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

The following articles in this issue may be read for CME credit:

| Clinical Presentation of Obstructive Sleep Apnea in Patients with Chronic Kidney Disease | 381 |
|**Objective:** Understand how OSA presents in patients with chronic kidney disease. |

| Atypical Headhanging Presentation of Idiopathic Sleep Related Rhythmic Movement Disorder: Three Cases with Video-Polysomnographic Documentation | 403 |
|**Objective:** Understand the clinical presentation of atypical headhanging. |
The risk-benefit balance of hypnotic medications remains an area of great clinical uncertainty, especially with long-term use. Issues of adverse effects on cognitive, psychiatric, and motor systems, together with risks of tolerance and dependence, necessitate caution even in short-term use. Several observational studies have even suggested hypnotics confer increased mortality risk. One recent study showed a strikingly increased mortality risk. However, it contains several methodological and inferential limitations, the dissection of which may be instructive for providers and researchers for whom this complex and concerning topic is relevant.

Kripke et al. analyzed a large database of diagnosis codes and prescription records with linked indications. They asked whether prescriptions for certain hypnotic sleep medications were associated with increased mortality over a 3-year observation period. From a database of over 200,000 individual outpatients seen between 2002 and 2006, about 10,000 had at least one hypnotic prescription, survived at least 3 months into the observation period, and did not already have a diagnosis of cancer. For each of these subjects, 2 controls were obtained from the remaining database, matched according to age, sex, smoking status, and observation period. The authors report 3.5-5.5 times higher mortality in the hypnotic group than the baseline 1.3% mortality of the control group.

The correlation of events in time does not necessarily imply a causal relationship. This is often referred to as the post hoc ergo propter hoc fallacy (“after this, therefore because of this”), and this fallacy remains an issue in modern clinical studies. Although the authors acknowledge this fallacy in the article’s supplement, the discussion in the main text not only argues that hypnotics caused the deaths, but it also implies that limiting hypnotic use would prevent deaths. In prior work, Dr. Kripke hypothesized that the underlying sleep disorder likely contributed to an inflated mortality hazard in Kripke et al. By comparison, in the prior 24 related studies listed in their supplemental material, the median hazard associated with hypnotics was < 1.5, and only 4 studies reported values > 2.0. Failing to address the underlying sleep disturbance is a major design flaw equivalent to concluding that chemotherapy prescriptions increase mortality without taking into account the mortality associated with the underlying malignancy that prompted chemotherapy. Given that their main outcome was mortality risk, it is unfortunate that cause of death data was not available to support potential mechanistic links.

Another important limitation relates to comorbidities. Major illnesses that carry mortality risk burden were 1.5-2 times more common in the hypnotic group of this population, compared to the control group. While the authors attempted statistical correction for these differences, the severity of the comorbidities was not available and thus the groups could have differed in this regard. Also, the extent to which comorbid sleep disorders, presumably much more common in the hypnotic group, might have synergistic risks with the medical conditions remains unknown. Psychiatric comorbidities that may have contributed to morbidity and mortality were not available and may also have differed between groups, as sleep complaints are a fundamental part of most psychiatric disorders. Finally, alcohol consumption may have serious interactions with hypnotic medications, in addition to health and accident implications, yet the control for alcohol use was limited to self-reported “yes,” “no,” or “unknown.” Given the concurrence of alcohol use, sleep complaints, and psychiatric disorders, it is possible that the hypnotic group was overrepresented in alcohol consumption not captured by this simplified categorization. Imagine, for instance, a person occasionally having 1-2 drinks per week, being “matched” with someone consuming 5-6 drinks per night.

The data speak only to prescription content, not the actual patterns of hypnotic use. The authors argue that non-compliance in the hypnotic group or undocumented use of hypnotics in the
control group would each lead to underestimation of the effect size. We agree. But it is unclear why the authors disregarded the (likely) possibility that patients in the hypnotic group may also be taking undocumented over-the-counter or prescription agents for sleep, which would exaggerate any mortality risk, either through drug interactions or as a marker of severity of a sleep disorder carrying its own mortality risk.

The authors emphasize the dose-response relationship between frequency of use and mortality risk. Yet no statistics are provided to support that claim, and the overlapping confidence intervals raise the possibility that there may be little or no dose effect. Even if the hazard ratios are statistically different, the dose-response profile would be highly unusual: a steep and immediate risk elevation observed at sparse dosing—fewer than 1.5 pills per month—followed by less than 1.5 fold change in risk over the next 10-fold increase in dose. Furthermore, the antihistamine diphenhydramine conferred a similar risk as benzodiazepines, non-benzodiazepine ligands, and barbiturates, each of which have different mechanisms, different drug-drug interactions and different side-effect profiles. Furthermore, some of these medications are used for other common indications, such as anxiety, epilepsy, and allergic rhinitis. Are we to surmise that patients using occasional benzodiazepines for anxiety or using occasional diphenhydramine for allergic rhinitis are dying at 4-6 fold increased risk?

The authors argue that the absolute gain in total sleep time with sleep medications is modest. We agree. However, total sleep time may not be as important as continuity (which is not necessarily reflected in total duration). Further, the greater subjective than objective sleep time benefits reported by patients taking sleep medications may be partly due to our limited techniques of objectively quantifying sleep physiology through current conventions of sleep staging, rather than simply modest objective efficacy. This uncertainty extends to the question whether pharmacological sleep recapitulates important or restorative aspects of normal sleep. For example, certain hypnotic agents impair cortical plasticity in animal models of sleep-dependent neuroplasticity. Resolving whether hypnotic medications faithfully replicate natural sleep physiology remains an important area of ongoing investigation.

Reporting alarmingly high death risks from commonly used medications generates intense media coverage and raises public concern. This paper’s discussion begins with the shocking claim that a half-million deaths in the USA in 2010 (about 25% of all deaths) may have been due to hypnotics. Given the numerous methodological flaws and logical fallacies of this paper, we find this claim to be irresponsible from scientific and ethical perspectives. From a Bayesian standpoint, extreme claims require extraordinary evidence. In this study, plausible arguments can be made that hypnotics are not causative for, and may not even be associated with, the observed mortality hazard.

Dr. Kripke is a long-standing critic of hypnotics. To be clear, many of his concerns are shared by the community of providers who care for those with sleep complaints, including the authors of this commentary. For example, long-term use of hypnotics is not recommended. Short-term use should be employed with caution, controlling for circumstances that might lead to unwanted effects, including driving safety and psychiatric wellness. Tolerance and dependence may develop. Further, non-pharmacological treatments have been shown to be equal to, or more effective than, hypnotic medications.

In summary, it remains plausible that hypnotics confer some degree of mortality risk, and substantive clinical and scientific questions remain about their biological impact on sleep and risk-benefit balance. But alarmist claims from mediocre data serve only to distract and detract from the many serious questions and concerns lingering in the arena of hypnotic medications. We encourage practitioners to openly discuss with insomnia patients the risk-benefit balance of pharmacological and behavioral approaches, as well as no treatment—which itself may confer health risks.

REFERENCES


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SUBMISSION & CORRESPONDENCE INFORMATION

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Address correspondence to: Matt T. Bianchi, M.D., Ph.D., Wang 720, Neurology Department, Massachusetts General Hospital, 55 Fruit St, Boston, MA 02114; Tel: (617) 724-7426; Fax: (617) 724-6513; E-mail: mtbianchi@partners.org

DISCLOSURE STATEMENT

Dr. Ellenbogen has received speaking fees from the American Academy of Neurology, Massachusetts General Hospital Academy, and the Massachusetts Department of Public Health. Dr. Bianchi has a patent pending on a home sleep monitoring device. Dr. Thomas is co-patent holder for electrocardiogram-based sleep technology, and for a carbon dioxide delivery device used to treat central/apnea, and he receives consulting fees from DeVilbiss.
Do No Harm: Not Even to Some Degree

Daniel F. Kripke, M.D.1; Robert D. Langer, M.D., M.P.H.2; Lawrence E. Kline, D.O.1
1Scripps Clinic Viterbi Family Sleep Center, La Jolla, CA; 2Jackson Hole Center for Preventive Medicine, Jackson, WY

W e are grateful to Dr. Bianchi and colleagues for summarizing questions about our recent paper associating hypnotics with excess mortality and cancer.1 We are grateful to the Journal for this opportunity to provide organized answers to these questions.

In the absence of adequate randomized trials extending for years, it is clinically important to assess the long-term risks and benefits of commonly prescribed hypnotics, using the best data now available and employing the most conservative analytic strategies possible. We have done that. Dr. Bianchi and colleagues asserted that we confused correlation with causality. We did not. We took pains to be clear that ours was an observational study and that some residual confounding was likely. Nonetheless, the robust associations of hypnotics with mortality and cancer that we found, increasing stepwise with increasing exposure, and virtually unchanged with multiple strategies for control, command attention and reassessment of common practice.

It has been hard to report calmly that hypnotic use was associated with 3.60- to 5.32-fold mortality risks. It would be wonderful if somebody could prove it is not so—and the risk could be overestimated—but scientific ethics require us to report what our data showed and to explain the possible implications. Though the main responsibility for warning falls on the manufacturers who were informed of these risks years ago and on their FDA supervision, we physicians have a duty to warn also. We cannot hide risks, even if they might frighten patients out of taking hypnotics. Patients have a right to know.

Some suppose that the increased mortality of hypnotic users was due to their insomnia, and that insomnia might explain the 3.60- to 5.32-fold mortality excess. It is true that because of the IRB’s interpretation of Pennsylvania law, we were unable to control explicitly for insomnia or depression. However, in our paper,1 we referenced several studies which have found that insomnia is NOT associated with significant mortality. We know of no evidence that insomnia significantly predicts mortality when hypnotic use, comorbidities, and other confounders are adequately controlled. A new example is found in the recently published representative national sample from Taiwan, where those with sleep disorders had significantly less cancer incidence than those without sleep disorders among participants who had not received zolpidem, HR = 0.69 (0.62-0.78 95% CI).2 Use of ≥ 300 mg/y zolpidem without benzodiazepines was associated with a cancer hazard ratio of 6.24 (4.13-9.43 95% CI), but even among the zolpidem users, those with sleep disorders had lower risk. Thus, sleep disorders could not conceivably explain the excess mortality or cancer associated with zolpidem prescriptions.

Our paper also referenced studies showing that depression does not confound the association of hypnotic use with mortality. In Belleville’s Canadian sample, control for depression only reduced the hypnotics and tranquilizers mortality odds ratio from 1.40 (1.13-1.75, 95% CI) to 1.36 (1.09-1.70, 95% CI), which was not significant.3 Depression was not even a significant mortality risk factor when benzodiazepine use and other covariates were controlled.4 In the Taiwan sample, the cancer hazard ratio for depression was 0.68 (0.53-0.88, 95% CI).2 Thus, confounding with depression could not explain mortality and cancer associated with hypnotic prescriptions.

What about sleep apnea as an explanation? Young and colleagues reported that apnea-hypopnea indices < 30 were NOT significantly associated with excess mortality in an adjusted model.5 With AHI ≥ 30, the risk ratio was only 3.0 (1.4-6.3, 95% CI). The Sleep Heart Health Study had even more surprising results, wherein women (who use more hypnotics than men) had no significant increase in mortality associated with any level of sleep apnea. Among men, significant excess mortality was associated with AHI ≥ 30 only among those age ≤ 70 years.6 Among both sexes of all ages combined, AHI ≥ 30 was associated with a hazard ratio of only 1.46 (1.14-1.86 95% CI). These apnea studies were not as extensively controlled for comorbidities as our study. Our hypnotic-associated risk ratios of 3.60 to 5.32 could not be caused by apnea risk ratios of only 1.46 or 3, even in the implausible event that all the patients prescribed hypnotics had AHI ≥ 30 but none of the controls.

Could excess comorbidities among hypnotic users account for our 3.60- to 5.32-fold hazard ratios? Let us recall the data. In our stratified analyses, we compared hypnotic users with controls having exactly the same classes of comorbidities, so comorbidity diagnoses were matched. Even had we not employed matching and alternative forms of adjustment to control for comorbidities, how could a 45% excess of comorbidities among the hypnotic users account for a 3.60- to 5.32-fold mortality hazard? It is true that we were unable to adjust for severity of comorbidities when they occurred, but since the diagnoses of comorbidities accounted for only a small amount of the mortality hazard, where is the evidence that severity of comorbidities or uncommon comorbidities could account additionally for a much larger portion of the mortality hazard?

No one has offered any explanation of how confounding could produce the significantly different hazard ratios we observed between hypnotics and different cancers. Sanofi Aventis
was cited in the *New York Times*, arguing that our 2.5 years mean follow-up was not long enough to study cancer initiation, but they have done no randomized zolpidem trials of 1 year or longer. Sanofi should be better satisfied with the new Taiwan study, with the high-dose zolpidem cancer hazard ratio of 6.24 observed after more than 8 years of follow-up.²

In answer to the query of Bianchi et al., one should not surmise that patients using drugs for occasional anxiety or allergic rhinitis “are dying at 4-6 fold increased risk,” since we explicitly stated that such indications for the compounds studied were excluded. The low-dose mortality hazard ratio for participants with NO comorbidities was only 1.93, but the hazard ratio for all those taking 1-18 doses per year was 3.60. Higher hazard levels of 4- to 6-fold were only observed in subgroups with specific comorbidities, in which the lower limit of the confidence intervals was always < 4.0.

As the authors of the commentary know, objective performance testing generally does not demonstrate any restorative benefits of hypnotic agents, whether by neuroplasticity or otherwise. The more favorable subjective responses are best explained by the amnesic properties of hypnotics, like the waters of Lethe, erasing memories of poor sleep.

Our critics pointed out that our mortality hazard ratios were much higher than those of most (but not all) previous studies. We suppose that the higher hazard ratios were observed because we explicitly identified the hypnotic drugs studied, whereas almost all previous studies confounded risks of hypnotics with any risks of tranquilizers, antidepressants, and other unidentified compounds. Also, previous studies had largely failed to monitor the quantity of hypnotics prescribed during the follow-up intervals to confirm which participants did or did not receive hypnotics during the observation. Methodologic improvements in our study compared to prior work may have yielded more accurate estimates.

Since the multiple controls for comorbidities that we employed, along with control for age, gender, smoking, etc., only reduced the raw death hazard ratio in hypnotic users from 4.86 to 4.56, it is highly unlikely that other confounding could explain all of the excess mortality associated with hypnotics. Is there any scientific evidence that uncontrolled confounders could produce such large hazard ratios, or is that just the speculation of people groping for a way to avoid bad news? There is no evidence that the neoplasm-specific risks we observed can be due to confounding, especially recognizing the parallel study from Taiwan. Furthermore, our critics recognized that limitations in our study design leading to underestimation of the hazard ratios would, to some extent, counterbalance residual confounding that might have resulted in some overestimation of the hazard ratios.

We remind readers that there are now 21 published studies suggesting excess mortality or cancer associated with hypnotic use, with no published studies suggesting mortality reduction or cancer prevention. It is good to recognize the limitations of published studies, but the current weight of evidence does not favor prescribing even 18 hypnotic doses per year. We encourage others to conduct replication studies and hope that new investigators can learn from the limitations of past work and do still better studies. Perhaps others have the ingenuity to devise ethical randomization for drugs consistently associated with excess mortality and cancer. For hypnotics with unknown mortality and cancer risks, there is a pressing need for randomized clinical trials to explore long-term hypnotic safety.

We concede that it is theoretically possible that there is no hypnotic causality underlying our mortality association findings. However, we do not advise patients to bet their lives that suspicion of causality with associations as robust as these is entirely mistaken. Perhaps our critics agree, saying, “it remains plausible that hypnotics confer some degree of mortality risk.” How much risk of death would they counsel patients to accept for the sake of using hypnotics? How much risk of cancer? Doesn’t a mortality or cancer hazard ratio “some degree” exceeding 1.0 signify more harm than good? Do our critics suggest to “some degree” ignoring the ethics of “Do no harm”??
The Lure of the Impact Factor and Journal of Clinical Sleep Medicine

Stuart F. Quan, M.D., F.A.A.S.M., Editor-in-Chief
Division of Sleep Medicine, Harvard Medical School, Boston, MA; Arizona Respiratory Center, University of Arizona College of Medicine, Tucson, AZ

Over the past several years as Editor-in-Chief of the Journal, I have received constant inquiries concerning the Journal’s impact factor, or lack thereof. I would then need to explain that to receive an impact factor, several years of tracking by Thomson ISI was required. Now, I no longer have to provide that explanation because last month, the Journal received its first impact factor from Thomson ISI, a very respectable 3.232. This ranks the Journal as third among the 7 non-review sleep journals receiving impact factors.

While the Deputy Editor, Associate Editors and Editorial Board as well as myself are pleased with this impact factor, I would like to reiterate that it is not the sole criterion for a scientific journal’s success. The impact factor is an indicator of how often papers in a journal are cited by other papers. Thus, it is one marker of whether the content of a journal is being disseminated and used by scientific investigators. In this regard, it would appear that papers published in the Journal are of some relevance to the sleep research community. However, the mission of the Journal is to help serve the needs of the membership of the American Academy of Sleep Medicine; the vast majority of whom are sleep clinicians. Thus, much of the content of the Journal is devoted to information that can be used in clinical practice. Consequently, for the Journal, the primary metric for success is whether or not the membership values and reads its contents. In this regard, I was pleased to learn that a recent membership survey gave the Journal high marks. Given the Journal’s mission, this is more important than a high impact factor.

As the Journal moves forward, a respectable impact factor will be valued, but the Journal will not succumb to the seductive lure of pursuing a high impact factor by employing policies targeted to inflate it. Rather we will continue to publish papers, reviews and commentary relevant to the practice of Sleep Medicine and of educational value to the membership of the Academy.

CITATION
Exercise Training Improves Selected Aspects of Daytime Functioning in Adults with Obstructive Sleep Apnea

Christopher E. Kline, Ph.D.1; Gary B. Ewing, M.D.2; James B. Burch, Ph.D.3,4; Steven N. Blair, P.E.D.3,5; J. Larry Durstine, Ph.D.5;
J. Mark Davis, Ph.D.5; Shawn D. Youngstedt, Ph.D.4,5,6

1Department of Psychiatry, University of Pittsburgh School of Medicine, Pittsburgh, PA; 2Department of Clinical Services, University of South Carolina School of Medicine, Columbia, SC; 3Department of Epidemiology and Biostatistics, University of South Carolina, Columbia, SC; 4WJB Dorn VA Medical Center, Columbia, SC; 5Department of Exercise Science, University of South Carolina, Columbia, SC; 6Department of Psychology, University of South Carolina, Columbia, SC

Study Objectives: To explore the utility of exercise training for improving daytime functioning in adults with obstructive sleep apnea (OSA).

Methods: Forty-three sedentary and overweight/obese adults aged 18-55 years with at least moderate-severity untreated OSA (apnea-hypopnea index ≥ 15) were randomized to 12 weeks of moderate-intensity aerobic and resistance exercise training (n = 27) or low-intensity stretching control treatment (n = 16). As part of a trial investigating the efficacy of exercise training on OSA severity, daytime functioning was assessed before and following the intervention. Sleepiness, functional impairment due to sleepiness, depressive symptoms, mood, and quality of life (QOL) were evaluated with validated questionnaires, and cognitive function was assessed with a neurobehavioral performance battery. OSA severity was measured with one night of laboratory polysomnography before and following the intervention.

Results: Compared with stretching control, exercise training resulted in significant improvements in depressive symptoms, fatigue and vigor, and aspects of QOL (p < 0.05). Sleepiness and functional impairment due to sleepiness also were improved following exercise versus control to a similar degree in terms of effect sizes (d > 0.5), though these changes were not statistically significant. No neurobehavioral performance improvements were found. Reduced fatigue following exercise training was mediated by a reduction in OSA severity, but changes in OSA severity did not significantly mediate improvement in any other measure of daytime functioning.

Conclusions: These data provide preliminary evidence that exercise training may be helpful for improving aspects of daytime functioning of adults with OSA. Larger trials are needed to further verify the observed improvements.

Trial Registration: Clinicaltrials.gov identification number NCT00956423.

Keywords: exercise training, obstructive sleep apnea, mood, sleepiness, quality of life, cognitive performance

Citation: Kline CE; Ewing GB; Burch JB; Blair SN; Durstine JL; Davis JM; Youngstedt SD. Exercise training improves selected aspects of daytime functioning in adults with obstructive sleep apnea. J Clin Sleep Med 2012;8(4):357-365.

The most common complaint among individuals with obstructive sleep apnea is impaired daytime functioning,1 which includes excessive daytime sleepiness and fatigue,2 as well as decrements in cognitive function,3 mood,4 and quality of life (QOL).5 Unfortunately, continuous positive airway pressure (CPAP), the standard first-line treatment for OSA, does not always improve daytime functioning. Improvements are related to compliance to CPAP use,6 as improvements in daytime functioning can be reversed by even a single night of CPAP non-use.7 Moreover, residual symptoms often remain despite optimal compliance.8

Exercise training has been shown to reduce OSA severity, even in the absence of significant weight loss.9-10 As a result, improvements in daytime functioning might follow.8 However, it is plausible that exercise training might improve daytime functioning in individuals with untreated OSA even in the absence of a reduction in OSA severity, since exercise training has been shown to improve cognitive function,11 reduce daytime sleepiness,12 increase energy and reduce fatigue,13 improve mood,14 and enhance QOL15 in various adult populations.

The limited available research is supportive of this hypothesis. In epidemiologic studies of individuals with OSA, physical activity has been significantly associated with higher levels of vigor, vitality, and QOL, and lower levels of fatigue.16,17 Conversely, lack of exercise has been associated with higher daytime sleepiness in obese males with OSA.18 Moreover, in an uncontrolled study of adults with OSA, six months of exercise training...
training elicited significant improvements in QOL, mood, and daytime sleepiness. We present here the daytime functioning outcomes from a randomized controlled trial in which the primary aim was to examine the efficacy of exercise training on OSA severity. The daytime functioning variables were regarded as secondary outcomes, and impairments in daytime functioning were not required for inclusion in the study. Nonetheless, we hypothesized that exercise training would result in moderate-sized improvements in these measures compared to the control treatment. An additional aim of the study was to determine whether daytime functioning improvements were mediated by exercise-induced reductions in OSA severity.

METHODS

A detailed description of the overall study methodology can be found elsewhere. The study utilized a randomized controlled experimental design involving assignment of sedentary adults with untreated OSA to an exercise training or stretching control treatment, with assessments of daytime functioning prior to and following a 12-week intervention. The study was approved by the Institutional Review Boards of the University of South Carolina and the WJB Dorn VA Medical Center, and participants provided informed consent before participation.

Participants

Participants in the current study are from the same cohort whose OSA severity and sleep quality data were previously published. Individuals aged 18-55 years who had at least moderate-severity OSA (apnea-hypopnea index [AHI] ≥ 15), were sedentary (i.e., self-reported exercise < 2 days/week), and were overweight/obese (i.e., body mass index [BMI] > 25) were eligible to participate in the study. Exclusion criteria included current treatment for OSA, uncontrolled hypertension (i.e., > 159/99 mm Hg), plans to lose weight, pregnancy, inability to exercise, and known or suspected significant cardiovascular, pulmonary, or metabolic disease. Medication use, including antidepressant or anxiolytic medications, was not an exclusion criterion as long as the medication dose was stable before (i.e., > 3 mo) and throughout the study.

Recruitment and Screening

Participants were recruited through local sleep clinics, media advertisements, and word of mouth. Initial eligibility was determined via a brief standardized phone screen. Individuals eligible following the phone screen were mailed a packet of questionnaires, including the Berlin Questionnaire. Individuals who were previously diagnosed with OSA or classified as “high risk” for OSA based on the Berlin Questionnaire were invited to the laboratory to review the protocol and provide informed consent. Individuals then were screened for OSA with one night of laboratory polysomnography (PSG), with an AHI ≥ 15 required for inclusion. As an additional inclusion criterion, individuals underwent a physical and physician-supervised graded exercise test for detection of underlying cardiovascular disease and/or adverse responses to exercise.

Enrolled participants visited the laboratory on 2 occasions before baseline assessment. During these visits, participants were familiarized with the experimental questionnaires and practiced the neurobehavioral performance battery used in this study. Following the introductory visits, participants completed baseline assessments of PSG, daytime functioning, and neurobehavioral performance, and were randomized to one of the 12-week treatments. Once the intervention was completed, the same assessments that were performed at baseline were repeated following a day of non-exercise. A summary of the study flow is provided in Figure 1.

Interventions

Prior to randomization, treatment allocations were prepared by an individual otherwise unaffiliated with the study and placed in sealed opaque envelopes. Participants were randomly assigned by a 3:2 ratio to an exercise training treatment or a stretching control treatment, respectively.

Descriptions of the exercise training and stretching control treatments are provided in Table 1. Although no change in OSA was expected from the stretching control treatment, it was chosen to control for the potential confounding influence of interpersonal interaction on outcomes related to the study. However, because blinding of treatment was not possible, both interventions were presented as active treatments. Expectancy regarding changes in daytime sleepiness, mood and health was assessed with 5-point Likert scales (1: much worse; 5: much better) at the time of randomization allocation.

Laboratory Polysomnography

A single night of laboratory PSG (Alice 5, Philips Respironics, Murrysville, PA), fixed at 8 h time in bed, was performed at baseline and post-intervention. A standard recording montage was used, which was previously described. Assessments were evaluated using standard criteria for the scoring of sleep stages and respiratory events by a single registered PSG technician blinded to treatment assignment.

An apnea was defined as a ≥ 90% reduction in airflow for ≥ 10 s, and a hypopnea was defined as a ≥ 30% reduction in airflow accompanied by a ≥ 4% drop in oxygen saturation (SpO2). The AHI (i.e., number of apneas and hypopneas per hour of sleep), oxygen desaturation index (ODI; i.e., the number of SpO2 reductions ≥ 4% per hour of sleep), and percentage of total sleep time spent with SpO2 < 90% (TST90) were retained for analysis.

Questionnaire-Based Measures of Daytime Functioning

Mood, sleepiness and QOL questionnaires were administered in the evening prior to overnight laboratory PSG at baseline and post-intervention. Questionnaires were introduced using a standardized script and administered in sequential order.

Mood

The Center for Epidemiological Studies—Depression scale (CES-D) is a questionnaire that assesses the frequency of 20 depressive symptoms, with scores ranging from 0 to 60. The questionnaire has excellent reliability and validity. Scores ≥ 16 indicate significant depressive symptoms. The Profile of Mood States (POMS) assesses a wide spectrum of mood dimensions. The questionnaire assesses the intensity of 65 different emotions/feelings on a 5-point scale (0:
Exercise and Daytime Functioning in OSA

not at all; 4: extremely). Subscale scores of fatigue and vigor, as well as a global Total Mood Disturbance (TMD) score, were retained for analysis.22

Daytime Sleepiness

The Epworth Sleepiness Scale (ESS) assesses the likelihood of falling asleep during 8 everyday sedentary activities. Response options for each activity range from 0 (would never dose) to 3 (high chance of dozing). Scores > 10 represent excessive daytime sleepiness. The ESS has a 5-month test-retest reliability of $r = 0.82$, differentiates between adults with and without OSA, and has been validated against the Multiple Sleep Latency Test.23

The 10-item Functional Outcomes of Sleep Questionnaire (FOSQ-10)24 is a shortened version of the 30-item FOSQ that estimates how daytime sleepiness affects one’s ability to perform certain tasks in the dimensions of general productivity, social outcomes, activity level, vigilance, and intimacy. Individual questions are rated on a scale of 1 (yes, extreme difficulty) to 4 (no difficulty), averaged among the 5 subscales, and

Figure 1—Summary of recruitment and participant flow through study

AHI, apnea-hypopnea index; GXT, graded exercise test; OSA, obstructive sleep apnea; PSG, polysomnography.
Table 1—Description of treatments

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Exercise training</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activity</td>
<td>Aerobic exercise</td>
<td>Stretching</td>
</tr>
<tr>
<td>Days/week</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Description</td>
<td>Supervised moderate-intensity aerobic activity (60% of HRR, monitored with heart</td>
<td>Supervised sessions</td>
</tr>
<tr>
<td></td>
<td>rate telemetry, performed primarily on the treadmill; 5-min warmup and cool down</td>
<td>involving 10-15</td>
</tr>
<tr>
<td></td>
<td>not included in dose calculations</td>
<td>stretches, held for</td>
</tr>
<tr>
<td>Weekly dose</td>
<td>150 min</td>
<td>60 min</td>
</tr>
<tr>
<td>Initial progression</td>
<td>Ramp of weekly aerobic dose from 50 min in week 1 to 150 min in week 5; full dose</td>
<td>Once weekly with</td>
</tr>
<tr>
<td></td>
<td>from week 5-on</td>
<td>one set of exercises</td>
</tr>
<tr>
<td></td>
<td></td>
<td>for weeks 1-2,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>twice weekly with</td>
</tr>
<tr>
<td></td>
<td></td>
<td>one set for weeks 3-4; full</td>
</tr>
<tr>
<td></td>
<td></td>
<td>dose from week 5-on</td>
</tr>
</tbody>
</table>

HRR, heart rate reserve.

Neurobehavioral Performance Battery

Neurobehavioral performance was assessed on a morning separate from laboratory PSG at baseline and post-intervention. All testing was conducted between 07:00-09:00, and participants arrived following an overnight fast. Participants went through abbreviated practice versions of each test before the full versions were administered.

Psychomotor Vigilance Task

The Psychomotor Vigilance Task (PVT; Ambulatory Monitoring, Inc., Ardsley, NY) is an electronic 10-min simple visual reaction time test that assesses sustained attention. Measures of median reaction time (RTmed), lapses (i.e., responses > 500 ms), and the reciprocal of the slowest 10% of responses (RRT10slow) were analyzed. Performance on this task has been shown to be impaired in adults with OSA.

Stroop Color-Word Test

The Stroop Color-Word Test (SCWT) is a test of cognitive interference in which participants are required to read aloud words or colors while timed during 3 different tasks: randomly ordered words (task A); randomly ordered blocks of colors (task B); and randomly ordered words with conflicting colors (e.g., the word red in green ink). An interference score, calculated as the ratio of time on task C to the time on task B, was retained for analysis. Performance on the SCWT is impaired in individuals with OSA.

Trail-Making Test

The Trail-Making Test (TMT) is a task that assesses frontal-lobe function. In Part A of the TMT, participants connect 25 consecutively numbered circles in ascending numerical order. In Part B, participants connect 25 circles, alternating between ascending sequences of numbers and letters (i.e., 1, A, 2, B). The difference between the time to complete Part B and Part A was retained for analysis. Performance on the TMT has been shown to be impaired in adults with OSA.

Statistical Analysis

Participant sample size was estimated based upon the primary outcome for the parent study, change in AHI. Statistical power was 83% to detect the expected change in AHI with a total of 40 participants randomized by a 3:2 ratio. The unbalanced treatment allocation allowed for similar power as a 1:1 allocation, but permitted a more thorough investigation into the possible benefits of exercise training on OSA severity and its associated consequences.

Data from all randomized participants were utilized for all analyses with one exception: because one participant’s baseline PVT scores were > 3 standard deviations different from the remaining sample, PVT data for this participant were excluded from analysis. Otherwise, all analyses were based on the intent-to-treat principle, and baseline data for participants who discontinued the study were carried forward for analysis. Participants who discontinued the study (n = 5) did not differ from those who completed the study on any demographic, OSA severity, or daytime functioning measures at baseline. Moreover, analyses restricted to those who completed the study (n = 38) did not differ from those presented here. All analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC). Data are presented as mean ± standard error.

Baseline participant characteristics were compared between treatments with independent sample t-tests. Changes in outcome variables were evaluated with generalized linear
models, with the post-intervention value for each variable as the dependent variable, treatment condition as the independent variable, and baseline value as a covariate. All statistical tests were 2-tailed. Results were considered to be statistically significant when \( p \leq 0.05 \). Due to the small sample size and the fact that the study was not powered to detect these secondary outcomes, no statistical adjustment was made for multiple outcome measures.

There are inherent limitations of a study with multiple outcome measures and small sample size, leading to increased probability of type I and type II errors, respectively. Therefore, effect sizes, which characterize the magnitude of a treatment effect and are independent of sample size, were also calculated for outcome variables. Hedges’ \( d \) effect sizes were calculated by dividing the difference between the baseline and post-intervention changes in the exercise training and control treatments by the pooled baseline standard deviation, then correcting for small sample-size bias.\(^{32}\) According to convention, effect sizes of \( d = 0.2 \), \( d = 0.5 \), and \( d = 0.8 \) were considered small, medium, and large in magnitude, respectively.\(^{32}\)

Because increased OSA severity has been associated with increased sleepiness and fatigue and reductions in vigor,\(^{1,18}\) basic mediational analyses were conducted to evaluate whether exercise training improved daytime functioning through reductions in OSA severity. Proposed mediators included AHI, ODI, and TST\(_{90}\). Mediation analysis was performed using MacKinnon’s product of coefficients test.\(^{33}\) Linear regression models were constructed to obtain coefficients associated with (1) the effect of the intervention on the proposed mediator (i.e., \( \alpha \) coefficient) and (2) the effect of the proposed mediator on the outcome measure (i.e., \( \beta \) coefficient). The product of coefficients was obtained by multiplying the \( \alpha \) and \( \beta \) coefficients, and asymmetric 95% confidence limits based on the distribution of the product of coefficients were created using the PRODCLIN program.\(^{33}\) Confidence intervals that did not include zero indicated a statistically significant mediation effect.

**RESULTS**

**Participant and Intervention Summary**

A summary of participant recruitment is provided in Figure 1. Forty-three participants were randomized to either an exercise training (\( n = 27 \)) or a stretching control treatment (\( n = 16 \)). Five individuals discontinued participation before study completion. Baseline participant characteristics are summarized in Table 2. No statistically significant differences between treatments were found for any of the demographic characteristics. Exercise training participants had significantly higher ESS scores than stretching participants at baseline (\( t_{15} = -2.74, p = 0.01 \)). No other baseline differences in daytime functioning were found between treatments. In addition, participants reported similar expectancy for improvements in mood, sleepiness, and overall health between treatments. Adherence, defined as the rate of attendance to prescribed sessions, did not differ between treatments (exercise: 87.0 ± 3.7%, control: 79.7 ± 5.3%).\(^9\)

**Effect of Exercise Training on OSA Severity**

Table 3 summarizes the effects of exercise training on OSA severity and body weight. As previously reported,\(^9\) exercise training resulted in a 25% reduction in AHI that was significantly greater than that following the stretching control (\( F_{1,40} = 9.54, p < 0.01 \)). There was also a reduction in ODI following exercise training compared to control (\( F_{1,40} = 5.05, p = 0.03 \)), but not for TST\(_{90}\). The change in body weight did not significantly differ between the two treatments.\(^9\)

**Effect of Exercise Training on Mood**

Table 4 provides a summary of the changes in mood between treatments following the intervention. Exercise training resulted in a significantly greater decrease in depressive symptoms compared with the stretching control treatment, as measured by the CES-D (\( F_{1,40} = 5.33, p = 0.03 \)). This corresponded with

### Table 2—Baseline participant characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Exercise Training</th>
<th>Stretching Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>27</td>
<td>16</td>
</tr>
<tr>
<td>Sex, male (%)</td>
<td>15 (56)</td>
<td>9 (56)</td>
</tr>
<tr>
<td>Age, y</td>
<td>47.6 (1.3)</td>
<td>45.9 (2.2)</td>
</tr>
<tr>
<td>Ethnicity, White (%)</td>
<td>22 (81)</td>
<td>10 (63)</td>
</tr>
<tr>
<td>Height, cm</td>
<td>173.3 (1.8)</td>
<td>171.7 (2.5)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>105.6 (3.0)</td>
<td>99.3 (5.1)</td>
</tr>
<tr>
<td>Prior OSA diagnosis, n (%)</td>
<td>14 (52)</td>
<td>10 (63)</td>
</tr>
<tr>
<td>Prior OSA treatment, n (%)</td>
<td>9 (33)</td>
<td>8 (50)</td>
</tr>
</tbody>
</table>

All data are presented as mean (standard error) unless otherwise noted. OSA, obstructive sleep apnea. No differences between treatments were found for any of the baseline demographic characteristics.

### Table 3—OSA severity and body weight prior to and following treatment

<table>
<thead>
<tr>
<th>Variable</th>
<th>Exercise Training</th>
<th>Stretching Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BL (SE)</td>
<td>POST (SE)</td>
</tr>
<tr>
<td>AHI</td>
<td>32.2 (5.6)</td>
<td>24.6 (4.4)*</td>
</tr>
<tr>
<td>ODI</td>
<td>24.5 (4.2)</td>
<td>21.5 (3.7)*</td>
</tr>
<tr>
<td>TST(_{90})</td>
<td>5.2 (1.2)</td>
<td>4.7 (1.1)</td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>105.6 (3.0)</td>
<td>104.7 (3.1)</td>
</tr>
</tbody>
</table>

All baseline (BL) and post-intervention (POST) data are presented as mean (standard error). \( d \) indicates Hedges’ \( d \) effect size. AHI, apnea-hypopnea index; ODI, oxygen desaturation index; TST\(_{90}\), percentage of total sleep time with oxygen saturation below 90%. *Statistically significant difference between treatments at post-intervention following control for baseline values (\( p \leq 0.05 \)).
A summary of changes in POMS-related mood measures is provided in Table 4. Exercise training significantly decreased fatigue \( F(1,40) = 3.83, p = 0.05 \) and increased vigor \( F(1,40) = 5.91, p = 0.02 \) compared to control. These findings were associated with moderate-sized improvements for both fatigue \( d = -0.61 \) and vigor \( d = 0.57 \). Although the global measure of mood disturbance, TMD, was not statistically significantly decreased following exercise training compared to control, a moderate-sized decrease was noted \( d = -0.42 \).

**Effect of Exercise Training on Sleepiness**

A summary of the changes in sleepiness following the treatments is presented in Table 4. Exercise training produced a moderate-sized reduction \( d = -0.67 \) in ESS compared to control, though this reduction was not statistically significant. Similarly, exercise training resulted in a moderate-sized improvement in FOSQ-10 score \( d = 0.61 \), despite the increase not being statistically significant.

**Effect of Exercise Training on Quality of Life**

A summary of changes in QOL is provided in Table 5. Compared to control, exercise training resulted in significant improvements in physical functioning \( F(1,40) = 4.57, p = 0.04 \), vitality \( F(1,40) = 5.00, p = 0.03 \), and mental health \( F(1,40) = 4.11, p = 0.04 \). Small- to moderate-sized improvements \( d > 0.35 \) following exercise training compared to control were noted for all SF-36 subscales except for bodily pain, social functioning, and role limitations due to emotional health.

**Effect of Exercise Training on Neurobehavioral Performance**

Table 6 summarizes the results relating to neurobehavioral performance. When compared with control, no significant changes between treatments were noted for any of the performance measures following exercise training. In addition, effect size calculations revealed no notable post-intervention difference in any neurobehavioral performance parameters except for a slightly greater reduction in TMT Difference score in the stretching control treatment compared to exercise training \( d = 0.23 \).

**Associations of Reduction in OSA Severity with Improvement in Daytime Functioning**

The intervention produced significant improvements in AHI and ODI, as previously reported (AHI: \( \tilde{\alpha} = 10.41 [3.61], p < 0.01 \); ODI: \( \tilde{\alpha} = 8.52 [3.79], p = 0.03 \)). Changes in AHI and ODI were significant predictors of reduction in POMS fatigue (AHI: \( \tilde{\beta} = -0.15 [0.07], p = 0.03 \); ODI: \( \tilde{\beta} = -0.17 [0.06], p < 0.01 \)), and reduced TST \(_{sp} \) predicted improvements in SF-36 physical function \( \tilde{\beta} = 1.15 [0.43], p = 0.01 \). Furthermore, reduction in ODI was a significant predictor of reduced PVT lapses \( \tilde{\beta} = -0.03 [0.01], p = 0.04 \). Mediation analyses indicated...
indicated that the effect of exercise training on POMS fatigue was mediated by reductions in AHI and ODI (αβ 95% confidence limits: AHI [0.21, 3.57], ODI [0.16, 3.25]). No other significant mediation effects were noted for any of the other daytime functioning variables.

**DISCUSSION**

As secondary outcomes of a randomized trial that evaluated the efficacy of exercise training on OSA severity, the aim of the current analysis was to investigate the effect of exercise training on the daytime functioning of individuals with OSA. Exercise training resulted in moderate effect-size improvements in depressive symptoms, vigor, fatigue, physical and mental health aspects of QOL, and sleepiness. Of all the variables that were improved following exercise training, only reduction in fatigue was found to be mediated by exercise-induced reductions in OSA severity.

Exercise training resulted in significant improvements in fatigue and vigor, with corresponding moderate-sized effects (d > 0.55). These findings are consistent with an extensive literature showing improvements in fatigue and vigor following exercise training in other populations. Moreover, the results of the present study extend the findings of prior uncontrolled research that indicated significant improvements in fatigue and vigor following exercise training in individuals with OSA, as well as strong epidemiologic associations of levels of fatigue and vigor with physical activity levels in individuals with OSA. The observed improvements in vigil and fatigue are similar to those achieved by CPAP. For example, a recent study found that three weeks of therapeutic CPAP produced moderate-sized improvements (d ~ 0.50) in fatigue and vigor compared to placebo CPAP.

Exercise training also elicited significant improvements in depressive symptoms and some aspects of QOL. A higher level in the vitality dimension of QOL has been associated with a higher level of physical activity in previous cross-sectional research of individuals with OSA, and a significant improvement in role limitations due to physical problems following exercise training was previously noted in a small uncontrolled study of apneics. Exercise training improved most of the QOL components that are most detrimentally affected by OSA, including physical functioning, general health perception, and vitality. The QOL improvements achieved with exercise training in the current study are comparable to those achieved with CPAP therapy.

