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Sleep Medicine: The Shot Heard Around the World

Meir Kryger, M.D.

Yale University School of Medicine, New Haven, CT; VA Connecticut Healthcare System, West Haven, CT

Background

There has recently been concern about the future of sleep medicine in response to the “disruptive technology” of home sleep testing (HST) and its embrace by the medical insurance industry in the USA. A reader might surmise that the first contract by an insurance carrier in Massachusetts to mandate HST as a first step in apnea diagnosis was the shot heard around the world that would change sleep medicine forever. The original shot heard around the world referred to the first skirmish of the American Revolution (incidentally only about 30 miles from the headquarters of the insurance carrier in Massachusetts) was simply a step in a process that had its genesis long before. Similarly, the genesis of this shot affecting sleep medicine was long ago, and the reader must recognize that this is a shot heard around America, not the around the World.

There have been many “disruptive” technologies and treatments in medicine, and in general they have improved patient outcomes. We can now prevent poliomyelitis and many childhood viral diseases; we can cure most bacterial, mycobacterial, and fungal infections; we seldom require surgery to treat diseases caused by gastric acid hypersecretion; we use “noninvasive” surgery using laparoscopic and thoracoscopic techniques to treat many patients who a generation ago would have required large incisions, dissections and excisions, and prolonged hospital admissions. We can now determine the presence of cancer in many cases using PET/MRI imaging.

Disruptions in Sleep Medicine

Sleep medicine is a young field, and there have already been several disruptions. In the field of sleep apnea some of the disruptions have been technical, while others were based on new knowledge. There have already been several shots heard around the world of sleep. Some of the shots have been quiet, while some have been very loud. Such shots might include the following: the description of CPAP; the first description of data acquisition for respiratory variables during sleep by a microcomputer; the notion that respiratory sleep data can be obtained outside the laboratory; the publication of data suggesting that apnea patients have more automobile accidents and increased mortality; the implementation of an integrated home sleep testing system; the monitoring of CPAP compliance; and the realization that sleep apnea is a very common problem.

Based on the latter, there was an explosion worldwide in the following decade in the capacity to diagnose sleep apnea. The ability and capacity to diagnose apnea clinically was related to local medical practice, funding, and available technology. Home sleep testing has been integrated as an important diagnostic option in the Veteran Administration Healthcare System. In some countries comprehensive polysomnography was used; in others the testing evolved to include (sometimes exclusively) limited-channel monitoring, and resources were directed towards treatment. In the United States (a notable exception being the Veterans Administration System), there was an entirely different path directed by two entities: the American Academy of Sleep Medicine that set the clinical benchmarks, and Centers for Medicare Services (CMS) which set the reimbursement benchmarks. At the end of the day, the decisions by CMS trumped the standards of the AASM.

There were several important milestones related to the definition of apnea and when CMS would pay for treatment that lead to the current situation:

• 1986—CMS defined sleep apnea as “at least 30 episodes of apnea, each lasting a minimum of 10 seconds, during 6-7 hours of sleep” using “facility-based, attended polysomnogram.”

• 2001—CMS defined sleep apnea as “AHI > 15, or AHI between 5 and 15 with documented symptoms of excessive daytime sleepiness, impaired cognition, mood disorders or insomnia, or documented hypertension, ischemic heart disease or history of stroke.”

• 2008—CMS for the first time defined apnea without requiring an in-lab PSG as “The AHI and/or RDI may be measured by polysomnography (PSG) in a facility-based sleep study laboratory, or by a Type II home sleep test (HST) monitor, a Type III HST monitor, or a Type IV HST monitor measuring at least 3 channels.” Initially there was no fee code for HST. Initial coverage for CPAP reimbursement was 12 weeks and the patient had to show compliance for CMS to pay for CPAP.

• 2009—Home sleep testing fees approved.

In these milestones and other decisions during the years, CMS actually ventured into the medical realm and de facto defined the disease (at least for the USA) and how it should be diagnosed and treated. The Medicare hypopnea has even found its way into the scoring manual published by the American Academy of Sleep Medicine as Hypopnea Rule A.

Chaos

Once home sleep testing fees were approved by CMS, entities not previously involved in sleep (doctors, clinics, companies marketing HST equipment and services) all of a sudden expressed tremendous interest in the field of sleep medicine (more...
precisely sleep apnea), and rapid transitions and sometimes chaos ensued. There was marketing of types II, III, and IV HST monitoring units and services to medical practitioners who often had no training in sleep and whose medical practice often did not involve patients who would benefit from such services. Since many of these new purveyors of sleep medicine services had little or no training in sleep, the interpretations of the studies were done by “board-certified sleep specialists” whose name, location, and state of medical licensure were often unclear or undecipherable on their reports. Doctors with almost no knowledge of sleep medicine were now ordering positive airway pressure (PAP) equipment from DMEs based on recommendations indicated on the HST study interpretations by doctors who actually never saw the patient and relied on questionnaires. Thus, the situation is such that some patients with a lifelong condition are currently being managed by clinicians out of their depth, and the patients are never actually seen by a practitioner with expertise in sleep.

Where Are We Now and What Does the Future Hold?

Out of chaos often comes order, and some patterns seem to be emerging. Home sleep testing is here to stay, because it does offer an excellent diagnostic option for many patients and health care systems. Does that mean that sleep labs are obsolete? Not at all. There are too many patients with sleep disorders who have problems that require in-lab evaluations including children, patients with complex comorbidities, patients requiring complex PAP titrations, and patients with a variety of diseases that cannot be properly evaluated with HST technology that is designed only to document apnea. In the author’s experience about 20% of HSTs are non-diagnostic and require additional, usually in-lab evaluation. However programs that offer only in-lab sleep testing may see their days numbered.

There will be new practitioners entering the sleep field from a variety of specialties. Some have taken the ABMS sleep certification exam. Indeed there was a large bulge in taking the exam whose results were available in early 2012. Most of the test takers were able to take the exam via the practice waiver, without having taken sleep medicine training. Thus, many will be in the field not ever having any comprehensive sleep training. There will be specific educational challenges so that these practitioners obtain the knowledge to evaluate and manage long-term sleep disorder patients.

It is likely that the trend of insurance carriers mandating screening or initial diagnosis of OSA by HST and covering testing only when done by their preferred provider will continue and expand. I believe that this is potentially harmful to patients because it takes sleep doctors out of an important loop in managing patients. The question remains whether insurance carriers have the expertise and know-how to evaluate whether their preferred HST provider has the proper equipment, staffing, and experienced interpreting physicians to offer patients what they deserve and expect. One challenge in the management of patients is not the diagnosis, but long-term adherence to treatment. With society’s focus on prevention, will insurance carriers fund true screening for apnea which in many cases is already a burden a decade before patients are formally assessed for the first time?16

Although on the surface, home sleep testing seems to be the most cost-effective approach to managing patients with sleep apnea without other comorbidities that may confound diagnosis, there is still debate about whether this approach is actually the most cost-effective.17 In addition to be able to rapidly respond to inevitable reimbursement shifts, it is likely that sleep medicine programs that are flexible in adopting new technologies (diagnostic and therapeutic) and that also maintain some in-lab capability and have long-term management programs will be the most successful. What is important that the target is understood: long-term patient outcomes. There will be innovations to come; we must evaluate them and, if effective, embrace them.

REFERENCES


SUBMISSION & CORRESPONDENCE INFORMATION

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DISCLOSURE STATEMENT

Dr. Kryger has indicated no financial conflicts of interest.
Restless legs syndrome (RLS) is a common neurological sensorimotor disorder characterized by an urge to move the legs during periods of rest or inactivity. The International Restless Legs Syndrome Study Group (IRLSSG) has described 4 mandatory clinical features to establish the diagnosis of RLS in a population-based sample.

Methods: We obtained data from the Tucson Cohort of the Sleep Heart Health Study, a prospective multicenter study. This cohort included 535 participants aged ≥ 40 years, who answered questions regarding RLS on the 2002 and 2006 sleep surveys. For this study, RLS was defined as the presence of all 4 International RLS Study Group criteria, with symptoms occurring ≥ 5 days/month and associated with at least moderate distress.

Results: Mean age of the predominantly Caucasian (90.8%) participants on the 2002 survey was 59.8 ± 9.7 years; 52.2% were women. RLS prevalence was 4.1% in 2002 and 7.7% in 2006. The yearly incidence of RLS was 1.7% (6.6% over 4 years). Multivariate analyses demonstrated that estrogen use (OR = 2.5, 95% CI: 1.17-5.10) and self-reported obstructive lung disease (OR = 2.8, 95% CI: 1.37-5.83) were independent risk factors predicting incident RLS. Incident RLS was associated with higher prevalence of insomnia (26.5% vs. 7.6%, p = 0.001), increased sleepiness (38.2% vs. 22%, p = 0.036); and higher sleeping pill use in 2006 (23.5% vs. 9.7%, p = 0.019).

Conclusion: The incidence of RLS in this population sample was 1.7% per year. Use of estrogen and history of obstructive lung disease were associated with a significantly higher incidence of RLS. RLS, in turn, was associated with insomnia and increased sleepiness.

Keywords: Restless Legs Syndrome, incidence, estrogen, obstructive airway disease, COPD

BRIEF SUMMARY

Current Knowledge/Study Rationale: Restless legs syndrome is a common neurological disorder. Several studies have looked at the prevalence of RLS but the incidence and correlates of RLS still need to be elucidated. The aim of the current study was to assess the incidence of RLS and its correlates in a prospective community-based cohort.

Study Impact: The study demonstrates a relatively high annual incidence of RLS and its association with estrogen use and obstructive lung disease. An awareness of this relationship would facilitate early diagnosis and management of RLS in these patient groups, which may, in turn, lead to a decrease in insomnia and sleeping pill use.
Table 1—Questions used to diagnose and measure the severity of RLS symptoms

(1) In the past year, while SITTING OR LYING DOWN, have you had any of the following symptoms?
   (1a) “An urge to move your legs?” (yes / no / do not know)
   (1b) “Unpleasant or uncomfortable feelings in your legs?” (yes / no / do not know)

(2) “Are they worse when you are sitting or lying down than when you are moving around or walking?” (yes / no / do not know)

(3) “Do the symptoms improve if you get up and start walking?” (yes / no / do not know)

(4) “These symptoms are most likely to occur when you are? (resting, sitting or lying down / exercising or just stopped exercising / standing or walking / having a leg cramp or Charley horse / do not know)

(5) “What time of day do they occur?” (daytime only (before 6 PM) / bedtime only / evening or nighttime only / both day and night (after 6 PM)).

   (5a) “If both day and night, do they get worse at night?” (yes / no / do not know)

(6) “How troublesome are the symptoms?” (hardly at all / a little / moderately / a lot / extremely).

(7) “How often do you get this symptom? (less than once a month / about once a month / 2-4 days a month / 5-15 days a month / most days (16-23 days a month) / daily (6 days a week or more))

Subjects were instructed to check one best answer. In accordance with IRLSSG criteria, a yes response was required to the first 3 questions. The symptoms had to be present during resting, sitting, or lying down positions (question 4) and had to occur primarily during the evening, nighttime, or bedtime (question 5). If the participant’s response was “both day and night” (question 5), then the symptoms had to be worse at night (question 5a). For the current study, RLS was defined as present if in addition to participants meeting the above criteria; the symptoms occurred at least 5 days a month (question 7) and were associated with at least moderate distress (question 6).

The aim of the current study was to assess the incidence of RLS and its correlates in a community-based cohort. We were especially interested in whether estrogen use or presence of obstructive pulmonary disorders results in a higher incidence of RLS. We used the data from the Tucson cohort of the Sleep Heart Health Study.

METHODS

Study Sample

The Sleep Heart Health Study (SHHS) is a multicenter, prospective cohort study implemented by the National Heart, Lung, and Blood Institute, primarily aimed at elucidating the relationship between sleep disordered breathing and cardiovascular diseases in participants aged ≥ 40 years in the United States. In the second examination cycle of the SHHS (SHHS-2) in 2002, questionnaire data were obtained regarding RLS symptoms. Approximately 4 years later in the Tucson cohort of SHHS, participants self-completed their follow-up survey which included these same questions. There were 535 participants who answered questions regarding RLS on both the surveys, and these were included in the analysis. The SHHS protocol was approved by the institutional review boards of all participating centers.

Participants were asked specific questions to determine the presence and severity of RLS (Table 1). We defined RLS as presence of all 4 IRLSSG criteria, with symptoms occurring ≥ 5 days/month and associated with at least moderate distress. These questions attempted to ensure that participants met IRLSSG criteria and had persistent and distressing symptoms. Participants whose responses suggested possible alternate diagnoses (discomfort from leg cramps/pain while exercising [claudication]) were excluded to decrease false positives.

Participants who had RLS based on these criteria in 2006, but not on first survey on RLS in 2002, constituted the incident RLS group.

Polysomnography

The participants also underwent overnight polysomnography in their homes, using a portable sleep-monitoring device that collected data on 12 channels, using electrodes attached to the head, face, and chest. Polysomnography was done during survey 1 (SHHS-2, 2002) only. Data obtained from polysomnography included: total sleep time, sleep onset latency, wake time after sleep onset, sleep efficiency, arousal index, and the apnea-hypopnea index. Sleep efficiency was defined as the percentage total time asleep divided by the total time in bed after lights off to the time of final awakening. The arousal index was defined as the total number of arousals in sleep divided by the total sleep time. Arousals were identified as abrupt shifts ≥ 3 sec in electroencephalogram frequency. Apneas were defined if airflow was absent or nearly absent for ≥ 10 sec; hypopneas were considered to be present if there was ≥ 30% reduction in airflow for ≥ 10 sec and were associated with ≥ 4% decrease in oxyhemoglobin saturation. The apnea-hypopnea index (AHI) was defined as the number of apneas plus hypopneas per hour of sleep.

Sleep Habits

Data regarding sleep habits was obtained during both surveys 1 (SHHS-2, 2002) and 2 (2006). For insomnia responses, the following 3 questions were used: Do you “Have trouble falling asleep,” “Wake up during the night, and have difficulty getting back to sleep,” and “Wake up too early in the morning and be unable to get back to sleep.” Response options were categorized into never, rarely (once a month or less),
sometimes (2-4×/month), often (5-15×/month), and almost always (16-30×/month). Insomnia was defined as a present if the subjects answered “almost always” to any of these questions. In order to determine the daytime consequences of insomnia, subjects were asked if they “Feel unrested during the day no matter how many hours of sleep you had” or “Feel excessively (overly) sleepy during the day.” Adverse daytime consequences were considered to be present if they had any of the above symptoms ≥ 5-15 times a month. Insomnia disorder was defined as presence of any of the insomnia symptoms along with adverse daytime consequences. Use of sleeping pills was defined as present if the response to the question “Do you use sleeping pills” was “often (5-15×/month)” or “almost always (16-30×/month).” Finally, participants were asked “How often do you snore?” Responses were classified as “do not snore,” “rarely (less than one night a week),” “sometimes (1 or 2 nights a week),” “frequently (3 to 5 nights a week),” “always or almost always (6 or 7 nights a week),” and “don’t know.” Participants were classified as frequent snorers if they snored ≥ 3 to 5 nights a week. The Epworth Sleepiness Scale (ESS), an 8-item self-report measure of sleepiness, was used to determine the level of daytime sleepiness. Scores range from 0 to 24, and values ≥ 10 are generally considered to indicate excessive sleepiness.

Other Variables
Ethnicity, gender, education, and marital status were obtained from data already collected by the Tucson SHHS cohort. Data regarding medical history, medication use (including estrogen use), BMI, smoking, and alcohol consumption were also obtained from survey 1 done in 2002. Obstructive lung disease was defined as present if patient reported having asthma, chronic bronchitis, COPD, or emphysema.

Analysis
The primary outcomes were the incidence and correlates of RLS. We evaluated the participants with no RLS at baseline (i.e., on 2002 survey). Among these, the participants who developed RLS on 2006 survey (incident RLS) were compared with those with no RLS on the 2006 survey. We compared baseline (survey 1) demographic factors, tobacco use, alcohol and medication use, presence of medical comorbidities and polysomnographic variables between those with and those without incident RLS using Student’s t-test or χ2 test. We then included the variables significant at level p < 0.1 to construct multivariate regression models to determine factors independently associated with incident RLS. We also investigated the relationship between incident RLS, insomnia, daytime consequences of insomnia, sleeping pill use, and daytime sleepiness (ESS score ≥ 10). Statistical significance was defined as 2-tailed p-value < 0.05.

RESULTS

Population Characteristics
There were 535 participants who answered questions regarding RLS on both surveys. Mean age of the study sample on survey 1 was 59.8 ± 9.7 years; 52.6% of the participants were women. Mean age was 59.4 ± 10.0 for women and 60.1 ± 9.4 for men (p = 0.49). It was a predominantly Caucasian population (90.8%). Mean BMI was 28.7 ± 5.6 kg/m².

Prevalence of RLS
Based on IRLSSG criteria alone, 71 participants (13.3%) had restless leg symptoms on survey 1 and 123 (23%) on survey 2. Prevalence of RLS (IRLSSG criteria, with symptoms occurring ≥ 5 days/month and associated with at least moderate distress) on survey 1 was 4.1% (22/535). Participants with RLS were older (65.09 ± 9.8 vs. 59.53 ± 9.7, p = 0.009), had higher prevalence of insomnia (22.7% vs. 5.7%, p = 0.009), higher sleep latency on PSG (49.47 ± 62.23 min vs. 27.34 ± 32.2 min, p = 0.014), and tendency towards poor sleep efficiency (77.08% ± 13.8% vs. 81.99% ± 10.14%, p = 0.056). Prevalence of RLS on survey 2 was 7.7% (41/535).

Incidence of RLS
The breakdown of incidence based on different frequency and severity criteria is shown in Figure 1. The annual incidence rate for RLS defined by IRLSSG criteria alone was 4.7%. In contrast, the annual incidence of RLS according to our definition which included occurrence ≥ 5 days/month and at least moderate distress was 1.7%. The comparison between the baseline characteristics of participants with and without incident RLS is shown in Table 2. All estrogen users were women. There was a higher prevalence of estrogen use and history of obstructive lung disease at baseline among those who developed RLS (Table 2). Conversely, estrogen users (n = 113) had...
higher incidence of RLS over 4 years than those who did not use estrogen (11.6% vs. 5.3%, p = 0.029). Similarly, patients with obstructive lung disease had higher incidence of RLS compared to those who did not have obstructive lung disease (12.5% vs. 5.0%, p = 0.009). Multivariable analyses confirmed significantly increased odds of developing RLS in estrogen users or those with a positive history of obstructive lung disorders (Table 3).

Participants with incident RLS had higher prevalence of insomnia disorder (insomnia with daytime consequences) and higher use of sleeping pill in the second survey in 2006 (Table 4).

**DISCUSSION**

To our knowledge, this study is the first community-based study to look at the incidence of RLS and define its correlates. We found an annual incidence of RLS of 1.7%, while the incidence based upon IRLSSG criteria alone without severity measures was 4.7%. Factors associated with increased odds of developing RLS over a period of four years were estrogen use and a history of COPD, both of which conferred an almost three-fold risk of developing RLS. Estrogen use was associated with a significantly elevated risk of developing RLS in the current study. This supports previous literature suggesting an association between estrogen use and RLS. Further evidence of a role of estrogen is provided by the peak prevalence of RLS in pregnancy occurring in the third trimester, when estrogen levels are the highest.12 Dzaja et al. reported an association of elevated estrogen levels, but not other hormone or ferritin levels with RLS in pregnancy.13 Moreover, the prevalence of RLS is higher in parous women and increases with each additional pregnancy.3 While the mechanism of this association is still obscure, it has been postulated that estrogen, by acting directly at the D2 auto receptor or via increased turnover of brainstem noradrenaline, may interfere with dopaminergic transmission in the basal ganglia, thus contributing to RLS pathophysiology.12,14,15

Another novel and important finding of the current study was the higher incidence of RLS in participants with a history of obstructive lung disease. The association between these two disorders was first suggested in 1970 when a case series reported comorbid COPD in eight consecutive patients referred for neurological evaluation for severe RLS.16 Lococo et al. compared 87 COPD patients to 110 age and gender-matched controls, and found a three times higher prevalence of RLS in patients with COPD.17 The severity of RLS symptoms was also higher in COPD patients compared to controls with RLS.17 Another study reported that RLS was more frequent in subjects with COPD,

---

### Table 2—Baseline clinical, demographic, and polysomnographic characteristics (Survey 1, done in 2002) of subjects with incident RLS compared to subjects who did not develop RLS

<table>
<thead>
<tr>
<th>Number of participants (Incident RLS/no RLS)</th>
<th>Incident RLS</th>
<th>No RLS</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>34/479</td>
<td>60.4 ± 8.9</td>
<td>59.5 ± 9.7</td>
</tr>
<tr>
<td>Gender, Female</td>
<td>34/479</td>
<td>64.7 (%)</td>
<td>51.4 (%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>32/461</td>
<td>22 (%)</td>
<td>25 (%)</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>33/474</td>
<td>18 (%)</td>
<td>9 (%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>30/449</td>
<td>7 (%)</td>
<td>3 (%)</td>
</tr>
<tr>
<td>Body mass index</td>
<td>34/478</td>
<td>27.3 ± 5.2 (kg/m²)</td>
<td>28.8 ± 5.6 (kg/m²)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>34/478</td>
<td>15 (%)</td>
<td>8 (%)</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>24/477</td>
<td>24 (%)</td>
<td>14 (%)</td>
</tr>
<tr>
<td>Benzodiazepine</td>
<td>34/477</td>
<td>9 (%)</td>
<td>4 (%)</td>
</tr>
<tr>
<td>More than 7 drinks of alcohol a week</td>
<td>34/478</td>
<td>14.7 (%)</td>
<td>14 (%)</td>
</tr>
<tr>
<td>Estrogen</td>
<td>34/477</td>
<td>38.2 (%)</td>
<td>20.8 (%)</td>
</tr>
<tr>
<td>Obstructive airway disease</td>
<td>34/479</td>
<td>41.2 (%)</td>
<td>20.5 (%)</td>
</tr>
<tr>
<td>Sleep latency</td>
<td>21/322</td>
<td>28.1 ± 27.9 (min)</td>
<td>27.2 ± 32.5 (min)</td>
</tr>
<tr>
<td>Sleep efficiency</td>
<td>24/349</td>
<td>82.5 ± 9.3 (%)</td>
<td>81.9 ± 10.2 (%)</td>
</tr>
<tr>
<td>Apnea hypopnea index</td>
<td>24/345</td>
<td>12.1 ± 15.9/h</td>
<td>13.0 ± 15.2/h</td>
</tr>
<tr>
<td>Wake after sleep onset</td>
<td>24/345</td>
<td>56.8 ± 35.6 (min)</td>
<td>60.9 ± 41.1 (min)</td>
</tr>
<tr>
<td>Total sleep time</td>
<td>24/349</td>
<td>383.8 ± 71.6 (min)</td>
<td>384.4 ± 66.1 (min)</td>
</tr>
<tr>
<td>Arousal index</td>
<td>24/345</td>
<td>16.4 ± 9.2/h</td>
<td>17.1 ± 10.0/h</td>
</tr>
<tr>
<td>Sleepiness (Epworth Sleepiness Scale score ≥ 10)</td>
<td>34/478</td>
<td>23.5 (%)</td>
<td>25.3 (%)</td>
</tr>
<tr>
<td>Epworth Sleepiness Scale score</td>
<td>34/478</td>
<td>7.1 ± 4.3</td>
<td>6.9 ± 4.0</td>
</tr>
</tbody>
</table>

*denotes statistically significant (p < 0.05).

### Table 3—Multiple logistic regression demonstrating odds for development of RLS

<table>
<thead>
<tr>
<th>Odds ratio</th>
<th>95% C.I.</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estrogen</td>
<td>2.446</td>
<td>1.172 5.104</td>
</tr>
<tr>
<td>Obstructive airway disease</td>
<td>2.820</td>
<td>1.365 5.828</td>
</tr>
<tr>
<td>Age</td>
<td>1.007</td>
<td>0.970 1.046</td>
</tr>
</tbody>
</table>

*denotes statistically significant (p < 0.05).
especially those with late stages of COPD, and was associated with more severe airway obstruction, hypercapnia, and hypoxia.\(^18\) Furthermore, an increased prevalence of RLS has also been reported in patients with other pulmonary conditions such as sarcoidosis\(^19\) and pulmonary hypertension,\(^20\) as well as in lung transplant recipients.\(^21\)

While the nature of the association between COPD and RLS is unclear, it may be hypothesized that hypoxemia is a contributing factor. Notably, recent literature demonstrates that hypoxic pathways may be activated in RLS. Hypoxic pathways may also be involved in the RLS pathophysiology associated with the well-documented brain iron deficiency state.\(^22\) The hypoxic pathways, particularly hypoxia inducible factor-1 (HIF-1), increase both tyrosine hydroxylase and the vascular endothelial growth factor (VEGF). Both of these changes have been documented in RLS. Connor et al. reported elevated tyrosine hydroxylase and phosphorylated tyrosine hydroxylase, the rate-limiting enzyme in the synthesis of dopamine, in nigro-striatal system in subjects with RLS.\(^23\) Another autopsy study demonstrated up-regulation of VEGF expression, as well as the HIF, in the brain microvasculature and substantia nigra neurons of RLS subjects.\(^24\) Hypoxic pathway is also activated in diverse cell types in subjects with RLS.\(^25\) Increased capillary network and VEGF have also been noted in tibialis anterior muscle of subjects with RLS.\(^24\) It is possible that hypoxia associated with COPD or other lung disorders could activate similar pathways and contribute to RLS.

In the current study, participants with incident RLS had a higher prevalence of insomnia (Table 4). This is consistent with prior studies that demonstrate various sleep disturbances, including increased sleep latency, increased awakenings, difficulty in maintaining sleep, and lower sleep efficiency in RLS.\(^25,26\)

Incident RLS was also associated with daytime sleepiness and sleeping pill use. Overall, neither the group with or that without incident RLS was sleepy (mean ESS < 10 for both, 7.8 ± 3.2 vs. 6.6 ± 3.9, respectively; p = 0.09). However, the proportion of sleepy people (ESS > 10) was higher in the RLS group (38.2%) than the other group (22%). These results are consistent with past studies, which demonstrate a weighted mean ESS score of 8.4 in RLS population, with 30% of RLS subjects having an ESS score > 10.\(^27\) The relatively modest degree of sleepiness is not, however, concordant with the profound sleep loss and insomnia reported by these patients. Sleepiness appears to increase in RLS, but unlike insomnia does not occur for most RLS patients. And when sleepiness occurs, it appears to be less than expected for the degree of sleep loss. We did not find a difference in sleeping pill use between sleepy (ESS > 10) or non-sleepy participants. As suggested by Fulda and Wetter, the factors predicting sleepiness in a subgroup of RLS subjects need to be elucidated.\(^27\)

Further studies are also needed to understand the potential consequences such as decreased productivity and increased traffic accidents, and the resultant economic and social burden of RLS-related sleep abnormalities. Notably, a recent study showed a decrease in workplace productivity by 20% to 50% in RLS subjects.\(^28\)

The study has several limitations. Firstly, the participants were predominantly Caucasian, and results may not be generalizable to non-Caucasian populations. Secondly, RLS was diagnosed by questionnaire and not confirmed by physicians. We tried to decrease false positives by excluding participants with symptoms suggestive of an RLS mimic (leg cramp symptoms or with symptoms associated with walking/exercising throughout the day). However, in view of the relatively low positive-predictive value of questionnaire utilizing self-report of symptoms, it is likely that false positives were included in the RLS group. Thirdly, we did not have data regarding iron status, renal insufficiency, parity, and family history of RLS in our participants. Notably, altered iron metabolism is well-known correlate of RLS and it is possible that some or many of our findings could be explained by iron deficiency. However, in absence of these data, the contribution of altered iron homeostasis to the results is impossible to predict. Finally, all SHHS participants were older than 40 years of age, and the incidence and correlates of RLS in a younger population may be different.

In conclusion, to the best of our knowledge, this is the first community-based study looking at incidence of RLS. Estrogen use and obstructive lung disease were associated with higher likelihood of developing RLS, which in turn was associated with insomnia, increased daytime sleepiness, and higher use of sleeping pills. Considering the disease burden of RLS, these

<table>
<thead>
<tr>
<th>Table 4—Prevalence of different sleep complaints and sleeping pill use in Survey 2 (done in 2006) in participants with and without incident RLS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of participants</strong></td>
</tr>
<tr>
<td><strong>(Incident RLS/no RLS)</strong></td>
</tr>
<tr>
<td>Prevalence of insomnia</td>
</tr>
<tr>
<td>Prevalence of insomnia disorder (Insomnia with daytime consequences)</td>
</tr>
<tr>
<td>Trouble falling asleep</td>
</tr>
<tr>
<td>Wake up during the night and have difficulty getting back to sleep</td>
</tr>
<tr>
<td>Wake up too early in the morning and be unable to get back to sleep</td>
</tr>
<tr>
<td>Use of sleeping pill</td>
</tr>
<tr>
<td>Snore frequently</td>
</tr>
<tr>
<td>Sleepiness (Epworth Sleepiness Scale score ≥ 10)</td>
</tr>
<tr>
<td>Epworth Sleepiness Scale score</td>
</tr>
</tbody>
</table>

*denotes statistically significant (p < 0.05).
results have important clinical and public health implications. Further studies need to be designed looking at incidence of RLS in diverse populations, assessing the effect of parity, iron status, family history, and renal function on incident RLS and the socioeconomic burden associated with this condition.

REFERENCES


ACKNOWLEDGMENTS

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Restless Legs Syndrome: What Have We Learned from Prevalence Studies and How Will Incidence Studies Further Clinical Knowledge?


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"...it must be remembered that the intensity of the symptomatology presents notable spontaneous oscillations."
Coccagna and Lugaresi, Int J Neurol, 1981

Restless legs syndrome (RLS), also known as Willis-Ekbom disease, is now generally appreciated in the medical literature as common and complex. Over 50 prevalence studies, most published since 2005, have been crucial in defining many important clinical aspects. In this issue of JCSM is one of the first general population-based incidence studies of RLS.1 How are incidence studies different, and how might they further clinical knowledge?

First, let us review the “Top Five” agreed upon findings from prevalence studies of RLS.2 Number 5: Prevalence in females is about twice as high as in males, beginning in the late teens or 20s. Number 4: Association with other conditions. Individuals with RLS are at least twice as likely to have scores indicating a depressive or anxiety disorder. This has major clinical implications in that common treatments for these disorders can worsen RLS,3 and prevalence rates of 1.9% to 4.6% for moderate-to-severe RLS in European and North American studies.2 Without differential diagnosis prevalence estimates are about 1.25 to 2 times higher. Importantly, the 2012 revision of the International RLS Study Group (IRLSSG) diagnostic criteria will include differential diagnosis as a 5th essential criterion, as is also planned for the International Classification of Sleep Disorders (ICSD-3) and the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) in 2013.

Incidence rate is an estimate of the number of new cases in a population over a given time period, as compared to prevalence, which estimates the total number of cases in a population at a given time. Incidence presents a temporal dimension to the disorder, rather than a single “snapshot” of it. While both typically assess disease associations and neither can prove etiology, incidence studies are usually more useful in identifying potential etiologic factors because incidence studies can identify factors associated with the new onset of a disorder, such as weight gain in obstructive sleep apnea.

The paper by Budhiraja et al. in this issue of JCSM is a significant contribution, showing that new cases of RLS are common, a yearly incidence of 1.7% for moderate-to-severe RLS (defined as RLS occurring at least 5 days/month and associated with at least moderate distress).1 Extrapolated to the adult population in Tucson, Arizona, this represents six to seven thousand new cases a year; to the US, four million a year. With the severity definition as above and exclusion of some mimics, this study found prevalence rates of 4.1% at baseline and 7.7% at follow up, which are within typical prevalence rates for the US. These findings are comparable to the only other general-population incidence studies of RLS, both published in the last six months. In two different German population-based cohorts, Szentkiralyi...
et al. reported incidence rates of 9 and 22 per 1000 person-years (= annual incidence of 0.9% and 2.2%). In Japan, Kagimura et al. found an annual incidence rate of 0.8%.

This is remarkable due to a lower RLS prevalence of 2% in this Japanese cohort. Incidence was significantly higher for women in only one of the four cohorts.

Perhaps the most striking finding from these incidence studies thus far is the remission rate—that is, the percent of cases where RLS criteria were not met at the follow-up survey. This was about half of the cases when all four cohorts are considered. An explanation was not evident, although data analysis did not focus on this aspect. In contrast, a large clinical case series that included affected family members reported RLS symptoms over time as follows: progressive in 36%, stable in 41%, diminished in 15%, and remitted in 8%. Persistence of RLS in one of the incidence studies correlated with frequency (≥ 2x/month), but not with severity (by the IRLS rating scale) or consistently by age or gender. Clearly, factors related to persistence and remission need further study.

Multiple correlates of new onset RLS were examined in the Budhiraja et al. paper, with self-reported obstructive lung disease (asthma, chronic bronchitis, COPD, or emphysema) and estrogen use found to be independent risk factors. They cite six studies that support an increased prevalence of RLS for estrogen use found to be independent risk factors. They cite six studies that support an increased prevalence of RLS for estrogen use found to be independent risk factors. They cite six studies that support an increased prevalence of RLS for estrogen use found to be independent risk factors. They cite six studies that support an increased prevalence of RLS for estrogen use found to be independent risk factors. They cite six studies that support an increased prevalence of RLS for estrogen use found to be independent risk factors. They cite six studies that support an increased prevalence of RLS for estrogen use found to be independent risk factors.

Conversely, a large population-based study of COPD found significantly more COPD in individuals with RLS, as defined by spirometry. Clinically, it is important to note that peripheral neuropathy is common in COPD and can mimic RLS, but it probably does not fully account for the increased prevalence. Budhiraja et al. suggest hypoxemia as the pathophysiological mechanism by which RLS is exacerbated in obstructive lung disease, via influence on brain dopamine pathways. Of note, there is not good evidence that serum ferritin levels or systemic inflammation (which limits its iron availability) explain the increase. Importantly, RLS represents a potentially treatable cause of sleep disturbance and decreased QOL in COPD.

Estrogen’s role in the exacerbation and pathophysiology of RLS is less clear. RLS is more common in women than men and is very common during pregnancy. While estradiol levels were found to be higher in pregnant women with RLS compared to those without RLS in one study, this was not confirmed in another study. Similarly, hormone replacement therapy use was found to be significantly more frequent in women with RLS in one study but not in two others. In a randomized study of hormonal therapy for postmenopausal women, RLS complaints were significantly less for those on estrogen + progesterone compared to baseline, but not different for those on estrogen or progesterone alone. Perhaps there is a genetically predisposed subset of women for whom estrogen is an exacerbating factor, but this relationship may be diminished when all women are considered.

Future incidence studies of RLS are likely to reveal additional clinical findings and etiologic clues. Because incidence studies provide a temporal dimension, these studies could provide new insight into the observation by Cocagna and Lugarosi more than 30 years ago of “notable spontaneous oscillations”—by helping answer why.
REM sleep behavior disorder (RBD) was initially described by Schenck et al. in 1986 as a REM sleep related parasomnia of older men. It is now recognized as a disorder of all ages and both sexes, though still predominately occurring in men.\(^2\)\(^3\) In adults, there is clear association of RBD with synucleinopathic degenerative disorders such as Parkinson disease, dementia with Lewy bodies, and multiple system atrophy.\(^4\)\(^5\) The condition is also a side effect of treatment with medications such as selective serotonin reuptake inhibitors (SSRIs).\(^6\)\(^7\)

The hallmark of RBD is preservation of muscle tone during REM sleep, allowing for motor dream enactment that is sometimes aggressive or violent in nature, leading to injury to self, others, or property. The pathophysiologic mechanisms of this disorder have been discussed by Boeve et al.\(^8\)\(^9\) There is dysregulation of inhibitory brainstem motor mechanisms. While the exact pathway in humans has not been determined, neuroimaging data from the few published human RBD cases associated with structural lesions have implicated the dorsal midbrain and pons. Studies in cats suggest involvement of the subcoeruleus region, while those in rats point to the sublaterodorsal nucleus of the pons. Studies in cats suggest involvement of the subcoeruleus region, while those in rats point to the sublaterodorsal nucleus of the pons.

Polysomnographic monitoring reveals increased muscle tone in the chin, arm, and leg electromyograms (EMGs). On video surveillance, the patient can be witnessed having activity of the extremities and body, often in an aggressive manner, sometimes associated with yelling. While RBD has important implications in adults from the standpoint of prognosis, the long-term implications in childhood are unknown.

There have been several small case reports of children with RBD. In 1975 Barros-Ferreira et al. reported a case of an 8-year-old girl with a brainstem tumor who had clinical signs of RBD with polysomnographic evidence of atonia before RBD was a defined entity.\(^10\) Schenck et al. described a 10-year-old girl who had clinical RBD after removal of a midline cerebellar astrocytoma; interestingly, her healthy 8-year-old brother had similar aperiodic movements in NREM and REM but without clinical sleep disturbance.\(^11\) Turner et al. reported a 16-year-old male with narcolepsy and clinical RBD.\(^12\) Schenck and Mahowald described 17 narcoleptic patients with RBD, of whom 3 were between the ages of 10 and 19 years.\(^13\) Nevimulasova et al. documented 2 girls, ages 7 and 9, with narcolepsy-cataplexy.

**Study Objective:** To describe our experience regarding the clinical and polysomnographic features of REM sleep behavior disorder (RBD) in childhood.

**Methods:** This was a retrospective chart review of children and adolescents with RBD and REM sleep without atonia. Demographics, and clinical and polysomnographic information were tabulated. Our findings were compared with those in the existing literature.

**Results:** The 15 subjects identified (13 RBD and 2 having REM sleep without atonia) had a mean age at diagnosis of 9.5 years (range 3-17 years); 11/15 (73%) were male. Nightmares were reported in 13/15 and excessive daytime sleepiness in 6/15. Two children had caused bodily harm to bedmate siblings. Comorbidities, which were multiple in some subjects, included anxiety (8/15), attention deficit disorder (10/15), non-specific developmental delay (6/15), Smith-Magenis syndrome (1/15), pervasive developmental disorder (1/15), narcolepsy (1/15), idiopathic hypersomnia (1/15), and Moebius Syndrome (1/15). Abnormal MRI scans were seen in 5/8 evaluated subjects. Treatments consisted of clonazepam (10/15), melatonin (2/15), and discontinuation of a tricyclic agent (1/15), with a favorable response in 11 of 13. Two of 15 patients with REM sleep without atonia did not require pharmacotherapy.

**Conclusions:** RBD in children may be associated with neurodevelopmental disorders, narcolepsy, or medication use. It seems to be modestly responsive to benzodiazepines or melatonin. The etiology is distinct from that of common childhood arousal parasomnias and RBD in adults; congenital and neurodevelopmental disorders, medication effect, and narcolepsy coexisted in some, but none had an extrapyramidal neurodegenerative disorder.

**Keywords:** REM sleep behavior disorder, parasomnia, polysomnography

**Citation:** Lloyd R; Tippmann-Keikert M; Slocumb N; Kotagal S. Characteristics of REM sleep behavior disorder in childhood. J Clin Sleep Med 2012; 8(2):127-131.
and parasagittal 16-lead EEG. Scoring of the PSG was conducted initially by certified PSG technicians, followed by independent review by 2 certified sleep specialists (RL + MTP or SK + MTP), utilizing standard criteria described by Rechtschaffen and Kales or the American Academy of Sleep Medicine Manual for the Scoring of Sleep and Associated Events. For patients diagnosed since 2007, sustained tonic muscle activity in REM sleep was defined as a 30-sec epoch of REM sleep with ≥ 50% of the epoch having chin EMG amplitude greater than the minimum amplitude seen in NREM. Excessive transient muscle activity (phasic activity) in REM sleep was defined as 50% of an epoch of REM sleep containing bursts of transient muscle activity. These bursts had to be 0.1-5.0 seconds in duration and ≥ 4 times as high in amplitude as the background EMG activity. This is comparable to the criterion utilized by Sheldon et al., where increased tone was defined as lasting > 3 sec and < 15 sec as per Rechtschaffen and Kales.

In all, 22 patients were identified with REM without atonia. Four were excluded because of seizures (2 with no 16-lead EEG and 2 with very abnormal EEGs throughout), and 3 because of sleep disordered breathing, leaving 15 subjects (12 Caucasian, 2 half-African American, and 1 Hispanic). In these 15 patients, the mean age at diagnosis was 9.5 years (range 3.7 to 17.9 years), with 11 of 15 (73%) being male. Demographic information is listed in Table 1. Two patients presented with excessive daytime sleepiness only and were found to have REM without atonia. Nightmares were either reported or suspected in 13 of 15 patients. Parents of this group described sleep disruption with crying out and flailing of the arms and legs that was suspicious for dream enactment behavior. Ten of 13 had recollection of vivid frightening dreams involving violence or parasomnia.

