>
<td>• Patients referred for presumed diagnosis of obstructive sleep apnea and willing undergo a polysomnogram</td>
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<tr>
<td>• Age 18-90 years</td>
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<tr>
<td>• Able to provide informed consent</td>
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<tr>
<td>• Able to return for one month follow-up</td>
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<tr>
<th>Exclusion criteria:</th>
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<tr>
<td>• Severe COPD signified by forced expiratory volume in 1 second &lt; 40% predicted or need for supplemental oxygen</td>
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<tr>
<td>• Known hypersensitivity to zaleplon</td>
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<tr>
<td>• Known severe hepatic or renal impairment (creatinine &gt; 3 mg/dL)</td>
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<tr>
<td>• Concurrent use of benzodiazepines.</td>
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<tr>
<td>• Concurrent use of drugs that may interact with zaleplon, including cimetidine, rifampin, or thioridazine.</td>
</tr>
<tr>
<td>• Predominantly central sleep apnea noted at the time of randomization (i.e., after the diagnostic portion of the split-night polysomnogram)</td>
</tr>
<tr>
<td>• New diagnosis of restless leg syndrome requiring treatment</td>
</tr>
<tr>
<td>• Known pregnancy or breast feeding mothers</td>
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</table>

if the total sleep time was a minimum of 120 minutes. Subjects with OSA were randomized (using nQuery Advisor 4.0 software) to receive zaleplon 10 mg or an identical-appearing placebo, followed immediately by commencement of the CPAP titration during the second portion of the PSG. CPAP was started at 5 cm H2O (4 cm H2O if the subject was uncomfortable with the initial CPAP setting) through an interface of the subject’s choosing and gradually increased in increments of 1 cm H2O until disordered breathing events were eliminated. At the conclusion of the polysomnogram, subjects used a visual analog scale to rate their initial experience with the PSG and CPAP. A board-certified sleep specialist reviewed all PSGs. For those prescribed CPAP, a standardized education packet regarding the use and care of CPAP equipment supplemented the sleep specialists’ education regarding CPAP use, and follow-up visit was scheduled. The follow-up visit target was 1 month, but varied because of differences in time necessary to secure CPAP (CPAP was obtained by subjects through a durable medical equipment vendor of their choosing) and travel distance to our center. All subjects were also encouraged to call our sleep center nurse phone line if they experienced any CPAP problems. At the follow-up visit, CPAP use information was downloaded from their device and subjects completed a second FOSQ. If subjects missed their return appointment, they were contacted by telephone to rescheduled a visit or were sent a mail package asking them to return a second FOSQ and their downloaded CPAP information (via their local vendor) using an enclosed self-stamped envelope. All patients, physicians, technologists, and nurses remained blinded with respect to zaleplon vs. placebo pretreatment throughout the study.

STATISTICS

A retrospective analysis of 274 OSA patients treated with CPAP in our sleep facility and who had downloaded compliance data revealed a mean CPAP use of 5.6 h (± 1.9) per night (non-published data gathered as part of our center’s database). Assuming the same standard deviation in our study groups and using α = 0.05, we calculated that 63 patients per study group would provide 80% power to detect a difference in nightly average CPAP use of 60 min (18% improvement) (nQuery Advisor 4.0 software) between groups. We used an intention-to-treat analysis for the pre- and post-CPAP data using a nonparametric analysis of variance (ANOVA). Similarly, nonparametric ANOVA was used to analyze the difference between groups at the time of follow-up regarding compliance and FOSQ. Non-normally distributed data are expressed as median and interquartile range (IQR), 25th and 75th percentiles. Where noted, mean ± standard deviation is used for some parametric data.

RESULTS

One hundred seventy-six eligible subjects were enrolled and randomly assigned to receive either placebo or zaleplon during split-night PSG (Figure 1). After enrollment, 42 subjects (27 in the placebo group, 15 in the zalenplon group) did not receive the assigned treatment for various reasons (Figure 1). As a result, 61 subjects comprised the placebo group and 73 subjects the zaleplon group.
Table 2—Baseline characteristics of study subject and diagnostic polysomnogram data

<table>
<thead>
<tr>
<th></th>
<th>Zaleplon</th>
<th>Placebo</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of subjects</td>
<td>73</td>
<td>61</td>
<td></td>
</tr>
<tr>
<td>Female (%)</td>
<td>18 (25%)</td>
<td>24 (39%)</td>
<td>0.049</td>
</tr>
<tr>
<td>Age (mean ± SD)</td>
<td>51.5 ± 11.6</td>
<td>47.7 ± 10.6</td>
<td></td>
</tr>
<tr>
<td>BMI (mean ± SD)</td>
<td>35.2 ± 8.2</td>
<td>36.9 ± 9.2</td>
<td>0.26</td>
</tr>
<tr>
<td>Neck (inches) (mean ± SD)</td>
<td>17.4 ± 1.8</td>
<td>17.3 ± 1.9</td>
<td>0.78</td>
</tr>
<tr>
<td>Epworth Sleepiness Scale</td>
<td>9 (7.3, 14)</td>
<td>10.5 (8, 15.1)</td>
<td>0.32</td>
</tr>
<tr>
<td>FOSQ</td>
<td>17.4 (14.7, 18.8)</td>
<td>16.3 (14.5, 17.8)</td>
<td>0.14</td>
</tr>
<tr>
<td>Sleep Efficiencya</td>
<td>73.4 (63.3, 84.5)</td>
<td>74.1 (64.8, 83.6)</td>
<td>0.93</td>
</tr>
<tr>
<td>Initial sleep latency (min)</td>
<td>10.5 (5.5, 22.2)</td>
<td>12.8 (8, 23.8)</td>
<td>0.19</td>
</tr>
<tr>
<td>Stage 1 (%)</td>
<td>17.3 (8.7, 23)</td>
<td>18 (11.7, 26.4)</td>
<td>0.41</td>
</tr>
<tr>
<td>Stage 2 (%)</td>
<td>53.5 (44.7, 63.9)</td>
<td>55.5 (43.5, 67.9)</td>
<td>0.70</td>
</tr>
<tr>
<td>Stage 3/4 (%)c</td>
<td>16.1 (4.3, 27)</td>
<td>13.7 (0, 26.3)</td>
<td>0.46</td>
</tr>
<tr>
<td>REM (%)</td>
<td>9.5 (4.7, 15)</td>
<td>7.85 (11.1, 13.3)</td>
<td>0.41</td>
</tr>
<tr>
<td>Arousal index</td>
<td>33.8 (23.1, 58.7)</td>
<td>35.5 (22.6, 59.4)</td>
<td>0.65</td>
</tr>
<tr>
<td>Periodic limb movement index</td>
<td>2.9 (0, 29.4)</td>
<td>0 (0, 28.4)</td>
<td>0.53</td>
</tr>
<tr>
<td>Apnea-hypopnea index</td>
<td>19 (9, 38.5)</td>
<td>17.5 (8.8, 33)</td>
<td>0.67</td>
</tr>
<tr>
<td>Minimum oxygen saturation</td>
<td>84 (80, 86.5)</td>
<td>84 (77, 87.6)</td>
<td>0.66</td>
</tr>
</tbody>
</table>

aData is expressed in median with interquartile range except where noted. 

aTotal sleep time/time in bed = sleep efficiency. 

bStaging slow wave sleep into stages 3 and 4 were standard at the time of this study. 

iQR, interquartile range (25th %ile, 75th %ile); BMI, body mass index (kg/m²); FOSQ, Functional Outcomes of Sleep Questionnaire.

Table 2 provides data on baseline demographics and the diagnostic portion of PSG for the 2 groups. Placebo group had slightly greater percentage of women and was slightly younger. There were no significant differences in body mass index, Epworth Sleepiness Scale (ESS) score, or FOSQ scores. There were no significant differences in various diagnostic PSG parameters, including AHI and minimum oxyhemoglobin saturation (Table 2).

Figure 1—Subject flow diagram

Subjects consented and randomized (n = 176)

Allocated to ZALEPLON (n = 88)
- Received allocated intervention (n = 73)
- Did not receive allocated intervention (n = 15)
- Failed to show for PSG (n = 2)
- Qualified for CPAP after 2:30 (n = 1)
- Did not meet CPAP criteria (n = 1)
- Refused study drug (n = 2)
- Technical error (n = 1)
- Disenrolled due to inability to fall asleep (n = 1)

Allocated to PLACEBO (n = 88)
- Received allocated intervention (n = 61)
- Did not receive allocated intervention (n = 27)
- Failed to show for PSG (n = 4)
- Qualified for CPAP after 2:30 (n = 2)
- Did not meet CPAP criteria (n = 8)
- Refused study drug (n = 4)
- Technical error (n = 1)
- Disenrolled due to inability to fall asleep (n = 2)

Began CPAP therapy (n = 54)
- Not prescribed CPAP (n = 6)
- Not accepting of CPAP (n = 13)

Began CPAP therapy (n = 50)
- Not prescribed CPAP (n = 4)
- Not accepting of CPAP (n = 7)

Did not return for follow-up (n = 5)

Did not return for follow-up (n = 4)

Analyzed (n = 49)

Analyzed (n = 46)
During CPAP titration, zaleplon use was associated with shorter initial sleep latency and decreased REM sleep compared to placebo (Table 3). There were no differences in the effective CPAP pressures, AHI for the entire titration, or the arousal index. Furthermore, there was no difference in overall subject satisfaction with the PSG and CPAP as determined by their responses on the visual analog scale (Table 3). All studies were completed without any adverse events and all CPAP titrations were considered “adequate” or greater per published clinical guidelines for CPAP titration.18

CPAP was not prescribed in 10 subjects (4 in the placebo group, 6 in the zaleplon group), because of the very mild nature of their OSA (mean AHI 5.9 ± 5.6 in these 10 subjects). An additional 20 subjects (7 in the placebo group, 13 in zaleplon group) refused CPAP therapy. Those who declined therapy were younger (median age of 41 vs 51 [p = 0.019]) and had lower BMI (median BMI of 31.5 vs 35.7 [ p = 0.009]), but did not differ in ESS, FOSQ, VAS, or AHI (data not shown). Nine subjects (4 in the placebo group; 5 in the zaleplon group) did not return for follow-up; they were not available by telephone and did not return a mail request for follow-up information (Figure 1). There were no significant differences in the age, BMI, FOSQ, ESS, or AHI between those who did and did not return for follow up (data not shown).

Ultimately, follow-up information was available in 46 subjects in the placebo group and 49 subjects in the zaleplon group, with 39 placebo group patients and 44 zaleplon group patients having CPAP devices with downloadable compliance capability (Table 4). Among these groups, no subjects discontinued CPAP therapy during the follow-up period. Using an intention-to-treat analysis, CPAP compliance and symptomatic improvements were not statistically different between the two groups (Table 4). ESS and FOSQ scores improved similarly in both groups (Table 5).

Overall, ESS score, AHI during the diagnostic test, and sleep efficiency during the CPAP titration was not associated with daily CPAP usage at follow-up (p = 1.0, 0.85, and 0.84, respectively).

**DISCUSSION**

Our study demonstrated that zaleplon administered just before CPAP titration during split-night PSG improved initial sleep latency without affecting minimum oxygen saturation or resultant CPAP pressure. Contrary to our hypothesis, use of zaleplon did not result in improved sleep efficiency or arousal indices, and thus perception of sleep quality during the PSG did not differ between the two groups. Although CPAP adherence was relatively high in both groups, use of zaleplon did not result in increased compliance. Improvements in OSA-related symptoms as measured by FOSQ and ESS were also similar in the zaleplon and placebo groups.

Our data conflict with Lettieri’s work involving the use of a hypnotic during CPAP titration. A retrospective assessment of 400 consecutive patients prescribed CPAP for OSA showed that of multiple parameters assessed, only age and use of a hypnotic
Zaleplon and CPAP Compliance

During the CPAP titration were associated with better short-term CPAP compliance. This association was significant for patients less than 50 years old, but not with older patients. The retrospective nature of their study did not allow control for selection bias (they only included patients who returned for follow-up; patients using hypnotic-sedative medications prior to PSG were excluded) or medication effects (they could not identify which patients received which hypnotic and could not verify use or non-use in 15% of their patients). In a prospective study, Lettieri and his colleagues also demonstrated that pre-treatment with eszopiclone prior to full-night attended polysomnography for CPAP titration improved CPAP compliance for those patients returning for follow-up. However, about one-sixth of their patients did not return, and the improvement in compliance was not demonstrated using an intention-to-treat analysis.

There are several potential explanations for the conflicting results. Twenty-nine percent of successfully randomized patients did not complete the study (77% of these subjects were not prescribed or declined CPAP), leaving our study potentially underpowered to detect a difference in CPAP compliance with zaleplon. In addition, the average rating of the initial CPAP experience in both groups was “very good” (“4” on a 5-point scale with “5” being “very satisfied”), making it challenging to discern an additive contribution of zaleplon when the control group was highly satisfied.

We also used a different hypnotic. Zaleplon is a pyrazolopyrimidine hypnotic/sedative that is unrelated to benzodiazepines but acts on the same GABA-A receptor site as the benzodiazepines. Zaleplon also possesses some anxiolytic effects. We opted for use zaleplon because of its short-acting hypnotic effect in an effort to mitigate any morning hangover that might result from administration in the middle of split-night PSG. Other studies have used related but longer acting nonbenzodiazepine, benzodiazepine receptor agonists, zolpidem, and eszopiclone. Multiple regression analysis of Drake’s study correlated improved CPAP compliance only with objective improvement in sleep efficiency, not with participants’ subjective improvement in their sleep quality. In our study, zaleplon improved initial sleep latency but did not affect other sleep parameters. This lack of objective improvement in sleep efficiency may also account for lack of improvement in CPAP compliance.

It is probably also important to note that the improvement in CPAP compliance in Drake’s study was from 4.09 to 6.12 hours per night. Lettieri’s prospective study using eszopiclone at the beginning of CPAP titration showed improvement from 3.9 to 4.8 hours per night of CPAP use. A prospective use of short-term eszopiclone use improved CPAP use from 2.4 to 3.6 hours. Other interventions that improved CPAP compliance were in cases where baseline or placebo group use was under 5 hours (Table 6). Our placebo group’s average compliance was already 6.5 h/night. These results imply that the benefit of adding hypnotic in improving CPAP compliance may be limited to those whose compliance is less than 5 hours. Thus, the benefit of adding zolpidem or eszopiclone for full-night CPAP titration

### Table 5—Outcome variables at follow-up

<table>
<thead>
<tr>
<th></th>
<th>Zaleplon median (IQR)</th>
<th>Placebo median (IQR)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>44</td>
<td>39</td>
<td>0.94</td>
</tr>
<tr>
<td>Days</td>
<td>35 (30, 41.5)</td>
<td>35 (29, 43)</td>
<td>0.72</td>
</tr>
<tr>
<td>Compliant days (%)</td>
<td>92.5 (82.8, 98.5)</td>
<td>91.7 (72.2, 97.7)</td>
<td>0.64</td>
</tr>
<tr>
<td>Hours/day</td>
<td>6.5 (5, 7)</td>
<td>6.5 (5, 8)</td>
<td>0.66</td>
</tr>
<tr>
<td>Follow-up Epworth Sleepiness Scale</td>
<td>6 (3, 9)</td>
<td>6 (3, 8)</td>
<td>0.48</td>
</tr>
<tr>
<td>Follow-up FOSQ</td>
<td>18.5 (16.5, 19.5)</td>
<td>17.9 (16.3, 19)</td>
<td>0.48</td>
</tr>
</tbody>
</table>

*SD was not provided.

### Table 6—Review of interventions’ impact on CPAP compliance

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Intervention Group’s PAP Use (hours/night, mean ± SD)</th>
<th>Baseline or Placebo Group’s PAP Use (hours/night, mean ± SD)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improved sleep efficiency during PSG</td>
<td>6.12 ± 2.25</td>
<td>4.09 ± 2.52</td>
<td>0.001</td>
</tr>
<tr>
<td>Zolpidem, placebo, or standard therapy during CPAP titration</td>
<td>4.43 ± 1.16</td>
<td>4.23 ± 2.14 (placebo)</td>
<td>0.361</td>
</tr>
<tr>
<td>Zolpidem or eszopiclone during CPAP titration</td>
<td>4.0 ± 1.7</td>
<td>3.2 ± 1.7</td>
<td>0.0007</td>
</tr>
<tr>
<td>Eszopiclone during CPAP titration</td>
<td>4.8 ± 1.5</td>
<td>3.9 ± 1.8</td>
<td>0.03</td>
</tr>
<tr>
<td>Eszopiclone – first 14 nights</td>
<td>3.57*</td>
<td>2.42*</td>
<td>0.005</td>
</tr>
<tr>
<td>Cognitive behavioral therapy</td>
<td>5.38 ± 2.55</td>
<td>2.51 ± 2.7</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>C-Flex (at one month)</td>
<td>4.7 ± 2.2</td>
<td>3.5 ± 2.8</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Use of BiFlex in previously non-compliant subjects</td>
<td>3.7 ± 2.0</td>
<td>2.9 ± 2.3</td>
<td>&lt; 0.05</td>
</tr>
</tbody>
</table>

*SD was not provided.
studies may hinge on baseline CPAP compliance of the patient population. For example, if CPAP compliance of patients with certain risk factors might be predicted to be less than 5 hours, adding hypnotic such as zolpidem or eszopiclone prior to CPAP titration may result in improved CPAP compliance at follow-up.

Our study may have been limited by the split-night format of our PSG. It is possible that approximately 4 hours of CPAP titration may have been insufficient for our subjects to fully subjectively experience the benefit of CPAP, especially considering some of that time was spent in less than optimum CPAP pressure. With a full-night CPAP titration study, more of the night may be spent at adequate CPAP pressure that may further improve subjective rating. However, given that our subjects felt the titration portion was at least “very good” (rating of 4 on 5-point scale), the split-night format seems less likely to be a major contributing factor. Furthermore, there were several studies looking at the impact of split-night studies that did not find any negative impact on CPAP compliance.  

CONCLUSION

In our double-blinded, placebo-controlled, randomized study, the use of zaleplon at the beginning of CPAP titration during split-night study improved initial sleep latency, but did not yield improvements in CPAP compliance. While there was a trend towards improved sleep efficiency, it did not reach statistical significance. Our study showed that use of zaleplon did not result in systematic changes to AHI, oxygenation, or CPAP titration pressures, and it may therefore be used safely in patients without contraindications during attended polysomnography, and because of shorter sleep latency, might allow for longer PSG recordings. However, benefit for CPAP treatment adherence may only accrue to patients in whom anticipated CPAP adherence is low.

REFERENCES


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DISCLOSURE STATEMENT

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Effects of Armodafinil on Simulated Driving and Self-Report Measures in Obstructive Sleep Apnea Patients prior to Treatment with Continuous Positive Airway Pressure

Gary G. Kay, Ph.D.; Neil Feldman, M.D., F.A.A.S.M.

Current Knowledge/Study Rationale: This study investigated a strategy for improving driving safety in OSA patients during the interval between the first contact of the clinician with the patient and the initiation of CPAP. The study was designed to assess the effect of armodafinil on simulated driving performance prior to the initiation of CPAP treatment and to determine the impact of this treatment on subsequent CPAP compliance.

Study Impact: Results demonstrate that 2 weeks of treatment with armodafinil improved simulated driving performance prior to the initiation of CPAP therapy and had no impact on subsequent CPAP compliance. The study also provided evidence of the marked improvement in driving performance following 6 weeks of treatment with CPAP (after discontinuation of the drug treatment phase of the study).

BRIEF SUMMARY

Methods: Sixty-nine newly diagnosed OSA patients, awaiting CPAP therapy, were randomized (1:1) to placebo or armodafinil (150 mg/day) treatment. Simulated driving tests and self-report measures were completed at baseline, after 2 weeks of drug treatment, and following 6 weeks of CPAP treatment. CPAP compliance was evaluated at the end of 6 weeks of CPAP.

Results: Compared to placebo, armodafinil improved simulated driving safety performance in OSA patients awaiting CPAP therapy (p = 0.03). Improvement was seen in lane position deviation (p = 0.002) and number of lane excursions (p = 0.02). Improvement was also observed on measures of sleepiness using the Epworth Sleepiness Scale (ESS) and sleep related quality of life. Following 6 weeks of CPAP, there was also significant improvement observed on multiple measures of simulated driving performance. CPAP compliance did not differ between armodafinil-treated and placebo-treated patients (p = 0.80).

Conclusions: Armodafinil was found to improve simulated driving performance in OSA patients with EDS prior to initiation of CPAP. Treatment with armodafinil showed no effect on subsequent CPAP compliance.

Keywords: CPAP, OSA, driving simulation, ESS, armodafinil

Citation: Kay GG; Feldman N. Effects of armodafinil on simulated driving and self-report measures in obstructive sleep apnea patients prior to treatment with continuous positive airway pressure. J Clin Sleep Med 2013;9(5):445-454.
A larger crossover study in the same patient population following acutely interrupted CPAP therapy, they were able to show that modafinil indeed prevented the decline in simulated driving performance, neurocognitive performance, and subjective sleepiness compared to placebo treatment.21

The current study was designed to assess the effects of 150 mg of armodafinil (the R-enantiomer of modafinil) on simulated driving performance in newly diagnosed OSA patients with excessive daytime sleepiness (ESS ≥ 12) during a 2-week period prior to initiating CPAP therapy. We chose an ESS ≥ 12 to obtain a study population with more clinically significant illness that might put them at risk for motor vehicle accidents. Unlike those who participated in the studies conducted by Williams et al.,20,21 our patients were CPAP naïve and studied for a different purpose. In clinical practice, patients newly diagnosed with OSA often must wait for weeks before initiating CPAP therapy. Delays can be the result of scheduling, waiting for insurance approval, or other causes. The obvious concern is that these patients are at higher risk for driving related accidents.2,3 In this regard, practitioners have asked whether it would be advisable to start a newly diagnosed OSA patient on a stimulant medication approved for treatment of residual EDS (e.g., armodafinil) while they are awaiting initiation of CPAP treatment.22 However, an additional concern is that prior use of stimulant treatment might negatively impact subsequent CPAP compliance. Therefore, in addition to determining the effect of armodafinil on simulated driving performance, the present study was designed to assess whether treatment with armodafinil, prior to initiation of CPAP, would affect subsequent CPAP compliance. Finally, the present study was also designed to assess simulated driving performance following 6 weeks of CPAP therapy.

METHODS

Patients

The study was advertised in local newspapers and was described in a local television news story. A total of 69 previously untreated OSA patients were enrolled in the study. Male and female subjects eligible for participation were 21-64 years of age, with a diagnosis of OSA confirmed by nocturnal polysomnogram (PSG) (apnea-hypopnea index [AHI] > 15), and with excessive daytime sleepiness (ESS ≥ 12). All subjects were newly diagnosed and awaiting CPAP therapy. Subjects were required to have a valid driver’s license and to have been actively engaged in driving for the past 3 years. Exclusion criteria included any unstable medical condition, circadian rhythm disorder, restless leg syndrome, narcolepsy, other significant sleep disorders, irregular sleep schedules, use of sedating antihistamines, selective serotonin reuptake inhibitors, muscle relaxants or hypnotics, consumption of more than 600 mg of caffeine per day, alcohol abuse, simulator sickness, and medical conditions or use of medications contraindicated for use of armodafinil.22 Subjects were admitted and randomized without regard for their driving history.

Study Design

The study design is shown in Figure 1. This was a double-blind, placebo-controlled, randomized, single-site study. The study was reviewed and approved by an institutional review board. All sub-

Figure 1—Study Design and Subject Disposition

Visit 1, Day 0  
Screening and Training  
Enrolled (n = 224)  
Driving Sim Screening & Training

Visit 2, Day 14  
Baseline  
Randomized (n = 69)  
Driving Sim Baseline Testing

Armodafinil (n = 35)  
Placebo (n = 34)

Visit 3, Day 28  
Driving Sim Testing  
Discontinuation of Medication  
CPAP Treatment Initiated (n = 69)

Visit 4, Day 42  
CPAP Follow-up

Withdraw/Terminated (n = 5)  
Adverse Event (n = 1)  
CPAP Intolerance (n = 2)  
Scheduling (n = 1)  
Positive Drug Screen (n = 1)

Visit 5, Day 70  
End of Study  
Driving Sim Testing  
Completed (n = 64)

Screen Failure (n = 155)  
Simulator Sickness (n = 32)  
AHI ≤ 15 (n = 21)  
Medical History (n = 21)  
Withdrew Consent (n = 10)  
ESS < 12 (n = 10)  
Other Sleep Disorders (n = 9)  
Abnormal Lab (n = 8)  
Time in Bed/Shift Work (n = 8)  
Concomitant Medication (n = 7)  
ECG Abnormality (n = 7)  
Lost to Follow-Up (n = 5)  
Prior OSA/CPAP HX (n = 2)  
Other Causes (n = 6)
jects gave written informed consent. This study was conducted in compliance with Good Clinical Practice, according to the International Conference on Harmonization Tripartite Guideline.

There were two phases to this study. In the first 2-week phase, subjects with OSA and EDS were randomized (1:1) to treatment with armodafinil (150 mg) or placebo. In the second phase, all subjects completing the first phase were treated for 6 weeks with CPAP.

During the 2-week screening period, the diagnosis of OSA was confirmed by nocturnal polysomnogram (AHI > 5) and subjects had to demonstrate at least moderate EDS (ESS ≥ 12). During the screening period subjects were given a brief introduction to the driving simulator (approximately 10 min). Upon completion of this screening drive, subjects were orally administered the Simulator Sickness Questionnaire (SSQ).24 Subjects with scores > 20 on the SSQ Nausea, Disorientation, Oculomotor, or Total scale were excluded. Subjects who passed the screening were shown an instructional orientation slideshow. This was followed by a 20-min training scenario, which provided additional standardized instructions for the scenarios used in the study. This was followed by an additional 20-min practice driving session.

Eligible subjects returned for their baseline visit (Visit 2). During the baseline visit, all study measures were administered. The driving simulation test was administered at approximately 10:00 and consisted of a 20-min vigilance driving scenario (VIG), a 20-min urban scenario (URB), and a 40-min country vigilance scenario (CV). Prior to beginning the driving simulation test, subjects completed a 10-min warm-up drive to reacquaint them with the driving controls.

Study medication was dispensed following completion of baseline testing. Subjects were randomly assigned on a 1:1 basis to receive armodafinil or matching placebo once daily in the morning (i.e., before 08:00 and 30 min prior to breakfast). Subjects were titrated to a fixed dose of 150 mg of armodafinil: 50 mg of armodafinil for the first 2 days of dosing, 100 mg of armodafinil for the second 2 days of dosing, and 150 mg of armodafinil for the remainder of the dosing period (10 to 24 days). A computer-generated randomization schedule was prepared using SAS Version 9.1.3 PROC PLAN.

Following the 14-day dosing period, subjects returned for Visit 3 procedures. A final dose of the study medication was dispensed at the clinic. Armodafinil dosing compliance was monitored by “pill count” on Visit 3 of the study (see Figure 1). Self-report measures (ESS, Functional Outcomes of Sleep Questionnaire [FOSQ], and Medical Outcomes Study 6-item Cognitive Functioning Scale [MOS-CF6]) were completed prior to beginning the driving tasks. In addition, subjects completed a 10-min warm-up drive. At approximately 10:00am, the subjects drove the 3 scenarios. Subjects returned on the evening of the same day or on the following day for a nocturnal polysomnogram with CPAP titration and were given instructions on proper use of CPAP. Two weeks following initiation of CPAP, subjects returned to the clinic for a follow-up clinic appointment (Visit 4), which addressed compliance and further instruction on proper use of CPAP as needed.

The final testing visit (Visit 5) was conducted after 4 additional weeks (6 weeks total) of CPAP. Subjects completed the same testing procedures that were completed at the baseline visit and following discontinuation of the study medication.

After completion of driving simulator testing, subjects were administered a battery of neuropsychological tests including measures of vigilance, psychomotor functioning, memory, and executive functions, including the computer-based cognitive test (CogScreen) used in the Apnea Positive Pressure Long-term Efficacy Study (APPLES).25 Results of the effects of armodafinil and CPAP on these cognitive measures will be reported separately.

Adverse events were monitored throughout the study, with severity (mild, moderate, or severe) and relationship to study medication rated by the investigator. Concomitant medications were recorded. Physical examinations (screening and end of study or final visit), vital sign measurements, and standard hematologic laboratory tests and chemistries were performed.

Cognitive Research Corporation Driving Simulator (CRCDS)

The CRCDS is a PC-based driving simulator which incorporates the Systems Technologies Inc. STISIM (Model 100W) software, three 21-inch LCD monitors to provide a wide field of view (105°), and a full-size steering wheel and pedals (ECCI Trackstar 6000GT). The CRCDS complies with current regulatory guidelines (U.S. FDA 21 CFR Part 11), which specify data integrity and system validation requirements. Two equivalent CRCDS simulators were used to conduct the study. The STISIM software used in the CRCDS has previously been used in studies of stimulant effects on driving performance26 and to study the effects of obstructive sleep apnea.1

The specific driving scenarios chosen for the study were designed to be sensitive to the known driving difficulties of untreated patients with OSA and are comparable to those used in prior studies of OSA patients. The subjects began by driving the VIG scenario, a 20-min scenario consisting of a 2-lane, rural highway with rolling hills, occasional oncoming traffic, a single crash likely event, and a secondary (divided-attention) vigilance task. For this task, subjects were instructed to rapidly press a button on the steering wheel when an infrequently presented target stimulus appeared in boxes at the upper left and right sides of the screen. The second scenario was the 20-min URB scenario. This scenario has considerably more traffic, pedestrians, and 3 crash likely events. The final drive was the CV scenario, a 40-min drive consisting of a 2-lane, rural highway with curves and hills but no sharp turns or stops, minimal oncoming traffic, no crash likely events, and a set speed limit (55 miles per hour). Driving data for the CV scenario was grouped into five 8-min time blocks (Epochs 1-5) to evaluate the effect of time-on-task.27

Self-Report Measures

The self-report measures selected for the study are among the most commonly used measures to assess outcome in sleep research, and included the Epworth Sleepiness Scale (ESS),28 the Functional Outcomes of Sleep Questionnaire (FOSQ),29 and the Medical Outcomes Study 6-item Cognitive Functioning Scale (MOS-CF6).30

CPAP Compliance

The Smart Card installed in the CPAP machine (Resmed Elite) was used to provide a measure of CPAP treatment com-
Clinical Population

Two hundred twenty-four (224) participants were screened, and 69 were randomized. The most common cause for screen failure was simulator sickness (n = 32; 14.3% of the subjects who were screened), followed by failure to meet the PSG criteria (i.e., AH1 ≤ 15; n = 21; 9.4%), failure to meet the medical history criteria (n = 21, 9.4%), low ESS score (n = 10; 4.5%), withdrawal of consent (n = 10; 4.5%), and positive urine drug screen (n = 9; 4.0%). One subject was excluded from the efficacy analysis (the mITT population) due to unwillingness to perform the driving simulation test at the end of Period 1. The same subject withdrew from the study at the beginning of Period 2 due to a work schedule conflict. Four other subjects discontinued during Period 2; one withdrew due to a treatment unrelated adverse event (cataract worsening); one for a positive urine drug screen, and 2 subjects could not tolerate CPAP. In the mITT population, 34 subjects were randomized to each of the 2 treatments. Treatment related adverse events are reported in Table 1.

The subject demographics are summarized in Table 2. Sixty-nine (69) subjects were randomized to armodafinil or matching placebo treatment for 14 days. The mean age of participants was 46.1 ± 9.8 years (range 23 to 64). The majority of subjects were males (85.5%). The distribution by race shows that 71.0% were non-Hispanic Caucasian, 18.8% African American, 8.7% Hispanic, and 1.4% Asian. College education (13 or more years of school) was reported by 72.4% of participants. Of the remaining subjects, 21.7% had completed high school and 5.8% had not graduated from high school. The mean AH1 at baseline was 43.12 ± 26.1 (range 15.07-114.6), and the mean body mass index (BMI) was 37.0 ± 7.5. The mean ESS score at baseline was 16.8 ± 3.0 (range 12 to 24). There were no significant differences between treatment groups on any of these variables.

Simulated Driving Performance

Effect of Armodafinil

There was significant improvement in the DSS (p = 0.03) for subjects who received armodafinil compared to those treated with placebo (see Table 3). For the DSS, a lower value indicates safer driving. Subjects who received armodafinil had a significantly lower DSS following treatment. In contrast, for subjects who were treated with placebo, the DSS increased from Baseline to Visit 3.

