Exploring the Effects of the Presence or Absence of Sleep Architecture and Critically Ill Patient Outcomes

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Dedication

This dissertation is dedicated to my spouse, Lee; my children, Elizabeth, Katelyn and Michael; and my parents, Jan and Larry.

Abstract

Background: Sleep disturbances and deprivation are known to exist in the critically ill patient. Over a 24-hour period, the critically ill can have 7-9 hours of sleep, but as much as 50% of that sleep can occur during daytime hours, signifying significant sleep fragmentation. Furthermore, some critically ill patients have been found to have abnormal brain waves that obliterate normal sleep architecture. These patients are without conventional sleep markers exhibiting no Stage II sleep spindles, minimal rapid eye movement sleep, and slow background brain wave reactivity. Disrupted sleep has been associated with delirium, weakened immune system, impaired wound healing, nitrogen imbalance, and negative cardiac, pulmonary, and neurological consequences which may all lead to negative patient outcomes.

Objective: The objective of this dissertation was to explore factors and outcomes associated with sleep disturbances in critically ill patients. The state of knowledge related to sleep and delirium in critically ill patients were explored. The tools and challenges of measuring sleep in patients while in the intensive care unit (ICU) were also explored.

Methods: Using a data base from retrospective chart review of 84 subjects, factors and outcomes related to the presence or absence of sleep in critically ill patients were explored. Literature reviews determined the state of knowledge related to sleep and delirium and the measurement of sleep in critically ill patients.

Results. Severity of disease was significantly associated the absence of sleep architecture in both the continuous electroencephalogram (cEEG) 1 to 2- and 1 to 5-day groups. Propofol was significantly associated with the presence or absence of sleep architecture in the day 1-2 group. After adjusting for age and medications, serum creatinine and neurologic physiologic state during days 1 to 2 of cEEG are factors associated with no sleep architecture using bi-variate analysis. Multivariate logistic regression adjusting for age and medications during Days 1-2 cEEG found abnormal serum creatinine to be statically significant. After adjusting for age and medications,

encephalopathy and developmental disability were factors significantly associated with no sleep architecture in the Day 1-5 group. . Multivariate logistic regression adjusting for age and medication during days 1-5 cEEG found the physiologic states of encephalopathy and developmental disability to be significantly associated with the absence of sleep architecture. The patient outcomes of increased mechanical ventilation days, ICU length of stay and hospital length of stay were associated significantly with no sleep architecture during Days 1-2 cEEG. In the 1-5 Days cEEG group, hospital length of stay was significantly associated with no sleep architecture. Post-hospitalization transfer location was associated with no sleep architecture for both cEEG groups. Discharge to home was associated with the presence of sleep architecture.

Conclusions: Certain patient characteristics are associated with the presence or absence of sleep architecture. The presence or absence of sleep architecture may impact patient outcomes. The exploratory study indicates that future prospective research with larger sample sizes and sleep architecture specifics is needed to advance the state of knowledge. While delirium theoretically may be related to sleep disturbances, more research is needed to determine if a correlation exists. Measuring sleep architecture in ICU patients can be challenging. Critical illness can impact the reliability and accuracy of sleep measurement tools including the gold standard polysomnography. Researchers need to be clear in their research goals and know the challenges related to the various sleep measurement tools.

Table of Contents

Table of Contents

Table of Contents

List of Tables

Page

List of Tables

Page

Chapter 1:

Introduction

One of the chief complaints of former intensive care unit (ICU) patients is sleep deprivation. Patients have indicated that the ICU environment disrupts circadian rhythms and disturbs sleep resulting sleep deprivation (Kiekkas et al., 2010; Lusk & Lash, 2005; DeKeyser, 2003, Fontana & Pittigloi, 2010). Qualitative research has shown that 54% of critically ill patients reported difficulty falling asleep in the ICU setting with close to half identifying noise as the causal agent (Hofhuis et al., 2010). However, many patients are unable to remember their ICU sleep experience related to their critical illness and/or medications making the sleep state in the critically ill difficult to determine.

Normal Sleep Architecture

Sleep is a complex process characterized by physiologic, behavioral and brain wave changes necessary for the restoration of cognitive, mood and physiologic functions (Kamdar, Needham, & Collop, 2012; Hardin, 2009). Normal sleep architecture consists of four to six 90 to 100 minute periods during which non-rapid eye movement sleep (NREM) and REM alternate in a cyclical fashion. The period of NREM is comprised of Stages 1–3, each stage having unique brain wave activity. REM sleep is distinguishable from NREM sleep by changes in physiological states, including its characteristic rapid eye movements and occurs approximately 90 minutes after sleep onset. All stages are necessary for a restorative sleep process.

Polysomnography

Polysomnography (PSG), commonly called a sleep study, measures brain waves, oxygen levels, electrocardiogram, and various muscle movements. PSG, considered the gold standard of sleep measurement, is able to determine the quality and quantity of sleep. However, utilizing PSG to determine sleep architecture in the critically ill patient is cumbersome, expensive, and potentially inaccurate. Illness, injury and medications may interfere with the ability to accurately

analyze PSG brain wave data. Studies employing PSG in critically ill patients often use extensive inclusion and exclusion criteria to insure complete and accurate sleep data, thereby limiting generalizability. Electroencephalogram (EEG) tracks and records brain wave activity. EEG data analysis can determine general patient sleep information but would have difficulty differentiating between wakefulness, Stage 1 and REM sleep (Estrada et al., 2006). EEG can be used be as a preliminary screening to determine if a patient has sleep architecture or normal brain waves that could sustain sleep.

Sleep in the Critically Ill Adult

Over a 24-hour period, critically ill patients can have an adequate 7-9 hours of sleep, but as much as 50% of that sleep can occur during daytime hours, signifying significant sleep fragmentation. Sleep fragmentation causes short bursts of sleep, resulting in a predominant N1 sleep stage with scarce time in restorative Stage 3 and REM sleep stages. For example, Friese et al. (2008) found that mechanically ventilated surgical patients average 8.25 hours of sleep, but 96% of the total sleep time was spent in stages 1 and 2. Sleep was disrupted by multitude of awakenings and arousals. Furthermore, some critically ill patients have been found to have abnormal brain waves that obliterates normal sleep architecture. These patients are without conventional sleep markers exhibiting no Stage 2 sleep spindles, minimal REM and slow background reactivity (Cooper et al., 2001; Drouot et al., 2011).

Sleep Disruption Outcomes

Even in healthy volunteers, sleep deprivation can lead to memory deficits, emotional imbalance, and slow reaction time with impaired attention, critical thinking, and recall (Maldonado, 2008). Disrupted sleep has been associated with a weakened immune system, impaired wound healing, nitrogen imbalance, and negative cardiac, pulmonary, and neurological consequences (Hardin, 2009; Bihari, 2012). By weakening upper airway musculature, sleep deprivation can interfere with efforts to wean patients from mechanical ventilation leading to

longer ICU length of stays (Celik et al., 2005). Additionally, sleep deprivation is theorized as a major contributor to delirium. Delirium is a state of confusion marked by a change in cognition associated with medical illness. Delirium in the critically ill has been associated with longer ICU and hospital lengths of stay, increased complications, longer mechanical ventilation time and higher mortality (Zhang et al., 2013). If sleep disruption and deprivation negatively impacts critically ill patients, having no discernable sleep architecture would also theoretically be associated with poor patient outcomes.

Summary

Disturbed sleep architecture has been associated with negative patient outcomes. Therefore, patients exhibiting no sleep architecture as determined by EEG monitoring would also be at risk for a higher rate of negative outcomes such as increased ICU and hospital stays, longer mechanical ventilation days, post-hospitalization discharge locations that are different from baseline (e.g., coming to the hospital from home but discharged to a nursing home), and higher mortality.

Purpose

The primary purpose of this dissertation is to describe the association between patient outcomes and no sleep architecture per EEG analysis in critically ill patients per a retrospective chart review from April 2015 to January 2016. Manuscripts presented reviews exploring the association between sleep and delirium in critically ill adults and the use of PSG in critically ill adult patients are also included.

Dissertation Aims

Aim 1. Determine the state of the knowledge related to an association between sleep and delirium in adult critically ill patients.

Aim 2. Determine the state of the knowledge in how to implement polysomnography in the critically ill and obtain comprehensive, accurate sleep data.

Aim 3. Explore factors associated with the finding of no sleep architecture in critically patients with EEG ordered as part of their plan of care.

Aim 4. Examine patient outcomes (mechanical ventilation days, hospital length of stay [LOS], ICU LOS, post-hospitalization discharge locations, and mortality) associated with no sleep architecture per EEG monitoring in critically ill patients.

Significance

The work presented in this dissertation will add to the limited body of research that explores the association between no sleep architecture and patient outcomes in critically ill patients. Next, a literature review will examine the association between sleep and delirium while providing recommendations for future research. While sleep disturbances are theorized to contribute to the delirium, limited research has been conducted measuring both sleep and delirium in critically ill patients. Additionally, the use of polysomnography in critically ill adult patients will be examined adding to the body of knowledge in regard to implementing this method of sleep data collection in the ICU environment.

Organization of Dissertation

This dissertation is organized into five chapters. Chapter 1 provides an introduction, purpose, aims, and organization of the dissertation. Chapter 2 consists of a manuscript that explores the state of the knowledge of an association between sleep and delirium in critically ill adult patients. This literature review will examine the strength of the association between sleep and delirium along with factors such as delirium measurement instruments, sleep measurement methods, age, diagnosis, ventilation, and sedation that may impact any findings. Chapter 3 examines sleep measurement in the critically ill patient with a focus on PSG. Barriers to implementing PSG along with inclusion and exclusion criteria used in studies to insure accurate, usable sleep data are explored. Chapter 4 reviews the finding of no sleep architecture in critically

ill patients with EEG ordered as part of their plan of care. A preliminary EEG screening for sleep

architecture for a sleep intervention study surprisingly found the majority of patients had no sleep architecture. An overview of the number of patients screened and the EEG findings is given. Chapter 5 discusses the research findings exploring an association between no sleep architecture and patient outcomes along with possible future research recommendations.

Chapter 2:

Sleep and Delirium in the Critically Ill Patient: A Comprehensive Literature Review

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Synopsis

Delirium, an acute brain dysfunction, is a common complication of the intensive care unit (ICU) having both short and long term negative consequences. Poor sleep quality as evidenced by decreased total sleep time, sleep fragmentation, and disturbed sleep architecture has been a prevalent finding in critically ill patients. Theoretically, delirium and sleep disturbances are believed to be related, although the exact relationship is unclear. Multiple factors seem to contribute to ICU sleep disturbances and/or delirium making the measurement and analysis of their relationship challenging. Understanding the strength of the correlation between sleep and delirium can guide nursing practice and the development of interventions to improve sleep and decrease ICU delirium. This review of the literature was conducted to determine the state of the knowledge on the association between sleep and delirium in critically ill patients. A search of Medline and CINAHL using the key words of "delirium", "sleep/sleep disorders" and "critical care/intensive care units" yielded nine articles and one dissertation after applying inclusion and exclusion criteria. Research directly related to both sleep and delirium in the ICU is minimal, but synthesizing the studies may help guide nursing interventions and direct future research to be conducted in this area important to critically ill patients.