The antidepressant effects of exercise have been well-documented in other populations. However, to our knowledge, no previous exercise training trials have investigated the effect of exercise training on depressive symptoms in adults with OSA. Given that depression is the most prevalent mental health condition observed in adults with OSA and the effects of CPAP on attenuating depressive symptoms are inconsistent, the results of the current study suggest that exercise training may be a useful nonpharmacologic therapy for reducing symptoms of depression in OSA patients.

In contrast to most other aspects of daytime functioning, there is minimal evidence that exercise significantly reduces sleepiness. In adults with OSA, epidemiologic research has associated higher daytime sleepiness with lack of exercise, and experimental research has documented a moderate reduction in ESS score (d ≥ −0.55) following 3 and 6 months of exercise training, respectively. The magnitude of improvement noted in the present study for ESS and FOSQ-10 scores following exercise training compared to control (d > 0.60) is consistent with prior research involving adults with OSA. Moreover, the ~2.5 point ESS reduction following exercise training in the present study is comparable to the effects of CPAP therapy. However, due to the lack of statistically significant improvement in these parameters of sleepiness, the results should be interpreted with caution.

Neurobehavioral performance was the only dimension of daytime functioning that did not appear to be at least modestly improved with exercise training. However, given the moderate efficacy of exercise at reducing AHI and ODI and the apparent lack of impairment in neurobehavioral performance in our study sample compared to normative values and previously published reports of individuals with OSA, it is not surprising that improvements in neurobehavioral performance were not observed.

Because this study relied upon effect sizes to demonstrate improvements in many aspects of daytime functioning following exercise training, the results should be considered preliminary. The lack of detection of statistical significance for many of these measures can be attributed to the sample size (N = 43), which was powered to detect expected reductions in AHI and ODI.
not necessarily the secondary outcomes of daytime functioning. However, it is noteworthy that effect sizes, which are independent of sample size limitations, revealed that exercise training produced moderate-sized improvements in most aspects of daytime functioning compared to the control treatment.

It has been hypothesized that individuals with OSA may be disinclined to exercise due to the impaired daytime functioning that is associated with the disorder, especially excessive sleepiness and fatigue. Thus, individuals who would be willing to exercise, such as the participants in the current study, may not be representative of the general OSA population. Conversely, individuals with significant daytime functioning impairment may be more likely to seek treatment than individuals with milder or absent daytime dysfunction. Our results suggest that participants were of similar impairment when compared to the overall OSA population, as the baseline daytime functioning of participants in the current study was similar to previously published OSA population samples (e.g., sleepiness; depressive symptoms).

Similarly, as with any intervention study, the self-selection of participants introduces a potential bias toward those who may benefit from the intervention being studied. Furthermore, with a study in which participants could not be blinded to their treatment, expectancy effects could plausibly have driven the improvements in daytime functioning. However, in the present study, both interventions were presented as active treatments, and no difference in expectancy for mood, sleepiness, or health improvements was noted between treatments following randomization. Therefore, that exercise training resulted in improved daytime functioning compared to a control condition of similar baseline expectancy suggests that the observed results were not driven by expectancy effects. Nevertheless, to reduce expectancy concerns, it would be prudent in future studies to include objective measures of sleepiness, such as the Multiple Sleep Latency Test or Maintenance of Wakefulness Test.

The different time commitments imposed by the two treatments is another potential limitation, as differing amounts of interaction with study staff could have theoretically influenced the subjective ratings of daytime functioning. However, we do not believe this factor significantly biased the outcomes of the present study. The treatment durations were chosen after carefully considering the advantages and disadvantages of having equal treatment durations. The stretching control and exercise training conditions were presented as “low intensity” and “moderate intensity” physical activity interventions, with the dosages of these activities in accordance with established guidelines.

Compared with participants in the exercise training treatment, stretching treatment participants had a greater opportunity for interpersonal interaction with study staff per hour of treatment while they were individually led through their flexibility program, such that total interaction was comparable or perhaps greater for the stretching group. Moreover, in our view, 150 minutes/week of flexibility exercises might have seemed excessive. We surmised that reduced treatment duration for the stretching intervention would provide an appropriate balance between controlling for behavioral confounds and having credible active treatments for which there were no differences in any of the expectancy measures.

Intermediate assessments of vigor, fatigue, and sleepiness were not performed in the current study. It is possible that initiation of an exercise program may produce temporary increases in fatigue and sleepiness along with decreased energy, and may discourage continuation of exercise training in participants who already are tired and sleepy from the underlying OSA. There were no anecdotal reports of this phenomenon in the current study, which might be explained by the gradual progression of exercise dose during the initial four weeks of the study. Such a progression is important for beginning any exercise program, but may be even more essential for individuals with OSA. Future research should employ more frequent assessment of sleepiness, fatigue/energy, mood, and QOL changes with exercise training in order to develop a better understanding of the time course of these changes.

It is unknown how exercise training would affect the daytime functioning of individuals currently being treated with CPAP therapy or oral appliances. Although the moderate efficacy of exercise training on OSA severity indicates that it is likely insufficient as a stand-alone therapy for OSA, this trial demonstrates the potential utility of exercise training to reduce daytime functioning decrements in OSA. Because CPAP or oral appliance use fail to completely normalize daytime functioning in many cases and most of the daytime functioning improvements following exercise training were independent of OSA improvement in the current study, combining exercise training with CPAP or oral appliance therapy may be an effective treatment option for augmenting improvements in sleepiness, fatigue, and QOL. Future trials involving combinations of exercise training with CPAP or oral appliance therapy are needed to determine whether exercise training results in additive improvements in daytime functioning relative to CPAP or oral appliances alone.

In conclusion, our results indicated that exercise training produced moderate improvements in selected aspects of daytime functioning that are impaired in individuals with OSA, including depressive symptoms, vigor and fatigue, and aspects of QOL. Because of the reliance of effect sizes to demonstrate improvement in some aspects of daytime functioning and the small sample size of the study, the results need to be verified by larger trials. Nevertheless, these data provide preliminary evidence that exercise may be a valuable therapy for improving aspects of daytime functioning in adults with OSA, regardless of changes in OSA severity.

REFERENCES

Obstructive sleep apnea syndrome (OSAS) is a complex, chronic disorder characterized by snoring, periodic apnea, hypoxemia during sleep, and daytime hypersomnolence. Its prevalence is 16% to 33% in men and 8% to 19% in women.2,3 Epidemiologic studies have confirmed that the morbidity of sleep-related respiratory disorders is increased in smokers, depending on their smoking history, and that habitual smoking appears to be associated with OSAS.3,4,5 The correlation between smoking and OSAS has not been studied in detail. In particular, the direct influence of smoking on OSAS and the correlation between the amount of cigarette smoking and the severity of OSAS have not been adequately demonstrated.

OSAS is characterized by repetitive upper airway collapse during sleep. Narrowing of the upper airway can be accompanied by breathing difficulty during sleep and is a predisposing anatomic factor for OSAS.6,7,8 Pathological conditions such as a redundant or long uvula and enlarged tonsils are thought to be the predominant causes of upper airway collapse during sleep and are indications for surgery to decrease snoring, apnea, and snoring-related cardinal symptoms. The upper airway mucosa can be easily affected by smoking, and longer exposure to smoking may cause abnormal histological changes to the upper airway mucosa. Therefore, evaluation of the uvular changes after exposure to smoking is important for understanding how smoking directly affects the uvular mucosa.

This study was designed to determine the relationship between smoking and OSAS. We reviewed the sleep studies of smokers and nonsmokers who were diagnosed with OSAS to...
examine the relationship of smoking to OSAS, especially the severity of OSAS. To better understand the influence of smoking on OSAS severity, we obtained uvular mucosa from OSAS subjects during snoring surgery and investigated smoking-induced histological changes in the upper airway mucosa resulting in narrowing of the upper airway.

MATERIAL AND METHODS

Subjects
This study included 122 patients referred to the Sleep Disorder Clinic in the Department of Otolaryngology and Head & Neck Surgery of Chung-Ang University College of Medicine (Seoul, Korea) between March 2005 and February 2008 with a diagnosis of OSAS due to a narrowed oropharynx, who underwent uvulopalatopharyngoplasty (UPPP). All patients gave their informed consent to participate. Surgical samples for histologic study were obtained from all patients who met the criteria for UPPP, the diagnosis of OSAS was established by overnight respisomnography, and a narrowed oropharynx was confirmed via the Müller maneuver using a flexible endoscope and lateral cephalometric roentgenogram. The records of 57 male patients with a clear smoking history and a normal anatomical cephalometric index except for a narrowed oropharynx were reviewed retrospectively, and the histological reports of their uvular specimens after UPPP were examined. Thirty-five patients treated with continuous positive airway pressure, 29 patients with hypertension, diabetes, or atherosclerotic vascular disease, and 11 patients who had an unclear smoking history were excluded.

Before UPPP, all patients underwent a pulmonary function test using forced spirometry. No patients had chronic respiratory diseases such as asthma or COPD. Patients with an active smoking history > 2 years before undergoing UPPP were considered current smokers, and patients with no smoking history were nonsmokers. Smoking history was quantified in number of pack years (PYs) as (packs smoked per day) × (years as a smoker), defined as 20 cigarettes smoked every day for one year. Smokers were divided into 2 groups: > 10 PY and ≤ 10 PY.

Sleep Study
All patients were examined prior to surgery by respisomnography ≥ 6 h using an Embleta PDS (Embla System, Reykjavik, Iceland) consisting of a pressure transducer system (pressure cannula), a thermistor sensor for oral and nasal airflow, a piezoelectric belt for thoracic and abdominal impedance, and a pulse oximeter (finger flex sensor) for O₂ saturation and pulse. Sen-

Surgical Specimens and Histological Study
Surgical specimens were obtained from the uvulas of the 57 patients who underwent UPPP and fixed in 10% paraformaldehyde. Histological studies were performed using morphometric and qualitative methods. One pathologist measured each factor within one window of a light microscope and read, interpreted, and classified the histological findings.

1. Morphometric study
We measured the following 6 factors with a light microscope (×100): (1) thickness of the epithelium, (2) thickness of the lamina propria, (3) degree of vascular dilation (0, no vascular dilation; 1, mild dilatation; 2, moderate dilation; 3, severe dilatation), (4) degree of fibrosis (0, no fibrosis; 1, mild fibrosis; 2, moderate fibrosis; 3, severe fibrosis), (5) amount of inflammatory cell infiltration, and (6) degree of submucosal gland proliferation. The number of submucosal glands was counted under a light microscope and graded according to the following scale: 1, number of submucosal glands < 3; 2, number of submucosal glands 3-10; 3, number of submucosal glands 11-30; and 4, number of submucosal glands > 30.

2. Qualitative Study
We noted the following histological findings in specimens under the light microscope (×100): hyperkeratosis, acanthosis in the epithelium, edema, vascular congestion in the lamina propria, hyperplasia in the submucosal glands, and atrophy of muscle tissues.

3. Immunohistochemistry
Immunohistochemical analysis was performed using the neuroendocrinological markers protein gene product (PGP) 9.5, substance P (SP), and calcitonin gene-related peptide (CGRP), to determine the expression of peripheral sensory nerves in patient uvulas or soft palates. The monoclonal antibodies used were PGP 9.5 (1:50; DAKO, Glostrup, Denmark), SP (1:100; Invitrogen, Carlsbad, CA, USA), and CGRP (1:200; Chemicon International, Inc., Billerica, MA, USA).

Briefly, 5-μm sections were fixed in acetone for 10 min at room temperature (RT). Non-specific protein staining was blocked with goat serum. Slides were treated with 0.5% hydrogen peroxide to eliminate endogenous peroxidase for 10 min at RT and incubated with primary antibody overnight at RT. After washing with Tris-buffered saline (TBS, pH 7.5), slides were incubated with horseradish peroxidase-conjugated secondary antibody (Thermo, Asheville, NC, USA) for 30 min at RT. Chromogen (3-aminio-9-ethylcarbazole) was applied to the specimens, followed by Mayer’s hematoxylin for counterstaining.

Statistical Analysis
ANOVA, independent sample t-tests, and Fisher exact test were used to assess the association between patient factors and respisomnography results. Statistical correlations were calculated us-
Influence of Smoking on OSAS

We investigated the relationship between smoking history and OSAS severity. For nonsmokers, the number of subjects in each OSAS severity group was evenly distributed. In contrast, more smokers were in the moderate (50%) and severe OSAS groups (43%) than in the mild OSAS group (7%), and the difference was significant (Table 3). Thus, smoking negatively affected patients, resulting in increased OSAS severity.

For patients with a > 10 PY smoking history, we observed an equal prevalence (50% each) of moderate and severe OSAS, and there were no patients with mild OSAS. The rate of moderate or severe OSAS in smokers with a > 10 PY smoking history was higher than in smokers with a ≤ 10 PY smoking history.

Table 1—Mean age and BMI according to smoking history and exposure to smoke

<table>
<thead>
<tr>
<th>Type</th>
<th>N</th>
<th>Mean Age (year)</th>
<th>p-value</th>
<th>BMI (kg/m²)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non smokers</td>
<td>29</td>
<td>41.48 ± 12.74</td>
<td></td>
<td>26.82 ± 4.31</td>
<td></td>
</tr>
<tr>
<td>Smokers</td>
<td>28</td>
<td>38.71 ± 11.14</td>
<td>0.387</td>
<td>25.87 ± 4.26</td>
<td>0.407</td>
</tr>
<tr>
<td>≤ 10 PY</td>
<td>12</td>
<td>30.58 ± 8.83</td>
<td></td>
<td>24.72 ± 4.91</td>
<td></td>
</tr>
<tr>
<td>&gt; 10 PY</td>
<td>16</td>
<td>44.81 ± 8.73</td>
<td>0.001*</td>
<td>26.74 ± 3.63</td>
<td>0.219</td>
</tr>
<tr>
<td>Total</td>
<td>57</td>
<td>40.12 ± 11.96</td>
<td></td>
<td>26.36 ± 4.27</td>
<td></td>
</tr>
</tbody>
</table>

BMI, body mass index; PY, pack year; N, number; *p < 0.05.

Table 2—Mean age, BMI, and AHI of patients by severity of OSAS

<table>
<thead>
<tr>
<th>Type</th>
<th>N</th>
<th>Mean Age (year)</th>
<th>BMI (kg/m²)</th>
<th>AHI</th>
<th>ODI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>11</td>
<td>37.73 ± 12.69</td>
<td>24.51 ± 2.45</td>
<td>9.95 ± 4.60</td>
<td>18.00 ± 12.20</td>
<td>0.927</td>
</tr>
<tr>
<td>Moderate</td>
<td>26</td>
<td>39.82 ± 11.84</td>
<td>25.59 ± 4.39</td>
<td>22.95 ± 3.60</td>
<td>32.73 ± 6.82</td>
<td>0.809</td>
</tr>
<tr>
<td>Severe</td>
<td>20</td>
<td>41.85 ± 11.47</td>
<td>28.37 ± 4.28</td>
<td>39.65 ± 13.49</td>
<td>51.74 ± 20.74</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>

OSAS, obstructive sleep apnea syndrome; BMI, body mass index; AHI, apnea hypopnea index; ODI, oxygen desaturation index; N, number; *p < 0.05.

Table 3—Results of the statistical analysis of smoking history and severity of OSAS, AHI, and ODI

<table>
<thead>
<tr>
<th>OSAS</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>p-value</th>
<th>AHI</th>
<th>p-value</th>
<th>ODI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non Smoker</td>
<td>9 (31%)</td>
<td>12 (41%)</td>
<td>8 (28%)</td>
<td></td>
<td>22.35 ± 11.11</td>
<td></td>
<td>34.43 ± 15.21</td>
<td></td>
</tr>
<tr>
<td>Smoker</td>
<td>2 (7%)</td>
<td>14 (50%)</td>
<td>12 (43%)</td>
<td>0.022*</td>
<td>30.32 ± 15.37</td>
<td>0.029*</td>
<td>38.76 ± 21.82</td>
<td>0.387</td>
</tr>
<tr>
<td>≤ 10 PY</td>
<td>2 (17%)</td>
<td>6 (50%)</td>
<td>4 (33%)</td>
<td></td>
<td>25.22 ± 8.21</td>
<td></td>
<td>30.29 ± 13.48</td>
<td></td>
</tr>
<tr>
<td>&gt; 10 PY</td>
<td>0 (0%)</td>
<td>8 (50%)</td>
<td>8 (50%)</td>
<td></td>
<td>34.14 ± 18.43</td>
<td>0.034*</td>
<td>45.12 ± 24.97</td>
<td>0.016*</td>
</tr>
</tbody>
</table>

OSAS, obstructive sleep apnea syndrome; AHI, apnea hypopnea index; ODI, oxygen desaturation index; PY, pack year; *p < 0.05.

RESULTS

Characteristics of Patients

We recruited 57 men who fulfilled the inclusion criteria: 28 with a smoking history and 29 nonsmokers. The mean age was 40.1 years (17-72 years). We classified the smokers into 2 groups on the basis of a 10-PY smoking history, with 12 in the ≤ 10 PY group and 16 in the > 10 PY group. The ages of smokers and nonsmokers were not significantly different, but patients with a > 10 PY smoking history were older than patients with a ≤ 10 PY smoking history (Table 1).

We classified OSAS severity as mild, moderate, or severe based on respiration results. The mild group had 11 patients (19.3%), the moderate group had 26 (45.6%), and the severe group had 20 (35.1%). Significant differences were not noted in mean age or BMI according to OSAS severity, contrary to AHI and ODI (Table 2).

The classification of patients according to smoking history or PY was independent of influences of other OSAS risk factors such as cardiovascular diseases, obesity, male sex, and history of chronic medication use. It has been known that old age may be one of the risk factors of OSAS and the age of smokers in the > 10 PY and ≤ 10 PY groups was significantly different in our data. However, no difference of mean age was observed according to severity of OSAS and smoking history (smokers vs nonsmokers). We found that nonsmokers had relatively less severe OSAS than with smokers, even though mean age of non-smokers was higher than that of smokers (Table 1). Therefore, the influence of age on OSAS severity would be excluded in our study and increased severity of OSAS in smokers with > 10 PY might be due to longer exposure to smoke.
We also found that OSAS severity according to AHI was higher in smokers, especially those who had a longer period of exposure to smoking (Table 3).

Unlike the AHI, the ODI was not significantly different between smokers and non-smokers. However, it was significantly higher in smokers with a > 10 PY smoking history compared to nonsmokers and smokers with a ≤ 10 PY smoking history (Table 3).

**Histological Changes in the Uvular Mucosa Due to Smoking in OSAS Patients**

We examined the histological findings of the uvular mucosa and OSAS severity in nonsmokers and smokers to assess the effect of smoking on upper airway narrowing. First, we evaluated the histological findings of the uvular mucosa by morphometric analysis and compared our findings with OSAS severity, irrespective of smoking history. We found that the lamina propria was significantly thicker in the uvular mucosa with increased OSAS severity (Table 4A, Figure 1). No significant differences were observed in terms of thickness of the epithelium, degree of vascular dilation, degree of fibrosis, amount of inflammatory cell infiltration, or degree of proliferation of the submucosal glands (Table 4A). The lamina propria of the uvula was thicker in smokers than nonsmokers, and there was a significant correlation between the thickness of the lamina propria and OSAS severity in smokers (Table 4B, Figure 2).

Second, we carried out a qualitative investigation of the histological findings of the uvular mucosa. We classified findings according to OSAS severity and analyzed the correlation with smoking history. We found that edema of the lamina propria was increased in moderate and severe OSAS patients (Table 5A), while findings of hyperkeratosis or acanthosis of the epithelium, vascular congestion in the lamina propria, hyperplasia of the submucosal glands, and atrophy of the muscle tissue were not observed in the uvular mucosa of OSAS patients (Table 5A).

Edema of the lamina propria was observed in the uvular mucosa of 14 smokers (n = 28, 50%) and was more definitive than the mucosal edema of nonsmokers (n = 29, 27%). In addition, the proportion of smokers with edematous lamina propria in the uvular mucosa was increased significantly according to OSAS severity, but the difference was minimal in nonsmokers (Table 5B).
Influence of Smoking on OSAS

The thickness of the lamina propria increased in the uvula mucosa of moderate and severe OSAS patients. (A) mild OSAS, (B) moderate OSAS, (C) severe OSAS (H & E, × 40).

Lamina propria thickness increased with longer smoking duration. The most severe thickening of the lamina propria was observed in the upper airway mucosa of smokers with a history of over 10 PY. (A) Nonsmoker, (B) < 10 pack years, (C) > 10 pack years (H & E, × 40).

DISCUSSION

In this study, we found that moderate and severe OSAS were more prevalent in smokers, and that smoking might induce narrowing of the upper airway through an increase in edema and thickness in the uvular mucosa. The severity of OSAS and the narrowing of the upper airway were particularly increased in smokers with a > 10 PY history of smoking.

Although proving an independent effect of smoking on snoring is difficult, some studies have recognized that smoking might have an effect on sleep related disorders.8-10,14 Previous epidemiologic studies have suggested that smoking may be an independent risk factor for habitual snoring,7-9,10,14 and that snoring frequency increases with the number of cigarettes smoked or the duration of exposure to smoking.15-22 However, most studies compared patients’ smoking history with OSAS prevalence or snoring-related diseases, and the relationship between...
smoking exposure and OSAS severity was not rigorously investigated or fully understood.

In this study, we attempted to verify the correlation between smoking and the severity of OSAS using medical records and patient specimens. We used consistent criteria to recruit patients in order to exclude the effects of other risk factors and to investigate the influence of smoking on OSAS. We excluded patients with systemic risk factors such as hypertension, diabetes, and cardiovascular or neurovascular diseases either currently or in the past. Age and BMI did not differ between smokers and nonsmokers; only male subjects were included to examine the influence of smoking more objectively.

We found that OSAS patients who were smokers had a higher AHI and ODI, and this increased with a longer smoking history, especially for smokers exposed to > 10 PY compared to nonsmokers. We determined that smoking increased the incidence of apnea and hypopnea and decreased oxygen desaturation during sleep in OSAS patients, and that longer exposure to smoking was a high-risk factor for severe OSAS.

Narrowing at the level of the oropharynx or palate is reportedly one of the most common predisposing factors for snoring and palatal surgeries, such as UPPP, uvuloplasty, and transpalatal advancement pharyngoplasty, which are popular modalities for correcting upper airway narrowing, resulting in decreased snoring at the level of the oropharynx. Anatomical variation has been less frequently reported at the uvula than at other oropharyngeal tissues; redundant uvular mucosa directly induces upper airway narrowing independent of other systemic factors.
Influence of Smoking on OSAS

We suggest that the uvular mucosa is the most suitable tissue of the oropharynx for comparing histological changes in OSAS subjects and for examining the local influence of smoking on upper airway narrowing and OSAS severity.

We found that increased thickness and edema of the lamina propria in OSAS subjects’ uvular mucosa were predominant if OSAS subjects were smokers and that the histologic changes in the uvular mucosa were intensified according to OSAS severity. These histological changes were consistent with the findings of previous studies. In our limited study, we did not obtain uvular mucosa from nonsmoking healthy volunteers without snoring history and did not compare histologic changes in the uvular mucosa among healthy volunteers, nonsmoking OSAS patients, and smoking OSAS patients. However, the changes were more definitive in smokers with OSAS, and when the uvular mucosa was exposed to smoke for a long period of time, it was thicker, with a more edematous lamina propria. We examined only the local influence of smoking on upper airway narrowing or collapse. The severity of OSAS results from a cascade of multiple physiological processes interacting with features such as muscle tone, craniofacial structures, anatomical variations, mucosal edema of the airway, and total lung function. Although it was difficult to analyze the systemic effect of smoking using patients’ clinical data, the patients included in this study were diagnosed with OSAS through radiographic methods, a pulmonary function test, flexible endoscopy, or respirometry; and patients who had normal lung function and normal cephalometric structure, except redundant oropharyngeal mucosa, were recruited irrespective of smoking status in order to exclude the systemic effect of smoking. Therefore, we suggest that smoking may result in thickening and edematous changes of the uvular mucosa, thus leading to increased OSAS severity through upper airway narrowing.

We also investigated how smoking might induce histological changes of the uvular mucosa in OSAS patients. Mucosal edema is closely related to mucosal inflammation, and tobacco fumes may be involved in the induction of neuroendocrinologic inflammation. The afferent peripheral nerves in the airway mucosa respond to stimulation by fumes by secreting tachykinin, CGRP, and SP, which are required for neuroendocrinologic inflammation. We found that CGRP-positive staining was substantially more prevalent in the uvular mucosa of smokers compared to PGP 9.5 and SP staining. In particular, CGRP staining was increased in the uvular mucosa of patients exposed to smoking for > 10 PY. CGRP-positive afferent peripheral nerves stimulate local vascular dilation, smooth muscle strength, and gland secretion; they also induce mucosal inflammation and edema. We determined that CGRP expression might be more specifically stimulated by smoke, and smoking may stimulate the secretion of CGRP from afferent nerves in the uvular mucosa, thereby increasing edema or thickness of the lamina propria in the uvulas of OSAS patients. In this study, we did not determine whether cessation of smoking can lead to the reversal or recovery of the histological changes seen in the uvular mucosa, and this remains unknown. Smoking is thought to lead to an increased risk of COPD, and patients with both COPD and OSAS suffer from more frequent episodes of oxygen desaturation and more total sleep time with hypoxemia and hypercapnia than OSAS patients without COPD. Therefore, we propose that smoking is an independent risk factor for OSAS subjects and that cessation of smoking may be required to prevent upper airway narrowing and systemic lung diseases that worsen OSAS.

In conclusion, we strongly suggest that smoking changes the uvular mucosa of OSAS subjects to become more thickened or edematous through CGRP-induced neurogenic inflammation, leading to increased OSAS severity through upper airway narrowing. Our findings suggest that longer exposure to smoking results in a higher prevalence of moderate or severe OSAS.
REFERENCES


SUBMISSION & CORRESPONDENCE INFORMATION

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Address correspondence to: Hyun Jik Kim, M.D., Ph.D., Department of Otolaryngology, Chung-Ang University College of Medicine, 224-1 Heukseok-dong, Dongjak-gu, Seoul, Korea 156-755; Tel: 82-2-8299-1782; Fax: 82-2-825-1765; E-mail: hyunjik@cau.ac.kr

DISCLOSURE STATEMENT

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A patent foramen ovale (PFO) can be detected in autopsy studies in 15% to 34% in the general population. It is reported in 26% of a randomly selected population cohort examined by transesophageal echocardiography (TEE). A higher prevalence has been reported in patients suffering from migraine or cluster headache, as well as in subjects with ischemic stroke. Case reports of thrombi-in-transit and a plausible physiologic mechanism support the notion that PFO are a potential cause for paradoxical peripheral and coronary embolization and decompression sickness.

Transesophageal echocardiography using contrast (agitated saline injection) has been demonstrated to have a high sensitivity and specificity for the detection of a PFO causing a right-to-left shunt when compared with autopsy studies and has, therefore, been considered the gold standard diagnostic test for the detection of a PFO. However, recent studies have shown contrast-enhanced TCD and TEE to be complementary techniques in the assessment of a PFO.

In fact, some evidence suggests that TCD may be more sensitive in the detection of RLS than echocardiographic imaging. Therefore, this technique may be able to exclude PFO causing RLS with a higher level of confidence than TEE and transthoracic echocardiography. Assuming no other (unusual) intracardiac or intrapulmonary shunts are present, a RLS detected on TCD is indicative of a PFO. Furthermore, TCD is considerably less invasive for the patient, and the Valsalva maneuver, which significantly increases microbubble appearance, can be performed more accurately. Further investigations demonstrated that the unilateral detection of RLS by power M-mode transcranial Doppler, used in this study, provided an equivalent sensitivity to a bilateral detection, while easier to handle. Recognizing the limitation that, in unusual circumstances, a RLS causes left-to-right shunting only, the presence of RLS demonstrated by TCD will, for the remainder of this discussion and manuscript, be assumed to be the consequence of PFO with RLS. Moreover, the term “PFO” will indicate PFO with RLS unless otherwise stated.

Obstructive sleep apnea (OSA) is a common condition affecting 17% to 26% of men and 9% to 28% of women over 30

**Background:** Patent foramen ovale (PFO) with right-to-left shunt has a prevalence of 10% to 34% in the general population. It can cause an ischemic stroke, transient ischemic attack, and paradoxical peripheral or coronary embolization. Its influence on migraine and several other diseases and conditions is currently under debate. Attention has recently been turned to the correlation between PFO and obstructive sleep apnea. Thus far, studies on the prevalence of right-to-left shunts as a surrogate for PFO in these patients were limited by small sample sizes and the results have been conflicting. Here, we evaluate the prevalence of right-to-left shunting (RLS) through transcranial Doppler ultrasound (TCD) in a large patient group with obstructive sleep apnea (OSA).

**Methods:** One hundred consecutive patients (mean age 59.5 y) with OSA underwent TCD with intravenous injection of agitated saline. The grading of right-to-left-shunts was in accordance with the Spencer PFO Grading Scale.

**Results:** RLS was detected in 72 of 100 patients (72%). Thirty-four out of these 72 patients (47%) had a shunt grade I or II; 15 (21%) had a shunt Grade III or IV; and 23 (32%) had a large shunt (Grade V or V+). In 47 of 72 patients (65%), a right-to-left shunt was detectable at rest without Valsalva maneuver.

**Conclusion:** The prevalence of a RLS in patients with OSA is high. Provided other intracardiac or pulmonary shunts were absent, the high prevalence of a RLS suggests a high prevalence of PFO in patients with OSA.

**Keywords:** Obstructive sleep apnea, patent foramen ovale, right-to-left-shunt, transcranial doppler

**Citation:** Guchlerner M; Kardos P; Liss-Koch E; Franke J; Wunderlich N; Bertog S; Sievert H. PFO and right-to-left shunting in patients with obstructive sleep apnea. J Clin Sleep Med 2012;8(4):375-380.
years of age with a higher prevalence in both the elderly and the overweight. Several disorders are associated with this condition: systemic and pulmonary hypertension, ischemic heart disease, cardiac arrhythmia, cerebrovascular disease, congestive heart failure, as well as cognitive dysfunction and an increased risk of accidents as a result of daytime sleepiness. Improvements in the degree of hypoxemia in patients with both OSA and PFO after closure of the PFO are conceivable. Data, to support this, however are limited to case reports. For example, subjective improvement in sleep apnea symptoms and objective improvement in polysomnographic testing after transcatheter closure of a PFO in a patient after ischemic stroke have been reported. Moreover, complete resolution of symptoms in a patient with OSA and desaturations during exercise has been described. It is not yet clear whether OSA, by virtue of increased mean transmural pulmonary artery pressure during apneic episodes, may allow an interatrial communication (PFO) that otherwise would be unrecognized, whether the PFO is a substantial contributor in the pathogenesis of OSA, or whether both apply. Recent research indicates that carbon dioxide retention and hypoxemia during nocturnal apneic episodes in patients with obstructive sleep apnea (OSA) lead to an elevation of pulmonary vascular resistance followed by an increase in right ventricular afterload and right atrial pressure. Under these conditions, right-to-left shunting via PFO may exacerbate the hypoxemia caused by apneic episodes. Importantly, it has not yet been determined whether OSA is associated with an increased prevalence of PFO. Previous studies examining the prevalence of PFO in patients with OSA have produced conflicting results. The aim of this study was to evaluate the prevalence of right-to-left shunting by means of TCD in a large group of patients with obstructive sleep apnea syndrome. Care was taken to include a nonselected cohort of consecutive patients representative of a general OSA population.

PATIENTS AND METHODS

Study Sample

One hundred consecutive patients first time diagnosed with OSA after clinical assessment and inpatient overnight sleep studies requiring nocturnal positive airway pressure treatment were screened for PFO.

Polysomnography

The diagnosis of OSA was made after performing a standard nocturnal polysomnography including electroencephalogram, electrooculograms, single-lead electrocardiogram, anterior tibial and submental electromyograms, finger pulse oximetry, and measurements of oro-nasal-airflow as well as abdominal and chest excursions. A single expert evaluated the polysomnograms manually. Respiratory events were counted as apnea if a cessation of airflow ≥ 10 sec occurred. Hypopnea was defined as ≥ 50% reduction of airflow, in association with an oxygen desaturation ≥ 4% from the baseline value, lasting > 10 seconds.

Continuous oxygen saturation (SaO₂) measurement allowed determination of the number of desaturations > 4% per hour sleep time (oxygen desaturation index, ODI). The frequency of apneas and hypopneas per hour of sleep (apnea hypopnea index, AHI) defined the OSA severity. AHI > 5 was considered pathological.

Shunt Detection and Assessment

To evaluate the presence of PFO, a transcranial Doppler was performed in every patient. We used the ST3 Digital Transcranial Doppler System Model PMD 150 (Spencer Technologies, Seattle, WA, USA), with Power M-Mode and injection of contrast medium, to discover RLS. The machine provides 33 gates of continuous Doppler information across a 66 mm depth range. There are 2 sections on display:

1. Digital Power M-Mode (mm): This shows all blood flow within a depth range. Blue represents blood flow away from the transducer, red towards the transducer. Brighter color corresponds to stronger signals. Blood flow signals cause a horizontal streak across the screen when located.
2. Spectrogram (cm/s): shows a Doppler spectral waveform that indicates the velocity profile of blood flow in the selected depth.

All examination data were stored internally and analyzed offline afterwards by a single experienced researcher.

Patients were placed in supine position with their head slightly elevated. An intravenous catheter (20-gauge) was inserted into the antecubital vein. The transcranial 2 MHz ultrasound probe was fixed unilaterally on the patients’ head, at the height of the temporal bone window, by using the Marc 600 Headframe System (Spencer Technologies, Seattle, WA). The Doppler signal of blood flow in the middle cerebral artery was located at a depth of 45-65 mm. At this point, the Valsalva maneuver was exercised with the patient: the patient was asked to take a deep breath and press against the closed epiglottis for 10 sec to increase the thoracic pressure. The maneuver was considered successful if a 30% reduction of mean flow velocity in the middle cerebral artery could be observed for the entire 10-sec period. Before recording, two 10-mL syringes were connected to the intravenous catheter by means of a 3-way stopcock: one containing 9 mL of 3.5% colloidal solution Haemaccel (TheraSelect, Marburg, Germany) and 1 mL of air, the other empty. The content was agitated by rapidly pushing it from one syringe to the other, resulting in a homogenous solution (the contrast agent).

In the following examination, 2 sessions were performed: in the first session the contrast bolus was rapidly injected (within 6-8 sec) with the patient at rest during physiological respiration. In the second session, the patient was asked to perform the Valsalva maneuver as previously practiced. Midway through the injection, the patient was instructed to start the Valsalva maneuver and hold it for 10 sec before breathing normally again. There was a 5-min break between the sessions to allow the recirculating bubbles to disperse. Embolic tracks were counted for a total of 60 sec after the end of each injection.

Microembolic signals can be distinguished from artifacts (caused by patient movement, swallowing, chewing, or manipulation of the probe) in the spectrogram by their characteristic sound and look. It is a short click-sound (< 300 ms) of high...
The Fisher exact test was used to compare categorical variables in the groups “no shunt” and “shunt.” Gender and preexisting illnesses (hypertension, diabetes, coronary artery disease, atrial fibrillation, COPD/asthma, stroke; Table 3) were included in the analysis (Table 4). Spearman rank correlation was calculated to test for a statistically significant association between shunt magnitude and clinical parameters. A p value < 0.05 was considered statistically significant.

**RESULTS**

There were 19 females and 81 males in the study population. The mean age was 59.5 ± 11.7 years, mean BMI 33.2 ± 6.4 kg/m² and mean AHI 44.2 ± 22.2/h (Table 2).

In 72 of 100 (72%) patients, a right-to-left shunt was detected. Forty-seven of 72 patients (65%) showed “at-rest shunting”—a right-to-left shunt during physiological respiration. A “provocative-only shunt”—a right-to-left shunt only after Valsalva maneuver—was present in 25 patients.

Out of these 72 patients, 34 (47%) had a small shunt (< 15 MES, conforming to grade I or II in the Spencer grading Scale); 38 patients (53%) had a large shunt (grade III to V+); and in 18 patients a curtain pattern was seen in TCD (V+).

There was no significant correlation with the following parameters: gender, BMI, AHI, ODI, AHI/ODI, nadir oxygen saturation, lowest oxygen saturation, or concomitant diseases, and the presence or absence of a shunt either at rest or with Val-
salva. In addition, there was no significant correlation between the shunt magnitude and any of the aforementioned parameters.

**DISCUSSION**

The study reveals right-to-left shunting in 72% of patients with OSA. Provided no other sources (i.e., an intrapulmonary or other intracardiac RLS) are present, the etiology of the RLS in these patients is PFO. This is approximately three times higher than the reported prevalence of PFO in the general population at autopsy. It is also significantly higher than the prevalence reported by TEE in a large randomly selected population cohort (26%).4 Of note, in the overwhelming majority in that cohort the PFO was diagnosed based on the presence of a RLS by contrast (agitated saline) injection. Our results confirm findings by Shoundy et al.27 The prevalence of PFO was 69% in patients with OSA analyzed by TEE (48 patients). In contrast, in a TCD-study (78 patients), Beelke et al. report a prevalence of only 27%, which lies within the range expected in the general population.28 However, this study only evaluated a selected group of patients with OSA. Patients with myocardial infarction, unstable angina, congestive heart failure, pulmonary embolism, transient ischemic attack, stroke, or migraine—all conditions frequently found in patients with OSA—were excluded. Thus the study population may not have be representative of the general OSA patient population. Transectral Doppler data regarding the prevalence of a RLS in a healthy population are limited and it could be argued that TCD is more sensitive or overestimates the true prevalence of RLS. However, though perhaps slightly more sensitive than TEE,10 the differences in reported prevalences between both modalities are small.

It has been hypothesized, that the high prevalence of PFO with RLS in OSA patients could be due to enhanced respiratory effort during apneic episodes causing a rise in right atrial pressure, allowing reopening of a patent but formerly closed foramen26; however, increased right atrial pressures in patients with isolated OSA have not yet been demonstrated. Likewise, increased right-sided pressure related to pulmonary hypertension may facilitate interatrial communication via the foramen ovale. Though it is controversial whether OSA alone (in the absence of concomitant pulmonary disease or daytime hypoxemia) can cause pulmonary hypertension, some recent data in patients whose sleep apnea was treated with continuous positive airway pressure causing a significant reduction in pulmonary artery pressure in the absence of changes in daytime hypoxemia or lung function tests does support the notion that OSA can lead to an increase (albeit mild) in pulmonary artery pressure.31 Finally, both mechanisms in concert may permit a patent foramen ovale to re-establish. To this effect, high pulmonary artery systolic pressure is often measured in patients with OSA32 and attributed to pulmonary vasoconstriction caused by hypoxemia.33 Though the prevalence of PFO in patients with pulmonary hypertension is reported to be similar to the general population,34 a study of patients with chronic obstructive pulmonary disease (COPD) shows a significantly higher pulmonary artery systolic pressure and an increased prevalence for PFO assessed by transesophageal contrast echocardiography (70%).35 Moreover, these patients experience significant systemic arterial oxygen desaturation after the Valsalva maneuver.

Similar observations have been made in OSA patients with PFO: these patients experience more oxygen desaturations in proportion to respiratory events (episodes of hypopnea and apnea) than patients without PFO. There appears to be a higher prevalence of PFO in patients with deep desaturations than in those with milder degrees (60% vs. 13%).36 The right-to-left shunt occurring during obstructive respiratory disturbances (i.e., patients pressing against closed upper airway) allows deoxygenated venous blood to enter the arterial system and thereby may decrease arterial oxygen saturation.

There is a high correlation between MES count in TCD and PFO size.37 Thus one may assume that a larger shunt in TCD is related to a larger defect. The role of PFO and shunt size in the severity of desaturation is still not fully understood. In the current study, a significant correlation between shunt size and AHI (which indicates severity of OSA) could not be found.

There was no significant associated between any of the evaluated clinical parameters to the presence a shunt or its magnitude. This corresponds with previous study results.27-28

Case reports suggest an association between OSA and PFO. For example, in support of the hypothesis that PFO may exacerbate hypoxemia and unfavorably affect physiologic sleep parameters, significant improvements of OSA symptoms were reported after PFO closure.23,24 Furthermore, favoring the notion that OSA may allow reestablishment of an interatrial communication, treatment of OSA with continuous positive airway pressure (CPAP) has been reported to suppress a previously existing shunt occurring through a PFO.38 It is conceivable that the higher prevalence of right-to-left shunting via a patent foramen ovale in patients with OSA may be responsible for a higher stroke incidence in patients with OSA.39 Hence, the importance of an association between PFO and OSA is not to be underestimated. Given the substantial and rising number of patients with OSA, the inves-

| Table 3—Concomitant diseases in study population |
|--------------|--------|
| Disease       | No. of patients |
| Hypertension  | 61     |
| Diabetes      | 18     |
| Coronary artery disease | 15     |
| Atrial fibrillation | 10     |
| COPD/asthma   | 9      |
| Stroke        | 6      |

<table>
<thead>
<tr>
<th>Presence of RLS</th>
<th>p-value</th>
<th>Shunt magnitude</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>0.3</td>
<td>0.3</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.1</td>
<td>0.19</td>
<td></td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>0.06</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>0.36</td>
<td></td>
<td></td>
</tr>
<tr>
<td>COPD/asthma</td>
<td>0.52</td>
<td>0.3</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>0.2</td>
<td>0.11</td>
<td></td>
</tr>
</tbody>
</table>

*Journal of Clinical Sleep Medicine, Vol. 8, No. 4, 2012*
tigation of the following aspects should be among the priorities in studying this patient population: First, it would be very important to prospectively establish whether individuals with OSA and PFO are more likely to experience strokes and, perhaps, are more likely to suffer from pulmonary or systemic hypertension than those with OSA and absent interatrial communication. Second, given the demonstrated procedural safety, the impact of percutaneous PFO closure on the incidence of strokes and other undesired associated conditions such as pulmonary hypertension and systemic hypertension in this patient population should be investigated. Though it would allow further elucidation of the physiology and association of OSA and PFO, a randomized comparison of patients with OSA and PFO treated with CPAP compared to no treatment is, of course, unethical.