Of the 7 variables (see Table 3) that comprise the DSS, a significant difference between armodafinil and placebo was found for Out of Lane CV (p = 0.02) and Lane Deviation CV (p = 0.002). Except for the 2 speeding variables (ES Time CV and ES Distance CV), which showed no response to treatment, the 3 remaining DSS variables; Excessive Ay CV (cornering speed), Total Tickets URB, and Total Crashes CV demonstrate numerically better performance for the armodafinil group than the placebo group.
Additional driving variables demonstrating a significant difference of p < 0.10 between armodafinil and placebo are found in Table 4. Of those comparisons, only Speed Deviation CV (p = 0.005) and Total Tickets V (p = 0.04) were found to be statistically significant (p ≤ 0.05). A trend towards significance was found for Time to First Crash CV (p = 0.045), Speed Deviation CV (p = 0.005) and Total Tickets V (p = 0.04) to the time between Visit 2 and Visit 3 (generally 2 weeks), compared to the time between Visit 1 and Visit 2 (< 24 h), compared to p = 0.15) with CPAP treatment. Many other driving simulator components showed a trend for improved performance (p = 0.06 to p = 0.10) with CPAP. Based on the interval between visits and the lack of a confounding treatment, assessment of the effect of CPAP on simulated driving performance was based on a comparison of the driving results from Visit 3 (end of drug treatment) and Visit 5 (after 4 weeks of CPAP treatment) for those subjects who were randomized to placebo.

The results for CPAP treatment on driving simulator performance are summarized in Table 5. The DSS showed a trend for improved performance with CPAP treatment (p = 0.07). Significant improvement was seen for Lane Deviation CV (p = 0.01). Only 1 of the DSS components, Total Tickets URB, failed to show a numerical benefit of CPAP treatment. All other DSS components showed a trend for improved performance (p = 0.06 to p = 0.15) with CPAP treatment. Many other driving simulator parameters showed significant improvement with CPAP, including: Time to First Crash CV (p = 0.045), Speed Deviation CV (p = 0.02), Crashes in the Construction Zone URB (p = 0.03), (i.e., < 24 h for 23 of 69 subjects). Experience in our laboratory has shown that the time between driving sessions significantly impacts simulated driving performance (i.e., very short intervals result in inflated retest scores). As a result of the unequal time interval between Visit 1 and Visit 2 (< 24 h), compared to the time between Visit 2 and Visit 3 (generally 2 weeks), the driving simulator results from the Baseline session (Visit 2) were not considered to be optimal for evaluating the effects of CPAP. Based on the interval between visits and the lack of a confounding treatment, assessment of the effect of CPAP on simulated driving performance was based on a comparison of the driving results from Visit 3 (end of drug treatment) and Visit 5 (after 4 weeks of CPAP treatment) for those subjects who were randomized to placebo.

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**Table 1—Treatment-related, treatment-emergent adverse events by system organ class (mITT)**

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Placebo (n = 35)</th>
<th>Armodafinil (n = 34)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiac Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palpitations</td>
<td>1 (2.9%)</td>
<td>2 (5.9%)</td>
</tr>
<tr>
<td><strong>Gastrointestinal Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>0 (0.0%)</td>
<td>2 (5.9%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1 (2.9%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Dry Mouth</td>
<td>0 (0.0%)</td>
<td>1 (2.9%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>0 (0.0%)</td>
<td>1 (2.9%)</td>
</tr>
<tr>
<td>Tongue Biting</td>
<td>0 (0.0%)</td>
<td>1 (2.9%)</td>
</tr>
<tr>
<td><strong>General Disorders and</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Administration Site Conditions</td>
<td>1 (2.9%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Feeling Jitter</td>
<td>1 (2.9%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td><strong>Nervous System Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>0 (0.0%)</td>
<td>1 (2.9%)</td>
</tr>
<tr>
<td>Headache</td>
<td>2 (5.7%)</td>
<td>2 (5.9%)</td>
</tr>
<tr>
<td>Hypoesthesia</td>
<td>0 (0.0%)</td>
<td>1 (2.9%)</td>
</tr>
<tr>
<td><strong>Psychiatric Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnormal Dreams</td>
<td>0 (0.0%)</td>
<td>1 (2.9%)</td>
</tr>
<tr>
<td>Affect Lability</td>
<td>1 (2.9%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>0 (0.0%)</td>
<td>2 (5.9%)</td>
</tr>
<tr>
<td>Depressed Mood</td>
<td>0 (0.0%)</td>
<td>1 (2.9%)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>0 (0.0%)</td>
<td>2 (5.9%)</td>
</tr>
<tr>
<td>Irritability</td>
<td>0 (0.0%)</td>
<td>1 (2.9%)</td>
</tr>
<tr>
<td>Mood Altered</td>
<td>1 (2.9%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td><strong>Skin and Subcutaneous Tissue</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disorders</td>
<td>0 (0.0%)</td>
<td>1 (2.9%)</td>
</tr>
<tr>
<td>Rash</td>
<td>0 (0.0%)</td>
<td>1 (2.9%)</td>
</tr>
<tr>
<td>Vascular Disorders</td>
<td>0 (0.0%)</td>
<td>1 (2.9%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0 (0.0%)</td>
<td>1 (2.9%)</td>
</tr>
</tbody>
</table>

Primary system organ classes are presented alphabetically; preferred terms are sorted within primary system organ class alphabetically. Patients with more than one occurrence in a category are only counted once.
**Table 3—DSS driving variables: change from Baseline to Visit 3 (mITT)**

<table>
<thead>
<tr>
<th>Driving Variable</th>
<th>Placebo (n = 34)</th>
<th>Armodafinil (n = 34)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DSS</td>
<td>0.42 (1.03)</td>
<td>0.07 (0.49)</td>
<td>0.03*</td>
</tr>
<tr>
<td>DSS Components</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lane Deviation CV</td>
<td>0.21 (0.37)</td>
<td>-0.09 (0.42)</td>
<td>0.002</td>
</tr>
<tr>
<td>Out of Lane CV</td>
<td>9.6 (18.3)</td>
<td>-0.2 (20.3)</td>
<td>0.02</td>
</tr>
<tr>
<td>Excessive Ay CV</td>
<td>26.4 (73.5)</td>
<td>4.8 (36.7)</td>
<td>0.13</td>
</tr>
<tr>
<td>ES Distance CV</td>
<td>0.01 (0.02)</td>
<td>0.00 (0.01)</td>
<td>0.25</td>
</tr>
<tr>
<td>Total Crashes CV</td>
<td>0.9 (3.0)</td>
<td>0.6 (4.5)</td>
<td>0.31</td>
</tr>
<tr>
<td>Total Tickets URB</td>
<td>0.5 (1.3)</td>
<td>0.2 (1.1)</td>
<td>0.43</td>
</tr>
<tr>
<td>ES Time CV</td>
<td>0.00 (0.02)</td>
<td>0.00 (0.01)</td>
<td>0.58</td>
</tr>
</tbody>
</table>

CV, country vigilance scenario, URB, urban scenario, ES, exceeded speed. *p ≤ 0.05.

**Table 4—Additional driving variables (p-values < 0.10): change from baseline to Visit 3 (mITT)**

<table>
<thead>
<tr>
<th>Driving Variable</th>
<th>Placebo (n = 34)</th>
<th>Armodafinil (n = 34)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lane Deviation CV E1</td>
<td>0.20 (0.42)</td>
<td>-0.05 (0.27)</td>
<td>0.006*</td>
</tr>
<tr>
<td>Lane Deviation CV E2</td>
<td>0.24 (0.51)</td>
<td>-0.14 (0.44)</td>
<td>0.001*</td>
</tr>
<tr>
<td>Speed Deviation CV</td>
<td>0.81 (1.99)</td>
<td>-0.44 (1.79)</td>
<td>0.005*</td>
</tr>
<tr>
<td>Speed Deviation CV E2</td>
<td>1.26 (3.34)</td>
<td>-0.79 (2.23)</td>
<td>0.004*</td>
</tr>
<tr>
<td>Speed Deviation CV E4</td>
<td>1.36 (4.03)</td>
<td>-0.89 (3.06)</td>
<td>0.017*</td>
</tr>
<tr>
<td>Time to First Crash CV</td>
<td>-177 (670)</td>
<td>52.9 (656)</td>
<td>0.0923*</td>
</tr>
<tr>
<td>Total Tickets VIG</td>
<td>0.47 (1.48)</td>
<td>-0.15 (1.13)</td>
<td>0.0358*</td>
</tr>
<tr>
<td>Average Speed CV E2</td>
<td>-0.69 (2.38)</td>
<td>0.15 (2.22)</td>
<td>0.0784</td>
</tr>
<tr>
<td>Total Crashes CV E2</td>
<td>0.2 (0.8)</td>
<td>0.0 (0.4)</td>
<td>0.0593</td>
</tr>
<tr>
<td>Out of Lane CV E2</td>
<td>2.2 (4.7)</td>
<td>0.0 (4.7)</td>
<td>0.0602</td>
</tr>
<tr>
<td>Divided Attention Omissions VIG</td>
<td>0.14 (0.25)</td>
<td>0.01 (0.30)</td>
<td>0.0792</td>
</tr>
</tbody>
</table>

For country vigilance scenario: E1 = 0-7:59 min, E2 = 8-15:59 min, E3 = 16-23:59 min, E4 = 24-31:59 min, E5 = 32-40 min. CV, country vigilance scenario, VIG, vigilance scenario. *p ≤ 0.05.

Out of Lane VIG (p = 0.03), Divided Attention Reaction Time VIG (p = 0.02), and Total Tickets VIG (p = 0.01). Analysis of time-on-task for the 40-min CV drive shows that for the five 8-min blocks (E1- E5), the most significant impact of CPAP was evident during the second 8-min block.

Analysis of the impact of CPAP compliance on simulated driving shows strong correlations between primary and secondary driving variables and hours of CPAP use. Correlations > 0.20 are shown in **Table 6**. CPAP compliance accounted for 26% of the variance (r = 0.51) in the DSS.

The relationship between baseline driving performance and PSG measures (AHI, mean O$_2$, minimum O$_2$ saturation, and arousal index) is shown in **Table 7**. This analysis shows that baseline AHI had the most impact on simulated driving performance, followed by minimum O$_2$ saturation and mean O$_2$.

**Patient Reported Outcomes**

Following treatment with armodafinil, there was a trend for improved self-reported sleepiness on the ESS (p = 0.066). Following CPAP, the improvement in ESS score was highly significant (p < 0.0001). ESS scores at Visit 5 were correlated with CPAP compliance (r = 0.33).

The FOSQ was administered to assess changes in quality of life. Following treatment with armodafinil, there was a significant improvement compared to placebo in 2 of the 5 FOSQ domains: General Productivity (p = 0.01) and Social Outcome (p = 0.005). Treatment with CPAP resulted in significant improvements in 3 FOSQ domains: General Productivity (p < 0.0001), Social Outcome (p < 0.0001), and Vigilance (p < 0.0001). FOSQ scores at Visit 5 for these 3 domains were correlated with CPAP compliance: General Productivity, r = 0.20; Social Outcome, r = 0.23; and Vigilance, r = 0.24.
The MOS-CF6 was administered at Baseline, Visit 3, and Visit 5. At Baseline, the placebo group reported more difficulty with cognitive functioning (65.4 ± 17.3) than subjects who were randomized to the armodafinil group (74.7 ± 13.6). Specifically, the placebo group reported more difficulty with problem solving, concentration, disorganization, and memory. At Visit 3, both groups reported less difficulty with cognitive functioning. However, the improvement for the placebo group (8.6 ± 18.1) was somewhat less (p = 0.06) than the improvement reported by the armodafinil group (9.3 ± 12.1). In contrast, CPAP treatment resulted in a highly significant reduction in self-reported cognitive function difficulty (p < 0.0001). The overall change from baseline in MOS-CF6 score for the mITT population following CPAP treatment was 17.4 ± 14.6.

After finishing the CV, subjects responded to 2 visual analog scales: (1) “How well do you think you drove for the last 60 minutes?” and (2) “How motivated did you feel to drive at your best during the last 60 minutes of driving?” From Baseline to Visit 3, subjects receiving placebo reported a decline (-10.9 mm) in their driving performance. In contrast, subjects receiving armodafinil reported an improvement (+1.9 mm) in their driving performance (p = 0.002). CPAP treatment resulted in a marked positive increase in “How well do you think you drove for the last 60 minutes?” (+12.5 mm, p = 0.0023). In response to the visual analog scale (VAS) measuring motivation, subjects receiving placebo reported a decline (-8.3 mm) in motivation. By comparison, those receiving armodafinil reported increased motivation (+4.3 mm, p = 0.0031). Following CPAP treatment, there was an improvement in motivation compared to baseline (+4.9 mm); however, the increase did not reach statistical significance (p = 0.107).

**CPAP Compliance**

The compliance results for the final 2 weeks of CPAP treatment were used to compare treatment compliance for the armodafinil and placebo groups. Results showed that hours of CPAP compliance did not differ for those subjects who had pre-
Clinician Assessment: CGI-s and CGI-c

The Principal Investigator, who was blind to both treatment group assignment and to CPAP compliance results, completed the Clinical Global Impression of Severity (CGI-s) rating at baseline and both the Clinical Global Impression of Change (CGI-c) and the CGI-s at subsequent visits. Mean CGI-s scores and score distributions were comparable at Baseline for the 2 treatment groups (placebo = 4.91; armodafinil = 5.06; 5 = markedly ill). Following treatment with armodafinil or placebo, the mean CGI-c score for the placebo group was 3.09 and for the armodafinil group 2.79. Although, numerically the change from baseline is more favorable for the armodafinil group, the difference between groups is statistically nonsignificant (p = 0.34). At the end of CPAP treatment, there was no difference in CGI-c scores between the 2 treatment groups (p = 0.82). However, for both groups there was a marked improvement in CGI-s (p < 0.0001) compared to Baseline. Of the 68 subjects in the mITT population, 41 (60%) were rated as normal, 14 (21%) were rated as borderline ill, and 4 (6%) were rated as mildly ill at the end of the study. At Baseline, the lowest rating was modestly ill (19%). Following CPAP, only 4 (6%) were rated as moderately ill, and 1 subject was rated as markedly ill (compared to 63% at baseline).

DISCUSSION

A primary objective of this study was to determine whether use of a new wake-promoting agent, armodafinil, prior to initiation of nasal continuous positive airway pressure (CPAP) therapy, would improve the simulated driving performance of patients with excessive daytime sleepiness (EDS) secondary to obstructive sleep apnea (OSA). Another objective of the study was to assess the impact of treatment with armodafinil prior to CPAP treatment on compliance with CPAP treatment.

The results demonstrate that armodafinil improved simulated driving performance prior to initiation of CPAP therapy. This improvement in driving performance was evident in the composite DSS, which was the primary study endpoint (p = 0.03). The DSS was shown to be sensitive to other stimulant agents in a prior study. In addition, according to the VAS, subjects appeared to be aware of their improved driving performance in response to treatment with armodafinil compared to placebo (p = 0.002).

The specific driving simulator measures which were most sensitive to the beneficial effects of armodafinil on driving performance were lane position deviation (p = 0.002), lane excursions (p = 0.02; Out of Lane), speed deviation (p = 0.005; Speed Variability), and total tickets (p = 0.036). Armodafinil also showed a trend to improvement (compared to placebo) on measures of reaction time on a divided attention task (p = 0.08) and time to first crash (p = 0.09).

Evaluation of the impact of CPAP on simulated driving was complicated by the unanticipated short interval (i.e., < 24 h) between the screening visit and the baseline visit. To eliminate this effect we assessed the impact of CPAP treatment by comparing the driving simulation results for Visit 3 (end of drug treatment) and Visit 5 (end of CPAP treatment) for the subjects randomized to placebo. Subjects who were randomized to armodafinil were excluded from this analysis to avoid the confounding effect of drug treatment.

In spite of the reduction in the number of subjects (n = 32), due to the exclusion of those treated with armodafinil, the results replicate the improvement in simulated driving performance previously shown following CPAP treatment.

The DSS showed a trend for improved performance following CPAP (p = 0.07). The only DSS component significantly affected by CPAP treatment was Lane Deviation (p = 0.01). This is consistent with the literature demonstrating SDLP to be the most sensitive measure to treatment with CPAP treatment. The Out of Lane measure and the Excessive Ay (cornering speed) measures showed a trend for better performance following CPAP (p = 0.06, and p = 0.07, respectively).

The mDSS, which is based on recent simulation research with OSA patients, showed significant improvement following CPAP (p = 0.038). The four mDSS components which showed a significant effect of CPAP include: Time to First Crash (p = 0.045), Out of Lane (p = 0.06), Lane Position Deviation E5 (p = 0.07), and Total Crashes (p = 0.15).

In addition to the driving measures already mentioned, the beneficial effect of CPAP was also evident on measures of speed deviation (p = 0.03), speeding violations on the vigilance scenario (p = 0.006), divided attention reaction time (p = 0.02), lane excursions on the vigilance scenario (p = 0.03), and crashes in the urban scenario construction zone (p = 0.03). Furthermore, subjects reported awareness of their improved driving performance following treatment with CPAP (p = 0.0023).

As expected, the benefits of CPAP are dependent upon treatment compliance. More than 25% of the variance in the DSS (rho = 0.55) at Visit 5 can be accounted for by CPAP compliance (i.e., hours of CPAP use in the last 2 weeks of the study). The strongest correlations between CPAP compliance and driving variables were found for measures of lane position deviation, speed deviation, and lane excursions. The benefit of CPAP on simulated driving performance is most evident on measures that assess weaving (i.e., maintenance of lane position) and speed control.

The results of the current study also touched on the question of the underlying causes of the driving problems associated with OSA. Regression analyses revealed that simulated driving performance was most strongly associated with baseline AHI, followed by minimum O2 saturation and mean O2 level.

Patient reported outcome scores also demonstrate the value of treatment with armodafinil prior to initiation of CPAP therapy. The improvement in self-reported sleepiness approached significance on the ESS (p = 0.066). Following two weeks of armodafinil, subjects reported significant improvement on sleep-related quality of life outcome scales (FOSQ Productivity, p < 0.001; and FOSQ Social Outcome, p < 0.001). On the other hand, the clinician-based ratings (CGI scales) showed a numerical advantage but not a statistically significant treatment difference in disease severity. Although subjects were less sleepy, they were still judged by the clinician as showing moderate disease severity.

Consistent with the benefits seen on measures of driving performance, the patient reported outcome measures and clinician...
ratings showed marked benefits of CPAP. The ESS dropped significantly following CPAP (p < 0.0001). ESS improvement was correlated with compliance (r = -0.33). Significant improvement was seen in three FOSQ domains (General Productivity, p < 0.0001), Social Outcome (p < 0.0001), and Vigilance (p < 0.0001). Similarly, CPAP treatment resulted in improved scores on the MOS-CF6. Subjects reported significantly less cognitive difficulties following CPAP (p < 0.0001). These benefits were also evident in the clinician’s rating of the patient’s condition following CPAP. Specifically, the clinician rating of disease severity (CGI-s) dropped significantly following CPAP (p < 0.0001).

Although treatment with armodafinil improved simulated driving performance in OSA patients, it is not our intention to encourage use of armodafinil as a substitute for treatment with CPAP. Our study was conducted to identify a safe alternative to CPAP during the waiting prior to the initiation of CPAP therapy (i.e., bridging therapy). However, it should be noted that treatment with armodafinil prior to initiation of CPAP did not have an impact on CPAP compliance (p = 0.80). This may allay the concerns that some practitioners may have as to whether treatment prior to initiation of CPAP would discourage subsequent use of CPAP treatment.

In summary, armodafinil was found to improve simulated driving performance in OSA patients with EDS prior to initiation of CPAP. The improvement in driving performance was most evident on measures of lane position control (including the number of lane excursions) and speed control. Subjects treated with armodafinil showed awareness of their improved driving performance. Treatment with armodafinil was not found to impact subsequent CPAP compliance. The improvement seen on driving simulator parameters in this study following CPAP is comparable to that reported in prior studies. Although the purpose of the current study was not to compare armodafinil to CPAP, a review of the study results shows a comparable effect size on DSS for treatment with armodafinil and treatment with CPAP (armodafinil vs. placebo, d = 0.42; Baseline vs. CPAP, d = 0.40).

ABBREVIATIONS

AHL, apnea-hypopnea index
ANCOVA, analysis of covariance
APPLES, Apnea Positive Pressure Long-term Efficacy Study
BMI, body mass index
CGI, clinical global impression
CGI-c, clinical global impression of change
CGI-s, clinical global impression of severity
CMH, Cochrane-Mantel-Haenszel
CNS, central nervous system
CPAP, continuous positive airway pressure
CRCDS, Cognitive Research Corporation Driving Simulator
CV, country vigilance driving scenario
DSS, Driving Safety Score
EDS, excessive daytime sleepiness
EEG, electroencephalogram
ESS, Epworth Sleepiness Scale
FOSQ, Functional Outcomes Sleep Questionnaire
mDSS, modified Driving Safety Score
mITT, modified intent-to-treat
MOS-CF6, Medical Outcomes Study 6-item Cognitive Functioning Scale
MWT, maintenance wakefulness test
nCPAP, nasal continuous positive airway pressure
OSA, obstructive sleep apnea
PSG, polysomnogram
PVT, psychomotor vigilance test
SDLP, standard deviation of lateral position
SSQ, simulator sickness questionnaire
STI, Systems Technology, Inc.
URB, urban driving scenario
VAS, visual analog scale
VIG, vigilance driving scenario

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SUBMISSION & CORRESPONDENCE INFORMATION

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DISCLOSURE STATEMENT

This was an investigator initiated research study supported by Cephalon, which provided no role in the conception and production of this study. Dr. Kay is President of Cognitive Research Corporation which provided the driving simulators and is an owner of CogScreen LLC which publishes the CogScreen test used to assess cognitive functioning in this trial. Dr. Kay has received research support from Merck, Schering-Plough, Novartis, Pfizer, Astellas, Watson, Shire, and Vivus. Dr. Feldman has received research support, consulting fees and speaker’s bureau honoraria from Cephalon, Jazz Pharmaceuticals, Merck, Pfizer, Sanofi, Novartis, Sanofi, Lundbeck, Eli Lilly, Evotec, Bristol-Myers Squibb, Takeda, Sepracor, and Apnicure.

The use of armodafinil (Nuvigil) in this clinical trial is considered off-label, since the approved FDA labeling states that: “In OSA, Nuvigil is indicated as an adjunct to standard treatment(s) for the underlying obstruction. If continuous positive airway pressure (CPAP) is the treatment of choice for a patient, a maximal effort to treat with CPAP for an adequate period of time should be made prior to initiating Nuvigil.”
Restless legs syndrome (RLS) is common in end-stage renal disease (ESRD), affecting up to 62% of patients, which is substantially higher than the 5% to 15% prevalence rate in the general population. Although a number of studies have evaluated RLS in patients with ESRD, very few have investigated the prevalence of RLS in patients with chronic kidney disease (CKD) who are not dialysis-dependent and its impact on sleep and daytime function. Merlo et al. reported an increased prevalence of RLS in CKD patients (10.9% vs 3.3%) in a case-control study that was limited by a relatively small sample size (138 CKD patients). Aritake-Okada et al. conducted a larger study on 514 Japanese patients with CKD. Although they found a higher prevalence of RLS in CKD patients (vs 5.9%), this prevalence is very low compared to non-Asian populations. Neither of these studies included patients with ESRD and consequently could not compare the prevalence of RLS across the full spectrum of kidney disease.

The coexistence of RLS in patients with CKD is likely to have clinical relevance. RLS has been associated with poor sleep and impaired daytime function both in the general population and patients with ESRD. Furthermore, RLS was associated with increased mortality in patients receiving treatment with chronic hemodialysis. The non-dialysis-dependent CKD population is much larger than the ESRD population, and its prevalence is growing. Establishing that the prevalence of RLS is increased in patients with CKD could heighten the treating physician’s awareness of this comorbidity and thereby provide an opportunity to potentially improve the quality of life and clinical outcomes in a relatively large group of patients.

The primary objective of the current study was to determine the prevalence of RLS across the full spectrum of kidney disease using the same methodology in patients with normal renal function, CKD, and ESRD. Our secondary objective was to assess the impact of RLS on sleep quality and daytime function. We hypothesized that the prevalence of RLS would increase progressively as kidney function decreased, and that RLS would have a negative impact on both sleep quality and daytime alertness in patients with CKD and ESRD.
METHODS

Patient Recruitment and Data Collection

Adult patients (≥ 18 years) were recruited from outpatient nephrology clinics and hemodialysis units in the Southern Alberta Renal Program in Calgary, Alberta from May 2008 to February 2012. Consecutive patients were invited to participate; all those who consented and were able to complete the questionnaires were included in the study. Some of the data have previously been published in a study that investigated the prevalence of sleep apnea and nocturnal hypoxia in CKD.13 The current study was designed to evaluate the prevalence and clinical significance of RLS in CKD with an expanded cohort of patients. The study was approved by the University of Calgary Conjoint Health Research Ethics Board. Written informed consent was obtained from all participants in accordance with the Declaration of Helsinki.

All patients completed a set of questionnaires administered either face-to-face or by telephone interview. First, a standardized questionnaire surveyed demographic information, sleep and medical history, and the use of medications, alcohol, caffeine, and cigarettes. Alcohol consumption was self-reported as the number of alcoholic drinks per week, and caffeine ingestion by the number of cups of coffee, tea, and cola per day. Cigarette smoking was defined as any current smoking habits. In addition, coexisting medical disorders were recorded, including hypertension, congestive heart failure, coronary artery disease (angina, myocardial infarction, and coronary artery bypass surgery), cerebrovascular disease (stroke or transient ischemic attack), diabetes, and chronic obstructive pulmonary disease (COPD). Second, the RLS Questionnaire devised by the International RLS Study Group (IRLSSG)6 was administered to determine the prevalence of RLS. Third, the Epworth Sleepiness Scale (ESS) was used to assess daytime sleepiness, where a score > 10 indicated excess sleepiness.15 Table 1 summarizes the demographic characteristics of the 500 patients we studied: 127 were eGFR ≥ 60; 242 had CKD (eGFR < 60); and 131 were ESRD patients. Patients in the eGFR ≥ 60 group were significantly younger than those with CKD and ESRD. Gender distribution was similar across the 3 study groups (40% female, 60% male). Median hemoglobin levels declined with increasing severity of kidney disease. Additionally, and as anticipated,18 the prevalence of hypertension, coronary artery disease, congestive heart failure, cerebrovascular disease and diabetes increased as kidney function declined. Overall, 24.2% of the cohort met the diagnostic criteria for RLS. Within the 3 study groups, the prevalence of RLS was 18.9% (eGFR ≥ 60), 26% (CKD), and 26% (ESRD). These differences were not statistically significant (χ² = 2.61; p = 0.271), and the trend analysis was also nonsignificant (p = 0.19). The prevalence of RLS in the CKD group was significantly higher for women than for men (women 34.7%, men 25.6%; χ² = 6.15; p = 0.04). Although women still had a higher prevalence of RLS among eGFR ≥ 60 and ESRD patients, this gender difference was not statistically significant.

Features of sleep disruption were reported more frequently by patients with, compared to those without, RLS (Table 2). Sleep latency was longer, and reports of feeling unrefreshed in the morning and of impaired memory and concentration during the daytime were more prevalent in those with RLS. The presence of poor sleep quality was also higher in this group, as reflected by the PSQI. Excessive daytime sleepiness (ESS > 10), on the other hand, was not significantly more prevalent in patients with RLS.
Finally, more patients with RLS reported a history of leg movements during sleep ($\chi^2 = 28.8; p < 0.001$). Similar findings were noted when the analysis was confined to the CKD group alone. Multivariable logistic regression analysis revealed that increasing severity of kidney disease was not significantly associated with the presence of RLS when controlled for confounders ($\chi^2$). Women were at higher risk of developing RLS (OR = 1.74, CI = 1.13-2.68, p = 0.012), as were patients with a positive family history of RLS (OR = 3.37, CI = 1.47-7.71, p = 0.004). Further, the comorbidities listed in Table 1 were not associated with the prevalence of RLS, other than female gender.

Regression models were used to evaluate the association between RLS and the PSQI and ESS scores ($\chi^2$). RLS was independently and positively associated with the PSQI score (OR = 2.63, CI = 1.60-4.00, p < 0.001) but not with the ESS score (OR = 1.49, CI = 0.853-2.6, p = 0.16), which further supports the observation that RLS does contribute to poor sleep quality but not to excessive daytime sleepiness. Some factors that were correlated with the ESS score were a previous diagnosis of sleep apnea (OR = 3.75, CI = 1.77-7.96, p = 0.001) and the presence of smoking, which was negatively correlated with the ESS score (OR = 0.51, CI = 0.273-0.951, p = 0.034). Factors linked to PSQI score were female gender (OR = 2.26, CI = 1.48-3.46, p < 0.001) and spending < 6 h in bed (OR = 4.29, CI = 1.09-16.9, p = 0.038). We repeated the logistic regression analysis in the CKD group alone, excluding both the eGFR ≥ 60 and ESRD groups, to evaluate the relationship between RLS and PSQI and ESS. As with the full cohort,

<table>
<thead>
<tr>
<th>Table 1—Clinical profile of all patients</th>
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</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
</tr>
<tr>
<td><strong>Gender (M/F)</strong></td>
</tr>
<tr>
<td><strong>BMI (kg/m²)</strong></td>
</tr>
<tr>
<td><strong>Hypertension (%)</strong></td>
</tr>
<tr>
<td><strong>Congestive heart failure (%)</strong></td>
</tr>
<tr>
<td><strong>Coronary artery disease (%)</strong></td>
</tr>
<tr>
<td><strong>Cerebrovascular disease (%)</strong></td>
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<tr>
<td><strong>Diabetes (%)</strong></td>
</tr>
<tr>
<td><strong>COPD (%)</strong></td>
</tr>
<tr>
<td><strong>Antidepressant meds (%)</strong></td>
</tr>
<tr>
<td><strong>Alcohol Intake (drinks/week)</strong></td>
</tr>
<tr>
<td><strong>Caffeine intake (cups/day)</strong></td>
</tr>
<tr>
<td><strong>Hemoglobin (g/L)</strong></td>
</tr>
<tr>
<td><strong>Prevalence of RLS (%)</strong></td>
</tr>
</tbody>
</table>

*Statistical significance. eGFR, estimated glomerular filtration rate (mL/min/1.73m²); CKD, chronic kidney disease; ESRD, end-stage renal disease; BMI, body mass index; COPD, chronic obstructive pulmonary disease. Continuous variables are reported as mean ± standard deviation.

<table>
<thead>
<tr>
<th>Table 2—Sleep characteristics of patients with and without RLS</th>
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</thead>
<tbody>
<tr>
<td><strong>Sleep latency (min)</strong></td>
</tr>
<tr>
<td><strong>Leg movements during sleep (%)</strong></td>
</tr>
<tr>
<td><strong>Un-refreshing sleep (%)</strong></td>
</tr>
<tr>
<td><strong>Poor memory or concentration (%)</strong></td>
</tr>
<tr>
<td><strong>PSQI score &gt; 5 (%)</strong></td>
</tr>
<tr>
<td><strong>ESS score &gt; 10 (%)</strong></td>
</tr>
</tbody>
</table>

RLS, restless legs syndrome; PSQI, Pittsburgh Sleep Quality Index; ESS, Epworth Sleepiness Scale. Continuous variables are reported as mean ± standard deviation.

<table>
<thead>
<tr>
<th>Table 3—Multivariable logistic regression analysis for independent predictors of RLS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Predictors</strong></td>
</tr>
<tr>
<td><strong>Kidney function</strong></td>
</tr>
<tr>
<td>eGFR ≥ 60</td>
</tr>
<tr>
<td>CKD</td>
</tr>
<tr>
<td>ESRD</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td><strong>Age</strong></td>
</tr>
<tr>
<td>1.01</td>
</tr>
<tr>
<td><strong>Family history of RLS</strong></td>
</tr>
<tr>
<td>3.37</td>
</tr>
<tr>
<td><strong>Anemia</strong></td>
</tr>
<tr>
<td>1.43</td>
</tr>
<tr>
<td><strong>Antidepressant meds</strong></td>
</tr>
<tr>
<td>1.83</td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
</tr>
<tr>
<td>1.06</td>
</tr>
</tbody>
</table>

OR, odds ratio; CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate (mL/min/1.73m²); ESRD, end-stage renal disease; RLS, restless legs syndrome.
Table 4—Multivariable logistic regression analysis for independent predictors of poor sleep quality and excessive daytime sleepiness

<table>
<thead>
<tr>
<th>Factor</th>
<th>Poor Sleep Quality (PSQI score &gt; 5)</th>
<th>Excessive Daytime Sleepiness (ESS score &gt; 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
</tr>
<tr>
<td>RLS</td>
<td>2.63</td>
<td>1.60-4.00</td>
</tr>
<tr>
<td>Kidney function</td>
<td></td>
<td></td>
</tr>
<tr>
<td>eGFR ≥ 60</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>CKD</td>
<td>0.679</td>
<td>0.388-1.19</td>
</tr>
<tr>
<td>ESRD</td>
<td>1.42</td>
<td>0.736-2.74</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>2.26</td>
<td>1.48-3.46</td>
</tr>
<tr>
<td>Age</td>
<td>0.997</td>
<td>0.983-1.01</td>
</tr>
<tr>
<td>Sleep restriction</td>
<td>4.29</td>
<td>1.09-16.9</td>
</tr>
<tr>
<td>Alcohol</td>
<td>1.02</td>
<td>0.975-1.07</td>
</tr>
<tr>
<td>Smoking</td>
<td>0.624</td>
<td>0.320-1.22</td>
</tr>
<tr>
<td>Caffeine</td>
<td>1.01</td>
<td>0.927-1.09</td>
</tr>
<tr>
<td>Sleep apnea</td>
<td>1.09</td>
<td>0.520-2.28</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>1.19</td>
<td>0.483-2.91</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>0.949</td>
<td>0.464-1.94</td>
</tr>
<tr>
<td>COPD</td>
<td>0.518</td>
<td>0.231-1.16</td>
</tr>
</tbody>
</table>

OR, odds ratio; CI, confidence interval; ESS, Epworth Sleepiness Scale; PSQI, Pittsburgh Sleep Quality Index; RLS, restless legs syndrome; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate (mL/min/1.73m²); ESRD, end-stage renal disease; COPD, chronic obstructive pulmonary disease.