**RESULTS**

Table 1—Demographics, presenting complaints, family history of parasomnia

<table>
<thead>
<tr>
<th>Subject</th>
<th>Gender</th>
<th>Presenting Sleep-Wake Complaint</th>
<th>Age at Onset</th>
<th>Age at RBD Diagnosis</th>
<th>Family History of Parasomnia</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>Fatigue</td>
<td>3</td>
<td>5</td>
<td>None</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>SIMD, EDS</td>
<td>5</td>
<td>14</td>
<td>None</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>Nightmares, awakenings</td>
<td>2</td>
<td>6</td>
<td>None</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>EDS</td>
<td>2</td>
<td>5</td>
<td>Somnambulism</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>Nightmares</td>
<td>4</td>
<td>11</td>
<td>Unknown</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>Nocturnal spells</td>
<td>1.5</td>
<td>3</td>
<td>None</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>EDS</td>
<td>11</td>
<td>16</td>
<td>None</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>Nocturnal awakenings</td>
<td>1</td>
<td>4</td>
<td>None</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>Nightmares, awakenings</td>
<td>6.5</td>
<td>7</td>
<td>None</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>EDS</td>
<td>6</td>
<td>9</td>
<td>Somnambulism</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>Nocturnal awakenings, EDS</td>
<td>15</td>
<td>18</td>
<td>None</td>
</tr>
<tr>
<td>12</td>
<td>M</td>
<td>EDS</td>
<td>10</td>
<td>12</td>
<td>None</td>
</tr>
<tr>
<td>13</td>
<td>M</td>
<td>SIMD</td>
<td>1</td>
<td>5</td>
<td>None</td>
</tr>
<tr>
<td>14</td>
<td>M</td>
<td>Fatigue, EDS</td>
<td>8</td>
<td>10</td>
<td>None</td>
</tr>
<tr>
<td>15</td>
<td>F</td>
<td>Fatigue, EDS</td>
<td>14</td>
<td>17</td>
<td>None</td>
</tr>
</tbody>
</table>

ADD, attention deficit disorder; ADHD, attention deficit hyperactivity disorder; DD, developmental delay; EDS, excessive daytime sleepiness; FTT, failure to thrive; LD, learning disability; NF-1, neurofibromatosis, type 1; OCD, obsessive compulsive disorder; PDD, pervasive developmental disorder; SIMD, sleep initiation and maintenance difficulties.
Characteristics of REM Sleep Behavior Disorder in Childhood

### Table 2—Comorbidities, neuroimaging, medication and treatment information

<table>
<thead>
<tr>
<th>Subject</th>
<th>Comorbid Sleep Diagnoses</th>
<th>Neurologic Diagnoses</th>
<th>MRI</th>
<th>Medications at Time of Evaluation</th>
<th>RBD Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NM, crying, restlessness, fatigue</td>
<td>None</td>
<td>Chiari 1</td>
<td>None</td>
<td>Clonazepam</td>
<td>Lost to FU</td>
</tr>
<tr>
<td>2</td>
<td>NM, hit sister, crying, EDS restlessness, nocturnal enuresis,</td>
<td>ADHD, Delayed secondary sexual maturation</td>
<td>None</td>
<td>DDAVP Imipramine</td>
<td>Iron sup discontinued Imipramine</td>
<td>Improved sleep, 5 month FU, exacerbated by SSRI</td>
</tr>
<tr>
<td>3</td>
<td>NM, restlessness, nocturnal enuresis, SIMD</td>
<td>Anxiety, Headaches, FTT, ADHD</td>
<td>Normal</td>
<td>Oxybutynin</td>
<td>Iron sup, Clonazepam</td>
<td>Improved sleep, 6 month FU</td>
</tr>
<tr>
<td>4</td>
<td>NM, crying, restlessness</td>
<td>Anxiety, PDD, autonomic dysregulation, FTT/G-tube</td>
<td>Pituitary cyst</td>
<td>Guanfacine, dextroamphetamine, sertraline, risperidone</td>
<td>Clonazepam</td>
<td>Improved sleep, 6 month FU</td>
</tr>
<tr>
<td>5</td>
<td>NM, EDS, hit brother, crying, restlessness,</td>
<td>ADHD, skull fracture, anxiety, PTSD with abuse</td>
<td>None</td>
<td>Guanfacine, Clonazepam</td>
<td>Improved sleep, 6 month FU</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Suspected NM, crying, SIMD, restlessness,</td>
<td>Speech apraxia, overactive impulsive, DD</td>
<td>Normal</td>
<td>None</td>
<td>Iron sup, Clonazepam</td>
<td>Improved sleep &amp; development at 3 &amp; 6 mo. FU</td>
</tr>
<tr>
<td>7</td>
<td>NM, crying, SIMD, restlessness,</td>
<td>Depression, ADD/LD, Moebius syndrome</td>
<td>Normal</td>
<td>None</td>
<td>SSRI, Clonazepam</td>
<td>Lost to FU</td>
</tr>
<tr>
<td>8</td>
<td>Suspected NM, restlessness, crying, EDS</td>
<td>ADHD, DD, Smith-Magenis syndrome</td>
<td>Venous anomaly</td>
<td>None</td>
<td>Clonazepam</td>
<td>Poor response</td>
</tr>
<tr>
<td>9</td>
<td>NM, crying, restlessness</td>
<td>ADHD, anxiety</td>
<td>None</td>
<td>Methylenidate, Quetiapine</td>
<td>Clonazepam,</td>
<td>Improvement w/Tx of anxiety, resolved on PSG at 18 mo</td>
</tr>
<tr>
<td>10</td>
<td>NM, crying, EDS, restlessness,</td>
<td>LD, Partial tumor resection Chemo/ radiation, VP shunt,</td>
<td>Pilocytic astrocytoma</td>
<td>None</td>
<td>Clonazepam</td>
<td>Improved sleep, 6 month FU</td>
</tr>
<tr>
<td>11</td>
<td>NM, snoring, erratic sleep schedule, EDS</td>
<td>Depression, anxiety, ADD</td>
<td>None</td>
<td>Fluoxetine, Melatonin</td>
<td>Improved sleep, 6 month FU</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>NM, restlessness, EDS/ narcolepsy</td>
<td>Obesity, difficulty concentrating</td>
<td>None</td>
<td>None</td>
<td>Ropinirole, Melatonin, Modafinil</td>
<td>Improved sleep, 3 month FU</td>
</tr>
<tr>
<td>13</td>
<td>NM, crying, restlessness</td>
<td>OCD, LD, ADHD anxiety, NF-1,</td>
<td>None</td>
<td>None</td>
<td>Clonazepam</td>
<td>FU pending</td>
</tr>
<tr>
<td>14</td>
<td>Nocturnal enuresis, EDS</td>
<td>Tourette, migraines, anxiety, NF-1,</td>
<td>Pilocytic Astro-cytoma</td>
<td>Gabapentin, Sumatriptan</td>
<td>None</td>
<td>Lost to FU</td>
</tr>
<tr>
<td>15</td>
<td>Mild snore, EDS/IH</td>
<td>Migraines, OCD</td>
<td>Normal</td>
<td>Fluvoxamine maleate, topiramate</td>
<td>None</td>
<td>Lost to FU</td>
</tr>
</tbody>
</table>

### Note
- ADD, attention deficit disorder; ADHD, attention deficit hyperactivity disorder; DD, developmental delay; EDS, excessive daytime sleepiness; FTT, failure to thrive; FU, follow up; IH, idiopathic hypersomnia; LD, learning disability; NF-1, neurofibromatosis, type 1; OCD, obsessive compulsive disorder; PDD, pervasive developmental disorder; PLMD, periodic leg movement disorder; SIMD, sleep initiation and maintenance difficulties; sup, supplement; TX, treatment.

Chasing; 2 had caused bodily harm to bedmate siblings. The 2 youngest (3 and 4 years) had speech apraxia and were unable to describe dream content.

Comorbid conditions and medications are listed in Table 2. They included anxiety (8/15), ADHD or inattentiveness (10/15), nonspecific developmental delay and learning disabilities (6/15), Smith-Magenis syndrome (1/15), pervasive developmental delay (1/15), non-accidental trauma with skull fracture in infancy (1/15), narcolepsy (1/15), idiopathic hypersomnia (1/15) and Moebius Syndrome (1/15). Magnetic resonance imaging of the brain was abnormal in 5/9 subjects who had undergone imaging, one with Chiari I malformation, 2 with midbrain pilocytic astrocytoma, one with a nonspecific vascular malformation in the right frontal region, and one with a pituitary cyst. Three patients were taking SSRIs. EEG monitoring was normal...
in all patients, with the exception of 2 who had the nonspecific finding of alpha intrusion.

Ten of the 15 patients were treated with clonazepam, with resolution of nightmares and abnormal motor behaviors in 8/10. Of the two who did not respond, one had Smith-Magenis syndrome with significant circadian rhythm disturbances; the other had severe anxiety with both day and night symptoms. Two of the 15 were treated with melatonin before bedtime and had resolution of nocturnal symptoms. One patient was treated with discontinuation of a concurrently administered tricyclic antidepressant, which initially improved her sleep symptoms. However, on follow-up 6 years later, she has been diagnosed with depression and ADHD and has had exacerbation of RBD symptoms on PSG monitoring. Two of the 15 patients did not require pharmacotherapy for REM without atonia on PSG in the absence of dream enactment behaviors.

**DISCUSSION**

Two children who presented with EDS only had REM without atonia and no history or demonstration of dream enactment. The remaining 13 children diagnosed with RBD, had unusual nocturnal motor behaviors described in various ways from restless sleep to frankly aggressive behaviors. Vocalization was common and consisted of yelling rather than the more common talking, crying, or mumbling observed in NREM parasomnias other than sleep terrors. Trying to distinguish NREM versus REM related parasomnias can be difficult based on history alone, but RBD was suspected in three of the patients who had a history consistent with dream enactment or injurious behaviors. In retrospect RBD could be considered in the differential diagnoses of all 13 affected patients, but other sleep disorders were considered initially, given the relatively low incidence of RBD.

Motor activity and recollection of vivid scary dreams can occur independently but together could be clues for consideration of RBD especially when motor activity is of a more aggressive nature. It is important to pay careful attention to the chin and leg electromyogram during review of the pediatric polysomnogram. Other PSG parameters were within normal limits with the exception of an elevated periodic limb movement index (> 5) in 6 of 15 patients. There are technical difficulties in diagnosing RBD in childhood, as seizures and obstructive sleep apnea can also lead to augmentation of muscle tone during sleep. While nocturnal seizures typically present in NREM sleep, they may occur rarely in REM sleep as well. The motor activity associated with seizures may be difficult to differentiate from RBD. Some children with sleep disordered breathing may also display excessive motor activity after an obstructive respiratory event, especially in REM sleep, making differentiation from RBD difficult.

Further, as pointed out by Thirumalai, et al., RBD may be prevalent in children with autism and other neurodevelopmental disorders. Unfortunately, these mentally handicapped children are frequently anxious and uncooperative; thus the diagnostically tool of nocturnal polysomnography is difficult to apply to the population that would likely benefit greatly from it. There was no correlation between onset of symptoms of neurodevelopmental disorders and age at diagnosis of RBD.

Fatigue and sleepiness were the most common presenting complaints and occurred in 9 of 15 patients. Two patients were diagnosed with a centrally mediated hypersomnia, one with narcolepsy and one with idiopathic hypersomnia. Long-term follow up is needed to see if any other patients develop an organic hypersomnia with RBD or REM without atonia being the earliest manifestation.

Learning difficulties, hyperactivity, and mood changes can be a manifestation of sleep disruption in children and were the most common comorbidities found in our study population. Neurobehavioral comorbidities have been described in adults with early onset RBD by Teman et al. who found a high incidence of past and present psychiatric diagnoses. It is difficult to determine the causal relationship, i.e., does the sleep disruption of RBD cause neurobehavioral problems, or do the neurobehavioral substrates predispose to RBD. Children with PTSD and abuse may have similar pathophysiologic mechanisms, though there would be increased risk of traumatic brainstem changes with physical abuse.

Medications which have previously been implicated in RBD (SSRIs and tricyclic antidepressants) were also identified in our patient population. Whether these are causative or trigger RBD in neurologically predisposed individuals warrants further investigation. RBD is associated with progressive, synucleinopathic extrapyramidal disorders in adults. In children, there seems to be no such association as congenital and neurodevelopmental disorders, medication effect, and narcolepsy predominate.

Some children (5 of 9 who had abnormal brain MRI scans) with structural lesions or risk for brainstem dysfunction were identified in our review. This was not unexpected in light of the described pathophysiologic mechanisms for RBD. While MRI imaging of the brain was performed for other reasons in our patients, it would be reasonable to consider obtaining an MRI if RBD is diagnosed.

Regarding treatment, most children were responded to a low dose (0.125 mg) of clonazepam, which was titrated upwards as needed, with only one child requiring a dose as high as 0.75 mg. Melatonin dosing ranged from 3 to 5 mg SR. The appropriate duration of therapy is unclear at this time. One child did demonstrate resolution on a follow-up PSG 18 months later, so periodic trials off medication would appear to be warranted, with monitoring for worsening upon discontinuation of medication.

Our study will hopefully increase the awareness of RBD in children and also advance the understanding of pathophysiologic of the condition. As has been recently been proposed by Luppi et al., RBD may be the end result of dysfunction in different pathways originating from the hypothalamus or brainstem. Three independent subgroups of patients with RBD/REM sleep without atonia can be seen in our study—those with narcolepsy or idiopathic hypersomnia (subjects #12, 15) likely had impaired hypocretin mediated activation of the ventral gigantocellular nucleus in the medulla, which in turn normally inhibits ventral spinal motor neurons. The second group was composed of subjects with autism and neurodevelopmental disorders, such as attention deficit disorder, Smith-Magenis syndrome, Moebius syndrome, neurofibromatosis type 1, and Tourette syndrome (subjects #2, 3, 5, 6, 7, 8, 9, 13, 14). Decreased activation of γ-hydroxybutyrate (GABA) mediated pathways is
common in children with autism. GABA is a key neurotransmitter in the ventral gigantocellular nucleus, and its deficiency might predispose to decreased ability to keep spinal motor neurons hyperpolarized during REM sleep. The third subgroup was composed of those receiving a selective serotonin reuptake inhibitor (subjects #2, 4, 11, 15). Serotonin suppresses REM sleep, but the exact nuclear locus and mechanism of this inhibition are unclear; nevertheless, the quality of REM sleep may be altered, with appearance of features of wakefulness/NREM sleep such as electromyographic tonus and motor behavior. It will be interesting to see if these pathophysiologic concepts can be applied to, and verified in, adults subjects with RBD as well.

**CONCLUSION**

RBD was previously believed to affect only older men. It is now known to be a disorder of both sexes and all ages, though more prevalent in older men. It most likely occurs more frequently in children and adolescents than previously recognized. Our study will hopefully increase the awareness of this parasomnia in childhood. Childhood RBD seems to fall into one of three categories:

1. Those with narcolepsy or idiopathic hypersomnia
2. Those who have received pharmacological agents that augment muscle tone during REM sleep, such as SSRI agents
3. Those with neurodevelopmental disorders or structural brainstem abnormalities such as autism, Smith-Magenis syndrome, Moebius syndrome, Chiari malformations, and midline tumors

RBD may be consequent inadequate inhibitory motor mechanisms in the brainstem during sleep. Some pathophysiologic mechanisms are proposed. The long-term implications of childhood RBD remain unknown. In the short term, it seems to be modestly responsive to benzodiazepines or melatonin.

**REFERENCES**


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**SUBMISSION & CORRESPONDENCE INFORMATION**

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**DISCLOSURE STATEMENT**

This was not an industry supported study. The authors have indicated no financial conflicts of interest.
REM sleep behavior disorder (RBD) is a parasomnia characterized by loss of normal muscle atonia in REM sleep. Patients may act out dreams, causing injury to themselves or their bed partner, resulting in relationship problems and decreased quality of life. Dream enactment in RBD occasionally has lethal results.

There are two main diagnostic categories of RBD. Secondary or symptomatic RBD occurs in association with comorbid neurological disease such as narcolepsy or neurodegenerative disease, most commonly Parkinson disease (PD), Lewy body dementia, and multiple system atrophy. Idiopathic RBD occurs in the absence of any associated neurological condition or medication.

RBD appears to be underdiagnosed, with prevalence estimated at 0.5% of the UK population. RBD occurs predominantly in men, the majority of patients presenting between 52 and 61 years of age.

RBD was first described in humans in 1986, and research in the area has accelerated in recent years, with advances in neuroimaging, and better recognition and understanding of the condition. However, an important clinical aspect of this disorder which has been neglected is diagnostic delay—a problem encountered in other sleep disorders, especially narcolepsy.

This study aimed to document the degree of diagnostic delay in RBD patients presenting to a tertiary referral center in the UK. The presence of comorbid sleep disorders and presence of a bed partner were hypothesized to reduce diagnostic delay.

Study Objectives: REM sleep behavior disorder (RBD) is a parasomnia in which normal muscle atonia of REM sleep is lost. The aim of this study was to confirm if diagnostic delay exists in RBD and identify any contributing factors.

Methods: A database was compiled of 49 patients with RBD seen at a tertiary referral center from 2005 to 2011 by retrospective review of referral letters and polysomnographic (PSG) reports. Patients with comorbid narcolepsy were excluded. A questionnaire was sent to investigate diagnostic delay, management, and comorbidities.

Results: Mean diagnostic delay was 8.7 ± 11 (median 4.5, IQR 1.75-11.75) years in 30 questionnaire responders. Common reasons for diagnostic delay included belief that symptoms were not serious enough to consult a doctor (59%), mild or infrequent occurrence of sleep behavior (56%), belief that symptoms may resolve (47%), and lack of knowledge of treatment options (47%). The bed partner was an important influence, with the decision to seek medical attention being made jointly by the patient and partner in 47%.

Conclusions: This study has demonstrated the existence of significant diagnostic delay in RBD, mainly due to lack of understanding of the disorder and its treatment by patients and members of the medical profession.

Keywords: REM sleep behavior disorder, parasomnias, sleep-related violence, delayed diagnosis, polysomnography, parkinsonian disorders, clonazepam, melatonin

Citation: White C; Hill EA; Morrison I; Riha RL. Diagnostic delay in REM sleep behavior disorder (RBD). J Clin Sleep Med 2012;8(2):133-136.

BRIEF SUMMARY

Current Knowledge/Study Rationale: REM sleep behavior disorder (RBD) is a potentially lethal parasomnia in which normal muscle atonia during rapid eye movement (REM) sleep is lost. Although diagnostic delay is documented in other sleep disorders, such as narcolepsy, diagnostic delay in RBD has not, thus far, been investigated.

Study Impact: This is the first study to focus specifically on diagnostic delay in RBD. The study demonstrates the existence of significant diagnostic delay, highlighting the need for greater awareness of the disorder and its treatment options amongst patients and medical professionals.

METHODS

A questionnaire (Appendix 1) was developed to explore aspects of diagnosis and management of RBD: symptom duration before diagnosis; factors delaying diagnosis; features of RBD contributing to seeking medical help; identification of potential triggers (stress, menstruation, medication); management of RBD—pharmacological and behavioral; medication adherence and side effects; control of RBD; and comorbidities including other sleep disorders. All questionnaires were anonymized and mailed to patients with a covering letter. Ethical approval is not required by NHS Lothian for case series or audit.

All patients with suspected RBD at a tertiary referral sleep center from 2005 to March 2011 were reviewed (n = 66). Patients were excluded if they had a diagnosis of RBD with narcolepsy (the etiology of RBD in this group may be multifactorial and differ from RBD without narcolepsy) or if they did not fulfil ICSD-2 criteria for diagnosis of RBD. The medical case
notes and polysomnographic sleep study (PSG) data of the remaining 49 patients were reviewed. Diagnosis was based on history (from both patient and partner where possible) and standard video PSG, in accordance with ICSD-2 criteria.

Statistical analysis was undertaken using SPSS17 (Chicago, Illinois). Student’s t-test, χ2 test, and Fisher exact test were used to assess parametric data, and Mann Whitney U test for non-normally distributed variables. All tests were 2-sided. Statistical significance was taken at p < 0.05. Results were reported as mean ± standard deviation (SD) or as a median with interquartile range (IQR 25-75). As not all patients answered every question, n is reported as the number of patients responding to each particular question.

RESULTS

Of 49 RBD patients included in the study, 44 (90%) were male and 5 (10%) female. The mean age at first referral was 55 ± 14 years for males and 36 ± 10 females (p = 0.006). Forty-one patients (36 male; 5 female) were diagnosed with idiopathic RBD, 6 (all male) with RBD secondary to neurological disease, and 2 (both male) secondary to medication (citalopram and bisoprolol; p = 0.6).

The response rate to the questionnaire was 65% (n = 32). Non-responders were significantly younger than responders (responders male 61 ± 9, female 38 ± 11 vs. non-responders (male 44 ± 16, female 34 ± 13, p < 0.0001), but did not differ significantly in terms of sex distribution or RBD type (data not shown).

Polysomnographic Data

PSG data were available for all 49 patients. Twenty-seven patients (55%) had evidence of dream enactment on video, with no significant sex (p = 0.16) or age (p = 0.41) differences. All patients were positive for REM sleep without atonia (RSWA).

Fifty-three percent of patients had an apnea-hypopnea index (AHI) > 15 per hour, indicative of moderate-to-severe sleep disordered breathing. This differed significantly by age (p = 0.005); those with AHI < 15 were younger than those with a higher AHI (47 ± 15 years v. 59 ± 13 years). There was no significant difference by sex (p = 0.17) or RBD type (p = 0.6).

Diagnostic Delay

Overall, the mean delay in diagnosing RBD was 8.7 ± 11 years (median 4.5, IQR 1.75-11.75; n = 30). There was a significant gender difference with women having a longer diagnostic delay than men (22 ± 11 years v. 7 ± 10 years, respectively; p = 0.03). There was no significant difference in diagnostic delay between the different types of RBD (p = 0.56): idiopathic RBD 9.4 ± 11.4 years, neurological RBD 8.7 ± 9.9 years, RBD secondary to medication 0.5 ± 0.7 years. Of the 32 people who responded, the most common reason for not seeking medical help was a belief that the symptoms were not serious enough to consult a doctor (59%; n = 19). Other common reasons were mild or infrequent occurrence of the sleep behavior (56%; n = 18), belief that the symptoms would eventually settle (47%; n = 15) and failure to realize that there might be treatment options for the condition (47%; n = 15). Thirty-one percent of patients (n = 10) were never asked about sleep by their doctor. There were no significant gender differences. There was no significant difference in reasons for diagnostic delay with RBD type or age, although those older than 50 years were more likely to experience delay due to their doctor not recognizing RBD, with a trend towards significance (p = 0.07). AHI and symptoms of possible obstructive sleep apnea did not play a role in bringing attention to RBD (p = 0.72): AHI < 15 8 ± 10 years (n = 12), AHI > 15 9 ± 12 years (n = 18).

Seventy-two percent (n = 23) of patients consulted a doctor specifically regarding their sleep behavior, with no significant age or gender differences observed. The decision to consult a doctor was most commonly a joint decision by both partners (47%, n = 15). All females making the decision to consult a doctor did so themselves (p = 0.023, n = 3); however, the low number of responders in this group should be noted.

Factors influencing the decision by patients to seek medical assessment of their nocturnal behavior are shown in Table 1. The most important factors cited by patients as having a strong or very strong impact on their decision to seek medical review were: (i) the partner noticing more regular abnormal sleep behaviors (88%, n = 23); (ii) the partner noticing an increase in the violence or force of the behavior (79%, n = 19); (iii) increased frequency of behavior (76%, n = 19); (iv) injury to the partner (55%, n = 12); and (v) increasing injury/violence (54%; n = 12). No significant age differences were evident (data not shown).

Table 1—Factors influencing patients’ decision to consult a doctor regarding abnormal sleep behavior

<table>
<thead>
<tr>
<th>Factor</th>
<th>Males (n = 29)</th>
<th>Females (n = 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injury to self</td>
<td>13</td>
<td>2</td>
</tr>
<tr>
<td>Injury to partner</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Increased frequency of behavior</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Increasing injury/violence</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Partner noticed more regular behavior</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Partner noticed increase in force of behavior</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Partner moved into separate bed</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>Impact on job</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Impact on relationship</td>
<td>8</td>
<td>0</td>
</tr>
</tbody>
</table>

Injury to self: No or small impact 13, Moderate impact 6, Strong or very strong impact 1. Injury to partner: No or small impact 2, Moderate impact 7, Strong or very strong impact 11. Increased frequency of behavior: No or small impact 0, Moderate impact 5, Strong or very strong impact 18. Increasing injury/violence: No or small impact 5, Moderate impact 4, Strong or very strong impact 11. Partner noticed more regular behavior: No or small impact 0, Moderate impact 2, Strong or very strong impact 22. Partner noticed increase in force of behavior: No or small impact 2, Moderate impact 2, Strong or very strong impact 18. Partner moved into separate bed: No or small impact 9, Moderate impact 2, Strong or very strong impact 6. Impact on job: No or small impact 11, Moderate impact 0, Strong or very strong impact 5. Impact on relationship: No or small impact 8, Moderate impact 6, Strong or very strong impact 7.
However, men were significantly more likely to consult on the basis of factors i and iii above (both $p = 0.002$).

The impact of RBD on the individual’s career was important in 53% of patients, with 9 of 17 patients rating this as having at least a small impact on their decision to seek treatment.

**Comorbidities**

Twenty-five of 31 responders (81%) reported that they had one or more comorbid sleep disorders. Thirteen patients (41%) had comorbid sleep apnea (defined as an AHI > 15), 8 of whom (62%) were using continuous positive airway pressure (CPAP) treatment. Six users (75%) found CPAP improved their RBD symptoms. No significant differences in mean diagnostic delay were found between those with or without comorbid sleep disorders (data not shown).

**Treatment**

Current treatment information was provided by 28 responders. Thirty-six percent were not on medication; 50% were taking clonazepam only, at doses in the range 0.5-2 mg per night; 4% were taking melatonin only, 2-6 mg per night; 7% were on combined clonazepam and melatonin therapy. One patient stated he was taking mirtazapine as his only treatment for RBD. In terms of medication use, there were no significant differences with age, gender or RBD type (data not shown).

**Lifestyle**

Thirty-eight percent of responders stated that lifestyle changes had been recommended to them ($n = 12$). Changes to sleeping arrangements were recommended to 14 of the 31 patients: sleeping in separate beds (19%), sleeping in a separate room (19%) and putting a guard around the bed (6%). Along with sleeping in separate beds or rooms, caffeine reduction (19%) was the most common lifestyle change. Other recommended changes included alcohol reduction and increased exercise (both 16%). Of the 12 patients who made lifestyle changes, 5 (42%) stated that lifestyle changes made a difference to their symptoms, and 6 (50%) stated they made no difference (1 patient did not answer). Lifestyle changes showed no significant association with sex, age, or RBD type (data not shown).

### DISCUSSION

This is the first study to specifically focus on diagnostic delay of an under-diagnosed and potentially lethal parasomnia. Our patient group is comparable to previously published series, with male predominance (90%) and mean age at first referral of 55 ± 14 years.

Although 72% of patients consulted specifically about their sleep behavior, the mean delay of 8.7 ± 11 years (median 4.5, IQR 1.75-11.75) shows that patients tolerated symptoms for some time before diagnosis. Additionally, 56% of patients classified their sleep behavior as initially mild/infrequent. The course of RBD often fluctuates, and these patients may delay seeking medical attention due to these periods of normal or only mildly disrupted sleep.

In this study, many patients initially dismissed their behavior as neither serious nor medically important. However, a large proportion consulted specifically about their sleep (72%, n = 23), showing the cumulative effect of chronic sleep disorders causing major disruption to patients’ lives. Common factors for delaying diagnosis included the belief that the symptoms were not serious enough to consult a doctor (59%) and failure to realize that treatment options were available (47%). Heightening public awareness of sleep disorders could reduce diagnostic delay and improve quality of life with many RBD, patients, but this is a challenging agenda.

The impact of RBD on the bed partner appeared to be the major driver for patients to seek medical advice. Four patients (13%) were unaware of their sleep behavior, thus delaying diagnosis. If the impact of RBD on the bed partner is more significant than the impact on the patient independently, under-diagnosis of patients who are single or have mild sleep behaviors may occur.

The absence of daytime symptoms may also delay presentation. In narcolepsy, patients with cataplexy have a shorter diagnostic delay than those without. If RBD patients do not have dramatic nocturnal symptoms such as violent dream enactment or injurious behavior, the condition may be tolerable. Dream enactment behavior is found in the normal, healthy population but is usually less violent and frequent than RBD. If this behavior is considered “subclinical RBD,” this may explain why increased frequency and severity of RBD symptoms were a strong or very strong prompt for presentation to a doctor in the majority of patients.

Diagnostic delay can be attributed to obstacles in health service provision. Lack of access to PSG can hinder diagnosis. In this study, failure to recognize the presence of RBD in primary care contributed to diagnostic delay in 31% of patients ($n = 10$). Thorough history-taking with direct questioning about RBD symptoms is required. To this end, an RBD screening questionnaire has been developed, and its routine use in clinical practice (particularly in at-risk populations such as PD) could aid prompt diagnosis. This may have particular bearing upon delayed recognition of neurodegenerative disease. Postuma et al. found a mean RBD diagnostic delay of 7.2 years, with 26 of 93 patients developing either PD or dementia at 11.5 ± 6.6 years from onset of symptoms.

No significant difference was found in mean diagnostic delay between those with or without comorbid sleep disorders, which suggests that the impact of RBD on the individual and their partner may be an independent factor in a patient’s diagnostic delay, not influenced by the presence of comorbidities.

Clonazepam, a sedating benzodiazepine which reduces phasic EMG activity, is considered first-line therapy in RBD, although the evidence for its use is not strong and it should only be used in selected groups. Clonazepam contributed to improvement in 77% ($n = 10$) of patients. This is lower than the quoted figure from some studies, but supports others. Only one responder was taking melatonin, the other major treatment option, and he reported that it improved his symptoms. Melatonin can be used either alone or in conjunction with clonazepam, but again there have been few studies examining its use in detail. Two of our patients were taking a combination of melatonin and clonazepam, and both stated this had improved their symptoms.

A number of limitations should be considered when interpreting the results of this study, namely small sample size, the
use of an unvalidated, self-administered questionnaire, and possible responder bias. In future studies, we would consider the use of a partner questionnaire in tandem with the patient questionnaire to further explore partner aspects of diagnostic delay.

This study has demonstrated the existence of significant diagnostic delay in RBD, mainly due to lack of knowledge of the disorder and its treatment options among both patients and medical professionals. We suggest that increasing knowledge of sleep disorders by targeting medical education and public awareness, particularly with RBD, would improve patients’ quality of life and limit potential harm to the patient and their bed partner. Additionally, it has been suggested that RBD is an early marker of neurodegenerative disease, and identifying these patients may allow for improved treatment with neuroprotective agents in the future.1,28,31

REFERENCES


SUBMISSION & CORRESPONDENCE INFORMATION

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DISCLOSURE STATEMENT

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Spanish Translation and Cross-Language Validation of a Sleep Habits Questionnaire for Use in Clinical and Research Settings

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Study Objectives: To translate, back-translate and cross-language validate (English/Spanish) the Sleep Heart Health Study Sleep Habits Questionnaire for use with Spanish-speakers in clinical and research settings.

Methods: Following rigorous translation and back-translation, this cross-sectional cross-language validation study recruited bilingual participants from academic, clinic, and community-based settings (N = 50; 52% women; mean age 38.8 ± 12 years; 90% of Mexican heritage). Participants completed English and Spanish versions of the Sleep Habits Questionnaire, the Epworth Sleepiness Scale, and the Acculturation Rating Scale for Mexican Americans II one week apart in randomized order. Psychometric properties were assessed, including internal consistency, convergent validity, scale equivalence, language version intercorrelations, and exploratory factor analysis using PASW (Version18) software. Grade level readability of the sleep measure was evaluated.

Results: All sleep categories (duration, snoring, apnea, insomnia symptoms, other sleep symptoms, sleep disruptors, restless legs syndrome) showed Cronbach α, Spearman-Brown coefficients and intercorrelations ≥ 0.700, suggesting robust internal consistency, correlation, and agreement between language versions. The Epworth correlated significantly with snoring, apnea, sleep symptoms, restless legs, and sleep disruptors) on both versions, supporting convergent validity. Items loaded on 4 factors accounted for 68% and 67% of the variance on the English and Spanish versions, respectively.

Conclusions: The Spanish-language Sleep Habits Questionnaire demonstrates conceptual and content equivalency. It has appropriate measurement properties and should be useful for assessing sleep health in community-based clinics and intervention studies among Spanish-speaking Mexican Americans. Both language versions showed readability at the fifth grade level. Further testing is needed with larger samples.

Keywords: Spanish translation/validation, sleep health disparities, psychometrics, Hispanic Mexican Americans, sleep habits and culture care

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Recent reviews reported the need for studies of sleep among Hispanics.24,25 This research need is time-critical because Hispanic Americans (e.g., Cuban, Mexican, Puerto Rican) are the second largest and fastest growing minority group and currently constitute 15% of the population; Mexican Americans represent the largest subgroup, comprising 66.7% of the Hispanic American population.26 Many factors combine to make sleep disorders research a high priority among Hispanics in the United States. Hispanics experience the following: higher rates of unemployment and less earned income when employed; greater likelihood of living in poverty; less likelihood of graduating from high school; greater food insecurity; are under- or uninsured; reduced leisure-time physical activity; acculturation pressures, immigration bias, limited access to care, diverse cultural constructions of health and illness; and higher rates of chronic conditions, including obesity, type 2 diabetes, and hypertension.27,28 These factors are associated with disordered or disrupted sleep in other cultural and racial/ethnic groups; thus studying sleep in Hispanics should enrich the overall understanding of their social, emotional, and physical well-being.

A major issue in the adequate and appropriate assessment of sleep disorders of Hispanics is that of language.29 Spanish is the second most common language in the United States and is the primary language spoken at home by more than 34 million people aged 5 or older.26 Disparities in quality and access to care have reportedly been narrowing for all groups except Hispanics due, in part, to language barriers.30 The aim of this paper is to report the psychometrics of a rigorously translated, back-translated, and cross-language validated version of the Sleep Heart Health Study Sleep Habits Questionnaire.31 The development of the Spanish version was guided by Brislin’s Translation Model to ensure that the instrument was linguistically and conceptually equivalent and suitable for use in clinical and research settings with Spanish-speaking Mexican Americans.32-34

**METHODS**

**Participants**

**Translation and Back-Translation**

Translators and back translators (N = 6) provided written informed consent (English and Spanish) prior to participating in the study and completed demographic information, including age, sex, race/ethnicity, years of education, current occupation and a questionnaire listing prior translation experience. Each translator was compensated $250 for their time.

**Cross-Language Validation**

Bilingual men and women volunteers (N = 50) were recruited by flyers posted in community, college and university settings, libraries, places of worship, community centers, and primary care clinics in neighborhoods with a high census of Mexican American/Hispanic residents. Participants completed demographic and health history data in English. English and Spanish versions of the Sleep Habits Questionnaire, the Epworth and an acculturation rating scale were completed 7 to 10 days apart in counterbalanced (randomized) order.35 Participants were provided written informed consent (English and Spanish) prior to participation and were compensated $30 for their time. All facets of this study were reviewed and approved by the university institutional review board.

**Instruments**

**Demographics**

Demographic information included age, sex, race/ethnicity, educational level, marital status, smoking status, alcohol, caffeine, prescription and other drug use, health history, and self-reported height and weight to calculate body mass index (BMI).

**The Sleep Habits Questionnaire**

The Sleep Habits Questionnaire was developed to survey Sleep Heart Health Study (SHHS) participants; a description of the study has been previously published.31 The Sleep Habits Questionnaire includes validated questions and response scales selected from the instruments of the Wisconsin Sleep Cohort Study24 and the Cleveland Family Study.25 The Cleveland study has demonstrated the validity and internal consistency of these questions among Caucasian and African American adults.30 The Sleep Habits Questionnaire includes instructions to complete it without discussing the questions with anyone, including a spouse. The questionnaire addresses several categories of sleep disorders examined in this study: (1) sleep duration (2 items); (2) snoring (3 items); (3) breathing pauses/apnea (4 items); (4) insomnia symptoms (3 items); (5) sleep symptoms, including insufficient sleep, daytime sleepiness, nightmares, leg jerks, leg cramps, and need for sleep aids (12 items); (6) sleep quality, including perception of depth and duration of sleep (3 items); and (7) restless legs syndrome (10 items). There is an additional category that assesses potential sleep disruptors, including sinusitis, room noise, temperature, pain, and frequent toileting (9 items).

The questionnaire can be used in its entirety for a comprehensive overview of subjective reports of sleep disorders, or in categories (e.g., snoring, insomnia symptoms, restless legs syndrome) for focused assessment in clinical and research settings. Snoring is ascertained by the question “Have you ever snored (now or at any time in the past)?”32 with possible responses “yes,” “no,” or “don’t know.” Participants answering “yes” were asked, “How often do you snore now?” with possible responses including “rarely–less than one night a week,” “sometimes–1 or 2 nights a week,” “frequently–3 to 5 nights a week,” “always or almost always–6 or 7 nights a week,” or “don’t know.” Breathing pauses during sleep are ascertained by the question, “Are there times when you stop breathing during sleep?”33 with possible responses “yes,” “no,” or “don’t know,” or if a physician ever told them they have sleep apnea. Participants are also asked how often there is someone nearby while they are sleeping, with possible responses of “never,” “sometimes,” and “always.” The questionnaire includes “Sleep Symptoms” containing 2 somnolence statements, “Feel excessively (overly) sleepy during the day,” and “Feel unrested during the day, no matter how many hours of sleep you had,” as well as “Not getting enough sleep,” the insomnia statements, “Trouble falling asleep,” “Wake up during the night and have difficulty resuming sleep,” and “Wake up too early in the morning and be unable to resume sleep,” and “Bad dreams or nightmares,” rated
on a 5-point scale from “Never” to “Almost Always.” These symptom questions have been widely used (e.g., the World Health Organization). Questions used to identify RLS were drawn from SHHS-2 and reflect NIH diagnostic criteria for the syndrome including description, frequency, time of day, active/ at rest status, and degree of discomfort.

**Epworth Sleepiness Scale**

The Epworth Sleepiness Scale is a validated self-completion tool that asks subjects to rate the likelihood of falling asleep in several common situations and was included with the sleep habits items. Sleepiness using the Epworth is assessed by the question, “What is the chance that you would doze off or fall asleep in each of the following situations?” followed by a list of 8 situations including “riding as a passenger in a car,” “watching TV,” and others. For each situation, possible responses include 4 ordinal categories ranging from “no chance” to “high chance.” The Epworth is a unitary scale, with a Cronbach α of 0.88 and test-retest reliability over 5 months of $r = 0.82$ in previous studies. The Epworth was used in tandem with the Sleep Habits Questionnaire to examine convergent validity. The Epworth measure, translated for this study in the same manner as the Sleep Habits Questionnaire, also demonstrated high reliability for the English (0.780) and Spanish (0.771) versions. The Spearman-Brown and intraclass coefficient for the English/Spanish translated Epworth demonstrated robust correlations as well (0.928 and 0.907, respectively).

**Acculturation**

Language serves as a general indicator of level of acculturation. The 30-item Acculturation Rating Scale for Mexican Americans II (ARSMA-II; English and Spanish versions) identifies language familiarity, usage, preference, ethnic identity, generation, reading, writing, cultural exposure, and ethnic interaction. It has an internal reliability of 0.88 and test-retest reliability of 0.72. Persons who score high in the “Traditional” category are more likely to identify with the Mexican culture, whereas persons with high scores in the “Assimilated” category identify more with the United States culture. High scores in the “Bicultural” category suggest the person identifies with both the Mexican and United States cultures.

**Procedures**

This English to Spanish translation of the Sleep Habits Questionnaire was guided by the adaptation of Brislin’s Translation Model to address cultural and functional equivalence, to make the translation and validation process more efficient and to ensure the integrity of the process. Cultural equivalence implies similarity of meaning and construct relevance across cultures.

