IMPROVING PATIENT SAFETY AND THE EVALUATION OF DISORDERS OF HYPERSOMNOLENCE IN THE SLEEP LAB

IMPROVING PATIENT SAFETY AND THE EVALUATION OF DISORDERS OF HYPERSOMNOLENCE IN THE SLEEP LAB

By

Margaret Blattner, MD PhD

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Project Advisors: Dr. Robert Thomas and Dr. Kiran Maski
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Table of contents:

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Overview: Background and Context

Improved understanding of the complex physiology that underlies sleep disorders and new technologies applied to the field of sleep medicine require a re-calibration of patient care standards and new approaches to meeting patient needs.

An in-lab sleep study is a common, non-invasive procedure that is widely considered very safe. The existing literature about patient safety events and risks associated with an in-lab overnight sleep study are 10-20 years old (1-3). However, new home-based sleep technologies appropriate for many healthy individuals ("home sleep tests"), result in selection of increasingly medically complex patients referred to a sleep lab for an in-lab assessment. Comorbid cardiac, pulmonary, and neurologic conditions are indications for in-lab, rather than home sleep testing, and sleep lab safety protocols that can be applied by sleep technicians without a medical background must meet the needs of these increasingly medically complex patients (Paper 1). Here, we describe the frequency of patient safety events in our sleep lab over three years, 9,558 studies.

In addition to maintaining high standard for patient safety in the sleep lab, increased scrutiny of existing sleep testing is needed to understand their utility for diagnosis of rare or complex sleep disorders. While the multiple sleep latency test for the evaluation of excessive daytime sleepiness has been the standard diagnostic tool for evaluation of narcolepsy and is broadly used clinically, there is an increasing body of literature suggesting that it is limited for evaluating all patients with excessive daytime sleepiness (4,5). Here, we characterize this standard test's limitation in a cohort of patients (n=42) with prolonged sleep duration (Paper 2).

Together, this work aims to define the frequency and characteristics of patient safety events in the sleep lab (Paper 1) and describe limitations of specialized testing in a subpopulation of patients with excessive sleepiness (Paper 2), as a foundation to build

appropriate or alternative protocols to optimize patient care and evaluation in an increasingly complex field.

Paper 1

A protocol for mitigating safety events in a sleep laboratory
M Blattner, K Dunham, R. Thomas, and A. Ahn
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SCIENTIFIC INVESTIGATIONS

A protocol for mitigating safety events in a sleep laboratory

Margaret Blattner, MD, PhD[1]; Kelley Dunham, RPSGT, RST[2]; Robert Thomas, MD, MMSc[3]; Anjali Ahn, MD[3]

[1]Department of Neurology, Beth Israel Deaconess Medical Center, Boston, Massachusetts; [2]NeuroCare Center for Sleep, Newton, Massachusetts; [3]Department of Medicine, Division of Pulmonary, Critical Care, and Sleep Medicine, Beth Israel Deaconess Medical Center, Boston, Massachusetts

Study Objectives: Polysomnography is a common outpatient procedure and the rate of adverse events is considered low. Due to the emergence and use of home sleep apnea testing, the patient population presenting for in-laboratory testing may have greater medical complexity, suggesting greater risk for in-laboratory adverse events. We believe that there is a greater need for standardized protocols to triage medically vulnerable populations and for formalized training of sleep technicians to respond to safety events.

Methods: The sleep laboratories affiliated with the Beth Israel Deaconess Medical Center system developed a referral triage protocol for patients undergoing polysomnography and a training protocol for sleep technicians with a formalized response to medical incidents. Safety events occurring from January 2016 to January 2020 were documented and patient demographics, referral characteristics, event characteristics, and outcomes were analyzed.

Results: Sixty-five safety events occurred over this period, with a rate of 1:147 studies. The most common events were chest pain (20/65, 31%), shortness of breath (13/65, 20%), and vital sign abnormalities (12/65, 18%). Patients experiencing events were 49% (32/65) female, with a median age of 57 years (range, 19–91 years); 60 of 65 (92%) had documented medical comorbidities, with a median of 3 documented medical or psychiatric comorbidities (range, 0–9). With the formalized response protocol, the time from incident identification to activation of the appropriate response was a median of 3 minutes (range, 0–47 minutes).

Conclusions: The incidence of in-laboratory safety events may be greater than previously described due to the widespread use of home sleep apnea testing. Implementation of formalized response protocols and sleep technician training may be necessary to meet the needs of an increasingly medically complex population.

Keywords: adverse events, polysomnography, sleep laboratory

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BRIEF SUMMARY

Current Knowledge/Study Rationale: Due to the emergence and use of home sleep apnea testing, the patient population presenting for in-laboratory testing may have greater medical complexity, suggesting greater risk for in-laboratory adverse events. We believe there is a greater need for standardized protocols to triage medically vulnerable populations and to train sleep technicians to respond to safety events. This study describes a generalizable protocol for triage and training and describes the breadth of safety incidents, responses, and outcomes in a sleep laboratory.

Study Impact: Safety events occurred at a rate of 1:147. The most common events were chest pain, shortness of breath, and vital sign abnormalities. These findings suggest that the incidence of in-laboratory safety events may be greater than described before widespread use of home sleep apnea testing. Implementation of safety event response protocols and sleep technician training may be necessary to meet the needs of a medically complex population.

INTRODUCTION

Polysomnography is a common overnight outpatient procedure requiring continuous cardiopulmonary monitoring by a trained technologist in a sleep laboratory. The traditional clinical sleep laboratory has been a place for noninvasive assessments of sleep disorders in relatively healthy individuals. Although safety risks are present,[1] prior studies have indicated an exceedingly low adverse event rate of 0.35% or 0.16%, where most adverse events are either cardiac in nature or related to falls.[2,3] These prior observational studies predate the advent of home sleep apnea testing and prior authorization requirements and may not reflect the current population now presenting for hospital-based sleep evaluation.

With the advent of prior authorization and home sleep apnea testing, the majority of relatively healthy adults seeking a sleep study evaluation are referred for home sleep apnea testing. It has been our observation that patients approved for in-laboratory sleep studies are older, require greater mobility assistance, and have significant neurological or cardiovascular comorbidities. As patients in sleep laboratories have increased medical and psychiatric comorbidities and require greater support, the risk for in-laboratory incidents may also increase.

Presently, sleep technicians are trained to apply sensors, monitor sleep patterns, and apply positive airway pressure therapy when warranted. Their training does not necessarily prepare them to quickly evaluate a patient with acute symptoms and appropriately determine the need for urgent medical evaluation. Given the increased clinical complexity of patients referred for laboratory-based studies and the minimal emergency training of sleep technicians, we identified a need for an explicit triage protocol for our laboratory-based sleep studies including more formalized cardiopulmonary training for our

sleep technicians. Additionally, isolated sleep laboratory safety events both at our sleep laboratory and nationally have demonstrated a critical need for formalized assessment and response protocols. This paper describes our approach to implementation of a comprehensive sleep laboratory safety protocol through triage of referrals, sleep technician training, and a formalized incident response protocol. We also describe the rate, characteristics, and outcomes of safety incidents observed in our sleep laboratory.

METHODS

In-laboratory sleep study location and resources

The Multi-Disciplinary Sleep Disorders Center at the Beth Israel Deaconess Medical Center (Boston, MA) utilizes 3 Massachusetts locations for in-laboratory sleep studies: one 8-bed hospital-based sleep laboratory (Beth Israel Deaconess Hospital Needham), one 2-bed hospital-based sleep laboratory (Beth Israel Deaconess Hospital Milton), and one 4-bed laboratory at a non-hospital-based affiliated sleep center. The Beth Israel Deaconess Hospital Needham and Beth Israel Deaconess Hospital Milton hospital-based sleep laboratories are located adjacent to the emergency department (ED) and have 24-hour in-house hospitalist coverage with rapid response (RR) and code teams. Both hospital-based sleep laboratories and the non-hospital-based laboratory are managed by an affiliated sleep center, NeuroCare Center for Sleep, in Newton, Massachusetts.