RLS in the CKD group was significantly associated with the PSQI score (OR = 2.39, CI = 1.20-4.79, p = 0.014), but not with ESS (OR = 1.89, CI = 0.792-4.48, p = 0.15).

**DISCUSSION**

We found that the prevalence of RLS was similar in patients with non-dialysis-dependent CKD and ESRD and was higher than what has previously been reported in the general population. Furthermore, patients with RLS had many more sleep-related symptoms than those without RLS, and RLS was an independent predictor of poor sleep quality as reflected by the PSQI scores. We believe that RLS is a common and clinically relevant sleep disorder in patients with CKD and ESRD.

Our observation of a high and similar prevalence of RLS in patients with early, non-dialysis-dependent CKD and ESRD supports the hypothesis that RLS is associated with kidney disease, but departs from it in that RLS was not correlated with the severity of kidney disease. This may indicate that RLS develops relatively early in the natural history of CKD and remains stable with progressive loss of kidney function. Up to now, RLS has been most strongly associated with ESRD among the renal disease population, which is also consistent with anecdotal evidence from clinical practice. This may reflect the paucity of studies that have formally evaluated the prevalence of RLS in patients with CKD. Alternatively, it is possible that RLS symptoms become more severe, and consequently more clinically apparent, as renal disease progresses. Unfortunately, our study cannot address this, as we did not measure the severity of RLS symptoms.

RLS was associated with many symptoms of sleep disruption and sleep loss in patients with kidney disease, namely increased sleep latency, feeling unrefreshed upon awakening, and impaired memory and concentration during the daytime. Furthermore, in our multivariable analysis, RLS was strongly associated with poor sleep quality, reflected by the PSQI score. This supports the clinical importance of RLS in this patient population. The pathogenesis of these sleep-related complaints can be attributed to the difficulty initiating sleep that is characteristically associated with RLS and the difficulty maintaining sleep that is often associated with periodic limb movement disorder (PLMD). Although we did not confirm the presence of this disorder by polysonmography, many patients with RLS (42.1%) reported a history of leg movements during sleep, which supports a diagnosis of PLMD.

Our study did not find excessive daytime sleepiness (reflected by the ESS) to be more prevalent in patients with RLS, nor was daytime sleepiness independently associated with RLS in our multivariate analysis. This finding concurs with previous research in which patients with RLS did not report excessive sleepiness, despite having chronic sleep loss. Gamaldo et al. observed that individuals with RLS had a higher level of daytime alertness than sleep deprived controls, and suggested that RLS-linked abnormalities in the dopaminergic activating system played a role in enhancing arousal. This may explain why patients with RLS in our study had poorer sleep quality but not excessive daytime sleepiness. It is also possible that some of our older, medically disabled patients may have slept voluntarily during the daytime and thereby not experienced involuntary sleepiness.

We chose to recruit patients with eGFR ≥ 60 as our control group in the belief that this would be the best way to control for the potential impact of non-renal factors on our outcome measurements. In some respects this was appropriate since all patients in the study were recruited from the same specialty clinics that were attended by the same healthcare providers. However, in other re-
spects, patients with eGFR ≥ 60 had significant limitations as a control group since they were a referred population with several comorbidities who had a renal abnormality. It would have been interesting to measure the prevalence of RLS using the same methodology in a healthy, community-based population. It is likely that the prevalence of RLS would have been lower, which may have impacted the outcome of our multivariate analysis.

Our study does have other limitations which should be addressed. First, reliance on self-reported data has its shortcomings, as misinterpretation of interview questions and errors in recall may result in inaccurate findings. However, the diagnosis of RLS is based on a clinical interview which we attempted to re-create by having all patients complete the questionnaires either face to face or by telephone. Second, some data such as total sleep duration, sleep efficiency, number of awakenings, and the presence of PLMD would have been more reliably collected by objective monitoring with polysomnography. This would have been costly and more inconvenient for patients which would have reduced our sample size or prolonged the time taken to complete the study. Third, additional measurements such as the IRLSSG rating scale\(^{22}\) that quantifies the severity of RLS symptoms would have enabled us to compare the severity of RLS across the full spectrum of kidney disease. Finally, information from iron studies were not collected, which would have been valuable as iron deficiency is a risk factor for RLS, especially among the elderly.\(^{23}\) The presence of anemia was recorded and served as an indirect indicator of absolute iron deficiency, in which there is insufficient iron for hemoglobin production.

Despite these limitations, the present study has established that RLS is common and a significant cause of sleep-related symptoms in patients with non-dialysis-dependent CKD and not just in patients with ESRD. Healthcare providers should be aware of this and consider RLS in any patient with kidney disease who reports poor sleep quality. Further research is required to determine whether the severity of RLS changes in individual patients as kidney disease progresses and how detection and treatment of RLS alters clinical outcomes in this patient population.

ABBREVIATIONS

RLS, restless legs syndrome
ESRD, end-stage renal disease
CKD, chronic kidney disease
COPD, chronic obstructive pulmonary disease
IRLSSG, International RLS Study Group
PSQI, Pittsburgh Sleep Quality Index
ESS, Epworth Sleepiness Scale
eGFR, estimated glomerular filtration rate
CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration
PLMD, periodic limb movement disorder

REFERENCES


ACKNOWLEDGMENTS

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SUBMISSION & CORRESPONDENCE INFORMATION

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DISCLOSURE STATEMENT

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Is Nocturnal Panic a Distinct Disease Category? Comparison of Clinical Characteristics among Patients with Primary Nocturnal Panic, Daytime Panic, and Coexistence of Nocturnal and Daytime Panic

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Japan Somnology Center, Neuropsychiatric Research Institute, Shibuya-ku, Tokyo, Japan

**Objective:** Many patients with panic disorder (PD) experience nocturnal panic attacks. We investigated the differences in demographic variables and symptom characteristics as well as response to treatment among patients with primary daytime panic (DP), primary nocturnal panic (NP), and the coexistence of DP and NP (DP/NP), and discuss whether NP is a distinct disease category.

**Method:** One hundred one consecutive untreated patients with PD were enrolled and subsequently divided into the NP, DP, and DP/NP groups. The presence of 13 panic attack symptom items as well as scores on the Panic Disorder Severity Scale (PDSS) and the Pittsburgh Sleep Quality Index (PSQI) were compared among the groups. After 3 months of regular treatment, PDSS scores were assessed again to evaluate response.

**Results:** Nocturnal panic attacks of the participants were mostly reported to occur in the first tertile of nocturnal sleep. The number of males, onset age, and presence of choking sensation were significantly higher, and the PDSS score was significantly lower in the NP group compared with the other groups. The DP/NP group showed the highest PDSS score, and participants in this group were prescribed the highest doses of medication among all groups. Only diagnostic subcategory was significantly associated with treatment response. The total score for PDSS and PSQI correlated significantly only in the NP group.

**Conclusions:** DP/NP could be a severe form of PD, while primary NP could be a relatively mild subcategory that may partially share common pathophysiology with adult type night terror.

**Keywords:** Panic disorder, nocturnal panic, the Panic Disorder Severity Scale (PDSS), the Pittsburgh Sleep Quality Index (PSQI)

**Citation:** Nakamura M; Sugiura T; Nishida S; Komada Y; Inoue Y. Is nocturnal panic a distinct disease category? Comparison of clinical characteristics among patients with primary nocturnal panic, daytime panic, and coexistence of nocturnal and daytime panic. *J Clin Sleep Med* 2013;9(5):461-467.
PD, subjective sleep disturbances, and response to treatment for PD among patients with primary NP, primary DP, and DP/NP. Based on the results, we discuss whether primary NP is a subcategory of PD distinct from DP or DP/NP.

METHODS

Participants

This retrospective study was approved by the ethics committee of the Neuropsychiatric Research Institute, and all patients gave written informed consent to participate.

The study comprised 101 consecutive untreated individuals seeking treatment for panic-anxiety symptoms (56 males, 45 females; mean age 36.9 ± 9.9 years) who visited the outpatient clinic of Japan Somnology Center and Seiwa Hospital, both of which are affiliated with the Neuropsychiatric Research Institute (Tokyo, Japan) from May 2003 to January 2008. Some of the patients (most with primary NP) were referred to our clinic with suspicion of obstructive sleep apnea syndrome (OSAS). However, results of clinical interviews and screening with a portable device as described below indicated that they had neither habitual snoring nor pathological apnea. Based on this, attending physicians judged that the core symptoms of these patients were panic-anxiety rather than OSAS. Eighty-nine of the patients met the diagnostic criteria of PD with and without agoraphobia by the DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition). The remaining 12 patients (all of them in the NP group) had limited panic attacks with ≤ 3 panic attack symptom items, and none of the NP patients reported experiencing nightmares with the episodes of panic anxiety during sleep.

After diagnosis of PD, all patients received regular pharmacological treatment over 3 months with fixed doses of medication for at least 1 month before the investigation. The treatment drug was determined individually based on the decision of the attending physician. No patients had abnormal findings on physical or laboratory examinations at their first visit, or had a current or previous diagnosis of other psychiatric disorders, psychoactive substance abuse, respiratory disease, cardiovascular disease, thyroid disease, or OSAS.

With regard to OSAS, all patients were screened with a portable device (Stardust, Respironics; Murrysville, PA, USA) including 4 channels (airflow monitoring with pressure sensor, respiratory movements, oxyhemoglobin saturation, and heart rate) for 1 night. All patients had a respiratory disturbance index < 5/h, and only a few had episodes of airflow limitation.

The disease course of PD was evaluated by psychiatrists with expertise in sleep disorders who performed detailed interviews with patients and their bed partners, if necessary. NP attacks were determined when a patient experienced an abrupt and uncomfortable sensation and fear immediately upon waking from nocturnal sleep, when symptoms were not attributable to frightening dreams, external interruptions, or other sleep disorders such as nightmares, night terrors, sleep paralysis, hypnompomnic hallucinations, or choking associated with sleep apnea.

We divided the patients into 3 groups with the main purpose of differentiating NP and NP/DP. Patients with primary DP in whom the rate of frequency of NP attacks to total panic attacks was less than 25% during the 3 months before the first visit, as noted by themselves and/or their bed partners, were placed in the DP group (n = 41). Patients with primary NP in whom the rate of the frequency of NP attacks to total panic attacks was ≥ 75% were placed in the NP group (n = 40), and patients with coexistence of DP and NP (rate of frequency of NP attacks was from 25% to 50% of all panic attacks) were placed in the DP/NP group (n = 20). No patient had a rate of frequency of NP attacks to total panic attacks of 50% to 75%.

Measurements

Before starting treatment, patients were interviewed regarding the occurrence of 13 panic attack symptoms listed by the DSM-IV-TR. The items were (1) palpitations, pounding heart, or accelerated heart rate; (2) sweating; (3) trembling or shaking; (4) sensations of shortness of breath or smothering; (5) feeling of choking; (6) chest pain or discomfort; (7) nausea or abdominal distress; (8) feeling dizzy, unsteady, lightheaded, or faint; (9) derealization or depersonalization; (10) fear of losing control or going crazy; (11) fear of dying; (12) paresthesia; and (13) chills or hot flashes. The Panic Disorder Severity Scale (PDSS), a self-rating scale, was used by patients to assess the severity of PD with 7 items scored on a scale of 0 to 4 and total score ranging from 0 to 28. This scale has sufficiently high reliability, with a Cronbach α of 0.86; a total score ≥ 16 corresponds to severe panic disorder in the Japanese version. Subjective sleep conditions were assessed using the self-rating Pittsburgh Sleep Quality Index (PSQI). The PSQI is an effective instrument to evaluate subjective sleep disturbance by measuring 7 domains. Scoring is based on a 0 to 3 scale for each domain. A global sum score (ranging 0 to 21) ≥ 5.5 indicates a poor sleep quality in Japanese (Cronbach α = 0.77) individuals.

Patients with NP were asked about the distribution of NP attacks in the first, second, and third tertiles of their nocturnal sleep. As with DP attacks, the frequency of NP attacks were assessed and expressed using the score on item 1 (frequency of panic attacks) on the PDSS (e.g., 0: no panic attacks, 1: < 1 attack per week and ≤ 1 attack per day, 2: 1-2 attacks per week and/or many attacks per day, 3: ≥ 2 attacks per week and ≤ 1 attack per day, 4: ≥ 1 attack per day, more days than not).

After 3 months of treatment for PD, PDSS was evaluated again in all patients to determine their therapeutic response. As an indicator of treatment response, we calculated the reduction rate of PDSS with treatment ([pre-treatment PDSS total score] – [post-treatment PDSS total score]) / [pre-treatment PDSS total score]).

Medication

All patients were treated pharmacologically. No types of psychotherapies such as cognitive behavioral therapy were used during the study. The following drugs were used: selective serotonin reuptake inhibitors, including paroxetine (10 to 40 mg/day), fluvoxamine (25 to 100 mg/day), and sertraline (25 to 50 mg/day); tricyclic antidepressants (25 to 75 mg/day of imipramine or amitriptyline); benzodiazepine anxiolytics including alprazolam (0.4 to 1.6 mg/day), ethyl lofazepate (1 to 2 mg/day), lorazepam (0.5 to 3 mg/day), clotiazepam (5 to 30 mg/day), and etizolam (0.5 to 3 mg/day); and benzodiazepine or benzodiazepine agonist hypnotics including triazolam (0.125 to 0.25 mg/day), flunitrazepam (1 to 2 mg/day), brotizolam...
(0.25 mg/day), zopiclone (7.5 to 10 mg/day), and zolpidem (5 to 10 mg/day). The daily doses of antidepressants were calculated according to the imipramine-equivalent dose, and those of anxiolytics and hypnotics were calculated on the basis of diazepam-equivalent dose.†

**Data Analysis**

Continuous variables including demographics were compared among groups using analysis of variance (ANOVA) followed by post hoc Bonferroni corrections. Statistical analyses of categorical variables (gender, distribution of NP in each tertile of nocturnal sleep period, and presence of each panic attack symptom) among groups were made using the \( \chi^2 \) test with cell contribution rate test as the post hoc rest error test. The post hoc cell contribution rate test is a form of standardized rest-error test that provides significance information among groups when the absolute value exceeds 1.96. Backwards stepwise multiple regression analysis was used to investigate factors associated with the reduction rate in PDSS score after treatment. Diagnostic subcategories which were dummy coded with \( d_1 \) (pure NP or not; 0: DP and DP/NP, 1: NP) and \( d_2 \) (pure DP or not; 0: NP and DP/NP, 1: DP), self-reported onset age of the disorder, gender, pretreatment total scores of PDSS and PSQI, and daily dosage of medication (antidepressants, anxiolytics, and hypnotics) were included as independent variables. The correlation between PDSS and PSQI scores in the 3 groups was estimated using Spearman rank correlation coefficient. A p value < 0.05 was considered statistically significant. Data analyses were made using SPSS version 10 (SPSS Inc., Chicago, IL, USA).

### RESULTS

**Descriptive Variables**

Based on detailed clinical interviews, it was confirmed that the first attacks occurred during the nocturnal sleep period in all NP patients, and during the daytime in DP and DP/NP patients. The NP group included a significantly larger number of male patients than DP and DP/NP groups (Table 1). The self-reported age of onset of PD was significantly different among groups (df: 2, F-value: 33.3, p < 0.01), and post hoc test revealed that the onset age in the NP group was significantly higher than that in the other 2 groups. Duration of PD morbidity was also significantly different among groups (df: 2, F-value: 5.07, p < 0.05), and the duration in NP group was significantly longer than in the DP group. In the DP/NP group, the duration did not differ significantly from the other 2 groups.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>DP (n = 41)</th>
<th></th>
<th>DP/NP (n = 20)</th>
<th></th>
<th>NP (n = 40)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>SD</td>
<td>%</td>
<td>M</td>
<td>SD</td>
<td>%</td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
<td>56.1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Onset age (year)</td>
<td>30.6**</td>
<td>6.8</td>
<td></td>
<td>26.5***</td>
<td>7.5</td>
<td></td>
</tr>
<tr>
<td>Duration of PD morbidity</td>
<td>2.0*</td>
<td>1.1</td>
<td></td>
<td>3.8</td>
<td>6.2</td>
<td></td>
</tr>
</tbody>
</table>

DP, day panic group; DP/NP, the coexistence of day panic and nocturnal panic; NP, primary nocturnal panic. †Post hoc cell contribution test showed a significantly lower rate of female (p < 0.05). *p < 0.05, **p < 0.01.

**Distribution of NP Attacks during Sleep**

NP attacks were reported to occur predominantly in the first tertile of nocturnal sleep in both the NP group (32/40, 80%) and the DP/NP group (14/20, 70%). The distribution of tertiles in which attacks mainly occurred did not differ significantly between these 2 groups (first/second/third tertile: NP = 32/6/2, DP/NP = 14/5/1, p = 0.64).

**Presence of Panic Attack Symptoms before Treatment**

Chi-square test revealed that the presence of all PD symptoms except palpitations, sweating, sensation of shortness of breath or smothering, and paresthesias significantly differed among the groups before treatment. Rest error test revealed that the NP group had the highest rate of feelings of choking (DP: 23/41, DP/NP: 15/20, NP: 35/40; p < 0.01; \( \chi^2(2) = 10.06, p < 0.01 \)). However, in this group, symptoms of trembling or shaking, chest pain or discomfort, nausea or abdominal distress, feeling dizzy, derealization or depersonalization, fear of losing control or going crazy, fear of dying, and chills or hot flashes were lowest. On the other hand, the DP group had a significantly higher rate for symptoms of trembling or shaking (DP: 18/41, DP/NP: 8/20, NP: 6/40), chest pain or discomfort (DP: 24/41, DP/NP: 12/20, NP: 9/40), nausea or abdominal distress (DP: 12/41, DP/NP: 5/20, NP: 2/40), feeling dizzy (DP: 20/41, DP/NP: 8/20, NP: 6/40), fear of losing control or going crazy (DP: 24/40, DP/NP: 12/20, NP: 9/40), fear of dying (DP: 27/41, DP/NP: 14/20, NP: 11/40), and chills or hot flashes (DP: 18/41, DP/NP: 6/20, NP: 7/40) compared with the other groups. In the DP/NP group, the rate of derealization or depersonalization was significantly higher than in the other groups (DP: 17/41, DP/NP: 12/20, NP: 7/40). In terms of the total number of symptoms, the NP group showed a significantly lower number than the other 2 groups (DP: 6.7 ± 1.8, DP/NP: 7.1 ± 2.2, NP: 4.3 ± 2.2; df: 2, F-value: 25.55, p < 0.01 vs DP, p < 0.01 vs NP/NP, respectively).

**PDSS and PSQI Scores before Treatment**

The total PDSS score and all sub-item scores of the PDSS were significantly different among the groups (Table 2). Post hoc tests revealed that all the sub-item scores as well as the total score in the DP/NP group were significantly higher than in the NP group. Scores for frequency of panic attacks, anticipatory anxiety, agoraphobic fear and avoidance, and total score were also significantly higher in the DP/NP group than in the DP group. The NP group showed significantly lower scores than the DP group in terms of agoraphobic fear and avoidance, interoceptive fear and avoidance, impairment of
work functioning, impairment of social functioning, and total score. On the comparison result of PDSS (after excluding the 12 patients with limited panic attacks), the total PDSS score of NP (7.7 ± 2.3) was also lower than DP and DP/NP (p < 0.01, p < 0.01, respectively).

The total PSQI score did not differ significantly among the groups (Table 3). However, the scores of subjective sleep quality (C1), habitual sleep efficiency (C4) and sleep disturbance (C5) differed significantly among the 3 groups. Post hoc Bonferroni testing showed that the score of C5 was higher in NP group than in DP group and DP/NP group, and that DP/NP group showed higher score of subjective sleep quality (C1) than that of NP group (Table 3). As with the PDSS score, the total score of PSQI did not differ among these 3 groups (excluding the 12 patients with limited panic attacks).

The total scores for PDSS and PSQI correlated significantly in the NP group (r = 0.59, p < 0.001), but not in the other groups (DP group, r = 0.30, p = 0.06; DP/NP group, r = 0.14, p = 0.59).

### Medications and Treatment Response

As shown in Table 4, the final daily doses of antidepressants, anxiolytics, and hypnotics differed significantly among the groups. Multiple comparisons by the Bonferroni test indicated that the DP/NP group received significantly higher daily doses of antidepressants and hypnotics than the other 2 groups. As for anxiolytics, the daily dose was not significantly different between the DP/NP group and DP group (p = 0.16), but was significantly lower in the NP group compared with the other 2 groups (p < 0.01 vs DP/NP, p < 0.01 vs DP).

After 3 months of treatment, all groups showed significant improvements in PDSS total score (p < 0.01 DP, p < 0.01 DP/NP, p < 0.01 NP) (Table 5). ANOVA revealed significant differences among groups for the reduction rate in PDSS score.

---

**Table 2—PDSS scores before treatment**

<table>
<thead>
<tr>
<th></th>
<th>DP</th>
<th>DP/NP</th>
<th>NP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M  SD</td>
<td>M  SD</td>
<td>M  SD</td>
</tr>
<tr>
<td>1:Frequency of panic attacks</td>
<td>2.4 0.7</td>
<td>3.0**;5;* 0.7</td>
<td>2.4 0.7</td>
</tr>
<tr>
<td>2:Distress during panic attacks</td>
<td>2.1 0.7</td>
<td>2.5** 1.0</td>
<td>1.8 0.7</td>
</tr>
<tr>
<td>3:Anticipatory anxiety</td>
<td>2.0 0.7</td>
<td>2.5**;5;* 0.8</td>
<td>1.8 0.7</td>
</tr>
<tr>
<td>4:Agoraphobic fear and avoidance</td>
<td>1.7 0.9</td>
<td>2.4**;3;* 0.6</td>
<td>1.2** 0.7</td>
</tr>
<tr>
<td>5:Interceptive fear and avoidance</td>
<td>2.2 0.8</td>
<td>2.2** 0.8</td>
<td>0.4** 0.5</td>
</tr>
<tr>
<td>6:Impairment of work functioning</td>
<td>1.1 0.8</td>
<td>1.2** 0.9</td>
<td>0.1** 0.3</td>
</tr>
<tr>
<td>7:Impairment of social functioning</td>
<td>0.9 0.8</td>
<td>1.3** 0.8</td>
<td>0.1** 0.2</td>
</tr>
<tr>
<td>Total Score</td>
<td>12.4 2.4</td>
<td>15.0**;3;* 2.8</td>
<td>7.7** 2.3</td>
</tr>
</tbody>
</table>

DP, day panic group; DP/NP, day panic and nocturnal panic group; NP, nocturnal panic group. *p < 0.05, **p < 0.01.

**Table 3—PSQI scores (pre-treatment scores)**

<table>
<thead>
<tr>
<th></th>
<th>DP</th>
<th>DP/NP</th>
<th>NP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M  SD</td>
<td>M  SD</td>
<td>M  SD</td>
</tr>
<tr>
<td>C1:Subjective sleep quality</td>
<td>1.3 0.7</td>
<td>1.7** 0.7</td>
<td>1.0 0.9</td>
</tr>
<tr>
<td>C2:Sleep latency</td>
<td>0.7 0.6</td>
<td>1.2 0.9</td>
<td>1.0 0.8</td>
</tr>
<tr>
<td>C3:Sleep duration</td>
<td>1.0 0.9</td>
<td>1.5 0.8</td>
<td>1.1 0.8</td>
</tr>
<tr>
<td>C4:Habitual sleep efficiency</td>
<td>0.7 0.8</td>
<td>0.9 0.7</td>
<td>0.4 0.6</td>
</tr>
<tr>
<td>C5:Sleep disturbances</td>
<td>0.9** 0.9</td>
<td>0.7** 0.7</td>
<td>1.5 0.8</td>
</tr>
<tr>
<td>C6:Use of sleeping medicine</td>
<td>0.6 1.0</td>
<td>0.9 1.3</td>
<td>0.6 1.0</td>
</tr>
<tr>
<td>C7:Daytime dysfunction</td>
<td>0.7 0.8</td>
<td>0.8 0.9</td>
<td>0.7 0.9</td>
</tr>
<tr>
<td>Total Score</td>
<td>5.9 3.0</td>
<td>7.6 2.5</td>
<td>6.2 3.1</td>
</tr>
</tbody>
</table>

DP, day panic group; DP/NP, day panic and nocturnal panic group; NP, nocturnal panic group. *p < 0.05, **p < 0.01.

**Table 4—Daily doses of medication**

<table>
<thead>
<tr>
<th></th>
<th>DP</th>
<th>DP/NP</th>
<th>NP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M  SD</td>
<td>M  SD</td>
<td>M  SD</td>
</tr>
<tr>
<td>Doses of antidepressants (mg)</td>
<td>85.6 19.4</td>
<td>116.1**;3;* 27.0</td>
<td>41.4** 16.3</td>
</tr>
<tr>
<td>Doses of anxiolytics (mg)</td>
<td>10.7 9.1</td>
<td>14.8** 10.5</td>
<td>1.9** 3.0</td>
</tr>
<tr>
<td>Doses of hypnotics (mg)</td>
<td>1.5 2.5</td>
<td>4.6**;3;* 3.8</td>
<td>0.1** 0.6</td>
</tr>
</tbody>
</table>

DP, day panic group; DP/NP, day panic and nocturnal panic group; NP, nocturnal panic group. The dose equivalents of psychotropic drugs were calculated according to the report by Inagaki A et al.16 The doses of antidepressants are presented in mg basis of imipramine, and those of anxiolytics and hypnotics are presented in mg basis of diazepam. *p < 0.05, **p < 0.01.
Moreover, the NP group showed a significantly greater reduction in score than the other 2 groups (p < 0.01). No significant difference in the reduction rate was found between the DP/NP group and DP group.

Stepwise multiple regression analysis showed that only the diagnostic subcategory (pure NP was dummy coded as d1) was significantly associated with the reduction rate in PDSS score (p < 0.01, B-hat = -0.32, with intercept B-hat = 0.76, p < 0.01).

### Discusssion

This study investigated differences in clinical features among three panic disorder subcategories stratified based on presence/absence of nocturnal or daytime panic attack. The results revealed significant differences in demographics, severity of the disorder, and response to pharmacological treatment among the groups.

Several epidemiological studies have shown that the prevalence of PD is higher in females than in males, and that the mean age of onset of PD is in the 20s and 30s. These demographic characteristics were recognized in the DP group and DP/NP group in our study. However, of note, the NP group showed a clear male predominance and significantly later age of onset than the other two groups. The patients with OSAS, which develops most frequently in middle-aged males, occasionally wake up with choking sensation during nocturnal sleep. However, OSAS was completely ruled out in the participants of the present study by examination with a portable device together with thorough clinical interviews. In addition, we excluded the possibility of upper airway resistance syndrome based on a lack of flow limitation on the air flow pressure sensor of the portable device. Moreover, the NP group had a significantly longer self-reported duration of the disorder than previously reported by Levitan, but had a milder severity of the disorder evaluated with the PDSS score at their first visit compared with the other two groups, even after excluding 12 patients with limited panic attacks, suggesting that a majority of NP patients remain stable in mild severity and symptoms do not become progressively more severe. Taking these findings together, primary NP can be considered a mild subtype of PD with slow progression that is likely to occur among a middle-aged male population.

Many previous studies have indicated that PD patients with NP attacks experience significantly more frequent and severe panic symptoms and more depressive and other psychiatric symptoms. However, in contrast to the findings in this study, sociodemographic characteristics did not differ between patients with and without NP attacks in these studies. The reason for this discrepancy is unknown. However, in most previous studies, the definition of NP was primarily made based on the answer to a one-item screening questionnaire such as “Have you ever been woken from your sleep by a panic attack?” Thus, it is possible that NP reported in previous studies included many patients with DP/NP who actually may have had a younger age of onset and a female predominance with higher PD severity, as seen in the present study.

Nocturnal panic attacks have been reported to occur during NREM sleep, especially during delta sleep. However, no study has ascertained the distribution of panic attacks among tertiles of nocturnal sleep. Interestingly, most patients with NP or DP/NP in the present study reported that their NP attacks occurred mainly in the first tertile. Although we did not perform polysomnographic evaluations of sleep structure among the patients, in general, delta sleep occurs mainly in the early part of sleep. Thus, our results could be consistent with the previous report showing that NP attacks are likely to occur during delta sleep. With regard to the nocturnal distribution of events, NP in our patients seemed to share common characteristics with sleep terrors, which occur during the transition period of arousal from slow wave sleep, mainly in the early part of the night. These two disorders also share common symptoms, such as autonomic symptoms including tachycardia, acute respiratory distress, sweating, and intense fear.

It has been reported that a considerable number of patients with sleep panic have a history of sleep terrors in their early childhood, and that respiratory symptoms frequently appear during episodes of night terrors in adults. Given these findings, it is possible that the pathophysiological mechanism of sleep panic attacks is related to that of adult type sleep terrors, although there is a clear difference in that patients are fully aroused and conscious during sleep panic episodes, while night terror occurs under the condition of clouded consciousness. Further research comparing polysomnographic variables and subjective symptoms between NP and adult type sleep terror is needed to clarify this issue.

In the present study, primary NP patients had fewer panic attack symptom items than patients in other groups. However, feelings of choking occurred in a significantly larger number of patients in the NP group than in the other groups. This finding is compatible with previous reports, suggesting that respiratory symptoms such as choking or shortness of breath are specifically common in NP. Thus, a respiratory symptom during sleep may be a primary symptom in the NP group.

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**Table 5—Change in PDSS score with treatment**

<table>
<thead>
<tr>
<th></th>
<th>Pre-treatment PDSS score</th>
<th>Post-treatment PDSS score</th>
<th>Reduction rate (%)†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>SD</td>
<td>M</td>
</tr>
<tr>
<td>DP</td>
<td>12.4</td>
<td>2.4</td>
<td>6.8</td>
</tr>
<tr>
<td>DP/NP</td>
<td>15.0</td>
<td>2.8</td>
<td>8.1</td>
</tr>
<tr>
<td>NP</td>
<td>7.7</td>
<td>2.2</td>
<td>1.7</td>
</tr>
</tbody>
</table>

DP, day panic group; DP/NP, day panic and nocturnal panic group; NP, nocturnal panic group. †Reduction rate = ([pre-treatment score] – [post-treatment score])/ [pre-treatment score]. *vs NP, **p < 0.01.
The milder form of PD in the NP group compared with the other groups was thought to be attributable to the lower score for agoraphobic or interoceptive fear and avoidance and lower scores for both impairment of work functioning and social functioning in this group. The reasons for these findings are unclear.

Overall, primary NP patients did not have a tendency toward disturbance in initiation and/or maintenance of sleep (insomnia), although they experienced attacks mainly during sleep. However, the severity of panic symptoms during sleep time in the NP group as manifested on the PDSS was significantly correlated with sleep disturbance measured with the PSQI. Considering that there was no significant correlation between PDSS and PSQI in either DP or DP/NP patients, the PD severity-dependent aggravation of sleep disturbance may be a specific clinical characteristic of primary NP.

In the present study, all three groups showed an improvement of PD symptoms with standard treatment including antidepressants, anxiolytics, and hypnotics. However, the dosages of antidepressants and benzodiazepine anxiolytics as well as hypnotics used for the treatment were significantly lower in the NP group than in the DP and DP/NP groups. Moreover, the reduction rate of PDSS with the treatment in this group was significantly higher than that of the other groups. In addition, among the descriptive variables, only the diagnosis of primary NP per se was significantly associated with a higher reduction rate of PDSS, possibly suggesting a better treatment response in this group. These findings could indicate that primary NP is most responsive to treatment among the three groups.

On the other hand, similar to the findings of a study by Argun and Kara, the DP/NP group in our study showed the highest values in terms of number of panic attack symptoms and total PDSS score. Moreover, among the three groups, the DP/NP group received the highest doses of both antidepressants and hypnotics as treatment. These findings strongly impress that DP/NP is the most severe and treatment-resistant subcategory of PD.