The translation and validation model is displayed in Figure 1. In Step 1, 3 independent translations were made simultaneously in a blinded fashion from source (English) to target (Spanish) language by 3 bilingual health providers of Mexican heritage with Spanish as their first language. During Step 2, each target language version of the questionnaire was back-translated in a blinded fashion to the source language by 3 new volunteer bilingual health providers of Mexican heritage with Spanish as their first language. In Step 3, a team member whose first language was Spanish completed a content analysis of the translations and back-translations to aid in assuring credibility, trustworthiness, and transferability of translation. Where differences in meanings were identified in the back-translations, the principal investigator and bilingual team members met with the translators and back-translators involved in Steps 1 and 2 to review differences and adapt the target language version (Spanish) in order to achieve the most accurate culturally equivalent mean-
Table 1—Characteristics of the cross-language validation studied sample (N = 50)

<table>
<thead>
<tr>
<th>Sex, n (%)</th>
<th>Male</th>
<th>24 (48)</th>
<th>Female</th>
<th>26 (52)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>Mean ± SD</td>
<td>38.8 ± 12.0</td>
<td>Range</td>
<td>20 – 62</td>
</tr>
<tr>
<td>Education, years</td>
<td>Mean ± SD</td>
<td>14.9 ± 3.4</td>
<td>Range</td>
<td>6 – 22</td>
</tr>
<tr>
<td>Marital Status, n (%)</td>
<td>Married/Partnered</td>
<td>34 (68)</td>
<td>Single/Divorced</td>
<td>16 (32)</td>
</tr>
<tr>
<td>Race/Ethnicity, n (%)</td>
<td>Hispanic (Mexican origin)</td>
<td>45 (90)</td>
<td>Hispanic (Other Latin America)</td>
<td>2 (4)</td>
</tr>
</tbody>
</table>

Readability Scoring

The Spanish translated instrument was assessed for grade level readability using the Huerta Reading Ease Score.45 Readability scores may range from 0 (most difficult) to 100 (least difficult) to read. Scores from 90 to 100 indicate very easy reading at an estimated 5th grade level; scores from 80 to 90 suggest easy reading at an estimated 6th grade level; while scores from 0 to 30 indicate very difficult reading at an estimated graduate college level.

Statistical Analyses

Differences in demographic and health history variables for the cross-language validation participants included analysis of variance for continuous variables and $\chi^2$ for nominal variables. Internal consistency reliability and conceptual equivalence were evaluated using Cronbach $\alpha$, Spearman-Brown, and intraclass coefficients. We used a standardized item $\alpha$ to measure the Spearman-Brown coefficients. Intraclass coefficients are used for test-retest reliability to determine the stability between English and Spanish versions when sample size is small.46 Spearman-Brown and intraclass coefficients will approach 1.0 when there is no variance within items. Spearman-Brown and intraclass coefficients of 0.80 to 0.89 are considered adequate, while coefficients $\geq$ 0.90 suggest good reliability.46,47 A one-way random effects model was used for intraclass correlations, which conceptualizes each observed subject as a component of subject factor; therefore, the intraclass correlation is interpreted as the proportion of subject variance associated with differences among the scores of the subject. Inter-correlations among sleep variables were conducted using correlation coefficients to determine convergent validity with the Epworth Sleepiness Scale. The criterion level for coefficient $\alpha$ was set at $\geq$ 0.70 to retain an item in an adequate scale. Exploratory factor analysis utilized principal component analysis without rotation to reduce the number of items to validate item consistency between the 2 language versions. For exploratory purposes, analysis included communalities $\geq$ 0.400 to determine central factors.48,49 All data analyses were performed using PASW (Version 18).

RESULTS

Translator and Back-translator Participant Characteristics

All 6 translators were of Mexican American heritage with Spanish as their first language. Two men and one woman translated the Sleep Habits Questionnaire from English to Spanish; then 2 other women and one other man reverse-translated the questionnaire from Spanish back to English. Translators and back-translators were 19 to 55 years of age. Their current occupations included physician, nurse, clinic staff members who work with Spanish-speaking patients, and 2 certified hospital translators (one translator and one back-translator). The bilingual experts and lay translators who reviewed the final translated version were no-cost volunteers of Mexican descent with Spanish as their first language.

Cross-Language Validation Participant Characteristics

Characteristics of the cross-language validation participants are displayed in Table 1. Ethnic distribution for the bilingual participants (N = 50; 52% women; mean age 38.8 ± 12 years) showed 90% to be of Mexican origin, 4% Central or South American, and 6% non-Hispanic white. The mean education level was 14.9 ± 3.4 years. The range of 6 to 22 years for education suggests a broad sampling for educational achievement. The largest subgroups of participants (n = 23 on the English and n = 25 on the Spanish versions) scored in the “Traditional” category on the ARSMA II,42 suggesting strong identification with Mexican culture. The remainder of the participants (n = 12 and n = 11 on the English and Spanish versions, respectively) scored in the “Bicultural” category, indicating strong identification with the cultures of both Mexico and the United States, and “Assimilated” (n = 13 and n = 12 on the English and Spanish versions, respectively), indicating strong identification with United States.
Spanish Translation of Sleep Habits

Internal consistency and correlation results for the Sleep Habits Questionnaire are displayed in Table 3. All sleep variables except sleep quality showed robust Cronbach $\alpha \geq 0.700$. The 3-item sleep quality category examines short versus long, light versus deep, and non-restful versus tranquil sleep on a 5-point Likert-type scale and showed a Cronbach $\alpha$ of 0.583 and 0.685 for the English and Spanish versions, respectively, suggesting moderate reliability. All categories of sleep variables for both language versions were highly correlated, with Spearman-Brown and intraclass correlations $> 0.800$, suggesting strong and comparable translation of the English to Spanish measures.

Proportion of Participants Comprising English and Spanish Sleep Disorder Categories

Table 4 displays the proportion of cross-language validation participants with and without sleep disorders by categories. Proportions were consistent between English and Spanish language versions, respectively, for short (18% vs. 20%) and long (14% each) sleep duration on weekdays, short (4% vs. 2%) and long (40% vs. 44%) sleep duration on weekends, snoring (40% vs. 44%), sleep apnea (8% each), insomnia symptoms (24% each), sleep symptoms (22% vs. 26%), sleep quality (28% vs. 32%), and restless legs (10% vs. 12%).

The means and standard deviations for the Epworth were 7.3 ± 4.8 (range 0–19) for the English version and 7.2 ± 4.5 (range 0–18) for the Spanish version. Proportions of par-
participant with an Epworth score >10 designating excessive daytime somnolence were 10% and 12% for the English and Spanish versions, respectively.

Convergent Validity Within and Between Language Versions

English Version Intercorrelations

Correlations for both language versions are displayed in Table 5. Correlations for the English language version are shown below the diagonal. For the English version, weekday sleep duration (average in h) was significantly negatively correlated with insomnia symptoms (r = -0.426, p < 0.01), sleep symptoms (r = -0.538, p < 0.01), sleep disruptors (r = -0.466, p < 0.01), and restless legs (r = -0.327, p < 0.05), and significantly positively correlated with sleep quality (r = 0.354, p < 0.05). Weekend sleep duration (in h) was negatively correlated with sleep symptoms (r = -0.304) and sleep disruptors (r = -0.328, each p < 0.05) and restless legs (r = -0.462, p < 0.01). Snoring was significantly positively correlated with apnea (r = 0.412, p < 0.01), sleep symptoms (r = 0.291, p < 0.05), and sleep disruptors (r = 0.306, p < 0.05). Apnea was negatively correlated with sleep quality (r = -0.317, p < 0.05). Insomnia symptoms were positively correlated with other sleep symptoms (r = 0.805, p < 0.01), sleep disruptors (r = 0.675, p < 0.01), and restless legs (r = 0.403, p < 0.01), and negatively correlated with sleep quality (r = -0.401, p < 0.01). Sleep symptoms (e.g., insufficient sleep) were positively correlated with sleep disruptors (r = 0.824, p < 0.01) and restless legs (r = 0.540, p < 0.01) and negatively correlated with sleep quality (r = -0.405, p < 0.01). Sleep quality was negatively correlated with sleep disruptors (r = -0.347, p < 0.01). Sleep disruptors were positively correlated with restless legs (r = 0.586, p < 0.05) and negatively correlated with sleep quality (r = -0.347, p < 0.05).

Spanish Version Intercorrelations

Correlations for the Spanish language version are shown above the diagonal in Table 5. Weekday sleep duration (in h) was negatively correlated with insomnia symptoms (r = -0.399, p < 0.01), sleep symptoms (r = -0.426, p < 0.01), and sleep disruptors (r = -0.334, p < 0.05), and positively correlated with sleep quality (r = 0.415, p < 0.01). Weekend sleep duration was negatively correlated with insomnia symptoms (r = -0.295, p < 0.05), sleep symptoms (r = -0.301, p < 0.05), and restless legs (r = -0.411, p < 0.01), and positively correlated with sleep quality (r = 0.295, p < 0.01). Snoring was positively correlated with sleep disruptors (r = 0.312, p < 0.05). As with the English version, apnea was negatively correlated with sleep quality (r = -0.319, p < 0.05). Insomnia symptoms were positively correlated with other sleep symptoms (r = 0.748, p < 0.01), sleep disruptors (r = 0.640, p < 0.01), and restless legs (r = 0.396, p < 0.01), and negatively correlated with sleep quality (r = -0.426, p < 0.01). Consistent with the English version, sleep symptoms were positively correlated with sleep disruptors (r = 0.820, p < 0.01) and restless legs (r = 0.609, p < 0.01) and negatively correlated with sleep quality (r = -0.456, p < 0.01); sleep disruptors were positively correlated with restless legs (r = 0.622, p < 0.01) and negatively correlated with sleep quality (r = -0.385, p < 0.01).

Approximately 87% (39 of 45) of the correlations between the English and Spanish versions were consistent in direction and magnitude of the relationships. Differences noted showed snoring to be negatively (English) and positively (Spanish) associated with weekend sleep duration; however, neither finding was significant. Snoring was significantly positively associated with apnea and sleep symptoms in English, while the Spanish version showed trends toward significance for apnea (r = 0.259, p = 0.07) and sleep symptoms (r = 0.247, p = 0.08).

Convergent Validity Between Language Versions

The Epworth scale provided convergent validity for 5 of 8 of the sleep categories (63%) for both language versions. For the English and Spanish versions, respectively, the Epworth was significantly positively correlated with snoring (r = 0.325 and r = 0.309, each p < 0.05), apnea (r = 0.340 and r = 0.354, each p < 0.05), sleep symptoms (r = 0.477 and r = 0.510, each p < 0.01), sleep disruptors (r = 0.505, p < 0.01 and r = 0.344, p < 0.05), and restless legs (r = 0.330 and r = 0.303, each p < 0.05). The Epworth was also noted to be significantly negatively correlated with weekday sleep duration (r = -0.334, p < 0.05) and positively associated with insomnia symptoms (r = 0.290, p < 0.05) on the English, but not the Spanish versions; however, the directions of the correlations for both versions were the same.

Construct Validity: Exploratory Factor Analysis

Exploratory factor analysis was conducted using principal components analysis without rotation that resulted in 4 factors.
Table 5—Intercorrelations among sleep variables and comparisons with Epworth for convergent validity

<table>
<thead>
<tr>
<th></th>
<th>Sleep Duration (Weekdays)</th>
<th>Sleep Duration (Weekends)</th>
<th>Snoring</th>
<th>Apnea</th>
<th>Insomnia Symptoms</th>
<th>Sleep Symptoms</th>
<th>Sleep Quality</th>
<th>Sleep Disruptors</th>
<th>Restless Legs</th>
<th>Epworth</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep Duration (Weekdays)</td>
<td>1</td>
<td>0.581**</td>
<td>0.012</td>
<td>-0.226</td>
<td>-0.399**</td>
<td>-0.426**</td>
<td>0.415**</td>
<td>-0.334**</td>
<td>-0.233</td>
<td>-0.161</td>
</tr>
<tr>
<td>Sleep Duration (Weekends)</td>
<td>0.593**</td>
<td>1</td>
<td>0.068</td>
<td>-0.180</td>
<td>-0.295*</td>
<td>-0.301*</td>
<td>0.295</td>
<td>-0.269</td>
<td>-0.411**</td>
<td>-0.068</td>
</tr>
<tr>
<td>Snoring</td>
<td>-0.070</td>
<td>-0.086</td>
<td>1</td>
<td>0.259</td>
<td>0.120</td>
<td>0.247</td>
<td>-0.139</td>
<td>0.312*</td>
<td>0.141</td>
<td>0.309*</td>
</tr>
<tr>
<td>Apnea</td>
<td>-0.087</td>
<td>-0.208</td>
<td>0.412**</td>
<td>1</td>
<td>-0.030</td>
<td>0.189</td>
<td>-0.319*</td>
<td>0.243</td>
<td>0.204</td>
<td>0.356*</td>
</tr>
<tr>
<td>Insomnia Symptoms</td>
<td>-0.426**</td>
<td>-0.238</td>
<td>0.236</td>
<td>0.182</td>
<td>1</td>
<td>0.748**</td>
<td>-0.426**</td>
<td>0.640**</td>
<td>0.396**</td>
<td>0.192</td>
</tr>
<tr>
<td>Sleep Symptoms</td>
<td>-0.538**</td>
<td>-0.304*</td>
<td>0.291*</td>
<td>0.237</td>
<td>0.805**</td>
<td>1</td>
<td>-0.456**</td>
<td>0.820**</td>
<td>0.609**</td>
<td>0.510**</td>
</tr>
<tr>
<td>Sleep Quality</td>
<td>0.354*</td>
<td>0.247</td>
<td>-0.057</td>
<td>-0.317*</td>
<td>-0.401**</td>
<td>-0.405**</td>
<td>1</td>
<td>-0.385*</td>
<td>-0.157</td>
<td>-0.034</td>
</tr>
<tr>
<td>Sleep Disruptors</td>
<td>-0.466**</td>
<td>-0.328*</td>
<td>0.306*</td>
<td>0.277</td>
<td>0.675**</td>
<td>0.824**</td>
<td>-0.347**</td>
<td>1</td>
<td>0.622**</td>
<td>0.344*</td>
</tr>
<tr>
<td>Restless Legs</td>
<td>-0.327*</td>
<td>-0.462**</td>
<td>0.199</td>
<td>0.265</td>
<td>-0.403**</td>
<td>0.540**</td>
<td>-0.100</td>
<td>0.586**</td>
<td>1</td>
<td>0.303*</td>
</tr>
<tr>
<td>Epworth</td>
<td>-0.334*</td>
<td>-0.221</td>
<td>0.325*</td>
<td>0.340*</td>
<td>0.290*</td>
<td>0.477**</td>
<td>0.057</td>
<td>0.505**</td>
<td>0.330*</td>
<td>1</td>
</tr>
</tbody>
</table>

Bolded are significant between the Epworth and items from the Sleep Habits Questionnaire for construct validity. *Correlation is significant at the p < 0.05 level (2-tailed). **Correlation is significant at the p < 0.01 level (2-tailed). Correlations for English are below the diagonal and correlations for Spanish are above the diagonal.

The factor loadings for items in the questionnaire are displayed in Table 6. Items 4 and 5 from each language version loaded on Factor 1 (Sleep Duration); Items 13, 14, 15 (Snoring) and 17, 18, 19 (Breathing Pauses/Apnea) loaded on Factor 2 (Snoring and Apnea); Items 21 a-e and h-j loaded on Factor 3 (Sleep Symptoms); Items 24 a-b, 25, 26, 27, 28, 29, 30, 30a, and 32 loaded on Factor 4 (Restless Legs). The bedtime, time to sleep, time arising in the morning, napping, reasons for napping, sleep quality, insufficient sleep, use of sleep aids, nightmares/bad dreams, sleep disruptors, age at onset of restless legs, and physician diagnosed restless legs did not centrally load on any of the factors. Based on these factor loadings, the structure of the Spanish version of the Sleep Habits Questionnaire is similar to the structure of the English version which supports construct validity across language. Categories included in Factors 2, 3, and 4 also correlated strongly with the Epworth Sleepiness Scale, which provided convergent validity. The Epworth was significantly negatively correlated with sleep duration on the English version, but not the Spanish version, or for weekend sleep duration on both language versions.
Table 6—Exploratory factor analysis of the Sleep Habits Questionnaire in English and Spanish

<table>
<thead>
<tr>
<th>Factor Structure</th>
<th>Item number and description</th>
<th>English</th>
<th>Spanish</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor 1: Sleep Duration</td>
<td>#4 Hours of sleep during the week</td>
<td>-0.498</td>
<td>-0.417</td>
</tr>
<tr>
<td></td>
<td>#5 Hours of sleep on weekends</td>
<td>-0.535</td>
<td>-0.493</td>
</tr>
<tr>
<td>Factor 2: Snoring and Apnea</td>
<td>#13 Snoring frequency</td>
<td>0.765</td>
<td>0.714</td>
</tr>
<tr>
<td></td>
<td>#14 Snoring loudness</td>
<td>0.776</td>
<td>0.662</td>
</tr>
<tr>
<td></td>
<td>#15 Snoring over time</td>
<td>0.640</td>
<td>0.432</td>
</tr>
<tr>
<td></td>
<td>#17 Witnessed apnea</td>
<td>0.711</td>
<td>0.586</td>
</tr>
<tr>
<td></td>
<td>#18 Self-reported apnea</td>
<td>0.802</td>
<td>0.613</td>
</tr>
<tr>
<td></td>
<td>#19 Apnea frequency</td>
<td>0.778</td>
<td>0.658</td>
</tr>
<tr>
<td>Factor 3: Sleep Symptoms</td>
<td>#21a Difficulty falling asleep</td>
<td>0.418</td>
<td>0.452</td>
</tr>
<tr>
<td></td>
<td>#21b Difficulty staying asleep</td>
<td>0.567</td>
<td>0.597</td>
</tr>
<tr>
<td></td>
<td>#21c Awakening early with inability to resume sleep</td>
<td>0.431</td>
<td>0.573</td>
</tr>
<tr>
<td></td>
<td>#21d Un-refreshing (non-restorative) sleep</td>
<td>0.503</td>
<td>0.559</td>
</tr>
<tr>
<td></td>
<td>#21e Excessive daytime sleepiness</td>
<td>0.400</td>
<td>0.606</td>
</tr>
<tr>
<td></td>
<td>#21f Nasal stuffiness/obstruction at night</td>
<td>0.467</td>
<td>0.588</td>
</tr>
<tr>
<td></td>
<td>#21g Leg jerks</td>
<td>0.754</td>
<td>0.775</td>
</tr>
<tr>
<td></td>
<td>#21h Nasal stuffiness/obstruction at night</td>
<td>0.577</td>
<td>0.598</td>
</tr>
<tr>
<td>Factor 4: Restless Legs Syndrome (RLS)</td>
<td>#24a Urge to move legs</td>
<td>0.841</td>
<td>0.836</td>
</tr>
<tr>
<td></td>
<td>#24b Unpleasant/uncomfortable feelings in legs</td>
<td>0.887</td>
<td>0.851</td>
</tr>
<tr>
<td></td>
<td>#25 Frequency of symptoms</td>
<td>0.857</td>
<td>0.823</td>
</tr>
<tr>
<td></td>
<td>#26 Degree of discomfort from symptoms</td>
<td>0.878</td>
<td>0.917</td>
</tr>
<tr>
<td></td>
<td>#27 Activity when symptoms occur</td>
<td>0.722</td>
<td>0.696</td>
</tr>
<tr>
<td></td>
<td>#28 Symptoms worsen when reeding</td>
<td>0.764</td>
<td>0.733</td>
</tr>
<tr>
<td></td>
<td>#29 Symptoms improve when walking</td>
<td>0.861</td>
<td>0.827</td>
</tr>
<tr>
<td></td>
<td>#30 Time of day symptoms occur</td>
<td>0.892</td>
<td>0.798</td>
</tr>
<tr>
<td></td>
<td>#30a If day and night, worse at night</td>
<td>0.406</td>
<td>0.524</td>
</tr>
<tr>
<td></td>
<td>#32 Family history of symptoms</td>
<td>0.640</td>
<td>0.637</td>
</tr>
</tbody>
</table>

Readability Scores for the Spanish-translated Sleep Habits Questionnaire

The Spanish-translated instrument was assessed in sections of sleep categories. Readability scores for the instrument were 89.1 (6th to near 5th grade reading level) for the snoring category, 91.7 for the sleep quality category, 95.7 for the for sleep duration category, 99.1 for the apnea category, and 99.7 for the restless legs syndrome category and the Epworth Sleepiness Scale (all 5th grade reading level).43 Readability scores could not be calculated for the sleep items that address insomnia symptoms, sleep symptoms (e.g., unrefreshing sleep, leg jerks), or sleep disruptors (e.g., nighttime toileting, noise in the surroundings). These categories, arranged with Likert-type scales for frequency of symptoms, do not provide enough words or sentences with punctuation marks to allow for readability calculations.

DISCUSSION

Overall, the Spanish-translated version of the Sleep Habits Questionnaire demonstrated acceptable psychometric characteristics. Both language versions showed high levels of content validity and conceptual equivalency. The rigorous translation process and review of the Spanish version by experts found the items and content to be conceptually similar to the English version. The Spearman-Brown and intraclass correlation coefficients, which measure the homogeneity of the scales, indicated strong correlation and agreement between language versions. The Epworth provided convergent validity for a majority of sleep categories on both language versions, and exploratory factor analyses provided construct validity across language. Thus, the Sleep Habits Questionnaire is suitable for use with clinical patients and in community-based studies that examine various categories of self-identified sleep disorders.

All Sleep Habits Questionnaire categories except for sleep quality demonstrated strong internal consistency reliability for both language versions, ranging from 0.734 (English) and 0.731 (Spanish) for the 2-item sleep duration variable to 0.900 (English) and 0.890 (Spanish) for the 10 restless legs items. The 3-item sleep quality category that assessed perception of length, depth, and satisfaction with sleep showed only moderate internal consistency for the English (0.583) and Spanish (0.685) versions. The quality of sleep items are determined by using a 5-point scale with short/long, light/deep, and poor/good anchors. This scaling feature may not provide enough definition or information for persons whose first language is not English to respond adequately to these items. Future studies will need to examine these items with additional bilingual and Spanish-only speakers to determine if the psychometrics for the sleep quality items remain consistent or fluctuate with other groups. Nevertheless, the coefficients between language versions are robust, suggesting good correlation and agreement. Furthermore, the readability scores suggest that each of the sleep categories, as well as the Epworth, are suitable to a fifth- to sixth-grade reading level. Translation issues and years of schooling have been posited as barriers to adequate health assessment of Spanish-speaking Hispanics in the United States.27-29

Proportions of participants with the presence of sleep disorders by categories showed consistency in reporting between language versions. Percentages of participants who report sleep disorders provide a foundation for prevalence rates among Spanish-speaking Mexican Americans. A majority of these rates are consistent with population studies undertaken in the United States, including the rates for insomnia symptoms, weekday short sleep duration, and, in particular, the high rates for snoring among the Hispanics in this study with Hispanics in other studies.4-5,8,16,24,25 Age, education, and acculturation category were not significantly associated with any of the sleep categories. Future studies will need to determine if these and other socioeconomic status variables, including naturalization or U.S.-born status, may play roles in the type and severity of sleep disorder category among Mexican American Hispanics.

Intercorrelations for both language versions show similar and consistent relationships and directions among variables that support what might be expected in clinical and research settings for persons with sleep disturbances, suggesting good criterion validity. For example, persons who snore would be more likely to have apnea and report daytime sleepiness (positive correlations). Persons who experience more sleep disruption due to noisy nighttime environment, pain, or the need for frequent toileting would be more likely to report shorter weekday and weekend sleep durations and poor sleep quality (negative correlations) and greater reports of insomnia symptoms, other sleep
between the English and Spanish versions. Notably, the comprehensiveness of this questionnaire relevant to the number and type of sleep categories have identified variables and their direction for both English and Spanish speakers that can be examined in future clinical and research studies. These covariates include insomnia symptoms, other sleep symptoms (e.g., insufficient or unrefreshing sleep), restless legs, daytime somnolence, and sleep disrupters.

Reasons for the limited number of English and Spanish variables (6 of 45) that did not significantly correlate are not known, but the lack of power due to the small sample size may have contributed to the lack of significance. In addition, there may have been unexpected circumstances that could have affected these few correlations. For example, snoring showed a positive correlation in English and a negative correlation in Spanish with weekend sleep duration. Weekend events or changes in weekend activities might possibly have influenced differences in snoring responses during the 7- to 10-day time frame. Future studies of this sort will need to include a brief question regarding change in lifestyle habits in repeated measures studies.

Items in the Spanish version loaded on the same factors in the English version (Sleep Duration, Snoring and Apnea, Sleep Symptoms, and Restless Legs). The four factors explained 68% of the variance on the English version and 67% of the variance on the Spanish version. Loadings for inclusion in this exploratory factor analysis were set at ≥ 0.400 to determine central factors, while loadings > 0.600 are considered high. Findings from this analysis suggest strong loadings for the measured variables most associated with each of the four extracted factors. Factor loadings and variance accounted for are consistent between language versions, supporting the construct validity between the English and Spanish versions.

Limitations

Limitations to this study include sample size and bilingual Spanish speakers of predominantly Mexican heritage residing in the Southwest. This sample of 50 bilingual volunteers is sufficient for initial analyses of reliability and validity, but is not adequate to demonstrate the critical relationships between sleep health and other comorbid conditions that should be studied in the Hispanic population. The design of a cross-language validation study is not appropriate for establishing the test-retest reliability of the Spanish version, providing normative data, or assessing cultural equivalence across other Spanish-speaking ethnic groups from Central and South America, Cuba, and Puerto Rico. Education and acculturation, included as a prelude to examining sociocultural factors on the development of this Spanish language version did not have an impact on the sleep categories for either language version. Future studies will need to examine if these and other socioeconomic, immigration, and access to care factors may be linked to type and severity of sleep disorder category among Mexican American Hispanics.

Acculturation status, age, and recruitment locations (clinics, community-based neighborhood centers and programs, and academic milieu) suggest the participants are representative of the general Mexican American population residing in Maricopa County, Arizona, who are clinic patients or who participate in community-based research studies. Notably, however, the high educational achievement reflected in their mean years of education (14.9) is not representative of academic levels generally seen among Mexican Americans (10th grade). Nevertheless, their range of education (6 to 22 years) suggests that the translated measure is relevant to a broad span of Spanish-speaking learners with a minimum of sixth grade education. These shortcomings will need to be addressed in future studies to determine the settings and populations in which use of the new instrument is most appropriate. Future studies will also need to determine item equivalence with confirmatory factor analysis.

Summary

This study examined the psychometric properties of the English to Spanish translated, back-translated, and cross-language validated Sleep Habits Questionnaire with bilingual community-dwelling adults predominantly of Mexican American heritage with Spanish as their first language. Results demonstrate that the Sleep Habits Questionnaire is a psychometrically sound measure with robust correlations within and between language versions for a broad range of subjective sleep disorder categories that can be self-administered in community and clinic settings. The Epworth provided convergent validity for the snoring, apnea, sleep symptoms, restless legs, and sleep disrupters categories, while loadings from exploratory factor analysis supported the structure of both English and Spanish versions of the instrument. The English version of the Sleep Habits Questionnaire has been used ubiquitously in clinical and population-based studies. Findings indicate that the Spanish-language version has robust and appropriate measurement properties and may be useful for assessing sleep health in community-based and intervention studies among Spanish speakers residing in the Southwest.

REFERENCES

Obstructive sleep apnea (OSA) is present in 2% to 4% of middle-aged adults and causes intermittent hypoxia, sleep fragmentation, and changes in sleep architecture. Continuous positive airway pressure (CPAP) is the recommended treatment for the majority of patients with OSA and has been shown to improve daytime sleepiness and mood, and reduce treatment for the majority of patients with OSA. In addition to improving health and quality of life for patients, spouses of OSA patients also report benefits from treatment, which means studying factors associated with adherence and represent moderately warm and controlling interpersonal behavior. Interventions to increase spousal collaboration in CPAP may improve adherence.

Study Objectives: Continuous positive airway pressure (CPAP) improves sleep and quality of life for both patients with obstructive sleep apnea (OSA) and their spouses. However, few studies have investigated spousal involvement in treatment adherence. Aims of this observational study were to assess perceptions of spousal involvement and evaluate associations between involvement and adherence.

Methods: Spousal involvement in CPAP adherence was assessed in 23 married male OSA patients after the first week of treatment. At 3 months, 16 participants completed a second assessment of spousal involvement. Types of involvement assessed included positive (e.g., encouraging), negative (e.g., blaming), collaboration (e.g., working together), and one-sided (e.g., asking). An interpersonal measure of supportive behaviors was also administered at 3 months to evaluate the interpersonal qualities of spousal involvement types. Objective CPAP adherence data were available for 14 participants.

Results: Average frequency of spousal involvement ratings were low for each involvement type and only negative spousal involvement frequency decreased at 3 month follow-up (p = 0.003). Perceptions of collaborative spousal involvement were associated with higher CPAP adherence at 3 months (r = 0.75, p = 0.002). Positive, negative and one-sided involvement were not associated with adherence. Collaborative spousal involvement was associated with moderately warm and controlling interpersonal behaviors (affiliation, r = 0.55, p = 0.03, dominance r = 0.47, p = 0.07).

Conclusions: Patients reported low frequency but consistent and diverse perceptions of spousal involvement in CPAP over the first 3 months of treatment. Perceptions of collaborative spousal involvement were the only type associated with adherence and represent moderately warm and controlling interpersonal behavior. Interventions to increase spousal collaboration in CPAP may improve adherence.

Keywords: Obstructive sleep apnea, continuous positive airway pressure, adherence, relationship quality, social support

Citation: Baron KG; Gunn HE; Czajkowski LA; Smith TW; Jones CR. Spousal involvement in CPAP: does pressure help? J Clin Sleep Med 2012;8(2):147-153.

BRIEF SUMMARY
Current Knowledge/Study Rationale: Patients often report spousal influence on treatment-seeking in OSA but few studies have systematically evaluated spousal involvement in treatment. The goal of this study was to evaluate how spouses are involved in CPAP treatment and the effects of perceived involvement on adherence to continuous positive airway pressure.

Study Impact: This study will inform sleep professionals about the ways spouses are involved in treatment and results suggest that increasing collaborative spousal involvement in CPAP use may improve adherence.

However, higher marital conflict and seeking treatment because of a spouse (rather than self-referral) have been associated with poorer adherence. The discrepancy in these findings may be due to the specific nature of spousal interactions with respect to CPAP use. In other words, the type of involvement may be integral to CPAP adherence. At this point, no study has systematically evaluated spousal involvement in CPAP. Elsewhere in the health literature, spousal involvement has been related to improvements in a range of health behaviors, including diet, exercise, and visiting the doctor, particularly when the involvement is viewed as positive and collaborative. The most effective types of spousal involvement include providing encouragement or helping make...
changes to facilitate the behavior. On the other hand, negative
types of involvement, such as criticism, have been associated
with psychological distress or ignoring the spouses’ request for
behavior change.\textsuperscript{18,22-25} In one study, feeling supported by the
spouse has been associated with higher CPAP adherence during
the subsequent night in patients with more severe OSA.\textsuperscript{26} How-
ever, the methodology used in the study (daily questionnaires)
limited the number of spousal behaviors assessed, and it was
not clear what type of supportive behavior was most beneficial.
Further research to describe and understand how spouses are
involved in improving CPAP treatment is vital to the design of
couples-based interventions, as well as for providing evidence-
based recommendations to OSA patients and their spouses.

The goal of this observational longitudinal study was to eval-
uate the frequency and nature of spousal behaviors aimed at in-
fluencing CPAP adherence over the first 3 months of treatment.
The second aim was to determine if perceptions of spousal in-
volve ment are associated with adherence. We hypothesized that
more frequent perceptions of positive and collaborative spous-
al involvement aimed at CPAP adherence would be associated
with higher adherence and that more frequent perceptions of
negative involvement would predict poorer adherence.

\section*{Methods}

Participants

Participants were recruited from patients undergoing over-
night diagnostic polysomnograms at an academic sleep dis-
orders center. Eligibility criteria included the following: age
18-65 years, male gender, diagnosis of OSA, married or living
with a romantic partner $\geq$ 1 year, and CPAP naive. Exclusionary
criteria included the following: spousal use of CPAP, chronic
obstructive pulmonary disease, oxygen therapy, congestive
heart failure, cardiomyopathy, psychosis, and use of other con-
current treatments for OSA (bariatric surgery, upper airway
surgery, and oral appliance). Patients with comorbid sleep dis-
orders (insomnia n = 2, periodic limb movements and/or rest-
less leg syndrome n = 8) were not excluded. The protocol was
approved by the University of Utah institutional review board,
and all patients completed written informed consent.

Procedure

All patients underwent 2 overnight polysomnograms: a diag-
nostic study and a CPAP titration. Patients were enrolled in the
study after the diagnostic study confirmed an OSA diagnosis.
All patients attended a physician’s appointment for education
and treatment planning as well as an individual 30-min mask
fitting and education session with a sleep technician prior to
the CPAP titration. The type of CPAP mask was determined by
the patient preference and assessment of fit by the technician.
Brand of CPAP machine, use of heated humidification, and set-
tings were determined by the sleep physician. Patients complet-
ed baseline questionnaires (demographics, relationship quality)
on the evening of their CPAP titration. Spousal involvement
was measured using a questionnaire administered by mail 7-10
days after starting CPAP to assess spousal involvement in the
first week of CPAP use. At 3 months, patients were contacted
again to complete follow-up measures (spousal involvement
and interpersonal behavior associated with CPAP). CPAP ad-
herence data were downloaded by the patients’ home care com-
pany at 3 months. Multiple attempts were made by the home
care company and research team to contact patients missing
adherence reports and arrange to retrieve the adherence data by
mail or in person.

Measures

Demographics were collected prior to treatment initiation in-
cluding self-reported age, marital status, income, and employ-
ment status.

Relationship quality was measured by the support and con-
FLICT subscales of the Quality of Relationship Inventory (QRI).\textsuperscript{27}
The support subscale contains items related to emotional sup-
port in the marriage, such as “To what extent could you count
on your spouse for help with a problem?” and “To what extent
could you count on this person to listen to you when you are
very angry at someone else?” The conflict subscale contains
items related to the frequency and extent of marital conflict,
such as, “How angry does your spouse make you feel?” and
“How often do you have to work hard to avoid conflict with
your spouse?” Subscales were scored as the average of the 7
support items and average of the 12 conflict items. Cronbach’s
$\alpha$ for the support and conflict subscales ranged from the 0.70s to
0.90s, indicating adequate internal consistency; test-retest reli-
ability correlations ranged from 0.48 to 0.79.\textsuperscript{28,29}

Perceptions of spousal involvement in CPAP was measured
using an adapted version of a 25-item measure of strategies
couples use to influence each other’s health behavior.\textsuperscript{30,31} The
original measure was developed using existing power/control
measures as well as focus groups of couples discussing influ-
encing each other’s health, then subscales were assigned by
6 independent raters. In this study, we excluded 3 items from
this measure because these items were not relevant to CPAP
treatment (e.g., offering to change with the patient, making
the change for the patient). Then, we adapted the remaining items
in the scale to specifically reference perceptions of spousal
efforts to influence CPAP use. Patients rated how often their
spouse used each strategy over the past week. Response options
ranged from 1 (never) to 5 (often, several times per day). We
also re-named the subscale titles for easier interpretation (with-
out changing the scoring of the measure). Subscales included
collaborative (e.g., changed something at home, discussed
CPAP), one-sided (e.g., gave space, dropped hints), positive
(e.g., told me she was happy), and negative (e.g., tried to evoke
negative emotion, withdrew). Some behaviors were combina-
tions of these categories. For example, helping make changes
at home to get the participant to use CPAP is considered posi-
tive and collaborative, whereas making the patient scared of
the consequences of not using CPAP is considered negative and
one-sided. Therefore, categories were not mutually exclusive
and many items were coded in two categories. Cronbach’s $\alpha$
for this scale (in the original form) has been reported as adequate
(0.72 to 0.78.)\textsuperscript{30} In our sample, the Cronbach’s $\alpha$ for the 4 scales
was similar (0.72-0.80). The adapted measure was administered
7-10 days after initiation of CPAP treatment and at 3-month
follow-up.

Patients completed an adapted version of the Support Actions
Scale-C\textsuperscript{32} at 3-month follow-up as a measure of interpersonal
qualities of behaviors associated with CPAP use. This measure was included to provide more specific information on the nature of interpersonal behaviors that were occurring between spouses in regards to CPAP. Based on the interpersonal circumplex, the measure included items that measure supportive behavior based on the 2 main axes of interpersonal behavior: affiliation and control.33 Thirty-two items of the 64-item measure were selected for use in this study. Items were selected by factor loadings on the octant scores and their relevance to transactions regarding CPAP. The instructions for this measure were adapted to interactions regarding CPAP use. Responses ranged from A (very unlikely) to E (very likely). Two dimension (affiliation and control) scores were computed. Excellent structural integrity and construct validity of the original 64-item measure with other measures of social support and circumplex measures of interpersonal behavior have been reported.32

Adherence to CPAP was measured using a memory card located in the CPAP apparatus which recorded the number of minutes per night the CPAP machine was turned on with the mask in place. Adherence downloads were ordered by the clinic’s CPAP follow-up technician approximately 90 days after patients began treatment. Downloads were conducted by mail or in person by the patients’ durable medical equipment company. Adherence was defined as average hours of CPAP use per night.

Data Analysis

Data were analyzed using SPSS (v. 19). Descriptive statistics were computed to describe the sample characteristics, frequency and intensity of spousal involvement subscales. Change in spousal involvement from week 1 to 3-month follow-up was evaluated using paired t-tests. Correlations between spousal involvement week 1 and adherence at follow-up were calculated using Pearson correlation coefficients. Significance was defined as p values < 0.05 on two tailed tests.

<table>
<thead>
<tr>
<th>Table 1—Baseline participant characteristics, N = 23</th>
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<tbody>
<tr>
<td>Mean (SD) or N (%)</td>
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<tr>
<td>Age, Mean (SD)</td>
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<td>&lt; 12 grade</td>
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<td>some college or associate’s degree</td>
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<td>bachelor’s degree</td>
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<tr>
<td>graduate degree or more</td>
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<td>Length of Marriage, Mean (SD)</td>
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<td>Share bed with spouse every night, N (%)</td>
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<td>Apnea hypopnea index, Mean (SD)</td>
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<tr>
<td>Range</td>
</tr>
<tr>
<td>Adherence at 3 months*, Mean (SD)</td>
</tr>
<tr>
<td>Range</td>
</tr>
<tr>
<td>Self report of “good adherence” to physician at follow-up***</td>
</tr>
</tbody>
</table>

*Objective adherence data were available for 14 patients with baseline data.

p values are > 0.20 for all variables. *One participant did not respond to this question. **Objective adherence data were available for 12 of 16 patients in the group with both time points and 2 of 7 patients with baseline spousal involvement measures only. ***Notes from follow-up with a sleep physician were available for 16 of 16 participants with both time points and 6 of 7 participants with baseline only.
Average adherence was 5.6 h (SD 1.3), and average number of days recorded was 88.4 (SD 45.9). Missing adherence data were due to inability to contact the participant to arrange a download of adherence data (n = 5), lack of placement of adherence card (n = 2), lack of adherence recording capabilities in the CPAP machine (n = 1), and moving out of state (n = 1).

Characteristics of Perceived Spousal Involvement

Ratings of perceived spousal involvement from week 1 are listed in Table 3. Results demonstrate a range of commonly endorsed items from all subscales. Of the 25 items on the spousal involvement scale, the most commonly rated items were from the positive scale, such as “Changed something at work or home to get me to use CPAP,” reported by 83% of patients with an average rating of 2.3 (approximately 1-2 times in the past week), and “Told me she was happy I was using CPAP,” reported by 65% of patients with an average rating of 2.2 (approximately 1-2 times in the past week). However, negative items were also endorsed by many patients. “Tried to make me scared of the consequences of not using CPAP” was reported by 57% of patients and had an average rating of 1.9 (approximately 1-2 times in the past week).

Change in Perceived Spousal Involvement over 3 Months

Average perceived spousal involvement scores total scores and subscores at 1 week and 3 months are presented in Figure 1.
Average rating of within each subscore was low, in the range of less than 1-2 times per week. Perceived spousal involvement frequency at 3-month follow-up was only different for the negative subscore, which was lower at 3 months ($p = 0.003$). When perceived spousal involvement types were scored as either present or absent over the previous week, patients endorsed 5.75 items on the spousal involvement scale over the first week, and 4 items on the spousal involvement scale at 3-month follow-up ($p = 0.07$).

**Associations Between Perceived Spousal Involvement and Adherence**

Perceived collaborative spousal involvement was positively correlated with adherence at 3 months ($r = 0.75, p = 0.002$, Figure 2). Total spousal involvement scores, positive, negative, and one-sided involvement were not associated with adherence.

**Associations Between Spousal Involvement, Ratings of Relationship Quality, and Interpersonal Behavior**

There was a trend for an association between perceived collaborative spousal involvement and ratings of relationship support ($r = 0.388, p = 0.07$), but this score was not associated with relationship conflict. With respect to interpersonal support behaviors (Support Actions Scale-C, adapted to focus on CPAP use), perceived collaborative spousal involvement was positively correlated with the affiliation scale ($r = 0.55, p = 0.03$) and demonstrated a trend with the dominance scale ($r = 0.47, p = 0.07$). This suggests the interpersonal quality of collaborative spousal involvement is warm yet has some degree of control. Total perceived spousal involvement score and other subscales (positive, negative, and one-sided) were not associated with relationship support, conflict, or interpersonal ratings.