**Limitations**

As described in the introduction, TCD cannot distinguish between a shunt occurring through a PFO and a shunt on a pulmonary level. Albeit the latter is rare, its role in the physiology of OSA is unknown. Likewise, a PFO causing exclusively left-to-right shunting may remain silent on TCD imaging. The clinical significance of this possibility is unclear. In addition, optimally, the prevalence of RLS in patients with OSA should be compared to that of a general population using the same imaging modality to minimize errors related to the imaging procedure itself.

**CONCLUSION**

The prevalence of a RLS assessed by TCD is high in patients with OSA. Provided no unrecognized other unusual intracardiac or intrapulmonary shunts are present in OSA patients, this is likely related to a high prevalence of PFO in this population. To confirm our findings, further studies comparing the prevalence of a RLS in OSA patients to that of a healthy population are warranted. It remains to be investigated whether PFO are risk factors for OSA or, to the contrary, if OSA helps maintain a PFO or leads to re-opening of a formerly closed foramen ovale. Lastly, further research is needed to determine whether PFO exacerbate the symptoms of sleep apnea or may be associated with a higher incidence of strokes in patients with OSA and, therefore, if a PFO closure should be considered in these patients.

**REFERENCES**


**SUBMISSION & CORRESPONDENCE INFORMATION**

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Address correspondence to: Prof. Dr. Horst Sievert, CardioVascular Center Frankfurt, Seckbacher Landstrasse 65, 60389 Frankfurt, Germany; Tel: +49-69-4603-1344; Fax: +49-69-4603-1343; E-mail: info@CVCFrankfurt.de

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Clinical Presentation of Obstructive Sleep Apnea in Patients with Chronic Kidney Disease


1Department of Medicine, Faculty of Medicine, University of Calgary, Calgary, Alberta, Canada; 2Alberta Kidney Disease Network, Alberta, Canada; 3Sleep Centre, Foothills Medical Centre, University of Calgary, Calgary, Alberta, Canada

Background: Obstructive sleep apnea (OSA) is an important and common comorbidity in patients with chronic kidney disease (CKD). However, few studies have addressed how OSA presents in this patient population and whether it is clinically apparent.

Objective: The objectives of this study were to determine if the prevalence and severity of sleep related symptoms distinguished CKD patients with OSA from those without apnea, and whether the clinical presentation of OSA in CKD patients differed from the general OSA population.

Methods: One hundred nineteen patients were recruited from outpatient nephrology clinics. All patients completed a sleep history questionnaire, the Epworth Sleepiness Scale (daytime sleepiness, ESS > 10), the Pittsburgh Sleep Quality Index (poor sleep quality, PSQI > 5), and underwent overnight cardiopulmonary monitoring for determination of sleep apnea (respiratory disturbance index ≥ 15). CKD patients with OSA (n = 46) were compared to (1) CKD patients without OSA (n = 73) and (2) OSA patients without CKD (n = 230) who were referred to the sleep centre.

Results: The prevalence of OSA symptoms and PSQI scores did not differ between CKD patients with OSA and CKD patients without apnea. Although the prevalence of daytime sleepiness was higher in CKD patients with OSA compared to CKD patients without apnea (39% vs. 19%, p = 0.033), both daytime sleepiness and other symptoms of sleep apnea were considerably less frequent than in OSA patients without a history of kidney disease.

Conclusions: The presence of OSA in patients with CKD is unlikely to be clinically apparent. Consequently, objective cardiopulmonary monitoring during sleep is required to reliably identify this comorbidity.

Keywords: Obstructive sleep apnea, chronic kidney disease, snoring, symptoms, daytime sleepiness

Citation: Nicholl DDM; Ahmed SB; Loewen AHS; Hemmelgarn BR; Sola DY; Beecroft JM; Turin TC; Hanly PJ. Clinical presentation of obstructive sleep apnea in patients with chronic kidney disease. J Clin Sleep Med 2012;8(4):381-387.
addressed these objectives by describing the clinical sleep profile of CKD patients with OSA and comparing this to CKD patients without OSA and to OSA patients without a history of kidney disease.

**METHODS**

**Patient Recruitment**

Adult patients (≥ 18 years) with CKD (as defined by an estimated glomerular filtration rate [eGFR] < 60 mL/min/1.73 m² according to the National Kidney Foundation Staging System) attending outpatient nephrology clinics were invited to participate in the study. eGFR at the time of the study visit was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. Exclusion criteria included current treatment with supplemental oxygen, tracheostomy, and inability to give informed consent. Patients currently treated with CPAP therapy were included in the study if their original diagnostic sleep study and sleep questionnaire were available for review and their eGFR at the time of OSA diagnosis was known. A control group of OSA patients without a history of kidney disease, but similar OSA severity (based on the respiratory disturbance index [RDI]), were referred to the Foothills Sleep Centre for suspected sleep apnea during the same time period were randomly selected from the clinical database. Selection was performed while blinded to other data from nocturnal cardiopulmonary monitoring, patient demographics, and symptoms. The study was approved by the University of Calgary Conjoint Health Research Ethics Board. Informed consent was obtained from all participants in accordance with the Declaration of Helsinki.

One hundred twenty-four CKD patients were recruited. Fifty-one met our criteria for a diagnosis of sleep apnea (RDI ≥ 15). Eight patients currently treated with CPAP were included in the study. Five patients with Cheyne-Stokes respiration (CSR) were excluded from further analyses. The remaining 46 CKD patients with OSA were first compared to the 73 CKD patients without OSA and then compared to 230 OSA patients without a history of kidney disease.

**Nocturnal Cardiopulmonary Monitoring**

Patients performed an unattended, overnight cardiopulmonary monitoring study at home (Remmers Sleep Recorder Model 4.2, Saga Tech Electronic, Calgary, AB, Canada). The monitor consists of an oximeter to record oxyhemoglobin saturation (SaO₂) and heart rate variability, a pressure transducer to record nasal airflow, a microphone to record snoring, and a body position sensor. The oximeter provides the data for an automated scoring algorithm, which calculates the RDI based on the number of episodes of oxyhemoglobin desaturation ≥ 4% per hour of monitoring. Nocturnal oxygen saturation was sampled at 1 Hz. The Remmers Sleep Recorder has been validated by comparison to attended polysomnography. We defined sleep apnea as an RDI ≥ 15 as this reflects moderate to severe sleep apnea which is likely to be clinically significant. The Remmers Sleep Recorder has a sensitivity of 98% and specificity of 88% for a designation criteria of RDI ≥ 15. The raw data were reviewed by a sleep medicine physician (PJH), blinded to patients’ kidney function and symptoms, who confirmed that the estimated RDI was accurate and determined whether apnea was central (CSR) or obstructive (OSA), based on the morphology of the airflow recordings. Nasal pressure recordings with a characteristic crescendo/descrescendo pattern and no evidence of airflow limitation were classified as CSR, whereas recordings without a crescendo/descrescendo pattern and with airflow limitation were classified as OSA.

**Subjective Measurements of Sleep Quality**

**Sleep History Questionnaire**

All patients completed a standardized sleep history questionnaire developed at Foothills Sleep Centre, which included a history of snoring, witnessed apnea during sleep and nocturnal choking, unrefreshing sleep, morning headaches, and memory impairment. Additionally, the questionnaire surveyed demographic information and medical history, including a history of obesity (body mass index [BMI] ≥ 30 kg/m²), hypertension, cardiovascular disease (angina, myocardial infarction, coronary artery bypass surgery, or congestive heart failure), cerebrovascular disease (stroke or transient ischemic attack), diabetes, chronic obstructive pulmonary disease (COPD), and medications.

**Daytime Sleepiness**

All patients completed the Epworth Sleepiness Scale (ESS). The ESS is a self-administered questionnaire designed to measure the general level of daytime sleepiness. Patients rate on a scale of 0-3 how likely they are to fall asleep in 8 different situations that are commonly encountered. Total ESS scores range from 0-24, with higher scores indicating more subjective daytime sleepiness. Specifically, an ESS score > 10 is considered indicative of subjective daytime sleepiness.

**Sleep Quality**

All CKD patients completed the Pittsburgh Sleep Quality Index (PSQI). The PSQI is a self-rated questionnaire that assesses sleep quality and disturbances over a 1-month time interval. Nineteen individual items generate 7 “component” scores: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medications, and daytime dysfunction. The sum of the seven component scores yields one global score, which ranges from 0-21. Higher scores indicate worse sleep quality, and PSQI global scores > 5 are considered indicative of poor sleep quality. PSQI data were not available for OSA patients without a history of kidney disease. All questionnaires were completed on the evening of overnight cardiopulmonary monitoring.

**Analysis**

Data are presented as mean ± standard deviation or number (percentage). CKD patients with OSA were initially compared to CKD patients without OSA, and secondly to OSA patients without a history of kidney disease. The unpaired t-test or the Mann-Whitney U-test was used for comparisons between continuous variables while the χ² test with Fischer exact test was used for dichotomous variables. Univariate and multivariate logistic regression models were used to identify
factors associated with OSA in CKD patients. Age, male
gender, comorbidities (obesity, hypertension, cardiovascular
disease, cerebrovascular disease, and diabetes), medications,
and sleep related symptoms were included in the model. All
model assumptions were tested and met. All statistical anal-
yses were 2-sided and performed with SPSS V.17.0 (SPSS,
Chicago, IL, USA). P-values < 0.05 were considered statisti-
cally significant.

**RESULTS**

**Chronic Kidney Disease: OSA versus No Apnea**

**Patient Characteristics**

The nocturnal cardiopulmonary monitoring findings and clinical
profile of CKD patients with and without OSA are shown in
Table 1. By definition, the RDI was higher in CKD patients
with OSA than in patients without sleep apnea. As expected,
the severity of associated nocturnal hypoxemia was greater in
CKD patients with OSA. Although CKD patients with OSA had
a higher prevalence of cardiovascular disease than those without
sleep apnea, they did not differ from non-apneic patients in
terms of gender, age, other comorbidities, or medication use.

**Sleep Related Symptoms**

Sleep related symptoms for all CKD patients are displayed in
Table 2. There were no differences in the prevalence of re-
ported snoring, witnessed apnea, nocturnal choking, unrefresh-
ing sleep, morning headaches, or memory impairment between
CKD patients with and without OSA. Although the mean ESS
was not different between groups, the proportion of patients
with an abnormal ESS score (ESS > 10) was greater in CKD
patients with OSA (39% versus 19%, p = 0.033). No differences
were observed between mean PSQI global scores or the propor-
tion of patients with an abnormal score (PSQI > 5).

On univariate analysis (Table 3), only obesity, cardiovascular
disease, and daytime sleepiness (ESS > 10) were associated
with OSA in CKD patients. Male gender and witnessed apneas
during sleep were of borderline significance. On multivariate
analysis, only male gender was significantly associated with
OSA in CKD patients.

**Obstructive Sleep Apnea: CKD versus No History of
Kidney Disease**

**Patient Characteristics**

The nocturnal cardiopulmonary monitoring findings and clinical
profile of OSA patients with CKD compared to those without a history of kidney disease are shown in Table 4. By study design, the RDI was similar between the two groups. However, the severity of associated nocturnal hypoxemia was greater in OSA patients with CKD than in OSA patients without a history of kidney disease. OSA patients with CKD were older and a greater proportion had hypertension and diabetes. However, there were no intergroup differences in

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**Table 1—Characteristics of chronic kidney disease patients, stratified by OSA status**

<table>
<thead>
<tr>
<th></th>
<th>All Patients</th>
<th>OSA</th>
<th>No Apnea</th>
<th>p-value*</th>
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<tr>
<td>N</td>
<td>119</td>
<td>46</td>
<td>73</td>
<td></td>
</tr>
<tr>
<td>Nocturnal monitoring</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RDI, /h</td>
<td>21.1 ± 25.1</td>
<td>43.3 ± 28.4</td>
<td>7.2 ± 3.8</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Mean SaO₂, %</td>
<td>91.5 ± 3.2</td>
<td>89.6 ± 3.3</td>
<td>92.7 ± 2.4</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>SaO₂ &lt; 90%, % monitoring time</td>
<td>22.6 ± 28.3</td>
<td>39.5 ± 30.3</td>
<td>11.9 ± 20.9</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Total monitoring time, h</td>
<td>7.2 ± 1.5</td>
<td>7.1 ± 1.7</td>
<td>7.3 ± 1.4</td>
<td>0.641</td>
</tr>
<tr>
<td>Reported sleep time, % monitoring time</td>
<td>81 ± 15</td>
<td>80 ± 16</td>
<td>81 ± 14</td>
<td>0.686</td>
</tr>
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<td>Demographics</td>
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<tr>
<td>Age, years</td>
<td>65 ± 12</td>
<td>67 ± 10</td>
<td>64 ± 13</td>
<td>0.277</td>
</tr>
<tr>
<td>Male</td>
<td>75 (63)</td>
<td>34 (74)</td>
<td>41 (56)</td>
<td>0.055</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>31.2 ± 8.3</td>
<td>34.0 ± 9.6</td>
<td>29.5 ± 6.8</td>
<td>0.004</td>
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<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
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<tr>
<td>Obesity</td>
<td>56 (47)</td>
<td>27 (59)</td>
<td>29 (40)</td>
<td>0.057</td>
</tr>
<tr>
<td>Hypertension</td>
<td>108 (91)</td>
<td>42 (91)</td>
<td>66 (90)</td>
<td>1.000</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>24 (20)</td>
<td>14 (30)</td>
<td>10 (14)</td>
<td>0.035</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>8 (7)</td>
<td>3 (7)</td>
<td>5 (7)</td>
<td>1.000</td>
</tr>
<tr>
<td>Diabetes</td>
<td>47 (39)</td>
<td>21 (46)</td>
<td>26 (36)</td>
<td>0.337</td>
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<td>COPD</td>
<td>6 (5)</td>
<td>3 (7)</td>
<td>3 (4)</td>
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<tr>
<td>Medications</td>
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</tr>
<tr>
<td>Sedatives</td>
<td>10 (8)</td>
<td>3 (7)</td>
<td>7 (10)</td>
<td>0.739</td>
</tr>
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<td>Antidepressants</td>
<td>5 (4)</td>
<td>3 (7)</td>
<td>2 (3)</td>
<td>0.373</td>
</tr>
</tbody>
</table>

Data are mean ± SD or number (percentage) of patients within group. OSA, obstructive sleep apnea; RDI, respiratory disturbance index; SaO₂, oxyhemoglobin saturation; BMI, body mass index; COPD, chronic obstructive pulmonary disease. *OSA versus No Apnea.
Sleep related Symptoms

Snoring, witnessed apnea, unrefreshing sleep, and morning headaches were reported less often by OSA patients with CKD than OSA patients without a history of kidney disease (Table 5). In addition, the prevalence of daytime sleepiness was lower in OSA patients with CKD than in OSA patients without a history of kidney disease (39% versus 63%, p = 0.005), though this result may be partly explained by selection bias since OSA patients with CKD were not referred for evaluation of sleep complaints.

DISCUSSION

The presence of OSA in patients with CKD was associated with only one of the traditional risk factors for sleep apnea, namely male gender. The prevalence of sleep related symptoms was lower in OSA patients with CKD than OSA patients without a history of kidney disease. More importantly, sleep related symptoms did not distinguish CKD patients with OSA from CKD patients without OSA.
Only two previous studies have evaluated the clinical presentation of OSA in non-dialysis-dependent CKD. Markou et al.\(^2\) reported a low prevalence of excessive daytime sleepiness (ESS > 10) of 11.4%, while the prevalence of snoring was found to be 40% in a cross-sectional study of 35 patients with CKD (eGFR = 26.8 mL/min/1.73 m\(^2\), 11-40). Their study was limited by a small sample size and they excluded patients with cardiovascular disease thereby limiting the generalizability of their findings as cardiovascular disease is a common comorbidity in this patient population.\(^1\) Roumelioti et al.\(^5\) reported a higher prevalence of excessive daytime sleepiness (ESS ≥ 10) of 29.3% in 89 CKD patients but used historical controls whose kidney function was undefined for comparison. Further, neither of these studies compared sleep related symptoms between CKD patients with OSA and non-apneic patients.

Our study addressed several of the limitations of these previous studies. First, we compared CKD patients with and without OSA. Second, our sample size was quite large, and all subjects were recruited from nephrology clinics, increasing the relevance of our findings to that patient population. Third, no inclusion or exclusion criteria were set with respect to age, gender, comorbidities, or medications, which improved the generalizability of our findings to the CKD population. In fact, our CKD population had a similar clinical profile to the Chronic Renal Insufficiency Cohort study.\(^2\)

The lack of excessive daytime sleepiness in a significant proportion of OSA patients with CKD has been reported in other

### Table 4—Characteristics of obstructive sleep apnea patients, stratified by chronic kidney disease status

<table>
<thead>
<tr>
<th></th>
<th>CKD</th>
<th>No CKD</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>46</td>
<td>230</td>
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</tr>
<tr>
<td><strong>Nocturnal monitoring</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>RDI, /h</td>
<td>43.3 ± 28.4</td>
<td>42.7 ± 12.5</td>
<td>0.888</td>
</tr>
<tr>
<td>Mean SaO(_2), %</td>
<td>89.6 ± 3.3</td>
<td>90.6 ± 2.7</td>
<td>0.052</td>
</tr>
<tr>
<td>SaO(_2) &lt; 90, % monitoring time</td>
<td>39.5 ± 30.3</td>
<td>30.1 ± 24.2</td>
<td>0.048</td>
</tr>
<tr>
<td>Total monitoring time, h</td>
<td>7.1 ± 1.7</td>
<td>7.0 ± 12.3</td>
<td>0.711</td>
</tr>
<tr>
<td>Reported sleep time, % monitoring time</td>
<td>80 ± 16</td>
<td>83 ± 13</td>
<td>0.268</td>
</tr>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>67 ± 10</td>
<td>51 ± 10</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Male</td>
<td>34 (74)</td>
<td>161 (70)</td>
<td>0.479</td>
</tr>
<tr>
<td>BMI, kg/m(^2)</td>
<td>34.0 ± 9.6</td>
<td>35.0 ± 8.2</td>
<td>0.544</td>
</tr>
<tr>
<td><strong>Comorbidities</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Obesity</td>
<td>27 (59)</td>
<td>156 (68)</td>
<td>0.297</td>
</tr>
<tr>
<td>Hypertension</td>
<td>42 (91)</td>
<td>129 (56)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>14 (30)</td>
<td>45 (20)</td>
<td>0.116</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>3 (7)</td>
<td>5 (2)</td>
<td>0.132</td>
</tr>
<tr>
<td>Diabetes</td>
<td>21 (46)</td>
<td>26 (11)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>COPD</td>
<td>3 (7)</td>
<td>41 (18)</td>
<td>0.075</td>
</tr>
<tr>
<td><strong>Medications</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sedatives</td>
<td>3 (7)</td>
<td>9 (4)</td>
<td>0.428</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>3 (7)</td>
<td>26 (11)</td>
<td>0.436</td>
</tr>
</tbody>
</table>

Data are mean ± SD or number (percentage) of patients within group. CKD, chronic kidney disease; RDI, respiratory disturbance index; SaO\(_2\), oxyhemoglobin saturation; BMI, body mass index; COPD, chronic obstructive pulmonary disease. *CKD versus No CKD.

### Table 5—Sleep-related symptoms of obstructive sleep apnea patients, stratified by chronic kidney disease status

<table>
<thead>
<tr>
<th></th>
<th>CKD</th>
<th>No CKD</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>46</td>
<td>230</td>
<td></td>
</tr>
<tr>
<td>Snoring, %</td>
<td>39 (85)</td>
<td>225 (98)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Witnessed apnea, %</td>
<td>16 (35)</td>
<td>179 (78)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Nocturnal choking, %</td>
<td>17 (37)</td>
<td>120 (52)</td>
<td>0.075</td>
</tr>
<tr>
<td>Epworth Sleepiness Scale</td>
<td>8.8 ± 5.2</td>
<td>12.2 ± 5.7</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Daytime Sleepiness (ESS &gt; 10), %</td>
<td>18 (39)</td>
<td>144 (63)</td>
<td>0.005</td>
</tr>
<tr>
<td>Unrefreshing sleep, %</td>
<td>19 (41)</td>
<td>192 (83)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Morning headaches, %</td>
<td>4 (9)</td>
<td>86 (37)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Memory impairment, %</td>
<td>23 (50)</td>
<td>143 (62)</td>
<td>0.248</td>
</tr>
</tbody>
</table>

Data are mean ± SD or number (percentage) of patients within group. CKD, chronic kidney disease; ESS, Epworth Sleepiness Scale. *CKD versus No CKD.
specific OSA populations, including those with stroke,10 heart failure,11 hypertension,12,13 and end-stage renal disease.14 There are a number of potential explanations for this observation that we can speculate on. First, it may reflect selection bias if the presence of sleep symptoms is not equally important in the recruitment of patients to the groups that are compared. Second, the complaint of subjective sleepiness may be overshadowed by other symptoms associated with chronic disease, such as anxiety or chronic fatigue, or side effects of their treatment such as medications. Third, the comorbid disease itself may hinder the development of excessive sleepiness through competing biologic mechanisms, such as augmented sympathetic activity in patients with chronic heart failure. Regardless of the explanation, the cumulative evidence indicates that daytime sleepiness is not a reliable diagnostic criterion for OSA in patients with many chronic medical disorders including CKD. Further, the absence of daytime sleepiness should not dissuade the clinician from considering a diagnosis of OSA in this patient population.

What are the clinical implications of our findings? OSA increases the risk of hypertension,10 cardiovascular,11 and cerebrovascular12 disease, all of which are important and highly prevalent complications of CKD.13 Further, OSA may also accelerate the deterioration of kidney function.14-20 As OSA can be effectively treated with CPAP therapy,21 it is important that this disorder be considered in this patient population and formally diagnosed. Male gender was the only significant predictor of OSA in our population of CKD patients. However, in conventional sleep medicine practice, the investigation of OSA is usually prompted by a constellation of sleep related symptoms including snoring, witnessed apneas during sleep, and daytime sleepiness, along with traditional risk factors for the disorder such as obesity and male gender.22 In our study, we found that we were unable to distinguish between CKD patients with OSA and CKD patients without OSA based solely on sleep related symptoms. Although the presentation of an obese male patient with CKD should prompt physicians to consider OSA, further clinical assessment for sleep apnea is unlikely to be helpful and objective cardio-pulmonary monitoring should be used to reliably diagnose the disorder.

Our study has limitations. First, the potential for selection bias exists as patients attending the nephrology clinics may have been more likely to participate if they suspected they had sleep apnea. We tried to limit the potential impact of this on our findings by emphasising that sleep related complaints were not required for recruitment. If such a bias did exist, it should have been reflected in a higher prevalence of sleep related symptoms in CKD patients with OSA which was not the case. Second, OSA patients with CKD were recruited differently than OSA patients with normal kidney function. Notwithstanding this difference, the primary purpose of describing the OSA group without kidney disease was to highlight the typical clinical stereotype of OSA, detected by the same methodology, and how infrequently CKD patients with OSA present in that way. Third, we did not objectively assess kidney function in OSA patients without a history of kidney disease. However, we were vigilant to ask all patients about kidney disease and excluded any whose history was suggestive of this.

Although male gender was the strongest predictor of OSA in patients with CKD, OSA is unlikely to be clinically apparent in this population. This is disconcerting, given the high prevalence of OSA in CKD and its potential impact on important clinical outcomes.1-7 Further studies are required to determine the validity and efficacy of OSA clinical prediction rules in patients with CKD. In the meantime, objective cardiopulmonary monitoring during sleep is required to reliably identify sleep apnea in this patient population.

REFERENCES


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Address correspondence to: Patrick J. Hanly, M.D., 1421 Health Sciences Centre, 3330 Hospital Drive NW, Calgary, Alberta, Canada; Tel: (403) 210-8694; Fax: (403) 283-6151; E-mail: phanly@ucalgary.ca

DISCLOSURE STATEMENT

An abstract for this study was presented at the annual meeting of the American Society of Nephrology in Philadelphia, PA, November 8-13, 2011. This was not an industry supported study. The authors have indicated no financial conflicts of interest.
Development of a Pregnancy-Specific Screening Tool for Sleep Apnea

Francesca L. Facco, M.D.1; David W. Ouyang, M.D.2; Phyllis C. Zee, M.D., Ph.D.3; William A. Grobman, M.D., M.B.A.1

1Northwestern University, Feinberg School of Medicine, Department of Obstetrics and Gynecology, Chicago, IL; 2NorthShore University HealthSystem, University of Chicago, Pritzker School of Medicine, Department of Obstetrics and Gynecology, Evanston, IL; 3Northwestern University, Feinberg School of Medicine, Department of Neurology, Chicago, IL.

Study Objective: The Berlin Questionnaire and Epworth Sleepiness Scale (ESS) are commonly used to screen for sleep apnea in non-pregnant populations. We sought to evaluate the Berlin and ESS in pregnancy and to determine whether an alternative screening approach could better detect sleep apnea in pregnant women.

Methods: Pregnant women at high risk for sleep apnea (women with chronic hypertension, pre-gestational diabetes, obesity, and/or a prior history of preeclampsia) completed a sleep survey composed of the Berlin and ESS, and participated in an overnight sleep evaluation with the WatchPAT100 (WP100), a wrist-mounted device designed to diagnose sleep apnea, defined as an apnea hypopnea index ≥ 5. Using multivariable statistics, demographic, clinical, and subjective symptoms that were independently associated with sleep apnea were determined and a prediction rule for the presence of sleep apnea was developed. The predictive capacity of this newly developed system was compared to that of the Berlin and ESS using receiver-operating curve (ROC) statistics.

Results: Of the 114 women who participated and had a valid WP100 study, 100 completed the Berlin and 96 the ESS. The Berlin and ESS did not accurately predict sleep apnea in this high-risk pregnancy cohort, with ROC area under the curves (AUC) of 0.54 (p = 0.6) and 0.57 (p = 0.3), respectively. Conversely, a model incorporating frequent snoring, chronic hypertension, age, and body mass index performed significantly better (AUC 0.86, p > 0.001).

Conclusion: The Berlin and ESS are not appropriate tools to screen for sleep apnea in high-risk pregnant women. Conversely, our four-variable model more accurately predicts sleep apnea in pregnancy.

Keywords: Pregnancy, sleep apnea screening

Citation: Facco FL; Ouyang DW; Zee PC; Grobman WA. Development of a pregnancy-specific screening tool for sleep apnea. J Clin Sleep Med 2012;8(4):389-394.

Sleep disordered breathing (SDB) describes a group of disorders characterized by abnormalities of respiration (e.g., pauses in breathing) or the quality of ventilation during sleep. Obstructive sleep apnea (OSA), the most common such disorder, is characterized by the repetitive collapse or partial collapse of the upper airway during sleep and the need to arouse to resume normal ventilation. The cardinal clinical manifestations of sleep apnea are loud and persistent snoring, bed partner-observed pauses in breathing, and excessive daytime sleepiness. OSA has clearly been linked to poor sleep and impaired daytime function, but there are also data linking OSA to other health outcomes, principally cardiovascular and metabolic disease.1-7

Pregnancy has been associated with several alterations in sleep and a high incidence of sleep disturbances.8 With regard to OSA, pregnancy-associated weight gain and fluid retention can lead to airway edema and increased airway resistance, which can result in snoring and OSA. This is particularly true for women who are overweight or obese (pre-pregnancy body mass index [BMI] ≥ 25), experience excessive weight gain during pregnancy, or suffer from excessive fluid retention during pregnancy (e.g., preeclampsia).8-10 The determination of whether a woman has sleep apnea is important, as this condition during pregnancy may be associated with an increased risk of gestational hypertension, gestational diabetes, preterm birth, and intrauterine growth restriction.11-14

Most studies examining sleep apnea in pregnancy have relied on a diagnosis made from subjective questionnaires (e.g., the Berlin Questionnaire and Epworth Sleepiness Scale [ESS]) that were designed for and validated in non-pregnant, predominantly male, middle-aged, and elderly populations.15 Indeed, there are some data suggesting that these tools are not as ac-
The objective of this study was to evaluate the performance of the Berlin and ESS in pregnancy, and to determine if an alternative screening algorithm could better detect sleep apnea in pregnant women.

**METHODS**

Women with singleton pregnancies at high risk for sleep apnea who were between 6 and 20 weeks of gestation were recruited at 2 university-affiliated hospitals. Women who were considered at high risk for sleep apnea were those with chronic hypertension (diagnosed prior to pregnancy), pre-gestational diabetes (type 1 or type 2), obesity (pre-pregnancy BMI ≥ 30), and/or a prior history of preeclampsia. All women were asked to complete a sleep survey, comprised of the Berlin and ESS, and to participate in an overnight at-home sleep evaluation with the Watch-PAT100 (WP100), a wrist-mounted, ambulatory device designed to diagnose sleep apnea.

The Berlin Questionnaire uses 10 self-administered questions about known risk factors for sleep apnea. The questions are grouped into 3 categories: Category 1 questions assess snoring behavior; Category 2 questions assess wake time sleepiness; and Category 3 questions assess for the presence of obesity (BMI ≥ 30) or chronic hypertension. Data from non-pregnant populations has demonstrated that a high-risk Berlin score has a sensitivity ranging from 68% to 86% and a specificity ranging from 46% to 95% for sleep apnea.

The ESS is used to assess daytime sleepiness symptoms, which are common among those with OSA. It consists of 8 questions regarding the tendency to fall asleep in certain situations (e.g., sitting and reading, sitting as a passenger in a car). ESS scores range from 0 to 24. Excessive daytime sleepiness is typically defined as a total score ≥ 10 or ≥ 12. Studies of sleep apnea in non-pregnant populations have shown that ESS scores are positively correlated with objective measures of sleep apnea.

Sleep apnea is diagnosed by measuring the total number of apneas (cessations of airflow) and hypopneas (reductions in airflow) per hour of sleep. An apnea-hypopnea index (AHI) ≥ 5 is diagnostic for sleep apnea. We used the Watch-PAT100 (WP100, Itamar Medical Ltd., Israel) to objectively assess for sleep apnea in this pregnant cohort (Figure 1). Several studies have shown that there is a significant correlation between the WP100 AHI and in-laboratory polysomnography evaluation, the gold standard for diagnosing sleep apnea. The WP100 measures peripheral arterial tone (PAT), oxygen saturation, pulse rate, and sleep duration (via actigraphy) continuously throughout the night. Apneas and hypopneas typically result in an increase in sympathetic tone, an increase in heart rate, and an oxygen desaturation; therefore, analysis of the WP100 signals allows for the determination of the AHI. WP100 studies were uploaded and an automated analysis was performed using zzz-PAT software scoring algorithms (version 4.0).

After informed consent was obtained, subjects were shown a brief video instructing them on the proper use of the WP100. They were then asked to wear the device for one night of home sleep and to complete the 2 sleep surveys (Berlin and ESS) either the night of, or the day following the sleep study. Pertinent demographic and clinical data were abstracted from the prenatal record.

Demographic and clinical characteristics of those with and without sleep apnea as determined by the WP100 were compared using the t-test and χ² test for continuous and categorical variables, respectively. The classification ability of the Berlin and the ESS with regard to the diagnosis of OSA were assessed with the area under the curve (AUC) derived from the receiver-operating characteristic curve (ROC). The questions of the Berlin were also individually analyzed to determine which, if any, accurately identified women with OSA. To develop a pregnancy specific prediction rule for sleep apnea, demographic, clinical, and subjective symptoms that were associated with sleep apnea with p values < 0.10 in univariable analysis were included as covariates in a multivariable logistic regression model, and those with p-values < 0.05 were retained in the final multivariable logistic regression model. A prediction model for the presence of OSA, using an integer-based score, was developed from the logistic regression model using a regression coefficient-based scoring method. Points were assigned to each predictor by multiplying the regression coefficient by 10 and rounding to the nearest integer. The area under the ROC of this scoring system was compared to that of the Berlin and ESS.

A test for screening or prediction should have an AUC ≥ 0.7. Therefore, using a β of 0.1, an α of 0.05, and assuming an estimated 30% prevalence of OSA in our high-risk population, 100 women were required for a statistically significant AUC of at least 0.7 to be detectable.

All analyses were performed using PASW 18.0 statistical software (SPSS Inc, Chicago, IL). The study was approved by the institutional review boards of Northwestern University and NorthShore University HealthSystem.

**RESULTS**

Of the 122 women who were recruited, 114 had a valid WP100 study; of these, 100 completed the Berlin and 96 completed the ESS. Mean (± standard deviation) gestational age at the time of the sleep study was 16.5 ± 3.7 weeks, and 28% of women had an AHI ≥ 5. The median AHI was 1.5 (interquartile range 0.5-6.0). Additional demographic and clinical characteristics of the 100 participants with a valid WP100 study and at least one screening survey, stratified by the diagnosis of OSA,
Women with OSA were older, had higher pre-pregnancy BMIs, were more likely to have chronic hypertension, and were less likely to have pre-gestational diabetes. Women with and without sleep apnea were equally as likely to have a positive Berlin score (39% vs. 32%, p = 0.49) and had similar ESS scores (7.5 ± 4.3 vs. 7.3 ± 4.5, p = 0.47). Both screening tests performed poorly with an AUC < 0.7: Berlin 0.54 (95% CI 0.41, 0.67, p = 0.6) and ESS 0.57 (95% CI 0.45, 0.70, p = 0.3). The Berlin had a sensitivity of only 39% (95% CI 22%, 59%) and a specificity of 68% (95% CI 56%, 78%). Similarly, an ESS score of ≥ 10 had 36% sensitivity (95% CI 19%, 57%) and 77% specificity (95% CI 66%, 86%). When we examined the individual Category 1 (snoring) and Category 2 (sleepiness) questions of the Berlin we found that only the snoring questions differentiated women with and without sleep apnea. Moreover, it was the frequency of snoring that was most differentiating. Women reporting frequent snoring (≥ 3 times per week) were > 4 times more likely to have an AHI ≥ 5 than those with less frequent or absent snoring (54% vs. 21%, OR = 4.4, 95% CI 1.4, 11.2).

Using the results of the univariable analysis (Table 1), a multivariable logistic regression analysis was performed that revealed that pre-pregnancy BMI, age, chronic hypertension, and frequent snoring were independent significant factors in the identification of OSA in this cohort of high-risk pregnant women. As described in the methods, a four variable-based prediction rule for the presence of sleep apnea was developed from the logistic regression model using a regression coefficient-based scoring method (Table 2). The β coefficients for frequent snoring and chronic hypertension were very similar (1.5 vs. 1.7); thus we simplified the scoring system by the changing

---

**Table 1—Subject characteristics**

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Entire cohort (N = 100)</th>
<th>AHI &lt; 5 (N = 72)</th>
<th>AHI ≥ 5 (N = 28)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall demographics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>33.0 ± 6.5 (range 17–45)</td>
<td>32.1 ± 6.8</td>
<td>35.4 ± 5.0</td>
<td>0.02</td>
</tr>
<tr>
<td>Pre-pregnancy BMI</td>
<td>31.9 ± 9.1 (range 16.1–63.0)</td>
<td>29.8 ± 8.6</td>
<td>37.1 ± 8.4</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>40%</td>
<td>40%</td>
<td>39%</td>
<td>0.9</td>
</tr>
<tr>
<td>Black</td>
<td>28%</td>
<td>26%</td>
<td>32%</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>17%</td>
<td>17%</td>
<td>18%</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>15%</td>
<td>17%</td>
<td>11%</td>
<td></td>
</tr>
<tr>
<td><strong>Clinical characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nulliparous</td>
<td>27%</td>
<td>25%</td>
<td>32%</td>
<td>0.47</td>
</tr>
<tr>
<td>Chronic hypertension</td>
<td>22%</td>
<td>13%</td>
<td>46%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Pre-gestational diabetes mellitus</td>
<td>54%</td>
<td>61%</td>
<td>36%</td>
<td>0.02</td>
</tr>
<tr>
<td>Pre-pregnancy BMI ≥ 30</td>
<td>56%</td>
<td>47%</td>
<td>79%</td>
<td>0.005</td>
</tr>
<tr>
<td>History of preeclampsia</td>
<td>23%</td>
<td>22%</td>
<td>25%</td>
<td>0.77</td>
</tr>
<tr>
<td><strong>Sleep characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive Berlin</td>
<td>34%</td>
<td>32%</td>
<td>39%</td>
<td>0.49</td>
</tr>
<tr>
<td>Berlin category 1 questions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Do you snore?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>58%</td>
<td>51%</td>
<td>75%</td>
<td>0.01</td>
</tr>
<tr>
<td>No</td>
<td>24%</td>
<td>32%</td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>Don’t Know</td>
<td>18%</td>
<td>17%</td>
<td>21%</td>
<td></td>
</tr>
<tr>
<td>Frequent snoring (≥ 3 nights/week)</td>
<td>30%</td>
<td>21%</td>
<td>54%</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>ESS data</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ESS score</td>
<td>7.5 ± 4.3 (range 0-19)</td>
<td>7.3 ± 4.5</td>
<td>8.0 ± 3.6</td>
<td>0.47</td>
</tr>
<tr>
<td>ESS ≥ 10</td>
<td>26%</td>
<td>23%</td>
<td>36%</td>
<td>0.19</td>
</tr>
<tr>
<td>ESS ≥ 12</td>
<td>18%</td>
<td>18%</td>
<td>16%</td>
<td>1.00</td>
</tr>
</tbody>
</table>

All data presented as mean ± standard deviation or %. ESS, Epworth sleepiness scale; AHI, apnea hypopnea index. *For ESS data N total = 96, 71 with AHI < 5, 25 with AHI ≥ 5.

**Table 2—Results of the multivariable prediction model for sleep apnea**

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Beta coefficient</th>
<th>Odds ratio</th>
<th>p value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequent snoring*</td>
<td>1.5</td>
<td>4.7</td>
<td>0.009</td>
<td>1.4, 14.7</td>
</tr>
<tr>
<td>Chronic hypertension**</td>
<td>1.7</td>
<td>5.3</td>
<td>0.006</td>
<td>1.6, 17.4</td>
</tr>
<tr>
<td>BMI</td>
<td>0.1</td>
<td>1.1</td>
<td>0.005</td>
<td>1.02, 1.2</td>
</tr>
<tr>
<td>Age</td>
<td>0.1</td>
<td>1.1</td>
<td>0.012</td>
<td>1.03, 1.2</td>
</tr>
</tbody>
</table>

*Referent category = snoring < 3 times/week. **Referent category = documented normotensive prior to pregnancy.
the score for chronic hypertension from 17 to 15, since this did not significantly alter the predictive capabilities of the model. Therefore, in this model, women receive 15 points if they report frequent snoring and another 15 points if they have chronic hypertension, and this sum is then added to the summation of their age and BMI. This model \([(15 \text{ if frequent snoring}) + (15 \text{ if chronic hypertension}) + \text{age} + \text{BMI}]\) had an AUC of 0.850 (95% CI 0.77, 0.93), p value in comparison against null hypothesis (AUC = 0.5) = < 0.001. It performed significantly better than the Berlin (p < 0.001) and ESS (p < 0.001) screening evaluations for OSA detection (Figure 2). The best discriminatory point, identified by the part of the ROC graph that was closest to the upper left corner, was a score of 75 (Table 3). OSA was identified in women who had a score greater than or equal to this value with a sensitivity of 86% (95% CI 66%, 95%) and a specificity of 74% (95% CI 62%, 83%).

Race did not meet the required p value in the univariate analysis and therefore was not included in our model; however, as a trial, it was added to the multivariate analysis. Race remained nonsignificant and did not alter the p values and odds ratios for the other 4 significant variables (data not shown).

**DISCUSSION**

In this prospective study we evaluated the performance of the Berlin and ESS as screening tools for sleep apnea in pregnancy. Our findings indicate that these screening tools are not reliable predictors of sleep apnea in high-risk pregnant women. Conversely, a simpler four-variable screening tool that includes self-reported frequent snoring, chronic hypertension, BMI, and age predicts sleep apnea with high sensitivity and specificity.

There are several possible reasons why the Berlin and ESS do not perform well in pregnancy. First, they both incorporate daytime sleepiness to differentiate individuals with and without OSA. While daytime sleepiness is a common symptom of sleep apnea in non-pregnant populations, it is a very common complaint during pregnancy even in women without OSA. Therefore, daytime sleepiness questions are not likely to be specific for sleep apnea in pregnancy. Second, the Berlin scoring algorithm uses BMI as a categorical variable (BMI ≥ 30), despite data that suggest a more linear relationship between BMI and OSA. For example, Young et al. found a four-fold increase in the prevalence of sleep apnea with each increase in the standard deviation (5.6 kg/m²) of the BMI. Our four-variable prediction model demonstrates that utilizing BMI as continuous variable significantly improves the ability to predict sleep apnea in pregnancy. Finally, age is not accounted for by either the Berlin or ESS. Yet epidemiological data demonstrate that sleep apnea prevalence increases steadily with age in midlife. Most studies that have evaluated the performance of the Berlin studied this instrument in older populations, which may lessen the importance of age as a relevant variable, given that the relationship between OSA and age attenuates for those older than 65.

There are data that support our findings regarding the poor predictive capacity of the Berlin in high-risk women. Olivarez et al. studied a group of women admitted to an antepartum service (the majority of whom had either chronic hypertension, pregnancy induced hypertension, or pre-gestational or gestational diabetes mellitus) and reported a sensitivity (35%) and specificity (64%) for the Berlin that were nearly identical to those found in our pregnant population. However, we recognize that the results of our study may not be generalizable to all pregnant women. The reliability of the Berlin and of our four-variable screening tool in a general or low-risk obstetrical population remains unknown and warrants further investigation. Regardless, the positive predictive values for all OSA screening tests will be significantly lower in such a population because there will be a lower prevalence of OSA.