Key Words: Delirium, Sleep, Sleep disturbances, Critical Illness

Sleep and Delirium in the Critically Ill Patient: A Comprehensive Literature Review

Delirium is an acute brain dysfunction that is a common complication experienced by critically ill patients. Delirium is characterized by the acute onset of cerebral dysfunction, change or fluctuation in baseline cognition, inattention, and either disorganized thinking or an altered level of consciousness.[1-6] Patients with delirium may be agitated and distracted with delusions (hyperactive delirium), or lethargic, inattentive, and withdrawn (hypoactive delirium). Mixed delirium is identified by a fluctuation between hyperactive and hypoactive delirium types.[1, 7] It has been documented that ICU patients have a high risk for developing delirium with incidences ranging from 11% to 80% depending on setting, population, and study design.[4,8,9] ICU delirium has been linked to poor short and long-term outcomes.[6, 10] Delirious patients are more likely to experience acute respiratory distress syndrome (ARDS), nosocomial pneumonia, cardiopulmonary edema, self-extubation, re-intubation, cardiac arrhythmias, and to be discharged to a skilled nursing facility.[11-13] Additionally, mechanical ventilation days and length of stay in the ICU and hospital may increase in patients diagnosed with delirium.[14, 15]

Sleep is a complex process characterized by physiologic, behavioral and brain wave changes necessary for restoration of cognitive, mood and physiologic functions.[16,17] Normal sleep architecture consists of two distinct stages: nonrapid eye movement (NREM) and rapid eye movement (REM). Human sleep patterns normally consist of four to six 90-100 minute periods where NREM and REM alternate in a cyclical fashion.[17,18] NREM is further divided into three stages: N1, N2, and N3 or slow wave sleep (SWS) each with their own characteristics and properties (See Table 2.1). Sleep fragmentation, short bursts of sleep resulting in predominant N1 sleep stage with minimal time in the restorative sleep stages SWS or REM, is a common ICU finding. Even when total sleep time (TST) for a 24-hour period is adequate (7-9 hours), 50% of TST may occur during daylight hours indicating significant sleep fragmentation.[17, 21,22]

Table 2.1

Normal Sleep Stages

Sleep Stage	% Total Sleep Time	EEG Characteristics	Brain Activity
N1 or light sleep (NREM)	2%-5%	Low voltage theta waves (4-8 Hz)	Entry into sleep from wakefulness
N2 (NREM)	45%-55%	Slower, high amplitude waves, K-complexes & sleep spindles	Deepening sleep; transition to N3
N3 or Slow Wave Sleep (SWS) or Deep Sleep (NREM)	15%-20%	High amplitude delta waves (0.5-2 Hz)	High arousal threshold; restorative; memory consolidation
REM	20-25%	Low voltage, high amplitude, mixed frequency beta & saw-tooth theta waves	Dreaming; perceptual learning

More than 50% of ICU patients have been found to suffer from sleep disruption as evidenced by abnormal sleep duration, patterns, and architecture related to critical illness or the ICU environment.[20] Former ICU patients identified lack of sleep or rest as the most frequent, burdensome, and annoying ICU experience during their ICU stay.[19]

Sleep deprivation can lead to memory deficits, emotional imbalance, and slow reaction time with impaired attention, critical thinking, and recall.[23] Disrupted sleep has been associated with a weakened immune system, impaired wound healing, nitrogen imbalance, and negative cardiac, pulmonary, and neurological consequences.[17, 24] Sleep deprivation may consequently lead to increased ICU length of stay and increased mortality.[1,5,6]

ICU delirium has been shown to be a multifactorial process with sleep disruption hypothesized to be a factor in its development. While exact delirium etiology is unknown, sleep deprivation and delirium affect the same regions of the central nervous system: the prefrontal cortex and posterior parietal cortex.[5,25] Delirium has been described as a neurobehavioral syndrome caused by dysregulation of neuronal activity.[23] An imbalance of neurotransmitters may

explain both delirium and sleep disturbances. A deficiency in the cholinergic system and excess dopaminergic stimulation may produce the attention deficit, motor activity, mood, and memory changes found in delirium. The cholinergic system is also involved in creating REM sleep. Low levels of cholinergic neurohormones may decrease REM sleep and contribute to delirium.[5,25] Melatonin hormone levels influenced by dopamine and light exposure can result in disruptions to the 24 hour circadian biological clock.[2,25] Dementia, old age, and psychotropic medication are known risk factors for delirium that are associated with impaired melatonin secretion or function.[26-28]

In view of the high prevalence of ICU delirium and the adverse outcomes for patients and society, determining and understanding the relationship between sleep and delirium is necessary to guide healthcare interventions and direct future research. The present review of the literature was conducted to determine the state of the knowledge on the association between sleep and delirium in adult critically ill patients.

Method

The keywords used in the search strategy completed in October 2018 were "delirium", "sleep/sleep disorders", "critical care/intensive care units". The search limits were 1) human and 2) English language. Articles identified using the keywords in Medline or CINAHL were reviewed using the following inclusion and exclusion criteria: Research articles were required to measure both sleep and delirium in an intensive care unit; review articles, case studies and articles using secondary data analysis of an included article's data were eliminated. The reference list of reviews, studies, and editorials were hand searched for additional studies. Titles and abstracts were screened in order to evaluate studies for inclusion according to eligibility criteria.

Results

One hundred thirty-three articles were identified through the database search. One article was located per the reference list of a review article. A total of nine articles and one dissertation met the inclusion criteria. Articles were excluded for the following reasons: not relevant to the research question (n=50) and duplicates (n=74). Table 2.2 summarizes the studies and their relevant components.

Table 2.2

Summary of Study Findings

Reference, Year	Study Aim	Subject n/ Setting	Study Design and Intervention	Sleep Measurement	Delirium Measurement	Stud
van de Pol et al.[34] 2017	Assess whether protocol reducing nocturnal sound levels decreases incidence of ICU delirium & improves sleep	n=211, pre-test n=210, post-test Medical Surgical ICU Netherlands	Interrupted time series; pre-test post-test prospective observational	RCSQ-end of night shift Extra question added related to noise	ICDSC Three times daily	Deli redu redu of sl
Boesen et al.[31] 2016	Assess sleep by PSG in relation to Delirium in MV non-sedated ICU patients	n=14 Mixed ICU	Pilot Study Prospective, observational	PSG-24 hours Scored American Associ-ation of Sleep Medication	CAM-ICU Once per shift CAM-ICU Twice daily	1 pa sleep delir PSG delir patie
Vacas et al.[38] 2016	Investigate feasibility & utility of monitoring sleep in ICU setting using portable EEG monitor	n=23 ICU USA	Pilot Study Prospective, observational	Portable EEG monitor Analyzed by board certified technician	ICDSC Once a day	asse Occ sign
Whitcomb et al.[30] 2014	Determine relationship between sedation, disruptions, & sleep using a sleep monitor to capture actual sleep	n=7 Medical, pulmonary ICU USA	Prospective cohort pre-test post-test design	Wireless sleep monitor 9pm-6am 1-6 nights	If RASS ≥-4, then	betw with 48% 30% 50%

Reference, Year	Study Aim	Subject n/ Setting	Study Design and Intervention	Sleep Measurement	Delirium Measurement	Stud
Patel et al.[32] 2014	activity compared with patient characteristics and real-time activity in the ICU Investigate the implementation of a bundle of non-pharmacological interventions, consisting of environmental noise and light reduction designed to reduce disturbing pts during night	n=167, pre-test n=171, post-test Medical Surgical ICU UK	Multicomponent sleep promotion bundle Prospective cohort pre-test post-test design	RCSQ-each morning of ICU stay. 1 questionnaire per patient randomly selected to be included in data analysis. Sleep in Intensive Care Question-naire. Nurse assess if patient asleep or awake each hour	CAM-ICU 0800,1400, and 1800 plus 0200 if appropriate CAM-ICU twice daily	18.5 60% 3.4% 9%) 1 su with sleej Post had sleej qual and with sleej repo
Kamdar et al.[33] 2013		n=122, pre-test n=178, post-test General ICU	Randomized clinical trial	RCSQ daily unless RASS≤-4, RCSQ not completed if.CAM-ICU + or nurse completed RCSQ if patient unable	NEECHAM scale 0800, 1400, 2200 When RASS≤2, CAM-ICU twice daily	& nu Post had inci befo p<.0 0.19 Mea deli (SD test
Van Rompaey et al.[36] 2012	To determine if a quality improvement intervention improves sleep and delirium/ Cognition	USA n=69, earplug intervention n=67 control	Prospective, observational design			
Trompeo et al.[29] 2011	Explore the use of earplugs during the night			Patient response to 5 sleep questions		

Reference, Year	Study Aim	Subject n/ Setting	Study Design and Intervention	Sleep Measurement	Delirium Measurement	Stud
	reduces delirium & improves the quality of sleep in the ICU	General ICU Belgium n=29	Prospective, observational design	PSG manually analyzed per Rechtschaffen and Kales criteria 1 night-10:00 pm-8:00 am	CAM-ICU every 12 hours	No s in sl grou over Few deli in pr post
Campo et al.[37] 2010	To assess the characteristics of sleep disruption in a cohort of surgical critically ill patients examining the hypothesis that severe impairments of rapid eye movement sleep are associated to delirium	General ICU Italy n=27	Prospective comparative design	PSG manually analyzed per Rechtschaffen and Kales criteria 1 night- 3:00pm-8:00am	CAM-ICU tid for max 3 days after continuous sed- ation ends, then CAM-ICU daily until negative	Slee lowe conf devel first usin bette REM mea 55)% Seve slee minu TST of di
Figueroa-Ramos[35] 2010	To determine whether sleep quality helps to predict noninvasive ventilation(NIV) outcome in patients with acute hypercapnic respiratory failure	Medical ICU France n=20 control n=20 intervention		Sleep Perception questionnaire- no psychometric testing. Missing data due to		
	To evaluate the effect of a SWT and SBT on the occurrence of delirium,	Trauma ICU				

Reference, Year	Study Aim	Subject n/ Setting	Study Design and Intervention	Sleep Measurement	Delirium Measurement	Stud
	sleep perception of sleep in trauma ICU patients	Puerto Rico		unresponsive patients.		seve 73.3 redu deli daily inde with REM Pati (intu pers day sign have defy patte minu 26 n succ (p=0 ICU patie 0% s patie

Reference, Year	Study Aim	Subject n/ Setting	Study Design and Intervention	Sleep Measurement	Delirium Measurement	Stud
						Slee cont grou SW expe (OR 0.45 drug (RH 4.65 3.09 and soor 1.82 grou

MV-Mechanical Ventilation, ICU-Intensive Care Unit, EEG-Electroencephalography, REM-Rapid Eye Movement, ICDS(
Care Delirium Screening Checklist, CAM-ICU-Confusion Assessment Method-Intensive
Care Unit, RCSQ- Richards Campbell Sleep Questionnaire, RASS-Richmond Agitation Sedation Score, PSG- polysomnog
Sleep Time

Study Characteristics

While all of the ten studies that were selected included sleep and delirium as variables, the purpose of the studies widely varied. Three prospective observational studies focused on the relationship between sleep disruption, delirium, and sedation.[29,30,31] Two studies examined outcomes related to the implementation of multicomponent sleep promotion protocols using pre- and post-test designs with sleep and delirium as outcome measures.[32.33] Noise reduction is often included in sleep promotion protocols. One study focused on the effect of noise reduction on the incidence of delirium and the quality of sleep.[34] Another study explored sedation reduction and ventilator weaning trials by comparing two groups that were sequentially assigned into either a sedation reduction wake up and spontaneous breathing trial or usual care.[35] Primary outcome variables were the occurrence of delirium, the number of days of delirium, and patient perception of sleep. A randomized clinical trial studied the use of earplugs related to sleep perception, confusion and delirium.[36] Another study used sleep and delirium as outcome measures related to late noninvasive ventilation failure (NIV) where NIV failure was defined as intubation, continued significant NIV for six days, or death.[37] A final study directly explored the relationship between ICU delirium and sleep disruption.[38]

Sample Characteristics

There was a marked variation in study settings, patient age, and diagnosis. The studies were conducted in eight different countries with the ICU settings varying from trauma[35], medical[33,37], medical/surgical[32,], medical/pulmonary[30], cardiosurgical[36] to general.[29,31,34,38] With the variety of ICU settings, the patient characteristics were also diverse. Trauma ICU patients were younger ranging in age from 23-58 years.[35] Campo and colleagues[37] had an average participant age of 82 years (range 72-85). Van Rompaey and colleagues[36] subjects ranged in age from 18 to 84 averaging 59 years. The mean age of the remaining studies was 60-68 years (range

18-81).[29-32, 34,37,38] While some studies shared the exclusion criteria of certain health variables, including neurological trauma or diagnosis of psychiatric diseases,[29,31,32,34,35,38] as well as alcohol or drug dependence,[29,32,35] the types of included diagnoses differed. One study, due to setting and inclusion requirements, had a patient population with a more homogenous diagnosis type- chronic or acute respiratory failure.[37] Outside of the trauma ICU, studies without a specific diagnosis for inclusion criteria had a wide range of primary problems among their subjects.[32,33] One study did not identify the primary diagnoses related to their subjects.[36] No significant gender differences were evident except in the pilot study where six out of seven subjects were male.[30] In four

studies, all subjects were either invasively or noninvasively mechanically [29,30-33,,37] ventilated. Two studies did not give information related to ventilation.[36,38] In the remaining studies, some, but not all subjects, were intubated.[31,34,37]

Sedation medications and opioids have been found to be correlated to both delirium and sleep disturbances. For this reason, some studies had criteria of no sedation at all or over a period of time (24-28 hours) before study enrollment.[31,32,36,37] Three studies did not include the use of these medications in their analysis.[30,33,38] Trompeo and colleagues[29] found that benzodiazepines and delirium were independent factors associated with severe REM sleep reduction. Van de Pol, van Iterson, and Maaskant[34] discovered a decrease in delirium and benzodiazepines use with the implication of a noise reduction protocol, but the quality of sleep was unaffected. Figueroa-Ramos,[32] in her sedation wake trial study, found that the control group with continuous sedation infusions had an 80% delirium rate. The patients using benzodiazepines and propofol had more hypoactive delirium. The sedation wake-up intervention group had only a 30% delirium rate with a preponderance of mixed delirium.