**DISCUSSION**

The goals of this study were to systematically evaluate spousal involvement in CPAP treatment and the effects of such involvement on adherence. We found that perceived spousal involvement was present in the majority of male OSA patients at low but consistent levels between 1 week and 3 months after initiation of CPAP therapy. Patients reported their spouse was involved in CPAP approximately 4-6 different ways occurring 1-2 times per week. Despite this low level, patients reported experiencing a variety of involvement types from their spouse. For example, the majority of patients reported positive and collaborative involvement, such as changing things at home to facilitate adherence. However, over half of the sample also reported their spouse used negative types of involvement at least once during the week, such as trying to evoke fear over the consequences of not using CPAP. We predicted that both the positive and collaborative involvement types would be associated with adherence. Consistent with this hypothesis, we found that patients with higher perceptions of collaborative involvement in week 1 had higher CPAP adherence at 3-month follow-up. We did not find an association between those involvement types that were positive, (including collaborative and one-sided items), negative, or one-sided.

In addition to the spousal involvement measure, we also used a measure of interpersonal behavior to more precisely define the qualities of collaborative involvement. Results of this analysis demonstrated that collaborative spousal involvement is associated with the perception of warm and controlling interpersonal behaviors (e.g., helping in a friendly manner). Using an interpersonal framework allows for comparisons between our results with other previously reported studies of spousal interactions using different measures and in different populations, including measures of social support. In this case, we found that collaborative spousal involvement has similar interpersonal qualities as instrumental social support, which has been associated with adherence behaviors in other illnesses such as end stage renal disease and diabetes. The benefits of collaborative involvement appear to be two-fold. In addition to providing support and encouragement, collaborative involvement provides opportunities for spousal involvement problem solving, which can lead to better outcomes in problem solving tasks. Dealing with initial problems is a common occurrence in CPAP use, with up to two-thirds of CPAP users reporting initial problems with this treatment. These problems often require adjusting the equipment or learning strategies to get used to sleeping with the machine. Therefore, collaborative involvement from the spouse may provide both support and structure needed to overcome these initial problems in early CPAP use.

The longitudinal nature of our study allowed for evaluation of spousal involvement over several months. We found that most of the spousal involvement types remained consistent between 1 week and 3 months of CPAP treatment. The only type of spousal involvement that decreased was negative spousal involvement. One of the reasons this may have occurred is that negative spousal involvement may have been ineffective at motivating adherence or possibly caused annoyance or frustration. Previous studies have found that criticism tends to be unrelated to adherence or related to poorer adherence and emotional distress.

Interpretation of results of our study are limited by a small sample size and attrition at 3-month follow-up. Furthermore, the high levels of adherence in our sample (average adherence > 5 hours) suggest there is a possibility of selection bias for those who entered the study and/or bias in the results due to attrition. Although not statistically significant, participants who dropped out of the study were less likely to share a bed every night, had higher AHIs and were less likely to have objective adherence.
reported. However, in notes from follow-up visits with a sleep medicine physician, there was no different between groups in whether the physician noted the patient self-reported having adequate or good adherence. In addition, the responses in this study are limited to the patient’s report of the spouse’s behavior. It is possible that patient observations may over or underestimate the frequency of spousal involvement. Indeed, one study of couples motivation and attitudes about health behaviors found spouse but not patient perceptions of spousal involvement to be related to behavior change efforts. Spousal involvement in CPAP adherence is likely an interaction between the patient and spouse’s perception. Therefore, future research should consider the perspectives of both patient and spouse. Another consideration is that the findings of the current study are not necessarily generalizable to women with OSA. Due to significant gender differences in both the provision of and reactions to spousal involvement, it should not be assumed that results from male patients can be generalized to female patients.

Future studies of spousal involvement should consider involving qualitative methods to gain more knowledge about the intricacies of spousal involvement in CPAP. The spousal involvement measure used in this study was developed in healthy couples discussing a range of health behaviors and did not take into account specific ways that spouses can be involved in CPAP usage (e.g., assisting with refilling the water reservoir or cleaning the machine). Many of the items administered in this study were rated with very low frequency. Not only could this have limited statistical power for the study due to restricted range, it may have not assessed potentially important behaviors because it was not developed with CPAP users. The measure also did not take into account individual differences in perceptions spousal involvement. For example, repeated reminders may be helpful for some patients and irritating to others. Therefore, investigation into both the specific types of involvement in CPAP treatment and also individual differences in perceptions of involvement should be taken into account in future research, particularly in the design of interventions.

In conclusion, this study demonstrates that the majority of married OSA male patients report that their spouse is involved in CPAP treatment in a variety of ways over the first three months of treatment. However, only collaborative spousal involvement was associated with higher adherence. Encouragement of collaborative involvement may lead to improvements in CPAP adherence through a blend of both support and structure for patients.

REFERENCES

Spousal Involvement in CPAP

ACKNOWLEDGMENTS

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SUBMISSION & CORRESPONDENCE INFORMATION

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DISCLOSURE STATEMENT

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Sleep apnea has been implicated as an independent risk factor for atherosclerotic coronary artery disease (CAD). An association between the severity of sleep apnea and total cholesterol levels has previously been reported. However, the association with small dense low-density lipoprotein (LDL) cholesterol concentration (subclass B), one of the strongest predictors of atherosclerosis, is unknown. We examined the relationship between sleep apnea and LDL subclass B, considering body size.

**Methods:** This is a cross-sectional observational cohort of participants enrolled in a cardiovascular health study. Sleep apnea was assessed with a validated portable monitor. Lipid panels included total cholesterol, triglycerides, high-density lipoprotein cholesterol, LDL cholesterol, and LDL subclasses A, B, and A/B. Sleep apnea was analyzed categorically using the apnea hypopnea index (AHI).

**Results:** A total of 519 participants were evaluated. Mean age was 58.7 ± 7.4 years; BMI was 29.6 ± 5.7; 65% were female; 59% were Caucasian, and 37% were African American. Among participants with abnormal waist circumference by ATP III criteria, moderate to severe sleep apnea (AHI ≥ 25) was not independently associated with LDL subclass B. In contrast, among participants with normal waist circumference, moderate to severe sleep apnea was associated with 4.5-fold odds of having LDL subclass B.

**Conclusions:** Sleep apnea is independently associated with an atherogenic phenotype (LDL subclass B) in non-obese individuals. The association between sleep apnea and LDL subclass B in those with normal waist circumference may account, in part, for the increased risk of atherosclerosis and subsequent vascular events.

**Keywords:** Sleep apnea, atherosclerosis, lipoproteins, phenotype

**Citation:** Luyster FS; Kip KE; Drumheller OJ; Rice TB; Edmundowicz D; Matthews K; Reis SE; Strollo PJ. Sleep apnea is related to the atherogenic phenotype, lipoprotein subclass B. J Clin Sleep Med 2012;8(2):155-161.
Eligibility criteria included age 45 to 75 years, residence in the greater Pittsburgh metropolitan area, ability to undergo baseline and annual follow-up visits, and absence of known comorbidity expected to limit life expectancy to < 5 years. The present analysis is based on 519 participants enrolled in Heart SCORE who participated in a substudy protocol to assess sleep apnea using a portable monitor. Participants in this substudy were not substantially different from participants in the larger study with regards to cardiac and metabolic risk (see Table S1 in the supplement). The design of the study was cross-sectional and observational. The institutional review board at the University of Pittsburgh Medical Center approved the study protocol, and all study participants provided written informed consent.

Data Collection
Detailed demographic and medical histories were collected at the baseline visit. Race and ethnicity were self-reported. A medical history included inquiries about a history of previously diagnosed hypertension, hyperlipidemia, and diabetes mellitus, as well as current medications. Lifestyle characteristics including smoking history, as defined by current or former (> 6 months ago) cigarette use, and use of alcohol were measured by self-developed questionnaires. Physical activity was assessed by the Lipid Research Clinics Questionnaire.10 Physical examination included measurement of vital signs and anthropometric measures of body fat distribution, including waist circumference and waist-to-hip ratio.11 Height and weight were measured to calculate BMI.

Hypertension was defined as either a systolic blood pressure ≥ 140 mm Hg or use of antihypertensive medications. Diabetes mellitus was defined as fasting glucose > 126 mg/dL or a history of previously diagnosed diabetes treated with diet, oral agents, and/or insulin. The metabolic syndrome and individual component abnormalities were defined according to criteria established by the National Cholesterol Education Program.12 This included abnormal waist circumference, defined as ≥ 88 cm for females and ≥ 102 cm for males.

Lipid Testing
Lipid panels included measurement of total cholesterol, triglycerides, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol (calculated). Laboratory assessment of lipoprotein levels and particle sizes was performed on venous blood drawn in the fasting state. Lipid levels and lipoprotein particle sub-fractions were quantified by a commercial laboratory using a vertical auto profile technique (VAP, Atlotech, Birmingham, AL).13,14 These samples were also labeled indicative of moderate to severe sleep apnea as defined by an AHI ≥ 15. Based on Adult Treatment Panel III (ATP 3) criteria for waist circumference, there was only a nominal trend, indicating that participants with abdominal obesity had higher AHI scores than with normal waist circumference (11.6 ± 11.4 versus 11.3 ± 12.1, p = 0.07). This trend was similar in males and females (Figures 1 and 2).

Sleep Apnea and Traditional Lipid Levels
In multivariable analysis adjusting for age, gender, race, smoking status, blood pressure, BMI, and statin use, lipid lev-
cally, 61% of participants with AHI ≥ 25 had LDL subclass B, compared to only 25% of those with AHI ≤ 4 (p < 0.0001) in unadjusted analyses. However, the relationship between AHI score and LDL subclass B differed substantially by waist circumference. Among participants with abnormal elevated waist circumference, there was a nonsignificant trend of higher AHI scores being associated with LDL subclass B. In contrast, among participants with normal waist circumference, a threshold value of AHI ≥ 25 greatly increased the probability of having LDL subclass B (71% of all participants). In both

Sleep Apnea and LDL Subclass B
The percentage of participants with LDL subclass B varied significantly in relation to AHI score (Figure 3). Specifi-
Similar relationship between sleep apnea and LDL subclass B (data not shown), although women tended to have less severe sleep apnea overall than men in the Heart SCORE cohort. Consistent results were observed in multivariable analysis adjusted for age, gender, race, BMI, smoking status, statin use, and abnormal blood pressure per ATP3 criteria (systolic blood pressure ≥ 130 mm Hg, diastolic blood pressure ≥ 85 mm Hg, or use of antihypertensive drug therapy). Specifically, among 256 participants with abnormal waist circumference, AHI was not independently associated with LDL subclass B (Table 2). In contrast, among 255 participants with normal waist circumference, AHI ≥ 25 (compared to a score of 0 to 4) was associated with a 4.5-fold odds of having LDL subclass B (adjusted odds ratio = 4.53, 95% confidence interval: 1.67-12.24, p = 0.003). The formal test of interaction between abnormal waist circumference (dichotomous) × AHI ≥ 25 in relation to prevalence of LDL subclass B was statistically significant (p = 0.02), and was a more sensitive indicator of interaction than continuous measures of waist circumference, waist-to-hip ratio, and BMI (p = 0.10, 0.83, 0.07, respectively). In aggregate, these data indicate that AHI ≥ 25 is independently associated with a substantially elevated risk of having proatherogenic LDL subclass B, but only among participants with normal waist circumference.

For males, abnormal waist circumference: > 102 cm. For females, abnormal waist circumference: > 88 cm.

For females, abnormal waist circumference: > 88 cm.
DISCUSSION

We have shown that sleep apnea is independently associated with an atherogenic phenotype (LDL subclass B) in a diverse community cohort. The interaction between sleep apnea and LDL subclass B may account, in part, for the increased risk of atherosclerosis and subsequent vascular events that are associated with sleep apnea. However, this association appears to exist principally among those with a normal waist circumference. We chose to present these data stratified by waist circumference as opposed to BMI because of the better correlation of waist circumference to visceral obesity than BMI.5,6 There was a nominal trend indicating that participants with abnormal waist circumference had higher AHI scores than those with normal waist circumference. Our community-based sample had primarily mild sleep apnea; however, if the sample were enriched with more severe sleep apnea, more striking differences in AHI scores may have been found. In participants with normal waist circumference, the odds of having LDL subclass B were more than 4-fold higher among those with moderate to severe sleep apnea (AHI ≥ 25).

Despite finding that sleep apnea was associated with an atherogenic LDL subclass, we did not find an association between total cholesterol, HDL, or triglycerides and the severity of sleep apnea. This was true for all participants and when stratifying the analysis by waist circumference or BMI. These null findings are compatible with previous reports.17-19 One possible explanation for the lack of association between AHI and HDL or triglyceride levels is that our diverse community-based population was enriched with African American participants (37%), who as a group are known to have high HDL and low triglycerides at the same weight as compared to Caucasians.20 An alternate explanation is that the effect of sleep apnea is primarily on LDL subclass B, which would not be reflected in measurements of traditional lipid levels. Lipid-lowering agents such as niacin and fibric acid derivatives can shift lipoprotein particle size through biochemical stress response possibly mediated by intermittent hypoxia, which results in increased free fatty acids that form LDL.24-26 In the setting of insulin resistance, increased free fatty acids are cleared from the circulation, resulting in an increased opportunity for oxidation and subsequent development of the atherogenic plaque. Clinically, insulin resistance is associated with increased LDL subclass B levels.27

It is biologically plausible that sleep apnea and consequent intermittent hypoxemia adversely affect LDL metabolism via one or more pathways. Li et al. have demonstrated in a mouse model that intermittent hypoxia will induce hyperlipidemia via sterol regulatory element binding protein (SREBP) 1, a master regulator of lipogenesis.28 Intermittent hypoxia has been shown to increase lipid loading in human macrophages.29 In addition, a recent report by Drager et al. has shown in a mouse model that chronic intermittent hypoxia inactivates lipoprotein lipase.30 Lipoprotein lipase deficiency is known to favor production of small dense LDL subclass B.31 Finally, in sleep apnea, there may be an additional effect of upregulation of cortisol independent of obesity, further promoting the production of LDL subclass B.32-34

The ability to detect an independent signal attributable to sleep apnea alone would be more likely in the non-obese sleep apnea population because the known effects of obesity on lipid profiles may mask or diminish the effect of sleep apnea on LDL subclass B.7 Similar to the observation by Harsch and colleagues relative to sleep apnea and insulin resistance, we found that the relationship of LDL subclass B was strong and only evident in non-obese participants (Figure 3 and Table 2).35

The prevalence of moderate sleep apnea (AHI ≥ 15) was somewhat surprising at 26% in a cohort of participants who self-reported a 6% prevalence of a coexisting sleep disorder.36 This slightly higher rate than previously reported can probably be explained by the methodology used to identify sleep apnea.37,38 In our study, we used nasal pressure without oximetry as opposed to a nasal pressure with oximetry to identify apnea and hypopnea. Determining the presence of sleep apnea by assessment of nasal pressure alone may be considered a limitation of the current study. A direct measure of intermittent hypoxemia was not assessed with this device. Also, with nasal pressure alone, obstructive apneas could not be discriminated from central apneas. However, the portable monitor (ApneaLink, ResMed Corp) that we used has been previously validated with acceptable performance to identify obstructive sleep apnea.15,16,39 This finding has been corroborated by Ayappa et al., who compared nasal pressure alone to full polysomnography in and out of the laboratory.40

We controlled for weight in our analyses, including stratification by normal versus abnormal waist circumference. Thus,

<table>
<thead>
<tr>
<th>AHI Score (compared to 0 to 4)</th>
<th>OR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal waist cm (n = 255)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 to 9</td>
<td>0.68</td>
<td>(0.30 – 1.57)</td>
<td>0.37</td>
</tr>
<tr>
<td>10 to 14</td>
<td>0.74</td>
<td>(0.23 – 2.35)</td>
<td>0.61</td>
</tr>
<tr>
<td>15 to 24</td>
<td>1.06</td>
<td>(0.40 – 2.82)</td>
<td>0.90</td>
</tr>
<tr>
<td>25 or more</td>
<td>4.53</td>
<td>(1.67 – 12.24)</td>
<td>0.003</td>
</tr>
<tr>
<td>Abnormal waist cm (n = 256)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 to 9</td>
<td>1.03</td>
<td>(0.46 – 2.30)</td>
<td>0.93</td>
</tr>
<tr>
<td>10 to 14</td>
<td>1.12</td>
<td>(0.48 – 2.61)</td>
<td>0.79</td>
</tr>
<tr>
<td>15 to 24</td>
<td>1.48</td>
<td>(0.58 – 3.77)</td>
<td>0.41</td>
</tr>
<tr>
<td>25 or more</td>
<td>1.45</td>
<td>(0.49 – 4.28)</td>
<td>0.50</td>
</tr>
</tbody>
</table>

Models were adjusted for age, gender, race, body mass index, smoking status, statin use, and abnormal blood pressure per ATP3 criteria (systolic blood pressure ≥ 130 mm Hg, diastolic blood pressure ≥ 85 mm Hg, or use of antihypertensive drug therapy).
weight alone did not explain the relationship with AHI and LDL subclass B, although the direct contribution of visceral adiposity as an important covariate\(^1\) could not be formally assessed in our analysis. Insulin resistance was not measured. However, we controlled statistically for multiple components of the metabolic syndrome in our analysis, thereby suggesting that the metabolic syndrome or impaired glucose control did not account for the elevated LDL subclass B relationship to the severity of sleep apnea. In addition, there were slight differences in smoking history, racial distribution, and physical activity levels between the sub-study population and the Heart SCORE cohort. However, since this was a convenience sample, differences in demographic and clinical variables would be expected.

In summary, we have shown in a large community sample that sleep apnea is common, underdiagnosed (6.4% self-reported the diagnosis of any sleep disorder), and associated with the atherogenic phenotype LDL subclass B. The relationship is principally evident and strong in non-obese compared to obese participants and appears to have a threshold effect, i.e., at AHI > 25. These results indicate that sleep apnea may be an important target for treatment in patients with moderate to severe sleep apnea because of the increased risk of atherosclerotic vascular disease that has been identified in patients with this severity of sleep apnea.\(^1,3\) Further research is required to better define the relationship of sleep apnea, atherogenic LDL subclass B and atherosclerosis, and whether treatment of sleep apnea can favorably modify the atherogenic phenotype.

**ABBREVIATIONS**

- CAD, coronary artery disease
- LDL subclass B, small, dense low-density lipoprotein cholesterol concentration
- Heart SCORE, Heart Strategies Concentrating On Risk Evaluation
- BMI, body mass index
- LDL, low density lipoprotein cholesterol
- AH, apnea hypopnea index
- ATP III, Adult Treatment Panel III
- HDL, high-density lipoprotein cholesterol

**REFERENCES**

Sleep Apnea Related to Atherogenic Phenotype


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ACKNOWLEDGMENTS


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Neurophysiological Two-Channel Polysomnographic Device in the Diagnosis of Sleep Apnea

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Study Objective: Our objective was to evaluate a portable device (Somté, Compumedics, Australia), which incorporates 2 neurophysiological channels (electroencephalography and electrooculography) with cardiorespiratory monitoring for the diagnosis of obstructive sleep apnea (OSA).

Method: Full polysomnography (PSG) and Somté recordings were simultaneously performed in 68 patients with suspected OSA. Data were analyzed blindly by 2 scorers.

Results: A good agreement between methods in sleep efficiency was observed (68.8% [18.4] with PSG vs 68% [19.1] with Somté [p: n.s.] for scorer 1, and 67.5% [19.1] vs 68.4% [18.5; p: n.s.] for scorer 2). The apnea-hypopnea index (AHI) obtained with Somté was lower than with PSG: 19 (17.8) vs 21.7 (19) (p < 0.001) for scorer 1, and 16.6 (16.7) vs 20 (18.8) (p < 0.001) for scorer 2. The sensitivity of Somté for a PSG-AHI > 5 was 91% for scorer 1 and 90% for scorer 2, while specificity was 77% and 90%, respectively. The areas under the receiver operating curve for different PSG-AHI cutoff points (≥ 5, ≥ 15, and ≥ 30) were 0.81, 0.90, and 0.86, respectively, for scorer 1, and 0.90, 0.88, and 0.83 for scorer 2.

Conclusions: These data suggest that Somté is an effective device to identify sleep and respiratory variables in patients with suspected OSA.

Keywords: Diagnosis, sleep apnea-hypopnea, polysomnography, portable polysomnography

Citation: Ferré Á; Sampol G; Jurado MJ; Cambrodi R; Lloberes P; Romero O. Neurophysiological two-channel polysomnographic device in the diagnosis of sleep apnea. J Clin Sleep Med 2012;8(2):163-168.

O
bstructive sleep apnea syndrome (OSA) is a highly prevalent disorder1 and a well-documented risk factor for impaired quality of life,2 cardiovascular disease and mortality,3,5 and accidents.6 A number of recommended methods are used for diagnosing OSA. In 1994, the American Sleep Disorders Association, now the American Academy of Sleep Medicine (AASM), defined 4 levels for sleep studies, based on the number and type signals recorded.7 Type 1, known as full attended polysomnography (PSG), is the “gold standard” for the diagnosis of OSA; however, this procedure is both labor- and resource-intensive, leading to long waiting lists in sleep laboratories.8 For these reasons, many laboratories have incorporated simpler tests in order to facilitate the diagnosis of OSA. Type 2 is an ambulatory PSG. The most widely used technique is the type 3 study or respiratory polygraphy,4 which allows for the assessment of cardiorespiratory variables only, without neurophysiological parameters. However, the lack of sleep variables in type 3 studies in patients with suspected OSA has two potentially relevant limitations. First, without data on sleep efficiency, the apnea-hypopnea index (AHI) is estimated based on recorded time in bed. Second, hypopnea is defined as a reduction of airflow usually associated with a desaturation; hypopnea episodes characterized by the presence of transient electroencephalographic arousals following airflow reduction but without desaturation are not identified. A number of studies have been conducted comparing type 3 devices with conventional PSG, which have shown good AHI concordance. Currently, patients presenting classic OSA symptoms (usually somnolence) are selected for these studies,10-17 which is a clinical characteristic associated with heightened sleep efficiency throughout the sleep study.18 Furthermore, some studies do not measure the number of hypopneas based on arousal criteria during the PSG.15,19,20 These study design choices favor results that will yield good AHI concordance with both methods.

Based on these considerations, we evaluated the potential value of a commercially available portable device (Somté, Compumedics, Abbotsford, Australia), which allows for the inclusion of 2 high-frequency channels when assessing cardiorespiratory variables. Previously, Cunnington et al.21 used this by adding an EEG channel and a leg movement channel in order to detect arousals, although they did not measured sleep efficiency or sleep stages. In this study, we have used an EEG channel and an EOG channel to score sleep stages in patients with suspected
snoring, electrocardiogram, leg movements, and body position recordings. All PSG data were collected and stored using an E-Series digital system (Compumedics, Abbotsford, Australia).

**Somté**

The Somté polygraph allows the recording of 2 neurophysiological signals. Recorded signals included EEG (C3/A2) and EOG (left eye movements channel referenced to right eye), airflow (nasal cannula), thoracic and abdominal movements, SaO₂, body position, heart rate, and snoring (Figure 1). The sleep study technician did not have access to the signals being registered during the study and was instructed not to alter any of the sensor attachments throughout the night.

**Scoring Criteria**

Sleep stages were scored using Rechtschaffen and Kales standard criteria. Arousals were identified on PSG recordings according to AASM standard criteria. Given the absence of EMG channel, the following modifications to these criteria were introduced when scoring Somté recordings:

1. **Sleep staging:** We identified NREM sleep stages using standard criteria without considering any reference to EMG activity. Based on the criteria used by Dauvilliers et al., REM sleep was identified when low amplitude, mixed frequency activity in the EEG channel (with or without sawtooth waves) was accompanied by rapid eye movements. The chosen EOG montage, referencing left eye movements to the right eye, maximized the signal amplitude of conjugate eye movements typical of REM sleep. REM sleep end was considered when K complexes or sleep spindles (N2 stage), delta waves (20% to 50% of the epoch, N3; > 50% of the epoch, N4), alpha activity, or body movement (> 50% of the epoch wakefulness) was present in the epoch.

2. **Arousals:** Arousals were identified according to standard criteria during NREM sleep; in REM sleep, they were coded when an EMG artifact rapid (> 16 Hz) and high amplitude (> 8 µV) activity lasting > 3 sec was identified on the EEG and/or EOG channels.

3. **Respiratory events:** Apnea was defined as a decrease in airflow amplitude (nasal cannula) to < 10% for ≥ 10 seconds. Differentiation was made between obstructive and central apneas according to respiratory effort channels (presence or absence of thoracoabdominal movement). Hypopnea was defined as ≥ 50% reduction in flow amplitude of the surrounding baseline for ≥ 10 sec associated with a cyclical dip in SaO₂ ≥ 3% or an arousal. The apnea-hypopnea index was defined as the sum of the number of apneas plus hypopneas divided by total sleep time.

**Statistical Analysis**

Descriptive variables were expressed as mean (standard deviation) or percentages. Paired or unpaired t-test was used to compare means. The agreement between the AHI obtained with PSG and Somté was evaluated using the Bland and Altman method and Pearson correlation. The diagnostic accu-
Diagnosis of Sleep Apnea

PSG. The κ coefficients of agreement between the 2 scorers for these cutoff points were 0.66, 0.70, and 0.85, respectively. With PSG, the κ coefficients for these cutoff values were 0.84, 0.65, and 1, respectively. There was a significant correlation between the AHI obtained with PSG and Somté \( r = 0.959 \) for scorer 1 and \( r = 0.937 \) for scorer 2; Figure 2). Figure 3 shows Bland and Altman plots comparing the AHI from the 2 methods, with only 4 (6%) outliers for scorer 1 and 5 (7%) for scorer 2. No systematic trend was found, and the mean observed difference was 2.6 (5.4) for scorer 1 and 3.4 (6.6) for scorer 2.

The areas under the receiver operating characteristic curve of the AHI obtained with Somté for different cutoff points of PSG are shown in Table 5.

Table 1—Population characteristics

<table>
<thead>
<tr>
<th>n</th>
<th>68</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>M39/F29</td>
</tr>
<tr>
<td>Age (years)</td>
<td>55.9 (14.5) (R: 15-81)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28.5 (4.8) (R: 15-81)</td>
</tr>
<tr>
<td>Epworth Sleepiness Scale</td>
<td>8.6 (9.5) (R: 15-81)</td>
</tr>
</tbody>
</table>

M, male; F, female; SD, standard deviation; BMI, body mass index; R, range.

Table 2—Sleep data

<table>
<thead>
<tr>
<th></th>
<th>PSG</th>
<th>SOMTE</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>E (%)</td>
<td>68.8 (18.4)</td>
<td>68.0 (19.1)</td>
<td>0.351</td>
</tr>
<tr>
<td>SL (min)</td>
<td>26.7 (48.1)</td>
<td>32.5 (57.4)</td>
<td>0.093</td>
</tr>
<tr>
<td>RL (min)</td>
<td>125.4 (78.2)</td>
<td>126.9 (80.4)</td>
<td>0.829</td>
</tr>
<tr>
<td>WASO (min)</td>
<td>95.4 (64.9)</td>
<td>87.7 (82.7)</td>
<td>0.010*</td>
</tr>
<tr>
<td>REM (min)</td>
<td>38.8 (27.6)</td>
<td>41.2 (29.9)</td>
<td>0.054</td>
</tr>
<tr>
<td>NREM (min)</td>
<td>255.7 (74.4)</td>
<td>253.2 (78.14)</td>
<td>0.303</td>
</tr>
<tr>
<td>N1 (min)</td>
<td>20.8 (12.7)</td>
<td>17.2 (14.0)</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>N2 (min)</td>
<td>186.2 (67.1)</td>
<td>189.9 (71.1)</td>
<td>0.168</td>
</tr>
<tr>
<td>N3 (min)</td>
<td>27.9 (19.2)</td>
<td>25.8 (22.5)</td>
<td>0.218</td>
</tr>
<tr>
<td>N4 (min)</td>
<td>19.4 (23.9)</td>
<td>17.0 (21.4)</td>
<td>0.056</td>
</tr>
<tr>
<td>NSC</td>
<td>2.3 (1.4)</td>
<td>2.3 (1.4)</td>
<td>0.708</td>
</tr>
</tbody>
</table>

PSG, nocturnal polysomnography; SD, standard deviation; Mean dif, mean difference; min, minutes; E, sleep efficiency; SL, sleep latency; RL, REM latency; WASO, wake after sleep onset; REM, REM sleep; NREM, no REM sleep; N1; stage 1; N2, stage 2; N3, stage3; N4, stage 4; NSC, number of sleep cycles.

Table 3—Respiratory events

<table>
<thead>
<tr>
<th></th>
<th>PSG</th>
<th>SOMTE</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>AI</td>
<td>7.0 (15.3)</td>
<td>9.2 (15.7)</td>
<td>0.006</td>
</tr>
<tr>
<td>HI</td>
<td>14.6 (12.6)</td>
<td>9.7 (9.1)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>AHI</td>
<td>21.7 (19.0)</td>
<td>19.0 (17.8)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

SD, standard deviation; AI, apnea index; HI, hypopnea index; AHI, apnea-hypopnea index; PSG, nocturnal polysomnography.
Table 4—Sensitivity, specificity, and positive and negative predictive values of Somté, and κ coefficient of agreement between scorers for different AHI cutoff values

| AHI | PSG n (%) | SOMTE Scorer 1 | | | | SOMTE Scorer 2 | | | |
|-----|-----------|----------------|---|---|---|---|----------------|---|---|---|
|     |           | n (%)          | Sens | Spec | PPV | NPV | LR+   | LR- | n (%) | Sens | Spec | PPV | NPV | LR+ | LR- |
| ≥ 5 | 55 (81)   | 53 (78)        | 91%  | 77%  | 94% | 67% | 4.12  | 0.11| 52 (80) | 90%  | 90%  | 96% | 60% | 9.5 | 0.11|
| ≥ 15| 36 (53)   | 32 (47)        | 86%  | 97%  | 97% | 86% | 24.7  | 0.14| 25 (36) | 83%  | 92%  | 89% | 88% | 10.5| 0.18|
| ≥ 30| 18 (26)   | 13 (19)        | 61%  | 96%  | 85% | 87% | 15.3  | 0.41| 12 (17) | 67%  | 100% | 100%| 89% | 2.3 | 0.33|

n, number; Sens, sensitivity; Spec, specificity; PPV, positive predictive value; NPV, negative predictive value; LR+, positive likelihood ratio; LR-, negative likelihood ratio; AHI, apnoea hypopnoea index; PSG, nocturnal polysomnography.

Figure 2—Scatter plots showing the linear correlation between PSG and Somté for AHI

Figure 3—Bland and Altman plots showing the mean difference (thick line) and the limits of agreement (2 SD; dotted line) for AHI with PSG and Somté
DISCUSSION

The study shows good agreement between the Somté system and full PSG results in adult patients referred for assessment of OSA. The two neurophysiological channels incorporated by the device allowed for an accurate estimation of both sleep parameters and respiratory events.

Population-based studies have shown that the majority of patients with OSA are not sleepy, and that the absence of somnolence is not associated with a better long-term prognosis. Additionally, other population-based and clinical series studies have reported high variability in sleep efficiency in OSA patients without somnolence, being sleep efficiency notably low in a subgroup of them. In line with these observations, our patients had a mean ESS < 10, and 26.4% of them showed a sleep efficiency < 60% during the sleep study. Furthermore, insomnia is also associated with low sleep efficiency; we now know that it is a frequent complaint in OSA patients and that a significant percentage of patients with insomnia have OSA. PSG in patients with OSA and insomnia shows lower sleep efficiency. For all these reasons, we believe that in some OSA patients, an accurate determination of AHI is only achieved if we obtain sleep efficiency during the sleep study.

To our knowledge this is the first time that sleep in patients with suspected OSA has been scored with only two neurophysiological channels. Thus, in comparing against PSG results, we found statistically significant differences for several sleep stages. However, these differences were small, similar to those reported when comparing inter-laboratory agreement in sleep staging with PSG and of no clinical significance in OSA diagnosis.

There are several definitions of hypopnea that include different requirements for concomitant oxyhemoglobin desaturation and/or arousal in association with an airflow signal change. There are differences in the measured AHI depending on the adopted definition. One of the factors contributing to these differences is the lack of inclusion of the arousal criteria, leading to a markedly lower AHI value than that obtained when it is included. Furthermore, several studies have shown improved somnolence and quality of life when OSA is treated with nasal CPAP and obstructive events and arousals are abolished. After monitoring for AHI, the frequency of arousals is independently associated with fatigue symptoms in OSA patients. For these reasons, the AASM has maintained as a valid option the definition of hypopnea as a reduction of airflow associated with an arousal. Our approach with Somté allowed us to identify arousal-related hypopneas, and the obtained AHI showed good agreement with the one obtained with PSG.

The study has strong points and limitations that must be emphasized. On the one hand, we have included a wide group of patients with different degrees of suspected OSA, 28% of whom are over 65 years of age. Also, PSG and Somté studies were performed simultaneously, avoiding inter-nights and postural variability, and the studies were manually scored as recommended. Furthermore, our data were analyzed by two scorers and the \( \kappa \) coefficients of agreement obtained for different AHI cutoff points were good or excellent according to accepted criteria. On the other hand, while studies with Somté were performed in our sleep unit, this device could be especially useful for home sleep testing, reducing the long wait time for diagnostic tests in patients with suspected OSA. However, the studies were unattended by sleep technicians, and we think that our results could be extrapolated to those obtained in a home study. Another limitation that we faced is that we studied patients referred to the sleep unit for suspected OSA; although many patients did not have somnolence, OSA prevalence was 80%. Our findings do not necessarily support the use of Somté as a tool for screening OSA in a general population with much lower pretest probabilities. Another constraint is that we relied on R&K criteria. While our main objective was to establish an effective correlation with sleep efficiency, we also established a good correlation with the various sleep stages. Towards this end, we would need to further review these results using new AASM coding criteria.

In conclusion, in our study the Somté recording device has shown high diagnostic accuracy for OSA. Our results suggest that this device could be a complementary diagnostic alternative to PSG and respiratory polygraphy. Further studies are required to define what clinical characteristics are needed for optimal implementation of this approach.

REFERENCES


Refill Rates of Accessories for Positive Airway Pressure Therapy as a Surrogate Measure of Long-Term Adherence

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Study Objectives: To identify and validate a surrogate measure of long-term adherence to positive airway pressure (PAP) therapy in patients with obstructive sleep apnea (OSA).

Design: Retrospective cohort study.

Setting: Academic center.

Participants: 220 consecutive patients with OSA.

Interventions: N/A.

Measurements: In patients with OSA who were receiving PAP therapy for >1 year, PAP adherence measured by device-download and defined by Medicare criteria was compared to refill rates for mask and other PAP therapy accessories. First, receiver operating characteristic (ROC) curves were constructed to identify a threshold value of refills per year that discriminated best between PAP adherent and non-adherent patients (derivation set; n = 100). Then the predictive accuracy of the threshold value of refills per year was tested in an additional 120 consecutive patients (validation set).

Results: From the derivation set, ROC curve with good discriminant characteristics (ROC 0.83; 95% confidence intervals [CI], 0.75, 0.91, p < 0.0001) was used to identify a threshold value of refills (0.7 refills/year) for distinguishing PAP adherent and non-adherent patients. Subsequently, when the threshold was applied to the validation set, the likelihood ratio for a positive test (weighted for prevalence) predicting adherence to PAP therapy was 7.3 (95% CI, 3.8, 14), and likelihood ratio for a negative test was 0.6 (95% CI; 0.4, 0.8).

Conclusion: Refill rate of PAP accessories exhibited good test characteristics for predicting long-term PAP adherence. Such a surrogate measure based upon insurance claims data can be a powerful epidemiological tool in bioinformatics-aided comparative-effectiveness research and to monitor clinical performance of health systems.

Keywords: Adherence, obstructive sleep apnea, sleep apnea, continuous positive airway pressure, adherence, adult, compliance, artificial respiration

Citation: Patel N; Sam A; Valentin A; Quan SF; Parthasarathy S. Refill rates of accessories for positive airway pressure therapy as a surrogate measure of long-term adherence. J Clin Sleep Med 2012;8(2):169-175.

Obstructive sleep apnea (OSA) is a prevalent condition that is most frequently treated with positive airway pressure (PAP) therapy.1,2 Non-adherence to PAP therapy, however, afflicts a high proportion of adults with sleep apnea (46% to 83%),3 and such poor adherence is associated with increased risk for fatal and non-fatal cardiovascular events.4 Consequently, assessment of adherence to PAP therapy has been advocated as a physician performance assessment tool in the management of patients with OSA.5 However, obstacles to the universal and consistent measurement of PAP adherence remain.5 Therefore, a reliable surrogate for measuring long-term PAP adherence—both within and across healthcare systems—is direly needed for more consistent assessment of the performance of healthcare systems and providers.

Adherence to medications can be measured both directly (by measuring metabolites of drug in urine) or indirectly by measuring claims data pertaining to medication refills.5 While the former methodology may be more accurate, the latter offers a more pragmatic yet reliable tool for assessing medication adherence and is universally accepted as an adequate surrogate.6 Superior medication refill rates have been associated with more favorable patient outcomes, such as reduced exacerbations in chronic lung disease, reduced hospitalizations in patients with cardiovascular disease and schizophrenia, and reduced relapse rates in patients with rheumatoid arthritis and multiple sclerosis.7-12 Similarly, although PAP device download affords the best measure of adherence to PAP therapy,13-18 information pertaining to refill of PAP accessories (masks, hoses, filters, humidifiers, and even PAP machines) due to wear and tear may potentially serve as a surrogate measure of adherence. To our knowledge, a systematic assessment of whether refills of PAP accessories can parallel objectively measured device-downloaded adherence data has not been performed.
between refills of PAP accessories and objective device-downloaded adherence, if validated, could better facilitate adherence monitoring in health systems and support quality improvement initiatives that target management of OSA.

In line with such rationale, we set out to identify and validate a surrogate measure of long-term adherence to positive airway pressure (PAP) therapy in patients with obstructive sleep apnea (OSA). We hypothesized that refill rates for PAP device accessories can predict long-term PAP adherence in patients with OSA.

**METHODS**

**Study Population**

This is an analysis of an historical cohort contained in an electronic disease-registry that was set-up for a quality initiative in 2003 at the Tucson VA Sleep Program. Two hundred twenty consecutive patients who had received PAP therapy > 1 year were included in the analysis as follows: (a) An initial derivation set of 100 consecutive patients with OSA receiving PAP therapy (> 1 year) in whom PAP adherence was measured by device-download. (b) A validation data set of the next 120 consecutive patients with OSA receiving PAP therapy (> 1 year) in whom PAP adherence was measured by device download.

OSA was diagnosed by polysomnography that revealed an apnea-hypopnea index > 5/h, with hypopneas defined as > 50% reduction in flow or effort and ≥ 3% oxygen desaturation.

Fourteen percent of the consecutive patients were excluded due to unavailability of the download that resulted in the 220 patients reported in this study. The study was approved by the University of Arizona Institutional Review Board and the VA Research and Development Committee.

**Gold Standard**

Adherence to PAP therapy was measured by device download using manufacturer software and mailed in memory cards (ENCORE Pro, Philips-Respironics, Murrysville, PA). The usage was expressed in minutes of use per day, and adherence was defined by Medicare criteria requiring ≥ 4 h of PAP use on 70% of nights (5 of 7, which translated into 21 of 30 days) during 30 consecutive days within the prior 90-day period. Unlike Medicare criteria that require such data from the first 90 days of therapy, the adherence reported here was collected from the prior 90 days of therapy because our objective was to measure a correlate of long-term PAP adherence. Additionally, adherence was also defined by a more strict criterion of device usage > 4 h/day on all days. For the latter, the total number of hours of usage during the prior 90-day period available in the device memory was divided by the total number of days (90 days), which yielded average use of PAP therapy. Patients with an average device use ≥ 4 h were considered to be adherent.

**Surrogate Measure**

Refills of masks, hoses, filters, humidifiers, chin straps, and even PAP devices were derived from the dispensation logs that were maintained for each patient in the prosthetics department of the integrated healthcare system at Tucson VA. The number of total refills during the entire follow-up period (ranging from 1 to 7 years) was divided by follow-up period expressed in years to yield the refills per year. Moreover, similar refill rates were calculated for each of the above-mentioned accessories. All of the patients were receiving care exclusively from the VA in Tucson. Patients at the VA in Tucson are “means tested” and seldom have third party insurance. Patients who died or disenrolled from the Tucson VA were included if they had been on PAP therapy for at ≥ 1 year of PAP therapy, as this was our a priori definition for long-term PAP adherence and served as an inclusion criterion. For those patients who expired, or disenrolled, after being on 1 year of PAP therapy, the duration of time that they were alive since the time they received PAP therapy was censored at the day of death (or disenrollment) and expressed in years.