This study has several limitations. First, since the Japan Somnology Center mainly treats patients with sleep-related disorders, referral bias could exist. Thus, the sample of NP in our study might not be a representative of the general NP population. Second, there might be recall bias, especially regarding subjective distribution of panic attacks in subjects. Third, the assessment of depressive symptoms may be necessary because depression is frequently comorbid with panic attacks and would affect the severity of panic symptoms. Fourth, this study was an observation-based study, and we need further study with simultaneous measurement of autonomic system markers with polysomnographic recordings to investigate the nature of the physiological change that occurs during episodes of NP.

In conclusion, NP attacks are likely to occur in the first tertile of the nocturnal sleep period both in NP and DP/NP. However, primary NP is thought to be a mild and treatment-responsive subgroup of PD, while DP/NP patients showed severe PD symptoms and the worse treatment response. Identification of these two NP categories would be helpful for making better treatment plans.

REFERENCES

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DISCLOSURE STATEMENT

This was not an industry supported study. The authors have indicated no financial conflicts of interest.
A Multi-Step Pathway Connecting Short Sleep Duration to Daytime Somnolence, Reduced Attention, and Poor Academic Performance: An Exploratory Cross-Sectional Study in Teenagers


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Background: A multi-step causality pathway connecting short sleep duration to daytime somnolence and sleepiness leading to reduced attention and poor academic performance as the final result can be envisaged. However this hypothesis has never been explored.

Objective: To explore concurrent correlations between sleep duration, daytime somnolence, attention levels, and academic performance in a sample of school-aged teenagers.

Methods: We carried out a survey assessing sleep duration and daytime somnolence using the Pediatric Daytime Sleepiness Scale (PDSS). Sleep duration variables included weekdays’ total sleep time, usual bedtimes, and absolute weekday-to-weekend sleep time difference. Attention was assessed by d2 test and by the coding subtest from the WISC-IV scale. Academic performance was obtained from literature and math grades. Structural equation modeling was used to assess the independent relationships between these variables, while controlling for confounding effects of other variables, in one single model. Standardized regression weights (SWR) for relationships between these variables are reported.

Results: Study sample included 1,194 teenagers (mean age: 15 years; range: 13-17 y). Sleep duration was inversely associated with daytime somnolence (SWR = -0.36, p < 0.01) while sleepiness was negatively associated with attention (SWR = -0.13, p < 0.01). Attention scores correlated positively with academic results (SWR = 0.18, p < 0.01). Daytime somnolence correlated negatively with academic achievements (SWR = -0.16, p < 0.01). The model offered an acceptable fit according to usual measures (RMSEA = 0.0548, CFI = 0.874, NFI = 0.838). A Sobel test confirmed that short sleep duration influenced attention through daytime somnolence (p < 0.02), which in turn influenced academic achievements through reduced attention (p < 0.002).

Conclusions: Poor academic achievements correlated with reduced attention, which in turn was related to daytime somnolence. Somnolence correlated with short sleep duration.

Keywords: Sleep deprivation, daytime somnolence, attention, academic performance, structural equation modeling

Citation: Perez-Lloret S; Videla AJ; Richaudeau A; Vigo D; Rossi M; Cardinali DP; Perez-Chada D. A multi-step pathway connecting short sleep duration to daytime somnolence, reduced attention, and poor academic performance: an exploratory cross-sectional study in teenagers. J Clin Sleep Med 2013;9(5):469-473.

Insufficient sleep time in school-aged teenagers is a common phenomenon. A recent meta-analysis of 41 studies on adolescent sleep patterns surveys showed that weekdays total sleep time was 7.4 hours, 8.3 hours, and 7.6 hours for North American, European, and Asian teenagers, respectively. In a recent study of Argentine teenagers, insufficient sleep was reported in 49% of the studied sample.

Sleep deprivation among teenagers is associated with a wide range of behavioral, cognitive, and mood disruptions, including hyperactivity, reduced school grades, and depression. Academic performance is strongly affected by insufficient sleep. Kahn et al. reported that the risk of failing one or more years at school doubled in poor sleepers as compared to normal controls. Similarly, lower grades usually correlate with later bedtimes on school nights and increased delay of sleep onset on weekends.

Insufficient or fragmented sleep can induce sleepiness, thereby impairing learning. In a previous survey using the Pediatric Daytime Sleepiness Scale (PDSS), we found that somnolence was independently and significantly related to poor grades in language or math after adjusting for age, gender, body mass index (BMI), and the presence of snoring or apneas. Daytime somnolence in sleep deprived children may lead to reduced attention, causing impaired learning and academic failure.
Based on the correlations between each pair of variables, we hypothesized that the effects of short sleep duration on poor academic performance may be mediated by increased daytime somnolence resulting in reduced attention. Our hypothesis proposes a multi-step causality pathway connecting short sleep duration to daytime somnolence in a first step, which in turn would lead to reduced attention, finally causing poor academic performance. We set out the present study to further explore this hypothesis by using structural equation modeling (SEM) on the data from a cross-sectional survey.

The main objective of using SEM was to assess the statistical significance of a multi-step pathway connecting short sleep duration to daytime somnolence and attention, ending up in academic performance, adjusting for the presence of potential confounding variables. We believe that such objective would not have been achievable by using simpler statistical methods. While frequently used in education sciences, SEM is not commonly used in sleep research.

**METHODS**

### Study Sample

Teenagers assisting to public schools in 3 suburban areas of low socioeconomic status in Buenos Aires, Argentina, were invited to participate in this study. Subjects in middle school (13 to 17 years old) attending morning classes were eligible for participation. Informed consent was obtained from parents and informed assent from participating students. A total of 1,264 students attended classes in the morning; 1,194 agreed to participate in this study (94% response rate).

This study was approved by the Institutional Review Board at Austral University.

### Evaluations

The research team went to selected schools and invited children to participate. Some days later, subjects who fulfilled inclusion criteria, wanted to participate, and had brought parents’ authorization completed a self-administered questionnaire. Finally, trained neuropsychologists conducted attention tests in the first available opportunity.

We used a survey including the Spanish version of the PDSS to evaluate sleepiness. The scale consists of 8 questions dealing with several aspects of daytime somnolence in students, such as feeling sleepy in classroom or while doing homework, being alert during daytime, problems for getting up from bed, feelings of tiredness during daytime, the need of being woken up, falling asleep after been woken up in the morning, or feelings of insufficient sleep. PDSS scores range from 0 to 32, with higher scores indicating more severe daytime somnolence.

Data on bedtime and waking time on weekdays, hours slept during weekdays and weekend, and nap time during the week and weekend were also collected. The absolute difference between total sleep times on weekdays and weekends was also calculated. Gender, height and weight data were collected. Age- and gender-adjusted z-scores were calculated for BMI according to the parameters derived by LMS transformation as proposed by Cole et al.

### Statistical Analysis

Bivariate correlations between studied variables were evaluated by Pearson coefficients. Multivariate analyses were then performed by SEM. A more thorough review of this technique can be obtained from other sources. SEM is a method for representing, estimating and testing a theoretical network of linear association between variables. It is a generalization of both regression and factor analysis and allows the consideration of unobservable (“latent”) variables, which may only be measured imperfectly by a series of indicators. In our study, the “latent” multidimensional variables were sleep duration, daytime somnolence, attention, and academic performance. Only indicators loading significantly to their corresponding latent variable were retained. This analysis was performed by built-in confirmatory factor analysis. Sleep duration reflected the combination of longer weekdays sleep time, earlier bedtimes and lower weekday-to-weekend sleep time absolute difference. Daytime somnolence resulted from the combination of PDSS survey items. Attention included correct marks and concentration index from D2 test as well as WISC-IV code sub-score. Finally, academic performance included math and language grades as indicators.

SEM assesses whether a sample covariance matrix (i.e., the associations between all possible pair of variables) is consistent with a hypothetical matrix implied by a predefined model. SEM evaluates how well a prespecified model of postulated relationships between pairs of variables “fits the reality.” Thus, SEM is highly dependent on predefined models. For our study, we constructed series of models before conducting the analysis. Such models were always built around the principal hypothesis, which postulated a set of linear correlations exist between sleep duration and daytime somnolence, daytime somnolence with attention, and finally, attention with academic performance. Models differed in the way of handling the confounding variables (i.e., all other variables measured in this study).

SEM is mainly a confirmatory technique rather than an exploratory one, and its use is recommended in order to determine if a certain model is valid, rather than to purely explore previously undefined models. Model’s validity is assessed by several indexes, such as the , the root mean square error of approximation (RMSEA), the Comparative Fit Index (CFI), and
Normed Fit Index (NFI). For our study, models with RMSEA > 0.08, CFI < 0.8, or NFI < 0.8 were rejected because of poor fit. For comparisons between models, the Akaike information criterion (AIC) was also employed. Results from SEM are presented in terms of age-, gender-, and BMI-adjusted positive correlation between PDSS somnolence score and attention (statistic = 2.99, p < 0.002). Reduced attention (statistic = 2.27, p < 0.02) influenced academic achievements through reduced attention (statistic = 2.27, p < 0.02), which in turn influenced academic achievement (SWR = -0.16, p < 0.01). Conversely, we found a negative direct correlation between somnolence and attention was negative (SWR = -0.13, p < 0.01). Interestingly, we also found a negative direct correlation between somnolence and academic achievement (SWR = -0.13, p < 0.01). Furthermore, reduced attention correlated with lower academic achievements (SWR = -0.12, p < 0.01). Other important correlates of language or math grade were age and gender, as shown in Table 2.

A possible multi-step relationship pathway from sleep duration to academic achievements was further explored by SEM. Through SEM we built a model which offered an acceptable fit according to usual measures ($\chi^2 = 794$, RMSEA = 0.0548, CFI = 0.874, NFI = 0.838). As depicted in the path diagram shown in Figure 1, an age-, gender-, and BMI-adjusted positive correlation between sleep duration and somnolence was found (SWR = -0.36, p < 0.01), whereas correlation between somnolence and attention was negative (SWR = -0.13, p < 0.01). Reduced attention correlated with lower academic achievements (SWR = 0.18, p < 0.01). Interestingly, we also found a negative direct correlation between somnolence and academic achievement (SWR = -0.16, p < 0.01). Conversely, the relationship between sleep duration and academic outcomes was not significant (SWR = 0.10, p = 0.2). A Sobel test confirmed that short sleep duration influenced attention through increased daytime somnolence (statistic = 2.27, p < 0.02), which in turn influenced academic achievements through reduced attention (statistic = 2.99, p < 0.002).

## DISCUSSION

Our results suggest a multi-step pathway connecting short sleep duration with increased somnolence, which in turn correlated with reduced attention, ending up in lower academic achievements, as disclosed by a complex, holistic statistical method. While several studies have suggested the existence
of associations between each pair of variables, this is the first time that all variables are connected in one single pathway by using an unselected large sample and a powerful statistical technique. Such a goal could not have been achieved by using simpler techniques such as correlation or multiple regression analysis. These results further suggest that improving sleep quality in teenagers could be an effective measure to increase academic efficiency.

Experimental studies have shown that sleep deprivation is related to inattentiveness, impaired learning, and reduced arousal. In a recent study, 16 subjects completed two sessions of five consecutive nights of restricted or unrestricted sleep in a crossover fashion. In comparison with subjects with normal sleep, sleep deprived participants performed worse on quizzes and displayed more inattentive behaviors. These data lend support to our initial hypothesis. According to this paradigm, short sleep duration would set up a “chain reaction,” with increased daytime somnolence and reduced attention as intermediate links leading to reduced academic efficiency. Interestingly, we observed that somnolence correlated negatively with academic performance by itself and also reduced measurement error.

SEM analysis is not devoid of pitfalls and limitations. Firstly, paths essentially represent correlation between variables, which by themselves do not prove causality in cross-sectional studies. Furthermore, temporal aspects of relationships between sleep duration, sleepiness, reduced attention, and academic performance could not be evaluated in this study, thus further limiting our ability to evaluate causality. Important variables connected with academic achievements such as motivation, memory consolidation, personality, presence of behavioral disorders, or other environmental factors were not assessed in our study. Therefore, our model should be regarded as a hypothesis-generating one to be further refined and enriched by adding other variables. Finally, many variables were self-reported, which could have also introduced some bias or uncertainty in the evaluations.

In summary, our results suggest that increased somnolence and reduced attention may be in the middle of a multi-step pathway connecting short sleep duration to poor academic outcomes. These results may have important implications for public health. Short sleep duration resulting from unhealthy sleep habits should be discouraged, as it may significantly impact cognitive performance.

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Validation of the Mayo Sleep Questionnaire to Screen for REM Sleep Behavior Disorder in a Community-Based Sample

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Objective: To validate a questionnaire focused on REM sleep behavior disorder (RBD) in a community-based sample.

Background: RBD is a parasomnia manifested by recurrent dream enactment behavior during REM sleep. While confirmation of RBD requires the presence of REM sleep without atonia on polysomnography (PSG), a screening measure for RBD validated in older adults would be desirable for clinical and research purposes.

Methods: We had previously developed the Mayo Sleep Questionnaire (MSQ) to screen for the presence of RBD and other sleep disorders. We assessed the validity of the MSQ by comparing the responses of subjects’ bed partners with the findings on PSG. All subjects recruited from 10/04 to 12/08 in the Mayo Clinic Study of Aging—a population-based study of aging in Olmsted County, Minnesota—who had also undergone a previous PSG were the focus of this analysis.

Results: The study sample included 128 subjects (104 male; median age 77 years [range 67-90]), with the following clinical diagnoses at baseline assessment: normal (n = 95), mild cognitive impairment (n = 30), and mild Alzheimer disease (n = 3). Nine (5%) subjects had RBD based on history and PSG evidence of REM sleep without atonia. The core question on recurrent dream enactment behavior yielded sensitivity (SN) of 100% and specificity (SP) of 95% for the diagnosis of RBD. These data suggest that the MSQ has adequate SN and SP for the diagnosis of RBD among elderly subjects in a community-based sample.

Conclusions: These data suggest that the MSQ has adequate SN and SP for the diagnosis of RBD among elderly subjects in a community-based sample.

Keywords: Sleep disorders, parasomnias, dementia, Alzheimer disease, dementia with Lewy bodies, parkinsonism

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Sleep disorders such as rapid eye movement (REM) sleep behavior disorder (RBD), periodic limb movements during sleep (PLMS), restless legs syndrome (RLS), sleepwalking (SW), obstructive sleep apnea (OSA), sleep related leg cramps (SRLC), and insomnia can result in adverse effects on mood, cognitive functioning, and quality of life, especially in those with a neurological disorder. Treatment of these disorders often results in improved quality of life. The presence of RBD also has diagnostic relevance in those with a neurodegenerative disease, as RBD is far more common in the synucleinopathies such as Parkinson disease, dementia with Lewy bodies, multiple system atrophy, or primary autonomic failure.3 Polysomnography (PSG) is necessary to establish the diagnoses of RBD, PLMS, and OSA, but may not be practical in some settings due to expense, limited availability, scheduling difficulties, incomplete coverage by third-party payers, or other factors.

A validated screening measure for key sleep disorders could assist in identifying patients who would benefit from a formal sleep medicine evaluation and PSG. Such a screening measure could also be useful for research purposes, particularly in epidemiologic studies of sleep disorders.

The Mayo Sleep Questionnaire (MSQ) is a screening measure that poses questions about RBD, PLMS, RLS, SW, OSA, and SRLC. It was designed to be used for clinical and research purposes in a variety of settings, and RBD is the focus of interest with this measure. As a screening measure, high sensitivity is desired. The history of the development of the MSQ has been previously described.2 We recently reported validation data on the MSQ compared to PSG focused on RBD in a large cohort of aged subjects, most
Mayo Sleep Questionnaire

The MSQ is a 16 question scale that screens for the presence of RBD, PLMS, RLS, SW, OSA, and SRLC based on responses from bed partners, who are asked if a behavior has been exhibited at least three times in the past. Some questions are ignored depending on certain questions are answered affirmatively. The MSQ was copyrighted in 2009 by the Mayo Foundation for Medical Education and Research, and permission is granted for non-commercial patient care and research purposes. It is available free to the public and can be downloaded from this website: http://www.mayoclinic.org/pdfs/MSQ-copyrightfinal.pdf. The data presented refer to the primary question on RBD (Question 1). If the bed partner provides a “yes” response to this question, subquestions 1b-1e are completed, as shown below:

1. Have you ever seen the patient appear to “act out his/her dreams” while sleeping? (punched or flailed arms in the air, shouted or screamed).

If yes,
   a. How many months or years has this been going on? (data on this subquestion were not analyzed in this analysis)
   b. Has the patient ever been injured from these behaviors (bruises, cuts, broken bones)?
   c. Has a bed partner ever been injured from these behaviors (bruises, blows, pulled hair)?
   d. Has the patient told you about dreams of being chased, attacked, or that involve defending himself/herself?
   e. If the patient woke up and told you about a dream, did the details of the dream match the movements made while sleeping?

The MSQ takes less than two minutes for the bed partner to complete. Further information about the administration of the questionnaire has been published previously. The definitions for sleep-related phenomena, polysomnographic procedures and their interpretation, validations procedures, and data analyses used in this study are also identical to those published previously.

Subjects

All subjects enrolled in the Mayo Clinic Study of Aging (MCSA) from October 1, 2004, (the incident date for the population-based recruitment protocol), to December 31, 2008, whose bed partner/informant completed the MSQ, and the participant had undergone a PSG over the period January 1, 2003, through December 31, 2008, were included in the study. The details of the study population, recruitment strategy, assessment protocol, etc., are presented elsewhere. Briefly, all subjects are community-dwelling residents of Olmsted County, Minnesota, aged 70-89 at baseline, who were recruited in a randomly-selected fashion. The participation rate was 62%, which is similar to many other community-based studies on aging (this point is explained in Roberts et al.). Subjects were classified as having normal cognition (NC), mild cognitive impairment (MCI), clinically probable Alzheimer disease (AD), or another syndrome based on published criteria. Almost all (126/128) subjects had undergone PSG for clinical purposes (110 for suspected OSA, 6 for suspected periodic limb movements causing insomnia or hypersomnia, and 10 for suspected RBD), while 2 (1 for suspected OSA and 1 for suspected RBD) had undergone PSG as part of a research study (NIA AG15866, Alzheimer’s Association IIRG-05-14560). Ten of the 11 suspected RBD subjects were male. Most had undergone PSG prior to enrollment in the MCSA.

Statistical Analyses

The sensitivity (SN) and specificity (SP) and associated 95% confidence intervals (95% CI) were calculated for Question 1. Secondary analyses were performed to test for potential differences in SN and SP based on the timing of MSQ in relation to the PSG (MSQ before PSG versus PSG before MSQ). Additional comparisons using $\chi^2$ or t-test analyses were also carried out to determine the optimum combination of responses that could differentiate true positives from false positives, and true negatives from false negatives, provided that adequate numbers in each cell warranted use of these statistical measures. The data and interpretation relating to RBD are presented below; the methodology, findings and discussion relating to the other sleep disorders assessed by the MSQ are presented in the supplemental material.

Ethics

All procedures and analyses have been approved by the Mayo Foundation Institutional Review Board.

RESULTS

Demographic Features and Clinical Diagnoses

The study sample was composed of 128 subjects, with the core demographic features and clinical diagnoses shown in Table 1. Most subjects were male, and most were in the 70- to 90-year-old age range. All subjects had bed partners who completed the MSQ (by definition), of whom 99% were spouses and the other two were unwed companions of the opposite sex. Ninety-five (74%) were normal controls, 30 (23%) had MCI, and 3 (3%) had mild AD.

As described in the supplemental material, most subjects were referred for PSG to verify clinical suspicion for OSA (117 of 128). This was reflected in the very high frequency of OSA in the sample: the mean (range) of AHI values was 23 (0-58); 126 subjects (98%) had OSA based on an AHI $\geq$ 10, and 125 (98%) had an AHI $\geq$ 15.

Validation of the RBD Questions

Since 20 subjects failed to attain REM sleep on their PSG, and hence REM sleep could not be scrutinized for assessing EMG tone, a total of 108 subjects had data that could be ana-
alyzed. Eleven of these 108 subjects had EMG tone considered equivocally increased (rated as a 2); hence 97 formed the basis for most analyses. Nine (9%) subjects had recurrent dream enactment behavior by history associated with unequivocally increased EMG tone during REM sleep, thereby confirming the diagnosis of RBD; there were no subjects diagnosed with RBD based on PSG criteria only (i.e., there were no subjects who had increased EMG tone during REM sleep plus apparent dream enactment behavior during REM sleep, but no prior history of dream enactment behavior). Four of the subjects had normal EMG atonia during REM sleep associated with a “yes” response to Question 1 by their bed partner—these represent false positive cases. Thirteen other cases with a “no” response to Question 1 had REM sleep without atonia but no history of dream enactment behavior. These were considered to be true negatives. There were no false negative cases.

The core question on recurrent dream enactment behavior yielded a SN of 100% and SP of 95% (Table 2). These values changed minimally when the 11 cases with equivocal EMG tone findings were considered together with the group with abnormal EMG atonia (rating of 1; SN 100%, SP 96%). These values also changed minimally when the 11 cases with equivocal EMG tone findings were considered together with the group with normal EMG atonia (rating of 0; SN 100%, SP 94%). There were 55 subjects who completed the MSQ prior to PSG, and 42 who completed the PSG prior to the MSQ; the SN and SP values were also similar regardless of whether the MSQ was completed before (SN 100%, SP 98%) or after (SN 100%, SP 92%) the PSG.

As shown in Table 3, there were 13 (13%) subjects whose response to question 1 was affirmative, of whom 9 (69%) subjects were considered true positive and 4 subjects (31%) whose response were considered false positive. The frequencies of affirmative responses to subquestions 1b, 1c, 1d, and 1e were different between the true positive and false positive groups, but the frequencies for the groups were often less than 5, which limited the ability to use $\chi^2$ or t-test analyses. The true positive group tended to have affirmative responses to each subquestion, at least 3 of the subquestions, as well as all 4 of these 4 subquestions. The one false positive case who responded affirmatively to 3 of these 4 questions had an AHI value of 37. There was no apparent difference between the false positive and false negative groups with regard to affirmative responses to questions 5 and 6 concerning obstructive sleep apnea, nor in PSG indices of OSA.

One might predict that subjects with Parkinson disease or dementia with Lewy bodies would be more likely to have RBD, and hence more likely to have affirmative responses to MSQ Question 1. Three of the subjects in this analysis had PD, and two did indeed have affirmative responses on MSQ Question 1, but neither case attained REM sleep on their PSGs, and thus RBD could not be confirmed. The other PD case had a negative response and normal EMG atonia during REM sleep. Another case was classified as multiple domain MCI at baseline, and had an affirmative response to MSQ Question 1, but also did not attain REM sleep on his PSG; he subsequently developed dementia, visual hallucinations, and parkinsonism and was diagnosed with DLB. Upon review of the clinical records of the 2 PD cases and the 1 MCI case who subsequently developed DLB, all carried the diagnosis of probable RBD prior to and after their PSGs, as the diagnosis of RBD was strongly suspected despite the lack of confirmation on PSG due to the absence of REM sleep.

Four of the subjects had PSG evidence of unequivocally increased EMG tone during REM sleep but no apparent dream enactment behavior on the PSG. In each case, the clinician did not record a history of recurrent dream enactment behavior at

<table>
<thead>
<tr>
<th>Table 1—Demographic and clinical data</th>
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<tbody>
<tr>
<td>Frequency</td>
</tr>
<tr>
<td>Age at PSG (years)</td>
</tr>
<tr>
<td>60-69</td>
</tr>
<tr>
<td>70-79</td>
</tr>
<tr>
<td>80-89</td>
</tr>
<tr>
<td>90+</td>
</tr>
<tr>
<td>Total</td>
</tr>
<tr>
<td>Median</td>
</tr>
<tr>
<td>Sex, Male</td>
</tr>
<tr>
<td>Bed partner, Spouse</td>
</tr>
<tr>
<td>Neurologic diagnosis</td>
</tr>
<tr>
<td>Cognitively normal</td>
</tr>
<tr>
<td>MCI</td>
</tr>
<tr>
<td>SD-amnestic</td>
</tr>
<tr>
<td>MD-amnestic</td>
</tr>
<tr>
<td>SD-non-amnestic</td>
</tr>
<tr>
<td>MD-non-amnestic</td>
</tr>
<tr>
<td>AD</td>
</tr>
</tbody>
</table>

AD, Alzheimer disease; MCI, mild cognitive impairment; SD, single domain; MD, multiple domain; PD, Parkinson disease; PSG, polysomnogram.

<table>
<thead>
<tr>
<th>Table 2—Sensitivity and specificity of Question 1 on the Mayo Sleep Questionnaire for PSG-proven RBD*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DEB and RSWA</strong></td>
</tr>
<tr>
<td><strong>No DEB</strong></td>
</tr>
<tr>
<td><strong>MSQ Q1 - Yes</strong></td>
</tr>
<tr>
<td><strong>MSQ Q1 - No</strong></td>
</tr>
<tr>
<td><strong>Total</strong></td>
</tr>
</tbody>
</table>

95%CI, 95% confidence interval; DEB, dream enactment behavior by history and/or PSG is present; MSQ, Mayo Sleep Questionnaire; PSG, polysomnogram; Q1, question one; RBD, rapid eye movement sleep behavior disorder; +RSWA, rapid eye movement sleep without atonia is present; SN, sensitivity; SP, specificity; *Caveats: 20 patients did not attain REM sleep on their PSG, and thus their data were not included; 9 (7% of cohort) met established criteria for the diagnosis of RBD; 11 patients had equivocal EMG findings in REM sleep and their data are excluded from the analysis shown above (2 with DEB and 9 without DEB), with their data included (n = 108), the SN remains 100% and SN is 96%; 13 patients had RSWA without a clinical history of DEB or any DEB present on PSG.
Table 3—Comparison between true positive and false positive responders in relation to MSQ and PSG variables

<table>
<thead>
<tr>
<th>MSQ Item</th>
<th>Number with affirmative response</th>
<th>DEB and RSWA (true positives)</th>
<th>No DEB (false positives)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Act out dreams</td>
<td>13</td>
<td>9 (69%)</td>
<td>4 (31%)</td>
</tr>
<tr>
<td>1b. Patient injury</td>
<td>2</td>
<td>2 (100%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>1c. Bed partner injury</td>
<td>5</td>
<td>4 (80%)</td>
<td>1 (20%)</td>
</tr>
<tr>
<td>1d. Dream content</td>
<td>12</td>
<td>9 (75%)</td>
<td>3 (25%)</td>
</tr>
<tr>
<td>1e. Actions mimic dream</td>
<td>11</td>
<td>9 (82%)</td>
<td>2 (18%)</td>
</tr>
<tr>
<td>≥ 3 of subquestions 1b-1e</td>
<td>5</td>
<td>4 (80%)</td>
<td>1 (20%)</td>
</tr>
<tr>
<td>All 4 of subquestions 1b-1e</td>
<td>2</td>
<td>2 (100%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>5. Snort/choke awake</td>
<td>6</td>
<td>3 (50%)</td>
<td>3 (50%)</td>
</tr>
<tr>
<td>6. Stopped breathing</td>
<td>8</td>
<td>5 (63%)</td>
<td>3 (36%)</td>
</tr>
<tr>
<td><strong>PSG Index</strong></td>
<td><strong>Number with PSG finding</strong></td>
<td><strong>Mean AHI</strong></td>
<td><strong>AHI ≤ 5</strong></td>
</tr>
<tr>
<td>Mean AHI</td>
<td>13</td>
<td>19.1 ± 8</td>
<td>26.7 ± 7</td>
</tr>
<tr>
<td>AHI ≤ 5</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>AHI ≥ 10</td>
<td>13</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>AHI ≥ 20</td>
<td>7</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

AHI, apnea/hypopnea index; DEB, dream enactment behavior by history and/or PSG; MSQ, Mayo Sleep Questionnaire; PSG, polysomnogram; RBD, rapid eye movement sleep behavior disorder; RSWA, rapid eye movement sleep without atonia.

the time that the PSG was performed, indicating that such patients had evidence of RSWA. The clinical diagnoses at the time of PSG were NC in 3 and MCI in 1. Recurrent dream enactment behavior evolved after the PSG in the MCI case, and he has since developed PD and is currently on carbidopa/levodopa therapy.

Another 7 cases had equivocally increased EMG tone during REM sleep but no apparent dream enactment behavior on PSG and could be considered as having “equivocal RSWA.” All were diagnosed at baseline as NC.

**DISCUSSION**

The MSQ satisfies all criteria that are typically considered as important for a screening tool to be useful, including high sensitivity and adequate specificity, good safety, low cost, easy administration, minimal inconvenience or discomfort upon administration, and acceptability of patients and clinicians.

An affirmative response to question 1 was 100% sensitive for RBD in this population of community-dwelling elderly individuals residing in Olmsted County, MN, and the specificity was adequate at 95%. We suggest that those subjects in whom question 1 of the MSQ is answered affirmatively by someone knowledgeable about the subject’s sleep behavior be classified as having “probable RBD” (pRBD).

Similar to our previous results, false positives occurred in those with OSA, which is consistent with the known phenomenon of apparent dream enactment behavior in those with untreated OSA. Based on these data, a history of one or more of the core features of RBD as reflected on subquestions 1b-1e, adequately differentiates those with true RBD from those without. If a goal is to use this tool to screen for RBD, then Question 1 alone is a highly sensitive means to do this. If a goal is to use this tool to differentiate RBD from OSA, the specificity of 95% is high, and the profile of responses on subquestions 1b-1e perform well to increase specificity further. PSG remains as the optimal method to make this determination, but depending on the goal of use for the MSQ, PSG may or may not be critical for some analyses or circumstances. These findings suggest that among older individuals residing in a community setting with normal cognition or mild cognitive impairment, the MSQ is an excellent screening tool for the presence or absence of RBD.

The three cases (2 PD and 1 MCI who evolved to DLB) who screened positive for RBD based on the affirmative response to Question 1 but did not attain REM sleep on PSG are also noteworthy. The clinicians caring for these cases diagnosed each of them with probable RBD and were treating them as such (all with melatonin to decrease RBD frequency/severity). Judging from these observations and strong association of PD and DLB with RBD, it is reasonable to presume that such cases also would have been true positive cases had they attained REM sleep on their PSGs.

The 11 cases with RSWA (four with definite RSWA, seven rated as equivocal RSWA) are also of interest. While some consider cases with this PSG findings to represent “subclinical RBD,” we do not believe a sufficient number of cases with RSWA have been followed prospectively to know whether most or all develop definite RBD. Thus, the PSG finding of RSWA is more appropriate to classify such cases until prospective analyses adequately address this issue.

**Utility as a Clinical or Research Tool**

The utility of a screening measure such as the MSQ for RBD among patients undergoing evaluation for a slowly progressive disorder affecting cognition and/or parkinsonism on a neurodegenerative basis has been reviewed previously. The high sensitivity and adequate specificity of the MSQ for RBD in both an aging and dementia cohort, and now in a separate community-based elderly cohort, suggest that its use would be appropriate in a variety of clinical settings involving elderly patients—primary care practices, memory disorder/behavioral neurology clinics, movement disorder clinics, geriatric medicine clinics, sleep disorder centers, etc.

The potential of the MSQ as a research tool is also promising, and only a few examples will be presented and re-empha-
sized here. Due to the ease of use as a screening tool and high SN and SP as demonstrated by these analyses, the MSQ could be incorporated into the standard assessment of participants in any aging research program, with a positive screen for RBD increasing the clinician’s suspicion for an evolving synucleinopathy. Since performing PSGs on a large number of subjects may not be practical, the MSQ may also be useful in determining the incidence or prevalence of RBD in epidemiologic studies, especially since the only prevalence data (0.05%) on RBD is based on a telephone questionnaire. Screening for RBD in population-based studies could also identify those with probable RBD for a variety of research questions. Many analyses have been conducted with the MSQ thus far in Olmsted County, Minnesota, and the utility of such screening appears promising. The MSQ has already shown utility in estimating the risk of developing mild cognitive impairment/dementia or Parkinsonism among those who screen positive for RBD in a community-based cohort of older subjects, in identifying and assessing the frequency of probable RBD among subjects with mild dementia, in studying the frequency and timing of probable RBD in those with Parkinson disease with or without dementia, in assessing the frequency of probable RBD in those with restless legs syndrome compared to essential tremor, and in assessing differential neurotransmitter denervation changes among Parkinson disease patients with and without probable RBD.

The MSQ can also be used prospectively to determine if those with probable RBD in middle or old age ranges who do not have cognitive or motor problems are at a higher risk of developing a PD, MCI, or DLB. This will be particularly important when synuclein-active agents are available to test for disease-modifying properties.