We used an AHI 5 to define the presence of sleep apnea in our cohort. While this is the standard definition of sleep apnea, there remains a lack of consensus regarding which AHI value (i.e., what severity of sleep apnea) is most clinically relevant. In non-pregnant populations, an AHI ≥ 5 is considered abnormal, given the known association with cardiovascular and metabolic morbidity, although higher AHI levels are associated with an even greater frequency of adverse outcomes.

<table>
<thead>
<tr>
<th>Value</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 50</td>
<td>100.0% (84.9%, 100.0%)</td>
<td>9.7% (4.3%, 19.5%)</td>
<td>30.1% (21.2%, 40.6%)</td>
<td>100% (56.1%, 100%)</td>
</tr>
<tr>
<td>≥ 75</td>
<td>85.7% (66.4%, 95.3%)</td>
<td>73.6% (61.7%, 83.0%)</td>
<td>55.8% (40.0%, 70.6%)</td>
<td>93.0% (82.2%, 97.7%)</td>
</tr>
<tr>
<td>≥ 100</td>
<td>25.0% (11.4%, 45.2%)</td>
<td>96.6% (91.5%, 99.9%)</td>
<td>87.5% (46.7%, 99.3%)</td>
<td>77.2% (67.0%, 65.0%)</td>
</tr>
</tbody>
</table>

Table 3—Sensitivity, specificity, and positive and negative predictive values (PPV, NPV) for various cutoff values of our four-variable prediction rule
On the other hand, even AH1 values < 5 have been reported by some to be associated with the development of hypertension.4 Given the lack of full consensus and the existing data, an AH1 ≥ 5 was chosen for this study, given that it is a commonly accepted diagnostic threshold. If in the future, this threshold were to be changed, all screening tools would need to be evaluated anew. In addition, we focused our study on identifying SDB in early pregnancy and our findings may not be applicable to new-onset, third trimester SDB. Many studies have reported that SDB symptoms increase and pregnancy progress.19,31 However, as we have yet to define what is clinically significant SDB in pregnancy, it remains unclear if SDB that is only present in late pregnancy (i.e., new-onset SDB) is as clinically relevant as SDB that is present in early pregnancy and persists or worsens as pregnancy progresses. Future studies are needed to understand the impact of and how to best assess for new-onset SDB in late pregnancy.

It should be noted that other approaches for the objective measurement of OSA exist. The gold standard for documenting OSA is in-laboratory polysomnography (PSG), and the lack of full PSG assessment of AH1 in our cohort is certainly a limitation of this study. Unfortunately, the expense and burden of this testing limits its utility. The cost and complexity of in-laboratory PSG have led to the development of simpler diagnostic techniques for sleep apnea, such as the WP100 device. The WP100 does not measure ventilation during sleep directly, but instead generates an AH1 by analyzing heart rate accelerations, increases in peripheral arterial tone, and decreases in oxygenation, all of which are associated with apneic and hypopneic events. The WP100 allows for home recordings, which, in addition to significantly lower costs, are less likely to be hampered by changes in environmental factors (i.e., bed comfort, noise, temperature) that are inevitably encountered when studying a patient in a sleep-laboratory setting. Studies in non-pregnant populations have shown that the respiratory indices, which such as the AH1, derived from the WP100 are strongly correlated with those obtained from PSG (r = 0.90), and have also demonstrated that the WP100 is an accurate and reliable ambulatory method for the detection of sleep apnea.23-25,32 It is well established that certain biological parameters measured by the WP100 are altered in pregnancy. Specifically, resting heart rate is known to increase while systemic vascular resistance decreases. However, the algorithm for scoring WP100 events takes into consideration that every individual, pregnant or not, has a different baseline heart rate and peripheral arterial tone and therefore, events are scored when there is a change in baseline (increase in heart rate, increase in peripheral arterial tone).32 Pulse oximetry and actigraphy measures, also used by the Watch-PAT, should not be different when measured in pregnancy. Therefore we believe that there is no good biologic foundation to suggest that the objective measures of the WP100 will correlate less well with PSG measures just because a woman is pregnant. Moreover, O’Brien et al. recently presented data comparing Watch-PAT to full PSG in pregnant subjects. Their results indicate that among pregnant women, WP AH1 correlated very well with PSG AH1(r = 0.76, p < 0.0001) and that the WP has excellent sensitivity (88%) and specificity (86%) for identification of SDB (AH1 ≥ 5).33 Future studies, using alternative objective assessments of sleep apnea, AH1 cutoff values, and patient populations, to reevaluate the

### REFERENCES


ACKNOWLEDGMENTS
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Address correspondence to: Francesca Facco, M.D., Northwestern University, Prentice Women’s Hospital, 250 East Superior Street, Suite 05-2175, Chicago, IL 60611; Tel: (312) 472-4671; E-mail: faccof@upmc.edu

DISCLOSURE STATEMENT
Presented as a poster at the 31st annual Society for Maternal-Fetal Medicine Annual Meeting, San Francisco, CA, February, 2011. This was not an industry supported study. The authors have indicated no financial conflicts of interest.
The purpose of fast-track programs in surgery is to enhance postoperative recovery. Fast-track programs usually involve modalities to optimize preoperative conditions, including the provision of detailed information about the cause of events peri- and postoperatively. In the operative period, the use of regional anesthesia and minimally invasive surgery are advocated. Multimodal pain control, antiemetic prophylaxis, early mobilization, and enteral nutrition are encouraged. Fast-track programs almost unanimously recommend use of opioid-free or opioid-reduced multimodal analgesia postoperatively.

One of the most prevalent postoperative symptoms following hysterectomy is disturbed sleep. Postoperative sleep disturbances may affect mood, resulting in decreased vigor and an increase in the subjective feeling of sleepiness and fatigue. Thus, postoperative sleep disturbance may be an important factor for postoperative recovery and consequently an important issue to be considered in programs to enhance postoperative recovery. However, fast-track programs seldom include concepts to improve sleep postoperatively; it was only recently that Krenk et al. suggested that prophylactic intervention to improve sleep architecture be included in fast-track methodology.

The impact of surgery and anesthesia on postoperative sleep after hysterectomy in a fast-track setting has not been carefully investigated. Hysterectomy is disturbed sleep. 2 Postoperative sleep disturbances are an important factor for recovery and consequently an important issue to be considered in programs to enhance postoperative recovery. However, fast-track programs seldom include concepts to improve sleep postoperatively. 

Study Objectives: To examine the impact of mode of anesthesia on perceived quality of sleep and to analyze the perceived quality of sleep in affecting recovery from surgery.

Methods: A randomized, controlled, open multicenter trial was conducted in 5 hospitals in Southeast Sweden. One-hundred eighty women scheduled for fast-track abdominal hysterectomy for benign conditions were randomized to spinal anesthesia or general anesthesia; 162 women completed the trial; 82 allocated to spinal anesthesia and 80 to general anesthesia. Symptoms and perceived quality of sleep after surgery were registered daily in the Swedish Postoperative Symptoms Questionnaire.

Results: Women in the general anesthesia group experienced bad quality of sleep the night after surgery significantly more often than the women who had spinal anesthesia (odds ratio [OR] 2.45; p = 0.03). This was almost exclusively attributed to a significantly higher consumption of opioids postoperatively in the general anesthesia group. Risk factors for bad quality of sleep during the first night postoperatively were: opioids (OR 1.07; p = 0.03); rescue antiemetics (OR 2.45; p = 0.05); relative weight gain (OR 1.47; p = 0.04); summary score of postoperative symptoms (OR 1.13; p = 0.02); and stress coping capacity (OR 0.98; p = 0.01). A longer hospital stay was strongly associated with a poorer quality of sleep the first night postoperatively (p = 0.002).

Conclusions: The quality of sleep the first night after abdominal hysterectomy is an important factor for recovery. In fast-track abdominal hysterectomy, it seems important to use anesthesia and multimodal analgesia reducing the need for opioids postoperatively and to use strategies that diminish other factors that may interfere negatively with sleep. Efforts to enhance quality of sleep postoperatively by means of preventive measures and treatment of sleep disturbances should be included in fast-track programs.

Clinical Trial Information: The study was registered in ClinicalTrials.gov Protocol Registration System (NCT00527332) with initial release September 7, 2007.

Keywords: Abdominal hysterectomy, fast track, general anesthesia, quality of sleep, postoperative recovery, spinal anesthesia

Citation: Kjaelhede P; Langstrom P; Nilsson P; Wodlin NB; Nilsson L. The impact of quality of sleep on recovery from fast-track abdominal hysterectomy. J Clin Sleep Med 2012;8(4):395-402.

BRIEF SUMMARY

Current Knowledge/Study Rationale: Surgery may cause significant sleep disturbances that may influence the postoperative recovery. This study sought to evaluate the impact of mode of anesthesia on perceived quality of sleep postoperatively and to analyze the perceived quality of sleep in affecting recovery after abdominal hysterectomy in a fast-trace program.

Study Impact: Perceived quality of sleep was significantly better after spinal anesthesia mainly due to the significantly lower need of opioids postoperatively. The quality of sleep is an important factor for postoperative recovery and efforts to enhance quality of sleep postoperatively by means of prevention and treatment of sleep disturbances should consistently be included in fast-trace programs.
studied. Surgery has been shown to cause circadian disturbances on several levels, including a disrupted sleep pattern. A substantial decrease in REM sleep occurs on the first postoperative night, followed by a profound rebound phenomenon on the second to fourth postoperative night, when REM sleep increases in both intensity and amount. Opioid use, whether acute (as when used postoperatively) or chronic, has been associated with abnormal sleep architecture. Gögenur et al. found that the subjective quality of sleeping was significantly worse during the first 4 days postoperatively after abdominal surgery. This might indicate that this period is the most important if sleep disturbance is to have an impact on postoperative recovery. Although Rosenberg-Adamsen et al. concluded that general anesthesia per se is not an important factor for sleep disturbance postoperatively when comparing general and regional anesthesia, the studies to which they referred used different anesthetic agents. In addition, their studies were not conducted on fast-track programs.

METHODS

This open, controlled, randomized multicenter study compared general anesthesia and spinal anesthesia in fast-track abdominal hysterectomy for benign conditions (the “GASPI study”) with focus on postoperative recovery. The trial showed a significantly better outcome for patients given spinal anesthesia, with fewer perceived symptoms postoperatively, faster recovery of quality of life, and shorter sick leave. In addition, the consumption of opioids was significantly lower in the spinal group, almost 5-fold lower on the first postoperative day. Based on these results and applying the philosophy of the fast-track concept, we hypothesized that women having abdominal hysterectomy for benign conditions conducted in spinal anesthesia perceive the quality of sleep postoperatively as being better than do women who have had a hysterectomy carried out under general anesthesia.

The aims of this secondary post hoc analysis of the GASPI study were to examine the impact of mode of anesthesia on perceived quality of sleep and to analyze the perceived quality of sleep in affecting recovery from surgery.

Fast-Track Program

The fast-track program is described in Figure 1.

Anesthesia

Both modes of anesthesia were standardized. In summary, general anesthesia was based on propofol 1-2 mg/kg given for induction, followed by a maintenance dose of 6-10 mg/kg/h given continuously as intravenous (IV) infusion. The patients were intubated after fentanyl 0.1-0.2 mg and rocuronium 0.6 mg/kg were administered and ventilated with oxygen in air. Rocuronium and fentanyl were repeated during anesthesia when the attending anesthetist saw they were needed. Twenty minutes before completing surgery 5 mg morphine was given IV.

The spinal anesthesia was administered using a 25-gauge needle in the L3/L4 or L2/L3 intervertebral space. The anesthetic consisted of 20 mg hyperbaric bupivacaine (5 mg/mL) and 0.2 mg morphine (0.4 mg/mL). Fifteen minutes after administration of anesthesia, the level of the neural blockade was determined with a cold test and registered. The patients were sedated throughout the operation with a continuous IV infusion of propofol 2-5 mg/kg/h. The patient received general anesthesia according to the protocol described above if the spinal anesthesia was insufficient for the surgery.

Surgery

Modes of skin incision and hysterectomy were decided on by the gynecologist prior to randomization. The hysterectomy was performed as a standard extrafascial hysterectomy according to the principles described by Thompson.

Postoperative Care

After surgery, the patient was transferred to the post anesthesia care unit (PACU) for postoperative monitoring of hemodynamic and respiratory stability, degree of sedation, pain, and nausea. When the vital signs were stable and the patient was awake, she was discharged from PACU to the gynecological ward where the monitoring was continued. Provided that measures were within clinically normal limits, the monitoring was registered once every hour for 12 h, then once every third hour until 24 h after surgery. The monitoring was identical after both modes of anesthesia. Mobilization was initiated in PACU and actively encouraged in the ward. Similarly, eating and drinking were recommended as soon as possible after surgery. The patient was discharged from the hospital when the standardized criteria for discharge were obtained (Figure 1).

Clinical data including data on complications were collected continuously during hospital stay and at the follow-up visit 5 weeks postoperatively. Duration of hospital stay was defined as the time from start of anesthesia to the time the patient left the hospital.

Assessment of Postoperative Symptoms

Postoperative symptoms were assessed by the Swedish Postoperative Symptoms Questionnaire (SPSQ). The patient completed the form on a daily basis, preferably in the evening during the first 7 days postoperatively, starting in the evening after surgery (day 0) and thereafter once weekly until the 5-week postoperative visit. The questions were both open-ended and closed-ended. The closed-ended questions could be answered.
Quality of Sleep and Fast Track Abdominal Hysterectomy

**Figure 1—Summary of the fast-track program and anesthesia**

**Preoperatively**

Thorough information concerning care, anesthesia, surgery, and criteria for discharge. Clear fluids orally until 2 h before surgery. Two g paracetamol were given orally one hour before surgery. No use of sedatives. Acupressure wrist bands, applied preoperatively and maintained throughout hospital stay, were used as preemptive antiemetic therapy. Antibiotic and antithrombotic prophylaxes were given according to department routine.

**Perioperatively**

Spinal anesthesia in intervertebral space L3/L4 or L2/L3 with hyperbaric bupivacaine 20 mg and morphine 0.2 mg intrathecally. Sedation with propofol.

General anesthesia induced with propofol, fentanyl and rocuronium, and maintained with propofol and oxygen in air. Rocuronium and fentanyl repeated when needed. Orogastric tube during surgery. Twenty minutes before ending the operation 5 mg morphine applied iv.

Fenylephrine used to treat hypotension if systolic blood pressure decreased > 30% from the baseline.

40 ml Bupivacaine (2.5mg/ml) injected subcutaneously and pre-fascially in the abdominal wall at concluding surgery.

The total amount of intravenous fluids aimed at 25 ml/kg on day of surgery.

Transurethral catheter inserted before start of surgery and left until the next morning.

**Postoperatively**

Patient transferred to PACU after surgery. Pain management with 1,330 mg paracetamol and 50 mg diclofenac initiated 3 times daily. Rescue pain management with morphine IV or orally offered if VAS score > 3 (VAS 0-10), but opioids avoided if possible.

Rescue antiemetic treatment with droperidol and if necessary combined with 5-HT<sub>r</sub> receptor antagonist.

Patient encouraged to drink and eat as soon as possible and actively mobilized.

Patient discharged to the gynecological ward when vital signs were stable. In the gynecological ward, monitoring of hemodynamic and respiratory stability, sedation, pain, and nausea once every hour during first 12 hours postoperatively, then once every third hour for another 12 hours.

**Standardized criteria of discharge**: the patient was mobilized, tolerated normal diet, had sufficient pain relief with oral analgesics (VAS ≤ 4), had voided spontaneously with < 150 mL residual urine (measured by a portable bladder ultrasound scan) and showed no signs of mechanical bowel obstruction or other postoperative complications. If the patient had insufficient bladder emptying at discharge the patient received a transurethral bladder catheter for another couple of days.

*5-HT<sub>r</sub>*; 5-hydroxytryptamine type 3; IV, intravenous; PONV, postoperative nausea and vomiting; PACU, post anesthesia care unit; VAS, visual analogue scale.

by choosing an answer from a set given on a Likert-type scale. The open-ended questions required written responses. The patient was initially asked if she at the moment of completing the form experienced a number of symptoms commonly reported after surgery (pain in the area of surgery, nausea, retching, headache, abdominal pain, tiredness, drowsiness, and blurred vision) and how she rated the intensity of each of these symptoms. The answers were rated on a 4-point scale: “none” (0), “yes, a little” (1), “yes, somewhat” (2), and “yes, a lot” (3). To estimate overall discomfort from the symptoms at the moment of completing the form, a sum score was calculated. The minimum sum score was zero and maximum 24. The higher the sum score, the greater the discomfort experienced. In order to obtain information about the quality of sleep postoperatively, we added the question in the SPSQ: How did you sleep during the recent night? The options for the answers were: “Excellent,” “Neither well nor badly,” and “Badly.”

**Assessment of Stress Coping Capacity**

The capacity to cope with stress was measured approximately 1 week preoperatively by the Stress Coping Inventory (SCI). The respondent rates how often she thinks she is able to cope with each of the 41 stressful situations described in the SCI form. The answers are rated on a 6-point Likert-type scale, ranging from “almost never” (1), “rarely” (2), “occasionally” (3), “rather often” (4), “very often” (5) to “almost always” (6). The minimum sum score is 41 and the maximum 246. The higher the SCI sum score, the greater the stress coping capacity. The SCI sum score was first calculated after termination of the study and thus blinded for the participant, staff, and investigators during the study period.

**Sick Leave**

At discharge from the hospital the patient was granted sick leave for 14 days. The research nurse contacted the patient by telephone the day after discharge and then once weekly until the visit 5 weeks postoperatively. At these contacts, the sick leave was prolonged by ≤ 7 days at a time until the patient considered she was able to return to work or felt sufficiently recovered. Duration of sick leave was defined as the time from the day of surgery to the day of return to work to the same extent as preoperatively. Women, who were on sick leave for reasons other
than the hysterectomy, were unemployed, or had disability pension were excluded from the analysis of sick leave.

Statistics

Power calculation and estimation of sample size were based on the primary outcome measure of the trial, duration of hospital stay, and have previously been described.9 No power calculations were done a priori for the secondary outcomes. The analyses were conducted according to the intention-to-treat principles.

Data are presented as mean and one standard deviation (SD) or as number and frequency (%). Univariate analyses were conducted by means of nonparametric tests (Mann-Whitney U-test and Yates corrected χ² test, as appropriate). Level of significance was set at 5%.

Factors associated with the perceived quality of sleep were analyzed by means of multiple logistic regression models. Adjustments were carried out simultaneously for factors known to be confounding factors of sleep disorders: age, BMI, mode of hysterectomy (surgical stress, i.e., extent of surgery), stay in PACU after midnight for monitoring, interval of monitoring of vital signs, and SCI sum scores. Subsequently, other factors were added one by one separately as potential confounders in order to analyze whether they were independent risk factors for perceived bad quality of sleep. Results are reported as odds ratio (OR) and 95% confidence interval (CI).

Analysis of covariance (ANCOVA) models were used to investigate associations between outcome measures and perceived quality of sleep the first night after surgery. For the analysis of association between duration of hospital stay and quality of sleep, adjustments were performed simultaneously for the confounders depicted above and for the SPSQ sum score and the occurrence of complications during hospital stay. For the analysis of duration of sick leave, complications occurring perioperatively and during a 5-week period postoperatively were added as independent factors, as was the physical work load. Subsequent post hoc analyses were done with Fisher protected least significant difference (PLSD).

Data were processed in the software StatView for Windows, Version 5.0.1 (SAS Institute Inc., SAS Campus Drive, Cary, NC, USA).

RESULTS

Demographic and descriptive data are presented in Table 1. The preoperative data were well balanced between the 2 groups, showing that the randomization process worked well. The clinical data and the outcome measures shown in Table 2 differed significantly in many aspects, often in favor of the SA group.

The self-reported perceived quality of sleep for the first 5 nights postoperatively is presented in Table 3. Significantly more women in the GA group reported that they slept badly the first night after surgery compared with women who had the operation in SA. This difference was almost exclusively attributed to the amount of opioids given postoperatively until the next morning. When adjusted for the amount of opioids, there was no statistical difference in the proportion of women who reported that they slept badly the first night between the GA and SA groups (OR 0.84; 95% CI 0.25-2.89; p = 0.79). The amount of opioids given postoperatively was an independent risk factor for experiencing bad quality of sleep the first night postoperatively (OR 1.07; 95% CI 1.01-1.14; p = 0.03). However, the statistically significant difference in quality of sleep between the 2 groups remained when adjustments were made for the fentanyl

Table 1—Demographic and descriptive data

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>General anesthesia (n = 80)</th>
<th>Spinal-morphine anesthesia (n = 82)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>45.5 ± 5.7</td>
<td>46.0 ± 5.7</td>
<td>0.57</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>26.3 ± 5.2</td>
<td>26.4 ± 4.3</td>
<td>0.57</td>
</tr>
<tr>
<td>Parity</td>
<td>2.0 ± 1.1</td>
<td>1.9 ± 1.3</td>
<td>0.30</td>
</tr>
<tr>
<td>Smokers</td>
<td>16 (20.0%)</td>
<td>13 (15.9%)</td>
<td>0.63</td>
</tr>
<tr>
<td>Physical work load (no. of women)†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sedentary</td>
<td>19 (26%)</td>
<td>34 (44%)</td>
<td>0.07</td>
</tr>
<tr>
<td>Medium</td>
<td>25 (34%)</td>
<td>21 (27%)</td>
<td></td>
</tr>
<tr>
<td>Heavy</td>
<td>30 (40%)</td>
<td>23 (29%)</td>
<td></td>
</tr>
<tr>
<td>SCI sum score</td>
<td>183.4 ± 23.3</td>
<td>186.2 ± 28.1</td>
<td>0.53</td>
</tr>
<tr>
<td>ASA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class I</td>
<td>59 (73.7%)</td>
<td>55 (67.1%)</td>
<td>0.45</td>
</tr>
<tr>
<td>Class II</td>
<td>21 (26.3%)</td>
<td>27 (32.9%)</td>
<td></td>
</tr>
<tr>
<td>Mode of hysterectomy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total abdominal</td>
<td>55 (68.8%)</td>
<td>51 (62.2%)</td>
<td>0.48</td>
</tr>
<tr>
<td>Subtotal abdominal</td>
<td>25 (31.2%)</td>
<td>31 (37.8%)</td>
<td></td>
</tr>
<tr>
<td>Mode of skin incision</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Midline</td>
<td>6 (7.5%)</td>
<td>7 (8.5%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Low transverse</td>
<td>74 (92.5%)</td>
<td>75 (91.5%)</td>
<td></td>
</tr>
</tbody>
</table>

Figures denote mean and one standard deviation or number and (%). †Information on physical work load was not obtained from all participants. *Univariate analysis. Mann-Whitney U-test or Yates corrected χ² test. ASA, the American Society of Anesthesiologist classification of physical status; SCI, Stress Coping Inventory.
Given perioperatively. In addition, fentanyl seemed to be an independent if weak protective factor for good quality of sleep (OR 0.02; 95% CI 0.00-0.90; p = 0.04). The use of a rescue antiemetic was also an independent risk factor for bad quality of sleep (OR 0.02; 95% CI 0.00-0.90; p = 0.04). The use of a rescue antiemetic was also an independent risk factor for bad quality of sleep even when adjusted for the use of opioids (OR 0.02; 95% CI 0.00-0.90; p = 0.04). Similarly, relative body weight gain on day 0 was a risk factor for bad quality of sleep in the night after surgery (OR 1.47; 95% CI 1.02-2.10; p = 0.04).

The SPSQ symptom sum scores measured day-by-day for the first 5 days postoperatively were concurrently statistically significantly associated with bad quality of sleep, even when adjusted for daily use of opioids. (OR Day 0 1.13; 95% CI 1.02-1.24; p = 0.02. OR Day 1 1.18; 95% CI 1.04-1.35; p = 0.01. OR Day 2 1.23; 95% CI 1.10-1.49; p = 0.001. OR Day 3 1.44; 95% CI 1.17-1.77; p = 0.0005. OR Day 4 1.57; 95% CI 1.23-2.00; p = 0.0003.)

None of the following variables were significantly associated with the quality of sleep the first night after surgery (data not shown): propofol, rocuronium, phenylephrine, administration of anesthesia that differed from the anesthesia specified in the protocol due to an initial effect insufficient for surgery, use of anti-pruritus medication, operating and anesthesia time, time in PACU, and intravenously given fluid perioperatively.

Of the confounding factors used in the multivariate models, only the SCI sum score was found to be an independent risk factor for occurrence of sleep of bad quality (OR 0.98; 95% CI 0.96-0.99; p = 0.01).

The ANCOVA models revealed that the quality of sleep the first night was strongly associated with duration of hospital stay ($F_{2,157} = 6.695; p = 0.002$) (Figure 2). Excellent quality of sleep was associated with a significantly shorter stay in hospital.

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**Table 2—Clinical data and outcome measures**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>General anesthesia (n = 80)</th>
<th>Spinal-morphine anesthesia (n = 82)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anesthesia differs from protocol due to insufficient effect for surgery (no. of women)</td>
<td>5 (6.3%)</td>
<td>8 (8.8%)</td>
<td>0.59</td>
</tr>
<tr>
<td>Estimated bleeding volume perioperatively (mL)</td>
<td>236 ± 382</td>
<td>190 ± 207</td>
<td>0.55</td>
</tr>
<tr>
<td>Operating time (minutes)</td>
<td>82.9 ± 31.0</td>
<td>76.6 ± 28.0</td>
<td>0.12</td>
</tr>
<tr>
<td>Time of anesthesia (min)</td>
<td>127 ± 34</td>
<td>120 ± 30.5</td>
<td>0.24</td>
</tr>
<tr>
<td>Time in PACU (h)</td>
<td>4.7 ± 2.6</td>
<td>3.9 ± 1.9</td>
<td>0.003</td>
</tr>
<tr>
<td>Remaining in PACU after midnight</td>
<td>2 (2.5%)</td>
<td>1 (1.2%)</td>
<td>0.62</td>
</tr>
<tr>
<td>Monitoring once/hour ongoing after midnight (no. of women)</td>
<td>39 (48.8%)</td>
<td>35 (42.7%)</td>
<td>0.54</td>
</tr>
<tr>
<td>Propofol (mg)</td>
<td>1257 ± 556</td>
<td>438 ± 278</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Fentanyl (mg)</td>
<td>0.3 ± 0.1</td>
<td>0.0 ± 0.1</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Rocuronium (mg)</td>
<td>60.3 ± 18.6</td>
<td>3.5 ± 12.8</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Phenylephrine (µg)</td>
<td>144 ± 343</td>
<td>884 ± 928</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Equivalent morphine dose (mg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 0</td>
<td>20.2 ± 9.1</td>
<td>4.0 ± 6.2</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Day 1</td>
<td>4.7 ± 7.8</td>
<td>2.5 ± 6.3</td>
<td>0.006</td>
</tr>
<tr>
<td>Day 2</td>
<td>1.8 ± 3.3</td>
<td>1.3 ± 4.1</td>
<td>0.02</td>
</tr>
<tr>
<td>Day 3</td>
<td>1.4 ± 3.0</td>
<td>0.8 ± 2.5</td>
<td>0.04</td>
</tr>
<tr>
<td>Day 4</td>
<td>0.9 ± 2.5</td>
<td>0.7 ± 2.5</td>
<td>0.19</td>
</tr>
<tr>
<td>Receiving rescue antiemetics (no. of women)</td>
<td>45 (56.3%)</td>
<td>44 (53.7%)</td>
<td>0.86</td>
</tr>
<tr>
<td>Receiving anti-pruritus medication (no. of women)</td>
<td>1 (1.3%)</td>
<td>33 (40.2%)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Relative body weight gain on Day 0 (%)</td>
<td>0.4 ± 1.3</td>
<td>0.6 ± 1.2</td>
<td>0.30</td>
</tr>
<tr>
<td>IV fluid perioperatively (mL)</td>
<td>1615 ± 989</td>
<td>1424 ± 495</td>
<td>0.25</td>
</tr>
<tr>
<td>Complications during hospital stay (no. of women)</td>
<td>9 (11.3%)</td>
<td>7 (8.5%)</td>
<td>0.75</td>
</tr>
<tr>
<td>Complications within five weeks (no. of women)</td>
<td>19 (23.8%)</td>
<td>22 (26.8%)</td>
<td>0.79</td>
</tr>
<tr>
<td>SPSQ symptom sum score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 0</td>
<td>10.7 ± 3.6</td>
<td>8.1 ± 5.1</td>
<td>0.0001</td>
</tr>
<tr>
<td>Day 1</td>
<td>7.7 ± 3.8</td>
<td>5.8 ± 3.5</td>
<td>0.002</td>
</tr>
<tr>
<td>Day 2</td>
<td>5.5 ± 3.2</td>
<td>5.4 ± 3.6</td>
<td>0.58</td>
</tr>
<tr>
<td>Day 3</td>
<td>5.2 ± 3.0</td>
<td>4.8 ± 2.9</td>
<td>0.43</td>
</tr>
<tr>
<td>Day 4</td>
<td>4.7 ± 2.8</td>
<td>4.3 ± 2.8</td>
<td>0.37</td>
</tr>
<tr>
<td>Duration of hospital stay (hours)</td>
<td>48.3 ± 16.6</td>
<td>45.8 ± 20.4</td>
<td>0.16</td>
</tr>
<tr>
<td>Duration of sick leave (days)</td>
<td>28.9 ± 12.7</td>
<td>26.2 ± 28.9</td>
<td>0.006</td>
</tr>
</tbody>
</table>

Figures denote mean and one standard deviation or number and (%). *Univariate analysis. Mann-Whitney U-test or Yates corrected $\chi^2$ test. Day 0 indicates time from surgery to the next morning 07:00. Day 1 indicates time from 07:00 to 07:00 the next day, etc. ASA, the American Society of Anesthesiologist classification of physical status; PACU, post anesthesia care unit; SCI, Stress Coping Inventory; SPSQ, Swedish Postoperative Symptom Questionnaire.
(42 ± 16 h) compared with 54 ± 10 h for those who perceived bad quality of the sleep. No such association was observed concerning duration of sick leave ($F_{2,143} = 1.667; p = 0.19$). The p-values of the Fisher PLSD post hoc tests are shown in Figure 2.

DISCUSSION

The study demonstrated that sleep the first night postoperatively is an important quality to be given careful consideration even in fast-track program, as it affects the postoperative recovery substantially. Abdominal hysterectomy under spinal anesthesia offered significantly better quality of sleep than did general anesthesia, which led to a significantly shorter stay in the hospital. However, this effect was almost exclusively attributed to a significantly lower consumption of opioids postoperatively in the spinal anesthesia group. As shown in this study, quality of sleep after surgery is a feature that influences the recovery. Many factors, some of which can be treated or interfered with, seem to be associated with this phenomenon in fast-track abdominal hysterectomy.

There are some methodological concerns in this study. The study was not powered to detect differences in secondary outcome measures, and the study should therefore be seen as exploratory and hypothesis generating. There is a lack of baseline information about quality of sleep, and thus no adjustment has been made to account for baseline differences. Additionally, the study was not powered to detect differences in secondary outcome measures, and the study should therefore be seen as exploratory and hypothesis generating. There is a lack of baseline information about quality of sleep, and thus no adjustment has been made to account for baseline differences.
been made for this obvious potential confounder. However, the study was randomized and the allocation showed even distribution between the two groups for all other investigated preoperative variables, including psychological and quality of life measurements. We therefore find it less likely that baseline quality of sleep would be unevenly distributed between the two groups. The quality of sleep was determined by posing a simple question that could be answered by choosing an answer from a set of three options given on a Likert-type scale. This might be considered as a crude method and may lack the properties needed to detect possible subtle differences. However, other authors have used a simple visual analogue scale for the purpose of measuring the quality of sleep.

Several factors contribute to disturbed sleep postoperatively. Use of opioids has been shown to change sleep architecture substantially in healthy subjects. This coheres with our findings that the amount of opioids given postoperatively was an independent risk factor for bad quality of sleep. Interestingly, we found that fentanyl improved quality of sleep. Fentanyl is a short-acting opioid and was given exclusively during surgery. Mustola et al. have recently shown that fentanyl given during general anesthesia reduces the surgical stress response. The injury caused by surgery provokes a complex stress response involving release of stress hormones, humoral mediators of the endocrine and metabolic system, and activation of the immune system. All these factors may influence sleep architecture adversely. Thus by reducing the stress response, fentanyl may consequently improve sleep architecture and quality of sleep. The relative body weight gain the first day after surgery was an independent risk factor for bad quality of sleep in the present study. Since we found no association between sleep and the volume of the IV fluid given perioperatively, the relative body weight gain may be an effect of increased release of stress hormones and inflammatory processes and thus may represent an increased stress response.

We found that quality of sleep in the first night postoperatively was associated with the length of hospital stay. This is to our knowledge the first report to show such a clinically important association. The standardized criteria for discharge were emphasized in the fast-track program. In the analysis, we adjusted for several confounders that might influence the hospital stay or quality of sleep. Still, we found a significantly longer stay in hospital for the group who perceived having had a bad quality of sleep the first night after surgery. This indicates that the quality of sleep is an important factor for postoperative recovery. Our results seem to support the conclusion stated by Rosenberg-Adamsen et al. that mode of anesthesia—spinal or general anesthesia—per se does not influence the quality of sleep postoperatively. An anesthetic technique that gives good and prolonged analgetic effect with minimum use of opioids postoperatively should be chosen in fast-track programs. It is a common clinical impression that symptoms such as pain and postoperative nausea and vomiting (PONV) causes disturbed sleep. Use of opioids and rescue antiemetics may be regarded as surrogate measures of pain and PONV. However, the drugs themselves may interfere with sleep, so it may be difficult to ascertain whether it is the symptom or the drug that affects the sleep. We found that postoperative symptoms in terms of the SPSQ symptom sum score, irrespective of treatment of symptoms, was a strong risk factor for bad quality of sleep the five first nights postoperatively. This is an important finding, indicating that fast-track programs should include the use of modalities designed to decrease troublesome postoperative symptoms in order to positively affect and maintain sleep of good quality.

In conclusion, the quality of sleep the first night after elective abdominal hysterectomy is an important factor for the recovery. In fast-track it seems important to use anesthesia and multimodal analgesia that reduce the need of opioids postoperatively and use strategies that diminish other factors that may interfere negatively with sleep. Efforts to enhance quality of sleep postoperatively by means of prevention and treatment of sleep disturbances should be included in fast-track programs. Further studies are needed.

ABBREVIATIONS

ACOVA, analysis of covariance
ASA, American Society of Anesthesiologist classification of physical status
BMI, body mass index
CI, confidence interval
5-HT3, 5-hydroxytryptamine type 3
GA, general anesthesia
IV, intravenous
OR, odds ratio
PACU, post anesthesia care unit
PLSD, protected least significant difference
PONV, postoperative nausea and vomiting
SA, spinal anesthesia with intrathecal morphine
SCI, Stress Coping Inventory
SD, standard deviation
SPSQ, Swedish Postoperative Symptom Questionnaire
VAS, Visual Analogue Scale

REFERENCES


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Address correspondence to: Preben Kjølhede, M.D., Ph.D., Department of Obstetrics and Gynecology, University Hospital, S-581 85 Linköping, Sweden; Tel: +46 10 103 00 00; Fax: +46 13 14 81 56; E-mail: Preben.Kjolhede@liu.se

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Atypical Headbanging Presentation of Idiopathic Sleep Related Rhythmic Movement Disorder: Three Cases with Video-Polysomnographic Documentation

Shih-Bin Yeh, M.D.¹; Carlos H. Schenck, M.D.²

¹Department of Neurology (and Sleep Center), Changhua Christian Hospital Yun Lin Branch and Department of Neurology (and Sleep Center), St Martin de Porres Hospital, Chiayi, Taiwan; ²Minnesota Regional Sleep Disorders Center and Department of Psychiatry, Hennepin County Medical Center and the University of Minnesota Medical School, Minneapolis, MN

Study Objectives: To describe three cases of sleep related, idiopathic rhythmic movement disorder (RMD) with atypical headbanging, consisting of head punching and head slapping.

Methods: Three consecutive patients (2 males [11 and 13 years old] and one female [22 years old]) presented with atypical headbanging of 6 years, 7 years, and 17 years duration. In 2 cases, typical rhythmic headbanging (with use of the head) shifted after 3-4 years to atypical headbanging, with frontal head punching that was quasi-rhythmic. In one case, atypical headbanging (head-slapping) was the initial and only RMD. There was no injury from the headbanging. Prenatal, perinatal, developmental, behavioral-psychological, medical-neurological, and family histories were negative. Clinical evaluations and nocturnal video-polysomnography with seizure montage were performed on all patients.

Results: Atypical headbanging was documented in all 3 cases; episodes always emerged late in the sleep cycle: from N2 sleep in 11 episodes, from REM sleep in 4 episodes, and from N1 sleep in 1 episode. Epileptiform activity was not detected. Clonazepam therapy was substantially effective in 1 case but not effective in 2 cases.

Conclusions: These 3 cases of idiopathic atypical headbanging expand the literature on this RMD variant, as to our knowledge only one previously documented case has been reported.

Keywords: Headbanging, jactatio capitis nocturna, sleep related rhythmic movement disorder, RMD, clonazepam, parasomnia, video-polysomnography, handedness, periodic limb movements/PLMs, central pattern generators, cyclic alternating pattern (CAP)

Citation: Yeh SB; Schenck CH. Atypical headbanging presentation of idiopathic sleep related rhythmic movement disorder: three cases with video-polysomnographic documentation. J Clin Sleep Med 2012;8(4):403-411.

BRIEF SUMMARY

Current Knowledge/Study Rationale: 3 cases of atypical headbanging with head punching and head slapping are reported since there has only been one previously reported case, with video-polysomnographic documentation, of this self-hitting variant of jactatio capitis nocturna (headbanging). Typical headbanging involves banging of the head with the head forwards or backwards against the bed or bedside wall.

Study Impact: These 3 cases, together with a previously reported case, should encourage inclusion of the distinction between typical vs. atypical headbanging in the Sleep Related RMD section for the revision of the ICSD-2 that has recently been initiated by the American Academy of Sleep Medicine.

METHODS

Over 2 years, a series of 3 patients was gathered; the patients had presented to the sleep center of S-BY on account of longstanding nightly punching or slapping of the head that emerged mainly during nocturnal sleep and rarely from daytime naps. These patients were unaware of what was happening during sleep, and had no impairment of daytime function. Their headbanging made the parents concerned about the risk...
for brain injury, which eventually prompted referral to the sleep clinic.

A comprehensive questionnaire covering lifetime sleep-wake, medical and behavioral-psychiatric history, and review of systems was completed by the parents for these 3 patients. Neurological examinations and psychiatric interviews were conducted. Neuropsychological testing was not performed, since there was no suspicion of at least mild pervasive developmental disorder or other problem in any patient, based on intact psychosocial functioning at home and at school, including interactions with classmates and friends. Brain MRI and awake and sleep EEG studies were performed. Serum liver function tests, BUN, creatinine, and fasting blood sugar levels were routinely performed; testing for heavy metals or other toxins was not done. There was no suspicion of substance abuse in any patient.

Overnight, hospital-based, vPSG monitoring, utilizing standard recording and scoring methods, and with EEG seizure montage, was then performed for the 3 patients. All medications were stopped ≥ 8 weeks prior to vPSG. The PSG monitoring included eye movements (electrooculogram); expanded EEG (12-channel seizure montage) with fast paper speed (1 cm/sec), submental and anterior tibialis electromyograms (EMG); oral-nasal airflow, chest and abdomen respiratory effort; electrocardiogram; and continuous, time-synchronized, audiovisual recording. Patient #1 had his parents sleep in the same room in a separate bed during his vPSG study. Patients #2 and 3 had their mothers sleep in the same room in a separate bed during their vPSG studies.

RESULTS

Case Presentations

Patient 1

An 11-year-old boy suffered from head-slapping during his night sleep since he was 5 years old. Episodes occurred as clustered events several times nightly during nearly every night, with each event lasting several seconds, with either or both hands slapping his parietal area. The patient was never aware of these events, but his parents were disturbed by the sharp and clearly slapping sounds during his night sleep. They were particularly concerned about whether brain injury would result from the strong and repeated head slapping. He was evaluated by a pediatric neurologist soon after the onset of the sleep related head slapping. Physical and neurological exams were normal. Awake and sleep EEG and brain MRI were unremarkable. Nevertheless, a nocturnal seizure disorder was diagnosed and sodium valproate was prescribed, with poor response, and then various other anti-epileptic medications were prescribed (including clonazepam) during the subsequent 5-6 years, without benefit. Another pediatric neurologist eventually diagnosed a sleep disorder rather than a seizure disorder. The patient was then brought to the sleep clinic for evaluation. Medical history was benign. He was a full-term baby. His general health was excellent, he achieved developmental milestones normally, and there were no behavioral or emotional problems. Family history was non-contributory.

Patient 2

A 22-year-old female suffered from headbanging since she was 1 year-old. Headbanging episodes always occurred during transitions from sleep to wake and were accompanied by crying, but there was never dream recall, nor recall for the events. She would turn to the prone position and bang her head into the pillow for several minutes. When her mother picked her up from bed and held her, she would continue to bang her head into her mother’s shoulder. Consultation with a pediatric neurologist did not identify any neurological disorder, but the sleep problem was not addressed. Head-punching during sleep began spontaneously at the age of 5 years, with episodes gradually becoming concentrated into nocturnal sleep, most often around midnight (and occasionally during daytime naps). She usually punched the front of her head with either hand, but mostly with the right hand. At times her mother observed that she would still bang her head into the bedside wall. Also, if her mother held her hand to prevent head-punching, she would then bang her head into the wall by her bed. Subsequently, the emergence of the episodes migrated into the early morning hours. When her mother observed that this problem had been escalating since age 16 years, she sought a neurologic consultation for her daughter. Physical and neurologic exams, brain MRI and EEG were unremarkable. Clonazepam 0.5 mg at bedtime reduced the frequency of these episodes from 10+ times nightly to 2-3 times nightly. When the neurologist increased the clonazepam dose to 2 mg at bedtime, the patient felt excessive daytime sedation, so the dose was reduced back to 0.5 mg. She then presented to the sleep clinic. Medical history was benign. She was a full-term baby, without any abnormal developmental, medical, neurological or behavioral-emotional history. Family history was negative. Physical

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and neurological exams were unremarkable and the patient denied any daytime sleepiness.