Studies have shown a potential relationship between disease severity and the development of either delirium[11] or sleep disturbances.[41,64] Van Rompaey and collegues'[36] results

showed a 9% increased risk of delirium as Sequential Organ Failure Assessment (SOFA) scores increased. Trompeo and colleagues[29] found significantly higher severity of disease scores upon admission in the severely REM deprived cohort with a corresponding increase in delirium incidence rate. However multiple regression analysis revealed that severity of disease was not independently significant from other variables.

Sleep and Delirium

Among the ten studies, findings related to the relationship between sleep and delirium were mixed. Trompeo and colleagues[29] measured sleep using polysomnography (PSG) to determine that a less than 6% of total sleep time (TST) consisting of REM sleep would equal a severe REM reduction. Patients with a severe REM reduction had a higher incidence of delirium. In a pilot study with seven patients measuring sleep with a wireless sleep monitor, the patient who on average was the most awake during the night (88%) with only a mean 2% REM sleep was determined delirious,[30] whereas a patient with decreased night TST, being awake 65.8% of the night, did not develop delirium. A patient with only a mean 0.5% REM sleep did not develop delirium per the patient's total average delirium score. Boesem and colleagues[31] found that out of 14 subjects, only one had identifiable sleep architecture. This subject tested negative for delirium. The other 13 subjects had atypical brain waves resulting in the inability to assess for sleep. These subjects tested positive, negative, or were non-assessable for delirium. One study explored how the use of earplugs during the night impacted sleep and delirium without directly analyzing the relationship between sleep and delirium.[36]

Five studies measured sleep using a patient report questionnaire to determine sleep satisfaction scores. Patel and colleagues[31] found that the cohort with the best sleep efficiency, sleep quality, increased night sleep time, and greater number of 3 hour periods of continuous sleep along with a reduction in daytime sleepiness had a significant reduction in the incidence of

delirium between groups (33% vs. 14% $p<.001$). In the better sleep group, patients recovered from delirium quicker with a mean length of time diagnosed with delirium lasting 1.2 days (SD 0.9) vs. 3.4 days (SD 1.4). Kamdar and colleagues[34] found a difference in delirium between cohorts, yet there was not a corresponding difference in sleep scores. Similarly, Figueroa-Ramos[32] found a significant difference in hypoactive delirium between groups (60% vs. 5%) with no corresponding difference in the patient's perception of sleep. In this study, the sedation reduction/breathing trial and usual care groups both self-reported sleep fragmentation, rating their sleep quality as "bad". However, a considerable amount of sleep data were missing due to over half of the subjects being unable to complete the sleep questionnaire. Van Rompaey and colleagues[33] used five questions to determine patients' sleep perception with only four out of 136 subjects unable to reply to the questions due to ongoing delirium. In this study, the intervention group using earplugs significantly rated their sleep higher in the first 24 hours than the control group without earplugs. Past the first 24 hours, sleep was not significantly better with earplugs and the amount of poor sleep increased for all patients. Van de Pol, van Iterson and Maaskant[34] had a 65.56% completion of the RCSQ from enrolled subjects. All subjects were assessed for delirium. The RCSQ was not used for delirious and unconscious patients, making the relationship between sleep quality and delirium difficult to ascertain.

Discussion

While sleep disturbances and delirium in critically ill patients have been linked theoretically, supporting evidence is minimal. Multiple factors may influence the development of sleep disruptions and delirium. By exploring potential common factors, the potential relationship between sleep disruptions and delirium may become more evident.

Sleep Measurement

21,42-44

However, PSG is rarely categorizing ICU sleep criteria has been found to be less studies, investigators only correlations of sleep

Polysomnography (PSG) is considered the gold standard for measuring the quantity and quality of sleep. PSG is electroencephalography (EEG) monitoring with the additional measures of electrocardiogram, respiratory effort, pulse oximetry and various muscle movement. implemented in patient care due to expense and technical difficulties in the ICU setting. Most studies using PSG have small patient populations and the duration of monitoring was often only for one night or 24 hours.[33] As Trompeo and colleagues[29] acknowledged, the limited patient PSG data makes characteristics difficult, such as the difference between a REM sleep reduction and a severe REM sleep reduction. While PSG may be considered the most reliable measure of sleep, two of the studies implementing PSG used the manual Rechtschaffen and Kales criteria[23] to analyze the data. These accurate and reliable in mechanically ventilated ICU patients compared to a computer-based method.[39] Part of the difficulty in analyzing PSG in the critically ill patients may be due to abnormal brain wave patterns, making the detection of sleep and wakefulness challenging.[17,42] Also in two PSG obtained readings for one night lasting 8 or 17 hours. Research has shown that up to 50% of ICU patients' sleep can occur during the daytime hours, thus investigators could potentially miss a significant amount of TST by measuring sleep only during the night making it difficult to make valid characteristics and delirium.

Three studies used the Richards-Campbell Sleep Questionnaire (RCSQ) to measure perceived sleep quality and noise levels. The RCSQ is a patient self-reported sleep instrument that measures: 1) sleep depth, 2) latency (time to fall asleep), 3) number of awakenings, 4) sleep efficiency (percent time awake), 5) sleep quality, and 6) nighttime noise. The RCSQ has been validated with PSG in alert and oriented critically ill patients which differs from patients suffering

from delirium.[45] The Patient's Sleep Perception Questionnaire was developed without psychometrics by Figueroa-Ramos to simplify gathering sleep data from intubated, critically ill patients, yet a large amount of sleep data is missing in this study related to patients being unable to complete the questionnaire.[35] Van Rompaey and colleagues[36] measured sleep using five questions instead of using validated patient sleep perception instruments stating that validated scales were burdensome to patients in that they were too long and required the patient's sustained attention.

Common memory problems in the ICU related to critical illness, sedation, delirium or dementia can negatively impact the validity and reliability of patient reported instruments. This is particularly relevant when the outcome variable is delirium. Using a patient reported sleep assessment tool may result in the inability to obtain sleep data due to critical illness or generating unreliable data with the delirious subjects. To overcome this dilemma, nurses have completed the RCSQ for subjects unable to do so for themselves due to delirium or communication hindrances after having tested the validity of nurse and patient reports using the RCSQ. However, nurses have been found to over report total sleep time when compared to PSG.[39] In the Van Rompaey and colleagues[36] study, the inclusion and exclusion study criteria included a Glasgow Coma Scale >10 and no sedation which insured that a vast majority of subjects in a study were able to answer patient sleep perception questions while limiting generalizability of results.

Two studies used unique methods to measure sleep. Whitcomb and colleagues[30] used a wireless sleep monitor that was developed for personal home use that had not been tested in clinical settings as a result, data validity was lacking. The feasibility of utilizing a portable electroencephalography (EEG) monitor to measure sleep in critically ill patients was explored by Vascas and colleagues.[38] In a sleep laboratory, the portable EEG monitor was able to recognize sleep stages, transitions and arousals in enrolled subjects. However, in comparing PSG and the

portable EEG monitor, the investigators found a difference in the accuracy of the portable EEG monitor to measure different sleep stages.

Delirium Measurement

Currently, there is no accepted bio-physiologic marker for delirium, although changes in brain waves per EEG monitoring has been explored.[45] Acute changes in baseline consciousness and cognition are hallmark features of delirium. Assessment of these changes usually depend on secondary sources (e.g., family, friends, health care staff and medical history) as the potentially delirious ICU patients are unable to recognize changes or provide accurate information. The Confusion Assessment Method-ICU (CAM-ICU) was developed to quickly and easily identify the presence or absence of delirium in mechanically ventilated and non-ventilated patients in the ICU with high reliability and validity.[47] As the presence of delirium is known to fluctuate, the five studies utilizing the CAM-ICU had 2-4 data points in a 24-hour period. The Richmond Agitation Sedation Score (RASS) along with CAM-ICU may be used to determine whether delirious subjects are in hypoactive (CAM-ICU positive, RASS 0 to -3) or hyperactive (CAM-ICU positive, RASS +1 to +4) delirium.[35] Hypoactive delirium has been linked to sleep deprivation and poorer outcomes compared to hyperactive delirium.[35]

In contrast, the Intensive Care Delirium Screening Checklist (ICDSC) is an eight-point system to determine risk for and presence of ICU delirium with a score of 4 or greater indicating the presence of delirium. Compared to the CAM-ICU, the ICDSC has moderate sensitivity and good specificity.[48] While the CAM-ICU is dichotomous, the ICDSC can be used as a continuous variable showing decreasing or increasing delirium symptoms.[48] Whitcomb and colleagues[30] used the ICDSC only once a day possibly missing delirium fluctuations. They did report a subject who was awake nearly 68% of a night, but did not have delirium since the subject's overall mean ICDSC score was 3.2. Using ICDSC, a subsyndromal delirium can be detected (ICDSC 1-3)

which is a state between no delirium (ICDSC=0) and clinical delirium (ICDSC=4).[49] Subsyndromal delirium has been found to potentially increase hospital length of stays and the need for convalescence care upon hospital discharge compared to patients with no delirium.[49]

One study utilized the NEECHAM Confusion Scale which was designed to identify signs of developing acute confusion and measure its severity.[50] The NEECHAM scale has been found to have strong reliability and validity in elderly non-critical care patients.[50,51,52] Minimal psychometric testing of this scale has been completed in the ICU setting particularly in mechanically ventilated patients[52.53] resulting in the pain, agitation, and delirium guidelines not recommending the use of NEECHAM in the ICU setting.[1] The 30 point NEECHAM scale has four categories for results: 30-27 "normal", 26-25 "at risk", 24-20 "early to mild confusion" and 19-0 "delirium or acute confusion". The meaning for patients and the predictive values of the "at risk" and "early to mild confusion" categories has not been explored. If these categories were found to have value in predicating delirium, this scale could be useful in testing interventions to prevent and treat delirium.

Age

Elderly patients have been found to be more prone to both sleep disturbances and delirium. In elderly patients, delirium is a prevalent complication related to hospitalization.[13,54] Post-surgical elderly patients with poor sleep patterns or sleep satisfaction were more likely to be diagnosed with delirium.[55-57] Even in healthy elders, there can be a measurable decrease in sleep with less SWS, REM sleep, and TST, and more awakenings, length of awakenings and daytime sleep hours.[55-58] At baseline, elderly patients are more likely to have poor perceived sleep or sleep satisfaction making a correlation between sleep disturbances and delirium difficult in this population. In the majority of the studies, age was not included in the final analysis. This was mainly because age was not significantly different between groups which does not capture the

relationship between sleep, delirium, and age. Van Rompaey and colleagues[36] found that the risk for mild confusion or delirium increased by 3% per year of life. Additionally, Figueroa-Ramos[35] did find that when group assignment, benzodiazepine, and propofol were controlled for every additional year in age, the odds of being delirious increased by 7%. However, the overall mean age was 32.5 years with the oldest subject being 58 years old; thus, no elderly patients were included in the study. Kamdar and colleagues[33] did include age in their analysis, but found no relationship between age, sleep disturbances and delirium. In the aged population, baseline cognitive dysfunction has been found to be a risk factor in the development of delirium and this rather than age itself may contribute to delirium.

Diagnosis

Various diagnoses have been linked to the development of delirium and sleep disturbances in the critically ill. The small pilot study did not include information related to diagnosis,[30] while in the other studies the types of diagnoses varied widely. Four studies eliminated patients with a history and/or current abuse of alcohol or drugs.[29,32] Undergoing substance withdrawal can lead to a hyperactive delirium, potentially confounding any analysis that developing delirium is related to sleep disturbances. Diagnoses of dementia[29,32,33,38] and various psychiatric[29,32] or neurological[29,31,34-36,38] disorders were also excluded. While acute neurological diagnosis (e.g., stroke) may impact wakefulness and higher cognitive function on the CAM-ICU, these patients can still be assessed for delirium and sleep. Using the ICDSC to assess for delirium has been found to be feasible for this patient population.[59] While not every item on the ICDSC is always valuable in the neuro-critically ill, the increasing or decreasing trend even at the low end of the scale gives valuable information related to the presence or risk of delirium.[59] Additionally, PSG analyses can be impacted by certain neurological diagnoses,[41,60,61] making the study of sleep and delirium in this patient population challenging.