The high SN (96-100%) for the MSQ and other various screening measures on RBD may appear to be “too good to be true,” as few screening measures in clinical medicine have SN so high. Yet the high SN likely reflects the rather unique features of the disorder—if any patient has RBD, the features are so consistent across individuals that any questions involving recurrent dream enactment behavior will likely be answered affirmatively and result in a positive screen. These other screening measures also involved study populations where males represented the clear majority of cases.

**REM Sleep Without Atonia**

The finding of RSWA in 11 of the subjects is also of interest. One might argue that subjects with RSWA could be viewed as “false negative” cases in our analyses since they had “no” responses to Question 1 on the MSQ, but since there was no history of dream enactment behavior at the time the PSG was performed and no dream enactment behavior present during REM sleep on the PSG, such cases were appropriately viewed as true negatives. The one case with RSWA plus MCI who subsequently began exhibiting recurrent dream enactment behavior as well as other features characteristic of PD underscores the potential clinical relevance of following patients longitudinally when RSWA is identified on PSG.

**Qualifications and Limitations**

The same qualifications and limitations to the MSQ and the analyses, as noted previously, are applicable to the current analysis. The MSQ was developed to screen for RBD and other key sleep disorders, and it should not be used as the sole mechanism for making a diagnosis of any of the sleep disorders queried by the measure. The validation also was performed retrospectively by using responses on the MSQ and comparing the responses to the gold standards of clinical assessment and PSG, which may be inaccurate. A prospective approach would be reasonable for future analyses. The analyses in this paper primarily involved older male individuals, yet this is similar to the other validation studies on RBD screening measures. The MSQ also does not distinguish between RBD due to a neurodegenerative cause or due to secondary causes such as medications. As a result, the SN and SP may vary depending on the setting and population of patients in a validation analysis. Optimally, future prospective validations of the MSQ should be used with standardized clinical assessments and PSGs in a variety of settings, including individuals with no sleep complaints and in samples with equal numbers of men and women. Nevertheless, our findings among elderly subjects in two separate cohorts with SN 98% to 100% and SP 74% to 95% suggest that the MSQ has adequate SN and SP for the diagnosis of RBD, and those who screen positive can be considered to represent “probable RBD” cases.

**ABBREVIATIONS**

AD, clinically probable Alzheimer disease  
AHI, apnea/hypopnea index  
DLB, dementia with Lewy bodies (as defined by the clinical syndrome)  
EMG, electromyography  
ESS, Epworth Sleepiness Scale  
FN, false negative  
FP, false positive  
LBD, Lewy body disease (as defined by pathology)  
MCI, mild cognitive impairment  
MSQ, Mayo Sleep Questionnaire  
OSA, obstructive sleep apnea  
PD, Parkinson disease  
PLMS, periodic limb movements during sleep  
PSG, polysomnography  
RBD, REM sleep behavior disorder  
REM, rapid eye movement  
RLS, restless legs syndrome  
RSWA, REM sleep without atonia  
SN, sensitivity  
SP, specificity  
SRLC, sleep related leg cramps  
SW, sleepwalking  
TN, true negative  
TP, true positive

**REFERENCES**


17. (RBD) a risk factor of dementia in idiopathic Parkinson’s disease?

21. and sampling, participation, baseline measures and sample characteristics.


ACKNOWLEDGMENTS

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Insomnia is a highly prevalent and often debilitating condition that reduces quality of life, increases risks for various mental and medical disorders and enhances healthcare costs for millions of individuals worldwide. Over the past several decades a burgeoning body of insomnia-focused research has advanced our understanding and ability to manage this condition. However, this body of research has not been without its limitations. As noted by Buysse et al., the insomnia research literature has been plagued by lack of standardization, particularly in regard to the methods and criteria used for assessing and characterizing insomnia symptoms, and perhaps more importantly, the more global insomnia disorder. This lack of standardization, in turn, has resulted in considerable variability in the selection of insomnia samples across studies. Consequently, comparisons of findings across studies are often difficult or impossible to conduct. This state of affairs has slowed our progress toward developing optimal insomnia management strategies and reducing the overall prevalence and public impact of this troublesome sleep disorder.

Fortunately, in recent years, there have been a number of efforts in the sleep research and professional community to remedy this situation. Included among these are the development and publication of research diagnostic criteria for defining insomnia, as well as the publication of consensus recommendations for standardizing assessment methods and measures in all insomnia research studies. Additionally, some investigators have proposed developing quantitative insomnia criteria based on indices of nocturnal sleep disturbance. Studies devoted to this objective have shown that a cutoff value > 30 minutes for sleep onset latency or wake time after onset derived from respondents’ sleep diaries has good sensitivity and specificity for discriminating insomnia sufferers from normal sleepers. Thus, adding such quantitative cut-offs to study selection criteria may add some precision to the participant screening process for insomnia research studies.

Yet, use of quantitative insomnia criteria based on such subjective sleep estimates may not represent optimal research practice when alternate objective sleep assessment methodologies are readily available. Since polysomnography (PSG) has long been considered the gold standard objective measure of sleep, there has been considerable interest in using quantitative PSG criteria for identifying insomnia research candidates. This has

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**Study Objectives:** In recent years, polysomnography-based eligibility criteria have been increasingly used to identify candidates for insomnia research, and this has been particularly true of studies evaluating pharmacologic therapy for primary insomnia. However, the sensitivity and specificity of PSG for identifying individuals with insomnia is unknown, and there is no consensus on the criteria sets which should be used for participant selection. In the current study, an archival data set was used to test the sensitivity and specificity of PSG measures for identifying individuals with primary insomnia in both home and lab settings. We then evaluated the sensitivity and specificity of the eligibility criteria employed in a number of recent insomnia trials for identifying primary insomnia sufferers in our sample.

**Design:** Archival data analysis.

**Settings:** Study participants’ homes and a clinical sleep laboratory.

**Participants:** Adults: 76 with primary insomnia and 78 non-complaining normal sleepers.

**Measurements and Results:** ROC and cross-tabs analyses were used to evaluate the sensitivity and specificity of PSG-derived total sleep time, latency to persistent sleep, wake after sleep onset, and sleep efficiency for discriminating adults with primary insomnia from normal sleepers. None of the individual criteria accurately discriminated PI from normal sleepers, and none of the criteria sets used in recent trials demonstrated acceptable sensitivity and specificity for identifying primary insomnia.

**Conclusions:** The use of quantitative PSG-based selection criteria in insomnia research may exclude many who meet current diagnostic criteria for an insomnia disorder.

**Keywords:** Insomnia, PSG, research, sensitivity, specificity

**Citation:** Edinger JD; Ulmer CS; Means MK. Sensitivity and specificity of polysomnographic criteria for defining insomnia. J Clin Sleep Med 2013;9(5):481-491.
been particularly true for studies designed to test various pharmacological insomnia therapies. For example, parameters such as sleep onset latency, wake time during sleep, and total sleep time derived from pretreatment nights of PSG monitoring have been commonly used in conjunction with clinical diagnostic assessments to select patients deemed appropriate for medication testing. In such cases, PSG measures most typically have been used to select patients with sufficient levels of sleep disturbance to evaluate the effects of medications with particular pharmacologic characteristics on specific aspects of sleep. This practice seems to fit well with the other mentioned developments focusing on increased precision in insomnia research. Moreover, PSG-based criteria have face validity since they overcome the inaccuracies and reporting biases that can encumber the subjective sleep estimates provided by many insomnia sufferers.

However, the practice of defining and selecting insomnia sufferers for clinical trials on the basis of PSG measures is not devoid of its own shortcomings and potential criticisms. As repeatedly noted in the AASM standards of practice literature and elsewhere, only a subset of those who meet diagnostic criteria for insomnia show objective sleep disturbances during PSG monitoring. Also, as noted in the May 2011 proceedings of a FDA-sponsored workshop concerned with the safety and efficacy of insomnia drugs, “...most of the existing studies are based on one night of polysomnography for sleep ... classification. And we don’t really know or haven’t systematically examined the reliability of that categorizing criterion.” Although subject selection for many clinical trials has been based on findings from two or more qualifying nights of PSG, the specific quantitative criteria used in these trials have varied considerably. Indeed, multiple distinctive criteria sets have been proposed, and there is no apparent consensus as to which of these is optimal. Furthermore, it remains difficult to evaluate these various criteria since there have been no studies to test the sensitivity and specificity of any PSG measures or criteria sets for discriminating insomnia sufferers from those without insomnia. Thus, whether PSG-based selection criteria add precision to insomnia research remains an open question.

The purpose of this investigation was to test the sensitivity and specificity of PSG measures for the selection of patients with primary insomnia. Specifically, this study tested the usefulness of common sleep measures such as sleep onset time, total sleep time, wake time after sleep onset, and sleep efficiency, derived from lab-based and home-based sleep monitoring for discriminating primary insomnia sufferers from normal sleepers. The sensitivity and specificity of these PSG measures for sample characterization were evaluated by consensus standards for judging their adequacy and were compared to the performances of concurrent measures derived from sleep diaries. Additionally, this study tested the sensitivity and specificity of a number of previously proposed PSG criteria sets for discriminating primary insomnia sufferers from the normal sleepers in our sample.

**METHOD**

**Design**

This study comprised a secondary analysis of archival data using a between-groups cross-sectional research design. The study sample included independent groups of age- and gender-matched non-complaining normal sleepers and persons with primary insomnia. The participants for this report were drawn from a larger parent study conducted to compare the nighttime sleep and daytime functioning of adult insomnia sufferers and normal sleepers. All study procedures were reviewed and approved by the institutional review boards of the VA Medical Center and Duke University Medical Center in Durham, NC. Each participant was required to provide written informed consent prior to enrolling and received a maximum of $250 for completing all procedures of the parent study.

**Participants**

Both non-complaining normal sleepers and insomnia sufferers were recruited in 3 waves between October 1992 and October 2001 via posted study announcements on bulletin board within the VA and Duke University Medical Centers, letters mailed to persons in the Duke University Center for the Study of Aging and Human Development Subject Pool, and flyers posted in the community. In addition, we recruited a subset of the insomnia sufferers through face-to-face solicitations of clinic patients presenting to our university sleep disorders center. During the first recruitment wave, we enrolled age- and gender-matched insomnia sufferers and normal sleepers between 60 and 79 years of age. The second recruitment wave was used to enroll similarly matched middle-aged (i.e., aged 40 to 59 years) insomnia sufferers and normal sleepers, whereas the final recruitment period was used to enroll samples of young adult (aged 20 to 39 years) insomnia sufferers and matched normal sleepers. All study candidates underwent a thorough screening process to ensure that they met study selection criteria. Screening procedures included structured psychiatric (SCID) and sleep interviews and a physician-conducted medical exam with thyroid (TSH level) screening. Candidates who passed these initial screening procedures underwent a minimum of 1 to 2 nights of qualifying polysomnography (PSG) conducted in either the sleep lab or in the candidate’s home. To be included in the study, insomnia sufferers had to meet DSM-IV criteria for primary insomnia. These criteria include the following: (a) A predominant complaint of difficulty initiating or maintaining sleep or nonrestorative sleep for ≥ 1 month; (b) The sleep disturbance (or associated fatigue) causes clinically significant distress and impairment in social, occupational, or other important areas of functioning; (c) The sleep disturbance does not occur exclusively during the course of another primary sleep disorder; (d) The sleep disturbance does not occur exclusively during the course of another mental disorder; (e) The sleep disturbance is not due to the direct physiologic effects of a substance or a general medical condition. We used these criteria for selection of our insomnia sample since they are widely used in clinical venues to identify insomnia sufferers, and currently no biological/medical assay exists for diagnosing insomnia. The normal sleepers selected for this study had to report general satisfaction with sleep in the absence of any reported sleep onset or maintenance difficulties. Exclusion criteria for all participants were: (a) terminal illness; (b) medical condition associated with compromised sleep (e.g., rheumatoid arthritis, thyroid disease); (c) abnormal TSH levels on a screening thyroid panel; (d) history of any prior psychiatric illness (lifelong perspective); (e) current major psychiatric illness.
Americans, 1 Hispanic American, and 1 Native American; the group included 59 Caucasians, 10 African Americans, 5 Asian the normal group was 50.9 years (SD 16.0 years). The insomnia sample was 51.8 years (SD 16.5 years), whereas the mean age of cerns (e.g., non-restorative sleep). The mean age of the insomnia -tenance difficulties, and 4 persons with other sleep/wake con
awakenings), 38 with a mixture of sleep onset and sleep main-
ported a 10.6-year (SD 9.3 years) history of sleep difficulties on non-complaining normal sleepers. The insomnia sample re-
for primary insomnia, and the remaining 78 (38 women) were as normal sleepers who met structured sleep interview criteria13,14 for a comorbid sleep disorder in addition to primary insomnia, as well as normal sleepers who met structured sleep interview criteria for any sleep disorder.

A total of 208 study participants were enrolled; most (> 95%) of these were recruited from posted announcements or solicitation letters. Of the 208 who entered the study, 9 withdrew from the study before undergoing PSG, and 45 were excluded from this investigation because they either failed to complete all scheduled PSG studies described below or because one or more of their PSG recordings were deemed un-scorable due to technical problems (e.g., loss of key electrodes). As a result, 25 (12.5%) participants had 5 nights of usable data, 11 (5.5%) had 4 nights of data, 5 (2.5%) had 3 nights of data, 3 (1.5%) had 2 nights of data, and 1 had only 1 night of usable data (0.5%). Of the remaining sample, 76 (38 women) met selection criteria for primary insomnia, and the remaining 78 (38 women) were non-complaining normal sleepers. The insomnia sample reported a 10.6-year (SD 9.3 years) history of sleep difficulties on average and comprised 11 persons with solely sleep onset complaints, 25 individuals with solely sleep maintenance complaints (either middle-of-the-night wakefulness and/or early morning awakenings), 38 with a mixture of sleep onset and sleep maintenance difficulties, and 4 persons with other sleep/wake concerns (e.g., non-restorative sleep). The mean age of the insomnia sample was 51.8 years (SD 16.5 years), whereas the mean age of the normal group was 50.9 years (SD 16.0 years). The insomnia group included 59 Caucasians, 10 African Americans, 5 Asian Americans, 1 Hispanic American, and 1 Native American; the normal sleepers included 67 Caucasians, 9 African Americans, 1 Asian American, and 1 Native American.

Polysomnography

As part of their requirements for the parent study, all participants were scheduled for 3 consecutive nights of polysomnography (PSG) conducted in their homes and an additional 3 consecutive nights of PSG in our university medical center’s sleep laboratory. PSGs were conducted using 8-channel Oxford Medilog 9000 or 9200 series ambulatory recorders. The monitoring montage included 2 electroencephalogram (EEG) channels (C3-A2, O2-Cz), bilateral electrooculogram (EOG), submental electromyogram (EMG), 2 channels of anterior tibialis EMG (right and left leg), and a nasal/oral thermistor. All PSGs were scored using traditional scoring criteria for assignment of sleep stages, identification of respiratory events (e.g., apneas, hypopneas), and identification of periodic limb movement and periodic limb movement-related arousals.15-18 Per pre-planned study protocols, the first or initial 2 PSG nights (home or lab) were used to screen out those exceeding the aforementioned hypopnea index or periodic limb movement arousal index cutoffs for study inclusion. Although PSG typically includes additional respiratory measures to detect breathing abnormalities (e.g., respiratory effort, oximetry), it was thought that monitoring of nas/oral airflow along with our thorough interview screening for apnea would be sufficient to identify most cases with an apnea-hypopnea index above the study’s exclusionary cut-off.

Laboratory personnel who were kept blind to the participants’ diagnoses (insomnia vs. normal sleeper) scored all PSG recordings. Each taped PSG record was scored directly on the screen of the Medilog playback unit using traditional scoring criteria.16 Results of PSG scoring were subsequently used to derive measures of time in bed (TIB: time between the electronically marked bedtime and final rising time on each recording), total sleep time (TST: the total time in stages 1, 2, slow wave sleep, and REM sleep), latency to persistent sleep (LPS: time between lights out and the first 10 min of sleep containing ≤ 2 min of wake time, stage 1 sleep, or movement time), wake time after sleep onset, (WASO: all time awake after the onset of sleep and before the final morning rising time), and sleep efficiency % (SE %; [TST ÷ TIB] × 100%). It should be noted that the sleep onset measure chosen for use here—LPS—differs from other measures of sleep onset that require a more limited number of epochs or shorter time periods of sleep for connoting the transition from wakefulness to sleep. We chose LPS since it has been used in many clinical trials as a measure of sleep onset and because it connotes not only the ability to achieve sleep but also to sustain it. Hence, it is a particularly relevant parameter for those with sleep onset complaints.

Sleep Diary Monitoring

In addition to PSG recording, participants were asked to complete sleep diary forms in the morning after each PSG night and during an additional 2-week period when they were not undergoing PSG monitoring. The diary forms asked participants about bed and rising times as well as how long it took them to fall asleep, how long they were awake in the middle of the night after first falling asleep, and how long they were awake in bed at the end of the night before getting out of bed. The diary forms additionally included items asking participants to rate the quality of each night’s sleep (1 = very poor; 5 = excellent) and how well rested they felt upon arising (1 = not at all; 5 = very well rested). These items were common to both sets of diaries. In addition, the diary forms completed by participants after each PSG night included an item that asked how much the PSG recording equipment disturbed their sleep each night (1 = very much; 5 = not at all). The diaries completed after each PSG served mainly to help PSG scorers corroborate participants’ bed and rising times as well as to assess the degree to which the sleep monitoring process was perceived to disturb participants’ sleep. In contrast, the 2-week diaries were used to obtain measures of participants’ subjective measures of time in bed, sleep onset latency (SOL), middle of the night wake time (MWASO), wake time at the end of the night (TWASO), total sleep time (TST), and sleep efficiency (SE % of time in bed spent asleep). These measures were calculated for each night of sleep recorded by participants on the 2-week diaries and then used to calculate mean values across the 2 weeks of diary monitoring.

Procedure

Consenting participants who met selection criteria underwent PSGs in a randomly determined order so that roughly half of the participants in each group (normals and insomnia) underwent
lab PSG, first whereas the other half underwent home studies first. All sleep studies were scheduled such that the home and laboratory PSGs were separated by ≥ 4 but ≤ 30 intervening days. During both series of studies, participants were instructed to maintain customary home bed and rising times, and they were instructed to note their actual bed and rising times each night using an event marker contained on the PSG recorders. They also recorded bed and rising times on a sleep diary they completed upon arising each morning after each PSG night. In addition, all home studies were scheduled for nights when participants planned to have no overnight houseguests. Participants were instructed to abstain from alcoholic beverages and to not consume caffeinated substances after 18:00 on study nights.

RESULTS

Preliminary Analyses

Before conducting our primary analyses, we computed the means and standard deviations of each of the 4 PSG sleep measures for each sample in each recording site. Table 1 shows these data along with results of a series of one-way ANOVAs computed to compare the normal sleepers and insomnia sufferers on these measures in each setting. These analyses showed the insomnia sufferers had significantly higher mean WASO and a significantly lower mean sleep efficiency in the lab setting than did the normal sleepers. In the home setting, the groups differed only on their sleep onset latencies. The home setting studies were representative of the larger participant group enrolled.

Hence, we used a more liberal α = 0.01 level for assigning statistical significance. Whereas this criterion level of significance is appropriate for main study analyses, it arguably is a high bar to reach in our tests of possible study confounding. Since a total of 20 LMM analyses were conducted, a Bonferroni-corrected α = 0.0025 (i.e., .05 ÷ 20) might be considered for assigning statistical significance. Whereas this criterion level of significance is appropriate for main study analyses, it arguably is a high bar to reach in our tests of possible study confounding. Hence, we used a more liberal α = 0.01 level for assigning statistical significance in these 20 LMM analyses. Despite selection of this lenient α level, results of all these analyses showed no significant main or interaction effect for the group factor. Hence, the sleep measures derived from the inclusion sample were representative of the larger participant group enrolled.

ROC Analyses

In order to ascertain how well our selected PSG measures discriminated insomnia sufferers from normal sleepers, we first compared these groups in regard to their means values of the home and lab PSG measures obtained. Table 1 shows these mean

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Insomnia</th>
<th>Normal</th>
<th>Insomnia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M (SD)</td>
<td>M (SD)</td>
<td>F</td>
<td>P</td>
</tr>
<tr>
<td>LPS</td>
<td>26.6 (63.3)</td>
<td>23.5 (19.1)</td>
<td>0.21</td>
<td>0.65</td>
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<tr>
<td>WASO</td>
<td>48.4 (36.0)</td>
<td>62.2 (33.8)</td>
<td>7.4</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>TST</td>
<td>384.1 (53.8)</td>
<td>378.1 (2.6)</td>
<td>0.52</td>
<td>0.47</td>
</tr>
<tr>
<td>SE</td>
<td>88.0 (8.9)</td>
<td>85.1 (9.2)</td>
<td>5.1</td>
<td>0.03</td>
</tr>
<tr>
<td>TIB</td>
<td>442.3 (66.5)</td>
<td>450.7 (50.5)</td>
<td>0.98</td>
<td>&lt; 0.32</td>
</tr>
<tr>
<td>STAGE1</td>
<td>17.6 (10.0)</td>
<td>19.0 (10.8)</td>
<td>0.90</td>
<td>0.34</td>
</tr>
<tr>
<td>STAGE2</td>
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<td>194.0 (40.3)</td>
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<td>0.70</td>
</tr>
<tr>
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<td>77.1 (28.1)</td>
<td>0.39</td>
<td>0.54</td>
</tr>
<tr>
<td>REM</td>
<td>80.2 (20.2)</td>
<td>78.5 (24.0)</td>
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<td>0.61</td>
</tr>
<tr>
<td>EPI</td>
<td>81.3 (31.0)</td>
<td>94.4 (33.3)</td>
<td>8.06</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>

Table 1—Comparisons of mean PSG values from lab and home monitoring.
values and results of statistical comparisons. These results show
the insomnia sufferers had more WASO, lower sleep efficiencies,
and a great number of sleep episodes in the lab than did normal
sleepers, whereas in the home setting, the insomnia group showed
higher WASO values and more sleep episodes than did the normal
group. As a follow-up to these simple mean comparisons we used
receiver-operating characteristic (ROC) curve analyses to graphi-
cally depict the relation between the sensitivity and specificity of
the test over all possible values of each mean PSG measure. In
these analyses, sensitivity for a particular mean PSG measure rep-
resented the probability of detecting insomnia when it is present,
and specificity represented the probability of not detecting insom-
nia when it was not present. The ROC curve was plotted for all
values, and the greater the distance of ROC curve above the diag-
onal reference line, the more accurate the test.19 The area under the
curve (AUC) served as one primary index of accuracy. The AUC
is the probability that a test result for a randomly chosen positive
case will exceed the result for a negative case. Swets20 has suggest-
ed that test accuracy be defined as “low” for AUC values under
0.7, “moderate” for AUC values between 0.7 and 0.9, and “high”
for values greater than 0.9. In addition, we calculated the Youden
Index for each of the sleep measures tested. The Youden Index
is an alternative index of diagnostic accuracy. It ranges from 0 to
1, with higher values representing greater separation between 2
distributions. Thus, distributions having complete overlap would
have a Youden Index of 0, while those having complete separation
would have a Youden Index of 1.

In conducting the ROC analyses, we focused initially on the
4 variables most reflective of an insomnia diagnosis: difficulty
falling asleep (LPS); difficulty staying asleep (WASO); sleep
duration (TST); and sleep efficiency (SE). Results of the ROC
analyses conducted with these home- and laboratory-based mea-
sures are summarized in Figures 1 and 2, respectively. The top
portions of Table 2 provide summary statistics for these analy-
ses including AUC values, Youden indices, optimal cutoffs for
group discrimination, and the sensitivity and specificity of these
cutoffs. Collectively, the figures and table show that none of the
home or lab PSG measures performed well in discriminating the
insomnia sufferers from the non-complaining normal sleepers.
The best discriminators among the home-based measures were
SE and LPS, whereas the best discriminators among those mea-
sures derived from lab recordings were SE and WASO. None-
theless, AUC estimates all fell in the “low” range, indicating
the poor test accuracy of these measures for use as quantitative
insomnia criteria. The inadequacy of these mean values for dis-
criminating the insomnia and normal groups is characterized by
the plots of data shown in Figure 3. This figure shows the distrib-
ution of mean values of TST and SE obtained from lab record-
ings. These plots show that there is appreciable overlap between
the insomnia and normal groups in regard to the distributions
of measures across the ranges of values observed. Similar plots
(not shown) for all of the remaining lab and home sleep mea-
sures included in Table 1 showed comparable results. As a con-
sequence, it is difficult to discern a single quantitative cutoff for
any of these mean values, even for measures showing significant
group differences by the ANOVA tests.

Since an insomnia diagnosis does not require the presence
of both a sleep onset and sleep maintenance complaint, we also
explored the possibility that PSG-based sleep measures may
better discriminate if the type of insomnia complaint (onset
versus maintenance) is used as the comparator. We conducted
2 additional analyses comparing normal sleepers to those with
a sleep onset complaint and to those with a sleep maintenance
complaint. For the purpose of these analyses, the sleep onset
group comprised the insomnia sufferers with sleep onset only
or mixed onset/maintenance complaints (total = 49), whereas
the maintenance group included those with maintenance com-
plaints with or without accompanying sleep onset concerns
(total = 63). Results of these tests (see supplemental material)
showed that all AUC values fell in the low range, suggesting
poor test accuracy. Thus, considering the type of insomnia com-
plaint did not increase the accuracy of PSG sleep variables for
discriminating insomnia sufferers from normal sleepers.

Relative Sensitivity and Specificity of Sleep Diary
Measures
Since measures derived from extended periods of sleep diary
monitoring have demonstrated sensitivity/specificity for defin-
ing insomnia3,4 we conducted ROC analyses using 2-week sleep
diary data collected by participants during a period when they
were not undergoing PSG. The bottom portion of Table 2 shows
the AUCs and Youden indices derived from ROC analyses of
these sleep diary measures. Also shown are the optimal cutoffs
for group discrimination as well as the sensitivity and specific-
ity of those cutoffs. The sleep diary measures were found to be
consistently more accurate than PSG in discriminating insom-
nia sufferers from normal sleepers, particularly the measures of
SE, SOL, and middle of the night wake time (MWASO).

Tests of Previously Reported PSG Qualifying Criteria
It is possible that mean values of individual sleep measures
provide a somewhat limited view of the detectable PSG dif-
fences between insomnia sufferers and those without sleep
complaints. Indeed, it may be useful to consider indicators of
the persistence of sleep difficulties among those with insomnia
relative to normal sleepers, and/or to simultaneously consider
multiple PSG measures to enhance group discrimination. In
this regard, several recently published studies conducted to test
cytopnic agents have described sets of PSG criteria used in con-
junction with clinical diagnoses to select primary insomnia pa-
tients as study participants. The specific criteria sets suggested
in these trials are shown in Table 3.20-28 As noted, most of these
criteria sets considered both average values of selected sleep
measures across 2 qualifying nights of PSG and the magnitude
of these measures on each night separately. As such, these se-
lection criteria not only reflect a specific level of sleep diffi-
culty on average, but also a degree of persistence in that sort
of disturbance. The criteria proposed by Mayer27 would seem
designed to identify those with sleep onset difficulties, whereas
those provided by Roth28 appear suited to select patients with
sleep maintenance complaints. The remaining criteria sets
shown would appear useful for identifying insomnia patients
with a mixture of sleep onset and maintenance difficulties.

In selecting these various criteria sets, we recognized that
they were not intended to be used in isolation to define insomnia,
but rather were employed in conjunction with clinical assess-
ments to identify individuals with a particular form or severity
of sleep disturbance. We also recognized that these criteria sets

Polysomnographic Criteria for Insomnia

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were originally intended for PSGs conducted with participants who were provided prescribed (fixed) amounts of time in bed rather than the participant-determined bed and rising times used in this study. Nonetheless, since these criteria sets by and large considered multiple sleep parameters across nights, we reasoned that they might provide better discrimination of our insomnia and normal sleeper groups than would individual measures tested in our above-described ROC analyses. To test this assumption, we conducted a series of cross tabs analyses to evaluate the accuracy of each of these criteria sets for discriminating our insomnia group from our normal sleeper group. In doing so, we selected relevant measures from the first 2 nights of PSG recording conducted in the laboratory and the initial 2 nights obtained in participants’ homes. The classification rules were then applied to the lab- and home-derived data separately so as to ascertain how the sleep setting effects influenced our classification results. We used our cross tabs analyses specifically to ascertain each criteria set’s sensitivity (i.e., the probability for detecting insomnia when it is present), and specificity (i.e., the probability of not detecting insomnia when it was not present).

Results of these cross-tabs analyses are presented graphically in Figures 4 and 5. Figure 4 depicts results for the various criteria sets when applied to lab-based PSG parameters, whereas Figure 5 shows results obtained with the home-based PSG measures. These figures demonstrate that none of the criteria sets showed good sensitivity and specificity in discriminating our insomnia and normal sleeper groups. Furthermore, the recording site—lab or home—from which PSG data were derived seemingly had little effect on classification results. The majority of the criteria sets showed satisfactory to good speci-
ficity but poor sensitivity for identifying our insomnia sufferers. In fact, less than a third of the insomnia sufferers met most of these selection criteria. The Walsh et al. PSG criteria, based on TST and MSLT sleep latency measures, had relatively poor sensitivity and specificity. Hence, none of the criterion sets seem to convey sleep characteristics that are specific to insomnia.

In addition to testing each criterion set as proposed, we considered the possibility that some components of these various criteria sets may be effective for discriminating the insomnia and normal sleeper groups. As the LPS criterion used across trials was standard, we chose to test this criterion in isolation and in combination with WASO and/or TST criteria. For the purpose of these analyses we conducted cross tabulations of each of the WASO and TST criteria shown in Table 3 to ascertain the best for group discrimination. Results of these analyses showed that the WASO criterion used by Krystal et al. and the TST criterion proposed by Roth et al. produced the best group separation. We then conducted cross tabulations of each of these criteria individually and in various combinations to ascertain their sensitivity and specificity for defining our insomnia group. Results of these analyses are shown in Table 4. These data show that none of the individual criteria or their various combinations had acceptable sensitivity and specificity for identifying our insomnia cohort. Thus, our efforts to optimize these published criteria sets proved unsuccessful.

**DISCUSSION**

The current study was conducted to test the usefulness of quantitative PSG criteria for the identification/selection of pri-
mary insomnia sufferers in research protocols. The availability of such criteria derived from objective sleep monitoring would be extremely useful for standardizing the samples used in insomnia research and thereby facilitate comparisons of results across insomnia research studies. Unfortunately, the analyses conducted herein to identify useful quantitative PSG criteria did not support any of the criteria sets examined. Our ROC analyses, for example, showed that mean values of LPS, WASO, TST, and SE, derived from series of lab or home monitoring, failed to accurately discriminate primary insomnia sufferers from normal sleepers. Our analyses also showed that none of the PSG-based insomnia selection criteria sets used in recent insomnia treatment trials demonstrated acceptable sensitivity and specificity for selecting those meeting diagnostic criteria for primary insomnia. In fact, all of these criterion sets showed a tendency to select 50% or fewer of the insomnia sufferers and, for most such sets, our normal sleepers met these criteria at roughly the same rates as did the insomnia sufferers. Moreover, none of the cutoffs included in these criteria sets considered individually or in various combinations accurately selected the insomnia cases. To ensure that we did not overlook other sleep architecture variables which might have performed better in terms of identifying those with insomnia, we conducted additional ROC analyses on other PSG variables including the total number of sleep episodes recorded as well as the times spent in stage 1, stage 2, REM, and slow wave sleep. We found low test accuracy across all of these PSG variables as well. See the supplemental material for the specific results of these analyses.

These findings contrast markedly from those reported for measures taken from sleep diaries. Lichstein et al., 3 for example, found that sleep diary measures of sleep onset latency or wake time after sleep onset ≥ 31 minutes occurring ≥ 3 times per week have good sensitivity and specificity for discriminating insomnia sufferers from normal sleepers. Likewise, we previously were able to identify specific mean values of sleep onset latency and WASO taken from two weeks of sleep diary monitoring that effectively separate primary insomnia sufferers from normal sleepers in younger and older samples.4 In the current study, we expanded on our previous diary findings by showing that individual mean diary values of SOL, SE, and MWASO taken from two weeks of conventional home diary monitoring far outperformed any of our PSG measures for group discrimination. The more limited period of PSG monitoring may have put the PSG measures at a relative disadvantage and, in part, accounted for their poorer performance herein. In addition, both diary data and a clinical insomnia diagnosis are based on self-report and therefore share method variance not shared by objective PSG monitoring. Both these methodological factors should be recognized when considering our findings.