**Statistical Methodology**

Adherence to PAP therapy was treated as a binary dependent variable (defined by Medicare criteria). In the derivation set of 100 patients, the sensitivity and specificity with which the total number of refills per year could discriminate PAP adherent and non-adherent status was assessed with receiver operating characteristic (ROC) curves. The area under the ROC curve, which summarizes the performance of the refills per year in predicting PAP adherence, was calculated. Cross-plots between sensitivity and specificity values were performed to objectively identify the threshold value with the best sensitivity and specificity to discriminate PAP adherent and non-adherent patients.

The threshold value of refills per year derived from the initial derivation data-set was then used a test to predict long-term PAP adherence or non-adherence in a validation dataset of 120 patients. True positive, true negative, false positive, false negative, sensitivity, specificity, positive predictive value, and negative predictive value were derived as per standard convention.

Likelihood ratio (LR) for refills per year as a diagnostic test to predict long-term PAP adherence was performed using conventional and prevalence weighted techniques for positive test (LR+) and negative test (LR-) results. The LR+ is calculated as LR+ = (sensitivity)/(1-specificity) and LR- = (1-sensitivity)/(specificity). In our case, LR+ greater than 1 indicates the test result (i.e., refills per year) was associated with the condition of interest (i.e., long-term PAP adherence), whereas LR- less than 1 indicates that refills per year was associated with non-adherence. LR+ greater than 1 would argue in favor of long-term PAP adherence; the bigger the number, the more convincingly the finding suggests that long-term PAP adherence exists. Findings whose LR+ lie between 0 and 1 argue against PAP adherence; the closer the LR is to 0, the less likely the patient is PAP adherent. Findings whose LR+ equal 1, or whose 95% confidence interval (95% CI) overlaps the value “1” lack predictive value. Because LR+ can change based upon the prevalence of the condition (in this case the prevalence of long-term PAP adherence), LR+ was weighted for prevalence as follows LR+ = (prevalence)(sensitivity)/(1-prevalence)(1-specificity).

Similarly, LR- was weighted for prevalence as follows LR- = (prevalence)(1-sensitivity)/(1-prevalence)(specificity).

Sensitivity analysis with adherence defined by a stricter definition of 4 h/night was also performed. Also, test characteristics for mask refills alone was performed. Sensitivity analysis with
PAP Refills and Adherence

or even device by themselves, because the mask refills constituted the bulk of refills. Specifically, masks constituted 54.7% of total refills, whereas filters (30.4%), hose (5.8%), device (5.3%), and humidifier (3.7%) constituted a minority of the total refills requested.

Derivation Set

In the derivation set, the refill rate of all PAP-related accessories was a median of 0.75/year (interquartile range [IQR], 0.17, 1.8) and for masks alone was a median of 0.4/year (IQR; 0, 0.8). Filters, hoses, humidifier, and PAP device constituted the remainder of the refills, with a median of 0.2/year (IQR; 0, 1.0).

In the derivation set, when adherence was defined by Medicare criteria, total refill rate of all PAP-related accessories was greater in adherent (median 1.5/year; IQR 0.5, 2.9) than in non-adherent patients (median 0.2/year; IQR 0, 0.74; p < 0.0001). Similarly, mask refill rate was greater in adherent (median 0.8; IQR 0.4, 1.2) than non-adherent patients (median 0.2/year; IQR 0, 0.5; p < 0.0001). Adherence to PAP therapy (measured as min of usage/day) was correlated with refill rate for PAP device and accessories (R = 0.42; p < 0.0001; Figure 1). Similarly, adherence to PAP therapy (measured as min of usage per day) was correlated with refill rate for masks (R = 0.5; p < 0.0001).

RESULTS

There were 220 patients (age 57 ± 11 years; 94% men) with a body mass index 37.4 ± 5.8 kg/m² (Table 1). Average therapeutic CPAP pressure was 10.7 ± 3.1 cm H₂O. Seven percent of patients received bilevel PAP therapy, while 93% received CPAP therapy. The mode of therapy did not influence adherence. In the derivation set, the duration of follow-up was 4.8 ± 1.2 years (range 1 to 7 years). In the validation set, the duration of follow-up was 4.7 ± 1.2 years (range 1 to 6.25 years). For both definitions of adherence, the duration of follow-up was not different between the adherent and non-adherent groups (p > 0.8). In the validation set, the proportion of patients who were adherent by Medicare criteria was 67%, and by the strict 4-h criterion was 54%. Of all the various types of refills, besides total refills per year, we selected mask refills alone rather than refill rates of hose, filter, humidifier, arbitrarily defined threshold levels of refills (total and mask alone) were also performed. We performed univariate linear regression with long-term PAP adherence (expressed as average min used per day) and determinants such as age, gender, BMI, days on PAP, Epworth score, AHI, total refills per year, mask refills per year, AHI at therapeutic pressure (residual AHI), and PAP pressure. Significant determinants (p < 0.05) were entered into a multivariate regression model (forced entry), and care was taken to prevent collinearity between determinants by performing collinearity diagnostics. Group comparisons of continuous variables were made by unpaired t-tests or nonparametric equivalents. p values < 0.05 were considered significant. All data are shown as mean and standard deviation (SD), or median and interquartile range (IQR). SPSS v12.01 (SPSS Inc., Chicago IL) was used for statistical analysis.

<table>
<thead>
<tr>
<th>Table 1—Characteristics of patients</th>
<th>Derivation set (n = 100)</th>
<th>Validation set (n = 120)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>58 ± 12</td>
<td>56 ± 13</td>
<td>NS</td>
</tr>
<tr>
<td>Gender (men; %)</td>
<td>94%</td>
<td>95%</td>
<td>NS</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>37 ± 6</td>
<td>36 ± 6</td>
<td>NS</td>
</tr>
<tr>
<td>Race (%)*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>60%</td>
<td>58%</td>
<td>NS</td>
</tr>
<tr>
<td>Hispanic</td>
<td>10%</td>
<td>12%</td>
<td>NS</td>
</tr>
<tr>
<td>African American</td>
<td>7%</td>
<td>6%</td>
<td>NS</td>
</tr>
<tr>
<td>Epworth score</td>
<td>11 ± 4</td>
<td>10 ± 5</td>
<td>NS</td>
</tr>
<tr>
<td>AHI (mean ± SD)</td>
<td>25 ± 22</td>
<td>24 ± 21</td>
<td>NS</td>
</tr>
<tr>
<td>AHI (median; IQR)</td>
<td>17 (10, 35)</td>
<td>17 (9, 33)</td>
<td>NS</td>
</tr>
<tr>
<td>AHI at therapeutic pressure</td>
<td>5 ± 3</td>
<td>5 ± 3</td>
<td>NS</td>
</tr>
<tr>
<td>PAP pressure</td>
<td>10 ± 3</td>
<td>11 ± 3</td>
<td>NS</td>
</tr>
<tr>
<td>Mask interface§</td>
<td></td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Nasal</td>
<td>65</td>
<td>62</td>
<td></td>
</tr>
<tr>
<td>Full Face</td>
<td>27</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Nasal pillow</td>
<td>8</td>
<td>8</td>
<td></td>
</tr>
</tbody>
</table>

*Self-reported race not reported or unknown is not shown; §Initial mask interface that was issued; AHI, apnea-hypopnea index; BMI, body mass index; NS, not significant; IQR, interquartile range; SD, standard deviation.

Figure 1—Long-term adherence to positive airway pressure (PAP) therapy downloaded from PAP device is plotted against refill rate of PAP device accessories (masks, hoses, filters, humidifier, chin strap, and even PAP devices). All adherence information is represented as minutes of use per day on all days of the week. Refill rate of PAP device accessories was closely related to adherence to PAP therapy (R = 0.42; p < 0.0001).
and the threshold value of refill rate associated with the best sensitivity and specificity are shown in Table 2.

### Validation Set
Test characteristics of threshold values of refill rates used to predict long-term PAP adherence in the validation dataset (n = 120) are shown in Table 3. The refill rate of all PAP related accessories had the best LR+[P] for predicting long-term PAP adherence by Medicare criteria. In general, the test performance characteristics of refill rate of all PAP related accessories were good for both definitions of long-term PAP adherence (Table 3). We also performed sensitivity analysis with regard to the threshold level of mask refills by arbitrarily selecting a threshold of 3, 2, and 1 mask per year as well, as for 3, 2, and 1 total refills (any PAP accessory including mask) per year. Such thresholds were associated with excellent LR+ (0.7 to 1.0) and PPV (2.5 to ∞), but the LR- (0.3 to 0.84) and NPV (0.37 to 0.7) suffered.

### Multivariate Regression
We performed linear regression with long-term PAP adherence (expressed as average min used per day) and age, gender, BMI, days on PAP, Epworth score, AHI, total refills per year, mask refills per year, AHI at therapeutic pressure (residual AHI), and PAP pressure. In univariate regressions, greater BMI, higher AHI, greater total refills, or greater mask refills per year were found to be significantly associated with adherence to PAP therapy (p < 0.0001). Multivariate regressions yielded greater AHI and greater total refills per year as being independently associated with greater adherence to PAP therapy (model...
Table 3—Test characteristics of the threshold values of refill rates used to predict long-term PAP adherence

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>LR+</th>
<th>LR-</th>
<th>LR+P</th>
<th>LR-[P]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medicare criteria&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.76 (0.65, 0.85)</td>
<td>0.79 (0.62, 0.90)</td>
<td>0.88 (0.77, 0.94)</td>
<td>0.63 (0.47, 0.76)</td>
<td>3.6 (1.9, 6.8)</td>
<td>0.3 (0.2, 0.5)</td>
<td>7.3 (3.8, 14.0)</td>
<td>0.6 (0.4, 0.9)</td>
</tr>
<tr>
<td>Refills/year&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.76 (0.54, 0.76)</td>
<td>0.76 (0.59, 0.88)</td>
<td>0.85 (0.73, 0.92)</td>
<td>0.53 (0.39, 0.66)</td>
<td>2.8 (1.5, 5.0)</td>
<td>0.5 (0.3, 0.6)</td>
<td>5.6 (3.0, 10.2)</td>
<td>0.9 (0.7, 1.2)</td>
</tr>
<tr>
<td>Masks/year&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.74 (0.61, 0.84)</td>
<td>0.70 (0.55, 0.81)</td>
<td>0.74 (0.61, 0.84)</td>
<td>0.70 (0.55, 0.81)</td>
<td>2.4 (1.6, 3.8)</td>
<td>0.4 (0.2, 0.6)</td>
<td>2.8 (1.8, 4.4)</td>
<td>0.4 (0.3, 0.7)</td>
</tr>
<tr>
<td>Four hours on all days&lt;sup&gt;d&lt;/sup&gt;</td>
<td>0.80 (0.68, 0.89)</td>
<td>0.64 (0.50, 0.77)</td>
<td>0.72 (0.60, 0.82)</td>
<td>0.74 (0.59, 0.85)</td>
<td>2.2 (1.5, 3.3)</td>
<td>0.3 (0.2, 0.5)</td>
<td>2.6 (1.7, 3.9)</td>
<td>0.4 (0.2, 0.6)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Mean values are in bold font, and 95% confidence intervals are within parentheses; PPV, positive predictive value; NPV, negative predictive value; LR+, likelihood ratio of a positive test; LR-, likelihood ratio of a negative test; LR+[P], likelihood ratio of a positive test weighted for prevalence; LR-[P], likelihood ratio of a negative test weighted for prevalence; <sup>b</sup>Threshold value of 0.4 per year; <sup>c</sup>Threshold value of 0.5 per year; <sup>d</sup>Threshold value of 0.9 per year; <sup>e</sup>Threshold value of 0.4 per year.

R² = 0.20; p < 0.0001. We did not load mask refills per year together with total refills per year, as they were collinear. When masks per year was loaded into the model (model R² = 0.27; p < 0.0001), greater masks per year was independently associated with greater odds of long-term PAP adherence.

**DISCUSSION**

Refill rate of PAP device accessories exhibited good test characteristics for predicting long-term adherence to PAP therapy (defined as > 1 year of therapy). Specifically, refill rate of all PAP accessories (mask, hoses, filters, humidifier, and even PAP devices combined) had the best predictive value for discriminating long-term PAP adherence and was superior to that of mask refill rate alone. Notably, refill rates were much greater in PAP adherent patients than in non-adherent patients, regardless of how adherence was defined—Medicare criteria or 4 hours per day on all days. To our knowledge this is the first study to systematically develop and validate a surrogate measure of long-term PAP adherence based upon refill rates of PAP accessories in a manner similar to that of accepted techniques of measuring medication adherence based upon refill rates.<sup>6</sup>

Non-adherence to PAP therapy afflicts a high proportion of adults with sleep apnea,<sup>3</sup> and such poor adherence is associated with increased risk for fatal and non-fatal cardiovascular events.<sup>3</sup> There are numerous interventions and factors that either promote or are associated with better adherence to PAP therapy.<sup>3,4</sup> However, in order for such reversible factors to be targeted, or interventions to be implemented, physicians and healthcare systems need to universally monitor PAP adherence. But there are many impediments to implementing such practices, including greater cost, lack of care coordination with durable medical equipment companies, differing software platforms across various manufacturers, and lack of patient cooperation (such as failure to bring or mail memory cards or even transmit data via phone or internet).

While objective measurement of short-term PAP adherence (90 days) is required in Medicare beneficiaries, there is no requirement for measuring long-term PAP adherence.<sup>28</sup> Although data suggests that long-term adherence patterns are established early,<sup>30</sup> this may not be true for all patients. Long-term adherence over one year may differ from adherence measured in the first month of treatment initiation.<sup>15</sup> In a time series analysis by Aloia and colleagues, slow decliners, slow improvers, and variable users constituted as much as 44% of a cohort of PAP users followed for one year.<sup>15</sup> Our validated surrogate measure of PAP adherence—based upon PAP accessory refills—was measured beyond 1 year and up to 7 years of PAP therapy and is therefore indicative of long-term PAP adherence.

Long-term PAP adherence has been shown to confer cardiovascular disease modification and survival benefits in observational cohort studies over a 10-year follow-up period.<sup>4</sup> Such benefits cannot possibly be achieved within the recommended 90 days of commencing PAP therapy.<sup>29</sup> Therefore, it follows that we should be cognizant of measuring long-term (> 1 year) adherence while keeping costs of such adherence monitoring low. Measurement of refill rate for PAP accessories can be a powerful tool in integrated healthcare systems or in Medicare beneficiaries to monitor long-term adherence to PAP therapy in a cost-effective manner. Such surrogate monitoring of PAP adherence can assist health services researchers to account for the effects of PAP therapy when measuring patient outcomes, healthcare utilization, and performance of healthcare systems.<sup>5</sup> Also, it is unclear as to whether the health systems that struggle to accomplish PAP adherence measurements over the first 90-day period can indeed effectively “monitor” adherence over the years that it takes to accomplish benefits. We believe that this implementation gap can be effectively filled by the surrogate measure of adherence that we have proposed and validated.

The test characteristics of all refills of PAP accessories reveal that this surrogate measure has good PPV and LR+[P] values for predicting long-term PAP adherence (Table 2). However, the NPV and LR-[P], although acceptable, are not as good. This discrepancy may be explained by the fact that some patients may have continued to use their old masks and PAP accessories over the long term. Therefore, unlike medications, resilient PAP accessories may have lower refill rates that may conceivably underestimate long-term PAP adherence (Figure 1).

**Limitations**

There are limitations to our study. First, the proposed surrogate measure for long-term PAP adherence is dependent on refill benefits of a given healthcare system. While the PAP accessory refill allowances of our integrated healthcare system is mirrored after the Medicare benefits, other systems may have more lenient or stricter refill benefits. Therefore, the threshold...
rate that we propose in this paper may not be generalizable to other integrated healthcare systems or healthcare systems that are not integrated. However, this problem can be surmounted by calibrating or validating the surrogate measure of long-term PAP adherence within other healthcare systems prior to implementation. Also, outcomes studies or physician performance assessments within a healthcare system should not be influenced by such sources of error. Moreover, our study was made feasible because we are an integrated healthcare system with PAP refill information made easily available from the electronic medical records-derived disease registry, which may not be as easily accomplished in systems that do not have such an integrated model. All of the patients were receiving care exclusively from the VA in Tucson, but we realize that they may not seek PAP refills through other sources. However such refills from outside the system are unlikely for the following reasons: (a) Patients at the VA in Tucson are “means tested” and seldom have third party insurance. (b) Even when such private insurance exists, the veterans are unlikely to seek refills from such sources because they would need to pay full price (online) or co-pays (private insurance-based) for such refills, whereas the refills from the Tucson VA’s prosthetics department are available at no cost.

Second, considering the time period of 1 to 7 years in our validation dataset, this surrogate measure is not recommended for the assessment of PAP adherence in the short term (61-90 days) or support continued coverage from Medicare. Third, our data were primarily derived from middle-aged to older men; this limits generalizability to women. Systems with greater representation of women may need to reproduce our results Fourth, while the threshold levels of the surrogate measure predicted long-term PAP adherence in a validation dataset, care should be taken in not using refills of PAP accessories as a prospective predictor of adherence on the basis of this study. Lastly, masks or total refill was associated with long-term PAP adherence, and therefore a causal effect cannot be implied.

CONCLUSION

Refill rate of PAP accessories exhibited good test characteristics for predicting long-term adherence to PAP therapy. Such a surrogate measure based upon insurance claims data can be a powerful epidemiological tool in comparative-effectiveness research utilizing bioinformatics of claims data from integrated healthcare systems or Medicare beneficiaries, and for monitoring performance of health systems and supporting quality improvement initiatives that promote PAP adherence.

REFERENCES


ACKNOWLEDGMENTS

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DISCLOSURE STATEMENT

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Relative Prolongation of Inspiratory Time Predicts High versus Low Resistance Categorization of Hypopneas

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Study Objectives: Sleep disordered breathing events conceptually separate into “obstructive” and “central” events. Esophageal manometry is the definitive but invasive means of classifying hypopneas. The purpose of this project was to identify noninvasive markers for discriminating high vs. low resistance hypopneas. Methods: Forty subjects with obstructive or central sleep apnea underwent diagnostic polysomnography with nasal cannula airflow and esophageal manometry; 200% resistance relative to reference breaths was used to define “high” resistance. Noninvasive parameters from 292 randomly selected hypopneas in 20 subjects were analyzed and correlated to resistance. The best parameter and cutoff for predicting high relative resistance was determined and tested prospectively in 2 test sets in the 20 remaining subjects. Test Set A: 15 randomly selected hypopneas in each subject; Test Set B: all hypopneas in 7 subjects. Results: In the development set, prolongation of inspiratory time during the 2 smallest breaths of a hypopnea (Ti) relative to baseline had the best correlation to high relative resistance. In the Test Set A, relative Ti > 110% classified obstructive events with sensitivity = 72%, specificity = 77%, PPV = 64%, NPV = 83%. Similar numbers were obtained for classification of hypopneas based on presence of flow limitation (FL) alone. When either relative Ti or presence of FL were used to define high resistance, sensitivity = 84%, specificity = 74%, PPV = 65%, NPV = 89%. Similar results were obtained for Test Set B. Conclusions: Relative prolongation of Ti is a good noninvasive predictor of high/low resistance in a dataset with both FL and NFL hypopneas. Combination of FL and relative Ti improves this classification. The use of Ti to separate obstructive and central hypopneas needs to be further tested for clinical utility (outcomes and treatment effects). Keywords: Sleep disordered breathing, obstructive sleep apnea, central sleep apnea, hypopnea, diagnosis

Citation: Mooney AM; Abounasr KK; Rapoport DM; Ayappa I. Relative prolongation of inspiratory time predicts high versus low resistance categorization of hypopneas. J Clin Sleep Med 2012;8(2):177-185.

BRIEF SUMMARY

Current Knowledge/Study Rationale: On polysomnography it is difficult to separate central from obstructive hypopneas without invasive monitoring. The purpose of the current project was to separate hypopneas into central (low resistance) and obstructive (high resistance) using non-invasive criteria derived from the flow signal alone.

Study Impact: An algorithm based on the inspiratory time and presence of inspiratory flow limitation on the airflow signal was useful in separating obstructive from central hypopneas. This non-invasive technique has the potential to improve clinical decision making and influence research design.

The etiology is much more problematic. Esophageal manometry combined with measurement of airflow is the accepted gold standard, as the ratio of effort to flow defines resistance. However, this technique is invasive, disruptive of sleep, and considered by most clinical laboratories as unrealistic for routine use.

Pulse transit time has been shown in a small study to be a useful noninvasive tool for recognition of central hypopneas, but this data is not routinely collected. Noninvasive techniques based on airflow exist to identify collapsible upper airway behavior; this collapsible behavior generally identifies elevated upper airway resistance. In particular, we and others have shown that the presence of inspiratory flattening on a nasal cannula/pressure transducer tracing strongly suggests flow limitation (FL) which...
Methods

Subjects

The dataset consisted of 40 subjects selected from patients seen in the NYU Sleep Disorders Center. These subjects were chosen with the target of obtaining a wide spectrum of hypopneas with (FL) and without (NFL) inspiratory flow limitation. Twenty-two of these patients had previously undergone an NPSG with esophageal manometry as part of other research protocols for suspected obstructive sleep apnea (19) or suspected central sleep apnea (3). The remaining 18 patients were recruited because they had a clinical presentation suggestive of central sleep apnea and on NPSG had > 25% of hypopneas without flow limitation. No patient was taking sedative or hypnotic medication, but 4 subjects were on narcotic medications at the time of study (3 in development set, 1 in test set). Aggregate patient characteristics are shown in Table 1.

The study was approved by the Institutional Review Board of New York University School of Medicine, and all subjects signed informed consent prior to being included in this study.
NPSG Protocol

Polysomnography was performed using the standard clinical protocol recommended by the AASM with the addition of esophageal manometry. A nasal cannula pressure transducer system transducer (Protech PTAF2) was used to measure airflow along with an oral thermistor to detect mouth breathing. An esophageal catheter consisting of a thin catheter ending in a 10-cm latex balloon (Ackrad Labs, NJ) was placed transnasally following lidocaine anesthesia, and positioned in the lower third of the esophagus. Esophageal pressure measurements were made with a 100 cm H₂O pressure transducer (Validyne, Northridge, CA). Chest wall and abdominal movement were monitored with uncalibrated respiratory inductance plethysmography. A single technician scored all sleep studies for sleep and respiration. Sleep was scored according to AASM criteria. Hypopneas were defined as events ≥ 10 sec where the square root of the airflow signal on the nasal cannula was reduced to < 70% regardless of desaturation or arousal, but not reduced to < 10% (in which case the event was rescored as an apnea). To become proportional to actual flow (which was needed to calculate resistance), the pressure change in the nose obtained with a nasal cannula needs to be linearized with a square root transform.

Data Analysis

Each hypopnea used in the development and test set (see below) was characterized as FL or NFL using visual assessment. Specifically we examined the shape of each breath on the airflow/time curve for inspiratory flattening, which we have previously shown to be a reliable surrogate for actual detection of flow limitation on a flow/pressure curve. While subtle changes in the inspiratory flow curve may be detected by some observers, our experience suggests that when these are inconsistent or ambiguous (e.g., Figure 1B, C), the correlation to the flow/pressure curve deteriorates. Each hypopnea was reviewed visually by 2 experienced researchers and classified as FL only if the 2 researchers agreed. For each hypopnea, the 2 consecutive breaths with the lowest flow were identified. Two consecutive reference breaths with the highest flow were identified from the 30 sec before or after the event. For each breath the following variables were extracted: Flow (peak value of square root of nasal cannula signal for NFL breaths, value of square root of nasal cannula signal during the plateau phase for FL breaths), ∆Esophageal Pressure (from end expiratory baseline [∆Effort]), Resistance (∆Effort / Flow), Inspiratory Time (Tᵢ), Duty Cycle (Tᵢ/Tₜot), and Inspiratory/Expiratory duration (Tᵢ/Tₑ). For each variable, the values for the 2 breaths within the hypopnea were averaged. Similarly, for each variable the values for the 2 reference breaths were averaged. Data were expressed as the ratio of hypopnea-to-reference values in order to represent relative effort, relative resistance, relative Tᵢ, relative Tᵢ/Tᵢot and relative Tᵢ/Tₑ.

Development and test sets

The 40 sleep studies available for analysis were divided equally into 2 sets—one for development and one for testing of the algorithms. Each set contained 10 patients whose diagnostic PSG suggested primarily obstructive sleep apnea, and 10 patients where the esophageal manometry suggested predominantly central sleep apnea (CSA) or Cheyne Stokes respiration (CSR). In the development set, 5 events with inspiratory flattening of the flow/time signal and 10 without inspiratory flattening (where available) were selected from each study. The development set contained 73 FL and 219 NFL events. Equal numbers of events (where available) were selected from each patient in order to avoid overrepresentation from any given patient while generating rules for categorization of events. Data for the test set subjects were not analyzed until after analysis on the development set (and final definitions of noninvasive criteria) were completed. Test Set A contained 15 randomly selected hypopneas from each patient in parallel fashion as extracted from the development set (5 events with inspiratory flattening of the flow/time signal and 10 without inspiratory flattening [where available]). Test Set A contained 72 FL and 185 NFL events. Test Set B contained all the hypopneas observed in a subgroup of 7 patients. Four of these patients had classical obstructive sleep apnea, and 3 of these patients had atypical sleep disordered breathing with periodic breathing and predominantly NFL hypopneas. Test Set B contained 223 FL and 410 NFL events. Events in the development set and all test sets were chosen randomly without respect to body position during sleep.

Reference definition of individual events as “high” and “low” resistance

As stated in the introduction, relative resistance or relative effort are alternative ways to define obstructive vs central events using the “gold standard” invasive methodology of esophageal manometry. However, events with a relative decrease in effort do not all have a low resistance, and can be associated with either a proportional decrease in airflow (unchanged resistance) or disproportional decrease in airflow (representing increased resistance); thus decreased effort can be associated with both central or obstructive pathology. For the present analyses, we chose to define events as obstructive vs. non-obstructive using relative resistance and not relative effort. The relationship between these parameters in our da-
tastaset is shown in Figure 2. The high correlation (0.87) suggests similar results would be obtained when either relative resistance or relative effort is chosen as the basis for a reference classification of hypopneas, but importantly, 63% of events with reduced relative effort, i.e., <100%, (a possible definition of “central”) have relative resistances in the 100% to 200% range. Thus, given our choice of relative resistance as the defining variable for separating “low” and “high” resistance events, a decision needed to be made with respect to the cut point separating inappropriately obstructive from central hypopneas. Whereas the breaths chosen within events were clearly during sleep, our reference breaths were chosen from periods surrounding SDB events that were usually but not always associated with subcortical arousal (e.g., heart rate acceleration without clear EEG arousal), cortical arousal, or awakening. A doubling of airway resistance has been described in normal subjects at sleep onset,22 and for this reason, or awakening. A doubling of airway resistance has been developed in normal subjects at sleep onset,22 and for this reason, development set using a cutoff of >200% relative resistance (solid line) to define obstructive events. Relative Ti >110% (i.e., prolongation of Ti) was the best cutoff to predict high relative resistance, with an AUC of 0.82. Using an alternative reference definition of obstructive events as relative effort >100% (dotted line), ROC analysis identifies a similar Ti (>104%) as the best cutoff to predict high effort, with an AUC of 0.76.

Table 2 shows a classification analysis for NFL events in the development set. Sensitivity, specificity, PPV, and NPV are listed for using relative Ti >110% to identify obstructive events defined as relative resistance >200%. The table also lists a classification analysis for using relative Ti >104% to identify obstructive events when these are defined as relative effort >100%. By either criterion, relative Ti shows a high negative predictive value: in NFL events, absence of relative lengthening of Ti strongly suggests that an event is not obstructive. However, in NFL events, relative lengthening has little predictive value (PPV = 32% to 36%).

Analyses and Statistics
Within the development set, correlations between relative resistance, relative effort and each relative noninvasive parameter (T_i, T_i/T_tot, T_i/T_e) were first examined only in NFL events. The noninvasive parameter with the highest correlation to relative resistance was submitted to ROC analysis in order to identify the best cutoff for noninvasive classification of resistance or effort. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for high relative resistance (>200%) were calculated for the NFL events of the development set and Test Set A. An additional analysis was performed after inclusion of FL events in Test Set A and stratified by sleep stage (NREM/REM). Analyses were repeated using presence/absence of FL as the noninvasive parameters, and for the combination of relative T_i and presence of FL. These analyses were repeated for Test Set B. To test the sensitivity of our definition of “obstruction,” Test Set A was also analyzed according to alternative definitions (effort >100% = obstructive, resistance >150% = obstructive).

RESULTS

Development Set
As previously shown,23 events with inspiratory flow limitation (FL) showed an overall high (289% ± 142%) relative resistance. Events without flow limitation (NFL) showed a significantly lower relative resistance than FL events (151% ± 100%, p < 0.001), but, as shown in Figure 3, there was a substantial overlap of relative resistance between FL and NFL events. Thus flow contour alone was not sufficient to noninvasively predict low relative resistance.

Figure 4 shows the relationship of the noninvasive flow parameters (relative T_i, relative T_i/T_tot and relative T_i/T_e) to relative resistance in NFL events. All 3 noninvasive parameters were significantly correlated (p <0.001) with relative resistance; the highest correlation was observed between relative T_i and relative resistance. This was also true when the noninvasive parameters were examined against relative effort (data not shown).

Figure 5 shows an ROC curve for all NFL events in the development set using a cutoff of >200% relative resistance (solid line) to define obstructive events. Relative Ti >110% (i.e., prolongation of Ti) was the best cutoff to predict high relative resistance, with an AUC of 0.82. Using an alternative reference definition of obstructive events as relative effort >100% (dotted line), ROC analysis identifies a similar Ti (>104%) as the best cutoff to predict high effort, with an AUC of 0.76.

Table 2 shows a classification analysis for NFL events in the development set. Sensitivity, specificity, PPV, and NPV are listed for using relative Ti >110% to identify obstructive events defined as relative resistance >200%. The table also lists a classification analysis for using relative Ti >104% to identify obstructive events when these are defined as relative effort >100%. By either criterion, relative Ti shows a high negative predictive value: in NFL events, absence of relative lengthening of Ti strongly suggests that an event is not obstructive. However, in NFL events, relative lengthening has little predictive value (PPV = 32% to 36%).
High vs Low Resistance Categorization of Hypopneas

As a test of the sensitivity of our findings to the definition of “high” relative resistance (> 200%), we repeated the classification analysis of Ti as a predictor of resistance using a cutoff of 150%.

Table 6 shows these data and suggests similar trends.

To incorporate all of the observations made above for noninvasive prediction, we present a combined classification analysis (Table 7) for predicting relative resistance > 200% for events.
### Table 3—Test Set A

<table>
<thead>
<tr>
<th>A NFL events only (n = 185)</th>
<th>Sens</th>
<th>Spec</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obstructive event defined as Relative Resistance &gt; 200% Test positive = Relative Ti &gt; 110%</td>
<td>63</td>
<td>83</td>
<td>52</td>
<td>89</td>
</tr>
<tr>
<td>Obstructive event defined as Relative Effort &gt; 100% Test positive = Relative Ti &gt; 104%</td>
<td>68</td>
<td>69</td>
<td>39</td>
<td>88</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>B NFL + FL events (n = 257)</th>
<th>Sens</th>
<th>Spec</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obstructive event defined as Relative Resistance &gt; 200% Test positive = Relative Ti &gt; 110%</td>
<td>72</td>
<td>77</td>
<td>64</td>
<td>83</td>
</tr>
<tr>
<td>Obstructive event defined as Relative Effort &gt; 100% Test positive = Relative Ti &gt; 104%</td>
<td>82</td>
<td>60</td>
<td>49</td>
<td>88</td>
</tr>
</tbody>
</table>

### Table 4—Test Set A, effect of sleep stage (REM/NREM) on test validity

<table>
<thead>
<tr>
<th>NFL events only (n = 185)</th>
<th>Sens</th>
<th>Spec</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>REM (n = 44)</td>
<td>Obstructive event defined as Relative Resistance &gt; 200% Test positive = Relative Ti &gt; 110%</td>
<td>50</td>
<td>88</td>
<td>17</td>
</tr>
<tr>
<td>NREM (n = 141)</td>
<td>Obstructive event defined as Relative Resistance &gt; 200% Test positive = Relative Ti &gt; 110%</td>
<td>64</td>
<td>81</td>
<td>57</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>NFL + FL events (n = 257)</th>
<th>Sens</th>
<th>Spec</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>REM (n = 57)</td>
<td>Obstructive event defined as Relative Resistance &gt; 200% Test positive = Relative Ti &gt; 110%</td>
<td>60</td>
<td>79</td>
<td>38</td>
</tr>
<tr>
<td>NREM (n = 200)</td>
<td>Obstructive event defined as Relative Resistance &gt; 200% Test positive = Relative Ti &gt; 110%</td>
<td>74</td>
<td>76</td>
<td>69</td>
</tr>
</tbody>
</table>

### Table 5—Test Set A, classification results using presence or absence of flow limitation alone

<table>
<thead>
<tr>
<th>NFL + FL events (n = 257)</th>
<th>Sens</th>
<th>Spec</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Events (n = 257)</td>
<td>Obstructive event defined as Relative Resistance &gt; 200% Test positive = Flow limitation present</td>
<td>56</td>
<td>88</td>
<td>74</td>
</tr>
<tr>
<td>REM (n = 57)</td>
<td>Obstructive event defined as Relative Resistance &gt; 200% Test positive = Flow limitation present</td>
<td>80</td>
<td>89</td>
<td>62</td>
</tr>
<tr>
<td>NREM (n = 200)</td>
<td>Obstructive event defined as Relative Resistance &gt; 200% Test positive = Flow limitation present</td>
<td>54</td>
<td>88</td>
<td>76</td>
</tr>
</tbody>
</table>

### Table 6—Effect of an alternative definition of resistance as > 150% in Test Set A

<table>
<thead>
<tr>
<th>NFL events (n = 185)</th>
<th>Sens</th>
<th>Spec</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease present = Relative Resistance &gt; 150% Test positive = Relative Ti &gt; 110%</td>
<td>48</td>
<td>85</td>
<td>64</td>
<td>75</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>NFL + FL events (n = 257)</th>
<th>Sens</th>
<th>Spec</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease present = Relative Resistance &gt; 150% Test positive = Relative Ti &gt; 110%</td>
<td>63</td>
<td>80</td>
<td>76</td>
<td>68</td>
</tr>
</tbody>
</table>

### Table 7—Test Set A, two-tiered classification analysis

<table>
<thead>
<tr>
<th>NFL + FL events (n = 257)</th>
<th>Sens</th>
<th>Spec</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obstructive event defined as Relative Resistance &gt; 200% Test positive = Flow limitation present or if NFL then Relative Ti &gt; 110%</td>
<td>84</td>
<td>74</td>
<td>65</td>
<td>89</td>
</tr>
</tbody>
</table>
in Test Set A using either the presence of FL or Ti > 110%. By these criteria, sensitivity rises to 84%, while specificity, PPV and NPV remain similar at 74%, 65%, 89%.

Figure 6 compares the validity of each test (1-presence of flow limitation alone, 2-relative prolongation of Ti > 110% alone, 3-either presence of flow limitation or relative prolongation of Ti > 110%) to predict relative resistance > 200%.

Test Set B
In contrast to Test Set A, which consisted of an equal number of hypopneas randomly selected from all patients, Test Set B evaluated all hypopneas in 7 patients. Four of the patients demonstrated classic loud snoring and flow limitation throughout the majority of the night. The other three patients had predominantly non-flow limited hypopneas occurring in a periodic pattern. There were 633 hypopneas in Test Set B (410 NFL, 223 FL). Table 8 shows that the 3 noninvasive predictors (presence of FL, relative Ti > 110%, and the combination of the two criteria) show good sensitivity, specificity, PPV, and NPV in the data from Test Set B.

DISCUSSION
The present analysis shows that useful predictions about whether a hypopnea is “obstructive” or “central” (defined by relative resistance) can be made from airflow alone. Our data show that the relative prolongation of Ti can be used to correctly classify the majority of hypopneas without use of invasive monitoring in a dataset enriched for ambiguous (non-flow limited) hypopneas. In this dataset, the combined assessment of relative Ti and inspiratory flow limitation had greater accuracy than either alone. An algorithm categorizing each hypopnea event first according to FL and then according to relative Ti, not only helps classify individual events, but may also help in the clinical classification of patients and thus potentially inform treatment decisions.

The present study was predicated on the assumption that there is a clear dichotomy between “central” and “obstructive” etiologies that can be applied to each individual hypopnea, and that this was represented by the relative resistance obtained using the invasive measurement of esophageal manometry. We acknowledge that there may be considerable overlap in the pathophysiology underlying a given event, and as a result there may not exist an unambiguously correct distinction between an obstructive and a central hypopnea. However, it is currently assumed that this distinction exists and has clinical significance as well as implications for treatment and prognosis; a dichotomous classification scheme is currently standard clinical practice.

In the absence of consistent definitions of hypopnea, we chose to use a very inclusive definition of hypopnea based on reduced airflow alone for our analysis, rather than one that disregards events without 4% desaturation or EEG arousal. In addition, our methodology for classifying hypopneas requires comment. The signals we used for flow are not calibrated. Thus all measurements (such as resistance) were not absolute, and needed to be related to a “baseline.” By calculating relative resistance, and relative Ti, we build on the logic used to define hypopnea using the accepted change in relative amplitude. We used high vs. low relative resistance as the variable to provide the reference categorization of each SDB event, with > 200% being the cut point between obstructive and non-obstructive (see justification in methods).

Having chosen a definition for “correctly” classifying hypopneas as “obstructive” or “central,” the second component of our analysis was to use the now classified events as a test of various noninvasive algorithms to accomplish the same classification. Although relative prolongation of Ti alone provided a highly specific marker for high resistance (similar to flow limitation), it lacks sensitivity. Using the presence of either flow limitation or the prolongation of Ti (relative Ti > 110%) improves sensitivity while maintaining NPV for classifying events as “obstructive.” An automated technique utilizing discriminant analysis of flow limitation and other features extracted from the airflow signal was recently reported to demonstrate similar accuracy in predicting relative changes in effort and supports our conclusions.

Figure 6—Comparison of the sensitivity, specificity, PPV, and NPV for each noninvasive predictor of high resistance, in Test Set A events (FL and NFL)

Table 8—Classification results using the 3 noninvasive predictors in Test Set B

<table>
<thead>
<tr>
<th>NFL + FL events (n = 633)</th>
<th>Sens</th>
<th>Spec</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>All hypopneas in 7 Patients (n = 633)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obstructive event defined as Relative Resistance &gt; 200%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test positive = Flow limitation present</td>
<td>71%</td>
<td>89%</td>
<td>81%</td>
<td>82%</td>
</tr>
<tr>
<td>Test positive = Relative Ti &gt; 110%</td>
<td>72%</td>
<td>81%</td>
<td>72%</td>
<td>81%</td>
</tr>
<tr>
<td>Test positive = Either FL present or Relative Ti &gt; 110%</td>
<td>84%</td>
<td>77%</td>
<td>71%</td>
<td>88%</td>
</tr>
</tbody>
</table>
The observed low sensitivity for detecting events in Test Set A with high relative resistance is predictable from the choice made in constructing this dataset. We specifically enriched the data set with hypopneas without flow limitation as we felt that these posed the highest ambiguity based on prior work. The sensitivity of our algorithm to high resistance events necessarily increases as one includes more patients (and events) that are flow limited and this is confirmed by the higher sensitivity seen in Test Set B that has greater number of FL events.

There are obvious advantages to an algorithm for separating obstructive from central events based on noninvasive measurements. Patient willingness, use of lidocaine, sleep effects, potential extension to home study data and, finally, cost, all favor a noninvasive test over esophageal manometry if comparable classification of events can be achieved. A possible limitation of our data is that quantitative flow was not measured using a pneumotachograph, and thus resistance cannot be quantitative determined. Our choice of the nasal cannula signal was intentional in this regard, as we were trying to develop a technique that was generalizable to routine clinical use, and pneumotachographs are generally reserved to specialized research applications. We and others have previously shown that the nasal cannula qualitative flow signal can accurately determine presence or absence of flow limitation. Furthermore, breath duration (used to define the respiratory variables we examined relative T, relative T/Tot, relative T/Tt) does not require quantitative airflow measurement. While quantitative resistance cannot be calculated from the nasal cannula signal, relative resistance should not suffer from this limitation.