Prior workflow and needs assessment

Our needs assessment was motivated by isolated sleep laboratory safety events both at our sleep laboratory and nationally. The need for a safety process was highlighted by the media announcement in the fall of 2015 of the wrongful death case at Emory Sleep Center in 2010 of a 25-year-old man who developed hypoxia and respiratory arrest during his sleep study.[4] An additional incident in our own sleep laboratory also in the fall of 2015 involved a patient with history of atrial fibrillation who developed chest pain and tachycardia and required transfer to an ED for management of atrial fibrillation with rapid ventricular rate. At that time, the protocol involved calling an intermediary nursing supervisor, and delays in that response resulted in the sleep laboratory technician transferring the patient to the ED directly.

Together, these situations motivated the development of clearer triage guidelines and training for our technicians in patients with acute reported symptoms (such as chest pain, shortness of breath) or abnormal critical findings (such as low oxygen saturation, low or high blood pressure, fast or irregular heart rate).

Additional protocols were created in response to potentially high-risk situations: for example, the development of explicit prescreening, arrival, and monitoring procedures for any patient with a tracheostomy. The tracheostomy protocol was prompted by an incident where a patient with congenital central hypoventilation syndrome and tracheostomy became transiently hypoxemic when placed on different ventilator settings. He recovered quickly when his home ventilator settings were reestablished. Another formal protocol was put in place for use of sedating medications. This arose from an isolated event in 2016 involving a patient taking zolpidem for the first time at study initiation, and then unexpectedly leaving in the middle of the study. Although the patient was felt to be alert and capable of making decisions, the next morning the patient's partner informed the laboratory that the patient had been found asleep in the car in the driveway without a recollection of leaving the laboratory or driving home. Following a critical review of this event, a detailed sedative use policy was created.

Prior to 2015 and the implementation of our protocol, management of acute symptoms during a laboratory-based sleep study included instructing the laboratory technician to contact the nursing supervisor and the on-call sleep medicine physician for patient complaints (shortness of breath, headache, or chest pain). There was no formal prestudy risk-stratification questionnaire or comprehensive prestudy vital sign measurement. No specific sedation or tracheostomy policy was in place. The RR and code teams were not explicitly involved by protocol.

To assess the skill level and comfort with responding to patient emergencies of the sleep technicians, an emergency workshop was held. The workshop incorporated patient simulations for emergency situations, such as chest pain, arrhythmias, and respiratory distress. The results from that workshop were unanticipated and surprising: Most technicians were not comfortable identifying what symptoms or complaints should prompt a call for emergent medical support.

Multistep, multicomponent, parallel-process modification

A number of organizational changes were made to the emergency protocols including removing the nursing supervisor from the emergency response protocol and instead utilizing the RR and code teams, creating an annual emergency training program for the sleep technicians, obtaining a code cart for the sleep laboratory hallway and manual blood pressure cuffs for sleep laboratory use, posting "Take Quick Action" forms in sleep laboratory and control rooms, and reviewing every incident for response appropriateness and choosing 1–2 incidents each year to complete a root-cause analysis.

Sleep laboratory referral process and study location triage (part 1)

The vast majority (> 95%) of polysomnograms are performed in the hospital-based sleep laboratory. The electronic sleep study order was modified to explicitly require referring physicians to include any special needs, such as mobility limitations, cognitive impairment, insulin requiring diabetes, seizure history, or use of supplemental oxygen (**Box 1**). The presence of 1 of these factors or conditions on the electronic order prompted triage to the hospital-based Beth Israel Deaconess Hospital Needham sleep laboratory, which was identified as having increased medical support. The electronic sleep study order was also modified to direct any patient identified as needing adaptive servoventilation to the sleep clinic prior to scheduling the sleep study. External referrals were reviewed for the same criteria before scheduling. This modification to the referral process preceded the data collection reported here.

Sedative use policy

A sedative use policy was created and included in the prestudy paperwork sent to patients. This policy explicitly instructed patients to take their sedative medication by 10:30 PM and stated that if a sedative was to be used for the first time during the sleep study, then the patient was encouraged to arrange a ride home the morning following the study.

Engaging the hospitalists and the RR and code teams

Implementation of protocols was coordinated with the hospital's RR and code teams to delineate responsibilities of the RR or code teams and the sleep technicians. This included designating a location and maintaining a code cart within the sleep laboratory.

Clinical symptom screening and triage upon arrival to the sleep laboratory (part 2)

A clinical symptom screening and triage protocol was developed, tested, and refined between 2016 and 2017. Upon patient arrival to the sleep laboratory, the technician performed prestudy vital signs assessment using an automated blood pressure cuff and oximeter and administered a prestudy clinical symptom questionnaire. Acceptable baseline blood pressure and oximetry ranges as well as actions for vital signs that are out of range were explicitly defined in a "Take Quick Action" triage sign (**Figure S1** in the supplemental material). The prestudy questionnaire identified high-risk conditions as well as acute symptoms within the past 24 hours (**Figure S2** in the supplemental material). If the patient answered "yes" to certain questions on the prestudy questionnaire, then the technician was prompted to call the on-call sleep medicine physician, the RR team, or the code team. The technician also explicitly discussed the sedative medication policy with the patient.

Emergency protocol revision and training of sleep technicians (part 3)

A "Take Quick Action" triage sign was developed that explicitly described the appropriate response for each incident (**Figure S1**). Sleep technicians were instructed to call the RR team for chest pain, shortness of breath, fall, seizure, stroke symptoms, voiced intent for self-harm, marked concern by patient or family member, or vital sign abnormalities (heart rate > 120 beats per minute for 2 minutes, wake SpO_2 < 90%, systolic blood pressure < 90 mm Hg or > 200 mm Hg). Sleep technicians were instructed to call the code team for cardiac arrest or difficulty arousing the patient. Other concerns were directed to the sleep physician on call. All incidents were reported to the sleep physician in the morning and communicated to the referring clinician.

Emergency training was implemented for all sleep technicians and included an annual review of emergency procedures and an annual review of electrocardiographic tracings and causes of respiratory distress, with the creation of an advanced electrocardiographic skills training program; the creation of a script for how technicians should respond in an emergency with a review of scenarios; the creation of a specific tracheostomy prestudy form (**Figure S3** in the supplemental material), and the creation of a sedative use protocol (**Figure S4** in the supplemental material).

Box 1—High-needs criteria listed in the electronic sleep study referral for triaging to a hospital-based sleep laboratory (presence of ≥ 1 criteria).

Mobility limitations or additional assistance
Wheelchair or walker
Group living facility
Incontinent
Need an attendant to accompany
Visual impairment
Medical history
Recent hospitalization
Home nocturnal oxygen requirement
Insulin required for diabetes
Cognitive impairment
Neuromuscular disease
History of seizures
Morbid obesity
Tracheostomy present
Class III or IV congestive heart failure
Cardiac arrhythmia
History of myocardial infarction or stroke in past 3 months
Moderate to severe pulmonary disease

Incident definition and tracking outcomes

Incidents were defined as situations in which the sleep technician was required to evaluate an unexpected situation or symptom and initiate a treatment plan to mitigate or minimize risk or harm. These included events with a phone call to emergency personnel (the RR team or code team), a phone call for security assistance for behavioral dysregulation, a phone call to the sleep physician on call for assistance concerning dangerous decision-making by the patient (leaving the study prematurely after taking a sedative-hypnotic, after an incident occurred, or after a new serious symptom or arrhythmia had been identified), or any injury to the patient during the time in the sleep laboratory (not including minor skin bruising or irritation during routine placement of electrodes). Incident characteristics were tracked and reviewed every 3–6 months to evaluate the need for updated protocols.