In 2 of the cases (#1 and #3), typical headbanging emerged first and subsequently evolved after a number of years—for no identified reason—into almost exclusively atypical headbanging consisting of head-punching. Case #2 had a history of exclusively atypical headbanging manifesting as head-slapping, but without ever demonstrating any typical headbanging (with use of the head). Pt. #3 had (non-rhythmic) crying that accompanied her headbanging episodes. In none of the 3 cases was there reported or elicited symptoms suggestive of other sleep pathology, such as sleepwalking, sleep terrors, dream-enactment, restless legs syndrome, propriospinal myoclonus, excessive movements, sleep bruxism or tongue-biting, sleep related scratching, snoring, non-restorative sleep, or daytime somnolence. None of the children considered his or her sleep to be disturbed or abnormal. They were all healthy children with normal IQs who were devoid of medical, neurological or psychological-behavioral problems. All brain MRIs and blood test results were unremarkable. There was no history of head injury or loss of consciousness. There was also no history of any wakeful tendency for verbal or physical aggression directed towards others or themselves (e.g., self-hitting, self-biting, self-cutting), and the patients were well-adjusted in all spheres of their lives. They all came from upper middle class, university-educated families. The female patient is currently a university student, and both boys are junior high school students. The uncle of one boy is a physician and Chief of Family Medicine at the hospital in Chiayi, Taiwan where the sleep center that evaluated the 3 patients is located.

All 3 cases were right-hand predominant, and although the head-punching and slapping were observed by the parents to occur with either hand, it was predominantly with the dominant right hand. With patient #2, the mother would occasionally observe simultaneous slapping of the head with both hands. With patient #1, one episode of strictly left-handed headbanging was followed by an episode with strictly right-handed headbanging during the vPSG study.

Parental concerns over brain injury from the repeated head-punching and head-slapping that occurred for years during sleep had prompted medical evaluation in the first 2 cases, and parental concern over intensification of the headbanging at age 16 in the third case had prompted medical evaluation. However, none of the patients complained of headaches, or had sustained head injury or other injury from their atypical headbanging. In contrast, the parents of all 3 patients, especially those of patient #2, complained of having their sleep repeatedly interrupted by their child’s head-slapping, even when they slept in a separate bedroom (as with patient #2). They would wake up several times nightly to check on the status of their children. Nevertheless, none of the parents complained of non-restorative sleep upon arising in the morning.

Misdiagnosis of nocturnal seizures occurred in the second case, with multiple unsuccessful antiepileptic medication trials lasting years that ultimately resulted in parental concern, when the diagnosis of a sleep disorder was established, about possible adverse long-term effects from these medications. Clonazepam therapy, often effective in RMD, was not effective in the first 2 cases but was substantially effective in the third case.

**Video-Polysomnographic Results**

During their vPSG monitoring, patients #1 and #3 demonstrated repetitive head-punching/hitting during their single vPSG studies. Patient #2 had 2 vPSG studies, since the first night was devoid of any episode; rhythmic head-slapping appeared during the second vPSG. Table 1 contains the clinical and vPSG data.

Patient #1 had normal sleep latency, moderately increased N1 sleep, and a substantial reduction of REM sleep of about 50%. Otherwise, sleep was unremarkable, apart from 4 episodes of quasi-rhythmic fist-punching over the frontal head. Figure 1 shows the PSG correlates of the first episode that emerged from REM sleep.

Patient #2 had normal sleep latency, substantially increased N2 sleep, and substantially reduced N3 sleep and REM sleep (by about 50% each stage). Periodic leg movements (PLMs) unassociated with arousals were present during both vPSGs. Sleep was otherwise unremarkable, apart from one precipitous episode of violent, rhythmic head slapping emerging from N2 sleep. Figure 2 shows the PSG correlates of the episode of violent head-slapping.

Patient #3 had a normal sleep latency, and a substantial reduction (by > 50%) of REM sleep (9.7%). Otherwise, sleep was unremarkable, apart from 11 episodes of head-hitting that emerged mainly from N2 sleep, but also from REM sleep and N1 sleep. Events emerging from N2 sleep (8 episodes) usually were immediately preceded by a K-complex. Figure 3 shows the PSG correlates of the final (11th) episode of head-hitting.

Table 2 contains the vPSG data for the documented headbanging episodes. During the vPSG studies, patient #2 showed the most rhythmic headbanging, whereas patients #1 and #3 showed both rhythmic and quasi-rhythmic headbanging. The hand or any other part of the body was never bitten during any episode. The EEG accompanying the atypical headbanging episodes remained consistently asleep and without post-episode arousals. This EEG finding is typical for RMD.

**Patient #1 RMD Headbanging Episodes**

Time of onset of episodes #1-4 was as follows: (03:36:33) (03:38:41) (05:10:02) (05:12:47). Onset-to-onset intervals for the successive episodes were: 2 min 8 sec; 1 h 31+ min; 2 min 45 sec. The first 3 episodes involved strictly right-handed headbanging and other hitting, and the last episode involved strictly left-handed headbanging. The same strength was shown in headbanging with either the right or left hand, as demonstrated by the video examples for the second (right hand) and fourth (left hand) episodes.

**Description of the second episode** (uploaded video): At 03:38:41 during REM sleep, while supine and with knees drawn up, the right hand in a fist punches the forehead with the back of the hand moderately hard 5 times in 8 sec, then there is a 5-sec pause, followed by one hit, then a 7-sec pause, then one hit, followed by a 12-sec pause, and finally he lifts the right hand as if ready to come down with another hit, but instead he puts the hand on his face briefly and then moves his hand over his chest. Episode ends at 03:39:15. The parent sleeping in a nearby bed aroused during this episode from the noise of the hitting, and upon cessation of the episode, the child and parent started talking.
Description of the fourth (final) episode (uploaded video):
At 05:12:47 during N2 sleep, while supine and knees drawn up, the left hand in a poorly formed fist hits the forehead with the back of the hand moderately hard 4 times in 4 sec, then there is a 6-sec pause, followed by one more hit, and the left arm is lifted up, extended in the air for 5 sec before coming back down. Episode ends at 5:13:01.

Patient #2 RMD Headbanging Episode
Description of the episode (uploaded video): At 04:53:38, during N2 sleep (Figure 2), while supine with knees drawn up, the right hand hits the right parietal skull with 8 very hard and fast slaps in 5 sec, ending at 04:53:43. The open hand was rotated so that the palm was pounding the head with full aggression. Early in the episode, the left arm drifts to the left.

Patient #3 RMD Headbanging Episodes
Time of onset of episodes was as follows: (05:26:27) (05:28:40) (05:32:28) (05:33:53) (05:42:55) (05:48:25) (06:37:49) (06:40:32) (06:41:45) (06:43:05) (06:46:44). Onset-to-onset intervals for each of the successive episodes were: 2 min 13 sec; 3 min 48 sec; 1 min 25 sec; 9 min 2 sec; 5 min 30 sec; 49 min 24 sec; 2 min 43 sec; 1 min 13 sec; 1 min 20 sec; 3 min 39 sec. Range: 1 min 13 sec to 49 min 24 sec.

Description of Episode #11 (uploaded video): At 06:46:44, during N2 sleep (Figure 3), while supine and the right knee drawn up, the right hand, without a fist being made, hits the forehead with the back of the hand moderately hard 6 times in 4 sec, followed by a 4-sec pause, then he hits the head 4 times in 3 sec, then a 4-sec pause, then hits herself 3 times in 3 sec, then a 3-sec pause, then hits herself 3 times in 2 sec, and the episode ends at 06:47:09. In this sequence, she never made a fist and never rotated her arm while hitting, so it appeared that she was hitting herself without purpose or without aggression with the back of the forearm/wrist—while the right wrist was extended (“cocked”) in a peculiar manner. During this episode, the left arm was fully extended and motionless. This form of hitting was uniformly present in all 11 headbanging episodes during the vPSG study.

**DISCUSSION**

**Clinical Findings**
Our 3 RMD cases with atypical headbanging involved the use of the hand for either striking the head with the fist/knuckles, slapping the head with an open palm, or striking the head with the back of the hand/wrist/forearm. In 2 cases, typical rhythmic headbanging (with use of the head) shifted spontaneously to
atypical headbanging after 3-4 years, with decay in rhythmicity. In one case, head-slapping was the initial and only form of atypical headbanging. Therefore, atypical headbanging reflects a dynamic process in which multiple forms of head-hitting with the hands during sleep can coexist, and can also shift from one form into another form during the long-term evolution of the RMD, and can shift from rhythmicity to quasi-rhythmicity.

The bizarre clinical presentation confused primary care physicians and pediatric neurologists, indicating how headbanging can be prone to misdiagnosis as a nocturnal behavior problem or a seizure disorder, with resulting inappropriate treatment. An important point for differential diagnosis is that punching or slapping the head with either hand, or both hands simultaneously, during the episodes speaks strongly against seizures because of the lack of stereotypy. At times RMD is the sole manifestation of nocturnal seizures.\(^5\)

We consider that the ICSD-2 diagnostic criteria for RMD in these 3 cases were satisfied in regards to “self-inflicted bodily injury,” since repeated (hard) blows to the head on a nightly basis for years posed a serious risk for injury. However, they did not satisfy either of the other 2 diagnostic criteria for RMD, involving complaints of sleep interference or impaired daytime functioning. All parents complained about their own sleep interference from their child’s headbanging, but without daytime impact. In regards to risk of injury from typical or atypical headbanging, not only the level of force and violence should be considered, but also “victim vulnerability factors” should be considered,\(^6\) as less forceful blows to the head could cause injury in the setting of hemophilia or other bleeding disorder; anticoagulant therapy; prior head injury;\(^7\) CNS disorder; or other medical vulnerability factors.\(^6\) The threshold for initiating treatment should be influenced by both these clinical risk-related factors. In this regard, the natural history of atypical headbanging in our 3 cases is unknown, and may involve progressive or episodic increase in severity over time, as shown by patient #3, with increased risk for injury.

Therefore, given the lack of any neuropsychiatric disorder that could be linked with atypical headbanging, such as autism or mental retardation,\(^8,9\) and given the lack of daytime aggressive tendencies or any psychodynamic factors that could promote sleep related self-hitting, as was previously reported in one case,\(^3\) our 3 cases represent idiopathic, sleep related RMD. There was never self-awareness during the episodes and no subsequent recall for the episodes. There was also no associated dreaming even though RMD emerged from REM sleep at times. The underlying mechanisms would most likely involve rhythmic (or non-rhythmic) activation during sleep and sleep-wake transitions, of subcortical central (motor) pattern genera-

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**Figure 1**— PSG correlates of repetitive head-punching by patient #1

Figure 2—PSG correlates of violent repetitive head-slapping by patient #2

Multi-channel artifacts caused by rhythmic, violent head-slapping from N2 sleep (4:53:37 a.m. to 4:53:43 a.m.). Polygraphic channels: same as for Figure 1.

Table 2—Atypical headbanging episodes: vPSG data

<table>
<thead>
<tr>
<th>Time, sleep onset</th>
<th>Time, onset of first episode</th>
<th>Latency, sleep onset to onset of first episode</th>
<th>RMD episode #</th>
<th>Sleep stage (duration)</th>
<th>Mean ± SD, duration of RMD episode (sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>23:56:22</td>
<td>00:17:49</td>
<td>3 h 40 min</td>
<td>#1</td>
<td>REM (47 sec)</td>
<td>33.2 ± 13.9</td>
</tr>
<tr>
<td>00:17:49</td>
<td>04:53:38</td>
<td>4 h 35 min</td>
<td>#2</td>
<td>N2 (3 sec)</td>
<td>5.0</td>
</tr>
<tr>
<td>23:41:32</td>
<td>05:26:27</td>
<td>5 h 44 min</td>
<td>#3</td>
<td>REM (20 sec)</td>
<td></td>
</tr>
<tr>
<td>05:26:27</td>
<td></td>
<td></td>
<td>#4</td>
<td>N1 (69 sec)</td>
<td></td>
</tr>
<tr>
<td>04:53:38</td>
<td>05:26:27</td>
<td></td>
<td>#5</td>
<td>REM (25 sec)</td>
<td></td>
</tr>
<tr>
<td>05:26:27</td>
<td>05:26:27</td>
<td></td>
<td>#6</td>
<td>N2 (39 sec)</td>
<td></td>
</tr>
<tr>
<td>05:26:27</td>
<td>05:26:27</td>
<td></td>
<td>#7</td>
<td>N2 (25 sec)</td>
<td></td>
</tr>
<tr>
<td>05:26:27</td>
<td>05:26:27</td>
<td></td>
<td>#8</td>
<td>N2 (33 sec)</td>
<td></td>
</tr>
<tr>
<td>05:26:27</td>
<td>05:26:27</td>
<td></td>
<td>#9</td>
<td>N2 (15 sec)</td>
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<tr>
<td>05:26:27</td>
<td>05:26:27</td>
<td></td>
<td>#10</td>
<td>N2 (18 sec)</td>
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<tr>
<td>05:26:27</td>
<td>05:26:27</td>
<td></td>
<td>#11</td>
<td>N2 (28 sec)</td>
<td></td>
</tr>
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</table>

Range (sec) 14-47 N/A 15-69
idiosyncratic head-hitting (IHH) is a non-epileptic paroxysmal movement disorder (NPMMD) that characterizes uncontrolled, repetitive, and self-directed head-hitting behaviors 

10,11 It is unknown how certain muscle groups are preferentially selected, and how vigorous and potentially injurious self-hitting behaviors (focused exclusively on the head) are repetitively activated. 

**Video-Polysomnographic Findings**

The vPSG results are compatible with those from 2 previous studies: (i) preponderance of atypical headbanging arising from N2 sleep was also found by Dyken et al.12; (ii) a study by Mayer et al. of 24 patients with typical RMD found that episodes were not restricted to sleep-wake transition, and in fact occurred most frequently in wake, N1, and N2, but also in REM sleep and N3 sleep.13 All 24 cases were free of brain pathology. Their findings were highly congruent with the findings in our 3 cases, apart from the difference between typical and atypical headbanging.

The PSG data for all 3 patients indicated that they were good sleepers, with normal sleep latency and high SE%. However, in all 3 patients, REM sleep% was consistently reduced by half of normal (9.7%-15.8%). Patient #2 (with PLMs on both nights): had low N3 and low REM sleep% both nights—with a robust increase of N2 (to 74%-77%), but no increase in N1 (1.2%-1.2%). The alterations in sleep architecture just described for the 3 patients may reflect a “first night effect” in the sleep lab. Nevertheless, there was probably no clinical consequence from these sleep architecture alterations, especially since none of the patients (or their parents) had a complaint about their sleep or waking state. The finding of a K-complex signaling the onset of all 8 episodes coming during N2 sleep in patient #3 is most likely explained by the onset of the activated phase of the “cyclic alternating pattern,” i.e., “A phase of the CAP” that facilitates release of abnormal behaviors.14 This K-complex finding was also reported in a 41-year-old man with leg-kicking RMD, whose episodes during all sleep stages and wake-sleep transitions were often preceded by high-voltage K-complexes15 (PLMs were absent in this patient).

**Previously Reported Case of Atypical Headbanging**

To our knowledge, there is only one previously reported case involving the same atypical variant of headbanging RMD as with our 3 cases, with self-punching of the forehead and face.3 A 24-year-old man had rhythmically pounded himself with his knuckles during sleep since the age of 2 years. From the ages of 2 to 15 years, he had placed one hand on his forehead and then repeatedly hit that hand with the other hand. At age 15 years, he started to directly pound his forehead without the protection of the other hand, and these episodes occurred multiple times nightly throughout sleep during virtually every night. Episodes were often brief, but could last as long as 45 minutes. He was always amnestic for these events. In contrast to our 3 cases,
this man sustained serious injuries, such as bleeding, suppura-
tive wounds, and facial scar-related disfigurement. Psychiatric
evaluation uncovered major psychodynamic problems, with his
harboring persistent rage towards his parents.

Two consecutive vPSGs (without mention of a seizure
montage) documented 20 episodes (18 during REM sleep) of
atypical headbanging that was “at all times rhythmic and ste-
erotypical” with variable strength “and at times were quite im-
pressive in their force; each strong blow produced a distinctive
hollow thud.” Although the man was right-handed, he struck
himself with both hands, “and at one point switching hands
in the middle of an episode.” The episodes from REM sleep
were marked by the head-pounding beginning 1-2 minutes af-
after REM-onset and persisting into N1 sleep in 11/18 episodes.
EEG during the episodes was unremarkable, sleep architecture
was intact, and there was no comorbid sleep disorder. There
was a positive family history for RMD involving an 18-year-
old cousin with persistent, typical headbanging.

Given this family history, together with the clinical and vPSG
findings, the authors concluded that their patient had a variant
of typical headbanging in which the hand rather than the head
was mobilized for banging. The unique self-destructive quality
of the head-pounding was speculated to result from a powerful
psychodynamic drive in which the patient’s latent rage towards
his parents was released during sleep, taking the form of the
familial predisposition to headbanging RMD. (Presumably in
this construct, if there were a family history of sleepwalking or
sleep terrors, then this psychodynamic rage would have been
released as a NREM parasomnia).

Final Comments
A number of findings and observations from our 3 cases of
atypical headbanging, together with the previously reported
case, should be highlighted:

1. Five forms of sleep related motor dyscontrol were docu-
mented:
(a) the head bangs itself rhythmically, frontwards and/or
backwards
(b) the head is banged rhythmically/quasi-rhythmically
by the upper extremity
(a) fist/knuckles punching
(b) slapping with the open palm
(c) hitting with the back of the hand/wrist/forearm
(ii) crying during RMD events
(iii) PLMs during NREM sleep (on 2 consecutive vPSG
studies in one patient)
(v) shifts in handedness in the self-hitting
(a) during the same episode
(b) across consecutive episodes
(c) simultaneous bilateral head-punching during atyp-
ical headbanging episodes

2. The shifting dominance of handedness emerging with
RMD, including atypical headbanging, calls attention to
shifting language dominance emerging with sleepstalking
(another form of motor dyscontrol in sleep) in some bi-
lingual sleepstalkers (Spanish, Euskera).16

3. The spontaneous shifting from typical to atypical head-
banging, with change in rhythmicity, after 3-4 years in
2 patients was also present in a case of complex RMD
involving a 16-year-old male who had spontaneous shifts
across 4 different types of RMD, including typical head-
banging.17

4. The long latencies from sleep onset to onset of headbang-
ing in all 3 patients during their vPSG studies, ranging
from 3 h 40’ min to 5 h 44’ min, together with the ab-
sence of wake-sleep transitional RMD, should be noted
and may suggest a unique profile for late nocturnal sleep
cycle atypical RMD without transitional RMD wake-
sleep release.

5. Aggressive and non-aggressive atypical headbanging, in
various forms, were documented by the vPSG studies.

6. The strong suppression of REM sleep (by > 50% of nor-
mal) linked with normal (or slightly prolonged) REM la-
tency, normal number of NREM/REM sleep cycles (4-5
cycles/patient), and very high sleep efficiency is rare, and
may be another feature of a unique profile for this group
of patients. Substantial REM sleep suppression is usually
a medication effect, or a result of a neurologic disorder,
sleep disruption related to sleep disordered breathing or
other factors, or very prolonged REM latency.

7. The breakdown in rhythmicity of RMD evident in the
evolution of typical headbanging (highly rhythmic) to
atypical headbanging (quasi-rhythmic, non-rhythmic)
suggests reduced precision of the CPG pacemakers in the
brainstem and spinal cord, by unknown mechanisms.

8. The knees were always drawn up during the atypical
headbanging episodes, which may be part of the symp-
tom complex for atypical headbanging, or may be a com-
mon supine sleeping posture for these patients.

9. Lack of neuropsychiatric disease with adult persistence
of atypical headbanging in patient #3 was also found in
various cases of adult persistence of typical headbanging
18-21 (and in other cases, as reviewed).22

10. Clonazepam therapy was reported to be effective in
isolated cases of typical headbanging17,20,23 but was effec-
tive in only 1 of our 3 patients. Imipramine was effec-
tive in 2 typical headbanging cases.7,21

In conclusion, our 3 cases together with the previously re-
ported case1 should encourage inclusion of the distinction be-
tween typical vs. atypical headbanging in the Sleep Related
RMD section for the revision of the ICSD-21 that has recently
been initiated by the American Academy of Sleep Medicine.

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Address correspondence to: Carlos H. Schenck, M.D., Minnesota Regional Sleep Disorders Center, Hennepin County Medical Center, 701 Park Ave. South, Minneapolis, MN 55415, USA; Tel: (612) 873-6288; Fax: (612) 904-4207; E-mail: schen010@umn.edu

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Restless Nocturnal Eating: A Common Feature of Willis-Ekbom Syndrome (RLS)

Michael J. Howell, M.D.1; Carlos H. Schenck, M.D.2
1Department of Neurology, University of Minnesota, Minneapolis, MN; 2Department of Psychiatry, University of Minnesota, Minneapolis, MN

Study Objectives: To determine the frequency of nocturnal eating (NE) and sleep related eating disorder (SRED) in restless legs syndrome (RLS) versus psychophysiological insomnia (INS), and the relationship of these conditions with dopaminergic and sedative-hypnotic medications.

Design: Prospective case series.

Setting: Sleep disorders center.

Patients: Newly diagnosed RLS or INS.

Intervention: RLS or INS pharmacotherapy with systematic follow up interview for NE/SRED.

Measurements and Results: Patients presenting with RLS (n = 88) or INS (n = 42) were queried for the presence of NE and SRED. RLS patients described nocturnal eating (61%) and SRED (36%) more frequently than INS patients (12% and 0%; both p < 0.0001). These findings were not due to arousal frequency, as INS patients were more likely to have prolonged nightly awakenings (93%) than RLS patients (64%; p = 0.003). Among patients on sedative-hypnotics, amnestic SRED and sleepwalking were more common in the setting of RLS (80%) than INS (8%; p < 0.0001). Further, NE and SRED in RLS were not secondary to dopaminergic therapy, as RLS patients demonstrated a substantial drop (68% to 34%; p = 0.0026) in the frequency of NE after dopamine agents were initiated, and there were no cases of dopaminergic agents inducing novel NE or SRED.

Conclusion: NE is common in RLS and not due to frequent nocturnal awakenings or dopaminergic agents. Amnestic SRED occurs predominantly in the setting of RLS mistreatment with sedating agents. In light of previous reports, these findings suggest that nocturnal eating is a non-motor manifestation of RLS with several clinical implications discussed here.

Keywords: Nocturnal eating, sleep related eating disorder, restless legs syndrome, Willis-Ekbom Syndrome, psychophysiological insomnia, dopaminergic therapy, sedative-hypnotics, benzodiazepines/benzodiazepine receptor agonists


Restless legs syndrome, or Willis-Ekbom Syndrome (labelled RLS), is characterized by an underlying discomfort, primarily in the lower extremities that compels the afflicted to move. These symptoms are relieved, although only momentarily, with movement and may interfere with sleep initiation or maintenance.1

RLS has been associated with non-motor phenomena. In particular, patients with RLS often describe other comorbidities such as mood and anxiety disorders,2 as well as other nocturnal compulsions such as nocturnal smoking that interfere with sleep.1 Further, patients with these non-motor manifestations of RLS have more severe motor restlessness as measured by the International RLS Rating Scale.3

Recently, an investigation demonstrated a high frequency of dysfunctional nocturnal eating (SRED) in patients with RLS. This community-based case-control study found that 33 of 100 RLS patients met criteria for SRED compared to only 1% of normal population controls.4 The authors pondered whether SRED was related to underlying RLS brain pathology or whether it was merely “killing time” during prolonged nocturnal awakenings, as previously suggested.1 Conversely it has been suggested SRED in RLS may be due to anti-RLS dopaminergic agents.6,7

Most investigations of nocturnal eating (NE; eating after an arousal from sleep, prior to terminal awakening) have focused upon SRED. However, we have noticed subtler non-dysfunctional forms of NE, commonly in the setting of RLS. Also, we have noted that many cases of zolpidem-induced SRED had been originally misdiagnosed as having psychophysiological insomnia (INS), a condition for which a benzodiazepine receptor agonist was prescribed, but later noted to have underlying motor restlessness as the cause of their sleep difficulties.

To establish whether NE is common in RLS and whether NE is a product of frequent nocturnal awakenings, we compared the frequency of NE as well as SRED among patients presenting with RLS and INS, a distinct condition of cognitive hypervigilance that manifests with frequent nocturnal awaken-
RATIONALE: 3 Amnestic SRED or other sleepwalking behaviors than patients with INS. Finally, we followed RLS patients prospectively to determine whether RLS patients were more likely to manifest either benzodiazepines or benzodiazepine receptor agonists, to determine whether RLS patients were more likely to manifest amnestic SRED or other sleepwalking behaviors than patients with INS. Finally, we followed RLS patients prospectively to evaluate the effect of dopaminergic agents on NE and SRED.

METHODS

Consecutive adult patients who presented to the University of Minnesota Medical Center, Sleep Disorders Center or the Minnesota Regional Sleep Disorders Center with a complaint of difficulty sleeping were screened for either RLS or INS. All patients completed a 9-page comprehensive sleep questionnaire that evaluated sleep and circadian rhythm phenomena, in addition to surveying for medical comorbidities and neuropsychiatric disease. Current and past medications were documented. One investigator (MJH) performed all clinical evaluations, using a structured interview and examination. ICSD-2 criteria were used to diagnose both RLS and INS. Patients were excluded if they met criteria for both syndromes or if they had other causes of sleep initiation or maintenance failure. The most common disorder of exclusion was Circadian Rhythm Sleep Disorder, Delayed Sleep Phase Type.

Once diagnosed with either RLS or INS, using a structured 1-page nocturnal eating questionnaire, patients were queried about the frequency and characterization of both nocturnal arousals and nocturnal eating. A prolonged nocturnal arousal was defined as lasting > 5 minutes. Previous exposure to dopaminergic or sedative-hypnotic medication was specifically asked and documented.

A patient was considered to have NE if they admitted to nocturnal eating at least once a month; inquiries were subsequently made into whether the feeding behavior was dysfunctional. SRED was diagnosed if recurrent nocturnal eating was present with one or more of the following criteria: (1) ingestion of unusual or inedible substances, (2) difficulty falling back asleep or nonrestorative sleep, (3) sleep related injury or potentially injurious behaviors, (4) morning anorexia, (5) or adverse health consequences. If NE was present, the food types and subjective nature of the feeding episodes were documented. In particular, the patient’s hunger, memory, and control of NE were all quantified. Bed partner report, if available, was also gathered. Further, RLS NE patients were asked whether they had restless symptoms at the time of the NE.

Both RLS and INS patients were then treated in a standardized fashion and followed prospectively. The patients sleep initiation and maintenance symptoms, restlessness, as well as NE and SRED were serially evaluated with a structured follow-up interview.

RESULTS

RLS patients were overwhelmingly more likely to demonstrate NE and SRED than patients with INS, despite being less likely to have prolonged nocturnal awakenings (Table 1). Further, patients with RLS were far more likely to have amnestic SRED or sleepwalking when exposed to sedative-hypnotics than patients with INS (Tables 2, 3). Examples of other parasomnias behaviors among RLS but not INS patients on sedating agents included amnestic sexual behavior and smoking.

Of the 12 RLS patients with sedative-induced SRED or sleepwalking, all had previously been misdiagnosed and treated as having insomnia. Eleven of the 12 discontinued BRA once the diagnosis of RLS was made. All 11 patients described a cessation of amnestic nocturnal events after stopping the BRA, with complete elimination of NE in 3 patients, while the remaining 8 patients had persisting wakeful NE that was subsequently responsive to dopaminergic therapy (see dopaminergic treatment below). Conversely, in most patients with INS, treatment (either CBT-I or sedative-hypnotic) was well tolerated. Only 2 INS patients had a report of BRA induced amnestic behavior, both isolated to one event, and are still on sedative-hypnotics.

Hunger data were available on 35 RLS patients with NE. Only 31% of these patients described hunger prior to the nocturnal feeding behaviors. Patients often described that they had...
an urge to eat that prevented them from falling asleep, but once food was ingested, sleep was reinitiated. Conversely, of the 3 INS patients for whom hunger data were available, 2 described hunger as a predominant driver for NE.

Among the RLS patients, gender was evenly distributed between NE+ and NE- patients, and there were non-statistically significant differences in age, BMI, and ferritin levels. RLS patients who were NE more likely to report prolonged nighttime awakenings than RLS patients who were not NE (Table 4).

Prospective therapy data indicates that NE is reduced by correction of RLS with dopaminergic agents (Tables 5, 6). Several different classes of RLS therapies were used, including gabergens and opioids, but dopaminergic treatment data were available on 44 patients. A striking reduction of both NE (30/44 to 15/44; \( p = 0.0026 \)) and SRED (18/44 to 9/44; \( p = 0.063 \)) was noted, and only one patient had a worsening of NE. Among RLS patients without NE there were no reports of de novo NE once dopaminergics were started. Among INS patients, 1 of the 2 patients with NE continued to have nondysfunctional NE after treatment with zolpidem. There were no de novo reports of NE among INS patients once pharmacotherapy was started.

Among RLS patients who had resolution of motor symptoms, all NE ceased as well. Only patients who continued to have motor symptoms also continued to have NE. Several of the patients (6/9) who described no improvement in NE were unable to tolerate dopaminergic therapy. Nausea and impulsive (non-eating) behaviors such as online shopping and excessive ethanol ingestion were cited as reasons dopaminergic treatment was discontinued.

**DISCUSSION**

“They often have to get up and walk, ‘like a caged bear,’ to quote one of my patients, or they go into the kitchen and get something to eat.”—Karl-Axel Ekborn, Neurology, 1960

This study augments previous reports, including Ekborn’s seminal 1960 publication, that NE is pervasive among patients with RLS (see quote above). Further, we have demonstrated that NE is not merely “killing time” as previously suggested, because patients with INS were more likely to have prolonged nighttime awakenings than patients with RLS but less likely to have NE. As expected, amnestic SRED was common in the setting of sedative-hypnotic use among RLS patients but not INS patients. Finally, our prospective data demonstrate that contrary to previous speculation, dopaminergic agents improve NE and SRED in RLS.

This study and a critical review of the literature suggest an intimate relationship between NE and RLS. Here the evidence and implications of such a relationship is presented.

**Epidemiology of NE/SRED and RLS**

RLS is a disorder affecting approximately 8% to 10% of the population and thus a common cause of sleep initiation and maintenance failure. Both RLS and SRED are more common in women. While our study demonstrated the high frequency of NE in RLS, RLS has been commonly noted among patients with SRED. This finding has been particularly profound among patients with medication-induced SRED. In fact, even among SRED cases where RLS frequency was not addressed, there is a peculiar incidence of conditions frequently comorbid with RLS, such as Parkinson disease and narcolepsy.

Like nondysfunctional nocturnal eating (a non-pathological variation of SRED), RLS may be mild or only minimally interfering with sleep onset. Further, RLS sensations are often difficult for patients to define, and current symptomatic criteria are not easily translated between languages. Moreover, the pervasive use of opioid and gabergenic agents may intermittently mask symptoms, and thus RLS may go unrecognized during routine clinical evaluation. While these drugs suppress motor symptoms, they may be taken without the ideal timing or dosing needed to optimize sleep maintenance, allowing for breakthrough nocturnal phenomena such as NE. Thus, the actual prevalence of the RLS clinical spectrum is likely larger than current estimates. These findings bear special significance for the obesity pandemic since according to this study and others, the majority of RLS patients have NE, and more than a third have SRED.

<table>
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<th>Table 4—RLS NE+ versus RLS NE-</th>
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<td><strong>NE</strong></td>
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<tr>
<td>Total Patients</td>
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<td>Gender (F/M)</td>
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<td>Age (mean)</td>
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<td>BMI (mean)</td>
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<td>Ferritin (mean)</td>
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<tr>
<td># Pts who average at least one prolonged (&gt; 5 min) nightly awakening</td>
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1Fisher exact test (2-sided); 2Type 2 T-Test with 2 tails.

<table>
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<th>Table 5—Targeted pharmacology data</th>
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<tr>
<td><strong>RLS</strong></td>
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<tr>
<td># Of pts with pharmacological treatment data</td>
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<tr>
<td>Pharmacotherapy</td>
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<td>Average duration of follow-up</td>
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<td>Pre Rx</td>
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<tr>
<td># (% Pt with NE)</td>
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<td># (% pt with SRED)</td>
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1Pramipexole, ropinirole, or carbidopa/levodopa. 2Benzodiazepine receptor agonists: either zolpidem or eszopiclone. NE: Defined as nocturnal eating > than once a month.
Amnestic SRED is Predominantly Mistreatment of RLS as INS

The majority of patients in the original SRED series, where NE behaviors were predominantly amnestic, were taking sedative-hypnotic medication.13 Conversely, in a later series of 26 SRED patients with full consciousness during nocturnal eating, all were sedative free,15 prompting the suggestion that amnesia in SRED is predominantly medication induced.25 Our investigation helps confirm that amnestic SRED is unusual in the absence of sedative-hypnotic medication (Table 3).

Further, our study demonstrates that among RLS patients NE is pervasive (61%). Conceptually, if RLS patients are predisposed for NE, then amnestic SRED would be the expected result when treated with agents that suppress memory as well as executive function. Thus it was not a surprise that 80% of our RLS patients who had previously been exposed to sedative-hypnotics had a history of amnestic SRED or other sleepwalking behavior (Table 2).

Nearly all of the sedative exposures that induced amnestic NE were from BRA. Only one RLS patient, who also incidentally had fully conscious NE without sedation, had fully amnestic NE induced by a benzodiazepine (clonazepam). These findings are of particular relevance, as benzodiazepines are occasionally prescribed for the treatment of RLS. Further investigations are needed to evaluate the frequency by which benzodiazepines may induce amnestic NE among patients with RLS.

While RLS is a condition distinct from INS, it can be easily misdiagnosed and thus mistreated as INS. In 2002, the first case series of 5 patients with zolpidem-induced amnestic SRED was reported. Incidentally, all 5 patients were noted to have RLS.16 Others have commented that RLS appears to be ubiquitous in the setting of zolpidem-induced SRED.21 In fact, we are unaware of any zolpidem-induced SRED report where RLS was explicitly considered and subsequently not discovered.16-21

Tellingly, NE (both conscious and amnestic) among our INS patients was rare (Table 3). Among our 25 INS patients treated with either a benzodiazepine or benzodiazepine receptor agonist, only 2 reported amnestic behavior. One patient described a prolonged SW event during which she left her home and vandalized an apartment complex with spray paint. Another patient described one episode of amnestic nocturnal eating 5 years prior. Both patients claimed that the events never recurred and are still on sedating medications. Prospectively, there have been no reports of amnestic behaviors among INS patients treated with sedative-hypnotics after an average treatment follow-up of 6 months.

These findings are consistent with previous reports where RLS, sleepwalking, and other complex sleep behaviors are rare (1% or less) in zolpidem-treated INS patients when RLS has been carefully excluded.26 Thus we conclude that in the absence of motor restlessness, sedative-hypnotics are safe agents for INS.

Intriguingly, among the 5 NE positive INS patients in this study, 2 reported a history consistent with atypical RLS. One patient described a family history of RLS as well as her own remote history of motor restlessness from several years prior. The other INS patient reported a need to ambulate around the bedroom in order to “cool off” from the heat of his cancer-related night sweats.

Other Non-Motor Compulsions in RLS

Compulsive nocturnal eating is not unexpected as investigators have described other non-motor nocturnal urges. Among 6 patients with NE and nocturnal smoking, 5 were noted to have RLS. These patients claimed that they would wake up and be unable to return to sleep without eating and/or smoking.27 In a follow-up study looking for sleep-related smoking among RLS patients there was a six-fold higher prevalence than among matched controls (12% versus 2%). Interestingly, among RLS patients with nocturnal smoking, SRED was common (83%), and both phenomena began simultaneously. In our study, consistent with these findings, pa-
tients with NE often described that NE developed in concert with motor restlessness.

Non-motor manifestations of RLS have more severe motor restlessness as measured by the International RLS Rating Scale.\(^3\) We noted that RLS patients with NE were more likely to have more frequent awakenings than RLS patients without NE (Table 4), consistent with the suggestion that non-motor manifestations of RLS are markers of more severe disease.

While we did not formally survey for nocturnal smoking, 3 RLS patients (all with NE or SRED) volunteered that they smoked on a nightly basis after an arousal from sleep. All 3 stated that the urge to smoke was different from daytime smoking urges in that they felt a profound sense the smoking was necessary to reinitiate sleep. This is not unexpected as cigarette smoking results in modulation of CNS dopamine activity,\(^28\) and thus may be therapeutic in RLS. None of our patients with INS reported nocturnal smoking behaviors.

Intriguingly 2 of our patients with RLS and NE described other nocturnal compulsive behaviors. The first patient reported that in parallel to her RLS symptoms, she had the peculiar urge to pick off her toenail polish; the second needed to look up bits of geographic trivia on the internet. These behaviors were not present during the daytime and occurred in parallel to motor restlessness. After several minutes of toenail picking or, for example, identifying the location of an island off the coast of Texas, they were able to fall back asleep. The first patient had noticed that all nocturnal compulsions abated with opioid therapy and the second with dopaminergics. We suspect that more thorough investigations of RLS patients will reveal other nocturnal compulsive behaviors.

**NE/SRED in RLS Is Relieved by and Not Caused by Dopaminergic Agents**

Similar to RLS,\(^1\) NE and SRED are related to dysfunction in the CNS dopamine circuits. Dopamine mediates behaviors such as motor restlessness, smoking, and binge eating.\(^1,20\) A polysomnography (PSG) study of 35 SRED patients demonstrated that 77% had PSG confirmation of wakeful RLS and periodic limb movements (PLM) during sleep.\(^15\) Further, rhythmic masticatory muscle activity (RMMA) and bruxism are dopaminergic phenomena\(^15,30\) associated with RLS\(^3\) and commonly seen in SRED.\(^13,15\)

It has been suggested that nocturnal eating in RLS patients may be caused by dopaminergic agents as these agents are known to trigger impulsive behaviors such as gambling.\(^6,7\) Conversely, dopamine agents suppress feeding behavior in animal models.\(^32\)

This report, following up previous investigations, provides strong evidence that dopaminergic agents help treat, and are not the cause of NE. A review of the original SRED series noted that dopaminergic therapy resolved the dysfunctional eating in 7 of 8 patients in whom the treatment was attempted.\(^13\) Later, 2 cases of SRED were noted to resolve with levodopa (in combination with buproprion and trazodone).\(^33\) In a separate survey of patients with both SRED and RLS, 10 reported that NE emerged prior to or concomitant with motor restlessness, and none reported that nocturnal eating emerged after the start of dopaminergic therapy. Also, RLS patients with SRED were not significantly more likely to use dopaminergic drugs than RLS patients without SRED. In fact, subjects whose nocturnal eating symptoms were under control were more likely to be on these agents than subjects who continued to have nocturnal eating.\(^4\) Further, a double-blind treatment trial of pramipexole for SRED demonstrated improved sleep and reduced nighttime activity, although, admittedly, nocturnal eating ingestions were not reduced in this small study.\(^14\)

In the series published here, we monitored therapy outcome in 44 RLS patients previously unexposed to dopaminergics with and without NE. In this population, the frequency of both NE (68% to 34%; \(p = 0.0026\)) and SRED (41% to 20%; \(p = 0.063\)) diminished by half with dopaminergics. Further, only one patient reported an exacerbation of NE after dopamine agents were initiated, and there were no cases of dopaminergics inducing de novo NE (Tables 5, 6).

Tellingly, our patients frequently noted a resolution of NE in parallel to resolution of RLS motor symptoms. One example was of a 63-year-old male who described a 10-year history of motor restlessness along with compulsive nocturnal eating that had resulted in weight gain. Both phenomena interfered with sleep onset and maintenance, and both had responded to 0.5 mg of pramipexole; however, augmentation became a problem, and dosages were increased to 3 mg. During periods of breakthrough motor symptomatology, he noted a greater frequency of nocturnal eating with subsequent weight gain. Gabapentin was added but provided only modest additional benefit, and he eventually failed both pramipexole and ropinerole due to augmentation and what he described as distressing sexual urges. He was subsequently treated with methadone 10 mg, which he states permanently resolved the motor restlessness and nocturnal eating.

Importantly, no patients with resolution of motor symptoms on dopaminergic agents had a persistence of NE.

Finally, treatment with dopaminergic agents appears to improve other non-motor manifestations of RLS. In a previous report, all RLS patients who had resolved nocturnal smoking had been treated with dopaminergic agonists.\(^3\) One of our RLS patients with nocturnal smoking was started on dopaminergics and reported a resolution of nocturnal, although not daytime smoking (the other 2 nocturnal smoking patients noted above were lost to follow-up).