Sedation

Benzodiazepines and opioids are frequently used for sedation in ICU patients; both have been found to disrupt sleep cycles by decreasing slow wave and REM sleep phases.[62] Additionally, sedation medications can potentially cause increased REM intensity over shorter time durations which can provoke nightmares and directly affect memory,[62,63] contributing to the disorientation and decreased attention span found in delirious patients. Benzodiazepine was found to be an independent factor, along with delirium, associated with severe REM sleep reduction.[29] Discerning whether patient symptoms can be contributed to sedation, opioids or delirium is difficult, which explains why some studies require these types of medications to not be administered to subjects 24-48 hours before subject enrollment.[32,36,373] However, withdrawal reactions can also lead to profound sleep disruption and delirium in critically ill patients and is mostly due to sedative agents for mechanical ventilation.[62] Discontinuation of sedation and sedation reduction protocols need to take into consideration that any new delirium noted may be related to withdrawal, along with the consideration that the patient is now awake enough to be assessed for delirium.[35] While propofol was not found to be a significant factor related to sleep or delirium in these results, a crossover study using PSG found that propofol was related to less REM sleep and further worsened already poor sleep quality.[64] Even dexmedetomidine has been shown to influence memory formation and learning and is hypothesized to interrupt normal sleep cycles via alterations in REM and NREM sleep.[62,63]

Ventilation

Among mechanically ventilated patients, delirium has been found to be a predictor for longer hospital stays, more days on the ventilator, and increased mortality, but the associations between mechanical ventilation, delirium, and sleep are not obvious.[14,15,65] Trompeo and colleagues[29] started one night of PSG recording after ventilator weaning was initiated at pressure

support ≤10 cm H_2O, positive end-expiratory pressure (PEEP) ≤ 5. All subjects were considered to have a reduction in REM sleep. Due to delirium being measured in the days following the one time PSG recording, a correlation between sleep, delirium and ventilation mode was unable to be discerned. During sleep, particularly in NREM stages, voluntary control of breathing is lost and reactivity to hypoxia and hypercapnia tend to decrease. This results in more arousals and sleep fragmentation which may explain the overall REM reduction found in these subjects on pressure support ventilation.[16] Pressure support has been shown to result in more sleep fragmentation compared to assist control (AC) or pressure control (PS) ventilation modes.[66,67] Yet in a different study, sleep was equally poor using AC or pressure support ventilator settings,[68] indicating the complexity of determining factors related to sleep disturbances. Noninvasive ventilation (NIV) failure after a minimum of 48 hours was correlated with impaired sleep and delirium when controlling for other variables.[36] NIV has been found to improve sleep in hypercapnic ICU patients compared to unassisted breathing.[36]

Other Factors

More than 60 different variables have been studied in relation to the development of delirium both in and out of the ICU making it difficult to determine the variables to include in delirium and sleep research.[4] Hospitalized patients who had three or more delirium related variables had a 60% increased risk of developing delirium,[70] yet critically ill patients can be subjected to 10 or more of these variables. However, not every ICU patient exposed to potential delirium risk factors develops delirium, highlighting the need for delirium research to be conducted specifically in the ICU setting.[4]

Recommendations

The paucity of research that measures both sleep and delirium in the critically ill patient is evident. While the theoretical underpinnings may seem strong, the evidence is weak. In going

forward in this area, several factors should be taken into consideration. Using self-reported sleep questionnaires has inherent difficulties when measuring delirium; however, PSG is expensive and problematic to initiate in the ICU. Measuring ICU sleep for less than 24 hours is considered a limitation due to the amount of daytime sleep found in previous studies. Improved, reliable sleep measurement tools such as actinography, bispectral index monitoring (BIS), or portable EEG need to be developed and tested. Some studies reported delirium scores from days before and after the one time PSG measurement. Any relationship between sleep data and delirium scores should be cautiously interpreted. It is well known that at any given time the ICU environment may change dramatically in light or noise impacting sleep.[39,71-73] The critically ill patients themselves and the resulting healthcare interventions can also change significantly from one day to the next. One 24-hour period or less of sleep measurement does not reveal a sleep pattern that can be correlated to ongoing delirium scores. However, more information is needed on how long sleep disruptions impact patients including the development and/or continuation of delirium.

The CAM-ICU delirium instrument has strong psychometrics, yet the use of the ICDSC and NEECHAM as continuous delirium variables may be able to better capture the course of delirium over time. Additional knowledge is needed regarding whether decreasing high ICDSC or NEECHAM delirium positive scores to lower delirium positive scores has patient significance. Furthermore, the evidence regarding whether subsyndromal delirium (ICDSD) or mild confusion (NEECHAM) are pertinent concepts and their potential impact on patients are in the infancy stages.

Delirium and sleep are both multifactorial and can fluctuate considerably even within 24 hours. Researchers have focused mainly on investigating the magnitude of the delirium or sleep disturbances on one day or by averaging the variables across multiple days. Although this research is informative, especially in these beginning stages of gathering evidence, there is much

that can be gained by examining intra-individual variability characterized by delirium measurement to delirium measurement over time.[68,74] This type of modeling will assist in exploring the extent to which important demographic variables such as age, diagnosis, sedation, mechanical ventilation, and severity of disease are simultaneously associated with the magnitude and day-to-day variability related to sleep and delirium in critically ill patients.

Conclusion

Whether sleep disturbances contribute to delirium or delirium contributes to sleep disturbances is debatable.[29] In fact, evidence regarding a relationship between sleep and delirium in ICU patients is inconclusive. However due to the prevalence and the high cost of delirium to the critically ill patient and society as a whole, the theoretical basis for a relationship between sleep disturbances and delirium should be addressed. Further research regarding the relationship between sleep disturbances and delirium in the critically ill patient is a necessary step toward the development and implementation of interventions to prevent delirium and sleep disruption.

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Chapter 3:

Polysomnography in the Critically Ill Adult

*to be submitted to Heart and Lung

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Synopsis

In patients who are critically ill, sleep disturbances may complicate recovery. Sleep is a dynamic function that impacts a person's ability to meets physical and mental needs. Sleep deprivation in healthy individuals has been linked to cognitive impairment, depressive mood and poor immune response. Neuroimaging studies have shown that sleep deprivation results in decreased cerebral metabolism, cerebral blood flow and brain oxygenation. Various sleep measurement modalities have been utilized to study sleep in the intensive care unit (ICU) environment including polysomnography, the gold standard of sleep measurement. However, obtaining usable PGS data in critically ill patients is expensive and it can be challenging to acquire scoreable PSG data. Studies employing PSG often have subjects with non-scoreable PSG data. To acquire scorable PSG data, researchers may employ extensive inclusion and/or exclusion criteria, limiting the patient population studied in relation to sleep in the ICU environment. This paper reviews the use of PSG with critically ill patients, considerations in implementing this method of sleep measurement in the ICU and challenges to obtaining comprehensive, accurate sleep data. Recommendations for practice and future research are proposed.

Keywords: ICU, sleep, sleep measurement, critical illness, polysomnography

Polysomnography in the Critically Ill Adult

In the intensive care unit (ICU), more than 50% of patients have been reported to suffer from sleep disruption (Bijwadia & Ejaz, 2009). Normal sleep architecture consists of two distinct phases: nonrapid eye movement (NREM) and rapid eye movement (REM). Normal human sleep patterns consist of four to six 90-110 minute periods where NREM and REM alternate in a cyclical fashion (Kamdar et al., 2013; Bijwadia & Ejaz, 2009; Hardin, 2009). NREM can be divided into three stages: N1, N2, and N3 or slow wave sleep (SWS), each with their own characteristics and properties. In the critically ill, total sleep time (TST) for a 24-hour period can be adequate, ranging from 7-9 hours, but up to 50% of TST can occur during daylight hours, reflecting a significant amount of sleep fragmentation. Sleep fragmentation is characterized by short bursts of sleep, resulting in predominance of N1 sleep stage with scant time in restorative Stage 3 and REM sleep stages. In a prospective, observational cohort study, mechanically ventilated surgical ICU patients were found to have fragmented sleep with abnormal sleep architecture (Friese et al., 2007). In these patients, TST averaged 8.25 hours, but 96% of TST was spent in stages 1 and 2, 0.29% SWS, and 3.3% REM sleep. Normal sleep architecture in healthy adults is distributed as stages 1 and 2, 50% to 60%; SWS, 13% to 23%; and REM sleep, 20% to 25%. In the ICU patients, sleep was disrupted by multitude of awakenings and arousals. It has been observed the amount of sleep fragmentation and overall disturbance varies within ICU patients, possibly related to diverse characteristics of critically ill patient populations, ICU environments, and disruptions associated with patient care interventions (Hardin, 2009). The purpose of this review is to review the use of polysomnography to measure sleep in critically ill patients in the ICU setting.

Consequences of Sleep Deprivation

One of the chief complaints of former ICU patients is sleep deprivation. Qualitative research has shown that 54% of ICU patients reported difficulty falling asleep in the ICU settings and 26% indicated that the shortness of sleep was a significant burden (Hofhuis et al., 2010). Sleep deprivation has been shown to lead to memory deficits and emotional imbalance. When sleep is limited to 4 hours per night for numerous nights, the cumulative sleep deprivation can lead to impaired attention, critical thinking, reaction time and recall (Maldonado, 2013). Disrupted sleep has been associated with weakened immune systems, decreased resistance to infection, impaired wound healing, nitrogen imbalance, and negative cardiac, pulmonary, and neurological consequences (Bihari, 2012; Hardin, 2009). Sleep deprivation can impair upper airway musculature undermining efforts to wean patients from mechanical ventilation and weaken the immune system while producing muscle pain, anxiety, and delirium (Celik et al., 2005). Patients have indicated that the ICU environment disrupts circadian rhythms and disturbs sleep, resulting in a lack of sleep (Kiekkas et al., 2010; Fontana & Pittigloi, 2010; Lusk & Lash, 2005; DeKeyser, 2003; Cornock, 1998). Overall, sleep deprivation may lead to longer ICU length of stays and increased mortality (Zhang et al., 2013; Ely et al., 2004). Sleep Measurement in the Critically Ill Patient

Accurate sleep measurement that considers the unique characteristics of critically ill patients is needed to acquire valid and reliable sleep data that can be used to determine the effectiveness of interventions in the ICU setting. The easiest and most cost-effective methods to measure sleep are patient self-report and nurse observation. A number of patient self-report sleep instruments are widely used to measure sleep among adult populations; however, in ICU patients, memory problems related to critical illness, sedation, delirium or dementia are common, and can negatively impact validity and reliability of these instruments (Bourne et al., 2007). To use

patient sleep assessment tools, critically ill patients need to be aware and remember their sleep experience. The Richard Campbell Sleep Questionnaire (RCSQ) takes into consideration the muscle weakness and difficulty critically ill patients have in maintaining focus by using a short visual analog scale. RCSQ strongly correlated with polysomnography (PSG) on sleep depth, number of awakenings, percent of time awake and quality of sleep (Richards, O'Sullivan & Richards, 2000). RCSQ correlated least well to PSG on the time to fall asleep or sleep latency. The lower correlation with sleep latency impacts how well RCSQ measures sleep efficiency or the amount of time asleep compared to the time in bed to sleep (Richards et al.,). In the critically ill patient who spends considerable time in bed even when not sleeping, sleep latency is as valuable a measure of sleep quality. Frisk and Nordstrom (2003) compared patient sleep assessment and nurse rated sleep assessment using the RCSQ. There was a strong correlation between the patient and nurse completed RCSQ scores. Patients in this study were conscious and oriented to place and time. Other studies have determined that assessment tools used by nurses to measure sleep time result in over-reporting of total sleep time when compared to PSG (Ritmala-Castran et al., 2016, Bourne et al., 2007, Richards, O'Sullivan, & Phillips, 2000). Nurses assess patient movement, eye opening, and interactions to determine sleep. Self-report and nurse observation depend on patient characteristics to accurately measure sleep. Critically ill patients who are not oriented, immobile, or sedated would not be good candidates for either method of sleep assessment limiting their usefulness to specific patient populations.