Other aspects related to our methodology require comment. First, since airflow was collected with a nasal cannula/pressure transducer system where the calibration is only valid across short time periods (3 min) we needed to define “baseline breathing” for each event rather than using one single baseline period per subject. We chose periods of breathing within 30 seconds of the hypopnea. Second, in order to maximize reproducibility of breaths chosen for analysis we use the 2 biggest breaths for use as reference and 2 smallest breaths within the hypopnea.

An interesting and striking finding in our study was the behavior of our algorithm specifically in REM. In this state, absence of flow limitation was almost always associated with low resistance. Thus, in REM there was little need to explore additional noninvasive parameters beyond flow limitation to classify hypopneas. One possible explanation is that the upper airway during REM is so susceptible to collapse that any increase in effort brings out flow limitation. In NREM the lesser collapsibility of the airway makes for more overlap between the level of effort and the expression of flow limitation.

A limitation of our dataset is the predominance of male patients. Gender related differences in load response and arousal threshold may affect the appearance of FL and relative prolongation of T,. However, data from Pillar, et al. show that despite the greater prevalence of flow limitation and the reduced ventilation seen in men with inspiratory resistive loading, men and women had similar prolongation of inspiratory time. Further testing in a dataset with more women may be desirable before generalizing our conclusions.

In conclusion, we describe a noninvasive algorithm applied to data derived solely from the nasal cannula flow signal which is easily automatable and has good sensitivity and specificity for prediction of relative resistance of hypopneas. The utility of this algorithm lies in its ability to noninvasively classify obstructive and central hypopneas in clinical and research data sets of NPSGs, and thus test the utility and implications of this distinction for diagnostic, therapeutic and long term-outcomes.

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High vs Low Resistance Categorization of Hypopneas


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Menopausal night sweats, which are hot flashes that occur at night, are common in postmenopausal women and are significantly more bothersome to women than daytime hot flashes, most likely because of the associated interference with sleep. Many women with night sweats will report daytime hot flashes, most likely because of the associated interference with sleep. In one case, what started as isolated nighttime awakenings slowly progressed to awakenings accompanied by typical menopausal night sweats. This led to the theory that the initial isolated nighttime awakenings in this patient may have been secondary to a menopausal etiology related to low serum estradiol levels. In the subsequent 2 cases, early follicular phase serum estradiol was confirmed to be low. It is theorized that isolated nighttime awakenings in some premenopausal women may be caused by low serum estradiol, triggering events physiologically related to menopausal night sweats. Further research is needed to determine if low early follicular phase serum estradiol is associated with nighttime awakenings in premenopausal women not experiencing night sweats.

**Keywords:** Insomnia, estradiol, menopause, awakenings, night sweat, hot flash


**BRIEF SUMMARY**

Current Knowledge/Study Rationale: It is known that women experience insomnia at significantly higher rates than men and that this disparity may be related to cycling hormones, however, the sleep-related physiology of this association is unknown. Three cases are presented here suggesting that insomnia due to nighttime awakenings in some cycling premenopausal women may be physiologically related to menopausal night sweats and may also improve with bedtime gabapentin, a treatment known to be effective for hot flashes and night sweats.

Study Impact: These cases may represent the first description of a novel sleep disorder unique to women found to have low serum estradiol and nighttime awakenings. This proposed sleep disorder has been coined LUNAs and may help to explain the higher prevalence of insomnia in women.

**CASE 1**

In 2006, a 48-year-old white female having regular monthly menses presented with a chief complaint of frequent nighttime awakenings for the previous 3 years. The patient reported having sudden awakenings from deep sleep, “as if I have been shocked awake,” followed by great difficulty returning to sleep. These unexplained awakenings occurred 2-3 times a night ≥ 3 nights a week. The sleep disruption was causing excessive daytime sleepiness, difficulty concentrating at work, and irritability. She had been taking oral contraception daily for about 12 years. A 6-month trial of trazodone at bedtime and a 4-month trial of amitriptyline at bedtime were both ineffective.

Two years after the awakenings started, in 2005, the patient underwent a nocturnal polysomnogram that was normal (respiratory distress index: 3.6/h and occasional periodic limb movements).

In 2006, the patient began noticing that after some of her typical unexplained nighttime awakenings, she would feel hot and occasionally sweaty. Her serum follicle stimulating hormone (FSH) and luteinizing hormone (LH) levels were found to be normal, at 3.0 and 1.1 mIU/mL, respectively, while she was still taking oral contraception. Under the presumption that the patient was now experiencing menopausal night sweats, her primary physician increased her dose of oral contraception. There was no improvement in her symptoms after 2 months. The patient was not interested in taking hormone replacement therapy. The patient denied symptoms of restless legs syndrome...
T Guttuso

(RLS), periodic leg movements of sleep (PLMS), or snoring during sleep. Gabapentin 300 mg at bedtime (qhs) was initiated in 9/2006, based on evidence of efficacy in the treatment of hot flashes and night sweats and improved sleep in such patients. The patient experienced benefit after the first dose of gabapentin, reporting a full night’s sleep without any awakenings or night sweats. This degree of efficacy persisted for about 2 weeks, at which time the isolated nighttime awakenings began to recur, sometimes accompanied by feeling hot and sweaty. The dose of gabapentin was increased to 600 mg qhs, which again resolved the symptoms. The patient also reported normalized daytime alertness, concentration, and mood. The side effect of early morning dizziness occurred infrequently and did not affect any activities of daily living. Attempts at discontinuing gabapentin resulted in recurring night sweats and awakenings.

Three months later, in 12/2006, oral contraception was discontinued. Regular monthly menses continued until 9/2007, when menses began occurring every other month until 4/2008 when menses stopped. In 10/2008, serum FSH and LH were clearly in the postmenopausal ranges, at 114.0 and 51.7 mIU/mL, respectively.

This case led to the hypothesis that nighttime awakenings in late premenopausal women may be caused by declining systemic estradiol triggering isolated nighttime sympathetic surges without any subsequent night sweats. This hypothesized novel sleep disorder associated with low serum estradiol causing nighttime awakenings was coined LUNAs.

**CASE 2**

A 42-year-old white female having regular monthly menses presented in 1/2010, complaining of 2 years of worsening nighttime awakenings, excessive daytime sleepiness, and irritability. The patient had experienced hot flashes and night sweats with her 2 pregnancies at 33 years and 38 years, which fully resolved postpartum. The patient denied any hot flashes or night sweats at the time of presentation. The patient reported that almost every night over the previous 2 years, she would have 2-5 nighttime awakenings occurring at predictable times and causing great difficulty returning to sleep. The patient also noticed that the awakenings were more frequent and severe for 1-2 days before her menses and the first 4-5 days of her menses every month. The patient denied symptoms of RLS or PLMS or snoring during sleep.

The nighttime awakenings were postulated to be LUNAs due to the patient’s age and the exacerbation of symptoms just before and during menses, the time of the menstrual cycle when serum estradiol is at its lowest.

Due to the favorable response of the patient in Case 1 to gabapentin treatment, gabapentin 300 mg qhs was initiated. The patient reported near full resolution of the nighttime awakenings within 2 days. A side effect of early morning sedation was mild and resolved within 4 days. About 2 weeks later, the nighttime awakenings began to return and gabapentin was increased to 600 mg qhs with good effect for about 6 weeks, when the dose again needed to be increased (to 900 mg qhs). The nighttime awakenings would recur when the patient forgot to take gabapentin. The daytime sleepiness and irritability reported before starting gabapentin resolved after about 3 weeks of gabapentin treatment.

On 6/29/11—while still having regular monthly menses and still taking 900 mg of gabapentin qhs—serum FSH, LH, and estradiol on day 3 of her menstrual cycle were 13.7 mIU/mL, 7.0 mIU/mL, and 32.2 pg/mL, respectively, and on day 14 were 13.7 mIU/mL, 39.1 mIU/mL, and 665.3 pg/mL, respectively. Ovulation was likely occurring on day 14 in this patient, evidenced by the high LH and estradiol levels.

**CASE 3**

A 46-year-old white female presented in 3/2011 with a chief complaint of nighttime awakenings, concentration problems, and daytime sleepiness and fatigue for the previous 6 years. The problem had progressed to the point that over the previous year she began needing to drink coffee throughout the day in order to stay awake at work. Almost every night she reported awakening around 02:30 for no apparent reason with great difficulty returning to sleep. These nighttime awakenings were not accompanied by feeling hot or sweaty. During daylight savings time, the awakenings would change by 1 hour for a few months and then return to 02:30. For 3 months prior to presentation, the patient noticed occasional spells of feeling very warm during the day without any flushing or sweating. The patient denied symptoms of RLS, PLMS, or snoring during sleep.

At 36 years of age, about 4 years prior to the nighttime awakenings, she experienced 2 weeks of severe hot flashes and night sweats after having an ovary removed for cysts causing abdominal pain.

The patient had regular monthly menses until 44 years of age, about 4 years after the nighttime awakenings started, when she developed heavy menstrual bleeding and had a 52 mg levonorgestrel intrauterine device (IUD) placed. The IUD did improve her heavy menses but did not affect her nighttime awakenings. Since the nighttime awakenings had been slowly worsening since the age of 40 and the patient was starting to experience daytime spells consistent with mild hot flashes, the nighttime awakenings were suspected to be LUNAs. For this reason, gabapentin 300 mg qhs was initiated for 3 nights and then increased to 600 mg qhs for better effect. The nighttime awakenings fully resolved within 4 days except for occasional awakenings at 02:30, after which the patient was quickly able to return to sleep. After 2 weeks of gabapentin treatment the patient reported greatly improved daytime alertness, concentration, and energy and was able to stop drinking coffee at work. The patient denied any side effects from gabapentin.

After 8 weeks of gabapentin therapy, while still having regular monthly menses, serum FSH, LH, and estradiol on day 2 of her menstrual cycle were 6.3 mIU/mL, 5.1 mIU/mL, and 50 pg/mL, respectively, and on day 14 were 4.7 mIU/mL, 4.8 mIU/mL, and 150 pg/mL, respectively.

**DISCUSSION**

Although it is proposed that the insomnia occurring in these 3 cases was caused by low serum estradiol levels triggering nighttime awakenings physiologically related to menopausal night sweats, in only 2 of these cases was estradiol assessed and shown to be low during the early follicular phase. It certainly is possible that the low serum estradiol in these 2 cases
was simply coincidental and not causally related to the occurrence of the nighttime awakenings. In addition, gabapentin’s positive effects on nighttime awakenings reported in these 3 cases may have been due to its known general sleep-enhancing actions and not to a specific effect on the nighttime awakenings theorized here to have been caused by low serum estradiol and coined LUNAs.

On the other hand, these cases, summarized in Table 1, may be the first report of a novel sleep disorder unique to women. A large meta-analysis showed insomnia to be more common in females than males, and for the disparity to increase with increasing age. Also, premenopausal women with irregular menstrual cycles, which often signal declining estradiol levels, are twice as likely to report insomnia symptoms such as nighttime awakenings as those with regular menstrual cycles. These findings support an association between declining serum estradiol and insomnia in women. The 3 cases reported here also support this association. None of the women noted nighttime awakenings until after 40 years of age, a time when estradiol levels in some women may be declining. The patient in Case 2 noticed clear worsening of her nighttime awakenings during the days of her menstrual cycle when serum estradiol was at its nadir. Indeed, Cases 2 and 3 were both found to have low serum estradiol on day 3 (32.2 pg/mL) and day 2 (50 pg/mL), respectively, of their menstrual cycles. In contrast, a normal day 2–7 serum estradiol in premenopausal women over 40 years of age is 73–78 pg/mL, while postmenopausal levels are <20 pg/mL.

Although serum estradiol was not assessed in Case 1, what began as isolated nighttime awakenings at 45 years of age slowly morphed into awakenings occasionally followed by night sweats at 48 years, implicating a similar physiological process underlying these conditions. Finally, all 3 patients’ nighttime awakenings resolved with a single bedtime dose of gabapentin, a therapy known to be an effective treatment for hot flashes and night sweats. The fact that the nighttime awakenings in Case 1 failed to respond to oral contraception drugs (OCDs) may have been due to the much lower estrogen dose found in OCDs (about 0.05 mg) than in hormone replacement therapy (about 0.60 mg), which is the only FDA-approved therapy for menopausal hot flashes and night sweats.

In summary, the proposed LUNAs are hypothesized to be physiologically related to night sweats and to occur in women several years before menopausal symptoms would typically be expected to occur. Further research is needed in premenopausal women with isolated nighttime awakenings to determine if early follicular phase serum estradiol levels are significantly decreased compared to age-matched control women without nighttime awakenings and to exclude other contributing conditions such as sleep apnea or PLMS.

Table 1—Summary of 3 cases

<table>
<thead>
<tr>
<th>Patient age at onset of nighttime awakenings</th>
<th>History of hot flashes or night sweats?</th>
<th>Low early follicular phase serum estradiol?</th>
<th>Subjective improvement of nighttime awakenings with gabapentin qhs?</th>
<th>Final qhs gabapentin dose</th>
<th>Transient gabapentin side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>45yo (Case 1)</td>
<td>yes</td>
<td>?</td>
<td>yes</td>
<td>600 mg</td>
<td>Dizziness</td>
</tr>
<tr>
<td>40yo (Case 2)</td>
<td>yes</td>
<td>yes (32.2 pg/mL)</td>
<td>yes</td>
<td>900 mg</td>
<td>Sedation</td>
</tr>
<tr>
<td>40yo (Case 3)</td>
<td>yes</td>
<td>yes (50 pg/mL)</td>
<td>yes</td>
<td>600 mg</td>
<td>None</td>
</tr>
</tbody>
</table>

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DISCLOSURE STATEMENT

This was not an industry supported study. Dr. Guttuso is the inventor on US Patent 6,310,098, which is owned by the University of Rochester, covering the use of gabapentin for treating hot flashes and night sweats. Dr. Guttuso does not receive financial compensation on the sales of generic gabapentin or brand name Neurontin for any use. Dr. Guttuso may receive royalties on the sales of a gabapentin-related drug only if such a drug is FDA-approved for treating hot flashes.
Insomnia is a common problem among patients with obsessive-compulsive disorder (OCD), and patients suffering from acute insomnia with psychiatric comorbidity are more likely to develop chronic insomnia without appropriate intervention. Here we report a case of obsessive-compulsive disorder with acute insomnia, successfully treated with early sleep psychiatric non-pharmacological intervention. The augmentation of medication runs a risk of exacerbating daytime impairment. Clinicians usually prescribe medication, such as antidepressants and hypnotics without reflections for such complaints. However, the use of these sedative agents is often problematic, especially when patients have kept a good QOL activity in daily life. The rapid recovery from acute insomnia in this case suggests that the appropriate use of actigraphy is a favorable non-pharmacological intervention in acute insomnia.

**Keywords:** Insomnia, Obsessive-Compulsive Disorder, actigraphy, subjective-objective discrepancy

**Citation:** Abe Y; Nishimura G; Endo T. Early sleep psychiatric intervention for acute insomnia: implications from a case of obsessive-compulsive disorder. *J Clin Sleep Med* 2012;8(2):191-193.

**REPORT OF CASE**

Mr. T., a 25-year-old man, had a long history of OCD with recurrent obsessive thoughts of touching dirt and compulsive cleaning since preadolescence. At the age of 18, he first consulted a psychiatrist for the purpose of treating his depressive symptoms after his father’s sudden death. His depressive symptoms improved and then stabilized for several years with the aid of pharmacologic treatment (sulpiride 30 mg, clorazepate 7.5 mg, and paroxetine 20 mg). After graduating from professional school, he was able to work as a computer engineer in an urban company, despite persistence of his obsessive symptoms. One winter, he was referred to our outpatient clinic by his general practitioner. His symptoms had already stabilized because of the same medication as a long-term maintenance treatment for OCD.

After 4 months of our follow-up, he was transferred to another section in his company. This change of social environment made him cogitate about his interpersonal relationship with other colleagues, which provoked acute insomnia symptoms, such as difficulty falling asleep and nighttime awaking. Additionally, he also suffered from daytime impairment related to his insomnia, especially hypersomnia and daytime sleepiness. He said, “I can’t concentrate on my work because I made efforts to get to sleep last night”, “I have to fight to stay awake during my work” and “I feel afraid of falling asleep tonight because of my insomnia”. Typically, the fear of insomnia was exacerbated. In other words, he was very afraid of losing his career position in his new section caused by the daytime impairments (e.g., losing concentration and diminished performance), which he attributed to his insomnia.

In order to improve acute insomnia symptoms, we treated him mainly with an early sleep psychiatric approach as a non-pharmacological intervention. Intentionally, we avoided increasing medication, because his principal concerns were strongly related with daytime impairment of insomnia. Adding another medication to improve sleep might run a risk of exacerbating daytime consequences of insomnia. In this situation, we treated him, making use of home-monitoring actigraphy and an oxy-
This anxiety and fear of insomnia diminished dramatically, and he was encouraged to visit our clinic 3 times for evaluation. His nighttime actigraphic records always suggested longer and more consolidated sleep than indicated by the subjective intensity of insomnia complaints. As a next step, one night he was asked to get installed a portable oxygen saturation tool. The obtained data showed that some presence of hypoxemia during his sleep, which could partially explain the fragility of his sleep function. Also, he was found drinking alcohol and smoking just before going to bed. Moreover, he often surfed the Internet, eating snacks during the night on weekends. We considered this information as important evidence to stop him from smoking and drinking before bedtime, and to urge him to keep regular habits, even at the weekend. With this intervention equipped with the home-monitored objective data, also based on sleep hygiene education (e.g., avoid bedside drinking, smoking, snacking, and surfing the Internet), his anxiety and fear of insomnia diminished dramatically, and he spontaneously recovered from acute insomnia.

DISCUSSION

Recently, sleep psychiatry (psychiatric therapeutic approach, both biologically and psychologically, based on sleep science) has gathered much attention worldwide. In this case, we attempted an early intervention in the vicious cycle of acute insomnia. This early sleep focused intervention prevented him from entering the chronic vicious cycle of psycho/physiological hyperarousal, which was supposed to play a central role in the pathophysiology of insomnia. Possible other reasons explaining his diminished quality of sleep in this case, were as follows: (1) presence of co-occurring subclinical depressive symptoms, (2) negative consequences of core OCD symptoms of sleep habits, and (3) concurrent diurnal side effects of long-term prescribed medication. Clinically, these aspects must always be taken into consideration for managing sleep disturbance comorbid with neurotic disorders, including OCD.

We emphasize several suggestions about acute insomniacs state. “I can’t sleep,” “I don’t get enough sleep”: This kind of complaint has often led to the easiest solution of direct prescriptions of hypnotics. The accumulation of hypnotics has eventually had negative consequences in their everyday QOLs, such as daytime sleepiness and diminished concentration. Traditionally, Morita Therapy, a unique psychotherapy originated in Japan was devised for treating classical neurotic disorder. That concept has evolved the phenomenology of insomniacs as a subjective fabricated nature, claiming that clinicians are liable to make an error by just giving hypnotics to help the patient’s feeling of sleeplessness without attempting radical cure on him.

In this case, theoretically we applied some conventional concepts of Morita therapy to the treatment, utilizing the latest home monitoring instruments. We have to understand the fundamental phenomenology of diminished quality of sleep, and then give feedback to the acute insomniacs themselves in an appropriate way. To explain this process in the Morita theory, we attempted to stop exacerbating “psychic interaction” of acute insomniacs. This method of feedback may have something in common with the current well-developing biofeedback and mindfulness-based cognitive behavioral therapy for insomnia.

Despite their nature of subjective-objective discrepancy, individuals suffering from acute insomnia are situated under a subjectively perceived overwhelming threat. We may stress that focusing on how sleep state misperception could be a central aspect of insomnia within the context of OCD. From this case study, it appears that the treatment was largely successful because the actigraphic records helped to correct the patient’s misperceptions. Overestimation of performance deficits may also be explained by psychophysiological hyperarousal model of insomnia. Perhaps such a focused intervention has a nonspecific and positive psychotherapeutic effect. This could also have implications about the possible application of actigraphy to treat sleep problems within anxiety disorders.

While actigraphy has been used in research studies for many years, methodological issues had not been systematically addressed in clinical research and practice. A home monitoring system, such as actigraphy, not only provides satisfactory objective evaluation, but also a supportive psychotherapeutic effect in diminishing fear and anxiety related with acute insomnia. Getting an individual to recognize at an early stage, and providing him with treatment pathway guided by actigraph to deal with, were crucial in this case.

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Narcolepsy is thought to be a disorder of REM sleep, with cataplexy representing episodes of REM-related muscle atonia intruding into the waking period. Narcoleptics often report episodes of dreaming during daytime naps, and the diagnosis of narcolepsy is based in part on a mean sleep latency ≤ 8 min with ≥ 2 REM sleep episodes on naps administered during a daytime multiple sleep latency test (MSLT). REM sleep is partially produced by cholinergic activation of the thalamus, and muscle atonia during REM sleep is triggered by the cholinergic effect on the medial medulla.3,4 Both nicotinic and muscarinic agonists, as well as acetylcholinesterase inhibitors, have been shown to increase REM sleep.5-7 Interestingly, although low levels of nicotine administration have been shown to increase REM sleep, high levels of nicotine seem to reduce REM sleep percentage and decrease total sleep time in both animals and humans.8

Of interest in our current case, transdermal nicotine patches in nonsmokers have been shown to reduce REM sleep percentage and decrease total sleep time.9,10 In addition, REM rebound has been shown after stopping nicotine.10,11

This report describes a case of narcolepsy with cataplexy masked by the chronic use of cigarettes and nicotine patches. It has been described that narcoleptic smokers report relief of symptoms by smoking tobacco cigarettes.1 In addition, a case describing partial treatment of sleepiness using a nicotine patch in an adolescent with narcolepsy was recently reported in this journal.2 Our case adds to the growing literature that nicotine may be used to manage symptoms associated with narcolepsy.

**Keywords:** Narcolepsy, cataplexy, nicotine, sleepiness, masked

**Citation:** Ebben MR; Krieger AC. Narcolepsy with cataplexy masked by the use of nicotine. J Clin Sleep Med 2012;8(2):195-196.

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The current case involves an 89-year-old female referred for evaluation of cataplexy-like episodes. The patient describes having infrequent episodes of cataplexy for several years, described as a sensation of temporary loss of strength in her neck and lower extremity muscles, associated with laughing or excessive situational stress. Over the past few years, they have become concerning to her family and friends, as three episodes of body collapse occurred in public, not associated with loss of consciousness or other trauma. Since her teenage years, she has always felt sleepier than other people, requiring frequent naps during the day, and also describes dreaming during naps. She has been a heavy smoker since early adolescence. After having children, her naps were less frequent while she cared for her 7 children. In her mid-30s, the first “cataplectic” event occurred and was temporally associated with smoking cessation. After this event, the patient chose to resume smoking about 20 cigarettes per day until her mid-70s when she quit cigarette smoking after being diagnosed with coronary heart disease. At that point, a formal sleep evaluation revealed a history of intermittent sleep paralysis and hypnagogic hallucinations.

The sleep study was conducted in 1995 and contained 7.5 h of sleep with a 4-min sleep onset REM period. An MSLT performed the next day found a mean sleep latency of 3 min, with REM sleep occurring in 4 of 4 naps. Of note, REM sleep occurred in the first epoch of sleep on all naps. HLA typing for narcolepsy found the patient positive for HLA-DQB1-0602 and HLA-DR15.

The patient was offered stimulants at that point; however, she declined them due to concerns regarding potential addiction and rebound effects. Since then, she has opted to use a nicotine patch, which has been effective in controlling her cataplexy. However, over the past 5 years, 3 episodes of cataplexy were noted, most commonly triggered by either surprise or public speaking (e.g., last event occurred when her name was announced for an award at a large conference). On multiple occasions the patient has declined the offer to change to a more standard pharmacotherapy for narcolepsy. Currently, she sleeps for 7-9 h nightly on a regular schedule and naps for 20-30 min, 5-7 times a week. Her family history reveals a mother with very similar symptoms who was told she had narcolepsy in the 1940s. Her mother’s condition was well managed on amphetamines until she passed away at the age of 83, in 1982. This familial linkage further strengthens the diagnosis of narcolepsy.12

In this case, it appears that both smoking and the use of a nicotine patch may have partially masked both cataplexy and sleepiness. Therefore, once smoking was discontinued, the patient exhibited both increased sleepiness and cataplexy. The fact that nicotine masked sleepiness is not surprising, given that...
nicotine has been shown to improve memory and attention in humans and animals, similar to amphetamines.13

The finding in our case is consistent with Bagai and Malow’s finding that a nicotine patch helped treat morning sleepiness in a narcoleptic patient without cataplexy.2 Moreover, in a 2009 survey of narcoleptics by Krahm et al., it was found that all narcoleptics who had smoked in the past reported reduced daytime sleepiness while smoking, and one survey participant reported reduced cataplexy while smoking. Interestingly, passive smoking was found to be more common in narcoleptics, but active smoking was not increased compared to normal controls.14 Our findings, as well as previous reports suggest that smoking and nicotine patches decrease the clinical manifestations of narcolepsy, with reduced cataplexy and daytime sleepiness. Based on these findings, we believe further investigation is warranted to look at the role of nicotine in treatment of both cataplexy and excessive daytime sleepiness in narcoleptics.

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Topiramate-Induced Somnambulism in a Migraineur: A Probable Idiosyncratic Adverse Effect

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Somnambulism (sleepwalking) is a disorder of arousal that falls under “parasomnia” group and is more common in children. These phenomena occur as primary sleep events or secondary to systemic disease or can be drug induced. Medications that can cause sleepwalking include neuroleptics, hypnotics, lithium, amitriptyline, and β-blockers. This report presents an unusual adverse effect of topiramate on sleep in a patient with migraine.

**REPORT OF CASE**

A 35-year-old woman suffering from migraine without aura for past 7 years was started on topiramate 25 mg daily for prophylaxis. The patient started the drug and had an uneventful sleep on the first day. The second day she took topiramate 25 mg at 22:00 and went to bed. About 2 h after sleep, her husband noticed that she was not in the bed and found her walking around in the room. She was not responding to his call and continued to walk in a “trance-like” state for about half an hour. Her husband forced her back to bed and she continued to sleep. Next day morning she was totally unaware of what had happened in the night. She consumed topiramate 25 mg on the third day and had similar episode on that night. The duration and time of the event were same as in the first night, as reported by the patient’s husband. She was apprehensive about continuing topiramate and stopped it on her own on the fourth day. She continued to walk in a “trance-like” state for about half an hour. Her husband forced her back to bed and she continued to sleep. She did not report any change in her stress levels during the days she was taking topiramate. There was no history suggestive of any sleep related breathing disorder or somniloquy. She did not report any flu-like symptoms after initiation of topiramate. She denied any prior history of somnambulism or family history of sleep disorders. She was not taking any other medications. A challenge with topiramate with polysomnography was suggested, but the patient was unwilling to take the medication again.

**DISCUSSION**

This 35-year-old woman with migraine is the second case of topiramate-induced somnambulism reported in literature. Interestingly the previous case report is also from India, involving a 27-year-old man with chronic migraine. The fact that sleepwalking occurred on the second day with a small dose of topiramate (25 mg) suggests an idiosyncratic reaction rather than a dose-dependent response. Frontal lobe epilepsy is an important differential diagnosis for somnambulistic episodes. But it is very rare for frontal lobe epilepsies to present only with pure somnambulism, and they are of briefer duration. There was no history of seizures in the past or family. There was no evidence of tonic clonic movements, automatisms, or urinary incontinence. Topiramate is also an antiepileptic, and to induce seizure such at a low dose is very unlikely.

Topiramate is a drug commonly prescribed for migraine prophylaxis and epilepsy by physicians and neurologists. Topiramate has also been reported to be useful for treatment of nocturnal eating syndrome and sleep-related eating disorder (SRED). Topiramate has multiple mechanisms of action, including voltage-sensitive sodium channel blockade, calcium channel inhibition, increase in potassium conductance, GABA mediated chloride current increment, glutamate-mediated neurotransmission inhibition, and carbonic anhydrase isoenzyme inhibition. Topiramate increases the GABA-mediated chloride flux in cultured mouse neurons. It exerts a negative modulatory effect on excitatory glutamate neurotransmission. The inhibitory effect is mediated by the kainate AMPA subtype of glutamate receptor.

The exact mechanism of topiramate induced somnambulism is not known. The initiation of NREM sleep is gradual and is characterized by slowing of the brain waves on EEG. Very high amplitude delta waves occur in stages 3 and 4 of NREM. Somnambulism typically occurs during the first 3 hours of sleep, when stages 3 and 4 of NREM are most prevalent. The effects of topiramate on sleep are practically unknown. Most of the
patients who undergo polysomnography are refractory seizure patients on multiple antiepileptic drugs. So the individual effect of antiepileptic drugs on sleep are difficult to ascertain. Riluzole, a glutamate antagonist, is known to enhance the duration of slow wave sleep in rats. Topiramate by its anti-glutamnergic effect may also increase the duration of slow wave sleep.

Migraine and sleepwalking have an interesting relation. Serotonin which plays an important role in migraine pathogenesis, is also involved in slow wave sleep. There is a six-fold higher prevalence of somnambulism in patients with migraine. The predisposing factors and physiological pathways of migraine and somnambulism appears similar. The cerebral serotoninergic system may play an important role in the pathophysiology of sleepwalking. Cape and Jones revealed that microinjection of serotonin during sleep in cholinergic basalis neurons increases EEG delta activity in rats. Moreover, in one-half of rats injected with serotonin, these authors observed anomalous wake episodes associated with high delta activity. These wake episodes were characterized by open eyes and quiet behavior and in fact resembled sleepwalking in humans.

Serotonin, GABA, and glutamate play an important role in wakefulness and sleep. Serotonin neurons are most active during wakefulness and fire most rapidly during continuous motor activity such as walking or running. GABA has a significant role in NREM sleep while glutamate plays a pivotal role in REM sleep. During NREM sleep, GABA has been hypothesized to play key roles in the deactivation of wake-related arousal systems and in the generation of intrinsic thalamocortical oscillations. The excitatory amino acid glutamate widely interacts with cholinergic and cholinceptive neurons to generate the exponential increase of mesopontine and pontine reticular activity associated with REM sleep activation. Glutamatergic cells of the pons transmit signals to inhibitory glycinergic and GABAergic cells of the medulla, which in turn, suppress somatic motor neurons to produce REM sleep atonia. Topiramate, a pro-GABA and anti-glutamate agent, is also known to increase serotonin levels in children with migraine. We hypothesize that topiramate by its pro-GABA and anti-glutamate effect promotes NREM sleep, and by increasing serotonin levels favors motor activity. This may result in the intrusions of motor activity during NREM sleep, resulting in sleepwalking.

The phenomenon of drugs used for treating a particular disorder precipitating the same disorder is not rare in medical literature. Zolpidem, though used in the treatment of insomnia, is also known to precipitate somnambulism. Medications used to treat migraine such as propranolol and amitriptyline have sometimes induced, but most often cured, sleepwalking or other parasomnias. Topiramate, though reported to be effective in treating SRED, now is reported to produce somnambulism. This may due to the differences in the etiopathogenesis of sleepwalking and SRED at the receptor and neurotransmitter level. Dopaminergic/serotonergic mechanisms may be more important in SRED, while GABAergic/glutaminergic mechanisms may be more important in somnambulism.

This adverse effect of topiramate on sleep needs further study, as it is a useful drug in the field of epilepsy, headache, and sleep. It will be worthwhile to counsel the patients, especially those with chronic migraine, about this rare side effect because of the potential medicolegal implications.

REFERENCES


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Obstructive sleep apnea syndrome (OSAS) is a common sleep related breathing disorder. Its prevalence is estimated to be between 2% and 25% in the general population. However, the prevalence of sleep apnea is much higher in patients undergoing elective surgery. Sedation and anesthesia have been shown to increase the upper airway collapsibility and therefore increasing the risk of having postoperative complications in these patients. Furthermore, the majority of patients with sleep apnea are undiagnosed and therefore are at risk during the perioperative period. It is important to identify these patients so that appropriate actions can be taken in a timely fashion. In this review article, we will discuss the epidemiology of sleep apnea in the surgical population. We will also discuss why these patients are at a higher risk of having postoperative complications, with the special emphasis on the role of anesthesia, opioids, sedation, and the phenomenon of REM sleep rebound. We will also review how to identify these patients preoperatively and the steps that can be taken for their perioperative management.

Keywords: Obstructive sleep apnea syndrome, perioperative complications, postoperative complications, STOP Questionnaire, Berlin Questionnaire


Obstructive sleep apnea is characterized by intermittent and recurrent episodes of partial or complete obstruction of the upper airway during sleep. These episodes disrupt sleep architecture, causing fragmented sleep and daytime sleepiness. OSAS has been shown to be associated with various health-related consequences, including increased rate of motor vehicle accidents, hypertension, diabetes mellitus, congestive heart failure, stroke, and all-cause mortality.1–9

Recently, numerous studies have demonstrated that surgical patients with sleep apnea are at increased risk of having perioperative complications, including hypoxemia, pneumonia, difficult intubation, myocardial infarction, pulmonary embolism, atelectasis, cardiac arrhythmias, and unanticipated admission to the ICU. The majority of patients with OSA are undiagnosed upon admission and are at risk during the perioperative period, presumably due to their underlying sleep apnea. Therefore, it is very important to identify these patients preoperatively so that one can initiate appropriate perioperative measures.

Epidemiology

OSAS is an extremely common sleep related breathing disorder, and its prevalence has been increasing throughout the world because of obesity and increasing age of the general population. Its prevalence is between 2% and 25% in the general population, depending upon how sleep apnea is defined. In an epidemiological study, Young et al. noted that the prevalence of sleep apnea, defined as apnea-hypopnea index (AHI) ≥ 5/h was 9% for women and 24% for men.10 However, the prevalence of OSAS (defined as AHI ≥ 5/h and daytime sleepiness) was 2% in women and 4% in men.10 The National Sleep Foundation (NSF) Sleep in America 2005 Poll found that 1 in 4 Americans are at high risk of having sleep apnea based on the Berlin Questionnaire.11 The prevalence of sleep apnea is much higher in surgical patients and depends on the type of surgery. In the bariatric surgery population, the prevalence of sleep apnea has been found to be > 70%.12,13 It is the standard of care for these patients to get a formal sleep evaluation prior to undergoing the bariatric surgery. However, patients who are coming for general surgery also have a higher prevalence of sleep apnea.14 Chung et al. used the Berlin Questionnaire preoperatively and found that 24% of surgical patients were at high risk for sleep apnea.15 We used the STOP-BANG Questionnaire in our elective surgical population and found that 41% of patients were at high risk for sleep apnea based on the questionnaire.16 In a cross-sectional study, 39 patients underwent nocturnal polysomnography (NPSG) prior to undergoing epilepsy surgery. It was found that 1 in 3 patients undergoing epilepsy surgery had sleep apnea.17 In another study, the prevalence of sleep apnea was found to be 64% in a small population of patients undergoing surgery for intracranial tumor.18 The majority of these patients are unaware of their sleep apnea prior to undergoing elective surgery. In an observational study, Finkel et al. noted that > 80% of surgical patients were unaware that they had sleep apnea prior to undergoing surgery.14

Pathophysiology

Surgical patients receive sedation, anesthesia, and opioids during the perioperative period. These medicines have been shown to increase pharyngeal collapse, decrease ventilatory response, and impair the arousal response, leading to worsening of sleep apnea in the perioperative period.
Impact of Sedation, Anesthesia, and Opioids

Patients with sleep apnea have recurrent episodes of partial or complete obstruction of the upper airway during sleep. These episodes usually occur when the negative pressure of inspiratory muscles exceeds the upper airway dilator muscle activity (critical airway pressure). General anesthetics have been shown to decrease the upper airway dilator muscle activity in a dose-dependent manner and thereby increase upper airway collapsibility. In 12 healthy subjects undergoing minor surgery, increasing depth of propofol anesthesia was associated with a progressive increase in critical airway pressure and upper airway collapsibility. This increased upper airway collapsibility was found to be secondary to progressive decrease in the genioglossus muscle activity. Upper airway collapsibility may cause worsening of the sleep apnea and increase the risk of hypoxemia, cardiac arrhythmias, and postoperative complications.

Anesthetic medicines also impair the arousal response, a protective defense mechanism against sleep apnea that helps in overcoming the airway obstruction. Anesthetics, opioids, hypnotics, and benzodiazepines may also cause respiratory depression and thereby decrease the minute ventilation. Studies have shown that halothane reduces the ventilatory response to hypoxemia and hypercapnia in humans. This depression is most likely secondary to a selective effect of halothane on the peripheral chemoreflex loop. Similarly, a subanesthetic dose of isoflurane has been shown to reduce the hypoxic ventilatory response via peripheral chemoreceptors.

Patients undergoing surgery frequently receive opioids for the pain control. Opioids have been shown to impair ventilatory function by affecting both peripheral and central carbon dioxide chemoreflex loops. Studies have shown that small doses of narcotics administered epidurally may also depress the respiratory function, even in healthy adults. The ventilatory depression of opiates appears to be affected by sex and ethnicity, as well. Morphine has been shown to reduce hypoxic and hypercapnic ventilatory response in women, but not in men. On the other hand, it raises the apneic threshold in men with no effect in women. The combination of opiates and benzodiazepines has been shown to cause more significant episodes of hypoxemia and apnea. This is most likely secondary to significant reduction of hypoxic ventilatory response to both opiates and benzodiazepines.

REM Sleep Rebound

Surgical patients have been shown to have highly fragmented sleep on postoperative nights 1 or 2, with a significant reduction in REM sleep, slow wave sleep, and increased stage 2 NREM sleep. These sleep disturbances usually occur secondary to surgical stress, pain, and the use of anesthetic and pain medications. The stress of surgical trauma leads to increased level of cortisol, and cortisol has been shown to cause significant reduction in REM sleep. Surgical trauma has also been shown to induce significant inflammatory response, characterized by the increased level of pro-inflammatory markers like tumor necrosis factor alpha (TNF-α), interleukin 1 (IL-1), and IL-6. These inflammatory markers, especially IL-1 and TNF-α, have been shown to suppress REM sleep.

There are studies that have shown that REM sleep is usually absent on postoperative nights 1 and 2. This is usually followed by a profound increase in the amount and density of REM sleep (REM sleep rebound) during recovery nights 3 to 5. The episodes of sleep disordered breathing and hypoxemia are usually worse during REM sleep due to hypotonia and unstable breathing. REM sleep is also associated with increased sympathetic discharge leading to tachycardia, hemodynamic instability, and myocardial ischemia.

It is well known that most complications after the surgery occur in the first postoperative week, especially between postoperative days 2 and 5, corresponding to periods of REM rebound. Episodes of hypoxemia after surgery have been reported to occur mostly between postoperative nights 2 to 5. These episodes may increase the risk of wound infection, cerebral dysfunction, and cardiac arrhythmias. In an observational study at Mayo Clinic, it was found that the incidence of acute myocardial infarction peaked on day 3 after surgery. Similarly, episodes of delirium, nightmares, and psychomotor dysfunction have been reported to occur between postoperative nights 3 to 5.

Evidence on Sleep Apnea as a Risk Factor for Perioperative Complications

We systematically searched the literature on PubMed, Embase, and Scopus databases to identify relevant studies on association between obstructive sleep apnea and perioperative outcome. We included studies conducted in adults who underwent elective surgery. We excluded bariatric surgery and sleep apnea surgery population. Two authors (TSV and RG) independently searched for the relevant articles published in the English literature from 1966 to December 2011. We used the combination of terms including surgery, perioperative outcome, perioperative complications, perioperative pulmonary outcome, perioperative risk, postoperative complications, and obstructive sleep apnea. Bibliographies of all selected articles and review articles were also reviewed to find any other relevant article. These 2 authors (TSV and RG) also independently assigned the Oxford level of evidence and the grade of recommendation to each article. There was 100% agreement between the 2 authors. We identified 11 articles on obstructive sleep apnea and perioperative outcome. These articles along with their Oxford level of evidence are reported in the Table 1 and Table 2.

Surgical patients are at higher risk of having complications for a variety of reasons, including ASA (American Society of Anesthesiologists) class, age, type of paralytics, current smoking, low albumin, duration of surgery, type of anesthesia, and other comorbidities—especially chronic obstructive pulmonary disease, coronary artery disease, and renal failure. The risk of postoperative complications also depends on the type of surgery. The rate of complication is higher in patients undergoing abdominal surgery and is also increased with aortic aneurysm repair, vascular, thoracic, and neck surgery.