RESULTS

Patient demographics, medical comorbidities, and referral characteristics

Patient demographic details, medical and psychiatric comorbidities, and study referral information are presented in **Table 1.** Incidents occurred equally in males and females (49% [32/65] female) with a median age of 57 years (range, 19–91 years). Over 90% of the patients with reported incidents had some

Table 1—Characteristics of patients and sleep referrals in reported safety events.

	Finding
Patient characteristics	
Median (range) age, y	57 (19–91)
Female sex, n (%)	32 (49)
Race, n (%)	
White, non-Hispanic	42 (65)
Black or African American	11 (17)
Hispanic	5 (8)
Other	1 (2)
Not documented	6 (9)
Comorbidities,[a] n (%)	
Any	60 (92)
Cardiac	35 (54)
CHF	8 (12)
Atrial fibrillation	8 (12)
Neurologic	24 (37)
Stroke	1 (2)
Parkinson disease	4 (6)
Psychiatric	24 (37)
Endocrine	20 (31)
Pulmonary	16 (24)
COPD	7 (11)
Asthma	4 (6)
Rheumatologic	3 (5)
Number of comorbidities, median (range)	3 (0–9)
Referral characteristics, n (%)	
Referral	
From sleep clinician	44 (68)
From non-sleep clinician	21 (32)
Study type	
Split polysomnogram	31 (48)
Diagnostic polysomnogram	21 (32)
Titration polysomnogram	12 (18)
Not documented	1 (2)
Suspected diagnosis	
Obstructive sleep apnea	58 (89)
Insomnia	2 (3)
Central sleep apnea	1 (2)
Parasomnia	1 (2)
REM sleep behavior disorder	1 (2)
None documented	1 (2)

n = 65. [a]Documented comorbidities: cardiac (hypertension, atrial fibrillation, coronary artery disease, CHF), pulmonary (asthma, restrictive lung disease, chronic obstructive lung disease, interstitial lung disease, cystic fibrosis), neurologic (dementia, history of stroke, epilepsy, pseudotumor, traumatic brain injury, Parkinson disease, occipital neuralgia, myotonic dystrophy, meningioma, congenital central hypoventilation syndrome), rheumatologic (rheumatoid arthritis, autoimmune hepatitis, psoriasis, fibromyalgia), psychiatric (depression, psychosis, bipolar, posttraumatic stress disorder, attention-deficit disorder, attention-deficit/hyperactivity disorder, substance abuse, developmental delay), and endocrine (diabetes, prediabetes, hyperparathyroidism, polycystic ovarian syndrome, hypothyroidism). CHF = congestive heart failure, COPD = chronic obstructive pulmonary disease, REM = rapid eye movement.

medical or psychiatric comorbidity, with a median of 3 documented comorbidities (range, 0–9). Of the incidents documented, 64 of 65 (98%) occurred in the hospital-based sleep laboratories, rather than in the non-hospital-based sleep laboratory. The 1 incident reported in the non-hospital-based sleep laboratory was a complaint of chest pain in a 30-year-old woman with a history of myotonic dystrophy and depression. Recorded vital signs were stable during the event; 911 was called, and the symptoms resolved after talking with the emergency personnel.

Incident reporting

After implementation of the new incident response protocols, the number of reported events increased from 6 reports in 2015 to 22 reports in 2016 (annual reports from 2016–2019 ranged from 11–22/year). Over the study period of January 2016–January 2020, there were 9,558 total in-laboratory polysomnograms completed. With 65 events reported over this time, the incidence of safety incidents was 1:147 for all in-laboratory sleep studies performed.

Incident characteristics and outcomes

The most common events were symptoms of chest pain (20/65, 31%) and shortness of breath (13/65, 20%) (**Table 2**). Technician-documented vital sign abnormalities were also noted (12/65, 18%). The action taken in response to incidents was based on the formalized protocol and was most often activation of the RR team (40/65, 62%). For the incidents with documented response time, the interval between incident identification and response activation was 3 minutes (range, 0–47 minutes). The median interval between the response activation (ie, calling the RR team) and the intervention (ie, evaluation by a physician) was 3 minutes (range, 0–25 minutes). Most patients were transferred to the ED for evaluation (41/65, 63%), and of these, 51% (21/41) either had sufficient sleep data prior to transfer, many with symptomatic complaints on awakening in the morning (14/21), or completed the study after ED evaluation and incident resolution (7/21). The patients who returned to the study after ED evaluation included 4 patients with acute symptom complaints on arrival triage (chest pain, headache, dizziness) and 1 patient with vital signs outside acceptable parameters on arrival. These patients were evaluated, treated, and discharged from the ED; with all patients, this was completed in < 2 hours and patients were allowed to return to the sleep laboratory for their study. The remaining 2 patients reported dizziness during the study

Table 2—Incident characteristics, time to response, and outcomes.

	Finding
Incident characteristics (n = 65)	
Patient-reported symptoms, n (%)	
Chest pain	20 (31)
Shortness of breath	13 (20)
Headache	8 (12)
Dizziness	5 (8)
Nausea	2 (3)
Technician-noted events, n (%)	
Suspected seizure	5 (8)
Syncope	3 (5)
Disorientation	3 (5)
Refractory coughing	1 (2)
Vital sign abnormalities, n (%)	
Tachycardia (> 120 beats/min)	5 (8)
Hypoxia (< 88% SpO_2) during wake	3 (5)
ECG abnormalities (heart block)	1 (2)
Hyper/hypotension (systolic pressure < 90 or > 200 mm Hg)	3 (5)
Action taken, (> 1 action, in some incidents)	
Rapid response team activated	40
Called sleep attending physician on call	11
Called hospitalist on call	8
Code activated	3
Called security	3
Technician brought patient directly to ED	2
No further action	1
Time from incident identification to response activation	
Median (range), min	3 (0–47)
Not documented, n	15
Time from response to intervention (arrival of physician or evaluation)	
Median (range), min	3 (0–25)
Not documented, n	27
Outcome/disposition, n (%)	
Admitted to the ED	41 (63)
Home (against medical advice)	4 (6)
Admitted to hospital floor	2 (3)
Discharged home without completing study	1 (2)
Not documented	2 (3)
Study completed,[a] n (%)	37 (57)
Study characteristics, completed studies (n = 37)	
AHI 3%, median (range), events/h	46.2 (0–134)
AHI 4%, median (range), events/h	19.1 (0–128)
Mean O_2, median (range), %	94 (80–97)
Minimum O_2, median (range), %	83 (50–92)

[a]Adequate testing completed before incident or able to complete the study following the incident. AHI = apnea-hypopnea index, ECG = electrocardiogram, ED = emergency department.

(10:00 PM–midnight), were transferred to the ED, and returned to the sleep laboratory when discharged from the ED (eg, following juice administration for low blood sugar).

Of the 40 events for which the RR team was paged, most were transferred to the ED (30/40, 75%). Of the patients who were not transferred to the ED, the RR team evaluation provided medical guidance that allowed for completion of the study. In 5 instances, patients had abnormal vital signs without any symptoms (2 with elevated blood pressure, 2 with hypoxia, 1 with tachycardia) and on review of medical history and discussion with the ordering physician, these studies proceeded. Two additional patients with a history of diabetes were found to have hypoglycemia as a cause for their complaints of lightheadedness or confusion, which improved with a snack. The remaining 3 patients complained of chest pain and/or shortness of breath, and again on review of symptoms, vital signs, and clinical history, the RR team recommended completion of the study with improvement of symptoms.

The completed studies for patients with incidents suggested a tendency toward severe sleep apnea, with a median apnea-hypopnea index of 46.2 events/h (range, 0–134 events/h), although there was considerable variability in sleep-disordered breathing in these patients (**Table 2**).

DISCUSSION

A process for evaluating and managing urgencies and emergencies in a traditional sleep laboratory is described. This approach includes triage of referrals, sleep technician training, and creation of a formalized incident response protocol. While these results suggest that serious medical complications during sleep studies are rare, preparedness and standardized response protocols allow for swift identification and activation of emergency response procedures when they do occur.