PSG is considered the gold standard for determining the quantity and quality of a patient's sleep. PSG is electroencephalogram (EEG) monitoring with the additional measures of electrocardiogram, respiratory effort, pulse oximetry, and various muscle movements. Differentiation between wakefulness, Stage 1 and REM sleep is difficult with just EEG (Estrada et al., 2006). The addition of electrooculogram (EOG) and chin or limb electromyogram (EMG)

leads, as part of PSG, allow accurate scoring of these sleep stages. EOG can detect slow eye movements that indicate sleep onset and Stage 1 sleep. EOG also detects rapid eye movements that distinguish REM sleep from other sleep stages. Rapid eye movements may occur during REM sleep and wakefulness, so muscle movements, as measured by EMG leads, are used to determine REM sleep. Being awake has the highest level of muscular activity in contrast to REM sleep, which has the lowest. PSG is rarely implemented as part of patient care in the ICU related to expense, need for trained personnel, and technical challenges. Patient characteristics and the ICU environment can interfere with obtaining brain wave recordings that are needed for the analysis of sleep (Sutter, Stevens, & Kaplan, 2013). Wounds or dressings may interfere with EEG electrode placement and the collection of accurate EEG data. EEG artifact may occur from patient sweating, muscle activity, and patient movement. Electrical interference can arise from common ICU equipment such as mechanical ventilators, pumps and beds (Sutter et al., 2013). Loose or dry electrodes can also interfere with EEG recordings and the repair of these connections throughout the day and night may in itself interfere with sleep. It is therefore not surprising that PSG is rarely implemented as part of patient care in the ICU due to expense, need for trained personnel, and these technical challenges.

Due to the expense and challenges of using PSG to measure sleep in the ICU, other technological methods have been trialed in various studies. Bispectral index (BIS) monitors brain waves provide a measurement of total sleep time (TST), but not sleep time at various sleep stages. Lower BIS values could indicate sleep in non-sedated patients (Tung, Lynch, & Roizen, 2002; Dahaba et al., 2011); however, neurological trauma, dementia, and delirium can lower BIS values and may falsely be interpreted as adding to total sleep time (Bourne, 2007). Another commonly used method to measure sleep is actigraphy. An actigraph is a motion-sensing accelerometer than can be worn like a wristwatch to record patient movement. Computer algorithms are used to

translate actigraph data into sleep parameters, associating periods of low activity with sleep and high activity with wakefulness. Actigraphy is easy to implement and noninvasive. In general populations, actigraphy can be used to measure sleep parameters including TST and number of arousals, with high predictive value compared to the gold standard PSG (Weiss et al., 2010; Kosmadopoulos et al., 2018). However, actigraphy tends to overestimate sleep by misidentifying lack of movement when awake as sleep (Weiss et al. 2010; Kosmadopoulos et al., 2018; Zhu et al., 2018). In the critical care setting, actigraphy is less predictive of sleep (Van der Kooi et al., 2012; Schwab et al. et al., 2018) because within days in a critical care setting, patients can develop myopathy (Argov & Latronice, 2015) leading to weakness and reduced motion. Reduced motion negatively affects the accuracy of the actigraphy (Bourne, 2007 Van der Kooi et al., 2012; Schwab et al. et al., 2018). Since actigraphy technology continues to develop and improve (Kosmadopoulos et al., 2014), in the future actigraphy may become a more reliable and valid option in the ICU to measure sleep.

Sleep measurement in the ICU setting is particularly challenging. The most critically ill patients are often sedated, confused or immobile. These patients may be at the most risk of the complications related to sleep deprivation, but all these factors are barriers to accurate sleep measurement. In general, sleep self-reports, nurse sleep assessments, BIS and actigraphy have limitations when compared to PSG, but it is not known if the expense and challenges to use of PSG in segments of the critically ill patient population are justified. Examining inclusion and exclusion criteria and the amount of usable PSG data in studies that implemented PSG with critically ill patients may elucidate the benefits of PSG to obtain sleep data in a diverse population of critically ill patients.

While PSG is considered the gold standard for sleep measurement, its use in the ICU setting is particularly challenging. The most critically ill patients who are often sedated, confused

or immobile may be at the most risk of the complications related to sleep deprivation. Yet these patients are the most difficult to obtain an accurate sleep measurement. Sleep self- reports, nurse sleep assessments, BIS and actigraphy have limitations on reliably measuring sleep in segments of the critically ill patient population. However, when the aim is to measure sleep in critically ill patients, the benefit of utilizing expensive and challenge ridden PSG to gather valid and reliable data is questionable. Examining inclusion and exclusion criteria and the amount of usable PSG data in studies that implemented PSG with critically ill patients may determine the benefit of PSG to obtain sleep data in a diverse population of critically ill patients.

Methods

Search Strategy

The keywords used in the search strategy were "critical care" or "intensive care unit" and "polysomnography". The search limits were 1) human 2) English language 3) adults and 4) year 2000 to present. Articles identified using the keywords in Medline or CINAHL were reviewed per inclusion and exclusion criteria. Research articles were required to measure sleep by polysomnography in an intensive care unit on critically ill subjects. Review articles and case studies were eliminated along with articles utilizing secondary data analysis. The reference list of reviews, studies, and editorials were hand searched for additional studies. Titles and abstracts were screened in order to assess studies for inclusion according to eligibility criteria.

Results

One hundred and forty-one articles were identified through the database search. A total of twenty-six articles met the inclusion criteria. Articles were excluded for the following reasons: not relevant to the research question and duplicates. Table 1 summarizes the studies and their relevant components. The number of subjects enrolled in the twenty-six studies ranged from nine to seventy. The average age of the subjects in the majority of the studies was in their sixth decade.

In one study, the average age was eighty-two years. Two studies had a younger population with an average age in the thirties. In twenty studies, the number of males enrolled was greater than females. In two studies, only male subjects were enrolled. The setting for the majority of the studies was a general ICU. Eight studies took place in a medical ICU with the rest in medical-surgical ICUs, surgical ICU, trauma ICU and a special ventilator weaning unit. PSG Data Quality in the Critically Ill Patients

Since 2000, twenty-six studies (See Table 3.1) implemented PSG with adults in the ICU setting (Cooper et al., 2000; Freedman et al., 2001; Richards et al., 2002; Gabor et al, 2003; Fanfulla et al., 2005; Alexopoulou et al., 2007; Basma et al., 2007; Friese et al., 2007; Toublanc et al., 2007; Beecroft et al., 2008; Roche Campo et al., 2010; Trompeo et al., 2011; Koudili et al., 2012; Su et al., 2012; Andrjak et al., 2013; Cordoba-Izquerdo et al., 2013; Watson et al., 2013; Elliott et al., 2014; Knauert et al., 2104; Van den Broecke et al., 2014; Boisen et al., 2016; Ersoy et al., 2016; Wiseman-Hakes et al., 2016; Boyko et al., 2017; DeMoule et al., 2017., & Huttmann et al., 2017). Sleep in the critically ill has been found to be fragmented and occurring throughout a twenty-four-hour period of time. Studies using PSG in the ICU setting typically measure sleep during one night. Eight studies measured sleep at night for 7-10 hours (Richards et al., 2002.; Fanfula et al., 2005; Bosma et al., 2007; Toublanc et al., 2007; Trompeo et al., 2011; Kondili et al., 2012; Audrejak, et al., 2013; Huttmann et al., 2017), potentially missing a significant portion of TST. One study gathered data for only two hours one night per subject (Su et al., 2012). Four studies used an expanded time frame of 16-18 hours for PSG implementation (Roche Campo et al., 2010; Cordoba-Izquerdo et al., 2013; Wiseman-Hakes et al., 2016; DeMoule et al., 2017). Some studies realizing the fragmented nature of sleep in the ICU environment sleep utilized PSG for 24 hours possibly revealing a more accurate sleep state (Cooper et al., 2000, Freedman et al., 2001, Gabor et al., 2003, Alexopoulou et al., 2007; Friese et al., 2007; Elliott et al., 2014; Knauert

et al., 2014; Boisen et al., 2016; Ersoy et al., 2016). Two studies implemented longer PSG times. Boyko and colleagues (2017) had 48 hours of PSG per subject. While Watson and colleagues (2013) gathered PSG sleep data from 40-72 hours per subject with an average of 54.8 hours. The expense and difficulty of implementing PSG in the ICU setting may be the reason only one-half of the studies used a 24-hour time frame for data gathering.

Table 3.1

Summary of Study Findings

Reference Year	**Study Aim**	**Inclusion/ Exclusion Criteria**	**# Enrolled/ # Data used in Analysis Reason for Discrepancy**	**Study Design a Intervention**
Cooper et al. 2000	Measure sleep in the critically ill on MV	Inclusion: ETT, MV >24 hr Exclusion: ICU stay <24 hr, unlikely survival, premorbid disease impacts sleep data, hemodynamic instability, general anesthesia or drug overdose or alcohol past 24 hrs	N=26 20 analyzed 6 discarded due to artifact	Prospective observational
Richards et al. 2002	Exam frequency & severity of OSA in Older, stable men with acute cardiovascular Disease	Inclusion: No OSA, hemodynamically stable, No severe dysrhythmias, ongoing chest pain, Infrequent pressor changes, <48 hrs critical care unit	N=70 64 analyzed 6 respiratory artifact	Prospective observational
Gabor et al. 2003	Determine impact ICU noise & pt care activites on sleep continuity in critically ill pts compatred to healthy volunteers in the ICU environment	Inclusion: ETT, MV for next 24 hrs Exclusion :previously published exclusion criteria for reliable PSG (See Cooper et al., 2000)	N= 7 critically ill & 6 healthy volunteers 13 analyzed	Comparative prospective

Reference Year	Study Aim	Inclusion/ Exclusion Criteria	# Enrolled/ # Data used in Analysis Reason for Discrepancy	Study Design a Intervention
Fanfulla et al. 2005	Compare effects of 2 ventilation settings on sleep architecture	Inclusion: Neuromuscular disorder, chronic respiratory failure, long term NIMV, admitted with clinical stability	N=9 9 analyzed	Comparative crossover 2 NIMV setting
Alexopoulou et al. 2007	Determine whether large number of end inspiratory occlusions influences sleep in speciifrc ventilator modes	Inclusions: good patient ventilator synchrony	N=17 17 night data analyzed Large amount unreliable sleep data during wakefulness in sedated patients	Comparative prospective
Bosma et al. 2007	Understand patient ventilator asynchromy as related to sleep disruption & optimizing patient ventilator interaction improves sleep	Inclusion: MV ≥3 days, Intact respiratory drive; Propofol DC minimal 36 hrs; Lorazepam DC minimum 72 hrs.; Morphine ≤0.01 mg/kg/hr; Alert; GCS ≥10 Exclusion: Spontaneous breathing trial done; Abnormal EEG 24 hrs before study; Central sleep apnea; Drug/alcohol abuse; General anesthesia <72 hrs; Haldol >10 mg/24 hrs, hemodynamically stable, infection, sepsis	N=16 13 analyzed 2 sepsis 1 hypoxia	Randomized Crossover clinic trial

Reference Year	Study Aim	Inclusion/ Exclusion Criteria	# Enrolled/ # Data used in Analysis Reason for Discrepancy	Study Design a Intervention
Friese et al. 2007	Describe quantity & quality of sleep & sleep architecutre	Inclusion: ICU LOS ≥2 days; No general anesthesia >24 hrs; Exclusion: Closed head injury; TBI; hemodynamically instability; sepsis; systemic inflammatory response syndrome; sleep disorder; frequent surgeries; lorazepam and morphine equivalents limits	N=16 16 analyzed	Prospective observational
Toublanc et al. 2007	Compare impact of assist control & pressure control ventilation on sleep quality	Inclusion: Intubated mechanically ventilated; acute on chronic respiratory failure; hemodynamically stable Exclusion: Sedative, narcotic, analeptic drugs <48 hrs	N=22 20 analyzed 1 electric artifact 1 respiratory distress	Prospective randomized crossover
Beecroft et al. 2008	Evaluate the accuracy between PSG, actigraphy & behavioral assessment by RN	Inclusion: Unrestrained; MV; vent setting not changed ≥24 hrs; Anticipate MV for 48 hrs Exclusion: Unlikely survival <3 mos.; hopeless prognosis; neurologic & sleep disorders; hemodynamic stability; GCS ≤10; Lorazepam & Morphine equivalent limits	N=12 12 analyzed	Prospective observational