**Is RLS a Link between SRED and the Night Eating Syndrome (NES)?**

A statement is necessary regarding the potential implication that these findings have to either unify or further distinguish the two major conditions of dysfunctional eating during the main sleep period. There are notable similarities and distinctions between NES (not to be confused with NE) and SRED. Both share a chronic course, familial associations, comorbid neuropsychiatric disease, and are frequently associated with weight gain and obesity.\(^35\) Investigations have suggested that NES is a circadian delay in meal timing resulting in evening hyperphagia, with or without nocturnal eating, and morning anorexia. NES is currently diagnosed if 25% of food intake is consumed after the evening meal (evening hyperphagia) and/or there are at least 2 episodes of nocturnal eating per week with clinical consequences.\(^36\)

SRED has historically been distinguished from NES by anamnestic eating alone without evening hyperphagia. However, changes in the definition of SRED\(^1\) expanded SRED to include non-anamnestic eating increasing the overlap between these 2 conditions. Thus at this point, the only feeding behavior that is...
Table 7—The relationship between NE/SRED and RLS

1. Nocturnal eating is pervasive among patients with RLS
   - Noted in Ekbom’s 1960 description.
   - Not merely “killing time” as patients with other causes of fragmented sleep rarely break the nocturnal fast.
2. Dysfunctional nocturnal eating (SRED) is common in patients with RLS.
3. RLS is nearly ubiquitous in cases of SRED.
   - Every SRED report in which RLS was explicitly considered, RLS was found
4. In most cases of sedative induced SRED the underlying disorder for which the sedative was originally prescribed was not INS, but instead RLS, a condition that is easily confused with INS.
   - Based on the findings of frequent NE in RLS, sedative-hypnotic medications, which suppress memory and executive function, would be expected to disinhibit amnestic SRED.
   - The rise of amnestic SRED reports parallels the widespread use of benzodiazepine receptor agonist use.
   - SRED is rarely noted when patients with underlying motor restlessness excluded from benzodiazepine receptor agonist treatment.
5. The compulsive nature of NE is similar in character to the motor manifestations of RLS, as they frequently arise, intensify, and subside in parallel.
   - Non-motor manifestations of RLS such as NE indicate more severe disease.
6. Polysomnographic studies demonstrate PLMs, RMMA, and bruxism in SRED. These phenomena are frequently noted in RLS and like RLS are associated with dopaminergic dysfunction.
7. Dopaminergic treatments for RLS improve, rather than exacerbate nocturnal eating and SRED.

undisputably labelled SRED by eating disorder investigators is unconscious or partially conscious nocturnal eating, which as we have demonstrated, appears to predominantly occur in the setting of sedative-hypnotic medications prescribed for RLS. Thus it is plausible that the most “pure SRED” cases are in fact related to adverse events from medication misapplications. This hypothesis can be tested in prospective studies.

The purported pathophysiological mechanisms of both NES and SRED are similar and complementary. NES is attributed to an abnormality in the circadian timing of caloric intake relative to sleep, while SRED has been characterized as a breakdown in nocturnal fasting mechanisms.35,36 Of course, these explanations are not mutually exclusive, and in this regard the high frequency of NE in RLS may, in fact, explain the circadian hypothesis of NES. RLS symptoms, both motor and non-motor, have circadian fluctuations, which reach a symptomatic crescendo during the late evening in parallel with the abnormal nighttime feeding in NES.36,37 Only one study has looked into the incidence of both conditions among RLS patients and noted that compared to SRED (33%), NES was rare (3%).4 However, this study utilized a now outdated definition of NES, excluding many NES patients under the revised criteria, particularly those whose predominant feature would be nocturnal eating.38 One notable study39 investigated NES patients with PSG and demonstrated an increased number of awakenings and reduced sleep duration, suggesting an underlying sleep disrupting process. No comment was made regarding the presence or absence of RLS or periodic limb movements.

While we did not specifically survey for NES (i.e., did not systematically question about or quantitate evening hyperphagia), several of our RLS patients described evening hyperphagia, suggesting that these patients could also be given the diagnosis of NES. In fact, many of our RLS patients who reported evening hyperphagia did not have NE. Persuasively, these patients were more likely to have RLS symptoms limited to the evening, interfering with sleep initiation but not sleep maintenance.

Clearly further investigations of are needed in patients with abnormal nocturnal eating. Ecological momentary assessment (EMA), a method where a portable electronic device periodically surveys appetite, food intake, sleep perception, and other symptoms, is an elegant method of evaluating circadian phenomena. EMA has been used by NES investigators40 and would be ideal for considering whether patients with SRED have evening hyperphagia and morning anorexia or whether NES patients have motor restlessness of RLS.

We speculate that NES and SRED may, in fact, be a unitary disorder, with restless nighttime eating existing on a spectrum and being interpreted differently by separate clinical fields. Regardless, collaborative investigations between sleep and eating disorder specialists will either unify these currently disparate disorders or with greater insight demonstrate fundamentally distinct pathologies. Engagement between collaborators will help reach the ultimate goal of identifying proper diagnoses and effective therapy for all patients.

Limitations and Future Directions

Clinical investigations of disorders with symptomatic criteria such as RLS and INS are heavily dependent upon self-report. In the future more objective measurements such as with polysomnography for periodic limb movements, or EMA for diurnal variations in motor and non-motor phenomena, are needed to further define the relationship between RLS and nocturnal eating.

RLS is a common, diverse disorder with many associations such as renal disease, iron deficiency, neuropathy, and pregnancy. RLS may be further subtyped according to age of onset.
family history, and treatment response. This study was not large enough to distinguish the prevalence of NE or SRED among these various subgroups. Future investigations are needed to help distinguish which RLS patients are at the highest risk for NE and SRED. These discoveries would be of particular therapeutic relevance, as benzodiazepines, which could potentially induce amnestic SRED, are often used in the treatment of RLS.

CONCLUSION

The evidence listed in Table 7 suggests that NE is often a non-motor manifestation of RLS and that mistreatment of RLS as INS is a crucial step in the pathogenesis of drug-induced SRED cases. The implications of establishing NE as a RLS symptom are then listed in Table 8.

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Address correspondence to: Michael J Howell, M.D., Department of Neurology, 717 Delaware St SE, Room 510L, Minneapolis, MN 55414; Tel: (612) 624-9025; Fax: (612) 624-8111; E-mail: howel020@umn.edu

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Sleep problems in children with fetal alcohol spectrum disorders (FASD) are reportedly common but not well characterized. Objectives were to: (1) assess sleep concerns in children with FASD using a caregiver-report survey, the Children’s Sleep Habits Questionnaire (CSHQ); (2) compare CSHQ results with those of previously reported community sample; and (3) describe pilot polysomnography findings in children with FASD.

Methods: Children with FASD were recruited from a behavioral intervention study, and participating caregivers completed the CSHQ. CSHQ results were compared with the original data from a previously published community sample of similar age. Participants with FASD and elevated CSHQ scores were offered overnight polysomnography.

Results: Thirty-three children with FASD (4.1-12.1 years) were enrolled; 85% of children with FASD scored above the clinical cutoff Total Score of 41, reflecting marked sleep disturbance. Elevated subdomain scores occurred primarily in areas concerning for pediatric insomnia. Those with comorbid ADHD had elevated CSHQ on additional subdomains with no difference in Total Scores. Compared with the community sample, children with FASD had higher Total Scores on the CSHQ (52 vs. 39, p < 0.001). Polysomnography, completed in 5 subjects, revealed mild sleep disordered breathing and fragmented sleep with elevated non-respiratory arousal indices.

Conclusions: Clinically significant sleep problems are present in children with FASD on both subjective and objective measures. Further investigation is needed to better describe these sleep disturbances and their impact on overall health and daytime neurobehavioral problems in this clinical population.

Keywords: sleep disorders; fetal alcohol spectrum disorders; prenatal alcohol; pediatric insomnia; school-age children; fetal alcohol syndrome; maternal pregnancy drinking

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BRIEF SUMMARY

Current Knowledge/Study Rationale: Sleep problems in children with FASD, a common condition, are reportedly prevalent and clinically problematic, but not well described. Systematic characterization of these sleep problems is needed to better approach assessment and treatment of sleep disturbances in this challenging population.

Study Impact: Given findings of highly prevalent pediatric insomnia, and pilot findings of mild sleep disordered breathing and sleep fragmentation, care of children with FASD (who may diagnostically overlap with non-teratogenic ADHD) should include a clinical sleep health assessment and low threshold for polysomnography. Identification and treatment of sleep problems in those with FASD may lead to improvements in problematic daytime function.
insomnia, periodic limb movement disorder, sleep disordered breathing, and increased daytime sleepiness on multiple sleep latency tests compared to controls. Improvement or resolution of ADHD symptoms with treatment of insomnia or other underlying sleep disorder has been reported.13,18

Despite the demonstrated link between sleep problems and daytime difficulties in typically developing and other clinical populations, few studies have directly addressed sleep problems in those with FASD.19 Only one study has been published performing multidimensional assessment of sleep and daytime problems in FASD using standardized measures. Indeed, higher rates of both sleep and sensory problems were found in those with FASD compared to controls in that study.19 However, these findings need to be replicated in other cohorts. Many of the health, behavioral, and neurocognitive manifestations of pediatric sleep disturbance are conditions that are also known to be common problems among those with FASD.1,3,7 If a connection between sleep problems and daytime function can be established in FASD through further studies, proven effective treatments for these sleep disorders could be implemented in children with FASD. Such treatments could provide lifelong benefit for children with FASD, including reduction of health care and societal costs.20

The primary goal of this research was to begin building a comprehensive profile of sleep problems in this remarkably prevalent, but under recognized clinical population of children with FASD. Thus, study aims were as follows: (1) to systematically describe parent-reported sleep habits in a representative group of children with FASD by using the Children’s Sleep Habits Questionnaire (CSHQ); (2) to compare these results to CSHQ results from a previously described community sample22; and (3) to obtain pilot and feasibility data from polysomnography (PSG) sleep assessment within a subgroup of the children with FASD. The authors hypothesized that children with FASD would show a higher rate of clinically concerning sleep problems on the CSHQ, compared with profiles of a typically developing community sample.

METHODS

Participants

Children with FASD

Thirty-three children were recruited from 34 participants enrolled in a behavioral intervention research study or related intervention training study in 2007. All participants enrolled in this subject pool were diagnosed with conditions within the umbrella category of FASD. All 34 families agreed to be enrolled, but one participant did not complete a sleep questionnaire and was therefore ineligible for the current descriptive study. All children in the subject pool were seen by an interdisciplinary team within the Washington State Fetal Alcohol Syndrome Diagnosti c and Prevention Network (FAS DPN), and received a formal diagnosis on the fetal alcohol spectrum. Of the 33 participants, 88% had clinically significant externalizing behavior or attention problems on the Child Behavior Checklist (CBCL), which are common difficulties among children with FASD.7 Eligibility for the current study included a diagnosis on the fetal alcohol spectrum with confirmed alcohol exposure based on the clinically reproducible 4-Digit Diagnostic Code4 (see below); registration in a clinical database of a statewide network of FASD diagnostic clinics; residence in a designated geographic catchment area in Washington State; aged 4 to 12 years at time of enrollment; and residence with the current caregiver for ≥ 4 months at enrollment with caregiver intent of maintaining that placement for at least the next 1.5 years to maximize retention in the larger behavioral intervention study.

Exclusion criteria for the larger study included other birth defect syndromes; known seizure disorder requiring daily medications; IQ < 55; diagnosed thought disorder; very serious conduct problems (e.g., fire-setting); and current primary caregivers with alcohol abuse. Potential participants for both studies were not recruited based on any pre-study sleep assessments. Research was approved by the Institutional Review Boards (IRB) of the Seattle Children’s Research Institute and Washington State Department of Social and Health Services, with further approval for comparison with de-identified community control data.

The 4-Digit Code is a standardized method for characterizing conditions across the fetal alcohol spectrum by using 4-point Likert scales to characterize 4 primary categories of definitional criteria.4 Higher scores indicate features in each category that are more similar to their classic representation in full FAS. These 4 categories include: (1) growth deficiency; (2) characteristic facial features; (3) central nervous system damage or dysfunction; and (4) level of prenatal alcohol exposure. Code combinations are collected into broader diagnostic categories, such as FAS or partial FAS. Non-FAS conditions seen in this study on the wider spectrum are grouped together as “static encephalopathy, alcohol-exposed” and “neurobehavioral disorder, alcohol-exposed” which other diagnostic systems may categorize as “alcohol-related neurodevelopmental disorders.”

Representativeness of Sample with FASD

Because participants with FASD were recruited from a behavioral intervention study, care was taken to ascertain whether this sample of participants reflected the larger FASD population. Demographics, behavior profiles on the CBCL, comorbid ADHD diagnoses and diagnoses on the fetal alcohol spectrum were compared between this sample and the much larger Washington State FASD clinical database.

Community Sample

As part of a separate, already concluded study, comparison data were drawn from a large community sample (n = 418) of typically developing children, aged 4-11 years, enrolled in any of 3 public elementary schools during the 1997-98 academic year.21 Sample characteristics and study methods for this community sample have been fully reported elsewhere,21 though original data on individuals were used for this study’s analyses. The community sample study was conducted to validate the CSHQ, so data were used in the current study only for descriptive comparison. The original community sample research project was approved by the IRB of Lifespan Hospitals, with further approval for current comparison to participants with FASD.
Measures

Demographic Data

Demographic information included children’s age, caregiver report of race/ethnicity, and gender. Family characteristics included measures of socioeconomic status (SES) based upon the Hollingshead Index and family structure (e.g., whether there was a father in household). Information on chronic medical conditions and medications was obtained via parent report as medical records were not consistently available. For participants with FASD, diagnostic category on the fetal alcohol spectrum was ascertained from clinical records.

Sleep Habits

Children’s sleep habits were subjectively assessed by using the CSHQ, a validated 33-item caregiver questionnaire. The CSHQ includes key sleep domains grouped into 8 subscales: (1) Bedtime Resistance; (2) Sleep Onset Delay; (3) Sleep Duration; (4) Sleep Anxiety; (5) Night Wakings; (6) Parasomnias; (7) Sleep Disordered Breathing; and (8) Daytime Sleepiness. Most CSHQ items are rated on a 3-point scale ranging from “usually” (5 to 7 times/week) to “sometimes” (2 to 4 times/week) to “rarely” (0 to 1 time/week). Two questions about daytime sleepiness are rated on a 3-point scale of “not sleepy,” “very sleepy,” or “falls asleep.” Excluding 2 items that were included in multiple subscales, the subscale inter-correlations for the community sample and larger Washington State FASD sample are provided for reference.24 For descriptive purposes, the group with FASD was further divided into those with and without caregiver report of ADHD for further descriptive comparison. Group characteristics of the community sample and larger Washington State FASD sample are provided for the reader’s reference but were not statistically focused on the CSHQ scores, formal comparisons were run only on CSHQ scores between the study and community sample groups for which raw data were available. Comparisons were carried out by using unpaired t-tests with 2-sided p-values and significance set at p < 0.05. Correction for multiple comparisons was not used in this exploratory study. Age, gender, SES, family structure, and presence of ADHD or other medical problems were found to vary by participant group, but none were found to correlate with CSHQ Total Score, so statistical adjustments for these factors were not performed in this pilot study. Preliminary evaluation for associations between and within CSHQ scores and markers of FASD severity was accomplished by using linear regression. All statistical analyses were performed using Stata, version 10 (College Station, TX).

For descriptive purposes, the group with FASD was further divided into those with and without caregiver report of ADHD for further descriptive comparison. Group characteristics of the community sample and larger Washington State FASD sample are provided for the reader’s reference but were not statistically compared with this study’s participants, given methodologic differences in original data collection.

Given the small number of children with PSG data, we report PSG parameters only as descriptive statistics, with published normative data from 388 typically developing children with a mean age of 6.8 ± 0.48 years (range 6.0-8.6 years) provided for reference.24

RESULTS

Sample Characteristics

Demographics

Within the group with FASD, mean age was 7.5 ± 2.2 years, with a slight predominance of males (Table 1). Fifty-eight percent were in adoptive families and 12% in foster families, while 18% of participants were living with one or both birth parents.
This was an ethnically diverse sample, with 61% reported as Caucasian/White, 9% African American, 6% Hispanic, 6% Native American, and 18% reported to be “mixed race.” Two participants had diagnoses consistent with the full FAS (6%), 3 with partial FAS (9%), 7 with “static encephalopathy/alcohol-exposed” (21%), and the remaining 64% with “neurobehavioral disorder/alcohol-exposed.” When compared to the community sample, the group with FASD was of similar age but had more males, less paternal presence in the household, and lower mean SES (Table 1).

Caregiver Report of ADHD

The study group with FASD had higher rates of caregiver-reported ADHD when compared with the community sample, in which children who were taking psychostimulant medications (presumably for ADHD) were excluded for purposes of the original CSHQ validation study design (Table 1).21

Representativeness of FASD Group

The current study’s FASD group is broadly representative of those found in the FAS DPN clinical database, which at the time of study enrollment included 1729 patients enrolled from 1993–2005.25,26 Sixty-one percent of the FAS DPN patients fell into the 4- to 12-year age range. Demographic, behavioral, and diagnostic characteristics of both the study and larger FAS DPN groups are similar, indicating that the current study cohort is reasonably representative of the larger WA State FASD database (Table 2).

Subjective Sleep Assessment

CSHQ

Caregivers of children with FASD reported higher levels of sleep complaints, with a mean Total Score of 51.7 ± 11.0 compared with 38.8 ± 5.6 among the community sample (p < 0.001) (Table 3). This pattern was consistent across all 8 subdomain scores, though the differences in sleep disordered breathing were smaller with more variability in scores. In addition, 85% of children with FASD attained a Total Score above the clinical cutoff of 41 for sleep dysfunction compared with only 30% of the community sample (p < 0.001). While age, gender, SES, family structure, and presence of ADHD and presence of other chronic medical conditions were found to vary by participant group, none of these factors were found to correlate with CSHQ Total Score (data not shown). Despite an average of an hour less sleep at night in the FASD group (Table 3), both groups showed age-appropriate absence of habitual daytime napping (data not shown).
Among those with FASD, CSHQ Total Scores did not vary greatly by presence or absence of ADHD, ascertained by parental report (Table 4). However, children with comorbid ADHD scored slightly higher on the following subscales: Sleep Duration, Sleep Disordered Breathing, and Daytime Sleepiness. A notably higher percentage of those with comorbid ADHD scored above the cutoff score of 41. In addition, caregivers of children with ADHD reported nearly an hour less sleep per night than those without ADHD.

**Correlation of CSHQ Scores with FASD Severity**

All participants with full FAS or partial FAS (n = 5) attained CSHQ Total Scores above the clinical cutoff of 41. In this relatively small sample, no associations emerged between the CSHQ Total Score and components of FASD diagnosis based on the 4-Digit Code reflecting: (1) growth deficiency (2) facial dysmorphology; (3) central nervous system dysfunction; and (4) level of prenatal alcohol exposure (data not shown).

**Objective Sleep Assessment (Polysomnography)**

All 28 children with FASD who had an elevated CSHQ Total Score were referred for a sleep medicine consultation. Ultimately, a sleep medicine evaluation and PSG were completed by 5 children (18%) with an elevated CSHQ Total Score (range: 46-72) (Table 5). Given the small sample size, these data are considered exploratory.

Median age of the 5 children with FASD at time of PSG assessment was 7.5 years (IQR: 6.3, 7.5), and 60% were male (Table 5). All 5 children had a caregiver-reported diagnosis of ADHD. There was a 14.3 ± 8.6 month mean time lapse between CSHQ and PSG, as sleep medicine consultations and PSG occurred based on family and clinical availability. All children tolerated PSG set-up and acquisition.

**Sleep Architecture**

There were no overt group differences between the 5 children and published normative values in sleep stage distribution, although ranges varied widely. Fragmented sleep, defined as...
an elevated total arousal index, was seen among the 5 children with FASD. Median total arousal index was 11.1/h (IQR: 10, 16), and all children with FASD had higher than control group mean values. Respiratory arousal index correlated directly with severity of respiratory disturbances as measured by AHI (estimated slope = 0.74; 95% confidence interval (CI): 0.6–0.9). Total arousal index was only moderately associated with AHI (estimated slope = 0.5, 95% CI: -1.1 to 2.1). Thus, not all arousals were directly associated with respiratory disturbances.

Respiratory Events

The median overall AHI was 2.8/h (IQR: 2.2, 4.0), higher than 2 SD above the reported mean AHI in control data. Elevation of AHI in the children with FASD primarily arose from obstructive apneic and hypopneic events, and not central events. All participants with FASD had very mild snoring during PSG. Mean end-tidal CO2 levels were 45.0 ± 3.5 mm Hg, higher than the reported control group mean of 40.7 ± 4.5 mm Hg. Similar to sleep architecture measures, respiratory parameters showed a wide range of distributions.

Periodic Limb Movements

Periodic limb movements occurred with similar frequency to published control data.

Seizures

No clinical or electroencephalographic seizures were identified among the children with FASD.

Medication Use

Of the 5 children with FASD who underwent PSG, 3 were receiving a single medication and one was receiving multiple medications at the time of study; only one child was medication-free. A medication “washout” was refused by all the caregivers for this clinical evaluation. Families were concerned about the impact of a medication washout on child and family function. Medications were prescribed by non-sleep medicine specialists with the aims of decreasing daytime hyperactivity (amphetamine and non-amphetamine based stimulants), stabilizing mood (valproic acid, buspirone), and/or assisting with sleep initiation/maintenance (clonidine, melatonin) per caregiver report. All medications used are known to affect sleep architecture but not thought to significantly alter respiratory parameters during sleep.27

DISCUSSION

Overall prevalence of sleep abnormalities was high among children with FASD, with ~85% scoring above a CSHQ cut-off for clinically significant sleep disorders. The elevation in average CSHQ Total Score for children with FASD was driven primarily by increased scores in subdomains related to the initiation and maintenance of sleep, best described as pediatric insomnia. Furthermore, within the FASD group, those with comorbid ADHD had further increased subdomain scores for Sleep Duration, Sleep Disordered Breathing, and Daytime Sleepiness compared with those without caregiver-reported ADHD, and they were also more likely to score above the Total Score threshold of 41 although mean Total Scores were not remarkably different. Exploratory PSG findings within a subset of these children with FASD aged 5 to 7 years, at a point in development when sleep should typically be at its most consolidated, demonstrate sleep disturbances best described as mild sleep disordered breathing primarily due to obstructive disturbances and hypoventilation, and fragmented sleep with slightly elevated arousal indices.

The results of the current study support prior clinical reports of elevated rates of erratically described “sleep problems” or “sleep disorders” among children with FASD in the range of 50% to 62% within heterogeneous clinical samples of children.
and adolescents diagnosed with FASD, ascertained using different diagnostic systems. In addition, this study augments the findings of a very recent systematic study focused on preschoolers, which also uses the validated CSHQ allowing us to directly compare results across groups. The current study expands the age range studied in FASD and adds exploratory data on objective polysomnography to characterize physiologic occurrences during what is reported to be very disturbed sleep in this population.

**Interpretation of CSHQ Results**

Reports of shortened sleep duration and frequent night wakings in children with FASD may be manifestations of SDB, other primary neurologic sequelae associated with in utero alcohol exposure, or comorbid neuropsychiatric disturbances. In this study, children with FASD scored higher on subdomains involving sleep onset (Bedtime Resistance, Sleep Onset Delay, Sleep Anxiety) and sleep maintenance (Sleep Duration, Night Wakings, Parasomnias). Except for the parasomnia category, this distribution of subjective complaints fits within a larger diagnostic category of pediatric insomnia, defined by a recent consensus statement as “repeated difficulty with sleep initiation, duration, consolidation, or quality that occurs despite age-appropriate time and opportunity for sleep and results in daytime functional impairment for the child and/or family.” All these subjective complaints may contribute to complaints of daytime sleepiness, another elevated subdomain among children with FASD. Similar to findings in a younger cohort, the mean CSHQ Subdomain Score assessing SDB was not appreciably different than the control mean despite preliminary objective evidence from PSG indicating the presence of mild SDB in children with FASD. Caregiver observations are not the best predictors of obstructive sleep apnea, which may account for this discrepancy. This supports the need for both subjective and objective data to best describe clinical sleep abnormalities at this juncture.

**Association with ADHD**

The clinical symptoms of FASD have some similarities to the diagnostic criteria for ADHD, resulting in likely diagnostic comorbidities. While exact prevalence rates of comorbid ADHD within the general population of FASD are unknown, the current study’s caregiver reported rate of 76% falls within the ranges seen in other clinical samples, finding 60% to 95% of ADHD in persons with FASD. It is important to note that the attentional deficits seen with prenatal alcohol exposure may not have the same neuropsychological profile on detailed testing compared with non-teratogenic ADHD. Unfortunately, these tests are not readily available to most practitioners. Nevertheless, while FASD without symptoms of ADHD is not common, most pediatric practitioners who diagnose ADHD do not assess for any degree of prenatal alcohol exposure. Thus, within the population labeled as ADHD, the rate of FASD is unknown. In studies of children with ADHD, it is possible that some of the observed sleep problems arise through unascertained prenatal alcohol exposure. Therefore, clarifying diagnostic labels and the presence of prenatal alcohol exposure will be important in future studies of sleep problems in clinical samples of both ADHD and FASD.

While a comorbid diagnosis of ADHD in children with FASD may contribute to sleep problems in this population, it is unlikely to be the sole explanation. First, sleep problems are common in general pediatrics and not exclusive to those with ADHD or FASD. Indeed, 35% of subjects in the community sample had CSHQ scores ≥ 41, despite the fact that those on psychostimulant medications (for presumed ADHD) were excluded from the community sample. Second, among the children with FASD in this study, those with and without ADHD still had higher Total Scores than controls, and higher than those with ADHD without known FASD. Meta-analyses of PSG findings in studies of children with a diagnosis of ADHD report both SDB and an elevation of periodic limb movements; our pilot data in a subset of children with FASD and comorbid ADHD reveal SDB and hypoventilation, but no participant had an elevation in periodic limb movements. While this study was not designed to pinpoint the etiologies of differences between prior findings and this report’s data, prenatal alcohol exposure is a potential culprit.

**Etiologic Possibilities for Sleep Problems in Children with FASD**

The preliminary PSG data can be used to explore the potential physiologic causes for subjective reports of pediatric insomnia and disrupted sleep in this clinical group, generating hypotheses to be evaluated using larger samples in studies that include carefully defined control groups.

One possible etiology is SDB, based on early evidence of elevated AHI and higher mean end-tidal CO₂ measurements. Breathing irregularities in children with diagnosed FASD may have a physiologic basis. Experimental rodent models of prenatal alcohol exposure describe altered ventilatory responses. Children with FASD have known craniofacial abnormalities leading to narrowed upper airways, and reports show abnormal cerebellar vermi (thought to be involved with respiratory control and muscle coordination) in alcohol-exposed children. Any level of respiratory abnormalities may also result in repeated cortical arousals during sleep, compounding sleep fragmentation.

Another possible etiology for subjective complaints of insomnia lies in frequent cortical arousals leading to sleep fragmentation, presumably unrelated to SDB. This has previously been shown in other studies of prenatally alcohol-exposed infants and children and in animal experiments, with potential mechanisms including potential circadian and sleep homeostatic disturbances as a direct result of alcohol’s teratogenic properties. The median number of cortical arousals in the current small sample undergoing PSG was high compared with controls when respiratory-related arousals were excluded. This suggests the increased occurrence of sleep fragmentation is not attributable only to SDB. It is possible, however, that some cortical arousals labeled as non-respiratory related were actually related to respiratory disturbances not detectable by current techniques.

**Limitations**

The current study is congruent with previous case series and a very recent systematic study of preschoolers in which high rates of concerning sleep problems were observed in children with FASD. Nevertheless, the data must be interpreted with
potential study limitations in mind. First, the potential overlap between ADHD and FASD has been addressed but bears further study. Second, only children with clinically significant daytime behavior problems were enrolled into the original intervention study, from which participants in the current study were recruited. However, behavior problems are relatively common among children with FASD, and the children in this study were otherwise representative of the larger FASD DPN clinical database which had similar distribution of CBCL scores. Third, participants with FASD were not only exposed to alcohol before birth, but as a group also had other elevations in prenatal and postnatal psychosocial risk compared with controls, illustrated by lower SES scores and less traditional household/caregiver structures. However, there was still a high prevalence of reported sleep problems among those with FASD and low psychosocial risk (data not shown), indicating that psychosocial risk alone was not likely to have caused the difference between groups. This study was not designed to examine the role of these potential differences on CSHQ, but future studies with larger samples, including matched controls, may be able to do so. Fourth, comparison with the community sample, while quite informative, has limitations because these samples were recruited for different studies. It is unknown whether the community sample includes children with FASD. However, FASD prevalence data would suggest that only about four participants in the community sample would have fallen under the umbrella of FASD. Also, such misclassification of FASD cases as “controls” would have biased the comparison towards the null and away from the results that were actually found in this study. Lastly, the interpretation of PSG data was limited by very small numbers, referral and self-selection bias, and prescribed medications. However, data are in line with a recent study of medication-free preschoolers with FASD. These pilot data illustrate the current state of clinical sleep medicine and difficulties in performing PSG in a group of children who are medicated for sleep problems. While these medications are prescribed without an evidence base, to discontinue medications for a study places caregivers and families at risk for recrudescence of worsened behaviors/sleep problems and their sequelae at home.

Future Directions

Though the results of the current study are based on a small sample and are preliminary, they cohere with data from existing basic science and clinical literature. The high prevalence of sleep problems observed in children with FASD suggests that children with FASD should routinely be evaluated for sleep complaints. Sleep problems in this heterogeneous group are likely impacted by multiple factors including the presence of comorbid ADHD, and screening for sleep problems should be done whether or not children show the classic characteristics of the full FAS, with referral to a sleep medicine specialist when appropriate. Sleep problems warrant assessment and treatment, possibly involving medications, as disturbed sleep may worsen the already compromised daytime behavior and adaptive function among children with FASD. An evidence base needs to be created upon which providers make decisions for treatment of sleep problems for those with FASD. Of special importance are study designs that include medication washout, if families can tolerate the functional impact of this procedure. Further elucidations of the mechanisms of alcohol’s teratogenic effects on sleep are needed. Findings from this study highlight the urgency for clinical study of disrupted sleep among the relatively common but often underrecognized population of children with FASD.

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Address correspondence to: Maida Lynn Chen, M.D., Seattle Children’s Hospital, 4800 Sand Point Way, NE, MS A-5937, Seattle, WA 98105; Tel: (206) 987-1861; Fax: (206) 987-2639; E-mail: maida.chen@seattlechildrens.org

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Sleep-Related Arousal Versus General Cognitive Arousal in Primary Insomnia

Kai Spiegelhalder, M.D., Ph.D.; Wolfram Regen; Bernd Feige, Ph.D.; Verena Hirscher, Dipl.-Psych.; Thomas Unbehaun, Dipl.-Psych.; Christoph Nissen, M.D.; Dieter Riemann, Ph.D.; Chiara Baglioni, Ph.D.

Department of Psychiatry and Psychotherapy, University of Freiburg Medical Center, Germany

Study Objectives: The present study aimed at further investigating trait aspects of sleep-related cognitive arousal and general cognitive arousal and their association with both objective and subjective sleep parameters in primary insomnia patients.

Methods: A clinical sample of 182 primary insomnia patients and 54 healthy controls was investigated using 2 nights of polysomnography, subjective sleep variables, and a questionnaire on sleep-related and general cognitive arousal.

Results: Compared to healthy controls, primary insomnia patients showed both more sleep-related and general cognitive arousal. Furthermore, sleep-related cognitive arousal was closely associated with measures of sleep-onset and sleep-maintenance problems, while general cognitive arousal was not.

Conclusions: Cognitive-behavioral treatment for insomnia might benefit from dedicating more effort to psychological interventions that are able to reduce sleep-related cognitive arousal.

Keywords: Cognitive arousal, subjective sleep parameters, polysomnography, primary insomnia

Citation: Spiegelhalder K; Regen W; Feige B; Hirscher V; Unbehaun T; Nissen C; Riemann D; Baglioni C. Sleep-related arousal versus general cognitive arousal in primary insomnia. J Clin Sleep Med 2012;8(4):431-437.

BRIEF SUMMARY

Current Knowledge/Study Rationale: Cognitive arousal is positively correlated with prolonged sleep onset latency in insomnia. There is a lack of data how cognitive arousal is associated with sleep maintenance parameters and how sleep is differentially influenced by sleep-related cognitive arousal.

Study Impact: Habitual sleep-related cognitive arousal was associated with subjective and objective measures of disturbed sleep initiation and disturbed sleep maintenance, while habitual general cognitive arousal was not. This might encourage the investigation of interventions that specifically target sleep-related cognitive arousal.

Insomnia is one of the most prevalent health complaints worldwide. It is defined by difficulties initiating or maintaining sleep or non-restorative sleep, accompanied by significant daytime impairments. Chronic insomnia affects up to 22% of the population and commonly occurs as a comorbid condition in other medical or mental disorders. Primary insomnia, an exclusionary diagnosis of poor sleep, ruling out psychiatric, medical, and additional sleep-related pathology, is estimated to affect up to 3% of the population.

Current models of primary insomnia highlight the role of cognitive, emotional, and physiological hyperarousal for the development and maintenance of the disorder. With respect to cognitive processes, patients’ cognitions are often dominated by worries and ruminations that are associated with a level of arousal that is incompatible with restorative sleep. Accordingly, previous studies have shown that cognitive arousal is positively correlated with prolonged sleep onset latency in insomnia patients. Furthermore, some studies included an experimental increase of pre-sleep cognitive arousal levels that resulted in difficulties falling asleep as well as in distorted sleep perception. Focusing on the content of these intrusive thoughts revealed that thinking about sleep and the anticipated consequences of poor sleep is very common in poor sleepers. In line with this, the attentional system of patients with primary insomnia has been described as particularly sensitive to sleep-related information. According to the attention-intention effort model, this focus on sleep-related information leads to a cascade of processes inducing the poor sleeper to direct effort and intention towards sleeping which is incompatible with the ability to obtain restorative sleep. Several studies have investigated attentional preference for sleep-related cues in primary insomnia using computerized tasks. The majority of this work supports the notion that poor sleepers show an attentional bias for sleep-related stimuli relative to good sleeper controls. Consistent with these results, altered emotional responses to sleep-related stimuli have been reported in people with insomnia as compared to good sleepers. Of note, studies on anxiety suggest a direct causal link from facilitated selective attention to worry.

Although an enhanced attentional focus towards sleep-related cues may be involved in the development and maintenance of chronic insomnia, several important questions have not been answered up to now. First, little effort has been made to investigate the relationship between cognitive arousal and objectively determined sleep parameters, and the studies that have been carried out have reported inconsistent results. For example, van Egeren et al found no significant correlation between pre-sleep cognitive activity and polysomnographi-
cally determined sleep onset latency. However, Wicklow and Espie\textsuperscript{19} reported that objective sleep onset latency, as measured by actigraphy, was positively correlated with pre-sleep cognitive activity. Second, existing studies restricted their analysis of sleep parameters to the sleep onset latency. However, cognitive arousal may also have an impact on sleep maintenance parameters, and the investigation of these may deepen the understanding of the interaction between rumination and sleep. Third, as suggested by Carney et al.,\textsuperscript{18} the distinction between general cognitive arousal and sleep-related cognitive arousal might be important because their impact on sleep parameters might substantially differ. More specifically, the authors suggested that sleep-related cognitive arousal might be more closely related to impaired sleep quality. Finally, only one study has evaluated the relationship between cognitive variables and sleep parameters in a clinically referred sample of primary insomnia patients.\textsuperscript{10} However, this investigation focused primarily on the distinction between worry and rumination as independent constructs and not on the distinction between sleep-related cognitive arousal and general cognitive arousal. Additionally, objectively determined sleep parameters were not used in this study.

The current study aimed at investigating sleep-related arousal and general cognitive arousal and their association with objective and subjective sleep parameters in patients with primary insomnia and healthy good sleepers. The first aim was to compare cognitive arousal levels in insomnia patients and good sleepers. Based on the above mentioned presumed role of hyperarousal in the development and maintenance of insomnia, we hypothesized that sleep-related and general cognitive arousal levels would be higher in patients with primary insomnia than in good sleeper controls. The second aim of the current study was to investigate the association between cognitive arousal levels and sleep parameters with the hypothesis that higher levels of sleep-related and general cognitive arousal would be associated with indicators of poor sleep.

METHODS

Participants

In the current investigation, 182 patients with primary insomnia according to DSM-IV criteria\textsuperscript{29} and 54 healthy controls according to the Research Diagnostic Criteria (RDC) for normal sleepers were investigated. The study sample is overlapping with the one that was investigated by Feige et al.\textsuperscript{19} and was obtained by reviewing the data of the archival database of the Sleep Center at the Department of Psychiatry and Psychotherapy Sleep Center, University of Freiburg Medical Center, for the period 1995-2008. Altogether, 4173 individuals were investigated in this period. Of these, 3937 individuals did not meet the following inclusion/exclusion criteria. All participants were either primary insomnia patients or healthy good sleepers. All participants were free of any psychoactive medication known to affect sleep at least one week prior to the sleep laboratory examination and did not receive cognitive-behavioral therapy for insomnia before taking part in the study. Participants with a PLMS (periodic leg movements during sleep) arousal index > 5.0 or an apnea index > 5.0 were excluded from the current analyses. Written informed consent was obtained from all subjects before participating in the investigation.

Procedure

Insomnia patients were referred to our sleep disorders clinic by their primary care provider or medical specialist. Healthy controls were recruited through local advertisements. Before entering the protocol, all participants underwent our standard physical and psychiatric examination, as well as a clinical interview by an experienced physician, excluding those with psychiatric or occult sleep disorder pathology (including hypersomnias, parasomnias, sleep-related breathing disorders, sleep-related movement disorders, and circadian rhythm sleep disorders). Additionally, all participants underwent a standard physical examination, including electrocardiogram (ECG), electroencephalogram (EEG) and routine laboratory investigations (blood cell count, liver, renal and thyroid function) to exclude those with serious medical conditions. All participants underwent 2 consecutive nights of PSG sleep monitoring at the sleep center. During these 2 nights, participants had to refrain from alcohol and caffeine. On the first day of their visit, all participants were asked to complete a self-rating measure of subjective aspects of sleep (the SF-A questionnaire, described in detail below) and the German version of the Pittsburgh Sleep Quality Index (PSQI). In the morning after each sleep recording some minutes after lights on, all participants were asked to complete a self-rating measure of subjective aspects of sleep (the FEPS-II questionnaire, described in detail below). After completion of the study, all patients received treatment according to current guidelines.

Questionnaires

All participants completed a questionnaire that was specifically designed to measure trait aspects of sleep-related and general cognitive arousal in patients with sleep disorders (“Fragebogen zur Erfassung allgemeiner und spezifischer Persönlichkeitsmerkmale Schlafgestörter,” FEPS-II,\textsuperscript{31} see Table 1 for the item list). Respondents were instructed to indicate for each item whether it was consistent with their habitual experience. The FEPS-II consists of 23 items presented on a 5-point Likert-type scale (“not at all” to “completely”) divided into 2 subscales, as yielded by factor analysis. “Sleep-related cognitive arousal” (originally named “focusing,” 11 items resulting in an overall value from 11 to 55) refers to the tendency to excessively think about unresolved problems (e.g., “When I sleep poorly on one night I know that it will interfere with my work performance on the next day”). The dimension “general cognitive arousal” (12 items resulting in an overall value from 12 to 60) captures the tendency to repetitively think about unresolved problems (e.g., “I often see problems that others don’t see”). The underlying rationale for the questionnaire is that dysfunctional, negative cognitions such as continually ruminating or worrying about not being able to sleep or about unresolved problems are important factors for the development and maintenance of insomnia. Internal consistency of the measure was demonstrated in 402 patients with sleep disorders and 346 healthy good sleepers for both sleep-related cognitive arousal.
Cognitive Arousal in Primary Insomnia

In the same investigation, test-retest reliability (1 to 4 months interval) was r = 0.82 for sleep-related cognitive arousal and r = 0.92 for general cognitive arousal.

The “Schlaffragebogen A” (SF-A) captures subjective aspects of sleep in the preceding night. The questionnaire includes subjective estimates of wake times (sleep onset latency and wake time after sleep onset [WASO]). Subjective sleep efficiency was calculated using SF-A wake times and PSG-documented bedtimes because bedtimes are not estimated by subjects on the SF-A. The German version of the Pittsburgh Sleep Quality Index (PSQI) was used to assess sleep habits and sleep quality in the preceding 2 weeks.

Statistical Analysis

Descriptive presentation of the data includes mean values and standard deviations. Independent t-tests were used to assess demographic and clinical differences between primary insomnia patients and healthy controls. To test for associations between sleep parameters and FEPS-II subscales, 12 general linear model analyses were performed for the full sample (including primary insomnia patients and healthy controls). The 12 outcome variables of these analyses were the SF-A- and PSG-derived sleep efficiency, WASO, and sleep onset latency for the first and second night. For each of these general linear model analyses, 5 predictor variables were used; the 2 FEPS-II subscales, the diagnosis (primary insomnia vs. healthy controls), age, and gender. For the overall effects, the level of significance was set at p < 0.004 (2-tailed) after applying Bonferroni α adjustment for multiple parallel tests (12 analyses). For single tests, the level of significance was set at p < 0.05 (2-tailed).