Overall events were rare, with 65 events over 3 years (9,558 studies), with a rate of 1:147; however, this incidence was higher relative to previously reported rates[3] and may reflect increased patient acuity over time. Patients undergoing in-laboratory polysomnography have shown an increasing number of medical comorbidities over the past 10 years[5] that likely contributes to the increased incidence of acute events in the sleep laboratory. Colaco et al[5] further suggest a "Polysomnogram Clinical Index" based on comorbidities as a way to anticipate needed services of more complex patients. Our center does not formally measure the Polysomnogram Clinical Index score, but essentially operationalized it such that anyone with a score of > 1 (or ≥ 1 high-risk criteria [**Box 1**]) is triaged to our hospital-based sleep laboratory. Because our hospital-based

laboratories have 10 beds and our free-standing laboratory has 4 beds, the majority of our sleep study population is able to be served in the hospital-based laboratory, allowing us to reserve the free-standing sleep laboratory beds for those with effectively a Polysomnogram Clinical Index score of 0 or no high-risk criteria.

Previous studies have reported falls during overnight studies. Kolla et al[3] report that 5 out of the 12 patients who experienced a fall were given zolpidem by their sleep physician. Those authors shared that at their sleep laboratory, sleep technicians did not receive the same fall-mitigation education that inpatient nurses receive, and that patients and families were not routinely educated in the sleep center about fall risks during sleep study testing. In our center, we did not have any falls reported during the study period, possibly due to the rate of sedative use and the inclusion of fall risk in the triage process. Between January 2016 and December 2020, 548 patients took zolpidem on the night of their study, accounting for approximately 5% of the total number of patients evaluated in the laboratory. Furthermore, any increased risk associated with zolpidem was likely mitigated by prestudy fall-risk screening and the use of attendants in individuals identified as high risk. Any patient identified as having mobility limitations during scheduling or prestudy screening was asked to be accompanied by an attendant during the night of the study.

While sleep technicians typically do not have advanced medical training or Advanced Cardiac Life Support certification, a protocol that includes clear triage and contact instructions can ensure that patients have access to timely evaluation and care. Events generally occurred in patients with multiple medical comorbidities, suggesting that a more complex in-laboratory patient population may require additional screening and support. For example, our center has a program for screening patients with atrial fibrillation. This has resulted in an increase in patients with this arrhythmia and typical associated comorbidities (heart failure, stroke) presenting to the sleep laboratory. If treating sleep apnea in heart failure becomes a clinical standard, then the complexion of the laboratory will change in predictable ways.

These results are generalizable at least to hospital-based systems, while independent testing facilities may see less severely ill patients. Our sleep laboratory has the luxury of in-hospital and free-standing sleep laboratory resources, allowing triaging higher-risk patients to the hospital setting. Independent diagnostic testing facilities that offer sleep testing services may not have this option and may benefit from affiliating with a hospital-based program for patients with the highest complexity. Non-hospital-based sleep laboratories may need to have different algorithms. A successful safety protocol will need utilization of available resources, such as an RR team or its equivalent. Free-standing centers may have no option but to trigger a 911 call.

False alarms are inevitable, and expensive, but patient safety is the key endpoint. False alarms, or unnecessary activation of the RR team, were rare in our center. Of the 40 incidents that resulted in activation of the RR team, 30 patients were transferred to the ED. Of the 10 patients who completed the study without transfer to the ED, 2 required intervention for hypoglycemia and 2 were given supplemental oxygen (temporary oxygen given to 1 patient following a seizure consistent with typical break-through episodes of refractory epilepsy as confirmed by a family member). The remaining 6 patients were evaluated at bedside without further intervention (6/40, 15%), although even in these patients, activation of the RR team was likely reasonable: for example, tachycardia in the setting of not taking prescribed β-blocker, or mild hypoxia following a break-through seizure before return to baseline neurologic status as confirmed by a family member. Avoidance of false alarms is critical in any system of evaluation, and knowledge of medical history can reduce unnecessary activations. For example, adequate knowledge of baseline cardiac status will minimize calling an emergency based on detection of apparently new atrial fibrillation or nonsustained ventricular tachycardia, and knowledge of complex partial or focal motor seizure history can alleviate technician discomfort with break-through events if these are reasonably frequent for a patient.

There are some limitations in our report. The first is that our center does not test children, in whom unique challenges for sick patients may be seen and need modified protocols—conditions such as neuromuscular disease and respiratory failure, epilepsy, and severe behavioral outbursts will require thoughtful interventions. Second, our center uses a hospital-based sleep laboratory for the majority of our in-laboratory studies, where much of the infrastructure for an RR to medically acute situations is in place. Given the limited number of patients in our affiliated free-standing sleep laboratories, this study does not fully address protocols for those facilities. However, the protocols for acute symptom assessment, sedative use policy, and tracheostomy procedures can be used in free-standing sleep laboratories.

Risk stratification can reasonably occur at multiple levels: ordering and scheduling, prestudy screening and vital sign measurement, and vigilance once the test has started. As routine diagnostic testing localizes primarily to the home environment, and improved sophistication of positive-pressure devices enables bypass of the traditional sleep laboratory, selection for more high-risk patients with increased medical comorbidities in the sleep laboratory is inevitable. Standardized triage and response protocols can optimize recognition and reaction to emergencies and maximize patient safety in the sleep laboratory.

ABBREVIATIONS

ED, emergency department
RR, rapid response

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Address correspondence to: Anjali Ahn, MD, 330 Brookline Avenue, KSB 23, Boston, MA 02215; Email: aahn1@bidmc.harvard.edu

DISCLOSURE STATEMENT

All authors have reviewed and approved this manuscript. Dr. Thomas discloses the following: (1) licensed patent (ECG-spectrogram) and royalties through Beth Israel Deaconess Medical Center to MyCardio, LLC; (2) an unlicensed patent for a CO_2 device to treat central/complex apnea; (3) licensed patent and royalties for an auto-continuous positive airway pressure algorithm through Beth Israel Deaconess Medical Center to DeVilbiss-Drive; (4) consulting for Jazz Pharmaceuticals, Guidepoint Global, and GLG Councils. The other authors report no conflicts of interest.

Paper 2

REM sleep distribution and timing in patients with prolonged sleep duration
M Blattner and R Thomas
(planned submission to Sleep Advances*, May 2022)*

REM sleep distribution and timing in patients with prolonged sleep duration

Margaret Blattner MD PhD (1), Robert Thomas MD MMSc (2)

Department of Neurology (1), Department of Medicine, Division of Pulmonary, Critical Care and Sleep Medicine, (2), Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA

Corresponding author: Dr. Blattner
Mblattne@bidmc.harvard.edu

Beth Israel Deaconess Medical Center
Sleep Neurology
330 Brookline Ave
Boston, MA 02215

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Author conflict of interest:

Dr. Blattner: No disclosures.

Dr. Thomas: 1) Licensed patent for ECG-spectrogram, to MyCardio, LLC; 2) Licensed patent for auto-CPAP algorithm to DeVilbiss-Drive; 3) Consulting for Jazz Pharmaceuticals, GLG Councils and Guidepoint Global; 4) Unlicensed patent: CO2 device for central/complex sleep apnea

Abstract:

Study Objectives: Evaluation of hypersomnia includes polysomnography followed by mean sleep latency testing. In most centers, the overnight portion of the study will be terminated in the morning, rather than allowing spontaneous awakening, to begin sleep latency testing. For patients with habitual prolonged sleep duration, this interruption may result in REM sleep on nap testing that reflects continuation of their biological night, rather than abnormalities in REM sleep regulation.
Methods: 42 consecutive extended sleep studies for patients with a total sleep time greater than 600 minutes were reviewed. For studies with sleep onset before midnight, we evaluated REM period onset after 6AM, distribution of late REM sleep, and the time of the final REM period onset.
Results: The median age was 31 years (range 16-76) with a median total sleep time of 661 minutes (range 601-851), of these 31/42 (74%) had sleep onset before midnight (12 AM) and were included in the analysis. 29/31 (94%) of hypnograms reviewed had REM sleep after 8 AM, 15/31 (48%) had REM sleep after 10 AM, with the onset of the final REM period ranging from 3:45AM-13:20PM for patients with sleep onset time before midnight (12 AM). Holding age, gender, and SSRI use constant, the odds of REM sleep occurring after 10 AM increased by 2.2% (95% CI [1.003, 1.042]) for every minute increase in total sleep time.
Conclusions: Termination of overnight polysomnography to initiate mean sleep latency testing, as is standard in many sleep labs, may influence the presence of REM sleep on MSLT for patients with prolonged total sleep duration. These results may have implications for the interpretation of MSLT for patients with long sleep duration.