Reference Year	Study Aim	Inclusion/ Exclusion Criteria	# Enrolled/ # Data used in Analysis Reason for Discrepancy	Study Design a Intervention
Campo et al. 2010	Determine if sleep quality may predict NIV outcomes in patients with acute hypercapnic respiratory failure	Inclusion hypercapnic acute-on-chronic respiratory failure treated by NIV, ≥65 yrs, Exclusion: encephalopathy, sedative or opioid, or neuroleptic drugs within 48 hrs, neurologic or psychiatric disease, hemodynamic instability.	N=27 19 analyzed 8 discarded for abnormal EEG pattern	Prospective, observational
Trompeo et al. 2011	Assess the characteristics of sleep disruption surgical critically ill patients examining the hypothesis that severe impairments of REM sleep are associated to delirium	Exclusion: abnormal EEG 24 before enrollment, anesthesia 72 hr previously, sepsis, hemodynamic instability	N=29 29 analyzed	Prospective, observational

Reference Year	Study Aim	Inclusion/ Exclusion Criteria	# Enrolled/ # Data used in Analysis Reason for Discrepancy	Study Design a Intervention
Kondili et al. 2012	Assess effect of propofol on sleep quality on vented critically ill patients	Inclusion: propofol titrated Ramsey score 3, MV at least 48 hrs, hemodynamically stable without vasoactive drugs Exclusion: Sedation or opioids other than propofol, GCS <11, APACHE >15, delirium, epilepsy/neurologic disease, sleep apnea, sepsis	N=12 11 analyzed Ventilator mode change	Randomized crossover Sedated with propofol & no sedation
Su et al. 2012	Examine effects of non-commercial music on sleep quality & relaxation indices in patients in ICUs	Inclusion: ≥18 yrs, APACHE ≤25, conscious & clear Exclusion: hearing impaired, physical restraint, alcoholism, infectious disease, hemodynamically instability	N=28 28 analyzed	Randomized controlled trial Music before sleep & no musi
Andrejak et al. 2013	Evaluate the effect on sleep of pressure control ventilation	Inclusion: Acute on chronic respiratory failure, Pressure control ventilation, no encephalopathy, no sedative, opioid, or neuroleptic drugs administered the last 48 hrs hemodynamically stable	N=35 26 analyzed 5 discarded in-accurate PSG data/excessive artifact; 4 for no ventilator data	Prospective, observational

Reference Year	Study Aim	Inclusion/ Exclusion Criteria	# Enrolled/ # Data used in Analysis Reason for Discrepancy	Study Design a Intervention
Cordoba-Izquerdo et al. 2013	Compare sleep quality between two ventilation types	Inclusion: Acute hypercapnic respiratory failure, expected >1 day NIV Exclusion: Hypercapnic coma, sleep altering medication, home treatment with NIV or continuous positive airway pressure, central neurologic disease, hemodynamic instability	N=25 24 analyzed 1 technical issues	Prospective randomized stuc
Watson et al. 2013	Quantify typical & atypical PSG in critically ill patients to develop & reliability test methodology characterizing atypical PSG	Inclusion: >18 yrs, expected >24 hrs MV Exclusion: Psychosis, anoxic brain injury, stroke, subdural hematoma, neurotrauma, cirrhosis	N=37 37 analyzed 36 atypical sleep (85% all recorded data) not analyzable by standard methods	Prospective observational
Elliott et al 2014	Describe intrinsic and extrinsic factors affecting sleep in critically ill patients & examine potential	Inclusion: >17 yrs, ICU stay >24 hrs Exclusion: sleep disorder, psychiatric illness, dementia, drug or alcohol withdrawal, central neurologic impairment	N=57 53 analyzed 2 request end PSG 1 palliative care 1 unable to analyze	Prospective observational

Reference Year	Study Aim	Inclusion/ Exclusion Criteria	# Enrolled/ # Data used in Analysis Reason for Discrepancy	Study Design a Intervention
	relationships with sleep quality			
Van den Broecke et al. 2014	Assess feasibility of sleep-disordered breathing at early phase acute coronary syndrome	Inclusion: ≥18 age, acute coronary syndrome Exclusion: Sleep breathing disorder, hemodynamic instability, acute heart failure, unable to provide consent	N=27 27 analyzed	Prospective observational
Boesen et al. 2016	Assess sleep quality by PSG in relation to delirium in MV nonsedated patinets	Inclusion: MV; ≥18 yrs age; no structural illness Exclusion: Propofol & benzodiazepine	N=14 14 analyzed 1 intermittent electrode malfunction; 1 PSG lost 4 hours	Observational Study
Wiseman-Hakes et al. 2016	Determine feasibility using PSG in ICU patients with TBI	Inclusion: GCS 3-8 in ER & 30 minutes later, Age 16-59 yrs, extubated; normal ICP, no infection, continuous IV sedation & analgesia off >48 hrs. Exclusion: Previous psychiatric or neurology disorder, sleep disorder, substance abuse, disease impacts sleep, pregnancy, severe eye injury, skull bone flap removal	N=15 13 analyzed 1 unable to analyzed 1 not tolerated	Cross sectional case control

Reference Year	Study Aim	Inclusion/ Exclusion Criteria	# Enrolled/ # Data used in Analysis Reason for Discrepancy	Study Design a Intervention
Boyko et al. 2017	Compare sleep in nondelirious ICU patients on MV during "quiet routine" night & usual night	Inclusion: Expected MV >48 hrs, Exclusion: Comatose, delirium, acute intracerebral events, circulatory shock	N=13 13 analyzed 8% recording total time had artifact	Random controlled trial cross over desig
DeMoule et al. 2017	Determine the impact of ear plugs & eye masks on critically ill patients' sleep	Inclusion: No sedation >24 hrs, RSS <3, expected ICU stay >48 hrs, morphine <0.01 mg/kg/min, norepinephrine <0.3 µg/kg/minute Exclusion: History sleep disorders, medicated psychiatric illness, central neurological impairment, liver disease encephalopathy, uncontrolled sepsis, severe hearing impairment or blindness	N=64 42 analyzed 3 withdrew 10 poor signal quality 9 unable to interpret	Prospective randomized stuc
Huttmann et al. 2017	Assess sleep quality in critically ill patients receiveing IMV on weaning unit	Inclusion: Tracheotomy, fully conscious, stable state, no clinical signs sepsis, meet criteria to wean Exclusion: Vasopressors, continuous sedation, anxiolytics, analgesics, delirium	N=21 19 analyzed 2 discarded PSG technology limits	Prospective observational Study

PSG polysomnography; MV mechanical ventilation; ETT endotracheal tube, ICU intensive care unit, NIV non-invasive ventilation, IMV inva ventilation; REM rapid eye movement, GCS Glascow Coma Scale, TST total sleep time, RSS Ramsey Sedation Scale, TBI traumatic brain inj Sleep Apnea, IV intravenous, hrs hours, PT patient; NIMW non-invasive mechanical ventilation; DC discontinue; EEG electroencephalogram emergency room; ICP intracranial pressure

Barriers to Using Full PSG Data

Eighteen of the twenty-six studies were not able to use or complete the PSG data for all of their subjects. Beyond the two studies with PSG lasting longer than 48 hours, the studies with the shortest observation times had the highest percentages of usable data. Only four studies had PSG for 16-18 hours with 67% of the subject's data used. Four of the studies with 24-hour PSG were able to use all the data: however, overall only 86.8% of subject's data were included in analysis. It may be that the longer the duration of the frame required for PSG, the more likely data will not be available for analysis. The two studies with the longest PSG intervals used all the enrolled subjects' sleep data. However, Boyko and colleagues (2017) reported that the PSG data had eight percent artifact. Watson and colleagues (2013) stated that eighty-five percent of all the recorded sleep data was atypical. This study was developing and exploring the reliability of a method to measure atypical sleep patterns. In other studies, the artifact and atypical sleep may have resulted in discarded data. Alexopoulou and colleagues (2007) used all their subjects' PSG data but did report a large amount of unreliable sleep data during wakefulness in sedated subjects. So the longer the interval of PSG, the more likely it seems that PSG data may be compromised, however, the standards used to determine what data is used or discarded is not clearly articulated.

The stated reasons for incomplete data included artifact, abnormal PSG, inaccurate PSG, missed ventilator data, respiratory distress, hypoxia, sepsis, subjects' withdrawal, poor signal quality and technology limits. A total of nine subjects withdrew or were withdrawn from five studies had after enrollment (Toublanc et al., 2007; Elliott et al., 2014; Knauert et al., 2014; DuMoule et al., 2017; Wiseman-Hakes et al., 2016). Elliott and colleagues (2014) had a total of three subjects withdraw from their study. One subject withdrew due to a transition to palliative care. No additional reasons for withdrawal were identified for five additional subjects withdrawing from the Elliott et al. (2014) and DuMoule et al. (2017) studies. Other reasons for

withdrawal include not tolerating PSG, respiratory distress, and patient deterioration. Some subjects may find the multiple electrodes uncomfortable and end their participation in the study. Additionally, if the signal quality is monitored throughout PSG, technicians may interrupt rest to reduce poor signal quality and artifact which could be a dissatisfier for subjects. Five studies had multiple subjects with unusable data due to artifact or poor signal quality (Cooper et al., 2000; Richards et al., 2002; Andrejak et al., 2013; Ersoy et al., 2016; DeMoule et al., 2017). Cooper et al. (2000) lost data from 6 out of 26 subjects due to artifact. Electrical artifact, technical problems and severe respiratory artifact were the reasons indicated for unused PSG data. The patients with severe respiratory artifact were also considered very edematous which may impact the quality of the PSG data. Andrejak et al. (2013) enrolled 35 subjects and data from six of those subjects was not used due to inaccurate PSG and/or excessive artifact. Additionally, DuMoule and colleagues (2017) missed data from ten out of 64 subjects due to poor signal quality. Artifact and poor signal quality can be related to ICU equipment, dressings, edema, diaphoresis, and electrode connection. Three of the studies impacted by artifact gathered PSG data from sixteen to forty-eight hours. One study collected sleep data for 48 hours and while no subject's data were discarded, eight percent of the total recording was artifact. The longer the study, the more important it seems the monitoring of the electrode signal to reduce artifact.

Although monitoring the electrode signal may reduce artifact, the use of a technician to monitor the signal is an added PSG expense that does not guarantee a complete reduction in artifact issues. Knauert and colleagues (2014) gathered sleep data for 24 hours per subject using a portable PSG in a medical ICU. No attendant monitored the PSG during the study and interpretable data was collected from 27 subjects out of the 29 enrolled. None of the data was affected by electrical artifact. Yet only one subject had a full 24 hours of data. Eight subjects had 18-24 hours of PSG data. Three had 6-12 hours and four had less than 4 hours of sleep data.

Having an attendant may have resulted in less truncated data. Future researchers may decide to utilize attendants based on the length of PSG sleep measurement and attendant expense.

Investigators were also not able to analyze data due to abnormal PSG information. The inability to interpret PSG data due to abnormal brain waves was present in eight different studies (Freedman et al., 2001; Alexopoulou et al.; 2007; Roche Campo et al., 2010; Elliott et al., 2014; Knauert et al., 2014; Wise-Hakes et al., 2016; DuMoule et al.; 2017; Huttmann et al., 2017). Two of these studies had over twenty percent of their data discarded related to atypical sleep or brain waves (Freedman et al., 2001; Roche Campo et al., 2010). Freedman and colleagues (2001) reported that PSG data from five subjects were not able to be analyzed due abnormal brain waves related to septic encephalopathy. EEG of patients with encephalopathy may show abnormal diffuse ongoing slow waves without sleep architecture (Kavanau, 2005). While Alexopoulou and colleagues (2007) had sleep data from during the night, the day sleep data from sedated subjects was unreliable.

Instead of analyzing abnormal EEG, Watson and colleagues (2013) explored developing a methodology to characterize atypical sleep in mechanically ventilated critically ill patients. In their study, thirty-six of thirty-seven subjects had atypical sleep. Eighty-five percent of all recorded data was not analyzable by standard methods like Rechtschaffen and Kales' sleep criteria or the American Academy of Sleep Medicine scoring standards. Eleven studies were able to utilize some PSG data from every subject in their analysis (Gabor et al., 2003; Fanfulla et al., 2005; Alexopoulou et al., 2007; Friese et al., 2007; Beecroft et al, 2008; Trompeo et al., 2011; Su et al., 2012; Watson et al., 2013; Van den Broecke et al., 2014; Boyko et al., 2017). However, some studies still included a subject's data even if part of the data was not usable for various reasons such as intermittent artifact or abnormal data (Alexopoulou et al., 2007; Watson et al., 2013; Boesen et al., 2016; Boyko et al., 2017). Certain medications are known to impact sleep

architecture leading to abnormal sleep (Oldham & Pisani, 2015). Benzodiazepines increase sleep efficiency but suppress REM and decrease slow wave sleep. Opioids also suppress REM and may lead to central sleep apnea. While in higher doses of propofol leads to a burst suppression brain wave pattern without the common sleep architecture elements. Only three of the studies including data from every subject had inclusion or exclusion data that specifically limited sedation, opioids or propofol. Two studies had parameters of no delirium and conscious/clear that lead to a limit to certain medications (Su et al., 2012; Boyko et al., 2017). However, benzodiazepine, opioid and propofol limitation does not seem to be a consistent contributor to analyzable sleep architecture.