Table 1—Items of the FEPS-II (English translation by the authors of the current investigation)

<table>
<thead>
<tr>
<th>Question</th>
<th>Subscale</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) When I have a problem, I keep on thinking about it.</td>
<td>G</td>
</tr>
<tr>
<td>2) When I lie awake in bed, I start thinking about difficulties I will have in the near future.</td>
<td>G</td>
</tr>
<tr>
<td>3) I do not pay attention to how long it takes for me to fall asleep.</td>
<td>SR (rev)</td>
</tr>
<tr>
<td>4) I often lie in bed and cannot shut off my thoughts.</td>
<td>G</td>
</tr>
<tr>
<td>5) I am often plagued by useless thoughts that keep running through my head.</td>
<td>G</td>
</tr>
<tr>
<td>6) It happens to me often, that I worry about a problem for a long time without coming closer to a solution.</td>
<td>G</td>
</tr>
<tr>
<td>7) When I wake up in the middle of the night, I know exactly that I cannot go back to sleep at once.</td>
<td>SR</td>
</tr>
<tr>
<td>8) I often worry too much.</td>
<td>G</td>
</tr>
<tr>
<td>9) Laying in bed I ponder problems that I can’t solve before the next morning.</td>
<td>G</td>
</tr>
<tr>
<td>10) When I wake up in the middle of the night, I have to know what time it is.</td>
<td>SR</td>
</tr>
<tr>
<td>11) If I don’t fall asleep within a short time it makes me nervous.</td>
<td>SR</td>
</tr>
<tr>
<td>12) I often see problems that others don’t see.</td>
<td>G</td>
</tr>
<tr>
<td>13) I am annoyed when I wake up in the night and can’t go directly back to sleep.</td>
<td>SR</td>
</tr>
<tr>
<td>14) The fear of not being able to fall asleep makes me feel nervous.</td>
<td>SR</td>
</tr>
<tr>
<td>15) Even if there are serious problems, I can relax.</td>
<td>G (rev)</td>
</tr>
<tr>
<td>16) When falling asleep I am often scared by confusing thoughts.</td>
<td>SR</td>
</tr>
<tr>
<td>17) Already during the day, I am worried that I will not be able to fall asleep in the evening.</td>
<td>SR</td>
</tr>
<tr>
<td>18) I do not ruminate about the past.</td>
<td>G (rev)</td>
</tr>
<tr>
<td>19) When I’ve had a troublesome day I brood over it for a long time while in bed.</td>
<td>G</td>
</tr>
<tr>
<td>20) When going to bed I already know that I can’t fall asleep.</td>
<td>SR</td>
</tr>
<tr>
<td>21) Even though I know that a solution is not feasible I keep on thinking about it.</td>
<td>G</td>
</tr>
<tr>
<td>22) When I sleep poorly on one night I know that it will interfere with my work performance on the next day.</td>
<td>SR</td>
</tr>
<tr>
<td>23) I am paying close attention to how long I am awake at night.</td>
<td>SR</td>
</tr>
</tbody>
</table>

G, general cognitive arousal; SR, sleep-related cognitive arousal; rev, reverse-scored items.

(α = 0.90) and general cognitive arousal (α = 0.91). In the same investigation, test-retest reliability (1 to 4 months interval) was r = 0.82 for sleep-related cognitive arousal and r = 0.92 for general cognitive arousal.

All participants underwent 2 consecutive nights of PSG sleep monitoring. A standard laboratory procedure and PSG montage were followed. Nocturnal sleep was recorded on 24-channel EEG-polysomnographs for 8 h from lights out (23:00) until lights on (07:00). All recordings included EEG (C3-A2; C4-A1), EOG (horizontal and vertical), and EMG (submental), and were scored visually by experienced raters according to the criteria of Rechtschaffen and Kales. During the first night, all participants were screened for apneas and periodic leg movements by monitoring abdominal and thoracic effort, nasal airflow, oximetry, and bilateral tibialis anterior EMG. Sleep recordings were evaluated for the following parameters of sleep continuity: total sleep time (TST); sleep efficiency: ratio of TST to time in bed * 100%; wake after sleep onset (WASO): difference between TST and sleep period time (time from sleep onset until final awakening); sleep onset latency: time from lights out until sleep onset (defined as first epoch of stage 2); arousal index: number of arousals per hour; number of awakenings. Sleep architecture parameters were amounts of stages Wake, 1, 2, slow wave sleep (SWS), and REM sleep as percentage of sleep period time.
Due to adaptation effects, it is a common practice to exclude the first sleep laboratory night from the analysis.\textsuperscript{36} However, in the current study, we analyzed both nights because the adaptation to the lab environment might be associated with increased arousal levels, possibly emphasizing our effects of interest.

**RESULTS**

**Sample Description**

The group of primary insomnia patients consisted of 106 women and 76 men (age: 42.7 ± 11.9 years). They had a mean score of 11.1 ± 3.2 on the PSQI. Sixteen patients suffered from sleep onset insomnia, 66 from sleep maintenance insomnia, and 97 from mixed insomnia. Three patients had a complaint of non-restorative sleep in the absence of difficulty initiating and maintaining sleep. Average duration of primary insomnia was 10.9 ± 9.5 years. The control group consisted of 38 women and 76 men (age: 42.7 ± 11.9 years). They had a mean score of 11.1 ± 3.2 on the PSQI. Sixteen patients suffered from sleep onset insomnia, 66 from sleep maintenance insomnia, and 97 from mixed insomnia. Three patients had a complaint of non-restorative sleep in the absence of difficulty initiating and maintaining sleep. Average duration of primary insomnia was 10.9 ± 9.5 years. The control group consisted of 38 women and 76 men (age: 42.7 ± 11.9 years). Mean PSQI score was 3.1 ± 1.7. There were no significant group differences for sex distribution ($\chi^2(1,234) = 2.09, p = 0.15$) or age ($t_{234} = 1.35, p = 0.18$). The patient group had significantly higher PSQI values than the control group ($t_{234} = 23.73, p < 0.001$).

**Group Comparison of Sleep Parameters**

Polysomnographic and subjective sleep data of the 2 groups are presented in Table 2. With respect to polysomnography, insomnia patients had a significantly lower sleep efficiency and total sleep time than healthy controls on both nights. Additionally, SWS % and REM % were decreased in primary insomnia patients. WASO, Wake %, and the number of awakenings were significantly increased. Furthermore, in the first night, S1 % was higher in insomnia patients. With respect to subjective data, insomnia patients had significantly lower sleep efficiency as well as significantly increased WASO and sleep onset latency in both nights.

**Group Comparison of Cognitive Arousal Levels**

With respect to the FEPS-II subscales, primary insomnia patients had significantly higher values than the control group for both sleep-related cognitive arousal ($t_{234} = 12.65, p < 0.001$) and general cognitive arousal ($t_{234} = 7.49, p < 0.001$; see Figure 1). The correlation between the 2 FEPS-II subscales across the whole group was $r = 0.62$.

**Association between Cognitive Arousal and Sleep Parameters**

The results of the general linear model analyses with the sleep parameters as dependent variables and the 2 FEPS-II subscales as well as the diagnosis as independent variables are presented in Table 3. Sleep-related cognitive arousal was significantly related to all sleep parameters apart from objectively determined sleep latency. More specifically, sleep-related cognitive arousal was negatively associated with sleep efficiency and positively with WASO and subjectively determined sleep latency. This indicates that increased sleep-related cognitive arousal is associated with poor sleep quality, even when controlling for general cognitive arousal and the diagnosis of the participants. General cognitive arousal was only related to objectively determined sleep efficiency in the second night, indicating that increased general cognitive arousal is associated with increased sleep efficiency when controlling for sleep-related cognitive arousal and the diagnosis of the participants. While there seems to be an association between general cognitive arousal and sleep latency of the second night, the corresponding overall effect of the general linear model did not reach statistical significance after applying Bonferroni correction.

**Association between Cognitive Arousal and Sleep Parameters for Insomnia Subgroups**

Additional analyses were conducted by restricting the insomnia patients group to (a) sleep-maintenance insomnia pa-
patients and (b) insomnia patients with objective short sleep duration. Concerning the differentiation in insomnia with and without short sleep duration, we split up the insomnia group using an 85% sleep efficiency criterion for the PSG data of the second night.3 For both sleep-maintenance insomnia patients and insomnia patients with objective short sleep duration, there were no major differences in the association between cognitive arousal and sleep parameters to the results reported in Table 3.

**DISCUSSION**

In the current study, we investigated the relationship between trait aspects of sleep-related and general cognitive arousal levels and both subjectively and objectively determined sleep parameters of two consecutive sleep lab nights. In line with our first hypothesis, primary insomnia patients reported both increased sleep-related arousal and increased general cognitive arousal compared to healthy controls. In line with our second hypothesis, increased sleep-related cognitive arousal levels were significantly related to measures of poor sleep. However, contrary to expectations, our analyses revealed that general cognitive arousal was not independently related to disturbed sleep.

Previous studies have primarily focused on the sleep onset period when investigating the association between cognitive arousal and sleep parameters in poor sleepers. Concerning this, we replicated previous findings of an association between cognitive arousal and subjectively reported sleep latency.10-17 However, there has been a lack of information about the association between cognitive arousal and sleep maintenance parameters. The current study filled this gap by investigating sleep efficiency and wake after sleep onset and their relationship to sleep-related and general cognitive arousal. The results showed that both increased WASO and decreased sleep efficiency are related to sleep-related cognitive arousal. This is in line with the clinical experience that patients with sleep maintenance disorders report a cognitive hyperactivity during the night similarly to patients with sleep onset insomnia.

Furthermore, our data support the assumption that sleep-related cognitive arousal is more closely associated with sleep disturbances than general cognitive arousal. In the current study, general cognitive arousal did not show any significant

![Figure 1—Mean FEPS subscale scores (with standard deviations) of 182 primary insomnia (PI) patients and 54 good sleeper controls (GSC)](image)

**Table 3—Results of the 12 general linear model analyses with sleep-related parameters as dependent variables and the FEPS-II subscales, the diagnosis, age, and gender as independent variables**

<table>
<thead>
<tr>
<th></th>
<th>General linear model fit</th>
<th>Sleep-related cognitive arousal</th>
<th>General cognitive arousal</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F</td>
<td>p</td>
<td>β</td>
<td>F</td>
</tr>
<tr>
<td><strong>SF-A, 1. Night</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep efficiency</td>
<td>7.28</td>
<td>&lt; 0.001</td>
<td>-0.22</td>
<td>19.06</td>
</tr>
<tr>
<td>WASO</td>
<td>5.59</td>
<td>&lt; 0.001</td>
<td>0.28</td>
<td>6.87</td>
</tr>
<tr>
<td>Sleep latency</td>
<td>5.50</td>
<td>&lt; 0.001</td>
<td>0.66</td>
<td>25.12</td>
</tr>
<tr>
<td><strong>SF-A, 2. Night</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep efficiency</td>
<td>8.60</td>
<td>&lt; 0.001</td>
<td>-0.18</td>
<td>16.00</td>
</tr>
<tr>
<td>WASO</td>
<td>7.00</td>
<td>&lt; 0.001</td>
<td>0.22</td>
<td>6.81</td>
</tr>
<tr>
<td>Sleep latency</td>
<td>6.43</td>
<td>&lt; 0.001</td>
<td>0.66</td>
<td>24.96</td>
</tr>
<tr>
<td><strong>PSG, 1. Night</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep efficiency</td>
<td>16.68</td>
<td>&lt; 0.001</td>
<td>-0.35</td>
<td>25.50</td>
</tr>
<tr>
<td>WASO</td>
<td>15.91</td>
<td>&lt; 0.001</td>
<td>1.39</td>
<td>22.16</td>
</tr>
<tr>
<td>Sleep latency</td>
<td>1.55</td>
<td>0.177</td>
<td>0.41</td>
<td>3.39</td>
</tr>
<tr>
<td><strong>PSG, 2. Night</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep efficiency</td>
<td>12.95</td>
<td>&lt; 0.001</td>
<td>-0.23</td>
<td>10.66</td>
</tr>
<tr>
<td>WASO</td>
<td>15.64</td>
<td>&lt; 0.001</td>
<td>0.64</td>
<td>7.06</td>
</tr>
<tr>
<td>Sleep latency</td>
<td>2.29</td>
<td>0.047</td>
<td>0.25</td>
<td>0.38</td>
</tr>
</tbody>
</table>

After the application of Bonferroni correction, the level of significance was set at p < 0.004 for the overall effects of the general linear models. PSG, polysomnography; SF-A, “Schlaffragebogen A”; WASO, wake after sleep onset.
relationship to poor sleep that was independent of sleep-related cognitive arousal. This could explain, at least partially, the conflicting results reported by van Egeren et al.\(^{14}\) and Wicklow and Espie.\(^{18}\) While the first study focused on increased cognitive activity in terms of general cognitive arousal, the second study investigated pre-sleep cognitive activity mainly characterized by thinking about sleep loss and its possible consequences. Consistent with our results, the first study did not find a significant relationship with sleep onset latency, while the second study reported significant correlations.

With respect to the clinical significance of our findings, it has to be noted that the explained variance is generally low for cognitive arousal levels. However, the mean group difference in the FEPS-HII subscale “sleep-related cognitive arousal” (12.4 points) corresponds to a sleep efficiency difference of 3.5% to 5.1%, a WASO difference of 10.2 to 17.7 minutes, and a difference in subjective sleep onset latency of 9.4 to 9.5 minutes (please refer to the β-values of Table 3). These data support the hypothesis that sleep-related cognitive arousal is a clinically relevant factor for sleep disturbances.

Several limitations of the present study have to be addressed. First, the observations in the current study are based on cross-sectional data; thus no causal relationship between cognitive arousal and sleep parameters can be inferred from this design. Second, previous studies showed that more than two nights are needed to derive stable estimates of both polysomnographic and diary-rated sleep in insomnia patients.\(^{37}\) Therefore, future studies are needed to investigate the association between cognitive arousal and sleep parameters across multiple nights. Third, the clinically referred patients in the current study are a heterogeneous group, including different insomnia subtypes and lifetime histories of medication use. However, this makes the patient group more representative of the population of clinically referred primary insomnia patients in general; this is especially important as some previous investigations in this field have recruited nonclinical samples, and the results of the current study were stable across different insomnia subgroups. Furthermore, in the current analyses, we did not discriminate between worry and rumination, although there is some evidence that these two cognitive processes are separate constructs with respect to their impact on sleep disturbances.\(^{10}\) Additionally, since we did not include a state arousal measure, the decisions of the current analysis are restricted to trait aspects of arousal. Moreover, standardized bedtimes of 8 hours duration have been used in the current study resulting in differences to participants’ habitual sleep patterns. However, most sleep parameters are more comparable between subjects when standardized bedtimes are used. Last, both insomnia patients and healthy controls tended to overestimate their PSG-determined total sleep time. With respect to insomnia patients, this result was unexpected, and we cannot rule out that this might have affected our results on trait aspects of cognitive arousal. However, previous studies conducted both by our group\(^{55}\) and others\(^{48}\) also reported that overestimating total sleep time is not as uncommon in insomnia patients as generally assumed.

Despite these limitations, the current study provides novel data suggesting that cognitive arousal plays an important role for both sleep-onset and sleep-maintenance problems and that sleep-related cognitive arousal is more strongly related to sleep disturbances than general cognitive arousal. Although the current study design does not permit inferences of causality, future studies are worthwhile to investigate the effects of cognitive techniques that specifically target sleep-related cognitive arousal. Concerning this, Harvey et al.\(^{18}\) suggested (a) identifying and evaluating patients’ sleep-related worries and thoughts, and (b) reducing monitoring for sleep-related threat by actively directing attention away from it. Dedicating more effort to these psychological interventions might improve the treatment efficacy of cognitive-behavioral therapy for insomnia.

References

Sleep disorders are highly prevalent across all age groups, and can result in significant multiorgan dysfunction, with serious health consequences. If diagnosed early and appropriately, most sleep disorders are treatable. However, despite the prevalence of sleep disorders and the relationship of these disorders to underlying medical conditions, physician performance on sleep-related knowledge or skills assessments, from medical students to medical schools, has historically attributed to the limited inclusion of sleep medicine in medical school curricula. A 1978 survey by the American Sleep Disorders Association showed that 46% of medical schools provided no education in sleep medicine. Ongoing concerns of government agencies and other professional groups about the paucity of sleep disorders-related medical education resulted in several strategies to increase sleep medicine education, including formation of a special task force of American Sleep Disorders Association on medical education in sleep and sleep disorders, and the Sleep Academic Award Program of the National Commission on Sleep Disorders Research. Although the
Sleep Academic Awardees have developed curricula models and have successfully implemented sleep education in their respective institutions, incorporating sleep medicine into the curricula of medical schools remains difficult, due to the inadequacy of curriculum, and time constraints of faculty and learners, and the limited availability of qualified physician-sleep educators.

Delivery of instruction over the Internet, including the use of online courses and learning-management systems, has been used to enhance access to content designed by experts in particular topic areas and to address inadequacies in the curriculum and time limitations of the teacher and learner. The results of a comprehensive meta-analysis on the effectiveness of Internet-based learning in the health professions found that the effects of Internet delivery of instruction were equivalent to those using traditional instruction methods. However, the authors of this review reported that few studies that compared Internet-based with traditional instruction also assessed the learners’ skills (<16%) or behaviors and patient effects (<8%); the review did not look at the cost of Internet-based compared to traditional instruction. Thus, the literature provides limited guidance to assist specialty educators whose clinical content is important but must decide if it is cost effective to deliver instruction online.

Therefore this study sought to address the issues related to curriculum content, learner and instructor time constraints, and the availability of experts by developing and evaluating an online sleep medicine curriculum. The evaluation included the short- and long-term performance-based learner outcomes and the costs associated with developing and implementing the online sleep medicine curriculum, as well as comparing these results with those of a traditional face-to-face workshop.

**METHODS**

**Curriculum Competencies and Design**

Four competencies previously identified by Strohl et al. as core knowledge and skills for medical education in sleep medicine served as the common curriculum content for third-year medical students and focused on the students’ ability to (1) articulate the putative nature of sleep medicine; (2) identify common sleep disorders with associated signs and symptoms; (3) perform a sleep history; and (4) manage common sleep disorders to improve sleep, reduce sleepiness, or both. Four instructional modules were developed with the competencies threaded across each: (1) sleep physiology and chronobiology, (2) sleep disordered breathing, (3) hypersomnias (excessive daytime sleepiness), and (4) parasomnias.

Specific objectives for each module were outlined. The face-to-face and e-learning modules were then developed in parallel to ensure concordance between formats. The learning modules were then pilot tested and revised based on feedback from fourth-year medical students who were completing an ambulatory-medicine rotation; the modules were modified as needed to enhance clarity and education impact. The final versions of both formats were then implemented. A PowerPoint presentation (Office 2003, Version 11, Microsoft, Redmond, WA) was the primary instruction method for both delivery formats, and each learning point was explicitly linked to the objectives. Content was drawn from a variety of resources, including sleep medicine textbooks, journal review articles, and existing electronic learning materials. The key objectives were further enhanced through incorporation of case scenarios and video clips. The online modules were finalized using Microsoft Producer (Producer 2003Microsoft) to support incorporation of video clips, images, and oral narration. The modules were posted on the Medical College of Wisconsin education website, ANGEL, (A New Global Environment for Learning) e-learning platform for courses and course evaluation for medical students.

**Study Design**

All third-year medical students rotating on the required pediatrics clerkship from July 1, 2005, to June 30, 2006, participated. The students were alternately assigned to the face-to-face or e-learning delivery format, with a balanced number participating in each format through the year. Students, per institutional review board-approved protocol, were informed that their participation and test results would not be included in their clerkship evaluation.

Prior to completion of the instruction, all students completed the online multiple-choice examination. At the end of the rotation, students also participated in a post-instruction standardized patient interaction that was focused on sleep and incorporated into an objective structured clinical examination (OSCE).

Students assigned to the face-to-face workshop met on a single occasion during the rotation for 2.5 hours. Two physician-sleep medicine educators served as the workshop instructors, providing the live narrative for the PowerPoint slides and interactive discussion throughout the workshop. No enduring materials were distributed.

The e-learning group was given access to the sleep-education modules beginning on the first day of the rotation after completing the multiple-choice pre-intervention test. They were encouraged to complete the modules by the end of the rotation. Faculty then audited the students’ write-ups of results obtained through the patient history and physical examination. Audits also included sleep content for those students who then participated in an ambulatory medicine rotation after they completed the pediatrics rotation.

**Learning Outcome Instruments and Data Collection**

The Kirkpatrick 4-stage training-evaluation model was used to frame instrumentation decisions at 3 levels: (1) satisfaction or reaction related to instruction, (2) learning, and (3) application or transfer of behavior to practice. Learner satisfaction (Level 1) was assessed for both e-learning and face-to-face formats, with evaluation survey items focused on clarity of objectives, organization, effectiveness of instruction, and impact on learning. The survey rating scales and the number of questions were not identical (due to different delivery formats), but similar items were grouped into Effective Instruction and Apply Knowledge, with the response data transformed to create equivalent scales (1 = positive).

Forty-seven multiple-choice questions were developed to assess key objectives (Level 2) per a test blueprint composed
of core instruction domains. These questions were tested with 134 fourth-year students who had no prior exposure to a sleep medicine curriculum. Using the item statistics, the most effective questions were retained to appropriately sample the content blueprint, resulting in a 20-item multiple-choice test that was administered before and after the instructional intervention. All students completed the online multiple-choice test on the first day of the rotation (pre-intervention test) and again within 2 weeks of completing the education and before they completed the clerkship (post-intervention test). The multiple-choice post-intervention test was locked, only appearing once the learner had viewed all 4 modules (e-learning group) or after the workshop (face-to-face group). The post-intervention test could be opened only once and was timed to lock out at 30 minutes.

A standardized patient case was developed to highlight students’ sleep-specific history-gathering skills and was included in the required end-of-clerkship OSCE (Levels 2-3). The patient scenario involved a grade-school–aged child with school-performance issues. The child was accompanied by a parent, who was trained to ask the medical student whether the child’s sleep disturbances, which the parent had observed, could be the cause of the child’s inattention at school. The medical student’s performance was rated using a checklist focused on sleep history—including sleep disordered breathing, sleepiness, and sleep quality and quantity—along checklist items for a focused physical examination.

Assessing the students’ learning retention and transfer and application of sleep medicine knowledge to patient care (Level 3) required history-and-physical write-ups for approximately 25% of the pediatric clerkship students who went on to complete a required ambulatory medicine rotation during the study period (2-12 months after completion of the sleep medicine education). A history-and-physical sleep-audit coding sheet, designed to assess students’ long-term knowledge retention and transfer of knowledge to patient care, was developed using validated screening history mnemonics such as BEARS19 (bedtime issues, excessive daytime sleepiness, awakenings during the night, regularity and duration of sleep, snoring) and ISNORED (Insomnia, snoring and sleep quality, not breathing, older or obese, restorative or refreshing sleep, excessive day time sleepiness, drugs).

As part of her or his ambulatory-medicine rotation, each student was required to complete 4 write-ups. These de-identified patient write-ups were audited for content regarding sleep disorders and sleep history. An audit form was used to score the presence or inclusion of sleep-related complaints and incorporation of a sleep-related assessment and care plan. The audit form—which used a checklist structure to record the presence or absence of sleep-related details in the history of present illness, review of systems, or past medical history (1 point)—and the presence of sleep-specific details in the assessment and plan (1 point) resulted in a maximum of 2 points per write-up and a total maximum score of 8 points per student (4 write-ups × 2 points).

Audit-coding consistency was assessed by 2 physicians, who independently coded a common sample of the history and physical examination to determine concordance (Pearson correlation, 0.6). The coded data from the audit sheets were transferred to an Excel spreadsheet (Microsoft) for analysis, with notations made regarding face-to-face or e-learning instruction format, to enable comparison of findings by delivery method.

**Development and Implementation Time and Cost Data**

Time logs submitted by physician authors and educators from project commencement to project completion provided longitudinal time records associated with curriculum development and revisions, including supplementary materials, production of the face-to-face and on-line education models, and face-to-face teaching time. Faculty costs, based on hours invested throughout the project, were calculated using the most recent Association of America Medical Colleges Faculty Database Report,20 so that data would be generalizable to other medical schools. Staff costs were calculated based on actual salaries, including fringe benefits; the college’s Office of Human Resources established these salaries through a comparative analysis with similar positions nationally. Supplies and expenses were tracked using the college’s internal budgeting and purchase-order system (e.g., CD-ROMs, duplication or materials, video production) during the study period by method.

**Statistical Analysis**

Student performance on the pre-intervention and post-intervention multiple-choice tests were compared based on the learning methods (e-learning vs face-to-face) using a repeated-measures analysis of variance (SPSS, version IBM, Chicago, IL). Audit data sets from the standardized-patient OSCE and patient notes were analyzed by the student i-test comparing face-to-face and e-learning groups.

**RESULTS**

Results are reported by Kirkpatrick evaluation model level, each with a specific sample size, because sample size varied by instrument due to the longitudinal nature of the data collection process (see Figure 1).

**Level 1: Satisfaction with Instructional Format**

Evaluations were submitted by 173 students prior to the end of the pediatric clerkship, with slightly more students completing their instruction via online learning (n = 111) versus the face-to-face format (n = 62) due to the students’ rotation schedules. The face-to-face learners rated instruction effectiveness (mean ± SD) (1.73 ± 0.80; p < 0.01) and application of sleep knowledge (1.77 ± 0.89; p < 0.05) more positively, compared with the online learners (instruction effectiveness: 2.12 ± 0.55; application of sleep knowledge: 2.04 ± 0.54) using a 5-point rating scale, with 1 being the most positive.

**Level 2: Knowledge of Sleep Medicine via Multiple-Choice Examination**

Data from the pre-intervention and post-intervention multiple-choice sleep medicine examination was available for 207 students: 100 face-to-face learners and 107 online learners. Overall, student performance on the multiple-choice examination revealed a significant pre-intervention-to-post-intervention increase from 53% to 73%. Performance increased significantly by group: face-to-face learners’ performance increased by 16% (from 52% pre-intervention to 68% post-intervention) and on-
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Figure 1—Diagram outlining the number (n) of students enrolled in Face to Face vs Online and the results of three levels of learning outcomes

Level 1. Satisfaction with Instructional Format n = 173

Face to Face n = 62
Online n = 111

Instructional effectiveness

1.73 1 = More Positive 2.12

1.77 2.04

Application of sleep knowledge

Level 2. Knowledge of Sleep Medicine (via MCQ) n = 207

Face to Face n = 100
Online n = 107

Pre test 52%  Post test 68%
p < 0.001

Pre test 55%  Post test 77%
p < 0.001

Level 3. Application of Learning

OSCE n = 190
(Max. of 35 Items)

Face to Face n = 93
Score = 23.3

Online n = 97
Score 23.9

Patient write ups n = 58
(0-2 Min-Max score)

Face to Face n = 32
Score = 0.89

Online n = 26
Score = 0.92

97 online) and were reported as the number of checklist items completed (maximum 35). No significant differences in OSCE performance were obtained by group: face-to-face learners 23.3 (SD 3.3), on-line learners 23.9 (SD 3.1).

Fifty-eight students who completed the pediatric sleep medicine education enrolled in the ambulatory-medicine rotation during the study period; write-ups were available for audits from all of these students. No significant difference was found using t-test analysis (p = 0.083) by learner group: the mean write-up score of the 32 face-to-face learners was 0.89 (SD = 1.28), the mean score of the 26 on-line learners (n = 26) was 0.92 (SD = 1.02), and the standard error of the mean was 0.2 for both groups.

Cost

A comparison of the costs of curriculum design and delivery, based upon delivery method, revealed that the development costs for physician authors were roughly equivalent (see Table 1). However, the educator-related costs associated with on-line curriculum design added an additional 160 hours to the costs during the first year. Total first-year development and instruction-delivery costs were equivalent: additional physician hours were required for the repeated delivery of the face-to-face curriculum ($21,640) and additional educator costs were required for support of on-going e-learning ($21,752).

CONCLUSIONS

The primary objective of this study was to determine the cost and learning effectiveness of online education compared with traditional face-to-face instruction, which is repeated with each clerkship rotation. This study demonstrates that, although online delivery requires a start-up cost comparable to that of traditional face-to-face instruction during the initial implementation year, these costs are offset when the curriculum is incorporated in a required clinical rotation because of the increased costs associated with the need to repeatedly present the same material throughout the year with the face-to-face instruction. Costs associated with online instruction after initial development are minimal, whereas physician delivery of face-to-face instruction is ongoing.

Learner satisfaction for the students who completed the face-to-face instruction was higher, but learner performance was equivalent between groups or was slightly better for online learners. Student satisfaction may be the result of the “absent instructor” phenomenon common with the non-moderated online format. Students in the face-to-face group were able to directly interact, to ask questions specific to their learning needs, and to have personal contact with sleep medicine physicians.

Study conclusions may be limited by several factors. (1) Student exposure to sleep medicine-related patients during the clinical portions of their clerkships (per clinical experience log data recorded by students through their third-year clerkships) shows minimal sleep-related patient exposure. (2) The number of students who completed write-ups of the results of their patients’ histories and physical examinations was limited. This was due to the time lag between the focused sleep education and the collection of the write-ups during the ambulatory-medicine rotation. Unfortunately, this could not be controlled by the authors; because there were no significant differences.

line learners’ performance increased by 22% (from 55% pre-intervention to 77% post-intervention) (p < 0.001, effect size [partial eta²] = 0.59).

Level 3: Transfer or Application of Learning Assessed via Performance in Relationship to the Standardized-Patient and Patient Write-ups

Students’ performance data from the results of the patient history and physical examination were available from the pediatric end-of-rotation OSCEs for 190 students (93 face-to-face,
between face-to-face and on-line learners, further analysis was not preformed. (3) An inherent deficiency is associated with the use of the log-based medical records of clinical encounters as a valid measure of transfer of knowledge. (4) The study was performed in a private medical school that is located in the upper Midwest and is attended by students who are demographically representative of all US students; hence, additional studies may be needed to determine the generalizability of our findings to students from medical schools in other locations and those in public institutions.

Cognizant of these limitations, this study does demonstrate the cost effectiveness of online learning as an economically and educationally viable instruction platform for clinical clerkships.

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### ACKNOWLEDGMENTS

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Address correspondence to: Dr. Hari Bandla, Associate Professor of Pediatrics, Section Chief, Pediatric Sleep Medicine, 5841 S. Maryland Avenue, C104 E, University of Chicago, Chicago, IL 60605; Tel: (773) 702-5216; Fax: (773) 834-4819; E-mail: hbandla@uchicago.edu.

### DISCLOSURE STATEMENT

This was not an industry supported study. The authors have indicated no financial conflicts of interest.
Mind’s Eye: A Case of Out-Of-Body Experiences

Miranda Occhionero, M.D., Ph.D.; Vincenzo Natale, M.D., Ph.D.; Monica Martoni, M.S., Psy.D.; Lorenzo Tonetti, M.S., Psy.D.
Department of Psychology, University of Bologna, Italy

Out-of-body experiences are the phenomena of seeing the image of one’s body from an external perspective. We report the case of a patient affected by psychophysiological insomnia who presents hallucinatory phenomenon, successfully treated with haloperidol.

We hypothesize that these hallucinations during psychophysiological insomnia are expression of an alteration of specific neurocognitive networks that regulate the cognitive arousal systems.

**Keywords:** Out-of-body experiences, psychophysiological insomnia, sleep assessment, dreaming


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**REPORT OF CASE**

SC, a 50-year-old female, reported a history of insomnia for approximately 3 years. To permit a correct diagnosis, the assessment protocol provides a sleep log, actigraphy, and anxiety (STAI) and depression (ZUNG) questionnaires. The patient evaluation was carried out through 4 sessions, during which other sleep disorders were excluded. The diagnosis was psychophysiological insomnia characterized by difficulty maintaining sleep (see Table 1).

The patient spontaneously reported that she had OBEs 3 times in the previous 6 months during nighttime awakenings. The description provided by the patient was extremely detailed and vivid. She described her body split: “I see myself as if I was from an airplane and looking down at a distance of about five feet. I feel split and I see myself down. I have my body down, I’m not in my body, I’m out of my body. My mind sees my body, I see the shape of my body. The part of mine that is over...it seems strange to me looks like an angel, an entity. I see the body there but I’m like air...”

The patient estimated that the duration of each phenomenon was very short, but not static and therefore not comparable to a photograph. She describes the experience as a small video with an abrupt, approximately half-minute onset and offset. An interesting aspect was related to the uncertain reality testing: the patient was not able to determine whether the hallucinatory experience occurred in the real world or in her mind. Certainly, she was aware of the real nature of the phenomenon.

Given the unpredictable and rare nature of the phenomenon, it was not possible to perform a PSG recording to understand the physiological condition (sleep or wake) in which the OBEs occur.

The patient also reported that in recent months, her dreaming activity had significantly increased. The dreams had become very complex in content and very vivid regarding visual hallucinatory aspects.

She judged these hallucinatory experiences to be very real, but she was not worried about them. This condition was accompanied by feelings of strangeness, wonder, amazement, and happiness at seeing her body sleeping on the bed. During the day, she believed that these phenomena could be indicators of a severe psychological disorder.

The emotional dissociation related to the dream should not leave amazed. Cognitive research on dream bizarreness (and OBEs are a case of bizarreness in the representation of self)
A marked improvement of the subjective symptoms was observed, without any OBEs reported.

At the time of assessment, the patient took one-half tab benzodiazepines (brotizolam 0.125 mg and 0.33 mg of lorzetam) before bedtime. These drugs did not produce any improvement of her symptoms. We considered appropriate to redefine the therapy with an integrated approach, combining pharmacological (neuroleptic at low doses) and psychological support. The rationale for this choice was to use the neuroleptic, which has a hypnotic effect and an ideation reduction effect. The latter action was intended to counteract the OBEs and the excessive oneiric activity. Seven months after the beginning of therapy, a marked improvement of the subjective symptoms was observed.

### DISCUSSION

The interesting aspect of this case report is the occurrence of OBEs, likely triggered by the frequent night awakenings. Visual hallucinations are quite common occurrences during hypnagogic and hypnopompic hallucinations and are a physiological aspect of these phases. Such experiences, however, are usually simple visual images characterized by the presence of lines, flashes, and simple geometric shapes. In this case report we observed OBEs which are quite rare in a clinical setting and could be considered a particularly case of recurrent complex visual hallucinations (RCVH). In our opinion, the drowsiness can be considered a gray area characterized by the psychophysiological proximity to sleep on the one hand, and the state of low perceptual and sensory stimulation on the other. Both of these factors (physiological and environmental) destabilize the control processes and the levels of consciousness typical of wakefulness. It is possible that this situation could facilitate hallucinatory experiences of self as a result of two components: (1) insufficient neurofunctional integration and lack of binding information from different neural networks responsible for the perception of one’s own body as an integral part of psychophysical self-awareness, and (2) the instability of psychophysiological arousal with rebound both on the maintenance of sleep and mental activity. Research on psychophysiological insomnia attributes a specific role to an excessive activation of the central and/or autonomic nervous system (hyperarousal hypothesis). According to this hypothesis, a high level of arousal could activate elaborative and mnemonic cortical processes. This condition could lead to the occurrence of hallucinations and excessively vivid oneiric activity as expressions of an alteration of specific neurocognitive networks that regulate the cognitive arousal systems. In selected cases with intense oniric activity and maintaining primary insomnia, pharmacological treatment with low doses of a neuroleptic should reduce cognitive hyperarousal given its well-documented effects on the fronto-limbic dopaminergic pathway.

### REFERENCES


### DISCLOSURE STATEMENT

This was not an industry supported study. The authors have indicated no financial conflicts of interest.
Periodic limb movements (PLM) during sleep are believed to be under the control of the sympathetic nervous system and may cause interrupted sleep and daytime sleepiness. The presence of microarousals occurring simultaneously, before or after the onset of this motor event, is a common finding. The transient increase in heart rate (HR) concomitant with these PLM-related arousal events is frequently observed in patients with and without sleep disorders.

**REPORT OF CASE**

A 67-year-old woman was referred to our sleep disorders unit, with complaints of snoring and suspected obstructive sleep apnea. Although she was not aware of breathing pauses during sleep, she reported that her sleep was interrupted by unexplained awakenings. She had a subjective feeling of daytime sleepiness as was apparent from the Epworth Sleepiness Scale (ESS) score of 17 from a maximum of 24. She described a tendency to fall asleep easily in different passive situations. Symptoms of restless legs syndrome (RLS) were not present. She reported retiring to bed at 22:00 and waking up at 06:00. Her body mass index (BMI) was 37. The results of her polysomnographic evaluation revealed an apnea-hypopnea index (AHI) of 8.9, showing mainly hypopneas related to REM sleep (REM AHI = 23.0; NREM AHI = 6.1). Esophageal pressure was not recorded, and scoring of respiratory effort-related arousals (RERAs) was not performed since airflow was recorded by a thermistor, which is not a reliable sensor for the measurement of RERAs.

She slept during the whole night on her back and snored continuously, with a maximum loudness of 69 dB. Continuous PLM were recorded only during the first third of the night and were scored according to standard criteria. Non-PLM were not recorded. There were 199 periodic leg movements, of which 136 (68.3%) were associated with EEG arousals. The PLM index was 28.6, and the PLM arousal index was 19.6. Although not all leg movements were associated with arousals, it was remarkable that continuous brady/tachycardia (between 50-75 bpm, compared to a baseline about 53-55 bpm) was recorded in concomitant with the periodic leg movements (Figure 1).

**DISCUSSION**

The present case highlights the close relationship between PLM and significant heart rate changes independent of the presence of arousals. A number of studies have demonstrated a temporal relation between PLM and HR changes. However, a variable portion of these electrocardiographic events were accompanied by cortical arousal. In one study of 8 PLM patients, it was found that HR changes associated with PLM occur whether or not there is an accompanying EEG arousal. The HR began to increase 3 cardiac cycles before the onset of PLM and peaked at 4 cardiac cycles after the onset of PLM. Sforza et al. found that PLM were associated with visible EEG microarousals lasting longer than 3 seconds in one-third of all PLM. These previous observations are in concordance with our findings. In the present case, a remarkable and continuous brady/tachycardia changes in parallel with PLM events not always associated with an EEG arousal pattern was evident. Since we did not score RERAs, it is theoretically possible that slight variations in airway resistance were associated with PLM related HR changes. Nevertheless, since prominent HR changes occurred only during the period where PLM were present, it is unlikely that the described HR pattern is related to a breathing abnormality.

Recently, it was shown that in patients with PLM during sleep, a periodic sympathetic activation underlying the increase in HR occurred synchronously with the rise in the EEG delta activity just before the onset of the motor event. This was followed by an increase in fast EEG activity and HR whether or not the PLM was associated with arousals. This chain of events is most probably under the general control of a common mechanism, i.e., “the cyclic alternating pattern,” which has been shown to have a gating control function on the generation of PLM. The recently reported association of incident cardiovascular disease with PLM during sleep in a large cohort of community dwelling elderly men living in the US, and the increased mortality risk in patients with systolic heart failure and PLMI ≥ 5 emphasize the need for further studies addressing the possible mechanisms by which PLM could be involved in the pathogenesis of cardiovascular disorders.
Note the continuous and prominent brady/tachycardia changes concomitant with periodic limb movements (PLM) during sleep. This compressed view of the HR changes across night allows a simple and rapid visualization of this typical HR pattern which accompanied the PLM activity during sleep. This patient also showed REM-related breathing abnormalities and continuous snoring while sleeping in the supine posture during the whole night. The amplified area, illustrates a 3-min epoch showing a sequence of PLM events as part of the period in which prominent HR changes were observed in parallel with the occurrence of PLM events. (RAT, right anterior tibialis; LAT, left anterior tibialis).

Figure 1—Sleep Disorder Unit - Loewenstein Hospital

REFERENCES


Address correspondence to: Arie Oksenberg, Ph.D., Sleep Disorders Unit, Loewenstein Hospital Rehabilitation Center, POB 3 Raanana, Israel; Tel: 972-9-7709122; Fax: 972-9-7709123; E-mail: arieo@clalit.org.il

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Sodium Oxybate for Narcolepsy with Cataplexy: Systematic Review and Meta-Analysis

Mashael K. Alshaikh, B.C.P.S.1,2; Andrea C. Tricco, Ph.D.; Mariam Tashkandi, M.D.; Muhammad Mamdani, Pharm.D.; Sharon E. Straus, M.D., M.Sc.; Ahmed S. BaHammam, M.D.; Sharon E. Straus, M.D., M.Sc.3,5; Ahmed S. BaHammam, M.D.; 1University Sleep Disorders Center, King Saud University, Riyadh, Saudi Arabia; 2Medication Safety Research Chair Fellow King Saud University, Riyadh, Saudi Arabia; 3Li Ka Shing Knowledge Institute of St Michael’s Hospital, Toronto, Ontario, Canada; 4Applied Health Research Centre, St. Michael’s Hospital, Toronto, Ontario, Canada; 5Division of Geriatrics, University of Toronto, Toronto, Ontario Canada

Study Objectives: To assess the efficacy and safety of sodium oxybate (SXB) in narcolepsy-cataplexy patients.

Design: Systematic review and meta-analysis.

Patients: Adults with narcolepsy-cataplexy.

Interventions: SXB.

Measurements and Results: Electronic databases (e.g., MEDLINE) and references of included studies were searched to identify randomized controlled trials (RCTs) assessing the efficacy and safety of SXB for patients with narcolepsy-cataplexy. Risk of bias was appraised using the Cochrane risk of bias tool. Meta-analysis was conducted in Review Manager Version 5. Six RCTs and 5 companion reports were included after screening 14 full-text articles and 483 citations. All were private-industry funded. SXB (usually 9 g/night) was superior to placebo for reducing mean weekly cataplexy attacks (n = 2 RCTs, mean difference [MD]: −8.5, 95% CI: −15.3, −1.6), increasing maintenance wakefulness test (MWT) (n = 2, MD: 5.18, 95% CI: 2.59-7.78), reducing sleep attacks (n = 2, MD: −9.65, 95% CI: −17.72, −1.59), and increasing Clinical Global Impression scores (n = 3, relative risk [RR]: 7.74, 95% CI: 3.2, 19.2), vomiting (n = 2, RR: 11.8, 95% CI: 1.6, 98.4), and dizziness (n = 3, RR: 4.3, 95% CI: 1.1, 16.4). Enuresis was not significantly different from placebo (n = 2, RR: 2.6, 95% CI: 0.8, 9.6). All meta-analyses had minimal statistical heterogeneity (p-value > 0.1).

Conclusion: Narcolepsy patients on SXB have significant reductions in cataplexy and daytime sleepiness. SXB is well tolerated in patients with narcolepsy, and most adverse events were mild to moderate in severity.