Key words: hypersomnia, MSLT, REM sleep, sleep architecture, circadian

Statement of significance: Multiple sleep latency test (MSLT) guidelines emphasize adequate sleep duration and timing of sleep, but not sleep duration. In patients with prolonged sleep duration, habitual sleep time can extend far into the MSLT testing period. Thus, what is sampled may reflect part of the biological night, rather than the implicitly understood biological day. The occurrence of ample REM periods beyond typical wake up times in patients with prolonged sleep duration, as we show, have implications for interpretation of the MSLT and question the biological wisdom of such testing for this subset of patients.

INTRODUCTION

Evaluation of hypersomnia includes overnight polysomnography (PSG) followed by multiple sleep latency testing (MSLT). In most sleep testing centers, the overnight portion of the study is terminated in the morning to begin sleep latency testing, even if patients have not woken up spontaneously. Protocols often allow for initiation of the MSLT after 6 hours of recorded sleep time [1,2]. The presence of REM sleep during the nap opportunities of an MSLT differentiates narcolepsy from idiopathic hypersomnia (IH). However, this differentiation based on PSG/MSLT is fraught with complications; the MSLT has an inadequate sensitivity of only 30-50% in patients with idiopathic hypersomnia [3,4] and the MSLT has poor reliability for IH, with only 25-50% of patients having diagnostic concordance on repeat MSLTs [5-7]. For patients with habitual prolonged sleep duration, especially in combination with mild circadian phase delay from habitual late light exposure, the interruption of typical sleep for initiation of the MSLT itself may result in REM sleep on nap testing that reflects continuation of their biological night, rather than true abnormalities in REM sleep regulation characteristic of narcolepsy.

Here, we report the timing and distribution of REM sleep in a cohort of patients with long sleep duration observed on diagnostic overnight polysomnography. These findings may help to better understand the limitations of the MSLT for accurate diagnosis in patients with prolonged sleep duration.

METHODS

Polysomnography

Consecutive diagnostic overnight polysomnography from patients with total sleep time of more than 10 hours (600 minutes) was retrospectively reviewed. All protocols were reviewed and approved by our institution's Institutional Review Board. Studies were collected from

12/2011-8/2020, and 59 studies documented total sleep duration more than 600 minutes. Studies were clinically obtained to evaluate excessive daytime sleepiness. Studies were excluded if there was more than mild sleep disordered breathing (AHI < 15/hr included). PAP titrations or split night studies were excluded from analysis. The rationale for excluding studies indicative of moderate-severe sleep apnea (titration, split night, and diagnostic studies with an AHI> 15/hr) is that sleep disordered breathing is fundamentally disrupting the sleep on the study night: these patients would be functionally sleep deprived. Prolonged sleep on the study night may be indicative of rebound sleep/ making up sleep rather than habitual prolonged sleep duration. Additionally, sleep apnea, and treatment of sleep apnea with PAP therapy, can alter sleep architecture. For example, patients with REM-dominant sleep apnea may have fragmented REM sleep, with a titration allowing for REM rebound. Overall, these studies are excluded because the physiology of sleep duration and sleep architecture is fundamentally different than patients with healthy sleep. Of these studies, there was data from 42 individuals (Figure 1). The majority of studies included in analysis were unrestricted/ extended diagnostic polysomnography ordered to evaluate habitual prolonged sleep duration, however, we also included studies that met criteria of 600 minutes of total sleep time that were not specifically indicated for reported habitual prolonged sleep duration, because our goal was to include as many long sleepers as possible with variable sleep diagnoses (not just those with a primary hypersomnia).

Of the 42 studies with total sleep time of greater than 600 minutes reviewed, 31 studies had sleep onset time prior to midnight. Of all long sleepers, 11/42 (26%) were excluded from analysis due to sleep onset after midnight. Demographic information and polysomnography data were analyzed for both the inclusive group and the subset of patients with sleep onset before midnight. Studies with sleep onset before midnight were included in the final analysis of REM sleep distribution. Clinical and demographic information was

obtained from retrospective patient chart review. As this cohort was derived for polysomnography review for inclusion, all polysomnography data was available (sleep onset time, sleep architecture) as well as some demographic data (age, gender), and clinical data (medication list) included in the sleep report. Not all patients in this cohort were followed by our sleep clinic after their sleep study, and final clinical diagnosis was missing for some participants. Final clinical diagnosis was determined from chart review when available. When the complete chart was not available, clinical diagnosis was based on the study diagnosis itself, as was the case for patients followed by other centers.

REM sleep timing analysis

For studies with sleep onset before midnight, we evaluated the number of REM periods present after 6AM, 8AM, and 10AM, and the time of the final REM period onset. All studies were initially scored by a certified sleep technician, and independently reviewed by a Board Certified Sleep Medicine Physician. Hypnograms were visually reviewed to confirm time of REM periods. These time points were selected for analysis based on standardized protocols in many sleep labs: proceeding with MSLT once 6 hours of sleep has been observed on PSG. Demographic and diagnostic values reported as median and range, as results are not normally distributed.

We defined the presence of one or more REM periods with onset after 10 AM ("REM sleep after 10 AM") as the primary outcome measure. We selected this cut off time as 10 AM corresponds to the approximate second nap opportunity on the MSLT and REM sleep in 2 or more of the naps meets criteria for narcolepsy, having REM sleep after 10 AM would increase chance of a false positive on an MSLT. The primary predictor is total sleep duration (in minutes) on PSG. We included age, sex, and SSRI use as covariates. We conducted multiple logistic regression to test the hypothesis that long sleep duration (defined by total

sleep duration > 600 min on polysomnography) was associated with one or more REM periods with onset after 10 AM. In the multiple logistic regression model, we included total sleep time as the independent predictor of REM sleep after 10 AM. Univariate analysis of possible predictive factors (age, gender, BMI) was completed and we found no significant association between any of the demographic and clinical factors and the primary outcome (REM sleep after 10 AM), this analysis is summarized in Supplemental Table 1. We included age and gender as demographic covariates, and SSRI use as medically relevant information (known to influence sleep architecture) as an additional covariate confounder. Using the ICSD3 definition of idiopathic hypersomnia, with total sleep time greater than 660 min, as a proxy for long sleep time, we then tested the hypothesis that this cut off value serves as a predictor for REM sleep after 10 AM. Statistical significance was determined at the $p< 0.05$ based on two-sided tests.

RESULTS

Clinical characteristics

Of the 42 studies with total sleep time of greater than 600 minutes reviewed, 31 studies had sleep onset time prior to midnight. In the full cohort and the subset of patients with sleep onset prior to midnight, the median age and sex distribution were similar, with median 30 years (range 16-76) and 74% female (**Table 1**). The rate of selective serotonin reuptake inhibitor use was 52% (18/31) in the subgroup with sleep onset before midnight. Final clinical diagnoses included idiopathic hypersomnia (13/31, 42%), mild sleep disordered breathing (14/31, 45%, median AHI 1.96/hour, range 0.09-13.57), and circadian rhythm disorders were present in 11/31 (45%).