Respiratory failure was the most common primary diagnosis in the studies able to use data from every subject. In two studies, all the subjects had respiratory diagnoses: acute respiratory failure secondary to surgical procedures (Trompeo et al., 2011) and chronic respiratory failure due to neuromuscular disease (Fanfulla et al., 2005). Gabor et al. (2003) described their patient population as having respiratory insufficiency or multiple trauma. More than half of the subjects were diagnosed with acute respiratory failure in the Cabello et al. (2008) study. The rest of the subjects had cardiac surgery, abdominal surgery or sepsis.

In the studies that were not able to use the data from all the enrolled patients, multiple diagnoses were identified. Some studies focused on specific diagnosis such as mild or moderate lung injury (Cooper et al., 2000), hypercapnia (Roche Campo et al., 2010), and acute on chronic respiratory failure (Andrejak et al., 2013; Cordoba-Izquerdo et al., 2013). Within other studies, subjects had various diagnoses. In the Freedman and colleagues (2001) study, the subjects had diagnoses of pneumonia, sepsis, chronic obstructive pulmonary disease, and acute respiratory distress syndrome. The Alexopoulou et al. (2007) study identified sepsis abdominal aorta aneurysm rupture, heart failure, pneumonia, cardiogenic shock and spinal cord injury as subject diagnoses. The DeMoule and colleague study (2017) reported diagnoses of acute respiratory

failure, pneumonia, chronic respiratory failure, sepsis, metabolic issues, trauma, neuromuscular disease and vascular disease. A number of studies that were unable to use all the PSG data identified no specific subject diagnoses (Kondili et al., 2012; Su et al., 2012; Elliott et al., 2014; Ritmala-Castran, 2016; Huttmann et al., 2017). Due to the wide variety of diagnoses or lack of diagnoses identified in studies, making an association between complete PSG data and diagnoses impossible.

Of particular interest, Wiseman-Hakes and colleagues (2016) is the only study to explore sleep in patients with a primary neurologic brain diagnosis. Often neurologic diagnoses are excluded in sleep studies due to the possible impact on brain waves. This study enrolled fifteen subjects and only one had PSG data that was not able to be analyzed. These subjects were extubated, had normal intracranial pressure and were off continuous intravenous sedation and analgesia for greater than forty-eight hours. These parameters may have contributed to the amount of usable data. In all the other studies, only two enrolled patients with a central neurologic injury. Alexopoulou et al. (2007) enrolled one subject with central nervous system damage and was able to obtain usable PSG data. With the other study the ability to use the data from the neurologic patient is unable to be discerned (Knauert et al., 2014). Particular diagnoses may or may not impact the ability to obtain usable PSG data. However, many acute diagnoses particularly neurologic have not been studied in relation to sleep architecture in the critically ill patient.

Mechanical Ventilation

Mechanical ventilation may not in itself interfere with the ability to acquire accurate PSG data. In eighteen of the studies, all the included patients were mechanically ventilated (Cooper et al., 2000; Gabor et al., 2003; Fanfula et al., 2005; Alexopoulou et al., 2007; Bosma et al., 2007; Toublanc et al., 2007; Beecroft et al., 2008; Cabello et al., 2008; Roche Campo et al., 2010;

Trompeo et al., 2011; Kondili et al., 2012; Anderjak et al., 2013; Cordoba-Izquerdo et al., 2013; Watson et al., 2013; Boesen et al., 2016; Ersoy et al., 2016; Boyko et al., 2017; Huttmann et al., 2017). Nine of these studies were able to use the PSG data from all the enrolled patients, possibly related to their inclusion and exclusion criteria (Gabor et al., 2003; Fanfulla et al., 2005; Alexopoulou et al., 2007; Beecroft et al., 2008; Cabello et al., 2008; Trompeo et al., 2011; Watson et al., 2013; Boesen et al., 2016; Boyko et al., 2017). In contrast, Roche Campo and colleagues (2010) were only able to use PSG data from 19 out the 27 mechanically ventilated enrolled subjects. Five studies comparing pressure-controlled ventilation to pressure support ventilation effects on sleep were not able to use the data from all the enrolled patients (Elliot et al., 2014; Andrejak et al., 2013; Roche Campo et al., 2010; Freedman et al., 2001; Cooper et al., 2000). Mechanically ventilated patients are some of the most studied related to critically ill sleep and may be why researchers have been able to learn methods to gather usable sleep data.

Discussion

With the omission of up to 60% of PSG data in the analysis, researchers may use inclusion and exclusion criteria to increase the probability that the PSG will be scorable. Sample exclusion criteria used by the studies able to utilize all the PSG data include: sedation in the previous 24 hours, opioids for 24 hours, neuroleptic medications, general anesthesia for 24 hours, neurologic diagnosis, epilepsy, delirium, Glasgow Coma Scale <10 or 11, hemodynamic instability, sepsis, Apache II scale >15, encephalopathy, drug overdose, anticipated death, psychiatric diagnosis, sleep apnea, and ventilator dyssynchrony with ineffective effort and apnea. The ICU sleep knowledge gained in these studies may not pertain to the most critically ill patients who may not have the physical resources to deal with the further stress of sleep deprivation.

Extensive exclusion criteria may not be the only available method to insure the ability to analyze the PSG data from all enrolled patients. Trompeo et al. (2011) conducted a study to

assess the characteristics of sleep disruption in a cohort of surgical critically ill patients who developed acute respiratory failure with the hypothesis that severe impairments of rapid eye movement sleep are associated with delirium. Before initiating PSG, the subjects needed to meet strict ventilator weaning readiness requirements. Additionally, the patients would be excluded or PSG not initiated for: sedation or analgesia within 24 hours, GCS <10, stroke, hemodynamic instability, general anesthesia in the past 72 hours, alcohol or drug withdrawal, psychosis, Alzheimer's, dementia, mental retardation, and Parkinson disease. Along with this extensive list of criteria, PSG was not performed if patients had an EEG in the previous 24 hours which determined to be "abnormal" with nonspecific slowing and/or residual drug effects (Trompeo et al., 2010). Information was not divulged regarding how many potential subjects were excluded related to an abnormal EEG. This study was able to use the PSG data from all 29 of its enrolled subjects. It is unknown whether all the PSG data was included in the analysis due to the comprehensive inclusion/exclusion criteria or the pre-screening EEG before PSG placement. However, having information regarding a potential subject's EEG may eliminate the need for extensive inclusion or exclusion criteria and allow subjects who may have been excluded to be studied; thereby possibly expanding ICU sleep information to a wider patient population. Converting Continuous EEG to PSG

Continuous electroencephalography monitoring (cEEG) could be implemented to pre-screen for the presence of normal brain waves and sleep architecture and then can easily be converted to PSG. This may limit unusable data due abnormal brain waves and limit expense by converting a ordered diagnostic procedure to PSG. Continuous EEG provides physiologic information regarding brain function, particularly in unresponsive patients (Oddo et al., 2009). Continuous EEG can be converted to PSG by adding components such as EOG and EMG electrodes. In the sleep laboratory setting, video-EEG PSG is used to diagnose nocturnal events

with complex behavior and movements as possible sleep or seizure in origin (Kryger, Roth, & Dement, 2005). Converting EEG to PSG is less expensive that implementing PSG in the ICU environment. Digital computer software to analyze EEG data would have to be expanded to be able to also analyze sleep architecture. Unfortunately, patients who have EEG order as part of their ordered care may have abnormal brain waves that obliterates normal sleep architecture. Drouot et al. (2011) and Cooper et al. (2000) found ICU patients without conventional sleep markers. Patients had atypical sleep with or without pathological wakefulness. Atypical sleep had no Stage 2 markers, minimal REM and slow background reactivity. Pathological wakefulness consisted of impaired reactivity on EEG to stimulus. As patients with ordered EEG are more likely to have some level of brain dysfunction, they have a greater risk of exhibiting atypical sleep. The implications on patient outcomes related to atypical brain wave patterns in patients who are not exhibiting sleep architecture is not clear. Further studies examining a possible relationship between no sleep architecture and patient outcomes such as hospital and ICU length of stay, mechanical ventilation days, morbidity, and mortality are needed. Additionally, using continuous EEG to determine if sleep architecture can be analyzed may allow researchers to study sleep in patient populations normally excluded from ICU sleep studies. Furthermore, the advance screening of brain waves for sleep architecture by c(EEG) can mitigate the expense of initiating PSG and obtaining unusable sleep data.

While using cEEG to screen critically ill subjects for sleep studies may insure complete PSG data, patients with cEEG ordered as part of their plan of care may have brain wave anomalies. Critically ill patients often suffer from an alteration of mental status. Continuous EEG can be used to evaluate those changes. Most abnormal EEG activity will have certain patterns: 1) epileptiform, 2) slow waves, 3) amplitude abnormalities and 4) deviations from normal (Weinhous, 2009; Buzea, 1995). Epileptiform activity is related to irritable areas of the cerebral

cortex that occurs with seizures-subclinical or otherwise (Sutter, Stevens & Kaplan, 2013; Oddo et al., 2009, Buzea, 1995). Brain damage related to acute or chronic lesions due to stroke, trauma, hemorrhages, tumor, and scar tissue from older injuries can all produce types of epileptiform discharges (Andraus, Andraus, & Alves-Leon, 2012). Generalized epileptiform activity found in both brain hemispheres are often related to metabolic disturbances or toxic agents, anoxic brain injury, and central nervous system infection (Andraus, Andraus, & Alves-Leon, 2012; Buzea, 1995). Slow waves have less than 8 Hz frequency and can be found in a focal area or generalized. Focal slow waves are associated with cerebral cortex damage related to tumors, infarcts, hemorrhages, abscesses or temporary events like transient ischemic attacks, migraines or partial seizures (Buzea, 1995). Generalized slow waves are normal during sleep, but abnormal during wakefulness. Wakeful slow waves can be seen with dementia, demyelinating disease, encephalitis and infections. Burst suppression is a brain wave pattern where high voltage burst activity alternates with flatline suppression activity (Ching et al., 2011; Wang & Agarwal, 2007). Burst suppression can be caused by toxic and metabolic disorders, sedation medications such as propofol and benzodiazepines, hypothermia and coma (Ching et al., 2011; Murphy et al., 2011; Weinhous, 2009; Buzea, 1995). The multiple possible brain wave disturbances that may interfere with PSG in critically ill patients accounts for the often extensive inclusion and exclusion criteria in ICU sleep studies.

Conclusions

Measuring sleep in the ICU environment is challenging. To obtain the most accurate and comprehensive sleep data, PSG is recommended. However, PSG is expensive and difficult to implement in critically ill patients. The loss of PSG data due to its inability to be analyzed can cause researchers to implement inclusion and exclusion criteria to try to guarantee usable EEG data, but excludes many typical ICU patients. Using EEG to pre-screen patients for sleep

architecture and converting continuous EEG to PSG may expand the ICU patient populations studied related to sleep architecture. By determining additional methods to accurately measure sleep, further knowledge regarding the impact of sleep disruption in the critically ill may be discovered.

Chapter 4:

Sleep Architecture and Outcomes in Critically Ill Patients: An Exploratory Study

**to be submitted to Heart & Lung*

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Synopsis

Background: Sleep is a complex process essential for the optimization of functioning. The absence of sleep in critically ill patients may potentially have negative consequences.

Objectives: Presence or absence of sleep architecture (SA) per continuous electroencephalogram (cEEG) monitoring and outcomes in critically ill patients were explored and factors associated with absence of SA were identified.

Methods: Retrospective chart reviews was determined the presence or absence of documented SA in patients who had cEEG as part of their care.

Results: Records (N=84) indicated that 61 patients had no SA over Days 1 to 2 of monitoring and 50 over Days 1 to 5 of monitoring. Propofol was associated with no SA during Days 1 to 2. Abnormal creatinine, adjusted for neurologic physiologic state, age and medications, showed an association with no SA Days 1 to 2 (OR 4.35, 95% C.I. 1.15-16.45, p=0.031). No SA Days 1 to 2 was associated with increased ICU length of stay (LOS), days of mechanical ventilation, hospital LOS and patient destination post-hospitalization.