### Table 2—Comparison of ROC AUCs, optimal cutoff values and sensitivity/specificity of PSG and diary measures for discriminating those with and without insomnia

<table>
<thead>
<tr>
<th>Sleep Measure</th>
<th>Home PSG</th>
<th>Lab PSG</th>
<th>2-Week Sleep Diary</th>
</tr>
</thead>
<tbody>
<tr>
<td>TST</td>
<td>0.567</td>
<td>0.551</td>
<td>0.715</td>
</tr>
<tr>
<td>SE</td>
<td>0.602</td>
<td>0.641</td>
<td>0.905</td>
</tr>
<tr>
<td>LPS</td>
<td>0.621</td>
<td>0.627</td>
<td>0.888</td>
</tr>
<tr>
<td>MWASO</td>
<td>0.565</td>
<td>0.667</td>
<td>0.851</td>
</tr>
<tr>
<td>TWASO</td>
<td>0.521</td>
<td>0.606</td>
<td>0.675</td>
</tr>
</tbody>
</table>

* TST, total sleep time; SE, sleep efficiency; LPS, latency to persistent sleep; SOL, sleep onset latency; MWASO, middle WASO; TWASO, terminal wake time.

### Figure 3—Distribution of mean PSG values in the two samples

- **Lab Values of Total Sleep Time (Minutes)**
- **Lab Values of Sleep Efficiency**

* Normal and Insomnia groups.*
nosis. In the clinical setting, it is common experience, in fact, to find relatively normal sleep among some insomnia patients undergoing PSG recording, although such findings may be attributed to the so-called “reverse night effect” or the possible presence of paradoxical insomnia. It is also recognized that PSG recording can be disruptive to normal sleepers and produce sleep results that overlap with the sleep disruption characterizing insomnia samples. Such factors may account for the minimal differences often found in PSG comparisons of insomnia and normal groups. In line with these observations, current practice parameters indicate that polysomnography is generally not required for the routine diagnosis of insomnia, and there are relatively limited indications for its use among patients with insomnia complaints.\(^5,6\) Although the studies referenced herein did not necessarily use PSG for purposes of identifying those with insomnia, it would have been useful to have found that these criteria were helpful for this purpose. However, consistent with the current practice parameters, our study findings suggest that relying mainly on quantitative PSG-based criteria for the selection of study participants in insomnia treatment research is not advisable.

### Table 3—Published PSG qualifying criteria used for selection of primary insomnia patients

<table>
<thead>
<tr>
<th>#</th>
<th>Authors</th>
<th>PSG Criteria Sets</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Zammit et al. (2004)</td>
<td>2 nights of PSG with: Mean LPS ≥ 20 min with no night &lt; 15 min Mean TST ≥ 420 min or mean WASO ≥ 20 min with neither night &lt; 15 min</td>
</tr>
<tr>
<td>2</td>
<td>McCall et al. (2006)</td>
<td>2 nights of PSG with: Mean WASO ≥ 20 min with each night &lt; 15 min Mean LPS ≥ 20 min with neither night &lt; 15 min</td>
</tr>
<tr>
<td>3</td>
<td>Roth et al. (2007)</td>
<td>2 nights of PSG with: LPS ≥ 10 min Mean wake time during sleep (WTDS) ≥ 60 min with each night &lt; 45 min 240 min &lt; TST ≤ 410 min</td>
</tr>
<tr>
<td>4</td>
<td>Lankford et al. (2008)</td>
<td>2 nights of PSG with: Mean WASO ≥ 45 min &amp; WASO &gt; 30 each night Mean latency to persistent sleep (LPS) &gt; 20 min &amp; LPS &gt; 15 min each night Mean TST ≤ 6.5 hours &amp; TST &lt; 7 hours each night</td>
</tr>
<tr>
<td>5</td>
<td>Walsh et al. (2010)*</td>
<td>2 nights of PSG with: 240 min ≤ Mean TST ≤ 410 min 4 min ≤ Mean MSLT Latency ≤ 16 min</td>
</tr>
<tr>
<td>6</td>
<td>Krystal et al. (2010)</td>
<td>2 nights of PSG with: LPS &gt; 10 min WTDS ≥ 60 min 240 min &lt; TST ≤ 390 min</td>
</tr>
<tr>
<td>7</td>
<td>Mayer et al. (2009)</td>
<td>2 nights of PSG with: Mean LPS &gt; 20 min &amp; LPS ≥ 15 min each night</td>
</tr>
<tr>
<td>8</td>
<td>Roth et al. (2006)</td>
<td>2 nights of PSG with: Mean WASO &gt; 40 with each night ≥ 30 min 180 min ≤ TST ≤ 420 min each night</td>
</tr>
</tbody>
</table>

*The Walsh et al. criteria also included cutoffs for the average sleep latency on the multiple sleep latency test, but only the nocturnal PSG criteria were examined herein.

### Table 4—Additional tests of the sensitivity and specificity of various PSG criterion sets considered individually and in combination

<table>
<thead>
<tr>
<th>Criteria Used</th>
<th>Sensitivity % Insomnia Identified</th>
<th>Specificity % Normals Identified</th>
<th>(\chi^2 (p))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Home</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LPS</td>
<td>36.5</td>
<td>80.4</td>
<td>6.82 (&lt; 0.01)</td>
</tr>
<tr>
<td>WASO</td>
<td>52.1</td>
<td>63.9</td>
<td>5.01 (0.03)</td>
</tr>
<tr>
<td>TST</td>
<td>74.0</td>
<td>26.8</td>
<td>0.014 (0.90)</td>
</tr>
<tr>
<td>LPS + WASO</td>
<td>17.7</td>
<td>89.7</td>
<td>2.20 (0.14)</td>
</tr>
<tr>
<td>LPS + TST</td>
<td>29.2</td>
<td>84.5</td>
<td>5.23 (0.02)</td>
</tr>
<tr>
<td>WASO + TST</td>
<td>40.6</td>
<td>70.1</td>
<td>2.43 (0.12)</td>
</tr>
<tr>
<td>LPS + WASO + TST</td>
<td>13.5</td>
<td>91.8</td>
<td>1.40 (0.24)</td>
</tr>
<tr>
<td>Lab</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LPS</td>
<td>29.5</td>
<td>75.8</td>
<td>0.67 (0.41)</td>
</tr>
<tr>
<td>WASO</td>
<td>46.3</td>
<td>72.6</td>
<td>7.33 (&lt; 0.01)</td>
</tr>
<tr>
<td>TST</td>
<td>73.7</td>
<td>18.9</td>
<td>1.47 (0.23)</td>
</tr>
<tr>
<td>LPS + WASO</td>
<td>14.4</td>
<td>91.8</td>
<td>1.92 (0.17)</td>
</tr>
<tr>
<td>LPS + TST</td>
<td>21.6</td>
<td>80.6</td>
<td>0.15 (0.70)</td>
</tr>
<tr>
<td>WASO + TST</td>
<td>39.2</td>
<td>76.5</td>
<td>5.59 (0.02)</td>
</tr>
<tr>
<td>LPS + WASO + TST</td>
<td>12.6</td>
<td>92.6</td>
<td>1.46 (0.23)</td>
</tr>
</tbody>
</table>

The LPS criterion tested was an LPS ≥20 min average across nights, with neither night having <15 min; the WASO criterion tested was a wake time during sleep ≥60 min each of 2 nights; the TST criterion tested was total sleep time ≥180 min but ≤420 min on each night.

In considering our results it should be noted that the effectiveness found for any test is dependent upon the “gold standard” against which it is judged. Insomnia is defined on the basis of a patient’s clinical complaints, and there currently exists no biological assay or medical test that reliably confirms an insomnia disorder. For the purposes of this study, we chose to use DSM-IV-TR criteria for primary insomnia in identifying and selecting our insomnia sample; yet the primary insomnia diagnosis is based solely on self-report and is widely accepted to include a somewhat heterogeneous patient group. Moreover, the reliability of this diagnosis across raters seems marginal at best.\(^30,31\) Reliance on the clinical insomnia diagnosis as the gold standard has limitations in its own right and likely contributes to the findings obtained herein. Indeed, it could be argued that the clinical insomnia diagnosis has poor sensitivity and specificity for identifying individuals with large amounts of WASO or prolonged sleep latency on PSG. Nonetheless, at this juncture, the clinical diagnosis remains the defining feature of insomnia. Thus, the use of clinical criteria for establishing the diagnosis seemed reasonable for the purposes of this study.

Of course, the role of PSG selection criteria may go beyond the purpose of mere identification of those who meet diagnostic criteria for a specified disorder. There is also the consideration of selecting study participants who have a sufficient level or severity of disease so as to assure that treatment effects can be clearly discerned and detected by whatever statistical methods are deemed appropriate for the study in question. In the case of insomnia, it is common practice in this regard to select patients with a certain amount of wakefulness as measured by sleep onset latency and/or wake time during the night. This practice has indeed been common in studies of both pharmacological and
psychological therapies. As the Food and Drug Administration has required the inclusion of PSG outcome measures in tests of new insomnia agents, it is not surprising that the use of quantitative PSG selection criteria have been commonplace in insomnia medication trials. Yet the findings concerning the PSG selection criteria sets listed in Table 3 showed a sizable proportion of insomnia patients fail to meet these criteria and thus would be excluded from such studies. This was the case even when we attempted to increase test precision by considering sleep onset and sleep maintenance insomnia subtypes separately. Such results, in turn, raise questions about how well findings for such trials generalize to the larger insomnia population. It is clear from the previously cited proceedings of the May 2011 FDA/PERI sponsored workshop that the FDA is now reconsidering the role and use of PSG in insomnia clinical trials, so perhaps the sleep research community should do so as well. Of course, PSG may remain a useful research tool for documenting objective changes in insomnia treatment studies. Indeed, as PSG remains the gold standard for sleep measurement, this procedure is perhaps the best suited one for measuring the impact of a treatment on the overall sleep process.

Admittedly, this investigation had some limitations that need to be considered. Although our sample was moderate in size, it was heterogeneous in terms of insomnia complaint (e.g., onset, maintenance, mixed) and was composed largely of research volunteers. The findings therefore may not generalize to clinical populations since research and clinical samples may differ markedly. Furthermore, the sample included mainly Cauca-
sians, so it is not known how representative the findings would be for other ethnic groups. We also should note that many of the criteria sets used latency to persistent sleep (LPS) as a consideration, and the definition of this parameter is typically considered the onset of a 10-minute period of uninterrupted sleep. The definition used for LPS in constructing our archival data set was slightly less demanding. Although our measure of LPS would be expected to correlate highly with the LPS measure use in pharmacology trials, the two measures are admittedly not identical. As a result, it is possible that our analyses may underestimate the performances of at least some of the criteria sets we tested. Yet most of these sets performed so poorly that it is reasonable to assume that the use of more rigorous LPS measures would likely not result in significant performance improvement. Finally, we should acknowledge that the PSG montage used provided inadequate screening for sleep disordered breathing, given the relationship between subtle respiratory disturbance and insomnia complaints, especially in women. Despite this and the other limitations noted, our findings suggest that the use of quantitative PSG-based selection criteria in insomnia research is a practice that should be questioned. Use of such selection criteria in isolation may set an unreasonable metric for patients to achieve, and thus, may exclude many with genuine insomnia disorders from empirical scrutiny.

REFERENCES


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DISCLOSURE STATEMENT

This was not an industry supported study. The authors have indicated no financial conflicts of interest.
C-Reactive Protein and Carotid Intima-Media Thickness in Children with Sleep Disordered Breathing

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Study Objectives: Obesity is a risk factor for sleep disordered breathing (SDB) in children. Plasma levels of high-sensitivity C-reactive protein (Hs-CRP) are predictive of cardiovascular morbidity in adults, and CRP levels are associated with overweight. Increased carotid intima-media thickness (IMT) is associated with several cardiovascular risk factors. We evaluated the effect of SDB on CRP levels and IMT in lean and obese children not selected for snoring.

Methods: 101 children (age 5-15 years) attending a weight clinic or scheduled for routine visit. IMT was measured with quantitative B-mode ultrasound scans. The apnea-hypopnea index (AHI) was measured overnight: AHI < 1 defined controls, AHI ≥ 1 to < 5 = mild SDB, and AHI ≥ 5 = obstructive sleep apnea (OSA).

Results: AHI was significantly associated with Hs-CRP concentration (r = 0.32, p = 0.002) in all 101 children irrespective of age and sex. Body mass index (BMI) was higher in OSA children than controls (25.5 ± 7.0 vs 22.1 ± 6.9, p = 0.05). Obese children had 3.3 times more probability of having OSA (HR 3.3, 95% CI 1.2-9.3, p = 0.02) than lean children.

Hs-CRP values were significantly higher in children with OSA than in children without (p = 0.011), but not when BMI z-score was added as covariate. IMT was not associated with AHI or SDB.

Conclusions: The results of this study suggest an association between OSA and Hs-CRP concentrations (mainly mediated by overweight and obesity), but not between OSA and subclinical atherosclerosis. There is scope for prevention in childhood before OSA syndrome causes the irreversible damage to arteries observed in adult patients.

Keywords: C-reactive protein, intima-media thickness, obstructive sleep apnea

Citation: Iannuzzi A; Licenziati MR; De Michele F; Verga MC; Santoriello C; Di Buono L; Renis M; Lembo L; D’Agostino B; Cappetta D; Polverino M; Polverino F. C-reactive protein and carotid intima-media thickness in children with sleep disordered breathing. J Clin Sleep Med 2013;9(5):493-498.

BRIEF SUMMARY

Current Knowledge/Study Rationale: Sleep apnea is often associated with cardiovascular disease and atherosclerosis. This study was done to evaluate the association between sleep apnea and low-grade inflammation in a pediatric population without confounding influence of risk factors, as in adults.

Study Impact: The study demonstrated that obstructive sleep apnea in children is not associated with subclinical atherosclerosis. The major clinical implication of our study is that there is scope for prevention in childhood before sleep apnea syndrome causes the irreversible damage to arteries observed in adult patients.

recruit inflammatory mechanisms like those activated by obesity, which suggests that the two disorders may amplify each other. One of the most relevant serum markers of inflammation, at least in adults, is the high-sensitivity C-reactive protein (Hs-CRP), which has recently emerged as one of the most powerful independent predictors of risk for future cardiovascular morbidity. However, a pediatric population would be a better cohort in which to evaluate a possible association between SDB and low-grade inflammation because in adulthood...
there is a strong confounding influence of other cardiovascular risk factors, complete elimination of which might be difficult if not impossible.

The prevalence of OSAS in children differs among studies with estimates ranging between 0.7% and 10.3%. A possible limitation of most studies regarding SDB or OSAS in children is that they focus on children, obese or lean, who underwent polysomnography (PSG) for primary snoring. Snoring children are not representative of the general population of children. In the present study, we measured plasma Hs-CRP levels in a cohort of lean and obese children (not recruited for snoring) who were investigated for SDB. We also evaluated whether SDB severity is associated with subclinical carotid atherosclerosis.

**METHODS**

**Patients and Methods**

All the children from 5 to 15 years recruited from a subset of a community sample scheduled for a standard routine visit by their ambulatory pediatrician and all the children in the same age range evaluated for overweight or obesity in a specialist setting care in September, October, November, and December 2009, were invited to participate in a study to evaluate their cardiovascular risk factors and to investigate sleep breathing disorders by full PSG. Carotid ultrasound was performed in all enrolled subjects and intima-media thickness (IMT) was used as a proxy of vascular health. The local Ethics Committee “ASL SA1” approved the study on April 2, 2007 (approval number n° 21/2007). A total of 150 children were invited to participate, and 130 (54% males) accepted. Written informed consent was provided by the children and their parents. No child had any acute or chronic disease, and none was on regular medication. There was no family history of premature cardiovascular disease. A complete medical history, including a standard symptom questionnaire and history of snoring or atopy, was obtained from the parents.

Twenty children with a history or tests positive for asthma or allergic rhinitis were excluded. An expert pediatrician assessed pubertal development, based on Tanner stage, by physical examination. All subjects underwent a physical examination, and tonsillar size was graded from 0 to 4. Nine children with a tonsillar size graded as 4 were excluded from the study, leaving a final cohort of 101 children.

**Anthropometric Measurements**

Anthropometric measurements were made with the children wearing only underclothes and no shoes. Height was measured to the nearest 0.1 cm using a wall-mounted stadiometer. Body weight was measured to the nearest 0.1 kg with a digital scale. Waist circumference was measured at the level of the umbilicus and the superior iliac crest at the end of a normal expiration, while the child stood upright. The body mass index (BMI) was calculated as the weight in kilograms divided by the height in meters squared. BMI percentiles for age and standard deviation scores for BMI were based upon the Center for Disease Control normative curves. Obesity was defined as BMI > 95th percentile. The children had to rest for 10 min in a quiet, comfortable room before blood pressure measurements.

**Pressure Measurement**

Blood pressure was measured in the sitting position, using the right arm, with a standard mercury sphygmomanometer. After the appropriate-size cuff had been applied (covering approximately 80% of the circumference of the upper arm), the cuff was gradually inflated to about 20 mm Hg above the point at which the radial pulse disappeared. The pressure within the cuff was then deflated at a rate of 2-3 mm Hg/sec while the physician auscultated with a stethoscope over the brachial artery. The physician recorded systolic blood pressure (SBP) as the first Korotkoff sound and diastolic blood pressure (DBP) as the fifth. Pressures were measured 3 times at 1-min intervals, to the nearest 2 mm Hg. The measurements were then averaged for statistical analysis. Mean blood pressure was calculated as diastolic pressure plus one-third of pulse pressure.

**Laboratory Analyses**

Blood for high-sensitivity assessments of plasma CRP levels and for other biochemical parameters was drawn the morning after each child underwent a standard PSG evaluation in the sleep laboratory. C-reactive protein was measured by nephelometry (BNTnII, Dade Behring, Liederbach, Germany), and glycated hemoglobin was measured with high-performance liquid chromatography (Variant II, BioRad Laboratories, Hercules, CA). Plasma insulin was measured with an analyzer for heterogeneous immunoassays (Elecsys 2010, Roche Diagnostics, Mannheim, Germany). Total cholesterol, triglyceride, high-density lipoprotein cholesterol, and glucose concentrations were measured by enzymatic assays (Roche/Hitachi 747, Roche Diagnostics GmbH, Mannheim, Germany). The low-density lipoprotein cholesterol concentration was calculated using Friedewald’s formula. Insulin resistance was calculated with the homeostasis model assessment-insulin resistance (HOMA-IR) index (fasting insulin × fasting glucose / 22.5), as described by Matthews et al.

**Ultrasound B-mode Imaging**

Carotid B-mode ultrasound examinations were performed with an Aloka, SSD 4000 and a 7 to 13 MHz linear array probe. The ultrasound protocol involved a detailed investigation of the distal 1.0 cm of the near and far walls of the right and left common carotid artery before the crest at the origin of the bifurcation. Different scanning angles (anterior, lateral, and posterior) were used to identify the greatest IMT in each wall. Quantitative measurements of the near and far wall IMT were performed at the end of each examination on digitally stored images using electronic calipers. The sonographers, unaware of the study aim, reviewed the images and selected the frame that contained the thickest IMT for each of the 4 carotid walls. The mean of these 4 maximum thicknesses was reported as carotid IMT. Common carotid IMT measurements were obtained in all children. To evaluate the repeatability and intraobserver variability of vascular measurements in children, we performed the carotid ultrasound scan in the same setting and with the same sonographer on 2 occasions (1 to 7 days apart) in 21 healthy
children of a previous study. The coefficient of variation was 3.9% for the IMT measurements.

**Polysomnography**

Children were evaluated in the sleep laboratories of the Respiratory Departments of the Cava de’ Tirreni Hospital, in a quiet darkened room with an ambient temperature of 22-24°C, in the company, in a separate bed, of one of their parents. No sedation or sleep deprivation was used before the study. Subjects arrived at the laboratory at 21:00, and studies were terminated at 07:00. Children underwent a standard multichannel overnight PSG (Compumedics Sleep, Abbotsford, Australia). Electroencephalogram (C3/A2, O1/A2), right and left electrooculograms, submental electromyogram, and tibial electromyogram were continuously monitored. Nasal/oral airflow was measured by thermistors (nasal pressure cannula with an oral thermistor bead). Chest and abdominal wall movements were assessed by inductance plethysmography. Heart rate was assessed by electrocardiography, and transcutaneous hemoglobin oxygen saturation by pulse oximetry (Pulsox, Minolta) with simultaneous monitoring of pulse waveforms. Snoring intensity was monitored with a microphone sensor placed at the level of the neck, and body position was continuously recorded. All polysomnograms were supervised and recorded by an experienced sleep technologist. All data were stored for off-line analysis and were subsequently reviewed by a single investigator, a physician with expertise in sleep medicine, to ensure consistency. The percentage of time spent in each sleep stage was expressed as percentage of the total sleep time (TST). Obstructive apneas were defined by a complete cessation of airflow with continued chest wall and abdominal movement of at least two breaths. Hypopneas were defined as a reduction in airflow ≥ 50% from the immediately preceding recordings, with a corresponding decrease in oxygen saturation of > 4% and/or arousal. Breathing disturbances in sleep were quantified as the apnea index (AI) and apnea-hypopnea index (AHI). The obstructive apnea index was defined as the number of apnea events per hour of TST, and AHI was defined as the number of obstructive apnea and hypopnea events per hour of TST. AHI values ≥ 5 episodes/h of TST or AI values > 1 indicated obstructive sleep apnea (OSA); AHI values ≥ 1 and < 5 indicated mild SDB; and AHI values < 1 indicated controls. These cutoff points are widely used in clinical practice in children and are associated with such meaningful clinical outcomes as hypertension. Clinically, the data support the threshold of AHI > 5 (or AI > 1) for the initiation of treatment for SDB in children. Arousals were identified by an abrupt shift in EEG frequency lasting > 3 seconds. Arousal index, defined as the number of arousals divided by the TST, and sleep efficiency, defined as the ratio of TST to nocturnal time in bed, were also measured.

**Statistical Analysis**

The sample size of the study has been calculated using the following assumptions:

- 0.055 mm as a relevant difference in carotid IMT between the groups
- standard deviation of 0.06 mm
- α error (2-sided): 0.05
- β error: 0.20

Using these criteria, a minimum of 19 children per group was necessary to test the hypothesis of a difference in carotid IMT among children with OSA, SDB, and controls.

Because plasma Hs-CRP levels were not normally distributed, logarithmic transformation was applied (LnHs-CRP). Correlations of Hs-CRP levels with AHI were evaluated by linear regression followed by calculation of Pearson correlation coefficients. Comparisons of demographic, biochemical, ultrasound, and PSG data among groups were made with independent t tests or analysis of variance, with p values adjusted for unequal variances when appropriate (Levene test for equality of variances). Because obesity would be expected to contribute to increased CRP levels, we developed a general linear model and performed an analysis of covariance with LnCRP as dependent variable, categorized SDB as fixed factor and age, sex, and BMI z-score as covariates. Logistic regression analyses were used to determine whether obese children were at increased odds of OSA. All p values reported were 2-tailed, with statistical significance set at > 0.05. All analyses were performed using the Statistical Package for the Social Sciences Software (version 17.0; SPSS, Inc., Chicago, IL).

**RESULTS**

In all 101 children enrolled in the study, AHI was significantly associated with LnHs-CRP concentrations (r = 0.32, p = 0.002), irrespective of age and sex. However, when BMI was added to the model, the association did not quite reach significance level (p = 0.075). Age was significantly correlated with DBP, also after correction for AHI and sex (r = 0.13, p = 0.041), but this association lost statistical significance after the addition of BMI to the model (p = 0.32). No statistical association was found between AHI and SBP.

Glucose concentrations were similar in obese and non-obese children, but obese children had significantly higher concentrations of serum insulin and a higher HOMA index, which indicates an early insulin-resistance status. Socioeconomic status, evaluated by the parents’ level of education, was significantly lower in obese children. SBP, DBP, and carotid IMT values were significantly higher in obese children (Table 1). Moreover, obese children had higher plasma concentrations of transaminases, especially alanine-transaminase, which could be markers of early hepatic steatosis (Table 1).

At logistic regression analysis, obese children had 3.3 times more probability of having OSA (hazard ratio 3.3, 95% CI 1.2-9.3, p = 0.02) than non-obese children. LnHs-CRP levels were significantly higher in OSA children than in children with mild SDB and controls (Table 2). Hs-CRP values were significantly higher in children with OSA than in children without OSA (p = 0.011; Figure 1), but statistical significance was lost after adjustment for BMI z-score.

**DISCUSSION**

In an effort to identify pathophysiological links between obstructive sleep apnea-hypopnea and early markers of cardiovascular disease in the pediatric age group, we evaluated biochemical parameters and conducted carotid ultrasonography and PSG in a group of obese and lean children not se-
lected for snoring. To our knowledge, this is the first study that puts together data regarding subclinical atherosclerotic markers, sleep-breathing disorder parameters, and low-grade inflammation biochemical markers in a pediatric population not affected by snoring. Here we demonstrate: (i) an association between AHI and CRP concentrations, mainly mediated by overweight and obesity; (ii) a significantly greater low-grade inflammation in children with OSA than in children without OSA; and (iii) that OSA is not associated with subclinical atherosclerosis.

Table 1—Anthropometric, biochemical, subclinical atherosclerosis markers and sleep disordered breathing in obese and non-obese children (crude data)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Obese children (n = 35)</th>
<th>Non-Obese children (n = 66)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, males</td>
<td>20 (57%)</td>
<td>34 (51%)</td>
<td>0.10</td>
</tr>
<tr>
<td>Age (months)</td>
<td>127.7 ± 31.9</td>
<td>126.6 ± 23.6</td>
<td>0.86</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>147 ± 15</td>
<td>142 ± 14</td>
<td>0.07</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>68.2 ± 21.6</td>
<td>38.0 ± 10.9</td>
<td>0.0001</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>97.5 ± 14.1</td>
<td>69.6 ± 9.8</td>
<td>0.0001</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>116.2 ± 13.8</td>
<td>98.3 ± 10.3</td>
<td>0.0001</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>75.5 ± 9.6</td>
<td>64.6 ± 9.9</td>
<td>0.0001</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>85.6 ± 5.2</td>
<td>83.5 ± 7.6</td>
<td>0.11</td>
</tr>
<tr>
<td>Insulin (µU/mL)</td>
<td>20.3 ± 16.3</td>
<td>8.6 ± 6.0</td>
<td>0.0001</td>
</tr>
<tr>
<td>HOMA</td>
<td>4.2 ± 3.3</td>
<td>1.8 ± 1.4</td>
<td>0.0001</td>
</tr>
<tr>
<td>Cholesterol (mg/dL)</td>
<td>151.6 ± 32.0</td>
<td>154.1 ± 29.4</td>
<td>0.71</td>
</tr>
<tr>
<td>HDL-cholesterol (mg/dL)</td>
<td>45.5 ± 11.1</td>
<td>57.5 ± 12.7</td>
<td>0.0001</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>94.8 ± 55.0</td>
<td>50.1 ± 27.2</td>
<td>0.0001</td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td>31.0 ± 20.7</td>
<td>16.3 ± 3.8</td>
<td>0.0001</td>
</tr>
<tr>
<td>AST (U/L)</td>
<td>26.4 ± 9.0</td>
<td>24.1 ± 4.5</td>
<td>0.0001</td>
</tr>
<tr>
<td>LnHs-CRP (mg/L)</td>
<td>1.4 ± 0.8</td>
<td>-0.7 ± 1.1</td>
<td>0.0001</td>
</tr>
<tr>
<td>Carotid IMT (mm)</td>
<td>0.52 ± 0.06</td>
<td>0.42 ± 0.05</td>
<td>0.0001</td>
</tr>
<tr>
<td>Apnea-hypopnea index</td>
<td>4.1 ± 5.1</td>
<td>1.0 ± 1.4</td>
<td>0.014</td>
</tr>
</tbody>
</table>

DBP, diastolic blood pressure; HOMA, homeostasis model assessment; ALT, alanine aminotransferase; AST, aspartate aminotransferase; IMT, intima-media thickness; LnHs-CRP, logarithmic transformed high sensitivity C-reactive protein; SBP, systolic blood pressure.

Table 2—Anthropometric, biochemical, and subclinical atherosclerosis markers in OSA (AHI > 5), mild sleep disordered breathing (AHI > 1 to < 5), and control children (AHI < 1) (crude data)

<table>
<thead>
<tr>
<th>Variables</th>
<th>OSA (n = 19)</th>
<th>Mild SDB (n = 57)</th>
<th>Controls (n = 25)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, males</td>
<td>9 (47%)</td>
<td>32 (56%)</td>
<td>13 (52%)</td>
<td></td>
</tr>
<tr>
<td>Age (months)</td>
<td>115.7 ± 28.6</td>
<td>125.3 ± 23.8</td>
<td>129.6 ± 25.7</td>
<td>0.16</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.5 ± 7.0</td>
<td>21.4 ± 6.4</td>
<td>23.6 ± 7.8</td>
<td>0.03</td>
</tr>
<tr>
<td>BMI z-score</td>
<td>1.6 ± 1.1</td>
<td>0.8 ± 1.2</td>
<td>1.0 ± 1.2</td>
<td>0.014</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>108.5 ± 16.6</td>
<td>101.7 ± 12.8</td>
<td>107.8 ± 15.3</td>
<td>0.07</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>71.4 ± 11.7</td>
<td>68.1 ± 8.8</td>
<td>66.8 ± 14.5</td>
<td>0.25</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>84.9 ± 5.8</td>
<td>83.8 ± 6.7</td>
<td>84.8 ± 8.2</td>
<td>0.54</td>
</tr>
<tr>
<td>Insulin (µU/mL)</td>
<td>13.7 ± 12.9</td>
<td>12.2 ± 12.7</td>
<td>13.2 ± 10.7</td>
<td>0.63</td>
</tr>
<tr>
<td>HOMA</td>
<td>2.8 ± 2.3</td>
<td>2.6 ± 2.8</td>
<td>2.8 ± 2.3</td>
<td>0.75</td>
</tr>
<tr>
<td>Cholesterol (mg/dL)</td>
<td>165.1 ± 23.8</td>
<td>151.2 ± 32.3</td>
<td>147.5 ± 28.1</td>
<td>0.09</td>
</tr>
<tr>
<td>HDL-cholesterol (mg/dL)</td>
<td>51.7 ± 13.2</td>
<td>53.9 ± 15.0</td>
<td>51.4 ± 9.9</td>
<td>0.54</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>84.1 ± 63.2</td>
<td>67.1 ± 45.1</td>
<td>55.1 ± 21.8</td>
<td>0.17</td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td>23.9 ± 15.6</td>
<td>21.4 ± 14.5</td>
<td>19.8 ± 13.4</td>
<td>0.51</td>
</tr>
<tr>
<td>AST (U/L)</td>
<td>25.3 ± 6.3</td>
<td>25.6 ± 6.9</td>
<td>22.9 ± 5.4</td>
<td>0.80</td>
</tr>
<tr>
<td>LnHs-CRP (mg/L)</td>
<td>0.91 ± 1.3</td>
<td>-0.11 ± 1.3</td>
<td>-0.02 ± 1.6</td>
<td>0.01</td>
</tr>
<tr>
<td>Carotid IMT (mm)</td>
<td>0.47 ± 0.09</td>
<td>0.44 ± 0.06</td>
<td>0.47 ± 0.06</td>
<td>0.16</td>
</tr>
</tbody>
</table>

ALT, alanine aminotransferase; AST, aspartate aminotransferase; DBP, diastolic blood pressure; HOMA, homeostasis model assessment; IMT, intima-media thickness; LnHs-CRP, logarithmic transformed high sensitivity C-reactive protein; OSA, obstructive sleep apnea; BP, systolic blood pressure; SDB, sleep disordered breathing.
Association between AHI and CRP Concentrations, Mainly Mediated by Overweight and Obesity

Linear regression analysis showed a significant association between AHI and LnHs-CRP in all children enrolled in the study. The novelty of this finding lies in the demonstration of this association in children not selected for snoring. In our cohort, logistic regression analysis showed that obese children had a three-fold higher risk of having OSA than non-obese children.

In adults, OSAS is associated with cardiovascular disease, and elevated CRP plasma concentration could be the link between the two disorders.19,20 In snoring children, Tauman et al. reported significantly higher CRP levels in children with OSA (AHI > 5) versus children with mild SDB (AHI > 1 and < 5) and control children (AHI < 1). Moreover, CRP levels were associated with SDB irrespective of relative BMI. The authors speculated that the strong epidemiologic links between CRP levels and atherosclerosis could indicate that the coincidence of SDB with higher CRP levels could increase the risk of atheroma formation among children with OSA.21 In another study of an adolescent cohort free of known cardiovascular disease, SDB was associated with increasing levels of CRP.22 In agreement with our research, AHI was closely related to CRP only when AHI exceeded 5, whereas no significant association was found in children with an AHI < 5. Differently, in a survey of Greek children, mean CRP values did not differ between control subjects and snorers with an AHI < 1, snorers with mild SDB, and snorers with OSA.23

In our study, the association between AHI and LnHs-CRP maintained statistical significance when the covariates sex and age were added to the model, but was just below significance level when BMI was added. These data indicate that a high BMI is important in promoting the link between SDB and a pro-inflammatory state in children.