Polysomnography

All patients had prolonged total sleep time based on inclusion criteria (>600 min). In the overall cohort, the median total sleep time was 661 minutes (range 601-851), and in the subgroup with sleep onset before midnight, this was similar (675 minutes, range 601-851) (**Table 2**). In the subgroup with sleep onset before midnight, sleep efficiency median was 90.9% (71-97%) typically with short sleep onset latency (10.5 min, range 0-70 min) and normal to slightly prolonged REM onset latency (126 minutes, range 20-680).

REM sleep distribution

Hypnograms from this cohort demonstrated REM sleep late into the morning at times typical for MSLT protocols (**Figure 2**). 30/31 patients (97%) had onset of their final REM period after 6AM, 29/31 (93%) with onset after 8AM, and 15/31 (48%) with final REM period onset after 10 AM (**Figure 3**). 14 of the 31 studies (45%) were terminated from sleep, suggesting incomplete sampling of the biologic night.

Six patients in this cohort had undergone PSG/MSLT prior to the extended PSG included in this analysis, of these three had "abbreviated" MSLT (with 4 rather than 5 nap opportunities due to a late start of the MSLT, to allow patients to achieve > 6 hours of sleep on the overnight PSG). Of these six studies, two had no REM sleep during the naps, two had REM sleep (1 and 3 nap opportunities), two did not specify (MSLT obtained elsewhere).

Association of sleep duration and late REM sleep

In this study, n=42 cases met inclusion criteria and were included in this analysis. The prevalence of the primary outcome, REM sleep after 10 AM was 20/42 (48%). Within this cohort, the median age was 30 years (range 16-76), 74% female, and SSRI use in 20/42 (48%). The unadjusted odds ratio of the association between sleep duration and REM sleep after 10 AM was OR=1.02 [CI 1.00-1.04], p=0.026. The adjusted multivariate model controlled for age, sex, and SSRI use; these three covariates had no significant impact on our

primary outcome (chi $^{2}_{3}$= 1.0, p=0.809). The adjusted odds ratio was 1.02 [CI 1.00-1.04], p=0.025. Holding age, gender, and SSRI use constant, the odds of REM sleep occurring after 10 AM increased by 2.2% (95% CI [1.003, 1.042]) for every minute increase in total sleep time. To make this more clinically accessible with sleep duration in 30-min rather than 1-min intervals, in the same analysis, holding age, gender, and SSRI use constant, the odds of REM sleep occurring after 10 AM increased by 93.5% (95% CI [1.09, 3.44]) for every 30-minute increase in total sleep time.

Additionally, univariate logistic regression was performed to assess the effect of total sleep duration greater than 660 min (based on ICSD3 criteria for idiopathic hypersomnia) on the likelihood of REM sleep after 10 AM, though this model did not achieve significance there was a trend towards a predictive association (OR=3.52, 95%CI [0.94, 13.17] p=0.06).

DISCUSSION

The MSLT naps are implicitly targeting the biological day, as REM sleep occurrence is normal in the biological night. While melatonin profiling may provide a more accurate estimate of the limits of the biological night, especially the offset, in clinical practice a fixed time is used by most sleep laboratories, with minor (e.g., 1 hour) deviations permitted to enable 6 hours of recorded sleep. These data suggest that termination of overnight polysomnography to complete the MSLT as is standard in many sleep labs, may influence the presence of REM sleep on MSLT for patients with prolonged total sleep duration. These results have implications for the interpretation of MSLT for patients with reported long sleep duration in clinical sleep practice, as well as the choice of the testing strategy itself.

This study demonstrates a high prevalence of REM sleep into the morning in long sleepers with sleep onset before midnight. REM sleep occurred after typical overnight PSG study termination (6AM) in 97% of patients with prolonged total sleep time. REM sleep was

typically present into the time of recorded naps in multiple sleep latency testing (8AM and later) with almost half of patients with final REM period onset after the start of the second nap (10 AM). We found a significant association between total sleep duration and the presence of REM sleep after 10 AM ($p=0.025$) when including age, gender, and SSRI use as covariates. Current diagnostic criteria for diagnosis of idiopathic hypersomnia is documented sleep duration > 660 minutes. Though sleep duration > 660 minutes was not significantly predictive of sleep onset after 10 AM, there was a trend towards significance ($p=0.06$), suggesting need for further studies and enriching our sample size.

One limitation of this study is that the final diagnosis is not available for a subset of patients (no final diagnosis documented in 6/42 (14%) of patients), as some of these patients underwent diagnostic testing here, but obtained sleep clinical care at other centers. For this reason, for the main analysis, we use total sleep duration as a proxy for a diagnosis of IH. Of note, it is difficult for a direct referral request (patients not primarily seen at the BIDMC Sleep Center) to have extended polysomnography approved without a very strong documented clinical history consistent with idiopathic hypersomnia. Thus, while this study contained all long sleepers with different sleep diagnoses, 13/31(42%) had a final diagnosis of idiopathic hypersomnia available to us. The limitations of the PSG/ MSLT for the diagnosis of idiopathic hypersomnia are well documented with poor sensitivity [3,4] and poor test-retest concordance [5-7]. The findings from this cohort of long sleepers with extended PSG documenting REM sleep well into the morning may suggest that the presence of REM sleep on nap testing is reflective of the typical sleep architecture or biologic night, rather than an abnormal REM sleep propensity. Further, this late REM sleep is present in a majority of long sleepers, with or without a final diagnosis of IH, and may contribute to misdiagnosis of narcolepsy rather than idiopathic hypersomnia. About half of our patients were using REM

suppressing medications, and what impact such drugs have on REM sleep architecture in patients with prolonged sleep is not well defined[8].

We intentionally specify evidence of moderate to severe sleep apnea on the overnight study as an exclusion criterion for analysis; in this case that represents 14/59 of the studies screened and may introduce a selection bias. However, we felt that this exclusion was necessary for the integrity of our primary research aim as sleep apnea and treatment of sleep apnea (during a PAP titration protocol) can alter both sleep architecture and sleep duration with a physiology entirely distinct from habitual long sleep duration. However, this exclusion would likely bias our analysis towards the null, as these studies would likely demonstrate later REM "rebound" sleep, and prolonged duration due to deprivation of normal healthy sleep. Another known limitation of this study is the sample size, though representing a relatively large group of rare long sleepers that is often not clinically accessible, limits the power to detect significant associations.

The MSLT represents a brief recording of sleep, and scheduling often does not account for either typical sleep duration (for patients whose typical sleep time extends into the testing period) or habitual patterns of sleep-wake (patients with circadian rhythm disorders, for example). There is no formal consensus on the minimal duration of sleep that must be observed the night before or the days leading up to the MSLT, though the recommendation is at least 7 hours/night, or the most effective means of recording sleep patterns before testing (sleep diary, actigraphy) [9,10]. While it is desirable that there be unconstrained sleep with steady wake and sleep times prior to an MSLT, patients with prolonged sleep duration may have difficulty adhering to this recommendation due to work, school, or family constraints.

We observed a high prevalence of circadian disorders in patients with prolonged total sleep time. While a diagnosis of IH requires exclusion of symptoms due to a circadian

rhythm disorder, there is high prevalence of circadian rhythm abnormality in patients with hypersomnia. This should be expected, as if the individual habitually sleeps late, light exposure will also be proportionately late, and in time, entrainment will occur at a later clock time. In this analysis, patients with sleep onset before midnight were excluded from analysis (9/42, 21%); not all of these patients had a clinical diagnosis of delayed sleep phase disorder. Of the remaining patients with prolonged total sleep time, 11/31 (35%) had co-morbid circadian rhythm disorders (predominantly delayed sleep phase syndrome). As in the case of routine MSLT referral, with extended/ unrestricted sleep studies, the expectation is that 2 weeks of sleep diary (minimally) or actigraphy be obtained preceding the sleep study to evaluate for sleep deprivation or circadian rhythm disruption, which may influence test results. In this cohort, this data is available for only a few patients and, while consistent with data obtained clinically, represents a limitation of this data set. Future analysis could include deeper evaluation of delta power, spindle density, or percentage of N3 sleep as surrogates for sleep deprivation.