Keywords: Sodium oxybate, Xyrem, randomized controlled trial, systematic review, meta-analysis, narcolepsy, cataplexy


Narcolepsy is a sleep disorder characterized by excessive daytime sleeping (EDS) associated with irresistible attacks of sleep, sudden loss of muscle tone (cataplexy), disrupted nocturnal sleep, hypnagogic/hypnopompic hallucinations, and sleep paralysis.1 Cataplexy is specific to narcolepsy and is the most accurate diagnostic marker of the disease. It is characterized by a sudden, usually bilateral, partial or complete loss of muscle tone that is provoked by emotional stimuli. Studies have shown that 65% to 75% of patients with narcolepsy have cataplexy.1,3 The prevalence of narcolepsy with cataplexy is approximately 25 to 50 per 100,000 people, with an incidence of approximately 0.74 per 100,000 person-years.2,3 It is often extremely incapacitating, interfering with every aspect of life, including work and social settings.1,4,5

Currently there is no cure for narcolepsy, with treatment focusing on symptom control. Pharmacological management of EDS commonly involves medications that increase wakefulness, including non-sympathomimetic stimulants, (e.g., modafinil) and sympathomimetic stimulants (e.g., amphetamine, methamphetamine, dexamphetamine, and methylphenidate). Several drugs have been used to treat cataplexy, such as tricyclic antidepressants and serotonin norepinephrine reuptake inhibitors; however, none of these medications are Food and Drug Administration (FDA) approved for cataplexy treatment.

SXB was recently approved by the FDA to treat patients diagnosed with narcolepsy and symptoms of cataplexy. It is currently authorized by the European Medicines Agency to treat narcolepsy with cataplexy as a whole disease in adults, and by the FDA to treat cataplexy in patients with narcolepsy, with an “expanded indication” for the treatment of excessive daytime sleepiness.6 It is the sodium salt of γ-hydroxybutyrate (GHB), an endogenous cerebral inhibitory neurotransmitter.7 Its mode of action is uncertain, but it may involve stimulation of γ-amino butyric acid B (GABA [B]) receptors.8,9 SXB is rapidly absorbed and eliminated, having a mean elimination half-life of 30-60 minutes.10 Strict regulations have been established with regard to the prescription and dispensing of the drug and patients usually receive extensive education on its use.

In this article, we aimed to systematically review the efficacy and safety of SXB on EDS, cataplexy, quality of life, and the associated side effects among people with narcolepsy and cataplexy through a systematic review and meta-analysis.
METHODS

The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) Statement was used to guide the reporting of this review.11

Eligibility Criteria

The inclusion criteria were randomized controlled trials (RCTs) of participants with narcolepsy and cataplexy, which examined the use of SXB. We did not limit inclusion by comparator, language, publication status (i.e., unpublished reports could be included), or year of publication. When multiple study publications reported data from the same population (i.e., companion reports), the trial reporting the primary outcome of interest was considered the major publication and the other report(s) was used for supplementary data.

The primary outcome was elimination of excessive daytime sleepiness (EDS) according to subjective or objective indicators. Objective laboratory tests included the multiple sleep latency test (MSLT), which is a validated objective measure of the ability or tendency to fall asleep.12,13 In addition, it allows documentation of sleep onset rapid eye movement sleep (SOREM). Another objective laboratory test is the maintenance of wakefulness test (MWT), which is a validated objective measure of the ability to stay awake for a defined time that measures the mean time latency of falling asleep during 4 to 5 sessions of trying to stay awake.12 Subjective validated scales included the Epworth Sleepiness Scale (ESS), which is a specialized, validated sleep questionnaire containing 8 items that ask for self-reported disclosure of the expectation of dozing in a variety of situations. Scores ≥ 10 indicate an abnormal result.14 The subjective outcome of elimination of cataplexy or reduction of the symptoms by > 50% from patient diaries was also included.

Secondary outcomes included quality of life using the short-form (SF-36) scale, Clinical Global Impression of change (CGI-C), and harms, including the type of adverse event and number of adverse events per treatment group.

Information Sources

Medical Subject Headings and text words related to SXB for narcolepsy with cataplexy were used to search MEDLINE (OVID interface, 1950 to October 2010), EMBASE (OVID interface, 1980 to October 2010), CINAHL (EBSCOhost interface, 1997 to October 2010), PsycInfo (Scholar’s Portal interface, 1806 to October 2010), and the Cochrane Central Register of Controlled Trials (Wiley interface, inception to October 2010). To supplement the search, we searched a clinical trial registry (www.clinicaltrials.gov), scanned the reference lists of included studies, searched the authors’ personal files, and contacted narcolepsy experts via email to identify further studies to be included, as well as the manufacturer of SXB (Jazz Pharmaceuticals).

Search

An experienced information specialist conducted all of the literature searches. The search strategy for the main electronic search (MEDLINE) is presented in the appendix; details on the other searches are available from the authors on request.

RESULTS

Study Selection

To ensure reliability, a training exercise was conducted prior to commencing the screening process. Two independent reviewers screened the search results for inclusion using a predefined relevance criteria form and obtained the full text of potentially relevant articles and screened them to determine inclusion, independently. Discrepancies at any stage were resolved by discussion or the involvement of a third reviewer. The level of agreement during screening was assessed using a kappa statistic.15 We determined a priori that an acceptable level of agreement would be > 60%.15

Data Collection Process

A draft data extraction form was developed, piloted, and modified as necessary. Two reviewers assessed study quality and extracted all of the data using the standardized data extraction form, independently. Discrepancies were resolved by discussion or the involvement of a third reviewer.

Data Items

The extracted data included study characteristics (e.g., study period, sample size, geographic location, setting), participant characteristics (e.g., population, narcolepsy diagnosis, mean age, gender), and results from the primary and secondary outcomes.

Risk of Bias in Individual Studies and Across Studies

The risk of bias in individual studies was assessed using the Cochrane risk of bias tool.16 This tool consists of 6 items pertaining to sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other sources of bias. The risk of bias across studies was assessed using the outcome reporting bias criterion from the Cochrane risk of bias tool. Publication bias was to be assessed using funnel plots,17 but there were too few studies included in each meta-analysis to assess publication bias sufficiently.

Summary Measures

The summary measures were the relative risk (RR) and the mean difference (MD).

Synthesis of Results

The studies were plotted in a forest plot to examine heterogeneity visually. Statistical heterogeneity was examined using the F and χ² statistics.18 Pooled estimates were derived using a random-effects model, and 95% CIs were derived based on a normal distribution.19 All analyses were conducted in Review Manager Version 5 (The Cochrane Collaboration, available from http://ims.cochrane.org/revman/download).
full-text articles were retrieved and examined for relevance, and 6 RCTs fulfilled the inclusion criteria,20-25 along with 5 companion reports (Figure 1).25-28 Two articles were excluded at the full-text level of screening because they were not RCTs,29,30 and one study was excluded because it did not report any relevant outcomes.31 There was excellent agreement between reviewers at level 1 screening (κ = 0.92, 95% CI: 0.81 to 1.03), and lower agreement at level 2 screening, due to the small number of studies included at this level (κ = 0.46, 95% CI: −0.08 to 1.00).

Study and Patient Characteristics

Except for 2 studies,24,25 all studies were published after 2002 (Table 1). Most of the studies were conducted in clinics in the USA, Canada, and Europe. Duration of the RCTs ranged from 4-8 weeks, except for one study25 that lasted for 12 weeks. SXB at a dose range between 4.5 to 9 g/night was the dose examined in most of the studies.24,25

The number of patients ranged from 20 to 228, and the percentage of females ranged from 50% to 65% (Table 2). The diagnosis of narcolepsy was based on classical symptoms of narcolepsy and an MSLT showing ≥ 2 SOREM periods. MSLT in one study was conducted at home.24 All studies excluded patients with other sleep disorders. One study that assessed the effect of SXB on excessive daytime sleepiness did not include cataplexy as an enrollment criterion.22 No paper analyzed all of the clinical features of narcolepsy or performed all diagnostic tests.

Table 1—Study characteristics

<table>
<thead>
<tr>
<th>Articles</th>
<th>Type of trial</th>
<th>n</th>
<th>Setting</th>
<th>Duration of trial in weeks (longest duration of FU)</th>
<th>Trial arms (dose in grams)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xyrem Int. Group 200520</td>
<td>RCT</td>
<td>228</td>
<td>42 sleep clinics in USA, Canada, and Europe</td>
<td>8 (8)</td>
<td>1) Sodium oxybate (4.5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2) Sodium oxybate (6)</td>
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<td></td>
<td>3) Sodium oxybate (9)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>4) Placebo</td>
</tr>
<tr>
<td>Xyrem Int Group21</td>
<td>RCT</td>
<td>55</td>
<td>14 clinical sites (location NR)</td>
<td>2 (2)</td>
<td>1) Sodium oxybate (3)</td>
</tr>
<tr>
<td></td>
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<td>2) Sodium oxybate (4.5)</td>
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<td></td>
<td>3) Sodium oxybate (6)</td>
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<td>4) Sodium oxybate (7.5)</td>
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<td></td>
<td>5) Sodium oxybate (9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6) Placebo</td>
</tr>
<tr>
<td>U.S. Xyrem Multicenter Study Group, 200223</td>
<td>RCT</td>
<td>136</td>
<td>18 clinical sites (location NR)</td>
<td>4 (4)</td>
<td>1) Sodium oxybate (3)</td>
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<tr>
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<td></td>
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<td>2) Sodium oxybate (6)</td>
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<td>3) Sodium oxybate (9)</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>4) Placebo</td>
</tr>
<tr>
<td>Black et al.21</td>
<td>RCT</td>
<td>278</td>
<td>44 clinical sites in USA, Canada, and Europe</td>
<td>4 (8)</td>
<td>1) Sodium oxybate (6 titrated to 9)/modafinil</td>
</tr>
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<td></td>
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<td>2) Modafinil/placebo</td>
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<td>3) Sodium oxybate (6 titrated to 9)/placebo</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>4) Placebo/placebo</td>
</tr>
<tr>
<td>Lammers et al.26</td>
<td>Cross-over RCT*</td>
<td>24</td>
<td>Leiden University Hospital, Netherlands</td>
<td>4 (4)</td>
<td>1) Sodium oxybate (60 mg/kg/night)</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td>2) Placebo</td>
</tr>
<tr>
<td>Scrima et al.25</td>
<td>Cross-over RCT*</td>
<td>20</td>
<td>Sleep Disorders Center, University of Arkansas for Medical Sciences</td>
<td>4 (12)</td>
<td>1) Sodium oxybate (50 mg/kg/night)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2) Placebo</td>
</tr>
</tbody>
</table>

*Data from crossover RCTs were abstracted prior to the groups crossing over to make the data consistent with the other RCTs. CR, companion report; FU, follow-up; Int, International; ITT, intention-to-treat; N, no; RCT, randomized controlled trial; U, unclear; USA, United States of America; Y, yes.
Risk of Bias

None of the included RCTs were assessed as having adequate sequence generation or allocation concealment (Table 3). All of the studies adequately blinded participants and addressed incomplete outcome data. Five of the 6 studies were free from selective outcome reporting. All of the studies scored unclear on other biases, as they involved private-industry funding. Four of the included studies were sponsored by the manufacturing company.

Efficacy Meta-Analysis Results

Four studies reported cataplexy attacks and 2 were included in the meta-analysis (Figure 2). The 2 other studies could not be included in the meta-analysis because the standard error was not reported and these data could not be obtained from the SXB manufacturer. The first study comprised 20 subjects, and the other study included 104 subjects. Compared with placebo, cataplexy attacks were statistically significantly decreased with 4.5 g/night of SXB (pooled results: MD: -8.5, 95% CI: -15.3 to -1.6). No statistical heterogeneity was observed, with an I² of 0% and a p-value of 0.36 on the test.

Two studies reported the benefit of SXB on excessive daytime sleepiness which was measured by MWT and both were included in the meta-analysis (n = 101 and 91 subjects; Figure 3). At a dose of 9 g/night, SXB increased sleep latency significantly in the MWT compared to placebo (pooled results: MD: 5.18, 95% confidence interval, CI: 2.59-7.78). No statistical hetero-

Table 2—Patient characteristics

<table>
<thead>
<tr>
<th>Articles</th>
<th>N</th>
<th>% female</th>
<th>Age in years: mean (SD)</th>
<th>Weight in kg: mean (SD)</th>
<th>Narcolepsy diagnosis</th>
<th>Occurrence of cataplexy and/or sleep attacks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xyrem Int. Group 2005</td>
<td>228</td>
<td>65.4</td>
<td>42.5 (range: 16 to 75)</td>
<td>87.5 (range: 46.3 to 170.6)</td>
<td>PSG, MSLT in past 5 years</td>
<td>Daily for at least 3 months</td>
</tr>
<tr>
<td>Xyrem Int. Group</td>
<td>55</td>
<td>58.0</td>
<td>47.7 (NR)</td>
<td>80.5 (NR)</td>
<td>American Academy of Sleep Medicine criteria</td>
<td>5 or more per week</td>
</tr>
<tr>
<td>U.S. Xyrem Multicenter Study Group, 2002</td>
<td>136</td>
<td>58.1</td>
<td>43.1 (NR)</td>
<td>82.9 (NR)</td>
<td>PSG within previous 5 years</td>
<td>3 or more per week over a 2-week baseline period</td>
</tr>
<tr>
<td>Black et al.</td>
<td>278</td>
<td>51.8</td>
<td>38.6 (14.6)</td>
<td>81.6 (17.4)</td>
<td>American Academy of Sleep Medicine criteria</td>
<td>Cataplexy not considered as enrollment criteria</td>
</tr>
<tr>
<td>Lammers et al.</td>
<td>24</td>
<td>45.8</td>
<td>36 (NR)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Scrima et al.</td>
<td>20</td>
<td>50.0</td>
<td>45 (20.6)</td>
<td>85.1 (23.3)</td>
<td>PSG, MSLT</td>
<td>10 or more on a daily log during a 2-week baseline period</td>
</tr>
</tbody>
</table>

ITT, intention-to-treat; MLST, multiple sleep latency test; NR, not reported; PSG, polysomnogram; SD, standard deviation.

Table 3—Risk of bias results

<table>
<thead>
<tr>
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</tr>
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<tbody>
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<td>Xyrem Int. Group 2005</td>
<td>No</td>
<td>unclear</td>
<td>yes</td>
<td>yes</td>
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<td>U.S. Xyrem Multicenter Study Group, 2002</td>
<td>Unclear</td>
<td>unclear</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>unclear</td>
</tr>
<tr>
<td>Black et al.</td>
<td>Unclear</td>
<td>unclear</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>unclear</td>
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<tr>
<td>Lammers et al.</td>
<td>No</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Scrima et al.</td>
<td>Unclear</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>unclear</td>
</tr>
</tbody>
</table>

Figure 2—Mean weekly cataplexy attacks meta-analysis

![Figure 2](image-url)

Risk of Bias

None of the included RCTs were assessed as having adequate sequence generation or allocation concealment (Table 3). All of the studies adequately blinded participants and addressed incomplete outcome data. Five of the 6 studies were free from selective outcome reporting. All of the studies scored unclear on other biases, as they involved private-industry funding. Four of the included studies were sponsored by the manufacturing company.

Efficacy Meta-Analysis Results

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Two studies reported the benefit of SXB on excessive daytime sleepiness which was measured by MWT and both were included in the meta-analysis (n = 101 and 91 subjects; Figure 3). At a dose of 9 g/night, SXB increased sleep latency significantly in the MWT compared to placebo (pooled results: MD: 5.18, 95% confidence interval, CI: 2.59-7.78). No statistical hetero-
Geneity was observed, with an I² of 0% ($\chi^2$ p-value = 0.69). The above 2 studies used different protocols for the MWT. While the Xyrem International Study group used the 40-min version of the protocol, Black and Houghton used the 20-min version of the protocol. Theoretically, this may influence the sleep latencies obtained, particularly in patients who do not fall asleep very fast.

One of the included trials examined combination therapy trial of SXB and modafinil. The mean MWT values were statistically different in the SXB monotherapy and modafinil monotherapy and combination therapy (SXB + modafinil) compared to placebo. The median ESS scores decreased significantly in a dose-related manner in the international trial in patients receiving SXB (4.5 g, 6 g, and 9 g/night) compared to placebo. Black and Houghton (combination-therapy trial) reported a significant reduction by 20% and 27% in the median ESS scores in the SXB monotherapy and SXB + modafinil combined therapy recipients, respectively. On the other hand, the ESS scores did not change significantly in the placebo or modafinil monotherapy recipients. However, we could not conduct a meta-analysis on the ESS score because the standard error was not reported, and these data could not be obtained from the SXB manufacturer.

Two studies reported the number of weekly sleep attacks and both were included in the meta-analysis with a total of 105 and 98 participants (Figure 4). Sleep attacks were statistically significantly decreased with 9 g/night of SXB compared to placebo (pooled results: mean difference, MD: -9.65, 95% confidence interval, CI: -17.72, -1.59); low heterogeneity was observed, with an I² of 13% ($\chi^2$ p-value = 0.28).

Three studies reported the Clinical Global Impression of severity and Change (CGI) of “very much improved” and all were included in the meta-analysis (n = 106, 69, and 105; Figure 5). CGI scores significantly increased with 9 g/night of SXB (pooled results: mean difference, MD: 2.42, 95% confidence interval, CI: 1.77-3.32). No statistical heterogeneity was observed, with an I² of 0% and a p-value of 0.7 on the $\chi^2$ test. In the combination-therapy trial “very much improved” was seen only in the arms SXB monotherapy and the combination therapy (SXB + modafinil), while the modafinil monotherapy arm did not differ from that in the placebo arm.

Two studies reported the percentage of REM sleep before and after SXB and were included in the meta-analysis with a sample size of 22 subjects and 20 subjects, but there were no significant differences between groups (pooled results: MD = -0.49, 95% confidence interval, CI: -2.42, 1.44; Figure 6). No statistical heterogeneity was observed, with an I² of 0% ($\chi^2$ p-value = 0.37).

Harms Meta-Analysis Results

All harms meta-analyses included SXB at 9 g/night versus placebo. Patients receiving SXB had statistically more adverse events versus placebo, including nausea (3 studies, relative risk...
[RR]: 7.74, 95% CI: 3.2, 19.2; Figure 7), vomiting (2 studies, RR: 11.8, 95% CI: 1.6, 89.4; Figure 8), and dizziness (3 studies, RR: 4.3, 95% CI: 1.1, 16.4; Figure 9). Enuresis was not significantly different from placebo (2 studies, RR: 2.6, 95% CI: 0.8, 9.8; Figure 10), yet there was a trend towards favoring placebo versus SXB. In the US Xyrem study, 10 patients (7.4%) withdrew because of adverse events.23 Side effects were significantly more common in the SXB recipients compared to
placebo and included nausea, vomiting, dizziness, and urinary incontinence. In the international Xyrem trial, 21 (9.2%) patients withdrew due to adverse events; however, in that trial, there was no difference in the incidence of urinary incontinence between SXB and placebo recipients. In the combination therapy trial, adverse events were reported in 70% of placebo, 54% of modafinil monotherapy, 60% of SXB monotherapy, and 79% of SXB + modafinil combination therapy. In this latter trial, 1, 2, 4, and 6 patients withdrew from the placebo, modafinil monotherapy, SXB monotherapy, and SXB + modafinil combination therapy, respectively, due to adverse events. Serious side effects were reported infrequently. Acute confusion was reported in one patient in the US trial at a dose of SXB 6 g/night. In the combination therapy trial, one patient developed a serious psychotic disorder related to narcissistic personality disorder.

**DISCUSSION**

This systematic review assessed the efficacy and safety of SXB in narcolepsy patients and included six randomized controlled trials. All patients were diagnosed as having narcolepsy based on established criteria. This is the first meta-analysis that we are aware of to assess the effect of SXB in narcolepsy patients. Due to the short follow-up (2 to 12 weeks), we were unable to investigate long-term efficacy and harms.

We found that SXB in all trials resulted in significant reduction in cataplexy attacks and EDS. SXB reduced the frequency of cataplexy in a dose-related manner compared to placebo. Two studies have demonstrated beneficial effects on cataplexy attacks even with a smaller dose of SXB (4.5 g/night). EDS was reduced and sleep latency increased when evaluated by MWT in the SXB arm compared to placebo. The improvement was dose-related; however, the benefits documented in the MWT were statistically significant only in the higher dose (9 g/night). The improvement in the EDS appeared after 8 weeks of treatment. Although SXB reduces the frequency of sleep attacks, it did not eliminate them completely. Surprisingly, in the study by Black and Houghton, modafinil monotherapy had no significant effect on sleep latency in the MWT and or on the ESS scores. These results contradict previous studies, which demonstrated that modafinil in comparison with placebo results in significant improvement in daytime sleepiness when assessed by ESS, MSLT, and MWT.

In a recent report, four patients with narcolepsy treated with sodium oxybate were followed for approximately 2 years. The beneficial effect on cataplexy and daytime sleepiness persisted during the follow-up period.

The Clinical Global Impression of Change (CGI) scores, which are commonly used measures of symptom severity, treatment response, and the efficacy of treatments were dichotomized to responders as “very much improved” or “much improved.” “Much improved” and “very much improved” were statistically significant in all the doses (4.5, 6, and 9 g/night) compared to placebo. It was interesting to note that in the combination-therapy trial, “very much improved” was seen only in the arms SXB monotherapy and the combination therapy (SXB + modafinil) versus modafinil alone. Only one study examined quality of life indicators. Improved quality of life was observed for SXB at 9 g/night versus placebo in all subscales of the Functional Outcomes of Sleep Questionnaire, except for intimacy and sexual relationships. A statistically significant and clinically relevant result was found for SXB at 9 g/night versus placebo.

Sleep is frequently disturbed in patients with narcolepsy. Polysomnographic studies have documented several changes in patients with narcolepsy including prolonged awakening after sleep onset, increased stage N1, increased stage shift, and reduced stage N3. Several studies have shown that nightly SXB improves subjective and objective measures of nocturnal sleep and sleep architecture, with robust increases in stage N3 and delta power. Two recent randomized trials have shown that SXB resulted in significant dose-related improvements in slow wave sleep, total sleep time, and a decrease in stage N1, wake after sleep onset, and nighttime awakenings.

SXB is generally well tolerated, with mild-to-moderate side effects that are dose-related. There is a concern about a narrow margin between efficacy and toxicity of SXB. In general, the incidence of side effects increases with dose, and most side effects subside upon reducing the dose.

Long-term follow-up data on adverse events are limited. A 12-month extension study reported adverse events in 93% of patients, including dizziness, headache, nausea, urinary incontinence, viral infection, somnolence, and pain. Dizziness was the only adverse event that was statistically more common in the SXB group.

All of the trials included in this systematic review excluded patients with sleep disordered breathing (SDB). Therefore, caution is advised when treating narcoleptics with concurrent SDB, and physicians should confirm that patients with concurrent obstructive sleep apnea are compliant with positive airway pressure therapy before starting SXB.

We identified two review articles assessing the efficacy and tolerability of SXB in patients with narcolepsy. The authors did not conduct a systematic literature search or meta-analysis and included fewer trials than we do here. The findings of both reviews were consistent with the findings of this systematic review. Both reported improvement in cataplexy and daytime sleepiness and good tolerability of SXB. Evidence-based practice parameters of the American Academy of Sleep Medicine for the treatment of narcolepsy and other hypersomnias of central origin considered SXB as an acceptable patient-care strategy that reflects a high degree of clinical certainty for cataplexy, daytime sleepiness, and disrupted sleep due to narcolepsy; our review supports this recommendation. For the treatment of hypnagogic hallucination and sleep paralysis, they considered the evidence as uncertain.

There are a number of limitations of this report. One limitation is the fact that the included studies have a relatively short follow-up period. Nevertheless, the effect of SXB in the assessed outcomes was obvious during the follow-up periods. Another limitation is the small sample sizes of the included trials. Limitations in the systematic review process include that it was limited to the English language; no unpublished trials were identified (although we did contact trial authors and searched for unpublished material), we could not obtain data for all the outcomes from the SXB manufacturer, and we were unable to formally assess for publication bias because too few trials were included in the meta-analyses.

On the basis of this review, it can be concluded that patients with narcolepsy on SXB have a significant reduction in cataplexy
based on diaries and significant improvement in daytime sleepiness based on objective (MWT) and validated subjective (ESS) assessment methods. Reviewed data suggest that SXB is well tolerated in patients with narcolepsy, and most adverse events were mild to moderate in severity. The study raises further questions that need to be explored in the future including: the long-term efficacy and tolerability of SXB, the effect of SXB in patients with concurrent sleep disordered breathing, and the effect of different dosages on patients with milder form of narcolepsy.

REFERENCES


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The authors thank Laure Perrier for the literature searches and Kevin Thorpe along with Maggie Hong Chen for their statistical analysis consultation and the University Sleep Disorders Center, King Saud University for logistic support. This review was conducted as part of a systematic review course taught Drs. Tricco and Straus through the Li Ka Shing Knowledge Institute of St Michael’s Hospital. This systematic review was funded, in part, by the National Plan for Science and Technology, King Abdulaziz City for Science and Technology at King Saud University.

SUBMISSION & CORRESPONDENCE INFORMATION

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Address correspondence to: Ahmed S. Bahammam, Professor of Medicine, Director, University Sleep Disorders Center, College of Medicine, King Saud University, Box 225503, Riyadh 11324, Saudi Arabia; Tel: +966-1-467-1521; Fax: +966-1-467-2558; E-mail: ashammam2@gmail.com, ashammam@ksu.edu.sa

DISCLOSURE STATEMENT

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Eczema: A Diagnostic Consideration for Persistent Nocturnal Arousals

Lourdes DelRosso, M.D.; Romy Hoque, M.D.

Department of Neurology, Sleep Medicine Program, Louisiana State University School of Medicine, Shreveport, LA

A 5-year-old girl with past medical history of eczema requiring the use of diphenhydramine and cetirizine for nocturnal relief from pruritus presented for evaluation of excessive daytime sleepiness (EDS), loud witnessed snoring, and witnessed apneas. A diagnostic polysomnogram (PSG) showed electrophysiologic evidence of obstructive sleep apnea (OSA), with a total sleep time apnea hypopnea index (TST AHI) of 3.5, and an arousal index 11.4. The PSG was interpreted as meeting criteria for periodic limb movements of sleep (PLMS), with a PLM index of 8.3 and a PLM arousal index of 2.5. The patient was referred for a tonsillectomy and adenoidectomy for treatment of her sleep disordered breathing.

Four months after her oral airway surgery, a repeat diagnostic PSG revealed a TST AHI of 0.3 with a PLM index of 24, a PLM arousal index of 7.9, and an overall arousal index of 11.8.

Figure 1 demonstrates a typical arousal noted in the repeat PSG. Note the movements seen in the legs. They meet criteria for PLMS but they lack clear periodicity.

Figure 1—Two-minute polysomnogram (PSG) window showing leg movements that meet criteria for PLMS but are due to leg scratching associated with eczema
Atopic dermatitis is a condition of the skin characterized by pruritus, dryness, and erythema. It typically begins at an early age, with 85% of patients affected within the first 5 years. Younger patients tend to have more frequent nocturnal sleep disruption due to eczema.

The patient’s nocturnal movements met electrophysiologic criteria for PLMS, but careful review of the video monitoring revealed that the movements and arousals were purposeful scratching associated with her atopic dermatitis. The stability of the arousal index despite a dramatic improvement in the TST AHI after oral airway surgery also showed that many of the arousals noted on both PSGs were not secondary to sleep disordered breathing.

Restless movements of the arms and legs preceded scratching movements of her arms, legs, and abdomen. The arousals associated with these scratching episodes were of insufficient duration to be scored as wake. The significance of these arousals is unknown, since the arousal index in children does not appear to be a sensitive marker of sleep disruption.

**Clinical Pearls**

1. Patients with eczema exhibit disturbed sleep with decrease sleep efficiency and increased nocturnal arousals.
2. The pattern of scratching and moving may be mistaken for PLMS on the PSG.
3. Compare the arousal index before and after intervention for sleep disordered breathing. If the arousal index has not improved despite a reduction in the TST AHI, other sleep disturbing diagnoses need to be explored.

4. Inspection of PSG video is mandatory for proper interpretation of sleep related movements.

**Citation**


**References**


**Disclosure Statement**

This was not an industry supported study. The authors have indicated no financial conflicts of interest.
An 80-year-old right-handed male with history of hypertension, mild peripheral neuropathy, moderate macular degeneration, and a history of migraine headaches in the past presents with new nocturnal visual images intermittently for the last year. He mentioned that he would wake up from sleep in the middle of the night and immediately see some colorful butterflies, multi-colored parrots, and occasional animals, mostly stationary but some in motion in his bedroom. These images would last for a few minutes, but once he turned on the bed lamp, all these animals would vanish instantly. He denies any other sleep related complaints. Although he has taken frequent naps in the daytime recently, but he blames it on his being bored.

On physical examination, his blood pressure was 136/80, pulse was 80/min, and respiratory rate was 18/min; BMI was 27. His neck circumference was 16 inches, and his Mallampati score was 3/4. The rest of his examination was unremarkable except for mild neuropathy. His EPSS (Epworth Sleepiness Scale Score) was 10.

His routine blood work and an MRI of the brain initiated by his primary doctor were within normal limits. His overnight polysomnogram with a 16-channel EEG showed normal sleep onset with a sleep efficiency of 66%, with multiple awakenings causing fragmentation of sleep. During one such awakening he complained of seeing the dog and wanted the lights to be turned on. The EEG during that time showed alpha rhythm in the background and no ictal discharges. His sleep architecture showed stage N1 25%, stage N2 60%, stage N3 5%, and stage REM 10%. His AHI was 56; lowest saturation was 84% with a respiratory event. There was no other evidence of parasomnias or any REM related atonia. There was no evidence of any epileptic focus noted in the EEG leads of the polysomnogram. After 3.5 h of baseline polysomnography, PAP titration with CPAP was initiated; at 10 cm H2O with humidification, all the respiratory events with arousal were eliminated.

QUESTION: Which of the following is the most likely diagnosis for the patient’s nocturnal imagery?
1. Peduncular hallucinosis
2. Complex nocturnal visual hallucinations
3. Lewy Body disease
4. Nocturnal seizures
5. Complex migraines
The patient’s nocturnal symptoms are consistent with complex nocturnal visual hallucinations (CNVH). Patients suffering from CNVH awaken from sleep at night and see vivid hallucinations for few minutes, but these hallucinations resolve instantly in bright light. These symptoms are not associated with any sleep paralysis. This patient had multiple awakenings from sleep at night because of the untreated sleep disordered breathing. These multiple awakenings along with the deafferentation of visual pathways from macular degeneration (as is reported in Charles Bonnet Syndrome) may have resulted in the CNVH. Treatment of the undiagnosed sleep disordered breathing with PAP therapy resolved the multiple fragmentations of the sleep and eventually stopped the hallucinations.

Complex visual nocturnal hallucinations are thought to be a “positive release phenomenon” from occipital lobes. Some authors hypothesize that the combination of the deafferentation of the visual pathways in presence of ambient light and the “thalamic gated theory of passive sleep” may result in the “positive occipital release phenomenon.”

This patient’s history and examination was not consistent with parkinsonism to suggest Lewy Body dementia (LBD). Patients with LBD have vivid hallucinations, which are present throughout day and night with some predilection to more evening occurrences. Our patient’s nocturnal symptoms occurred only during awakening from sleep for few minutes and resolved when the room lights were turned on.

There was no stereotypy or amnesia of these events to suggest seizure events. Patients suffering from complex visual nocturnal hallucinations from an epileptic focus experience generally brief, repetitive, stereotypical images that are not distinct and as clear as seen by most patients suffering from CNVH. These visual symptoms were not preceded or followed by any headaches to suggest migraines. The visual symptoms associated with complex migraines are mostly simple hallucination rather than the complex, detailed, and vivid hallucination seen in NCVH. Brainstem strokes can result in peduncular hallucinosis (PH). However, the visual symptoms in PH are not present only during sleep and tend to occur more in the evening. PH does not resolve when the room lights are turned on and is rarely polymodal. PH can appear in any part of the visual field.

REFERENCES

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Address correspondence to: Gautam Ganguly, M.D., Neurology Consultants Medical Group, 12291 E Washington Blvd, Ste#303, Whittier, CA 90606; Tel: (562)698-6296; Fax: (562)693-6752; E-mail: gangulyg@hotmail.com

DISCLOSURE STATEMENT
Dr. Ganguly is a neurologist who joined private practice group of Neurology Consultants Medical Group, a group practice comprising 4 other neurologists. There is no conflict of interest in the preparation of this manuscript. Neither the Neurology Consultants Medical Group nor its partners have any intellectual or financial proprieties in the making of the manuscripts. Dr. Ganguly is affiliated to the USC-KECK school of medicine as Clinical Assistant Professor of Neurology. There are no contractual obligations between USC-KECK School of medicine and Dr. Ganguly except for clinical assignments for overseeing residents in outpatient departments three to four times a year. Again there is no conflict of interest.
Book Review: Sleep and Mental Illness


Frank M. Ralls, M.D.1,3; Swala K. Abrams, M.D.2

1Division of Pulmonary, Critical Care, and Sleep Medicine, Department of Internal Medicine and the 2Department of Psychiatry, University of New Mexico School of Medicine; and the 3University of New Mexico Hospital Sleep Disorders Center, Albuquerque, NM

Sleep and Mental Illness is a book with a unique goal: to show the importance of sleep in mental illness. Sleep restriction and poor sleep quality are endemic in our culture, and behavioral health concerns are widespread as well. A resource that addresses the interplay of these diverse morbidities is welcome and deserves a spot in the libraries of medical specialists of all kinds. The text is divided into three main sections covering basic science, neuroendocrinology, and clinical science. Many chapters are well-written and well substantiated with up-to-date references, although a few are not written to the same standard of quality. In this review, we will highlight some of the strengths as well as some of the weaknesses that we perceived.

In the neuroendocrinology section, chapter 10 discusses endocrine relationships across the reproductive cycle and is particularly well done. The reader is taken through the life cycle of a woman and important topics including biological rhythms, menstrual-cycle related mood symptoms, pregnancy, postpartum mood disorders, and menopause are competently and clearly addressed. Chapter 13 reviews the International Classification of Sleep Disorders and includes a good summary. Chapter 14 provides a nice review of Spielman’s “3P” model of insomnia. There are other excellent chapters such as those reviewing the important topics of dementia, Prader-Willi syndrome, traumatic brain injury (TBI), and more. Other positive elements include the thorough discussion of wakefulness-promoting neurotransmitters and the role of hypocretin, although we were left confused as to whether one author considered hypocretin 1 and 2 both to be present in humans.

Weaknesses in a few chapters seem mainly related to overgeneralizations and assumptions based on inadequate data and the use of outdated primary literature, which may be misleading to beginners and frustrating to those already well versed in the topics of mental illness and sleep. Occasionally, assumptions are made that do not necessarily fit the current standard of practice. The basic sciences section aims to cover a large range of sleep topics and several chapters seemed repetitive, containing only slightly different approaches to the same topic. Some of the chapters do not reflect the most current findings. A few specific examples: At least two chapters mention Dement and Kleitman’s 1950s classification of sleep, which includes NREM 4 sleep. The 2007 American Academy of Sleep Medicine (AASM) Manual for the Scoring of Sleep and Associated Events has combined the previously separate criteria for NREM 3 and NREM 4 into unified criteria defining a stage N3, thus rendering the earlier classification system obsolete for many. Another chapter makes statements about neurochemistry and pharmacology based on references to literature published in the 1960s and 1970s, such as “monoaminergic activity is responsible for the occurrence of some, if not all, types of depression,” which ignores the advances made in understanding the specific roles of serotonin, dopamine and other neurotransmitters in affective disorders.

In the section on neuroendocrinology, chapter 8 explains that normal aging is associated with corresponding decreases in slow wave sleep (SWS) and that elderly subjects commonly exhibit low or absent SWS. However, other chapters place an emphasis on decreased SWS as a correlate of mental illness without the caveat that this also accompanies normal aging without associated psychopathology. The authors of chapter 9, who are based in Australia, discuss metabolic changes in serious mental illness and state that weight gain and obesity are present in schizophrenic patients independent of their medications. In contrast, our experience in the U.S. suggests that untreated schizophrenics are often too disorganized to successfully obtain food or eat and therefore more likely to be thin and malnourished; one wonders if this is the result of cultural differences. Moreover, in the manic phase of bipolar disorder, the patient is often too busy to eat. Major depression by DSM 4 criteria includes changes in appetite, which is often reduced, and consequently weight loss is a common sign of significant depression. References to susceptibility to schizophrenia being conferred by a polymorphism in the promoter region for quinone reductase 2 (QRT2) are made in chapter 11, which are at this point are most likely premature. The author was possibly citing Harada’s 2003 paper, which suggested that individuals with the deletion of the 29 base pair sequence in the promoter region of the NQO2 gene may confer susceptibility to a certain form of schizophrenia. The study had a small sample size and further study is required to imply a testable genetic link to schizophrenia.

In the clinical science section, the author of chapter 24 rescues previous statements and simplifies sleep in schizophrenia to what it is: an intimate dimension of the clinical picture for which more effort and research attention should be devoted. Chronic psychosis commonly imparts undesirable symptoms
of passivity, apathy, negativism, and isolation, while Steven Bartels (1991) showed that fewer than 50% of schizophrenics exhibited any hostility. Of those who were judged to be hostile, contributing factors included housing instability, paranoid hallucinations or delusions, schizoaffective diagnosis, alcohol use, and bizarre behavior. Despite this, one author in this section states that schizophrenic dreams are most consistent with overt hostility, a formulation that does nothing more than reinforce society’s false assumption, often depicted in television melodrama, that schizophrenics are violent. The resultant victimization is perhaps a greater public health concern than perpetration. Teasing out the difference between a dream waking the patient from sleep and a hallucination usually requires significant expertise, and this important distinction was not clearly made.

Also in this section, a difference in practice standards between some authors and current best practice in the United States appeared evident. Some drugs that are mentioned are not available in the U.S.; for example, the sale of nefazodone was discontinued here and in Canada in 2004 by Bristol-Myers Squibb due to rare instances of hepatotoxicity resulting in liver transplant or death, and agomelatine, not yet FDA approved for the U.S. market, is still undergoing Phase III trials by Novartis. Vocabulary is used at times that is part of British parlance and relatively unfamiliar in North American conversation, however this presents an opportunity for expansion of our own cultural competence (and that’s “jolly good”).

In conclusion, the book *Sleep and Mental Illness* contains some very good chapters and reinforces a key principal that quality sleep is an invaluable asset to the quality of life of those with mental illness. It rightly emphasizes that neuromodulators involved in sleep are also part of current thinking on the pathogenesis of mental illness. Moreover, important sleep issues are addressed in special populations such as Alzheimer patients and those with Prader-Willi syndrome.
Nirav Patel, M.D., M.P.H., F.C.C.P., F.A.A.S.M., born in Nadiad, India, raised in London, England, and resident of Wyomissing, Pennsylvania, and physician specializing in sleep disorders, pulmonary medicine and critical care, passed away suddenly on May 17, 2012, of a myocardial infarction from coronary atherosclerosis. He was 37 years old. Dr. Patel's career was devoted to helping patients with sleep and pulmonary disorders. He was recognized as not only an outstanding clinician, but also as a superb teacher and researcher.

Dr. Patel dedicated his research career to advancing our understanding and awareness of the public health impact of sleep disorders. He was especially interested in poverty’s negative effects on sleep. He believed that sleep was a link between social inequality and adverse health outcomes. His research examined insufficient sleep attainment by people in disadvantaged groups (such as minorities and the poor)—a situation he called “sleep disparity”—and the reasons why these groups often have worse long-term health outcomes. He worked tirelessly to help increase awareness of the negative effects of inadequate sleep, such as increased risk of diabetes, motor vehicle accidents, and cardiovascular disease, through participation in community health fairs, his work as a board member of the Pennsylvania Sleep Society, and his numerous research publications. In 2008, he organized a “Population Sleep” conference at the University of Pennsylvania, which was attended by over a hundred participants from across the nation. He was instrumental in adding sleep questions to the Public Health Management Corporation (PHMC) annual survey, a key regional assessment of public health in the Philadelphia area. Despite his brief career, he has published extensively: His research, consisting of 36 manuscripts and 26 abstracts, has been published in leading journals in the sleep and pulmonary medicine communities, such as the journal SLEEP, and has been presented at international conferences.

Dr. Patel began his medical education at Guys, Kings & St Thomas University Medical School, King’s College in London, United Kingdom. He moved to the Philadelphia area in 2001, where he completed his internal medicine training at Albert Einstein Medical Center. He then came to the University of Pennsylvania for a fellowship in pulmonary medicine, critical care and sleep medicine. He joined the faculty of the Division of Sleep Medicine in 2008 where he was an Assistant Professor of Medicine. He also completed a Masters of Public Health at the University of Pennsylvania in 2009. Throughout his training and subsequent career, he loved caring for and learning about complex medical conditions. This passion led to numerous awards, including the Howard Rogers Prize for Medicine and the Exemplary House Physician award from University Hospital Lewisham (United Kingdom). Dr. Patel was also a member of the 2006 winning team for the nationwide American College of Chest Physicians “Chest Challenge” competition.

Dr. Patel left the University of Pennsylvania in 2009 to take a position at Respiratory Specialists in Wyomissing, Pennsylvania, where he also attended at The Reading Hospital Medical Center and St. Josephs Medical Center. He quickly developed a reputation as a kind, committed and hard-working physician who received awards for outstanding physician house staff teaching and showed that his love of learning extended to a desire to share that knowledge with others. Despite his significant clinical workload, he continued to be actively involved in public health, pulmonary and sleep medicine research activities, which recently resulted in his being considered for Adjunct Assistant Professor of Medicine at the University of Pennsylvania.

Those of us who knew Dr. Patel remember his vitality, commitment and incredible perseverance. In 2006, he was a passenger in a severe motor vehicle accident that resulted in debilitating elbow injuries which ultimately required five separate operations and left him with chronic pain and reduced arm mobility. Despite this traumatic, near-death experience, he maintained his optimism, love of life and family, and commitment to patient care and research. We are fortunate to have had his star burn so brightly in our presence even for this short time.

His philosophy in life was to never to put off till tomorrow what you can do today. His interests included connecting with people, traveling, and sports. His passion, however, was being there and helping people. Dr. Patel is survived by his wife, Minal, son Ariyan (age 5), daughter Rhea (age 3), and by his parents and sister, of London, England.