Low-Grade Inflammation Is Significantly Greater in Children with OSA than in Children without OSA

In our cohort, Hs-CRP values were significantly higher in children with OSA than in children without OSA. However, the addition of the covariate BMI z-score to the model abolished the significant difference between the two groups. This finding is in line with the well-known association between obesity and both SDB and a pro-inflammatory state also in children. In another study conducted in a clinical sample of obese children, SDB was associated with elevation of proinflammatory cytokines.16 In the latter study, Hs-CRP levels were elevated in obese children with SDB and the elevation was due to both SDB and obesity.

The increased CRP concentrations in children with OSA could indicate a link between the intermittent hypoxemia and sleep disturbance of SDB and inflammatory responses. The association in children of elevated CRP levels with OSA suggests that AHI > 5 facilitates the activation of low-grade inflammatory processes and that, together with overweight-obesity, may be responsible, at least in part, for the morbidity associated with SDB.

Association between SDB and Subclinical Atherosclerosis Markers

Primary snoring was associated with higher blood pressure and reduced arterial distensibility in a small cohort of Chinese children.24

In adults, carotid markers of subclinical atherosclerosis are significantly higher in OSAS.25 In our study, SDB was not associated with carotid IMT, a proxy of subclinical atherosclerosis. It is feasible that, in the pediatric age group, OSA, especially when associated with obesity, is able to elicit a low-grade inflammatory response, but, differently from adults,26,27 it does not cause clear signs of carotid atherosclerosis. However, SDB and obesity may be part of a negative profile of cardiovascular risk that continues into adulthood, thereby facilitating development of cardiovascular morbidities.

A limitation of the present study is the high prevalence of overweight/obesity and OSA in our cohort. However, the South of Italy has the greatest prevalence among western countries with 41.8% of children and teenagers being overweight or obese.28

In conclusion, our study demonstrates that SDB is associated with low-grade inflammation in children, but this association was mediated by BMI. Our study also reaffirms that overweight and obesity play a role in promoting low-grade inflammation and disturbances of sleep-breathing, and it provides the first demonstration that SDB and carotid atherosclerosis are not associated in children. Taken together, these findings confirm the importance of early intervention in childhood, before the onset of OSAS-induced ultrasound-detectable atherosclerosis and before OSAS causes the irreversible damage to arteries observed in adult patients.

ABBRVIATIONS

AHI, apnea-hypopnea index
AI, apnea index
BMI, body mass index
DBP, diastolic blood pressure
HOMA-IR, homeostasis model assessment-insulin resistance
Hs-CRP, high-sensitivity C-reactive protein
IMT, intima-media thickness
LnHs-CRP, logarithmic transformed high sensitivity C-reactive protein
OSA, obstructive sleep apnea
OSAS, obstructive sleep apnea syndrome
PSG, polysomnography
SBP, systolic blood pressure
SDB, sleep disordered breathing
TST, total sleep time

REFERENCES


Nocturnal Temazepam in the Treatment of Narcolepsy

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Narcolepsy is characterized by fragmented nighttime sleep and frequent arousals. One treatment approach to improve daytime symptoms is to consolidate nighttime sleep through decreasing arousals. Sodium oxybate is the first FDA-approved medication that follows this approach. Benzodiazepines are known to also decrease arousals at night and have been proposed to help with sleep fragmentation. In one report, clonazepam was shown to improve cataplexy in 10 of 14 patients with narcolepsy although no improvement in daytime sleepiness was reported. The purpose of this case review was to share our experience of nocturnal temazepam on daytime sleepiness in patients with narcolepsy as measured by the Epworth Sleepiness Scale (ESS).

Keywords: Narcolepsy, temazepam

REPORT OF CASES

In this retrospective case series, the records of patients diagnosed with narcolepsy and treated with temazepam were examined. Diagnosis was based on a combination of polysomnography, multiple sleep latency testing, and clinical presentation in accordance with the diagnostic criteria from the International Classification of Sleep Disorders, 2nd edition. All 7 patients had a history of cataplexy, but only 5 had ongoing attacks more often than once a month. Doses of temazepam ranged from 15 mg to 30 mg and were administered once nightly prior to bedtime for a minimum of one week. All other medications and doses were unchanged during the temazepam titration. Each patient had a quantified measure of daytime sleepiness through the ESS both prior to initiation of temazepam and at each tolerated dose. Baseline ESS and ESS at the highest tolerated temazepam dose were compared using a paired sample t-test. Seven patients were included in this review. The age of patients ranged from 9 to 71 years, with a mean age of 35 years. They were diagnosed with narcolepsy for a mean of 14 years (range 1 to 49 years). Six patients reported a decrease in daytime sleepiness on temazepam, with a mean change in ESS score of -5.1 points (range -10 to 1, see Figure 1). The mean ESS score was 16.4 prior to initiation of temazepam and was 11.3 on the highest tolerated dose. This difference was statistically significant (p = 0.007). Although not quantified, four patients who had frequent cataplexy at the time of initiation of temazepam reported a subjective improvement in frequency of cataplexy, three of whom had improvement in their subjective sleepiness. Six of the 7 patients elected to remain on the temazepam. See Table 1 for further information on sleep characteristics of individual patients.

DISCUSSION

Nocturnal temazepam may be an option to improve excessive daytime sleepiness in patients with narcolepsy. Based on our experience, temazepam appears to improve subjective sleepiness as measured by ESS scores and anecdotally improves the frequency of cataplexy. Narcolepsy patients are known to have fragmented sleep and frequent sleep stage shifts. Therapeutic guidelines recommend sodium oxybate as a treatment option for cataplexy. Large clinical trials suggest benefit to excessive daytime sleepiness and cataplexy may in part be mediated by the drug’s ability to consolidate sleep. Temazepam may have a similar action in patients with narcolepsy by consolidating sleep. Unlike sodium oxybate, temazepam is not known to increase slow wave sleep. Our study is limited by the retrospective approach and the small sample size. The population is mixed, including both pediatric and adult patients, as well as patients with and without cataplexy. We also did not perform polysomnography immediately prior to and following temazepam use and therefore do not have data to further speculate regarding the mechanism. Finally, we used the ESS as a measure of daytime sleepiness as opposed to the more objective MSLT. One prior study using triazolam showed no change in MSLT, which emphasizes the importance of objective measures for sleepiness. However, triazolam is also a short-acting agent, so might not work as well as temazepam.

Of note, the five adult patients in our study had a mean decrease in ESS score of 7 points. Our two pediatric patients...
had a mean decrease of only 1 point. One of these patients had an increase in ESS. Given the fact that adults with narcolepsy have more arousals from sleep than children, this difference in response to temazepam would be expected if the improvement in daytime functioning is a result of increased sleep consolidation. Interestingly, one pediatric patient did report improvement in frequency of cataplexy. Although temazepam may be an option in the future treatment of narcolepsy patients, further prospective, placebo-controlled trials are needed to establish the effectiveness of temazepam therapy in both children and adults.

REFERENCES


SUBMISSION & CORRESPONDENCE INFORMATION

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DISCLOSURE STATEMENT

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Sleep Disturbance in Pediatric PTSD: Current Findings and Future Directions

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1Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford University, Stanford, CA; 2Harvard College, Cambridge, MA; *Mr. Kovachy and Dr. O’Hara are co-first authors.

Many studies have provided strong evidence of a fundamental and complex role for sleep disturbances in adult posttraumatic stress disorder (PTSD). Investigations of adult PTSD using subjective and objective measures document sleep architecture abnormalities and high prevalence of sleep disordered breathing, periodic limb movement disorder, nightmares, and insomnia. PTSD treatment methods do appear to significantly improve sleep disturbance, and also studies suggest that treatments for sleep disorders often result in improvements in PTSD symptoms. Further, the most recent evidence suggests sleep abnormalities may precede the development of PTSD. Given the importance of sleep disorders to the onset, course, and treatment of adult PTSD, examination of sleep disturbances far earlier in the life course is imperative. Here we review the literature on what we know about sleep disturbances and disorders in pediatric PTSD. Our review indicates that the extant, empirical data examining sleep disturbance and disorders in pediatric PTSD is limited. Yet, this literature suggests there are significantly higher reports of sleep disturbances and nightmares in children and adolescents exposed to trauma and/or diagnosed with PTSD than in non-trauma-exposed samples. Sleep questionnaires are predominantly employed to assess sleep disorders in pediatric PTSD, with few studies utilizing objective measures. Given the important, complex relationship being uncovered between adult PTSD and sleep, this review calls for further research of sleep in children with PTSD using more specific subjective measures and also objective measures, such as polysomnography and eventually treatment trial studies.

Keywords: Pediatric, PTSD, sleep disturbance, subjective measures, objective measures

Citation: Kovachy B; O’Hara R; Hawkins N; Gershon A; Primeau MM; Madej J; Carrion V. Sleep disturbance in pediatric PTSD: current findings and future directions. J Clin Sleep Med 2013;9(5):501-510.

Traditionally, sleep disorders have been understood as a secondary symptom of posttraumatic stress disorder (PTSD). Further, it was presumed that treatment of the overarching disorder would eliminate these sleep disturbances.1 Studies now suggest that sleep disturbances, including insomnia, nightmares, sleep disordered breathing (SDB), and periodic limb movement (PLM), play a central, complex role in PTSD with accompanying diagnostic, treatment, and neurobiological implications. However, far more empirical data exist on the prevalence and nature of sleep disturbances in adults diagnosed with PTSD than in youth diagnosed with PTSD.

Significance of Sleep Disorders to PTSD: Summary of Evidence From Adult Studies

Sleep disturbances are a frequent occurrence in adults with PTSD, with one study finding 70% to 91% of PTSD patients have sleep disturbances.2 In a comparison to healthy controls, patients with PTSD report much higher initial, middle, and terminal insomnia.3,4 Ohayon and Shapiro found that 18.8% of patients with PTSD reported nightmares, as opposed to their non-patient comparison group, in which only 4.2% reported nightmares.4 SDB and PLM are sleep disorders that have also been frequently observed among PTSD patients. Sleep architecture profiles also appear different in patients with PTSD (for review see Kobayashi3).

Further, after a trauma, individuals who would develop PTSD experienced shorter, more frequent REM sleep periods, which were associated with both insomnia and PTSD severity.5,7 Similarly, a prospective investigation of car accident victims revealed that severity of sleep complaints 1 month after the accident was significantly associated with the subsequent development of PTSD a year after the accident.8 The culminating evidence from investigations of adults with PTSD suggests that not only are specific sleep disorders and specific sleep architecture profiles more prevalent in PTSD, they may also precede and/or predict the development and severity of PTSD.6,12

Further evidence of the important yet complex relationship between sleep disturbances and adult PTSD stems from treatment results for both disorders.13 Evidence suggests that although PTSD-focused treatment may lead to some improvement in co-occurring sleep disorders, it does not lead to complete remission of the sleep disorder and may also leave patients vulnerable to recurrence of PTSD symptoms.14,15 These findings highlight the intrinsic severity of sleep problems, or alternatively, our gap in knowledge in identifying targets for sleep treatments. They also challenge the notion that sleep disorders in PTSD are merely secondary symptoms best treated by treatment of the overarching disorder.

The utilization of specific treatments for sleep disturbances that accompany PTSD appears to lead to significant improve-
Sleep Disturbances in Pediatric PTSD: Evidence from Subjective Measures

To date, the most extensively used methods for measuring sleep disturbances in children with PTSD are self-report questionnaires, parent-report questionnaires, and clinical interviews. Many studies use the Child Post-Traumatic Stress Reaction Index (CPTSD-RI), a self-report questionnaire that assesses for nightmares and sleep disturbances, along with other PTSD symptoms.

In children exposed to trauma, the frequency of sleep disturbances as measured by self-report or parent-report is higher than in non-trauma exposed populations of children (see Tables 1 and 2, for additional review see Charuvastra and Cloitre29). Noll et al. examined sleep in 78 sexually abused children and 68 control comparison children using 6 self-report questions that asked about trouble falling asleep, staying asleep, middle of the night awakenings, nightmares, and feeling rested.29 The subjects were 6 to 16 years at the time of abuse, and the mean age for the participants at the time of the study was 20.41 (SD = 3.38). The results revealed significantly more sleep disturbances, including insomnia and nightmares, in the sexually abused group and more instances of PTSD in the sexually abused group.29

Children exposed to war trauma and/or violence often have sleep disturbances27,30,31 Thabet et al. examined 403 children aged 9-15 years living in refugee camps and found that 20.3% reported sleep disturbances “sometimes” and 31.6% reported sleep trouble “mostly, most of the time.”31 Similar rates of sleep disturbance were found among 311 Middle East refugee children aged 3-15 years. Specifically, sleep symptoms, such as nightmares and difficulties falling and staying asleep, were reported as “frequent” by nearly 20% of the children’s parents.32 Following a playground sniper attack in Los Angeles, Pynoos et al. found that 77.1% of children on the playground reported sleep disturbances one month following the trauma.32 Nineteen children who were on the playground were followed longitudinally. At 14-month follow-up, 57.9% of this sample still reported sleep disturbances.31 A sample of 120 preadolescent Kuwaiti boys and girls (9-12 years old) who were initially assessed for exposure to war-related trauma during the Iraqi occupation and Gulf war of 1990 were reassessed for general health and sleep, using the Pittsburgh Sleep Quality Index (PSQI), approximately 10 years later. Findings showed direct effects between exposure to war-related trauma and sleep difficulties, even after controlling for stressful life events experienced in the interim.34

A national phone survey of adults (N = 560) administered within 5 days of the 9/11 terrorist attacks in New York City attacks found 10% reporting that their children were experiencing difficulty falling or staying sleeping.33 Approximately one-fifth of residents living close to the World Trade Center, including children and adolescents, suffered symptoms of PTSD.34 A longitudinal study of preschoolers (N = 116) who were exposed to the World Trade Center attacks found that three years following the exposure, children who were exposed to “high-intensity” events of the attacks (e.g., witnessing the towers collapse, injured people, dead bodies, or people jumping out of the building) were approximately 5 times more likely to have sleep problems (assessed using the Child Behavior Checklist or CBCL) than those who had not been exposed to high-intensity events.37 Furthermore, a dose-response relationship was found,

Pediatric PTSD and Sleep Disorders

Currently, our knowledge about the fundamental sleep disorders, sleep dysregulation, and sleep architecture abnormalities that occur in children with PTSD is limited. Few studies have investigated the prevalence of pediatric PTSD. One investigation by Kilpatrick et al. found that 3.7% of males and 6.3% of females in a nationally representative sample of 4,023 children aged 12 to 17 years met DSM-IV diagnostic criteria for PTSD.25,26 However, studies specifically examining children exposed to trauma reveal much higher rates of PTSD. For example, in a Pynoos et al. study of 159 child witnesses of a sniper attack, 60.4% were diagnosed with PTSD.27 In children exposed to trauma, PTSD may be very prevalent and underestimated.
such that the greater the number of high-intensity events a child was exposed to, the greater the risk for sleep problems.  

Studies with children who experienced natural disasters similarly reveal associated sleep disturbance.  After a typhoon in South Korea, 13% of a local sample of elementary school children (N = 261) experienced sleep disturbances.  Following a lightning strike during a children’s soccer game, 17% of exposed children (N = 29) experienced difficulty falling asleep and 21% had restless sleep.  In an important recent longitudinal investigation, Brown et al. assessed sleep disturbance and fear of mares also appear to play a role and may contribute to sleep disturbance.  After a typhoon was exposed to, the greater the risk for sleep problems.

Table 1—Nightmares and sleep disturbance in average populations of children

<table>
<thead>
<tr>
<th>Controls</th>
<th>Year</th>
<th># of Subjects</th>
<th>Age Range</th>
<th>Measurements</th>
<th>Nightmares</th>
<th>Sleep disturbances</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simonds and Parraga 1984</td>
<td>1984</td>
<td>309 subjects from the general population</td>
<td>4 to 18</td>
<td>Parent-report sleep questionnaire</td>
<td>16.5% had nightmares</td>
<td>N/A</td>
</tr>
<tr>
<td>Yang et al. 1987</td>
<td>1987</td>
<td>846 Chinese high school students sampled</td>
<td>12 to 18</td>
<td>three questionnaires: one for students, one for parents, and one for teachers</td>
<td>9.5% had nightmares</td>
<td>14.9% had difficulty falling asleep</td>
</tr>
<tr>
<td>Kahn et al. 1989</td>
<td>1989</td>
<td>972 children from Brussels elementary schools</td>
<td>8 to 10</td>
<td>Parent-report sleep questionnaire</td>
<td>night fears (night terrors and nightmares) occurred at least twice a month in 15%</td>
<td>14% of children sleep poorly</td>
</tr>
<tr>
<td>Vignau et al. 1997</td>
<td>1997</td>
<td>763 students chosen at random from French high schools</td>
<td>15 to 23.</td>
<td>Self-report questionnaire</td>
<td>6.8% often had nightmares</td>
<td>22.5% reported bad sleep; 20.6% reported often having trouble falling asleep; 34.6% reported trouble waking up</td>
</tr>
<tr>
<td>Blader et al. 1997</td>
<td>1997</td>
<td>987 children</td>
<td>5 to 12</td>
<td>Parent-report sleep questionnaire</td>
<td>N/A</td>
<td>11.3% had sleep onset delays; 6.5% had night waking; 17% had morning wake problems</td>
</tr>
<tr>
<td>Lee et al. 1999</td>
<td>1999</td>
<td>144 6th to 8th graders</td>
<td>11 to 14</td>
<td>Self-report sleep questionnaire</td>
<td>20% reported nocturnal awakenings from nightmares</td>
<td>N/A</td>
</tr>
<tr>
<td>Liu et al. 2000</td>
<td>2000</td>
<td>2,004 elementary school children in Shandong Province in China</td>
<td>6 to 17</td>
<td>Parent reported sleep problems</td>
<td>12.5% of parents reported that their children had nightmares sometimes or often</td>
<td>6.1% trouble sleeping</td>
</tr>
<tr>
<td>Tomás Vila et al. 2008</td>
<td>2008</td>
<td>887 children</td>
<td>6 to 17</td>
<td>Pediatric Sleep Questionnaire (PSQ)</td>
<td>12.8%</td>
<td>10.5% insomnia</td>
</tr>
<tr>
<td>Hvolby et al. 2008</td>
<td>2008</td>
<td>211 healthy Danish children</td>
<td>6 to 11</td>
<td>Parent-report sleep questionnaire</td>
<td>N/A</td>
<td>7.5% had difficulties falling asleep</td>
</tr>
</tbody>
</table>

In both adult and child PTSD samples, self-reported nightmares also appear to play a role and may contribute to sleep disturbance in this disorder. According to the DSM IV, three of the main symptomatic groups for PTSD after exposure to a trauma are re-experiencing trauma symptoms, avoidance symptoms, and hyperarousal symptoms. Many nightmares experienced by PTSD patients are re-enactments of the trauma and thus account for the first DSM-IV PTSD symptomatic group.

Many studies find nightmares occur in about 10% to 20% of the general pediatric population (Table 1). In addition, younger children tend to have more nightmares than adolescents (Table 1). In pediatric PTSD and trauma-exposed populations, parent-report, self-report, and clinician-administered questionnaires reveal higher reports of nightmares than in average populations (Table 2). Carrion and colleagues utilized a structured interview, the Clinician Administered PTSD Scale for Children and Adolescents (CAPS-CA), to assess posttraumatic symptomatology in a group of youth exposed to interpersonal violence. Sixty-four percent of the subjects frequently experienced distressing nightmares that were not only frequent but also intense in nature. Chimienti et al. compared the sleep reports from parents of Lebanese children, ages 3 to 9 years, who had experienced a trauma (n = 312) to reports from parents of children who had not experienced a trauma (n = 727). Thirty-six percent of parents in the trauma-exposed group reported nightmares in their children, which was significantly different from the 23% of parents in the no-trauma group who reported nightmares in their children.
Several studies have documented similar rates of nightmares in children after a trauma, with some studies reporting prevalence rates as high as 50% to 80%,13,18,24 Arnberg et al. found that 50% of a group of sixth-grade children (ages 11 to 12 years) who were involved in a serious bus accident reported nightmares 9 months after the accident, compared to only 8% of indirectly affected children (classmates of the children in the crash).43 Cumulatively, these data strongly indicate high prevalence of nightmares among children exposed to trauma (Table 2). However, it should be noted that use of control groups is rare in these studies.

Some investigators have published their experiences with use of prazosin, clonidine, and guanfacine in individual case studies of children with PTSD, demonstrating modest improvement in sleep assessed subjectively, mostly in reducing nightmares.46-50 Behavioral treatments form the cornerstone of treatment of pediatric PTSD, yet little work has been done evaluating the impact of such treatments on sleep symptoms specifically. One behavioral treatment, image rehearsal therapy (IRT), a treatment for nightmares with demonstrated effectiveness in adult patients with PTSD, has been modified for treatment in adolescent populations.51 Krakow et al. adapted IRT for adolescent girls (ages 13-18) sentenced to Wyoming Girls School. They were able to decrease nightmare frequency and subjective distress, though nightmares with demonstrated effectiveness in adult patients of such treatments on sleep symptoms specifically. One behavioral treatment, image rehearsal therapy (IRT), a treatment

For example, most studies measure subjective sleep disturbances in children and adolescents who were exposed to trauma and/or diagnosed with PTSD than in non-trauma-exposed samples. However, there is considerable variability among these studies in the amount of sleep disturbances reported, ranging from 3% to 77.1%, and in the amount of nightmares reported, ranging from 20.3% to 80.8% (Table 2). This variability may reflect the use of unspecific, brief sleep questionnaires and the different study methods used across studies, including different populations examined, differing levels of PTSD severity and diagnosis, nature and duration of trauma, sample size, age, and other cultural and demographic variables.

For example, most studies measure subjective sleep disturbances in children exposed to a trauma. Thus, not all subjects examined have developed or will develop PTSD even if they experience some PTSD symptoms after the trauma. In fact, in some of the studies, only a minority of the sample have diagnosable PTSD.38,41,43,44,52 Other studies do not distinguish between disturbance of individuals who have been exposed to a trauma and individuals who have developed PTSD.32,39,42,45 In addition, the nature, intensity, and duration of the trauma experienced by the populations vary greatly across studies. Some subjects directly experienced a traumatic event, while others were witnesses. Additionally, whether the trauma is an acute event (e.g., lightning strike) or a chronically ongoing trauma (e.g., sexual or physical abuse) could significantly influence the degree and type of sleep dysregulation reported. Studies also varied in the temporal duration between the trauma exposure and the time of the sleep assessment, which may also contribute to variable outcomes.

A significant limitation to these approaches is that the measures used to assess sleep are often designed for clinical assessment of PTSD symptoms and as such, contain only a minimal subset of questions addressing the child’s sleep. Many studies examined in this review assess sleep in pediatric PTSD using the CPTSD-RI,27,30,31,38,32 which is the pediatric version of the PTSD-RI intended to diagnose PTSD in pediatric populations. The CPTSD-RI asks the subject to rate degree of sleep disturbance and nightmares but does not ask more targeted questions about the nature and frequency of these sleep disturbances. Some ask nonspecifically about any sleep disturbance covering the general sleep patterns of the child, while others may be more specifically oriented to circadian tendency, SDB, or insomnia. Even when subjective assessments focus on a specific sleep disorder, they can vary with respect to the type and quality of sleep disturbance they assess. However, subjective sleep measures can be extremely valuable for indicating that the child’s sleep is indeed disturbed.

While some pediatric studies will simply employ subjective measures of sleep that are validated for adults,44 e.g., the PSQI, several subjective assessments of pediatric sleep exist. In a recent review, Spruyt and Gozal identified 183 available measures, of which 57 had been psychometrically evaluated to some degree.53 These questionnaires are self-report or parent-report. As pointed out by Spruyt and Gozal, there is little consensus as to which questionnaire is most appropriate to evaluate sleep in pediatric populations. As these measures often focus on a specific sleep disturbance or disorder, it makes comparisons among studies difficult. However, each of these scales can provide information that is useful depending upon the clinical or research setting.53

Potential subjective specific sleep measures which can enhance the understanding of sleep disorders in pediatric PTSD include the Child Behavior Checklist (CBCL),54,55 the Pediatric Sleep Questionnaire (PSQ),56 the Sleep Disturbance Scale for Children (SDSC),57 Sleep Disorders Inventory for Students-Child and Adolescent form (SDIS),58 Childhood Sleep Habit Questionnaire (CSHQ),59 the Nightmare Frequency Questionnaire (NFQ),60 the Nightmare Distress Questionnaire (NDQ),60 and sleep diaries.

The CBCL is a parent-report subjective questionnaire that assesses child behavior difficulties and includes certain items on sleep including: “sleeps less than most kids,” “sleeps more than most kids during day and/or night,” “trouble sleeping,” “nightmares,” and “talks or walks in sleep.”54,55 In a sample of 122 youth, ages 7-17 years, with anxiety disorders (19%), major depressive disorder (MDD) (9%), both anxiety and depression (26%), or no history of any psychiatric disorder (46%), Gregory et al. examined how sleep items in the CBCL corresponded to sleep measured via sleep diaries (4-6 days), actigraphy (1 week), and polysomnography (2 consecutive nights).62 After controlling for age, gender, and diagnostic status, specific items (e.g. being overtired, sleeps less, sleeps more, and trouble sleeping items) correlated well with objective sleep measures of sleep latency and number of arousals. However, some items did not correlate with objective measures; for example, “sleeps more” was not associated with total sleep time (TST) as assessed by objective polysomnography.62 Overall, the CBCL can be a valuable tool in assessing broad sleep disturbance subjectively. However, similar to the PTSD scales mentioned above, the CBCL ultimately is not designed to thoroughly evaluate sleep, and thus cannot always provide important information on the source of sleep disturbances such as breathing related sleep disorders.

As Spruyt and Gozal53 point out, 3 well-validated subjective assessments of pediatric sleep include the PSQ, the SDSC, and the SDIS. The PSQ is a 22-item questionnaire, well documented to be a reliable and valid measure for assessing snoring, insomnia, sleepiness, and associated daytime behaviors. It is consid-

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erred to be a valuable alternative when polysomnography is not realistically available to measure specific sleep disorders in pediatric populations. Similarly, the SDSC is a 27-item parent questionnaire designed to assess disorders of initiating and main-

### Table 2—Nightmares and sleep disturbances in children exposed to trauma

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Subjects</th>
<th>% Diagnosed with PTSD</th>
<th>Age Range</th>
<th>Measurements</th>
<th>Nightmares</th>
<th>Sleep Disturbance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dollinger et al.</td>
<td>1986</td>
<td>29 children, victims of lightning strike disaster</td>
<td>N/A</td>
<td>10 to 12</td>
<td>Child Interviews and expansion of Missouri Children’s Behavior Checklist (parent-report)</td>
<td>24%</td>
<td>17% difficulty falling asleep, 21% restless sleep</td>
</tr>
<tr>
<td>Pynoos et al.</td>
<td>1987</td>
<td>159 children after sniper attack on school playground</td>
<td>60.4%</td>
<td>5 to 13</td>
<td>PTSD-R1 (self-report)</td>
<td>62.9% on playground, 55.6% at school, and 41.5% not at school</td>
<td>77.1% on the playground 55.6% of students at school that day; 48.8% of students not at school that day</td>
</tr>
<tr>
<td>Chimienti et al.</td>
<td>1989</td>
<td>1,039 Lebanese children</td>
<td>N/A</td>
<td>3 to 9</td>
<td>Parent-questionnaire or interview assessing 37 symptoms of fear and anxiety behaviors</td>
<td>trauma: 36% no trauma: 23%</td>
<td>N/A</td>
</tr>
<tr>
<td>Thabet and Vostanis</td>
<td>1999</td>
<td>239 Palestinian children who experienced war trauma</td>
<td>72.8%</td>
<td>6 to 11</td>
<td>CPTSD-R1 (self-report)</td>
<td>42.2% few/some; 13.1% frequent/most of the time</td>
<td>44.1% few/some; 3.0% frequent/most of the time</td>
</tr>
<tr>
<td>Thabet and Vostanis</td>
<td>2000</td>
<td>234 children who experienced war conflict</td>
<td>40.6% at first assessment, 10.0% at 1-year follow up</td>
<td>7 to 12</td>
<td>CPTSD-R1 (self-report)</td>
<td>13.1% at first assessment, 8.6% at 1-year follow up</td>
<td>3% at first assessment, 1.8% at 1-year follow up</td>
</tr>
<tr>
<td>Montgomery and Foldspang</td>
<td>2001</td>
<td>311 refugees from Middle East</td>
<td>N/A</td>
<td>3 to 15</td>
<td>parent structured interview with modules asking frequency of nightmares, trouble falling asleep, and trouble staying asleep</td>
<td>frequent 19% Sometimes 18.6%</td>
<td>Frequent problems falling asleep: 19.9%. Frequent problems staying asleep 18%</td>
</tr>
<tr>
<td>Carrion et al.</td>
<td>2002</td>
<td>59 children with a history of trauma and PTSD symptoms</td>
<td>24.0%</td>
<td>7 to 14</td>
<td>PTSD scale for Children and Adolescents</td>
<td>64.4%</td>
<td>Sleep problems: 59.3%</td>
</tr>
<tr>
<td>Thabet et al.</td>
<td>2004</td>
<td>403 children from Gaza refugee camps.</td>
<td>97.6%</td>
<td>9 to 15</td>
<td>CPTSD-R1 (self-report)</td>
<td>29.3% sometimes 22.5% most of the time</td>
<td>20.3% sometime 31.6% most of the time</td>
</tr>
<tr>
<td>Lee et al.</td>
<td>2004</td>
<td>261 elementary school kids exposed to Typhoon Rusa 4 months after disaster</td>
<td>35.0%</td>
<td>7 to 12</td>
<td>CPTSD-R1 (self-report)</td>
<td>20.3% re-experiences nightmares or bad dreams</td>
<td>13% sleep difficulties</td>
</tr>
<tr>
<td>Thabet et al.</td>
<td>2009</td>
<td>412 children from Gaza Strip</td>
<td>30% of boys 31.6% of girls</td>
<td>12 to 16</td>
<td>Structured clinical interview for DSM IV-PTSD module</td>
<td>80.8% distressing dreams</td>
<td>63.6% had sleep difficulty</td>
</tr>
<tr>
<td>Wittman et al.</td>
<td>2010</td>
<td>32 children examined after traffic accident</td>
<td>6.3% had full PTSD and 3.1% had subsyndromal PTSD 6 months post-accident</td>
<td>7 to 16</td>
<td>Self-report of nightmares in interview</td>
<td>34.4%</td>
<td>N/A</td>
</tr>
<tr>
<td>Amberg et al.</td>
<td>2011</td>
<td>sixth-grade children in a bus crash (10 directly affected; 92 indirectly affected)</td>
<td>N/A</td>
<td>11 to 12</td>
<td>Questionnaires (self-report) design to assess PTSD symptoms</td>
<td>50% of the directly affected subjects and 8% of indirectly affected group</td>
<td>N/A</td>
</tr>
</tbody>
</table>
taining sleep, insomnia, SRBDs, arousal disorders, sleep-wake transition disorders, sleepiness, and sleep hyperhidrosis in children. The SDS evaluates SDB, excessive sleepiness, PLM, delayed sleep phase syndrome, and narcolepsy. It was designed for children aged 2-18 years, it is a parent-report questionnaire, and it includes computer scoring. However, it was developed to be used as a screening tool to determine which children should be referred to a sleep physician and not for the assessment of sleep disorders per se (although the scale is moderately accurate at determining the specific sleep disorder a subject has).

The CSHQ is a 45-item parent-report subjective questionnaire with 7 components assessing bedtime behavior, sleep onset, sleep duration, anxiety related to sleep, sleep and night waking behavior, SDB, parasomnias, and morning waking and daytime sleepiness. In a community sample of 469 children and 154 children with diagnosed sleep disorders, aged 4-10 years, sensitivity and specificity were 0.80 and 0.72, respectively. The CSHQ has also been employed to examine sleep in children aged 2 to 5.5 years old with autism diagnoses (n = 68), developmental delay (n = 57), and normal development (n = 69). This indicates that the CSHQ can be clinically utilized in even younger populations than children aged 4 to 10 years and in populations with developmental disorders. However, as yet, the CSHQ has not been utilized in pediatric populations of PTSD.

To assess frequency of nightmares and the level of associated daytime distress these nightmares cause, several questionnaires are employed. The Nightmare Frequency Questionnaire (NFQ) consists of 2 brief sections, and was validated in a sample of adults with PTSD who experienced sexual assault. Further, correlations between frequency of nightmares as determined by the NFQ and by prospective nightmare dream logs were highly significant. However, the NFQ has not yet been validated for pediatric populations. While the NFQ measures nightmare frequency, the Nightmare Distress Questionnaire (NDQ) is a 13-item questionnaire that measures the distress individuals experience during the day about their nightmares. It has been employed in pediatric as well as adult samples. One investigation in children aged 5 to 11 years used simple, child-appropriate questions as follows: (1) Have you ever had a nightmare?; (2) How frequently do you experience nightmares?; (3) How scary would you rate the nightmare to be? While these methods have not been psychometrically evaluated in children, the NFQ would provide a more complete understanding of the nightmares and the subsequent distress associated with the nightmares in pediatric PTSD populations.