Given the limitations in the current protocols for patients with habitual prolonged sleep duration, alternative testing protocols are required to ensure accurate and efficient diagnosis of hypersomnia, as is performed in several European centers [11,12]. One option for documenting the long sleep of idiopathic hypersomnia is an extended or unrestricted PSG that continuously records patients' sleep for 24-32 hours in a sleep lab. These protocols have better sensitivity (>90%) and specificity (about 85%) for IH [11,12], but they are resource intensive and available in only a few sleep centers around the world. Actigraphy may also represent an avenue for estimating sleep duration in hypersomnia [13], though this is limited by accessibility, difficulty in obtaining unconstrained sleep for 2 weeks or more, and lacks the rich information about sleep architecture available with polysomnography.

In healthy sleepers, the timing of REM sleep during the night reflects sleep homeostatic processes as well as mediation from the suprachiasmatic nucleus, such that REM sleep has a strong circadian rhythm. REM sleep latency depends on circadian phase, and REM sleep propensity is greatest in the second half of the night[14]. We see REM sleep late into the morning in this cohort of long sleepers, suggesting possible failure of circadian processes that mediate healthy REM sleep timing, or suppression of REM sleep during the day. For healthy sleepers, there are circadian promoters of wakefulness, such as cortisol, which are prominent in the morning. For long sleepers, future studies are needed to determined daily patterns in circadian biomarkers, including cortisol, to determine if pathological prolonged sleep duration, as is seen in IH, is a problem of the sleep homeostatic drive or the circadian pacemaker.

Meantime, until more targeted diagnostic approaches are widely available, these data support the need for cautious interpretation of PSG/MSLT findings in patients with prolonged sleep. In borderline cases, dim light melatonin offset testing via salivary melatonin may help guide testing decisions or the timings of the first nap, within pragmatic limits of sleep laboratory flexibility. Clinicians should consider how protocols may influence results and interpret the PSG/MSLT in the context of habitual sleep time and duration; estimating the duration of sleep through unrestricted polysomnography may be preferred in such instances.

ABBREVIATIONS:

AHI (apnea-hypopnea index)

IH (idiopathic hypersomnia)

MSLT (multiple sleep latency test)

PSG (polysomnography)

REM (rapid eye movement)

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Table 1: Cohort demographics of all long sleepers with sleep onset before and sleep onset after midnight on the night of the sleep study. There was no significant difference between age, % female, or BMI in these groups ($p<0.05$ for all comparisons).

	Sleep Onset Before MN (n=31)	Sleep Onset After MN (n=11)
Age, median (range)	30 (16-76)	31 (19-56)
Sex, % female	23, 74%	9, 82%
BMI, median (range)	26 (17-48.1)	30(18-49)
SSRI use, n, %	18, 52%	8, 73%
Final Clinical Sleep Diagnosis (may be more than one), n, %		
IH	13, 42%	4, 36%
Sleep disordered breathing*	14, 45%	7, 64%
Circadian rhythm disorder	11, 35%	8, 73%
Phase delay	7, 23%	7, 64%
Shift work	3, 10%	0
Irregular rhythm (non-24)	1, 3%	1, 9%
Other sleep disorder**	7, 23%	0
None documented	5, 16%	1, 9%

*Mild OSA (AHI < 15/hour)

**Other sleep disorders included insomnia (2), RLS or periodic limb movement disorder (3), REM behavior disorder (2), medication-related hypersomnolence (1), and narcolepsy type 1 (1).

Table 2: PSG characteristics of the cohort with sleep onset before midnight and after midnight on the PSG night. Further characterization of the onset time of the final REM period was determined for patients with sleep onset before midnight.

	Sleep onset Before MN (n=31)	Sleep onset after MN (n=11)	
Total Sleep Time, minutes, median (range)	675.5 (601-851)	639 (619-691)	p=0.1
Number of REM periods, median (range)	6 (1-9)	5 (2-7)	**p=0.04**
REM latency, minutes, median (range)	126 (20-680)	202 (103-436)	**p=0.03**
REM %, median (range)	22 (11.5-41.6)	20.9 (7.4-30.4)	p=0.1
Onset of final REM period, median (range)	10:00 (3:45-13:20)	12:00 (8:45-13:30)	

Supplemental Table 1: Univariate logistic regression analysis of possible demographic and clinical factors and REM sleep after 10 AM, for selection of covariates of the multiple logistic regression model. For all of these, number of observations, n=42.

Factor	**OR [95% CI]**	**p**
Age	1.00 [0.95, 1.05]	0.995
Sex (female)	0.52 [0.12, 2.34]	0.40
BMI	1.04 [0.96, 1.13]	0.34
SSRI use	1.29 [0.37, 4.49]	0.69
PLMI	0.99 [0.92, 1.06]	0.74
IH diagnosis	1.22 [0.34, 4.38]	0.76
Sleep Onset Latency	1.01 [0.98, 1.04]	0.43
REM latency	1.00 [1.00, 1.01]	0.28
REM %	0.97 [0.89, 1.06]	0.56
Number of REM periods	1.21 [0.83, 1.77]	0.33

Figure 1: Consort Diagram depicting screening, inclusion, and exclusion from this analysis. NeuroCare database of sleep studies obtained for evaluation of patients at Beth Israel Deaconess Medical Center searched for sleep studies with sleep duration > 600 minutes. Duplicate studies, PAP titrations, and split night studies, and diagnostic studies with more than mild sleep disordered breathing (AHI > 15) excluded. Cohort included in the analysis (n=42).

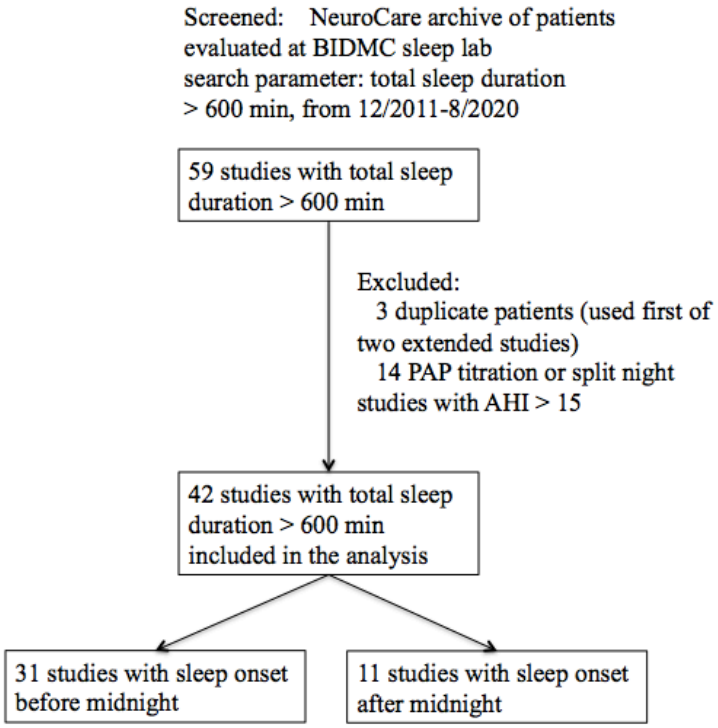


Figure 2: Hypnograms of long sleepers and MSLT timing. Extended uninterrupted hypnograms of selective long sleepers (a-c) relative to schematic of overnight polysomnography and multiple sleep latency testing (d). PSG here included from a 21-year-old female with idiopathic hypersomnia, total sleep time 710 min (a), an 18-year-old female with idiopathic hypersomnia, total sleep time 607 min (b), and a 32-year-old female with idiopathic hypersomnia, total sleep time 669 min (c).