Gupta et al. have shown an increased risk of postoperative complications (39% vs 18%), higher rate of transfer to ICU (24% vs 9%), and increased length of hospital stay in patients with obstructive sleep apnea compared with control subjects matched for age, sex, and body mass index (BMI). In this study, these investigators also reported that OSA patients who
### Table 1—Studies reporting association between obstructive sleep apnea and perioperative complications

<table>
<thead>
<tr>
<th>Author</th>
<th>Type of Study</th>
<th>Number of Patients</th>
<th>Diagnosis of OSAS</th>
<th>Type of Surgeries</th>
<th>Complications</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gupta et al.98</td>
<td>Case control study</td>
<td>101 patients with OSA and 101 matched controls</td>
<td>Polysomnography (PSG)</td>
<td>Orthopedic (hip or knee replacement)</td>
<td>Reintubation, hypoxemia, acute hypercapnia, myocardial infarction, arrhythmia, delirium, and ICU transfer</td>
<td>Patients with OSA had higher rate of postoperative complications (39% vs 18%). These patients also had increased hospital length of stay.</td>
</tr>
<tr>
<td>Auckley et al.105</td>
<td>Historical cohort study</td>
<td>81 patients with completed Berlin Questionnaire</td>
<td>Berlin Questionnaire</td>
<td>Elective surgery (type of surgeries is not included in the abstract)</td>
<td>Hypoxemia, hypercapnia, reintubation, atelectasis, pneumonia, arrhythmia, thromboembolism</td>
<td>Patients with high-risk of sleep apnea based on the Berlin Questionnaire had a higher rate of postoperative complications (20% vs 4.5%).</td>
</tr>
<tr>
<td>Sabers et al.106</td>
<td>Case control study</td>
<td>234 patients with OSA and 234 matched controls</td>
<td>Polysomnography</td>
<td>Non-otorhinolaryngologic outpatient surgical procedures</td>
<td>Unplanned hospital admission, bronchospasm, upper airway obstruction, hypotension, atrial fibrillation, pulmonary edema</td>
<td>No significant difference in the rate of unplanned hospital admissions (23.9% vs 18.8%) or other adverse events (2.1% vs 1.3%)</td>
</tr>
<tr>
<td>Kaw et al.100</td>
<td>Case control study</td>
<td>37 patients with OSA and 185 matched controls</td>
<td>Polysomnography</td>
<td>Cardiac</td>
<td>Encephalopathy, postoperative infections, and ICU length of stay</td>
<td>Patients with sleep apnea had higher rate of encephalopathy, postoperative infections (mediastinitis), and increased ICU length of stay.</td>
</tr>
<tr>
<td>Hwang et al.102</td>
<td>Historical cohort study</td>
<td>172 patients underwent home nocturnal oximetry</td>
<td>Home nocturnal oximetry</td>
<td>Abdominal, ENT, Thoracic, Vascular, Gyn, Neurosurgical, Urologic, Cardiothoracic, and Orthopedic</td>
<td>Arrhythmia, hypoxemia, atelectasis, GI bleed, pneumonia, pulmonary embolism,</td>
<td>Patients with ODI4% ≥ 5/h had a higher rate of postoperative complications than those with ODI4% &lt; 5/h (15.3% vs 2.7%).</td>
</tr>
<tr>
<td>Gali et al.104</td>
<td>Prospective cohort study</td>
<td>693 patients with completed Flemons Criteria and SACS score</td>
<td>Flemons Criteria and SACS score</td>
<td>Orthopedic, Gyn, ENT, Urologic, Thoracic, Plastics, Neurosurgery, General abdominal</td>
<td>Arrhythmia, MI, ICU admission, pneumonia, need for the ventilator support</td>
<td>Postoperative respiratory events were associated with high SACS and PACU events</td>
</tr>
<tr>
<td>Liao et al.99</td>
<td>Retrospective matched cohort study</td>
<td>240 patients with OSA and 240 matched controls</td>
<td>International Classification of Disease (ICD-9) codes</td>
<td>Cardiac, ENT, Orthopedic, Spine, Urologic, General, Gyn, and Plastic</td>
<td>Hypoxemia, pulmonary edema, bronchospasm, arrhythmia, confusion</td>
<td>Patients with OSA had a higher incidence of postoperative complications (48% vs 36%)</td>
</tr>
<tr>
<td>Vasu et al.96</td>
<td>Historical cohort study</td>
<td>135 patients with completed STOP BANG Questionnaire</td>
<td>STOP BANG Questionnaire</td>
<td>Orthopedic, Abdominal, Head and Neck, ENT, Gyn, Vascular, Cardiothoracic</td>
<td>Hypoxemia, pneumonia, pulmonary embolism, atelectasis, hypotension, atrial fibrillation</td>
<td>Patients with high-risk of sleep apnea based on STOP BANG Questionnaire had a higher rate of postoperative complications (19.6% vs 1.3%) and the hospital length of stay.</td>
</tr>
</tbody>
</table>

PSG, polysomnography; ICU, Intensive Care Unit; SACS, Sleep Apnea Clinical Score; PACU, Postanesthesia Care Unit.

Table 1 continues on the following page
received continuous positive airway pressure (CPAP) therapy prior to surgery had a reduced rate of serious complications and a one-day reduction in the length of hospital stay. In another case-control study, Liao et al. found that patients with OSA had higher rate of postoperative complications (44% vs 28%).

Interestingly, they also noted that OSA patients who were not compliant with their CPAP had the highest rate of postoperative complications. Kaw et al. also demonstrated that patients with OSA had higher incidence of encephalopathy, postoperative infections (mediastinitis), and increased ICU length of stay. Similarly, Memtsoudis et al. in their case-control study found that orthopedic and general surgical patients with sleep apnea were at a higher risk of having perioperative pulmonary complications.

Hwang et al. demonstrated that the rate of postoperative complications was increased in proportion to episodes of over-
night desaturation during home nocturnal oximetry. In this study, 172 patients underwent home nocturnal oximetry during preoperative evaluation for elective surgery. The number of episodes per hour of oxygen desaturations (oxygen desaturation index) ≥ 4% (known as the ODI 4%) was calculated for every patient from the home nocturnal oximetry. Patients with an ODI 4% ≥ 5/h had a significantly higher rate of postoperative complications than those with ODI 4% < 5/h (15.4% vs 2.7%). Interestingly, the rate of postoperative complications increased with increasing ODI severity. Patients with an ODI 4% of 5-15 had a 13.8% incidence of complications, compared to 17.5% of those with an ODI 4% > 15.

In a recent cohort study, 471 patients who underwent non-cardiac surgery within 3 years of polysomnography were evaluated for postoperative complications and hospital length of stay. It was found that patients with sleep apnea had higher rates of postoperative complications and hypoxemia. We used the STOP-BANG Questionnaire preoperatively to identify patients at high risk for OSAS. We found that patients at high risk of OSAS had a higher rate of postoperative pulmonary and cardiac complications than patients at low risk (19.6% vs 1.3%). We also noted that patients at high risk of OSAS had significantly higher length of stay in the hospital compared to patients at low risk. Gali et al. used Flemons criteria and SACS (sleep apnea clinical score) to identify patients at high or low risk for obstructive sleep apnea. They also noted that patients with high SACS and PACU (postanesthesia care unit) events had a higher rate of postoperative respiratory events. Similarly, Auckley et al. used the Berlin Questionnaire to identify the high-risk patients. They demonstrated that patients at high risk of sleep apnea had more postoperative complications (20% vs 4.5%); however, this difference was not statistically significant.

There are two studies that have been conducted in patients undergoing ambulatory surgery to assess the impact of obstructive sleep apnea. These studies found that the presence of OSA did not increase the rate of unplanned hospital admissions in patients who underwent outpatient surgical procedures. Stierer et al. used a prediction model in a cohort of ambulatory surgical population to assess the probability of sleep apnea. They demonstrated that patients with ≥ 70% propensity for OSA had increased rate of difficult intubation, increased oxygen requirement, and intraoperative tachycardia.

How to Identify Patients with Sleep Apnea

Nocturnal polysomnography (NPSG) is considered to be the gold standard to identify patients with obstructive sleep apnea. However, in the perioperative setting, it is difficult to implement due to a variety of factors, including its prolongation of the process of surgery and contribution to the overall cost. In many hospital settings, it may also not be readily available. There are other methods that have been shown to identify patients who are at risk for obstructive sleep apnea including questionnaires, nocturnal pulse oximetry, and home sleep testing.

Questionnaires

There are many questionnaires that are available to identify surgical patients who are at high risk of having obstructive sleep apnea. Three of these questionnaires have been validated in the surgical population: the Berlin Questionnaire, ASA checklist, and the STOP-BANG questionnaire. The Berlin questionnaire is the most widely used questionnaire to identify patients at high risk for OSA. It contains 11 questions that are organized in 3 symptom categories and has been validated in the primary care patients. It has a sensitivity of 86% and positive predictive value of 89% for identifying patients with respiratory disturbance index (RDI) > 5/h in the primary care clinic. Recently, Chung et al. validated the Berlin questionnaire in surgical population and found that it had a sensitivity of 74.3% to 79.5% and a negative predictive value of 76% to 89.3% in identifying patients with moderate-to-severe OSA. However, this questionnaire has complex scoring system and is time consuming.

The American Society of Anesthesiologists (ASA) checklist also appears to be very useful and promising and has been proposed by ASA Task Force to identify patients with OSA. It contains 12 items for adults and 14 items for children. The ASA checklist has been shown to have a sensitivity of 78.6% to 87.2% and a negative predictive value of 72.7% to 90.9% in identifying surgical patients with moderate-to-severe OSA.

Recently, the STOP-BANG (Snoring, Tiredness during daytime, Observed apnea, high Blood Pressure, Body mass index, Age, Neck circumference, Gender) questionnaire was validated as a screening modality for OSAS in the preoperative setting. It is a concise, self-administered, and easy-to-use questionnaire that consists of 8 yes/no questions. Patients are considered to be at high risk of OSAS if they answer yes to ≥ 3 items. The sensitivity of the STOP-BANG questionnaire at an AHI ≥ 5, > 15, and > 30 cutoff values was 83.6%, 92.9%, and 100%, respectively; corresponding negative predictive values (NPV) were 60.8%, 90.2%, and 100%. This questionnaire has a moderately high level of sensitivity, specificity, and NPV to detect patients with moderate (AHI > 15) to severe (AHI > 30) sleep apnea in the surgical population. Therefore, if the patient is ranked as a low risk for OSA by the STOP-BANG scoring model, practitioners can exclude the possibility that the patient would have moderate-to-severe sleep apnea with a good degree of accuracy.

Abrishami et al. conducted a systematic review to identify and evaluate the different screening questionnaires for sleep apnea. They noted that the Berlin and STOP-BANG questionnaires had high sensitivities and specificities in predicting moderate or severe sleep apnea. However, they found that the STOP and STOP-BANG questionnaires had the highest methodological validity, and these questionnaires are very easy to use.

Nocturnal Pulse Oximetry

Nocturnal pulse oximetry has also been used for the screening of OSA. Malbois et al. compared the sensitivity of nocturnal oximetry to ambulatory monitoring in order to identify patients with sleep apnea prior to undergoing bariatric surgery. They demonstrated that nocturnal oximetry with a 3% desaturation index as a screening tool for OSA could rule out significant OSA (AHI > 10) and also detect patients with severe OSA. This cheap and widely available technique could accelerate preoperative work-up of these patients.
morning headaches. A focused physical examination should be
ness, witnessed apneas, frequent awakenings at night, and
evaluation of sleep apnea. One should obtain history pertinent
amination preoperatively with the special emphasis on the
erative management (operative evaluation, intraoperative management, and postop-
ary guidelines, perioperative care can be subdivided in 3 parts: pre-
scoring system to assess the perioperative risk. Based on these
employed in patients at high risk for OSA. These questionnaires
simple and easy to administer preoperatively and have been
validated in the surgical population. There should be an action
plan for the management of high-risk patients during the peri-
operative period. In few circumstances, anesthesiologists and
surgeons may decide to obtain formal sleep evaluation for the
management of sleep apnea prior to performing surgery.

**Intraoperative Management**

Intraoperative management usually focuses on surgical mea-
ures and the type of anesthesia. One should minimize the surgi-
cal stress and the duration of surgery as these factors have been
shown to increase the perioperative complications. Whenever
possible, consider using regional or local anesthesia instead of
general anesthesia. These patients should be extubated when
they are fully awake, preferably in the semi-upright position.

**Postoperative Management**

Patients at increased perioperative risk from OSA should be
very closely monitored in the post anesthesia care unit (PACU)
for hypoxemia or other complications. They should have con-
tinuous monitoring of oxygenation with the help of pulse ox-
ometry. Whenever possible, these patients should be placed in
the non-supine position after the surgery to decrease the se-
verity of apnea. These patients are very susceptible to opioids
and benzodiazepines and one should minimize the use of these
medicines in the perioperative period. Consider using NSAIDs,
acetaminophen, tramadol, and regional analgesia for pain con-
rol. Dexmedetomidine can be very useful for sedation because
of its opioid sparing effect and the lack of respiratory depres-
sion. Patients with the known diagnosis of sleep apnea should
use their CPAP after surgery. There is no randomized controlled
trial that has demonstrated that CPAP is beneficial in the post-
operative setting. However, one may consider using auto-CPAP
in high-risk patients after surgery, although it might be difficult
for the CPAP-naïve patient to get used to it in the perioperative
period. Once again, the use of auto-CPAP has not been formally
studied in this population, and there may be a need to conduct a
randomized controlled trial to assess the efficacy of auto-CPAP.
These patients should also get formal sleep evaluation after dis-
charge from the hospital.

**Evidence for Perioperative use of CPAP**

CPAP acts as a pneumatic splint and helps in opening the
collapsed upper airway at night. The application of CPAP also
improves functional residual capacity (FRC) and oxygenation
with reduction in work of breathing. CPAP has been shown to
improve excessive daytime sleepiness in patients with OSAS.
There is some evidence that the perioperative use of CPAP may
help in reducing postoperative complications. In a case control
study, Gupta et al. noted that OSA patients who were compli-
ant with their CPAP had reduced rate of complications and also
decreased hospital length of stay. Similarly, Liao et al. noted that
OSA patients who were not compliant with their CPAP were
at the greatest risk of having postoperative complications.

| Table 3—Perioperative management of patients at high risk of obstructive sleep apnea syndrome |
| Preoperative Evaluation |
| 1. History |
| 2. Physical Examination |
| 3. Screening Questionnaires like Berlin, ASA, or STOP BANG to identify high-risk patients |
| 4. Consider a formal sleep evaluation in very high-risk group |
| Intraoperative Management |
| 1. Minimize the surgical stress |
| 2. Reduce the duration of surgery |
| 3. Consider regional or local anesthesia instead of general anesthesia |
| 4. Anticipate difficult intubation |
| 5. Consider awake extubation preferably in semi-upright position |
| Postoperative Management |
| 1. Minimize the use of opioids and sedation after the surgery |
| 2. Consider using acetaminophen, NSAIDs, or regional analgesia for the pain control |
| 3. Continuously monitor oxygenation in the postoperative period |
| 4. Patients with a known diagnosis of sleep apnea should use their CPAP after the surgery |
| 5. High-risk patients for sleep apnea should use Auto CPAP during the postoperative period |
| 6. Follow-up at the sleep center for the management of sleep apnea upon discharge from the hospital |

**Home Sleep Testing**

Ambulatory monitoring is another modality that can be em-
ployed in patients at high risk for sleep apnea. However, this is
recommended only in patients with a high pre-test probability
of sleep apnea and is not recommended in patients with coex-
isting cardiopulmonary complications. It also has its limita-
tions in terms of ease of use by the patients. There is one study
that has shown the effectiveness of ambulatory monitoring in
confirming the diagnosis of OSA in 82% of adult surgical pa-
ents, identified as high risk prior to undergoing surgery, in a
large academic medical center. It would be helpful to evaluate
this modality of diagnosing OSAS in specific surgical patient
population.

**Perioperative Management**

The American Society of Anesthesiologists published prac-
tice guidelines in 2006 on the perioperative management of
patients with obstructive sleep apnea. It also proposed OSA
scoring system to assess the perioperative risk. Based on these
guidelines, perioperative care can be subdivided in 3 parts: pre-
operative evaluation, intraoperative management, and postop-
erative management (Table 3).

**Preoperative Evaluation**

Patients should undergo thorough history and physical ex-
amination preoperatively with the special emphasis on the
evaluation of sleep apnea. One should obtain history pertinent
to sleep apnea including snoring, excessive daytime sleepi-
ness, witnessed apneas, frequent awakenings at night, and
morning headaches. A focused physical examination should be
conducted to evaluate neck circumference, body mass index,
modified Mallampati score, tongue volume, tonsillar size, and
nasopharyngeal characteristics. It is important to administer
screening questionnaires like the Berlin, ASA, or STOP-BANG
to identify patients at high risk for OSA. These questionnaires
are simple and easy to administer preoperatively and have been
validated in the surgical population. There should be an action
plan for the management of high-risk patients during the peri-
operative period. In few circumstances, anesthesiologists and
surgeons may decide to obtain formal sleep evaluation for the
management of sleep apnea prior to performing surgery.
Squadron et al. demonstrated that the use of CPAP leads to reduction in the incidence of endotracheal intubation and other severe complications in patients who develop hypoxemia after elective major abdominal surgery.117 In a randomized controlled trial, Kingen-Milles et al. found that the prophylactic use of nasal CPAP was associated with a reduction in pulmonary complications and hospital length of stay in patients undergoing thoracoabdominal aortic aneurysm repair.118 In another study, Zarbock et al. also noted significant reduction in the rate of pulmonary complications with the prophylactic use of nasal CPAP in patients undergoing elective cardiac surgery.119 A recent meta-analysis of nine randomized controlled trials in the abdominal surgical population reported reduction in the rate of atelectasis, postoperative pulmonary complications, and pneumonia with the perioperative use of CPAP.120

Conclusions
Obstructive sleep apnea syndrome (OSAS) is a common type of sleep disordered breathing, with a high prevalence in the surgical population. The majority of patients with sleep apnea are undiagnosed and are therefore unaware of their OSAS at the time of the surgery. These patients are at increased risk for perioperative complications. Sedation, anesthesia, opioids, and REM sleep rebound have been shown to cause worsening of sleep apnea in the perioperative period that may lead to increase in the rate of perioperative complications. It is important to identify these patients preoperatively so that appropriate actions can be taken during their perioperative care. Screening questionnaires such as the Berlin, STOP-BANG, or ASA checklist are easy to administer preoperatively and have been shown to identify high-risk patients. There should be a standard protocol for the perioperative management of high-risk patients in order to reduce the rate of complications. These high-risk patients should also have a formal sleep evaluation for the long-term management of their sleep apnea after the discharge from the hospital.

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Dissemination of CBTI to the Non-Sleep Specialist: Protocol Development and Training Issues

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Strong evidence supports the efficacy of cognitive behavioral therapy for insomnia (CBTI). A significant barrier to wide dissemination of CBTI is the lack of qualified practitioners. We describe challenges and decisions made when developing a CBTI dissemination program in the Veterans Health Administration (VHA). The program targets mental health clinicians from different disciplines (psychiatry, psychology, social work, and nursing) with varying familiarity and experience with general principles of cognitive behavioral therapies (CBT). We explain the scope of training (how much to teach about the science of sleep, comorbid sleep disorders, other medical and mental health comorbidities, and hypnotic-dependent insomnia), discuss adaptation of CBTI to address the unique challenges posed by comorbid insomnia, and describe decisions made about the strategy of training (principles, structure and materials developed/recommended). Among these decisions is the question of how to balance the structure and flexibility of the treatment protocol. We developed a case conceptualization-driven approach and provide a general session-by-session outline. Training licensed therapists who already have many professional obligations required that the training be completed in a relatively short time with minimal disruptions to training participants’ routine work responsibilities. These “real-life” constraints shaped the development of this competency-based, yet pragmatic training program. We conclude with a description of preliminary lessons learned from the initial wave of training and propose future directions for research and dissemination.

Keywords: Dissemination, insomnia, cognitive behavioral therapy

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A commentary on this article appears in this issue on page 219.

A significant barrier to wide dissemination of CBTI is the lack of qualified practitioners. Graduate and postdoctoral fellowships are excellent vehicles to train behavioral sleep medicine specialists, who usually practice within or in association with a sleep center. However, there remains a need for shorter yet effective training of licensed clinicians to deliver CBTI within a broad array of clinical settings, where many insomnia patients seek care. Mental health providers who work in a variety of settings, including mental health and primary care services, are ideally suited to deliver CBTI. Difficulties initiating and/or maintaining sleep usually do not resolve with general psychotherapy, and untreated insomnia among patients with comorbid psychiatric and medical conditions contributes to illness severity and hinders response to treatment, underscoring the need to train mental health providers to deliver CBTI. Fortunately several clinical trials have indicated that CBTI is effective in patients with depression, posttraumatic stress disorder (PTSD), and pain. The task is therefore to train mental health clinicians from different disciplines (psychology, social work, and nursing) with varying familiarity and experience with general medicine specialists, who usually practice within or in association with a sleep center. However, there remains a need for shorter yet effective training of licensed clinicians to deliver CBTI within a broad array of clinical settings, where many insomnia patients seek care. Mental health providers who work in a variety of settings, including mental health and primary care services, are ideally suited to deliver CBTI.
principles of cognitive behavioral therapies (CBT) to deliver CBT for insomnia (CBTI).

Successful, competency-based training of psychotherapists requires both didactic content (course work and/or a workshop) and ongoing expert consultation and feedback training (usually closely supervised delivery of treatment until competency is reached). The latter has been found to be particularly important. We describe a CBTI dissemination project that encompasses both elements, focusing on the challenges we met in developing the training content. The dissemination project targets mental health clinicians in the Veterans Health Administration (VHA)—the health care component of the U.S. Department of Veterans Affairs (VA) and the largest integrated health care system in the United States. It is part of a series of dissemination efforts designed to translate evidence-based psychotherapies into clinical practice within the VHA system. The didactic portion of the training requires attendance at a clinical workshop that provides ample opportunity for experiential learning and extensive modeling of therapeutic techniques. It also provides a comprehensive treatment manual to be used as a reference resource and supporting materials designed to help therapists implement the treatment. The consultation training component is anchored in the review and ratings of taped therapy sessions by experts in CBTI, using a competency rating scale developed by the authors for this dissemination effort to standardize the rating of the taped sessions. The consultation training involves weekly small group phone calls, led by a CBTI expert training consultant, to provide feedback after review of the tapes and to discuss emerging clinical issues. Regular feedback regarding the taped sessions and the weekly consultation provide a process for continued correction and improvement of training participants’ skills. Such close consultation is also ethically necessary during hands-on training of new psychotherapy skills. We began the project with a pilot training of clinicians who had successfully completed VA’s competency-based training program in CBT for depression (described in Karlin BE, Brown GK, Trockel M, et al. Dissemination of cognitive behavioral therapy for depression in the Veterans Health Administration. Manuscript submitted for publication.) Subsequently, we expanded the CBTI training program to meet the needs of all mental health providers (regardless of their background in CBTI) within the VHA if they meet the following prerequisites: (1) they are licensed, credentialed, and routinely provide psychotherapy; (2) they receive approval and release time from their supervisors to participate in the training; (3) they demonstrated the need for CBTI services in their setting; and (4) they express commitment to regularly use CBTI after successful completion of the training.

Training licensed therapists who already have many professional obligations, meant the training has to be completed within a relatively compressed timeframe with minimal disruptions to training participants’ routine work responsibilities. These real-life constraints contributed to the decisions we made as we developed this pragmatic training program. We were faced with the following questions: (a) How much to teach about the science of sleep? (b) How much to teach about comorbid sleep disorders? (c) Which comorbidities other than sleep disorders to cover and how to adapt treatment to address the unique challenges these comorbidities present? (d) How to address hypnotic-dependent insomnia? Decisions had to be made pertaining to the strategy of training. In that regard, we describe the following decisions about principles, structure, and tools for CBTI dissemination. These include: (e) Which version of sleep restriction therapy (SRT) to use? (f) How to teach cognitive therapy strategies to those clinicians with limited prior training in cognitive therapy? (g) How to structure the treatment protocols, balancing between the simplicity of a session-by-session protocol and the benefits of a flexible case conceptualization-driven approach? (h) How to facilitate and streamline the assessment and case conceptualization? and (i) What tools should be used to assist the training and facilitate clinical care? These challenges are relevant to any large-scale pragmatic dissemination effort. Of course, initial impressions and training plans often change once actual dissemination efforts begin, and such was the case in this project. The article concludes with a description of preliminary lessons learned from the initial wave of training and proposal of future directions for research and dissemination.

How much teaching about the science of sleep should be included?

Competency in CBTI requires the clinician to be versed in the science of sleep, content that is not typically well covered (if covered at all) in most mental health graduate training programs. Our challenge was to identify the essential aspects of sleep science that could be taught within the limited time available for pure didactic learning given the experiential, “how-to” focus of the workshop, without overwhelming the learners. Our guiding principle was to focus on aspects of sleep science most directly relevant to the implementation of CBTI, including the initial assessment and case conceptualization. The content development workgroup identified three core areas of sleep science to be taught: (a) the two-process model of sleep (circadian process and homeostatic sleep drive) and how these processes work together to maintain wakefulness during the day and sleep at night; (b) how hyperarousal interacts with the two-process model and contributes to the insomnia experience; and (c) the basics of sleep architecture and its relevance to understanding sleep quality. This focused education in sleep science differs from the requirements for Behavioral Sleep Medicine (BSM) certification, which includes the equivalent of a one-year post-doctoral sleep fellowship (or comparable equivalency). BSM training includes much broader didactics in the science of sleep and greater exposure to experiential training in the provision of a range of behavioral sleep medicine interventions in addition to CBTI. Below we provide rationale for the choice of each of the sleep science didactic components.

Understanding of the two-process model is essential for competent administration of CBTI. Knowledge about homeostatic drive helps training participants present the rationale behind SRT and some stimulus control (SC) instructions, such as avoiding naps. Knowledge of the circadian process helps training participants explain the rationale for keeping a fixed rise time and guides the placement of the SRT-determined time in sleep?
behaviors that may necessitate referral to sleep specialists. Trainees can use their understanding of how the two processes work together to regulate sleep to help their patients understand some of the reasons they have a sleep problem, dispel their myths about insomnia, and increase their trust in the provider. This knowledge also prepares training participants to anticipate and address challenges their patients may experience when implementing SRT and SC.

Understanding the regulation of sleep is incomplete without considering hyperarousal and how it interacts with the two-process model of sleep. Training participants need to understand that a strong homeostatic drive and placement of the TIB window to be congruent with the patient’s chronotype may not be enough to promote sleep when arousal is high. Training participants are encouraged to explain how these three factors interact and contribute to the development of conditioned insomnia. This information provides the training participants with a framework for presenting the components of CBTI and for addressing emerging adherence issues. The didactic training includes modeling by experts and rehearsal opportunities to practice explaining these processes in a clear and simple manner tailored to each Veteran’s experience of insomnia and comprehension level.

The didactic training includes education about sleep architecture (sleep stages, the arousal threshold associated with each, and the distribution of sleep stages across the night). This information enhances training participants’ understanding of their patients’ experience of insomnia and helps them explain sleep-state misperceptions. The didactic training also includes education about the contribution of sleep fragmentation to perceptions of sleep quality, and this knowledge can be used when explaining SRT as a procedure for reducing sleep fragmentation. Education about the effects of aging on sleep architecture is included because it helps clinicians correct inaccurate beliefs about sleep and shape realistic expectations about treatment goals. Understanding sleep architecture is also important for differentiating between nightmares, ubiquitous among Veterans with comorbid PTSD, and other parasomnias and parasomniac behaviors that may necessitate referral to sleep specialists.

How much teaching about comorbid sleep disorders should be included?

Competent delivery of CBTI requires knowing when comorbid sleep disorders are contraindications for CBTI, when they necessitate adaptation of CBTI to ensure patient safety, and when referral to specialized sleep medicine treatment is indicated. To be parsimonious and ensure appropriate focus, the workgroup decided to limit training to the assessment of comorbid sleep disorders most prevalent among VHA patients: obstructive sleep apnea (OSA), circadian rhythm sleep disorders, and restless legs syndrome (RLS). The training provides information and tools for identifying these sleep disorders, encourages referral to and collaboration with sleep specialists when a comorbid sleep disorder is suspected, and discusses when and how to modify CBTI to enhance outcome and ensure patient safety. Assessment scripts and assessment tools are provided to help clinicians identify the presence of these disorders. Relevant assessment tools consist of the STOP questionnaire to assess the likelihood of severe OSA and the Restless Legs Questionnaire. We also include information on how to adapt CBTI in the context of untreated or undertreated OSA to address the greater risk of daytime sleepiness in response to strict SRT. However, OSA associated with severe daytime sleepiness was deemed a contraindication for CBTI. We instruct training participants to assess and encourage adherence with continuous positive airway pressure devices when applicable. We chose not to discuss adaptations of CBTI for working with RLS sufferers, because our collective clinical experiences suggest standard CBTI protocols are effective with such patients. We encourage collaboration with sleep specialists (either sleep medicine or behavioral sleep medicine specialists) for all comorbid sleep disorders.

We decided that significant focus on severe Circadian Rhythm Sleep Disorder necessitating circadian rhythm entrainment was beyond the scope of CBTI training and recommend referral to sleep specialists. However, we do encourage training participants to assess chronotype using assessment guidelines and the Morningness/Eveningness questionnaire because of its relevance to the implementation of SRT (placing the TIB window to be congruent with it). We also included content for assessing common parasomnias that may be relevant to the treatment of insomnia in patients with comorbid PTSD.

With the exceptions noted above, we decided not to teach strategies and techniques that fully trained BSM specialists use for managing sleep disorders other than insomnia. This has allowed the focus to remain on our primary aim—teaching CBTI to competency. The training emphasizes and encourages collaboration and referral to sleep specialists, including BSM-certified behavioral sleep specialists, for dealing with comorbid sleep disorders. Training in a wider range of BSM services could be the focus of “advanced training” for those who complete the CBTI focused training. Dissemination projects with a broader aim may need longer and more extensive training. We believe that clinicians providing CBTI, whether trained in all aspects of behavioral sleep medicine or not, may contribute positively to patient care by identifying comorbid sleep disorders and recommending appropriate referrals.

Which comorbidities other than sleep disorders to cover and how to adapt treatment to address the unique challenges these comorbidities present?

To make the training most relevant to clinicians in VHA, we focus training on comorbidities most likely to present within the system. These include Major Depressive Disorder (MDD), PTSD, chronic pain, and mild traumatic brain injury (mTBI). For each comorbidity, we incorporate training foci that augment standard insomnia assessment and CBTI implementation. No empirical support exists for providing CBTI during active substance abuse/dependence. The modest data that do exist support the use of CBTI with recovering alcoholics. We recommend that CBTI be provided to patients with abuse/dependence disorders, but after some initial period of sobriety is achieved. We include education on the short-term and long-term effects of alcohol (and nicotine) use on sleep given its widespread use among Veteran patients.

Some assessment considerations are common to depression, PTSD, and pain. For example, we highlight the increased prev-
male and the importance of assessing its presence and adequacy of its treatment in all three comorbidities. We also educate the training participants on the sleep effects of medications used for each disorder. We encourage assessment of two other features common in these three disorders: (a) hopelessness (Does patient believe poor sleep will not improve because it is just a symptom of depression/PTSD/pain-brain injury?) and (b) the functional significance of bed- or night-related behaviors. In MDD and chronic pain, going to bed may be an escape from emotional or physical pain or daily demands. In PTSD, bed- or night-related behaviors include avoidance of silence or sleep/bed because of nightmares or nocturnal hypervigilance. For MDD, we also discussed the need to determine if sleep is used in an attempt to escape from emotional pain, whether anhedonia and/or low motivation contribute to difficulty getting out of bed in the morning, whether rumination interferes with sleep, and whether diurnal variations in mood affect likelihood of staying in bed too much. For mTBI, we recommend assessing comorbid psychiatric disorders because a large-scale study found that the psychiatric disorders comorbid with mTBI might be better predictors of insomnia than the mTBI itself.

With respect to treatment considerations, we highlight some of the unique presentations of insomnia that occur in each of the comorbid disorders and may affect adherence to CBTI recommendations. In all modifications we selected, we strove to maintain fidelity to the efficacious components of CBTI (SC, SRT) and to the efficacious strategies for comorbid psychiatric or pain disorders. For example, to help patients with MDD or chronic pain with difficulty in following the SC guideline about getting out of bed at the same time each morning, we teach providers to use behavioral activation (planning rewarding daily activities—a component of CBT for depression and for pain). In most instances, CBTI and CBT for depression, pain, and PTSD are complementary and conceptually compatible. However, particular attention was required to address how to implement CBTI in the context of excessive nighttime hyperarousal, as seen in PTSD. Veterans with PTSD often report engaging in compensatory behaviors, such as sleeping with weapons or performing perimeter checks when concerned about safety in the middle of the night. Although these behaviors may increase a sense of safety in the short term, they perpetuate insomnia in the long term by promoting hyperarousal. Therefore, we encourage clinicians to teach patients with PTSD to lock up their weapons and refrain from checking behaviors when unable to sleep and to use instead thought-challenging or relaxation techniques outside of bed to cope with the short-term increase in anxiety and at the same time help break the association between bed and hyperarousal.

We provide additional training about how to adapt standard CBTI by modifying existing components, adding components, or changing the relative emphasis of the different components. For example, when hyperarousal is very high in the context of disorders, such as MDD or PTSD, methods for reducing it may need to be emphasized. Therefore we provide training on the use of worry time and acceptance-based techniques during the day to handle ruminations that might arise in bed, whether they were related to dysfunctional beliefs about sleep or to a tendency to replay past traumatic memories. We alert training participants to the possibility that among chronic pain patients, progressive muscle relaxation may increase pain and need to be adjusted or an alternative relaxation technique substituted. For patients with mTBI, we recommend using simplified sleep diary and handouts to suit the patient’s concentration problems. Another example is training on when and how to modify SC and SRT through use of alternatives such as sleep compression and countercontrol. This may be indicated for some chronic pain patients who may find it too physically demanding to move to another room or even get out of bed when unable to sleep. We demonstrate the use of cognitive restructuring when disorder-specific beliefs and thoughts interfere with sleep or adherence with CBTI. The training includes education about sleep in various disorders to help training participants change patients’ inaccurate beliefs. For instance, we include education about the effects of pain and attention to pain on the likelihood of falling back to sleep when awakened by pain.

The consensus of the workgroup was that training in structured therapies for addressing nightmares, such as Imagery Rehearsal Therapy (IRT), was premature for national dissemination and implementation until further work clarifies its efficacy for addressing combat-related nightmares. In addition, adding IRT to the intensive CBTI training would likely be overly complex. However, we developed the CBTI protocol and training to include important nightmare-related content and skills training, given the frequency of nightmares and other PTSD-related sleep symptoms in Veterans. This includes training in helping Veterans avoid rumination about the meaning of disturbing dreams, use of SC to help extinguish the association between bed and arousal associated with nightmares, and methods for calming the mind when out of bed following a nightmare awakening to facilitate return to sleep. Furthermore, we recommend that clinicians refer patients with more severe nightmare-related symptoms to an exposure-based PTSD psychotherapy, particularly when other PTSD symptoms are also present, or for consideration of treatment with prazosin, shown in multiple randomized controlled trials to be efficacious for nightmares.

How should hypnotic dependent insomnia be addressed?

Nearly 50% of patients presenting for treatment for insomnia are prescribed a medication for sleep, and the majority will continue to use sleep medications almost nightly for periods of a year or longer. It is therefore likely that many candidates for CBTI are currently taking some form of pharmacotherapy for their insomnia, and many of these patients have been receiving this treatment for extended periods of time. The majority of studies suggest that hypnotic-dependent patients respond about as well to CBTI as do medication-free patients. Therefore, the consensus of the workgroup was to not exclude medication-dependent insomnia sufferers from treatment with CBTI. However, it was recognized that two aspects of sleep medication use may require adaptation of CBTI. The first is the potential risks associated with getting out of bed in the middle of the night (SC) or in the morning (during SRT) when hypnotic effects may still be present.
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consult the prescribing physician or another physician on the treatment team about such risks and to use a more liberal TIB prescription, when implementing SRT in order to minimize risk of carryover sedation. The second issue is patients’ PRN use of medications, whereby they go to bed without their normal medication to “see how they do” without it. This practice may result in heightened sleep-related performance anxiety, low sleep-related self-efficacy, and psychological dependence on the medication. We included didactic content about these issues, as well as about patients’ ambivalence about their use of hypnotic use. However, training participants were discouraged from contradicting physician’s instruction of PRN use and were advised to discuss the patient’s schedule of hypnotic use with the prescribing physician.

The issue of whether to include specific focus on medication discontinuation led to extensive discussion among workgroup members. Ultimately, there was consensus not to include content related to medication discontinuation, due to feasibility issues and a sense that this would have required significant additional training time and costs for the dissemination program. Therefore, instructions in validated protocols for hypnotic discontinuation had to remain beyond the scope of this training. It was further recognized that the VHA system has expert pharmacotherapy capacity to address the issue of a safe medication taper. We encourage CBTI training participants to refer all patients requesting medication taper to their prescribing physicians, offer to support the patient during the taper, and collaborate with physicians when psychological dependence appears to be hindering success with the tapering plan. For that reason, training includes didactic information about hypnotic medications, relevance of medication half-life, and the timing of administration for the safe application of CBTI. In addition, the training also discusses the concepts of rebound insomnia and psychological dependence, as well as the utility of a gradual taper and strategies for supporting patients during the tapering process.

**STRATEGY OF TRAINING: DECISIONS REGARDING PRINCIPLES, STRUCTURE, AND TOOLS OF CBTI FOR DISSEMINATION**

**Which version of SRT to use and how to adapt it when needed?**

The very term “sleep restriction therapy” can induce anxiety in many insomnia patients who already feel they are not getting enough sleep. This anxiety may become a significant obstacle to adherence. Therefore we offered several alternative terms, such as “time in bed restriction,” “sleep quality training,” and “sleep efficiency training.” The alternative terms facilitate a focus on curtailing the excess time in bed, without implying reduction in sleep time, improving the quality of sleep, and making sleep more efficient. Such terms are less likely to promote anxiety and more likely to foster adherence.

We chose to develop an initial time in bed (TIB) schedule based on Spielman et al., 49 using one to two weeks of pre-treatment sleep diaries. We opted for the original SRT method, 49,50 because it is most commonly used in CBTI studies and is more likely to yield rapid results than subsequently developed alternatives that involve longer initial TIB. 51-53 Although the original SRT method used 4.5 hours as the minimum prescribed sleep opportunity, to ensure patient safety we recommend a 5-h minimum, as recommended by several authors. 54,55 We modified Spielman’s original recommended criteria for extending, reducing, or maintaining TIB. We operationalize the TIB adjustment to take into account the patient’s sleep need. With permission from Arthur J. Spielman, PhD, we adapted a sleep algorithm 56 to assist the novice therapist in determining whether to extend, hold, or decrease time in bed and how much. The algorithm is based on sleep efficiency (SE) and a 4-item questionnaire to assess sleep need based on daytime and evening fatigue, sleepiness, napping, and the patient’s perception of sleep adequacy. If SE is ≥85%, the modified algorithm calls for a 30-min increase in TIB when sleep need is high and a 15-min increase when sleep need is moderate. If SE is <80% and the sleep need is low, there is a 15-min reduction in TIB. The 85% and 80% SE cutoffs we adapted were originally proposed by researchers testing SRT in older adults 51,52,53 and have been subsequently recommended in several therapists’ guides. 58,59 Even though the original protocol recommended adjustment every 5 days, 49 we recommend weekly evaluation for adjustments in TIB for pragmatic reasons, since therapy sessions are usually spaced more than 5 days apart.

The calculation of daily sleep diaries can be time-consuming. We therefore developed a sleep calculator, whereby the therapist enters the diary values into an easy-to-use spreadsheet. The calculator determines the weekly means and graphs the weekly data over time. The graphs can be shared with the patient to highlight progress and help shape awareness of change, particularly early in therapy when the fatigue and sleepiness effects of treatment are strongest.

As in the SRT 60 and SC 62 protocols, we recommend that patients avoid naps. We also provide guidelines for modifying this and other aspects of SRT and SC when patients experience daytime sleepiness. For such cases, we provide napping guidelines. If napping does not alleviate daytime sleepiness sufficiently to permit the patient to function safely during the day and evening, we recommend relaxing SRT. For example, setting the initial TIB to be average TST plus 30 min 2,63 or using sleep compression, 64 a variant of SRT that involves gradual, rather than abrupt reduction of TIB. These variations of the standard SRT were also recommended for certain frail patients, patients with chronic pain, and patients who respond to SRT with high levels of anxiety. Training includes discussion of when SRT is contraindicated, such as in patients with severe untreated sleep apnea. The general recommendations we provide as alternatives to SRT include SC and strategies to reduce arousal. For patients who respond to SRT with very high levels of anxiety or are otherwise resistant to the idea of reducing TIB, we recommend motivational enhancement and anxiety reduction strategies, including cognitive therapy to prepare for future implementation of SRT.