Sleep diaries are well documented to be an important means to assess sleep-wake and circadian rhythm patterns, and have been effectively used in pediatric populations, including children with autism spectrum disorders. Yet, in pediatric populations, discrepancies between sleep time scored by actigraphy and sleep time reported in sleep diaries have been identified. The authors suggest that this may occur because actigraphy measurement can overestimate wake after sleep onset time and underestimate total sleep time in pediatric populations. The authors also found that sleep characterization by sleep diary was well correlated with sleepiness and fatigue, but actigraphy recordings were not. Sleep diaries are considered important for the fuller characterization of sleep-wake patterns when employed in conjunction with actigraphy.

Subjective assessments of healthy and traumatized children do not always specify the frequency of sleep disturbances, which can be important for differentiating normal sleep from a clinically significant condition. Also, subjectively assessed sleep disturbances can reflect a broad range of sleep disorders, such as PLM, insomnia, restless leg syndrome, circadian rhythm disturbance, and SDB. Sleep questionnaires do not always provide sufficient information to identify which sleep disorders the subjects may suffer from, although more specific, targeted sleep questionnaires are evolving, such as the Pediatric Restless Legs Syndrome Severity Scale, to better characterize specific sleep disorders in youth. Even the most comprehensive subjective sleep measures cannot fully characterize sleep architecture, or capture the full spectrum of sleep disorders potentially underlying any identified sleep disturbance. However, when objective studies of sleep are not a realistic option—because of funding issues, population dynamics, or large samples in epidemiological studies—specific subjective sleep measures can provide a valuable, valid, and reliable assessment of sleep. As such, subjective measures of pediatric sleep could be used to significantly increase our understanding of sleep in psychiatric disorders in children who are undergoing clinical assessment. Further, a comprehensive clinical interview in combination with pediatric sleep questionnaires and diaries represents a particularly reliable and valid approach for identifying specific sleep disorders, such as circadian rhythm disorders and insomnia.

Subjective measures and questionnaires also identify a significant problem in pediatric PTSD that needs further examination: namely, children with PTSD report having more sleep disturbances and nightmares than do normal populations of children. Given the methodological limitations of the subjective understanding of pediatric PTSD and sleep, studies employing more specific sleep questionnaires and interviews to assess nightmares and objective measures to assess sleep disturbance would provide a more complete understanding of the sleep dysregulation in pediatric PTSD. To date, however, very few studies have utilized objective measures to record sleep in children with PTSD.

Sleep Disturbances in Pediatric PTSD: Evidence from Objective Measures

Actigraphy and polysomnography are the most common methods of objectively measuring sleep. Actigraphic methods measure sleep-wake activity, which during the night includes TST, sleep onset latency, sleep efficiency, and number of awakenings. Studies using actigraphy in children with psychiatric disorders tend to support the findings of subjective sleep questionnaires. In a sample of 122 children aged 7 to 17 years diagnosed with MDD, an anxiety disorder, or both, those who reported “trouble sleeping” were also more likely to have longer sleep onset latency as recorded by actigraphy. Sadeh et al. performed actigraphic measurements on 39 children (7 to 14 years old) in a psychiatric inpatient unit. The children were divided into 3 groups, those who had experienced physical abuse, sexual abuse, or no abuse. Children who experienced physical abuse had significantly more fragmented sleep than the children who had experienced no abuse or sexual abuse. The physical abuse group had a quiet sleep percentage (the percent of sleep with-
out movement) of 58.3%, which was significantly lower than the 67.8% of quiet sleep of the group with no abuse and 67.3% of the sexual abuse group. These results suggest physical abuse may lead to greater fragmentation of sleep and poorer overall sleep quality. Although the authors used actigraphy on 8 children with PTSD, they did not differentiate between those with and without PTSD in their analysis, so no direct relationship between disturbed sleep and childhood PTSD can be inferred.72

Using actigraphy, Glod et al. measured sleep over 3 consecutive nights in a sample of 19 abused children (13 were diagnosed with PTSD), 10 depressed children, and 15 non-abused controls.73 The children were aged 6 to 12 years. The abused children with PTSD had significantly higher sleep onset latencies compared to both the depressed and the control groups. Further, the nocturnal activity in the group with PTSD and abuse was almost twice that of controls. Although abused children with and without PTSD had significantly more sleep impairments than controls, when the authors compared the abused PTSD and non-PTSD groups, they found more sleep impairments in the non-PTSD group. This suggests that the sleep disturbances observed may be more related to abuse than to the presence of PTSD per se. Still, the sample sizes were quite small in both these studies,72,73 and more in-depth, larger studies are required to further address this important issue.

Overall, the extant data from actigraphic investigations of pediatric PTSD suggest that this population experiences increased sleep onset latency, nocturnal activity, and fragmentation of sleep. That said, it remains to be determined which specific aspects of sleep-wake activity, specifically nocturnal activity, are disturbed in children with PTSD, given the limited amount of research using actigraphy to investigate sleep in children with PTSD.

Polysomnography is considered the gold standard for characterizing sleep architecture. It provides measurements of sleep architecture including REM sleep, stages 1 and 2 sleep, slow wave sleep (SWS), REM latency, sleep latency, and sleep efficiency. To date, there are no studies that have specifically employed polysomnography to measure sleep disturbances, disorders, and architecture in children with PTSD. However, several polysomnography studies have been conducted on adults with PTSD. These studies reveal high rates of SDB and PLM in adult PTSD patients—disorders that could help explain the sleep disturbances frequently reported by adults with PTSD.9,74,75 Further, among this population, abnormalities in REM and SWS are frequently observed. Yet, the results of the studies are sometimes inconsistent. A recent meta-analytic review of twenty polysomnographic studies7 found overall modest differences in sleep in adult patients with PTSD. Adult PTSD patients typically exhibit less SWS, higher REM density, and more stage 1 sleep than do controls.5,28 The authors suggest that their findings support previous findings of centrally measured hyperarousal in PTSD patients.5,74,75 The authors also found a significant moderating effect of age, with reduced TST in the younger patients and decreased SWS and REM density in older adults, suggesting different sleep architecture profiles at different stages of the lifespan. These age effects suggest the modest differences observed in the sleep of adults with PTSD cannot be taken as evidence that substantial differences may not exist in the sleep of children with PTSD. Further, the authors were not able to fully disentangle the effects of age and time since the index trauma.5 Since children likely are closer to the index trauma temporally, by virtue of their age, the effects on sleep and sleep architecture may be more profound.

The meta-analysis also identified comorbid depression as an important moderating factor of the relationship between PTSD and sleep disturbances. Specifically, studies in which adult PTSD patients had lower rates of comorbid depression tended to show greater sleep abnormalities. As such, comorbid psychiatric symptoms may contribute to differences in sleep in patients with PTSD.

Better characterization of sleep in children exposed to trauma may provide further insights into the development of PTSD in adults as well as guidance for areas of potential intervention or prevention. To date, we are aware of no polysomnographic study of pediatric PTSD. Polysomnography studies of healthy populations of children provide a base for comparison.76-78 One study by Ohayon et al. examined many studies of control populations of all ages. They found that TST, SWS, and REM latency decreased as age increased for the entire lifespan as well as for childhood through adolescence. Additionally, their meta-analysis revealed that stage 2 sleep percentage slightly increased with age. Across the life span, sleep latency and stage 1 sleep percentage increased with age and sleep efficiency decreased with age, although no significant changes with age were found within childhood and adolescence. Lastly, they found that REM sleep time increased until adolescence and then decreased throughout adult life.79

While there are no polysomnography studies on children with PTSD, Forbes et al. utilized polysomnography to investigate groups of children from 7 to 17 years old: 24 with anxiety disorders, 128 with major depressive disorder, and 101 with no psychiatric disorder.79 The authors found that the children with anxiety disorders had less SWS, greater sleep onset latency, and more awakenings than the control or major depressive disorder group. While this study examined children with any anxiety disorders and not specifically PTSD, the general trends are consistent with those found in adults with PTSD.79

Longitudinal studies have implicated a connection between childhood sleep problems and future neuropsychological functioning and psychiatric symptomatology, including depression and anxiety.81-84 For example, one study found in a sample of 6,000 twins pairs followed at ages 3, 4, and then again at age 7, that sleep disturbance reported at ages 3 and 4 predicted anxiety at age 7.82 In yet another investigation, the sleep and behavioral/emotional problems of 499 children were measured by the CBCL. Reported sleep problems at age 4 were predictive of behavioral/emotional problems in mid adolescence.83 A bidirectional and interactive relationship between sleep and stress-related psychiatric symptoms and disorders has been proposed.85,86 The authors suggest that patterns of sleep disturbance early in life may actually increase vulnerability to the subsequent development of stress-related behavioral and psychiatric disorders, while stressful events and associated symptoms may increase the risk for the development of sleep disturbance and sleep disorders later in life. Indeed, recent empirical evidence suggests that nightmares increase the risk for the development of PTSD.86 Specific aspects of sleep wake patterns, sleep macroarchitecture, and microarchitecture including sleep spindles may serve as important biomarkers of developmental and psychiatric disorders.87-90 For example, Buckley et al. found that children with autism spectrum disorder
had reduced REM sleep and increased REM latency relative to typically developing children and those with developmental delay, and have begun to consider pharmacological approaches for augmentation of REM in autism spectrum disorder. Similar approaches may be valuable for increasing our understanding and treatment of pediatric PTSD.

Polysonmography is required to measure sleep macro and microarchitecture, and as a result, we know little about these features in pediatric PTSD. Further, while a comprehensive clinical interview, combined with sleep questionnaires and sleep diaries, can help diagnose circadian rhythm disorders and insomnia, subsets of the bioparameters measured by polysonmography, such as electroencephalogram (EEG), electrooculogram (EOG), submental electromyogram (EMG), expiratory/inspiratory nasal airway pressure, nasal/oral airflow, finger pulse oximetry, electrocardiogram (ECG), movements of the rib cage and abdomen, snoring, and body position, are integral to the diagnosis of many sleep disorders, including sleep apnea, REM disturbance, and PLMs. Sleep disturbance can reflect very different sleep disorders. Highly effective treatment approaches are available for many of these sleep disorders, not only ameliorating and alleviating the sleep disturbance itself, but also improving daytime functioning. Treatment of sleep complaints in adult PTSD patients has been shown to be effective at reducing symptoms of insomnia and nightmares as well as improving daytime PTSD symptoms. However, most of the current research discussing treatment of pediatric PTSD does not address sleep disturbances, and we are aware of no sleep treatment studies in pediatric PTSD. Indeed, due to a lack of objective sleep measures, we often lack knowledge as to which specific sleep disorders underlie the sleep disturbance observed in youth with PTSD, and as a consequence, appropriate targeted treatments are not always provided.

However, conducting full objective, overnight measures of sleep, such as polysonmography in children with PTSD, has significant challenges. These pediatric patients often have extreme difficulty with novel procedures and strange environments that are typically involved when conducting polysonmography. Techniques, such as systematic desensitization, in which individuals learn to cope and overcome their anxiety regarding a process in a sequence of steps in a hierarchy of increased exposure to the source of the anxiety, eventually leading to overcoming anxiety regarding the procedure or process, may represent a valuable approach to enhancing the ability of children with PTSD to overcome their fear regarding polysonmography assessment.

Conclusion and Future Directions
To date, studies have predominately used subjective questionnaires and interviews to measure sleep disturbance in children with PTSD. These investigations strongly suggest that there are higher rates of sleep disturbance and nightmares in pediatric PTSD populations than in normal pediatric populations. Consistent with subjective reports of sleep disturbance, studies using actigraphy document increased sleep onset latency, nocturnal activity, and sleep fragmentation in pediatric PTSD populations.

The current understanding of sleep disturbances in pediatric PTSD and their connection to development of PTSD over the lifespan is limited and warrants further investigation. Although studies to date have demonstrated sleep disturbance as a fundamental issue in trauma-exposed pediatric populations, the current research into pediatric PTSD and sleep disorders is limited in that (a) almost all measures of sleep in this population are from subjective questionnaires or interviews; (b) these subjective measures often do not provide specific information about the nature, duration, and frequency of sleep disturbances; (c) thus, these measures do not provide sufficient enough information to assess which sleep disturbances trauma-exposed populations are experiencing and if there are abnormal sleep architecture patterns as well; (d) in pediatric PTSD the effect of comorbidity with other psychiatric disorders that are associated with sleep disturbance, such as depression, needs exploration; (e) no studies with large sample sizes have examined the sleep of this population using actigraphy, and none have employed polysomnography, a method that can identify the specific sleep mechanisms disrupted and provide a better understanding of the associated sleep disorders; and (f) the longitudinal implications of sleep disturbance in childhood for PTSD onset across the lifespan have not been investigated.

Future investigations employing full polysomnography are critical for diagnosing the underlying sleep disorders in pediatric PTSD. Actigraphy does provide an objective assessment of activity during the night, providing reasonable estimates of total time in bed and sleep efficiency. However, it does not provide qualitative information on the type of activity nor does it provide many of the bioparameters that are routinely derived from polysomnography and are required for the diagnosis of many sleep disorders. Only full polysomnography provides measures of sleep stage and architecture, using recordings of EEG, EOG, submental EMG, and typically includes expiratory/inspiratory nasal airway pressure, nasal/oral airflow, finger pulse oximetry, ECG, movements of the rib cage and abdomen, snoring, and body position. These measures are integral to the diagnosis of most sleep disorders, including sleep apnea, REM disturbance, and PLMs. Further, as identified by polysomnography, abnormal sleep architecture patterns in pediatric PTSD populations may serve as a critical biomarker for onset of PTSD and other sleep disorders after a trauma.

As a result, a multi-method, longitudinal study examining phenomenology and utilizing polysomnography on children with PTSD would greatly contribute to our current understanding of sleep disorders in pediatric PTSD. Once the specific sleep disorders in pediatric PTSD have been objectively determined, treatment development and outcome studies would be crucial for not only reducing negative symptoms in patients but also for identifying sleep disturbance as a biomarker for development of PTSD. In adults, studies have already demonstrated that sleep disruption does predict severity and onset of PTSD. Treating sleep dysregulation early in life, as well as after a trauma at any age, could have significant implications for reducing risk of PTSD onset both in childhood and across the lifespan.

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A 58-year-old woman presented with restless legs syndrome (RLS). RLS had been present for 12 years and was initially problematic only at bedtime. Treatment with ropinirole 0.5 mg each night resulted in complete resolution of symptoms at that time. In recent years, symptoms had grown more severe and extended earlier in the day, prompting an increased dosage of ropinirole. At the time of presentation, she was taking 0.5 mg ropinirole at noon and 1 mg at bedtime. Despite this, she experienced discomfort as early as 10 a.m., escalating throughout the afternoon. She also reported considerable difficulty with sleep onset and maintenance, with 5-6 awakenings each night due to RLS, one of which was often prolonged (up to 3 hours).

Review of systems was notable for loud snoring and “tired” mood with low energy and poor concentration. Medical history included anxiety, for which she was being treated with sertraline; uterine cancer, recognized due to dysfunctional uterine bleeding and treated with a hysterectomy; and hyperlipidemia. Social and family history were unremarkable. Her only medications were ropinirole as above, sertraline 150 mg, and simvastatin 40 mg. Physical examination was normal apart from a BMI of 48 (normal: 18-25), indicative of obesity. Polysomnography demonstrated reduced sleep efficiency (64%) due to several prolonged awakenings. It also showed severe obstructive sleep apnea (OSA) with an apnea-hypopnea index of 32/h. Serum iron studies were obtained:

- Ferritin: 85 ng/mL (normal: 12 ng/mL to 250 ng/mL)
- Iron: 28 μg/dL (normal: 26 μg/dL to 98 μg/dL)
- TIBC: 298 μg/dL (normal: 262 μg/dL to 474 μg/dL)
- Transferrin saturation: 9% (normal: 20% to 50%)

**QUESTION**

In addition to treatment of sleep apnea, what further evaluation or management do you recommend?

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**Normal Ferritin in a Patient with Iron Deficiency and RLS**

Susan Mackie, M.D.; John W. Winkelman, M.D., Ph.D., F.A.A.S.M.

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ANSWER

Iron supplementation is indicated. Although ferritin is within the normal range and above the cut-off generally used for iron supplementation in RLS (i.e., > 50 ng/mL), the transferrin saturation is abnormally low.

Oral ferrous sulfate 325 mg twice daily was begun. Six weeks later repeat iron studies showed:
- Ferritin: 125 ng/mL
- Iron: 125 µg/dL
- TIBC: 322 µg/dL
- Transferrin saturation: 39%

Accompanying this normalization of iron measurements, the patient reported complete resolution of daytime RLS symptoms. Because of this improvement (which was noted prior to initiation of treatment for OSA), the earlier dose of ropinirole was stopped. Nocturnal symptoms were also substantially alleviated, and the patient reported fewer overnight awakenings.

DISCUSSION

There is broad consensus that iron status should be evaluated in all patients with RLS. Many clinicians believe that serum ferritin > 50 ng/mL is an adequate marker of iron sufficiency, and recently published practice parameters for the treatment of RLS do not mention measurement of other iron markers. However, hematologists nearly universally recommend that ferritin not be used as a lone assay of iron status. Ferritin is increased in a number of conditions unrelated to iron status. This may cause a falsely normal value in an individual with truly low iron stores. Thus, an opportunity to ameliorate symptoms using iron supplementation may be missed. The ratio of serum iron to total iron binding capacity (a.k.a. transferrin saturation) may reveal decreased iron stores in such situations despite a falsely normal ferritin. Transferrin saturation < 20% is indicative of iron deficiency.

Ferritin is an acute phase reactant and as such, inflammation increases ferritin independent of any true effect on iron stores. Therefore, ferritin is most likely to be spuriously normal in the setting of inflammation. On the other hand, and in contrast to iron deficiency, the inflammatory state is distinguished by normal transferrin saturation. Thus, a low value is indicative of true iron deficiency.

Obesity, commonly observed in sleep medicine clinics, is perhaps the most common inflammatory state. Although seldom associated with overt anemia, obesity has been consistently associated with the elevated ferritin levels characteristic of inflammation.

Obesity is also a risk factor for both iron deficiency and RLS. Iron deficiency among obese RLS patients may therefore be especially common. As in this patient, ferritin is likely to be a misleading indicator of iron status in this group.

Iron deficiency is a known risk factor for augmentation during treatment with dopamine agonists. Augmentation is an iatrogenic worsening of RLS due to the medication, frequently characterized by shorter time to symptom onset at rest or migration of symptoms earlier in the day. Augmentation may have been a factor in this patient’s recent intensification of symptoms. If ferritin alone had been measured, the contribution of iron deficiency to this process would have been overlooked.

In addition to obesity, several other conditions that are common among RLS patients and pertinent to this patient deserve mention in this context. Obstructive sleep apnea, major depressive disorder, and chronic partial sleep deprivation have all been associated with increased levels of serum inflammatory markers. These problems are nearly ubiquitous in sleep medicine clinic, and all may be under-recognized by a clinician focused on treatment of RLS.

In this patient, obesity, obstructive sleep apnea, incompletely treated mood symptoms, and sleep deprivation due to RLS may all have contributed to normal ferritin despite iron deficiency. Low iron stores were, in turn, likely contributing to augmentation. In addition to identification and treatment of iron deficiency, adjustment of dopaminergic therapy to include multiple daily doses or a continuous release formulation could be helpful in this circumstance. Down-titration of the SSRI medication could also be of benefit. Objective documentation of symptoms before and after treatment interventions using a validated measure such as the International Restless Legs Scale (IRLS) is appropriate. Although the IRLS was not obtained in this patient, clinical interview confirmed that supplemental iron alone was sufficient to facilitate reduction in the ropinirole dose in this instance.

In light of the myriad subtle conditions in which ferritin alone may be falsely reassuring, clinicians are encouraged to evaluate iron status in all patients with RLS using both ferritin and transferrin saturation. This approach minimizes false negative conclusions about iron deficiency and maximizes the opportunity to provide symptom relief with iron supplementation alone.

PEARLS

1. Iron status should be evaluated in all patients with RLS.
2. In addition to ferritin, it is helpful to obtain transferrin saturation, which is the ratio of serum iron to TIBC.
3. Supplemental iron is recommended if ferritin is < 50 ng/mL or transferrin saturation is < 20%.

CITATION


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This was not an industry supported study. Dr. Winkelman has served as a consultant/advisor from Pfizer, UCB, Zeo Inc., and Sunovion. He reports having received research support from GlaxoSmithKline, Impax Pharmaceuticals, and UCB. The other author has indicated no financial conflicts of interest.
Article Summary

Question: What is the effect of continuous positive airway pressure (CPAP) therapy versus Sham CPAP therapy on neurocognitive function in patients with obstructive sleep apnea (OSA)?

Design: Multi-center, randomized, double blinded, sham controlled trial; ClinicalTrials.gov Identifier: NCT00051363.

Allocation: The Data Coordinating Center used a computerized permuted block design to randomize participants to the 2 study arms.

Blinding: Participants and most personnel were blinded to treatment assignments, with the exception of site coordinators, polysomnography (PSG) technologists, and the database administrator/data manager.

Follow-up period: 6 month follow-up; the first participant was enrolled in 11/2003 and the final completion month was 8/2008.

Setting: 5 clinical sleep centers in the United States (academic and private settings).

Subjects: 1,098 participants (556 active CPAP, 542 sham CPAP, 35% women, mean age 52 years in active CPAP group) who were diagnosed with OSA with apnea hypopnea index (AHI) ≥ 10 events per hour were randomized. The primary exclusion criteria were: 1) prior OSA treatment with CPAP or surgery; 2) anyone in the household with current/past CPAP use; 3) sleepiness-related automobile accident within past year; 4) oxygen saturation < 75% for > 10% of the diagnostic PSG total sleep time; and/or 5) conditions (including known neurocognitive impairment), disorders, medications, or substances that could potentially affect neurocognitive function and/or alertness. Subjects were recruited primarily from patients scheduled in a regular sleep clinic for evaluation of possible OSA and from local advertising. Although recruitment source was not tracked, it was estimated that initial contact with ~70% of the subjects occurred as a result of advertisement.

Intervention: Participants were randomized to receive CPAP treatment or sham CPAP. Outcomes: The primary outcomes were 3 neurocognitive variables, each representing a neurocognitive domain: 1) Pathfinder Number Test-Total Time assesses attention and psychomotor function; 2) Buschke Selective Reminding Test-Sum Recall assesses verbal learning and memory; and 3) Sustained Working Memory Test-Overall Mid-Day Index assesses an executive and frontal-lobe function (E/F). The secondary outcomes were 7 neurocognitive and 2 sleepiness measures (the maintenance of wakefulness test and the Epworth Sleepiness Scale).

The sample size was based on pilot study results for the Pathfinder Number Test. A target of 1,100 total participants (assuming 90% power, 2-sided α = 0.05, 20% study dropout, and allowing for 3 interim analyses) was estimated to achieve an effect size of 0.2, translating to the clinically significant difference of 26 msec in reaction time between the Active and Sham CPAP groups. An effect size of ≥ 0.2 is also a clinically significant between group difference for the other two primary outcome measures.

Patient Follow-Up: intention to treat analysis, 79% completed follow-up in active arm, 74% in sham arm.

Main Results: There was no statistically significant difference between the groups in the primary outcomes at 6 months. When stratified by measures of OSA severity (AHI or oxygen saturation parameters), the primary E/F variable and one secondary E/F neurocognitive variable revealed transient differences between study arms for those with the most severe OSA that did not persist at 6 months. When primary neurocognitive analyses were restricted to CPAP-adherent individuals (mean nightly active or sham CPAP adherence ≥ 4 h for the 2 months prior to each neurocognitive testing visit), no differences in means were detected between arms for any of the primary outcomes at any visit.

Participants in the active CPAP group had a significantly greater ability to remain awake whether measured subjectively by the Epworth Sleepiness Scale or objectively by the maintenance of wakefulness test.

Conclusion: In adults with OSA, CPAP therapy did not improve neurocognitive measures at 6 months compared with those on sham CPAP therapy.

Sources of Funding: APPLES was funded by NHLBI (HL68080). The APPLES pilot studies were supported by grants from the American Academy of Sleep Medicine and the Sleep Medicine Education and Research Foundation to Stanford University and by the NINDS (N44NS002394) to SAM Technology. Respironics®, Inc. supplied the active- and sham-CPAP devices and equipment.

For Correspondence: Clete A. Kushida, M.D., Ph.D., F.A.A.S.M.; Email: clete@stanford.edu
The effect of Continuous Positive Airway Pressure (CPAP) treatment for Obstructive Sleep Apnea (OSA) on neurocognitive function (APPLES) is an NIH-funded, impeccably designed and executed RCT from experts in the field which is essentially a negative study. The primary aim of this five year, multi-site investigation was to determine, with sufficient statistical power, whether neurocognitive function is improved by CPAP treatment for OSA.

From the point of view of the primary endpoints, the finding of a small deterioration in the Sham condition at 2 months, in the domain of frontal lobe and executive function (E/F), rather than any large improvement in the Active arm is intriguing. There remains a chance that it was a type 1 statistical error. However this seems unlikely because as the authors delved deeper into the efficacy analysis, the difference in outcomes favoring Active at 2-months appeared to strengthen overall, particularly in participants with more severe OSA and sleep dysfunction at baseline. One might speculate that the improvements in sleepiness seen in those adherent with therapy were mediating the lack of deterioration in E/F and furthermore that these benefits were less able to be built upon from 2 to 6 months (as the sleepiness was already “cured”). As the authors note, perhaps the study sample was fundamentally biased towards those with more cognitive reserve and thus the potential for improvement with treatment reduced. Additionally, the greater reduction in adherence observed in the Sham group, and the subsequent loss of statistical power of the efficacy analyses, may also reignite the debate as to what is an appropriate Sham for CPAP; sugar pills are well tolerated (93% adherence) and preferred by participants over CPAP. Regardless, the data support the authors’ conclusion that the relationship between OSA and neurocognition, particularly in more severe disease, is real and complex.

The authors and the journal are also to be commended for the publication of the results contained in the Appendices. These comprehensive data substantially increase the information available to the scientific community from the study. I would attest that had an APPLES a day been found to substantially increase neurocognitive function, rather than the equivocal, arguably negative overall effect that was demonstrated, the paper would have been far shorter, published in a higher impact general medical journal and these valuable data would have struggled to see the light of day. Negative studies are vital contributors to the body of knowledge about how and why CPAP works in OSA.
LETTER TO THE EDITOR

The new research by McCarty et al. titled “Vitamin D, Race, and Excessive Daytime Sleepiness” was very interesting as well as somewhat confusing. The authors reported that more than half of their patients with somatic pain and sleep disruption had vitamin D deficiency. So in this cohort, the most prevalent sleep disorder was expected to be insomnia secondary to medical condition; however, the majority of patients in the study cohort suffered from obstructive sleep apnea ([OSA] 74%) and restless leg syndrome ([RLS] 30%), whereas insomnia was only 16%.

The authors acknowledge that the study did not consider the severity of OSA or RLS. Could these primary sleep disorders be the cause of the excessive daytime sleepiness (EDS) and vitamin D levels an epiphenomenon to this primary process?

The major source of vitamin D in humans is exposure to UV radiation. Even the vitamin D level in this cohort of white patients differed according to sunlight exposure between the winter and summer months, but black patients had chronically low vitamin D. Increased frequent nocturnal awakenings from any of the primary sleep disorders can lead to sleep fragmentation, thereby causing EDS and less exposure to sunlight. EDS may be the barrier to vitamin D formation, thereby causing low vitamin D levels in these patients. This results in an inverse relation between vitamin D and EDS as was seen in the vitamin D non-deficient group.

In the vitamin D deficient group, it was surprising not to find any correlation between EDS and vitamin D deficiency except for black patients. This negates the hypothesis that vitamin D deficiency in nonblack patients caused OSA by increasing chronic rhinitis or tonsillar hypertrophy. This also suggests that vitamin D level may not be the determinant factor in this cause of EDS.

The editorial¹ to this paper suggested a possible role of melanin and skin pigmentation and sleep patterns. Melanin is a neurotransmitter secreted from the lateral tegmentum that works against orexin and consolidates REM sleep. At this moment, other than mere speculation, more studies are need to help us understand the role of melanin secreted during nocturnal REM sleep and vitamin D absorption during daytime with sunlight exposure.

African American patients are also known to have high prevalence of sleep disordered breathing, noncompliance to treatments, and high risk for vitamin D deficiency for their increased skin pigmentation. Was this the reason for the findings we see in Figure 2, where major part of the black patients had a vitamin D level < 15 and also had high excessive daytime sleepiness? It may be difficult to extrapolate any inference of any relationship between vitamin D and EDS from this small cohort of black patients with so many variables.

I applaud the authors for their keen observation, but the study was inconclusive about the cause-effect relationship between vitamin D and EDS, partly because of the complexity of the cohort and the multiple unknown variables. However, this study demands a well-designed future study addressing all the variables that will help us understand this matter more.

CITATION


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2. National Institutes of Health: Vitamin D; Dietary supplement fact sheet
We agree with Dr. Ganguly’s initial comments about our recent publication, that a relationship between the Epworth Sleepiness Scale score (ESSs) and circulating 25-OH Vitamin D is interesting, but disagree that the research as presented was confusing. Instead, we would suggest a more accurate assessment is that the identified relationships are complex and requiring of further study. These points were stated fairly clearly in the discussion.

To be included in this cohort, subjects merely had to admit to the presence of moderate or severe musculoskeletal pain either interfering with sleep or interfering with daytime function. Dr. Ganguly raises the point that one would expect “insomnia secondary to medical condition” to be the most prevalent sleep disorder, whereas insomnia was only reported in 16% of our sample. In response to this, we can only state that, according to the judgment of the physician caring for the patient (DM), the most appropriate clinical diagnoses were given at the time of the encounter, and these diagnoses were abstracted and reported during the process of research-related chart review. These data were provided merely to provide some degree of background information to clinicians who wish to see if the population we studied was at all comparative to clinical populations they serve. The fact that the data don’t adhere to Dr. Ganguly’s expectations is noted, but is also arguably irrelevant to the major findings presented.

Next, Dr. Ganguly raises multiple questions about the underlying mechanism of EDS within the cohort we studied, stating that EDS may be related to each subject’s underlying sleep disorders, tendency toward noncompliance, whether melanin may somehow be involved, and so forth. The issue of causation was clearly addressed in the discussion section of the paper—an association between two variables does not guarantee causation. It is crucial to emphasize, however, that this study was never designed to provide conclusive data on causation. To this point, we gently remind Dr. Ganguly that causation cannot be investigated at all if an association is not recognized to exist. We hope this paper helps initiate the scientific conversation about the possible role of Vitamin D deficiency in the pathophysiology of sleep disorders, as well as the potential role of Vitamin D supplementation in the treatment and/or prevention of diseases encountered by Sleep Medicine specialists.

We agree with Dr. Ganguly that more research is needed to help resolve these unanswered questions.

CITATION
McCarty DE; Marino AA. We’ve only just begun: a conversation started shouldn’t be mistaken for the last word. J Clin Sleep Med 2013;9(5):519.

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The subject of mental illness makes some physicians uncomfortable, and as such, many avoid this group of patients entirely or are unable to see beyond the most obvious symptoms of the psychiatric illness. One example of this is the schizophrenic patient presenting to the Emergency Department (ED) in the early morning with a chief complaint of “I can’t sleep because the devil won’t stop pounding on my chest. I know he is trying to steal my heart!” Once identified as mentally ill, this patient may be quickly transferred to the psychiatric ED without the realization that he was complaining of cardiac chest pain but expressing the symptom in a manner consistent with his thought disorder; what may be missed is a devastating ischemic event. Specifically in terms of the practice of sleep medicine, the importance of sleep in the psychiatric patient is too often vastly underestimated and misunderstood. While the effects of psychiatric illness on sleep symptomatology are commonly taught, the concept that poor sleep may greatly exacerbate mental illness frequently is not given the attention it deserves in medical school and beyond. Poor sleep will often precipitate manic or psychotic decompensation and cause otherwise treatable depression to continue as a smoldering illness. Consequently, the sleep medicine physician must develop an appreciation for the bidirectional interactions between sleep/wake disorders and mental illness. More broadly, a basic understanding of sleep physiology and how sleep disorders (particularly insomnia) affect the mind are essential to every practicing health professional.

In summary, Foundations of Psychiatric Sleep Medicine starts the reader on an adventure that begins with the very first page and does not end until all 415 pages of informative and well-written text are fully digested. We can easily imagine this book finding a place on the bookshelf (or the first time through, the night stand or next to a favorite reading chair) of every physician interested in psychiatry, sleep, and the many interactions between these two disciplines.
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