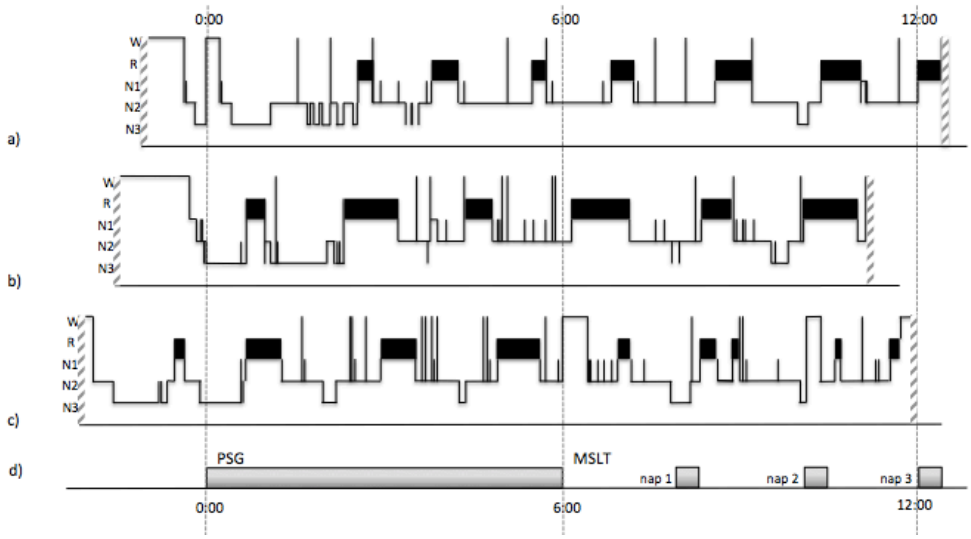
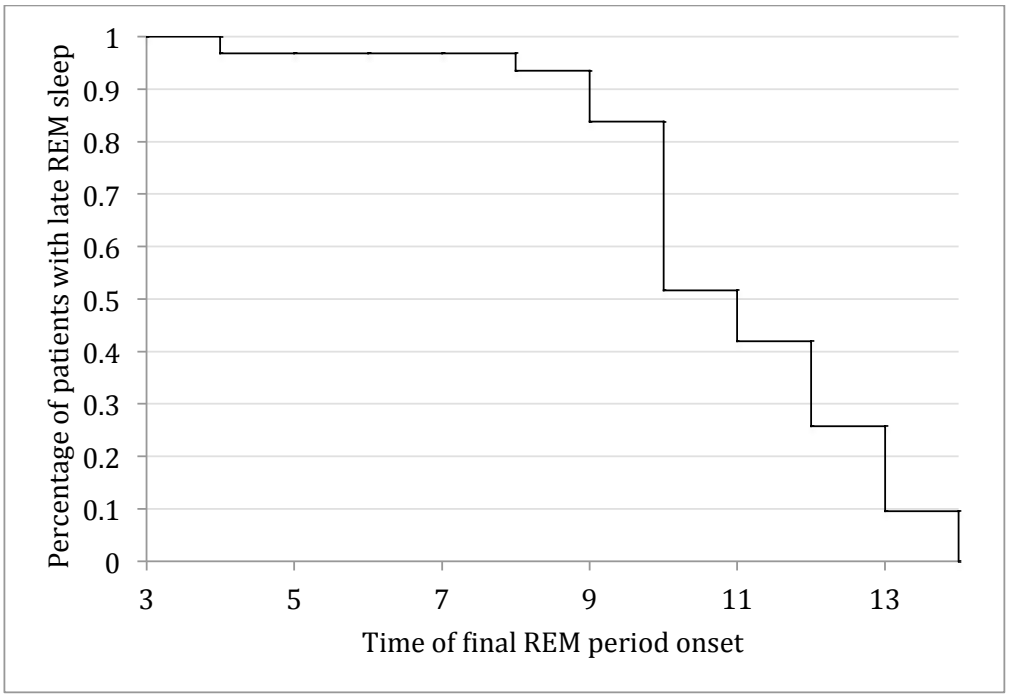


Figure 3: Time of onset of final REM period in long sleepers with sleep onset before midnight (n=31).



Summary and Conclusions

This work suggests that, while rare, patient safety events do occur during sleep studies, and that having protocols in place can result in efficient and appropriate evaluation (Paper 1). Further, the existing broadly applied sleep tests for hypersomnolence have limitations in special populations that require thoughtful interpretation and novel diagnostic approaches (Paper 2).

Overall patient safety events in the sleep lab were rare, with 65 events over 3 years (9,558 studies), with a rate of 1:147 studies; however, this incidence was higher relative to previously reported rates (0.68% relative to previously reported 0.16-0.35%) (2,3) and may reflect increased patient acuity over time. The incidence of in-laboratory safety events appears to be greater than previously described, potentially due to the widespread use of home sleep apnea testing. Implementation of formalized response protocols and sleep technician training may be necessary to meet the needs of an increasingly medically complex patient population. Based on this study, we identified "high needs" areas to emphasize in sleep technician training and have implemented a multi-factor screening for every patient in the sleep lab. When patients are admitted to the sleep study, all patients (those identified as "high needs" and not) complete a symptom survey questionnaire including common concerning symptoms, such as chest pain, shortness of breath. In addition, a set of vital signs is obtained and there are highly visible signs in the technician workroom reminding of concerning vital sign parameters and emergency workflow ("Take Quick Action").

While the multiple sleep latency test is broadly applied for the clinical evaluation of hypersomnolence, the outcomes of this test are known be influenced by habitual sleep time (circadian delay or shift work) or sleep deprivation (4.5). In this study, we evaluate sleep architecture in patients with prolonged sleep duration and demonstrate that REM sleep extends throughout the nap testing time frame in this population (Paper 2).

By appreciating that patients coming into the sleep lab are medically complex (Paper 1) and may have complex sleep pathology complicating interpretation of standard sleep lab tests (Paper 2), sleep lab protocols can be adapted to adequately address patient safety during the sleep study, and physicians interpreting these studies can consider them in clinical context to improve diagnostic accuracy.

Discussion and Perspectives

To our knowledge, this work reports the most up-to-date and comprehensive safety data from a sleep lab (Paper 1). However, there are some limitations of this study. As discussed, this center evaluates only adults in the case of patient safety events and mitigation; there are unique challenges for children, which require modified protocols from those presented here. Second, our center uses a hospital-based sleep laboratory for the majority of our in-laboratory studies, so the protocols presented reflect utilization of an existing rapid response in-hospital protocol; many sleep centers are free-standing so modification of these sleep lab safety protocols would be needed. As with all patient safety protocols, ongoing event tracking and monitoring of outcomes is needed to update and maintain safety protocols. Future directions also include development of an algorithm to predict high-risk patients, based on patient referral characteristics and medical history. While this analysis was not included in this study, one hypothesis may include the mobility limitations and the medical comorbidities we list as triage or "high needs" criteria in Paper 1 Box 1.

Hypersomnolence with true prolonged sleep duration is rare. Because our sleep center has the ability to perform unrestricted/ prolonged diagnostic sleep studies as part of the clinical evaluation, this study reports extended sleep data from a relatively large cohort of long-sleepers (Paper 2). In patients with a circadian phase delay and shift work, the MSLT is impacted by habitual sleep time/ circadian phase (4,5); this study provides evidence that this test may also be influenced by sleep duration. One limitation of this study is the retrospective chart review for gathering patient clinical data, as pre-test data is not standardized for all evaluations. For example, while habitual sleep time is reported for many of these patients, confirmatory sleep diary information is missing for many.

Together, this work serves as a foundation to build appropriate and alternative protocols in the sleep lab to optimize patient safety and evaluation of an increasingly

complex sleep disorders population. Next steps include development and validation of novel testing protocols for these patients, and a future goal of specific biomarker identification.

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Note: References for the Overview*,* Summary*, and* Discussion *sections listed below. References for Paper 1 and Paper 2 are included in the respective sections, formatting consistent with journals targeted for submission.*

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