**How to teach cognitive therapy strategies to clinicians with no prior exposure to cognitive therapy?**

Comprehensive training in cognitive therapy theories and practice as it applies to depressive and anxiety disorders was considered not feasible within the context of this training effort.
Moreover, a comprehensive CBT manual which includes more extensive content and worksheets on the theory and application of cognitive therapy with Veterans and Military Service members has been developed and is now widely available to VA clinicians and others. Instead the workgroup decided to focus on providing the basic model linking cognitions, emotions, and behaviors, and then focus on strategies for reducing cognitive hyperarousal, sleep-interfering cognitions, and beliefs about sleep that may hinder adherence with CBTI. These include strategies for thought restructuring (guided discovery, downward-arrow technique, cost-benefit analysis, thought records), coping cards, and behavioral experiments. In other modules of training, we included modeling and ample opportunities for practice through dyadic and small group work and large group discussions of the experiential work. Even though this sleep-focused training in cognitive strategies will not prepare training participants to apply cognitive therapy when treating other mental disorders, the workgroup reasoned that the focused attention on sleep-related beliefs and cognitions will adequately prepare them to enhance adherence with the behavioral strategies of CBTI.

Using case conceptualization to enhance learning and competency

Case conceptualization is the foundation for any good therapy, including CBTI, and is an important component of the VA CBT-I protocol, thus allowing for flexible patient centered administration. To promote the development and application of case conceptualization in the therapy, the workgroup developed a case conceptualization form that facilitates the synthesis of information gathered during the assessment and design of a treatment plan. The case conceptualization form is part of the protocol. It asks training participants to identify (a) factors that may weaken the homeostatic drive, such as extended TIB, excessive napping, and dozing off before the intended sleep period; (b) factors that may weaken the circadian process, such as irregular sleep schedule or a mismatch between chronotype and the habitual sleep opportunity window; (c) evidence of sleep-interfering hyperarousal, such as sleep effort, dysfunctional beliefs about sleep, and difficulty quieting the mind in bed; (d) sleep-interfering behaviors, including use of substances and other poor sleep hygiene practices, such as nocturnal eating, exercising, and exposure to sleep-disruptive environmental factors. The form also asks training participants to consider (a) how comorbidities, if present, contribute to insomnia and/or hinder treatment adherence, and what disease specific sleep symptoms other than insomnia may need attention (e.g., early morning awakening in depression, confusional arousal and nightmares in PTSD, nocturnal pain); (b) how prescription and non-prescription medications impact sleep and whether they raise a safety concern; (c) which predisposing, precipitating, and perpetuating factors of insomnia are present. The case conceptualization form asks training participants to write down plans for addressing each identified factor and to rank order the list of factors. Thus, the form was designed to promote a flexible, individualized treatment.

How to facilitate and streamline the assessment?

To facilitate and streamline the assessment process, we have developed an intake form and recommended a set of assessment questionnaires. These include the Dysfunctional Beliefs About Sleep Scale to assess sleep-interfering beliefs and cognitions; the Morning/Eveningness Questionnaire to discern the patient’s circadian tendency so that if there is a mismatch between a patient’s circadian tendency and sleep/wake schedules, it can be recognized; the brief STOP screening questionnaire to assess the likelihood of severe OSA; and the Restless Legs Syndrome Rating Scale to help determine the severity of RLS, when it is suspected. The workgroup thought it is safe to assume that mental health providers would be able to assess comorbid mental conditions without additional instruction or special assessment instruments. Daily sleep diary is a mandatory assessment and treatment tool that guides the implementation of CBTI. The workgroup was faced with the decision as to which of the many versions of a sleep diary to choose. We agreed the format and items used should provide quantitative information to allow estimation of TST and SE. We also thought it would be useful to choose a diary version that is likely to enjoy widespread use both within and outside of the VA health care system. Given these considerations the workgroup chose and obtained permission to use the “Consensus Sleep Diary” developed recently to standardize insomnia assessment in research and clinical venues.

How to structure the treatment protocol?

A session-by-session treatment protocol is easy to learn and is particularly important in research when samples tend to be homogeneous and prescreened. The main disadvantage of this approach is that it does not lend itself to flexible clinical implementation in a real-life setting, in which the patient population is heterogeneous. We opted for a semi-structured approach allowing the case conceptualization to drive the order in which the treatment components are introduced. The workgroup decided on a 6-session protocol that allows early termination when treatment aims are attained earlier and longer treatment when clinically indicated. The first session is dedicated to assessment and the last includes a relapse prevention component. The therapist spends time after the assessment to complete the case conceptualization form and design a treatment plan. The second and subsequent sessions begin with a review of the completed sleep diary. In most cases the second session consists of SRT and SC, but when sleep-related anxiety and sleep effort are high, when daytime sleepiness is severe and/or when other clinical and/or safety concerns render SRT contraindicated, the clinician may chose to focus on other clinically relevant components and, when applicable, to use motivational enhancement and other therapeutic techniques to prepare them for the implementation of SRT. Subsequent sessions include review of sleep diary entries, adjustment of the TIB based on the patient’s progress, addressing adherence, and introducing other treatment components as needed. The treatment structure is outlined in Table 1.

What patient handouts can assist the training and facilitate clinical care?

The workgroup agreed that clinically relevant patient handouts could be an effective way to facilitate training. Taking into account the possibility that many patients may shun supplemental reading materials we limited the number of es-
Dissemination of CBTI

is completed, and again at follow-up approximately 6 months after the end of training. Variables measured include: participating therapists’ ratings of the trainers, the quality of the training program, perceived knowledge and skills acquisition, intent to apply skills learned in their therapy practice, self-efficacy in applying general and CBTI specific therapy skills, attitudes regarding use of CBTI, estimated percentage of respondents’ patients who would benefit from CBTI, and the percentage of their patients with whom they plan to use CBTI. We also assess the effects of CBTI on patients’ insomnia severity.70,71 In addition, therapist training outcome, as measured by a competency rating scale developed by the authors for this dissemination effort, and patient clinical outcomes are core components of the program evaluation efforts. Although a detailed report of evaluation results would be premature and beyond the scope of this paper, it does seem useful to comment on initial lessons learned from the first pilot cohort of therapists enrolled in the training program.

Twenty-three therapists (9 social workers, 2 advanced practice nurses, 11 doctoral level psychologists, and 1 psychiatrist) with previous training in cognitive behavioral therapy for depression participated in the first pilot training workshop and are actively treating VHA patients with CBTI and undergoing weekly consultations. The workshop lasted 1.5 days. The training participants overwhelmingly reported that the program met stated objectives (all but one therapist), their educational expectations (all but 2 therapists), and provided them with new psychotherapy skills/techniques that were relevant to treating insomnia in their practice population (all but 2 therapists). The

**PRELIMINARY LESSONS LEARNED AND FUTURE DIRECTIONS**

Lessons learned from the first training cohort

Ongoing formative and summative program evaluation is a central component of the dissemination effort, as with other VA initiatives for dissemination of evidence-based psychotherapies.26 We use survey measures to collect data prior to the training, immediately after the workshop is completed, and again at follow-up approximately 6 months after the end of training. Variables measured include: participating therapists’ ratings of the trainers, the quality of the training program, perceived knowledge and skills acquisition, intent to apply skills learned in their therapy practice, self-efficacy in applying general and CBTI specific therapy skills, attitudes regarding use of CBTI, estimated percentage of respondents’ patients who would benefit from CBTI, and the percentage of their patients with whom they plan to use CBTI. We also assess the effects of CBTI on patients’ insomnia severity.70,71 In addition, therapist training outcome, as measured by a competency rating scale developed by the authors for this dissemination effort, and patient clinical outcomes are core components of the program evaluation efforts. Although a detailed report of evaluation results would be premature and beyond the scope of this paper, it does seem useful to comment on initial lessons learned from the first pilot cohort of therapists enrolled in the training program.

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training participants particularly highly valued the experiential aspects of the training, such as skills exercises in small groups. They further reported that additional time would be valuable to fully assimilate the amount of information presented in didactic presentations and experiential exercises. Some therapists indicated that additional training and practice to feel more comfortable explaining a scientifically sound model of insomnia to their patients would be particularly valuable. As expected given the high frequency of comorbidities in the VHA patient population, training participants also expressed significant interest in and value related to the content on implementing CBTI with patients with comorbidities (especially PTSD) and indicated that additional time addressing these issues would be valuable.

Based on this early formative feedback from the pilot training, we have extended the training workshop (3 days vs. the initial 1.5 days) to allow more time for therapists to assimilate the content and provide more opportunity for experiential skills practice, including demonstration and practice on how to present a scientifically sound model of insomnia and rationales for the treatment components to patients. Because the subsequent cohorts of clinician training participants are not required to have prior familiarity with cognitive therapy, the extended training expands training in cognitive therapy strategies relevant to insomnia. Additional content related to implementing CBTI with patients with PTSD and other comorbidities (significantly addressed in the protocol and therapist manual, as described above) was incorporated into the expanded training workshop. The plan is to centrally train approximately 1,000 mental health clinicians from a variety of clinical settings, including primary care, over a span of three years with an approximate annual budget of 1.3 million dollars. Furthermore, mechanisms are being developed to eventually decentralize the training to broaden dissemination and promote sustainability, such as continued “virtual office hours” for graduates. At the time of this writing, this dissemination of CBTI within the VA health care system represents, to our knowledge, the largest initiative to disseminate and implement CBTI in this nation.

**Conclusions and Future Directions**

The ultimate goal of any CBTI dissemination project is to fill the gap between the number of professionals presently trained in CBTI and the vast, currently unmet, demand for clinicians competent to alleviate the distress of insomnia. This article described the development of a CBTI training protocol for mental health clinicians who work in the VA health care system and have little or no prior sleep specialty training. The issues we encountered in developing this dissemination initiative will be relevant to future dissemination efforts, as those too will have to contend with “real-world” practical issues and tailor training to the training participants’ backgrounds, experiences, knowledge, and disciplines, clinical settings, and patient populations. Real-world practical issues may include time available for training, need to minimize disruptions to training participants’ ongoing workload and to the system in which they work, and, of course, available funds. To ensure availability of CBTI to meet the needs of the largest group of patients possible, we aim to train mental health clinicians regardless of professional discipline. The decision about which training participants to target in future dissemination projects will have to be based on the needs of the specific system(s) within which training will take place. Some decisions we made were specific to the needs of Veterans. For example, we included extensive training on adapting CBTI to patients with comorbid PTSD. We have also adapted the training and the treatment protocol taking into consideration Veterans’ culture and other such issues. The specific target population of future dissemination projects may suggest de-emphasizing this aspect of training and emphasizing other aspects instead. Training that targets primary care patients may de-emphasize this aspect of training and emphasize other aspects instead. Training that targets primary care patients may emphasize medical comorbidities, and place greater emphasis on collaboration with primary care providers. Program evaluation of our CBTI dissemination project is ongoing, as is the validation of our competency rating scale. Once finalized, these and other materials developed for this dissemination initiative will be freely available to others so that they can be used or adapted in future disseminating projects. The continuous evaluation of therapists’ adherence and competence on training cases provides information about the strengths and development areas of each therapist and areas that require additional training and feedback. This information will be used for quality assurance.
purposes. To fully evaluate the success of any dissemination project of an evidence-based psychotherapy, it is important to evaluate long-term utilization and sustainability, patient outcomes and the maintenance of treatment fidelity over time, all of which are planned for this program and are included in other EBP dissemination initiatives in VHA. We hope this dissemination and training initiative will enable CBTI to cross the boundaries of clinical research laboratories and specialty clinics to serve the great clinical need of Veterans with insomnia. Importantly, we believe this initiative can serve as a model of dissemination of CBTI, making it available to the many patients who can benefit from this effective therapy.

**REFERENCES**


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SUBMISSION & CORRESPONDENCE INFORMATION

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There has been considerable research indicating that the prevalence for insomnia is high, that cognitive behavior therapy for insomnia (CBTI) is an effective treatment, and that it maintains its effectiveness during follow-up periods for as long as two years.\(^1,2\) Despite this, there have been difficulties in disseminating CBTI so that more individuals would benefit.

The article by Manber et al. in this issue on the training and dissemination effort taking place at the Veterans Health Administration (VHA) is ambitious and tackles some of the most difficult aspects of disseminating effective treatments. The VHA is the largest integrated health care system in the United States and is in the midst of undertaking an evidence-based psychotherapy dissemination program\(^3\) for a number of disorders including depression, PTSD, and now insomnia treated with CBTI. With regard to CBTI, VHA mental health clinicians who are already credentialed to treat mental health problems are being recruited for training and supervision in CBTI.

There are many noteworthy aspects of this training program, but one that stands out is the commitment to what the authors call, “case conceptualization.” This commitment to personalized assessment, etiology, and the mechanisms underlying effective treatments is praiseworthy. There is sometimes a danger in attempts to disseminate treatments by simplifying or abbreviating them. In the process of doing so, we may lose sight of insuring that the mechanisms for the treatments’ effects are retained.\(^4\) Not infrequently, the treatment of insomnia is made more difficult when it is complicated by the presence of comorbidities that are common in returning veterans, and simplified versions of the treatment may not work under those conditions.

To emphasize a personalized approach in the VHA program, a case conceptualization form was developed that prompts the training clinicians to identify items that affect possible etiological factors. This includes descriptions of activities that may have weakened homeostatic drive, activities that may have weakened circadian drive, and evidence of both sleep-interfering hyperarousal and sleep-interfering behaviors. In addition, those being trained are taught to attend to the role of comorbid disorders and the effects of ongoing medication. Further, the Spielman model of predisposing, precipitating, and perpetuating factors of insomnia\(^5\) is integrated into treatment planning.

The material discussed in the paragraph above is part of a training experience that begins with a workshop. As described in the article there is considerably more covered during the workshops. The Manber et al. article provides detail on a number of issues that had to be decided to keep a balance between the time commitments of busy professionals and the methods of expanding the clinician’s expertise to include CBTI.

The workshop, although important, may not be the most important pedagogical technique described. Equally important, if not more so, all trainees see patients using the CBTI approach and are supervised by behavioral sleep medicine clinicians. Such a mentoring approach is common in many training environments. It would seem to be essential in any attempt to build clinician competence.

The short-term process results look excellent. The long-term test of the program will depend on whether the authors meet their goal of training 1000 VHA clinicians to implement CBTI, whether the clinicians’ commitment to treating insomnia with CBTI can be sustained, whether the training experience serves as a gateway to becoming expert in the full range of behavioral sleep medicine clinical activities, and whether competency as measured by patient outcomes is achieved.

A strength of the program is that this CBTI dissemination effort has the potential to impact a growing societal problem in treating insomnia that is comorbid with other medical and emotional problems. Perhaps the success of the VHA CBTI program will be encourage other integrated health systems, such as HMOs, to implement their own programs.

**REFERENCES**

Dr. Bootzin has indicated no financial conflicts of interest.
Development and Growth of a Large Multispecialty Certification Examination: Sleep Medicine Certification—Results of the First Three Examinations


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This paper summarizes the results of the first three examinations (2007, 2009, and 2011) of the Sleep Medicine Certification Examination, administered by its six sponsoring American Board of Medical Specialty Boards. There were 2,913 candidates who took the 2011 examination through one of three pathways—self-attested practice experience, previous certification by the American Board of Sleep Medicine, or formal Sleep Medicine fellowship training. The 2011 exam was the last administration in which candidates who had not previously been admitted could take it without completion of formal Sleep Medicine fellowship training. As expected, the number of candidates admitted to the 2011 examination through the practice experience pathway increased, and the overall scores of these candidates were on average lower than the other candidates. Consequently, the pass rate for all first takers of the 2011 examination (65%) was lower than that observed from the 2009 examination (78%) and the 2007 examination (73%). For each administration, candidates admitted through the fellowship training pathway scored the highest; over 90% of them passed the 2011 and 2009 examinations.

Keywords: Sleep Medicine Certification Examination, American Board of Medical Specialty Boards

Citation: Quan SF; Buysse DJ; Ward SLD; Harding SM; Iber C; Kapur VK; Rowley JA; Sateia MJ; Silber MH; Sorscher AJ; Vaughn BV; Wilmans M; Woodson BT; Zee P; Mills LE; Hess BJ. Development and growth of a large multispecialty certification examination: sleep medicine certification—results of the first three examinations. J Clin Sleep Med 2012;8(2):221-224.

INTRODUCTION

The Sleep Medicine Certification Examination was administered for the third time in November 2011 under co-sponsorship of six member boards of the American Board of Medical Specialties (ABMS)—the American Board of Internal Medicine (ABIM), which is the designated administrative board, the American Board of Family Medicine (ABFM); the American Board of Otolaryngology (ABOto); the American Board of Pediatrics (ABP); the American Board of Psychiatry and Neurology (ABPN); and the American Board of Anesthesiology (ABA). The 2011 examination was the first time that ABA candidates were admitted.

Identical to the previous two administrations of the examination in 2007 and 2009, there were three admission pathways to the examination available to prospective candidates. Pathway A was self-attestation, subject to possible audit, of the equivalent of 12 months of full-time, post-training practice experience providing clinical care to patients with sleep disorders, accumulated over a maximum of five years prior to examination application. Candidates also had to attest that they (1) evaluated a minimum of 400 individual patients with sleep disorders, (2) interpreted and reviewed raw data of at least 200 polysomnograms, and (3) interpreted and reviewed raw data of at least 25 multiple sleep latency tests. Pathway B required that candidates hold a valid American Board of Sleep Medicine (ABSM) sleep medicine certificate. Pathway C required successful completion of a one-year fellowship in Sleep Medicine. As previously described, the ABMS approved certification of Sleep Medicine in 2005. At that time, Sleep Medicine practitioners consisted of either individuals certified by the ABSM (Pathway B) or those who were not certified by any formal process (Pathway A). Few
had received any formal training in Sleep Medicine, and none of the training programs had been accredited by the Accreditation Council for Graduate Medical Education (ACGME). During initial discussions to plan for the new examination, Pathways A and B were made available in order to allow for current Sleep Medicine practitioners to become certified. However, in 2004, ACGME accreditation requirements for Sleep Medicine fellowships were approved, and shortly thereafter, a number of Sleep Medicine fellowship programs received ACGME accreditation. Thus, it was decided that during these preliminary planning meetings to develop the Sleep Medicine examination, Pathways A and B should be made available for only a limited amount of time—specifically, three examination cycles. This would allow sufficient time for current Sleep Medicine practitioners who had not undertaken fellowship training to become certified by passing the new examination. The 2011 administration marked a milestone in the history of Sleep Medicine because it was the last time that new candidates were admitted to the examination through either the self-attested practice experience pathway or through previous certification by the ABSM. Beginning with the 2013 examination, only physicians who have completed an ACGME accredited Sleep Medicine fellowship (Pathway C) will be admitted to take the examination. However, candidates admitted through one of the other pathways and who were not successful in passing the examination will still be eligible to retake the examination without additional formal training.

EXAMINATION METHODOLOGY

An overview of the process for developing and scoring the examination was previously described.3 The test blueprint defining the primary medical content domains for the Sleep Medicine Certification Examination was the same for the 2007, 2009, and 2011 administrations. The ABIM website contains further information about the test blueprint (http://www.abim.org/pdf/blueprint/sleep_cert.pdf) as well as the test development process (http://www.abim.org/about/examInfo/developed.aspx). For each of the three administrations, the Sleep Medicine Certification Examination contained 240 single-best-answer multiple-choice questions and was administered by computer. However, beginning with the second (2009) administration, candidates’ overall scores were computed using 200 of the 240 questions. This was done to help ensure that each examination was parallel in content and psychometric characteristics to the prior administration, thus maintaining high-quality measurement characteristics. The additional 40 questions were considered experimental questions, a common practice in the testing industry to identify which questions performed well enough to be retained for future test takers. Because of the large number of candidates who registered for the examination, 2009 also marked the first time that multiple forms of the examination were administered, and that examination was given on two separate days. Modern test theory was used to ensure that candidates’ overall scores had the same meaning regardless of the form taken; scores were standardized and reported on a scale with a mean of 500 (SD = 100).

All candidates were held to an absolute content-based standard for passing the examination, rather than a relative standard that is dependent on their performance in comparison with other candidates. A standard was set for each examination year because the composition of the admission pathways changed from the previous administration (e.g., there were fewer candidates admitted to the first 2007 examination through the fellowship training pathway). The standard was established by the committee using the modified Angoff method, a validated and established method for examination standard setting.3 In short, for each examination, the committee discussed the characteristics of minimally qualified or borderline candidates. Next, the 200 questions used for scoring the examination were reviewed, and group members individually identified the expected performance of borderline candidates for each question. Finally, these judgments were systematically combined to derive a minimum passing score for all examinees on the standardized score scale.

EXAMINATION PERFORMANCE AND RESULTS

A total of 2,457 candidates took the 2011 examination for the first time (Table 1). This represents a 15% increase in the number of first takers compared with the number of first takers in 2009 (N = 2,140), and a 31% increase compared with the number that took the first 2007 examination (N = 1,882). Taking the 2011 examination for the first time were 1,512 (62%) ABIM candidates, 527 (21%) ABPN candidates, 234 (10%) ABOto candidates, 108 (4%) ABFM candidates, 71 (3%) ABP candidates, and 5 (< 1%) ABA candidates. Except for the inclusion of ABA candidates, the relative proportion of candidates from each Board is consistent with the proportions observed in 2009 and 2007.

<table>
<thead>
<tr>
<th>Year</th>
<th>N</th>
<th>% Pass</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>2007</td>
<td>1882</td>
<td>73%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2009</td>
<td>2140</td>
<td>78%</td>
<td>500</td>
<td>100</td>
</tr>
<tr>
<td>2011</td>
<td>2457</td>
<td>65%</td>
<td>466</td>
<td>103</td>
</tr>
</tbody>
</table>

The 2011 data exclude a few candidates whose examination outcomes were pending at the time this article was being prepared. Mean scores are not reported for the 2007 candidates because that examination was scored using all 240 questions, whereas in 2009 and 2011 candidates’ scores were computed using 200 of the available 240 questions. Modern test theory was used operationally for the first time in 2009 so comparisons between 2011 with 2009 scores are possible, but these cannot be compared with 2007 scores.

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lower pass rate for ABSM-certified candidates was surprising only minimally met the examination entry criteria. The slightly pass rates for the practice experience pathway were expected, way were highest (and similar to those observed in 2009). The candidates admitted through the fellowship training path-

minimally, for those who completed a fellowship. This was

in 2009, pass rates decreased for each pathway in 2011, although was the last year candidates could be admitted to the examina-

tion without fellowship training. Compared with the pass rates in 2009, the lower pass rates in 2011 can be attributed primarily to the lower ability of those candidates.

Table 2 presents the number (and percent) of first takers admitted through each pathway and their pass rates and mean scores for the first three administrations. Both in absolute numbers and proportionally, there were fewer first takers admitted through the fellowship training pathway in 2011 (293, 12%) compared with those in 2009 (352, 16%). This is somewhat surprising given that the number of fellowship positions accredited by the ACGME has increased steadily over the past six years. One possible explanation is that the number of candidates classified as fellowship trained in 2009 was inflated by including those who had completed non-ACGME accredited fellowships. Not unexpectedly, there were numerically and proportionally fewer first takers previously certified by the ABSM in 2011 (526, 21%) compared with 2009 (573, 27%) and 2007 (683, 36%). In contrast, the absolute number and proportion of first takers from the self-attested practice experience pathway was much higher in 2011 (1638/67% compared with 1215/57% in 2009 and 1034/55% in 2007). This was expected because 2011 was the last year candidates could be admitted to the examination without fellowship training. Compared with the pass rates in 2009, pass rates decreased for each pathway in 2011, although minimally, for those who completed a fellowship. This was largely due to the lower ability of these first takers compared with first takers in 2009. Specifically, the ability and pass rate of candidates admitted through the practice experience pathway were the lowest; conversely, the ability and pass rate for the candidates admitted through the fellowship training pathway were highest (and similar to those observed in 2009). The pass rates for the practice experience pathway were expected, given that many of these candidates had no formal training and only minimally met the examination entry criteria. The slightly lower pass rate for ABSM-certified candidates was surprising and not readily explainable, but does indicate such candidates who delayed taking the exam, on average had slightly less ability. Nevertheless, ABSM candidates as expected performed markedly better than practice pathway candidates. The strong performance of fellowship-trained candidates not only provides independent evidence for validity of the examination scores but also supports the relevance of clinical training experienced during an ACGME fellowship.

Two important considerations when assessing the psychometric characteristics of an examination are the reliability of scores and the reproducibility of pass/fail decisions. Score reliability was assessed using the coefficient α. Coefficient α provides an estimate of the amount of variability in candidates’ scores that is due to true differences in ability rather than random influences such as guessing. The consistency of the pass/ fail decision, which is related to score reliability, is an estimate of the proportion of candidates who would receive the same pass/fail decision if repeatedly tested with equivalent examinations. The coefficient α for each of the three examinations exceeded 0.90, which meets testing industry standards. This value indicates that the variability in scores is largely due to differences in the true abilities of the candidates. Pass/fail decision consistency for 2011, 2009, and 2007 was 0.88, 0.89, and 0.89, respectively, which indicates that approximately 90% of the candidates that took any one of the three examinations would receive the same pass/fail decision if retested with an equivalent examination.

CONCLUSION

The data presented here indicate that the first three ABMS Sleep Medicine Certification Examinations performed very well. Candidates’ scores were reliable, and the resulting pass/fail decisions were consistent. The differences observed in the performance of the candidates from the three pathways provide some evidence for the validity of the examination scores. Furthermore, the overall pass rates observed from each administration were judged to be reasonable, and the performance of each of the three admission pathways was generally as expected.

The administration of the 2011 ABMS Sleep Medicine Certi-
fication Examination marked a milestone in the history of the specialty that began with the first Accredited Clinical Polysongrapher examination in 1978. In the 31 years that have elapsed, the practice of Sleep Medicine has evolved to incorpo-
rate new knowledge, diagnostic paradigms, and treatment. The practice of Sleep Medicine will continue to change. The challenge in the future for the Sleep Medicine Test and Policy comm-

Table 2—Number (% of first takers, pass rates, and mean scores for each admission pathway—2007, 2009, and 2011 administrations

<table>
<thead>
<tr>
<th>Pathway</th>
<th>2007</th>
<th>2009</th>
<th>2011</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>% Pass</td>
<td>Mean SD</td>
</tr>
<tr>
<td>Practice Experience</td>
<td>1034 (55%)</td>
<td>59%</td>
<td>-</td>
</tr>
<tr>
<td>Certified by ABSM</td>
<td>683 (36%)</td>
<td>93%</td>
<td>-</td>
</tr>
<tr>
<td>Fellowship Training</td>
<td>165 (9%)</td>
<td>82%</td>
<td>-</td>
</tr>
</tbody>
</table>

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pool of questions and by eventually incorporating high-fidelity testing methods that better simulate the practice of the specialty, such as using multimedia to include actual polysomnograms in the exam rather than using static illustrations.

REFERENCES


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This was not an industry supported study. Dr. Quan is Editor-in-Chief of Journal of Clinical Sleep Medicine. Dr. Buysse has consulted for Merck, Philips, and Transcept and has participated in speaking engagements for Servier and Astellas. Dr. Iber has consulted for Apnex medical. Dr. Zee has consulted for Sanofi-Aventis, Merck, Philips-Respironics and Purdue. Dr. Hess and Ms. Mills are employees of the American Board of Internal Medicine, the organization responsible for the development, administration, and scoring of the Sleep Medicine Certification Examination. The other authors have indicated no financial conflicts of interest.
A Modern Artifact in the Sleep Laboratory
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Division of Neurology, Department of Medicine, Sunnybrook Health Sciences Centre, University of Toronto, Canada

After reviewing this article, readers should be able to identify a novel modern artifact seen in the sleep laboratory. A 34-year-old woman was referred to the sleep laboratory for a continuous positive airway pressure (CPAP) titration to treat sleep apnea. When the polysomnogram (PSG) was reviewed, a novel pattern was observed which was most obvious in the electromyography (EMG), audio snore channels, and electroencephalogram (EEG) (Figure 1A).

The pattern was composed of 100-µV low frequency (5-9 Hz) sharply contoured waveforms with intermittent high frequency (20-50 Hz) sinusoidal waves. They occurred throughout the night and lasted approximately 1-20 sec. Review of the audio recording revealed an intermittently rhythmic sound during the discharges.

Q: What is the cause of these abnormal traces in the PSG?

Figure 1A—30-second epoch of polysomnography including a burst of interference seen most clearly in the EMG and snore channels.

Before sleeping, the patient placed her mobile phone (iPhone, Apple Inc.) approximately 12 inches away from the headbox (Figure 1B). Over the night, several bursts of interference were seen, which were prominent in the EEG, EMG, and audio channels because the artifact falls within the filtered range. These patterns also occurred in the ECG, but were less apparent as the ECG sensitivity is typically set a few orders of magnitude less than the EEG or EMG. Typically, interference is easily detected when present in multiple channels simultaneously. An incidental cardiac artifact is noted in the EEG, which could be reduced by referencing the EEG to linked mastoids (A1+A2).

In this case, interference did not correspond to phone calls or received messages and could have been caused by the phone’s intermittent communication with its provider.

This finding can lead to clinical confusion for clinicians and technologists. The staging of the sleep may be misinterpreted because the frequency of the interference in the EEG can mimic spindles (11-16 Hz). Therefore, short bursts may bias towards scoring stage N2 sleep. The high amplitude, short bursts of activity can mimic elevated tone in REM sleep as is observed in the REM sleep behavior disorder. In a recent Emergency Medical Journal article, authors described a case of a phone causing interference in an ECG that may have been confused for a malfunctioning pacemaker. Interference may also obscure significant events. In Figure 1A, approximately 18 seconds of a 30-second epoch were masked. During periods of interference like this brief epileptiform activity, transient EMG activity, or cardiac arrhythmias may occur.

Mobile device interference with medical equipment has been investigated to determine safety. As technology improves, interference with equipment is becoming less of a concern. In a 2004 study, investigators tested a variety of mobile devices. In older equipment, at distances of 17-32 inches, they observed significant interference, though newer technologies are less problematic. ECG and EEG were most susceptible to mobile device interference. Other recent publications have noted that cellphones close to a person’s head can delay objectively measured sleep onset latency and also alter sleep architecture. This effect may be modulated by cellphone low-frequency signals that are in the same range as the visible human EEG that define sleep staging. In overnight or daytime PSG studies, patients are more likely to bring other devices (laptops, tablets, etc.) into the recording environment to occupy themselves before, or between, sleep periods. The effect of these technologies on medical equipment is unknown, and could conceivably interfere at short distances.

### CLINICAL PEARLS FOR MOBILE PHONE INTERFERENCE

- Clinicians and technicians should be aware of potential interference.
- Simultaneous abnormal activity across multiple channels can help identify this source of interference, and technical artifacts in general. Reviewing audio and video recordings can also help provide important clues.
- To minimize confounding results, patients should be instructed to keep mobile devices at least 32 inches away from laboratory equipment.
- With rapidly changing technology, there are many potential sources of interference from consumer devices.

### REFERENCES


### ACKNOWLEDGMENTS

All work performed at Sunnybrook Hospital.

### DISCLOSURE STATEMENT

This was not an industry supported study. The author has indicated no financial conflicts of interest.

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**Figure 1B**—Patient’s mobile phone (circled on left) is placed about 12 inches from the PSG headbox (circled on right).
Sleep is an overlooked area of metabolic processes and an important modulator of endocrine function. Despite a large body of evidence suggesting that obstructive sleep apnea (OSA) is an independent risk factor for type 2 diabetes, the underlying pathogenesis of impaired glucose metabolism (IGM) in OSA remains less well understood. The recent findings of Papaioannou and colleagues showed no clinically significant abnormalities of appetite regulating hormones in OSA that would suggest a cause for IGM. While the study provides an important insight into the phenotypic spectrum of OSA, it also raises questions related to possible yet unexplored more complex pathomechanisms linking appetite hormones with IGM in OSA.

From a pathophysiological point of view, insulin resistance (IR) and beta-cell dysfunction both play a role in the development of IGM. While research has documented that OSA can contribute to IR independent of obesity, there is a paucity of information on leptin resistance-related IR in OSA that may potentially impair glucose homeostasis. Leptin is a well-known adipose tissue-derived hormone that binds to receptors in the brain and inhibits expression of neuropeptide Y (NPY). Most obese humans produce large quantities of leptin but are insensitive to its effects. The suggested mechanisms underlying leptin resistance include defective leptin receptors and/or post-receptor signal transduction, reduced numbers of leptin receptors, interactions between leptin and plasma circulating factors, and other factors that override the leptin satiety signal. It is plausible that OSA-stress-related release of NPY from sympathetic nerves and activation of its Y2 receptors in the adipose tissue might stimulate fat angiogenesis and the proliferation and differentiation of new adipocytes, resulting in abdominal obesity, while closing a vicious cycle of increasing leptin-insulin resistance. Considering different receptor-mediated effects of NPY, the plasma level of NPY might not necessarily be the best parameter to assess NPY effects in peripheral tissues.

In our study, we demonstrated that OSA is associated with specific cytokines that reflect link between OSA and glucose metabolism. Specifically, nocturnal oxyhemoglobin desaturations in OSA were closely associated with interleukin-6 (IL-6) production in obese women with IGM, but not in controls with normal glucose metabolism matched individually for sex, age, adiposity, and apnea-hypopnea index. Moreover, cross-sectional data from our study showed additional close associations of IL-6 with leptin-to-leptin receptor ratio and markers of adiposity only in IGM. These findings support the role that IL-6 plays in obesity and extend it to possible pathophysiological processes linking obesity to IGM via leptin resistance and hypoxic stress in OSA.

Further prospective studies are needed to explore the dynamic interactions among appetite regulating hormones, their receptors, and glucose homeostasis in OSA to develop novel interventions to prevent metabolic sequelae of OSA.

CITATION


REFERENCES


ACKNOWLEDGMENTS

Dr. Pallayova received grant support (November 10, 2008 - November 9, 2009) from the European Respiratory Society (Fellowship Number LTRF 15 - 2008), and was supported through a National Institutes of Health grant (November 10, 2009 - June 30, 2010). The sponsors had no involvement in the writing of this manuscript, or submission of this manuscript for publication.
Dr. Pallayova has indicated no financial conflicts of interest.
Could Leptin Mediate Insulin Resistance Through Cytokine Signaling?

Michael Polkey, Ph.D.¹; Mary J. Morrell, Ph.D.²

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We thank Dr. Pallayova for her interest in our work,¹ and for drawing our attention to hers.² We think the two studies are not really comparable, first because we did not measure circulating inflammatory cytokines, but also, perhaps more importantly in our view, because her cohort did not contain a control group. We believe her hypothesis, that tissue mediates effects of NPY may differ from circulating effects, is novel, and deserves further investigation. Interestingly, a recent observation indicates that circulating NPY seems to relate to the presence of hypertension (a manifestation of sympathetic activation) rather than OSA.³ However, at present, we are not aware of data which would support Dr. Pallayova’s hypothesis directly.

CITATION


REFERENCES

The Importance to Assess the True “Periodicity” of Leg Movements during Sleep in Narcolepsy

Raffaele Ferri, M.D.; Oliviero Bruni, M.D.; Marco Zucconi, M.D.; Giuseppe Plazzi, M.D.

Sleep Research Centre, Department of Neurology I.C., Oasi Institute (IRCCS), Troina, Italy; Centre for Pediatric Sleep Disorders, Department of Developmental Neurology and Psychiatry, Sapienza University, Rome, Italy; Sleep Disorders Center, Department of Neurology, Scientific Institute and University Ospedale San Raffaele, Milan, Italy; Department of Neurological Sciences, University of Bologna, Bologna, Italy

We have read with interest the paper “Periodic Limb Movements during Sleep in Children with Narcolepsy” by Jambhekar and colleagues recently published in the Journal of Clinical Sleep Medicine. These authors have made a very simple analysis of periodic leg movements during sleep (PLMS), based on the current AASM criteria for their scoring and have found that only 4 patients had a PLMS index ≥ 5/h (9%). The authors have then considered the 16 patients (36%) that had “any PLMS” (PLMS index > 0/h) in whom they claim that sleep was significantly more disrupted than those without PLMS (PLMS index = 0), based on the finding of a higher arousal index while none of the only two additional sleep parameters provided (total sleep time and sleep efficiency) was significantly different. In this comparison, the authors also found that the mean sleep latency at the multiple sleep latency test was shorter. The authors then conclude that children with PLMS and narcolepsy have more sleep disruption and shorter mean sleep latencies than those with narcolepsy but without PLMS.

Beside the general interest of the topic, this article was disappointing from several points of view. First of all, the analysis of PLMS has undergone in recent years a profound improvement, and it appears now clear that the classical PLMS index is inadequate to detect real periodicity in the LM activity during sleep. Based on newer and detailed methods of analysis, we have already published two papers on the topic of PLMS in narcolepsy, one in adults and another in children, completely omitted by Jambhekar and colleagues. We have shown that periodicity is almost absent in narcoleptic children, associated with a decrease of arousal indexes; in adults the periodicity of LM is also decreased and clearly lower than that expected for restless leg syndrome patients (RLS). In fact, in another paper in adult narcoleptic patients, we have also shown that the occurrence of real PLMS appear to be connected with the presence of RLS, which can be found in about 15% of individuals with narcolepsy/cataplexy. Moreover, the distribution of LM activity during the night in adults is clearly different from that expected for PLMS in RLS.

In the paper by Jambhekar and colleagues, an unusually average low value of PLMS is reported (PLMS index 1.3/h, SD 2.5) that was not compared to that of normal controls because no such a group was included in the analysis. These values are clearly lower than the values reported by other studies even in normal controls and might indicate that if a control group was included the authors would have found no differences with their patients; this makes the conclusions of this study weak and doubtful.

A tentative explanation of the results of Jambhekar and colleagues can be attempted by considering also our recent report on LM activity during quiet wakefulness preceding sleep in normal controls and RLS patients. In this study we have found that the distribution of leg intermovement intervals during wakefulness is very similar, if not identical, to that of the first peak at about 2-4 s in the same type of analysis performed during sleep, when also the true periodic peak appears, starting at approximately 10 s and reaching its maximum at approximately 20 s. The striking similarity between these two peaks prompted us to hypothesize that, when occurring during sleep, such a peak might be the expression of LM activity, spaced by short intervals, occurring during arousals. In children, and in narcoleptic children in particular, only this peak can be found during sleep which might be correlated with the amount of arousal activity, which was also found to be increased in narcoleptic children.

Thus, in our view, the main result reported by Jambhekar and colleagues, i.e., a higher number of arousals in children with “PLMS,” might be considered the cause of the occurrence of LM activity rather than the effect.

We believe that the conclusions of this type of methodologically limited studies should be considered with great caution as they can only introduce doubtful and not sound data to the current literature on PLMS. Their recent possible re-evaluation as a pos-
R Ferri, O Bruni, M Zucconi et al

Possible risk factor for cardiovascular consequences is plagued by the presence in the literature of noncontrolled studies that have included in their “PLMS” analysis a wide variety of different LM activities, ranging from the true periodic LM to isolated leg jerks or arousal-related irregular activity, because several of these movements meet the criteria for PLMS, as coded by the AASM or WASM/IRLSSG rules. It should be noted that the classical PLMS index can be considered as a reliable indicator only when LM activity is really periodic; however, finding a high PLMS index by no way can represent a proof that the LM activity is actually periodic. This can be done only by applying more detailed and accurate methods of analysis, including the “periodicity index.”

REFERENCES

Every Breath You Take: A Song Parody for Polysomnography Technologists

Adam J. Sorscher, M.D.
Department of Psychiatry (Sleep Medicine), Dartmouth Medical School, Hanover, NH

(Tune: “Every Breath You Take” by The Police)

Every breath you take
Every snort you make
Every limb you shake
Every lead you break
I’ll be watching you

And if you gasp, cough or wheeze
Or if perchance you should sneeze
If you start to seize
While you’re catching some Zzzzzs
I’ll be watching you

(chorus)
Oh can’t you see, you’re in stage 3
My poor heart aches, every time you wake

And in the night if you groan
Or make an unearthly moan
Supine or prone
You’re not alone
Cause I’ll be watching you

(bridge)
It’s 3 am and I’m standing over your face
Your chin tone’s down, it’s vanished without a trace
I look around, I re-reference; I attempt to replace
But it’s no use, this titration is a big disgrace
I keep on begging you, begging you baby please!

Every breath you take
Every limb you shake
Every snort you make
Every bathroom break
I’ll be watching you!

To view video performance of this song parody, go to youtube and type in Adam Sorscher, the author’s name, in the search box.

CITATION

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Thank You Journal of Clinical Sleep Medicine Reviewers for 2011

Over 200 individuals submitted reviews online for the Journal of Clinical Medicine in 2011. The Editors extend their sincere thanks and appreciation to the following individuals who volunteered their time and expertise for this important task.

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