Conclusions: This study supports sleep as an important part of critically ill patients' outcomes/recovery. More research is needed to guide practice and develop evidence-based sleep interventions.

Keywords: Sleep Architecture, electroencephalogram (EEG), outcomes, intensive care

Sleep Architecture of Patients in Intensive Care and Patient Outcomes

Introduction

Sleep is a complex process with physiologic, behavioral and brain wave components essential for the optimization of cognitive, mood and physiologic functions (Kamdar, Needham, & Collop, 2012; Hardin, 2009). Sleep in critically patients often does not follow typical processes or sleep phases, potentially leading to negative patient consequences. Sleep normally cycles between nonrapid eye movement (NREM) and rapid eye movement (REM) stages. NREM consists of three distinct phases: N1, N2, and N3 or slow wave sleep (SWS). Normal sleep architecture will cycle through NREM and REM stages over 90-100 minutes four to six times per night. However, patients in the intensive care unit (ICU) have been found to have significant variation from normal sleep architecture (Pisani et al., 2015).

Sleep deprivation can be characterized by decreased total sleep time (TST), difficulty falling asleep (sleep latency), staying asleep (sleep efficiency), multiple arousals, and multiple short sleep episodes (sleep fragmentation). Up to fifty percent of critically ill patients have reported sleep disturbances during their ICU stay (Bijwadia & Ejaz, 2009). While critically ill patients often have a normal TST, a large portion of that sleep occurs during day hours. Their sleep is exemplified by poor sleep efficiency with multiple arousals and fragmentation. Sleep fragmentation consists of brief spurts of sleep, resulting in primarily N1 sleep stage with minimal time in restorative SWS and REM sleep stages. Friese and colleagues (2007) found that mechanically ventilated surgical ICU patients had fragmented, abnormal sleep architecture. Their TST averaged 8.25 hours, but 96% of TST was in stages 1 and 2, 0.29% SWS, and 3.3% REM sleep. Healthy adults' normal sleep architecture consists of stages 1 and 2, 50% to 60% sleep time; SWS, 13% to 23%; and REM sleep, 20% to 25%.

Sleep as a physiological activity repairs and restores the body. Sleep disturbances have been found to increase the risk of hypertension (Fernandez-Mendoza et al., 2012; Vgontzas et al., 2009), impair insulin metabolism (Spiegel et al., 2005; Strand et al., 2015), weaken pulmonary mechanics (Chen & Tang, 1989; Series, Roy & Marc, 1994; Tadjalli & Peever, 2010), delay wound healing (Lange, Dimitrov & Born, 2018; Wright et al., 2015), decrease the immune response (Lange et al., 2003; Faraut et al., 2012) and adverse psychological and neurological processes (Anderson et al., 2018; Banks & Dinges, 2007; Trautmann et al., 2018; Tucker et al., 2010). Impaired sleep increases the sympathetic nervous system response, resulting in the increased release of epinephrine and norepinephrine and the suppression of insulin. These physiologic changes result in increased heart rate and blood pressure along with impaired glucose metabolism (Joo et al., 2012; Takase et al., 2004). The psychological and neurocognition complications can lead to anxiety, depression, irritability, and a decreased pain threshold.

As an additional stressor in patients already impacted by critical illness, disrupted sleep may be a potential impediment to successful recovery and outcomes. Sleep disturbances in critically ill patients may lead to increased morbidity and mortality. Overall, impaired sleep may result in negative patient outcomes such as prolonged mechanical ventilation, ICU time, and hospital days. These negative patient outcomes can lead to a change in patients' transfer locations post discharge that are different from their prehospitalization places of residency.

Determining whether sleep disturbances exist in critically ill individuals can be difficult in the ICU setting. Polysomnography (PSG), considered the gold standard of sleep measurement, integrates brain wave analysis, eye and muscle movements to determine the amount of sleep in various sleep stages. Normally, sleep progresses through the non-rapid eye movement stages into rapid eye movement sleep. The slow wave and rapid eye movement sleep stages are the most restorative. Polysomnography distinguishes between stage 1 and rapid eye movement sleep stages

by using eye movement and muscle movement electrodes. Stage 1 is light sleep moving from wakefulness to sleep and is not known for its restorative properties. Electroencephalography (EEG) or continuous EEG (cEEG) is able to distinguish stage 2 and stage 3 or slow wave sleep without the electrooculography (EOG) and electromyography (EMG) electrodes. These stages progress through to REM sleep. cEEG can determine if sleep has progressed past the initial sleep level towards more restorative sleep levels. While polysomnography is expensive and difficult to maintain in the ICU environment, cEEG monitoring is often implemented with critically ill patients. cEEG would not be able to determine the length of sleep time or the amount of time in stage 1 or REM sleep. However, cEEG monitoring can be used to determine if normal sleep architecture is present beyond stage 1.

More information on the relevance of sleep disturbances on critically ill patient outcomes is needed. The purpose of this study is to explore the potential relationship between the presence or absence of sleep architecture per cEEG monitoring and outcomes in critically ill patients. Additionally, factors that may be related to the presence or absence of sleep in critically ill patients per cEEG monitoring are explored.

Methods

This secondary data analysis used data from a retrospective chart review of patients who had cEEG ordered as part of their plan of care between April 2015 and January 2016. The original study explored the effect of white noise on the sleep of critically ill patients. The findings of cEEG were used to pre-screen patients for any sleep architecture and if sleep architecture was observed, then patients were recruited for the white noise study. The cEEG findings unexpectedly showed that very few patients had sleep architecture. The study was consequently revised to a retrospective chart review to gather data about sleep architecture and possible factors that may be related to the presence or absence of sleep in critically ill patients. Chart reviews of 84 patients

who had received care in a single neurologic/medical/surgical intensive care unit in the Midwest were included in analyses. Data were collected each day that the patient had cEEG while in the ICU. Patients were excluded if a phenobarbital infusion was ordered because of its effects on cEEG (Dubey, Kalita, & Misra, 2017).

Design

A retrospective and longitudinal exploratory study design was used to address the study aims of this secondary data analysis.

Measures

Based on a review of the literature, potential predictor variables (factors potentially related to the presence or absence of sleep architecture) were recorded from the electronic health record. Baseline demographic data included gender, age, race, and ethnicity.

Sleep Architecture. Data documenting the presence or absence of sleep architecture were obtained from the electronic health record notes of the epilepsy physician group who ordered the cEEG. The cEEG used a 10-12 electrode system. Continuous EEG is able to capture/recognize sleep stages 2 with the characteristic sleep spindles and k complexes and stage 3 slow wave sleep. Stage 1 and REM sleep cannot be definitively differentiated from each other using cEEG without electrodes to measure eye and muscle movement. A patient was determined to have the presence of sleep architecture if any sleep stage was identified at any time during cEEG monitoring. In this exploratory study, sleep data were grouped into categories of data for 1-2 days (Days 1 to 2) and data from days 1 to 5 days (Days 1 to 5). These data groupings were not mutually exclusive. The category of sleep data from Days 1 to 5 included data from patients with sleep data from Days 1 to 2 and, additionally, days 3, 4 and 5. This category explores the effect the presence or absence of sleep architecture over a longer period of time while keeping the power of a small study size.

A day of sleep data corresponds to a single day, although the day may not comprise the data for the full 24 hours.

Primary Diagnosis Category. The primary patient diagnosis was categorized into one of the following groups: Neurologic, Respiratory, Medical, Cardiac, Infections and Substance Abuse.

Severity of Illness. The severity of illness was measured by the Acute Physiology, Age, Chronic Health Evaluation (APACHE) III score (Knaus et al., 1991). The PI calculated the APACHE III score (range 0-71) at the time of the chart review using the values from within the first 24 hours of the ICU admission. The greater the APACHE III score, the more severe the illness is considered. Some subjects did not have the elements needed to calculate the APACHE II score, thus the score was not included in logistic regression models.

Physiologic State. Patient subjects were identified as belonging to a physiologic state category if they had a primary or secondary diagnosis or comorbidity written in their medical record related to the category. Patients could have more than one physiologic state. The categories included: Neurology, nephrology, hepatic, infection, sepsis, anoxia, alcohol abuse, drug abuse, dementia, cancer, encephalopathy, developmental disability, and seizure.

Lab Values. Serum lab value results were obtained while patients were being monitored by cEEG and recorded as "normal" or "abnormal;" including both high *or* low values. Due to the limited number of subjects, lab values were considered as a potential predictor variable for sleep architecture only if all subjects had the same lab ordered and results obtained. These labs included serum levels of sodium, potassium, and creatinine.

Medications. Opioid and benzodiazepines medications were converted to Morphine and Ativan equivalents using online calculators (Equivalent Opioid Calculator, 2017; Equivalent Benzodiazepine Calculator, 2017) and recorded daily on the days patients had cEEG measured.

Median values of Propofol along with Morphine and Ativan equivalents were calculated with the 25^{th}-75^{th} interquartile. Propofol, Morphine equivalents and Ativan equivalents were placed into dosage groups. Morphine equivalent was grouped as none, <40mg, and ≥40 mg. Ativan equivalent was grouped as none, < 2mg, and ≥2 mg. Propofol was placed into dosage groups of none, <2500 mcg, and ≥2500mcg. The dosage groupings of these medications were used in statistical models. Due to the small number of patients administered Dexmedetomidine, the medication was measured as none or used.

Outcomes. Mechanical ventilation days were measured from day of intubation to day of extubation, or death. Hospital length of stay was calculated as the time from admission to the hospital to discharge or death. ICU length of stay was calculated as the number of days from ICU admission to ICU discharge or death. Discharge destination from the hospital (e.g., home, nursing home, transitional care) was also recorded.

Ethical Considerations

The parent study protocol and secondary analyses were approved by the institutional review board (IRB) of the large Midwestern tertiary care center, and the university with which the principal investigator was affiliated.

Statistical Analysis

Data analyses were conducted with SAS version 9.4 (SAS Institute, 2018). All data were analyzed descriptively using univariate statistics (e.g., medians, means), and bi-variate statistics such as Fisher Exact tests or independent t-tests; Mann Whitney U tests or Chi^2 tests. Tests were considered statistically significant at $p \leq 0.05$. There were no corrections made for multiple statistical tests. Multiple regression models were developed using influential factors from bi-variate analyses ($p \leq 0.2$) or chosen because of clinical relevance. Candidate factors for logistic regression models were selected if they were associated with the outcome using $p \leq 0.2$ in bi-

variate analyses, and if there was at minimum one subject in both the sleep architecture and no sleep architecture categories.

Results

Demographic and Medical Characteristics

Overall characteristics. The average age of the 84 subjects was 53.8 years; 50% were male. The most prevalent race was Caucasian (85%). Other races represented included Black (10%), Asian (4%), and American Indian/Alaskan Native (2%). By far, the most common primary diagnosis was neurologic in nature (68%). A neurologic physiologic state was the most prevalent with 62% of the subjects having this secondary diagnosis or comorbidity. The next two common physiologic states were infection (35%) and encephalopathy (33%). (See Table 4.1).

Table 4.1

Demographic and Medical Characteristics Overall and by Presence or Absence of Sleep Architecture Grouped Days 1 to 2

Variable	*Overall*	*SA on Day 1 to 2*	*No SA on Day 1 to 2*	*P value*	*SA on Day 1 to 5*	*No S 1 to*
N	*84*	*23*	*61*		*34*	*50*
Age in years, mean (SD)	53.8 (19.1)	47.4 (19.3)	56.2 (18.6)	0.060	50.0 (19.5)	56.3
Male sex, n(%)	42 (50)	11 (48)	31 (51)	0.807	17 (50)	25 (
Apache III, mean (SD)*	62.0 (26.5)	44.1 (23.6)	68.8 (24.5)	**<.001**	51.5 (28.5)	689
Race				0.554		
Caucasian, n(%)	71 (85)	18 (78)	53 (87)		28 (82)	43(8
Asian, n(%)	3 (4)	1 (4)	2 (3)		1 (3)	2 (4
Black, n(%)	8 (10)	3 (13)	5 (8)		4 (12)	4 (8
American Indian/Alaskan Native, n(%)	2 (2)	1 (4)	1 (2)		1 (3)	1 (2
Primary Diagnosis Category				0.770		
Neurologic n(%)	57 (68)	17 (74)	40 (66)		24 (71)	33 (
Respiratory n(%)	3 (4)	1 (4)	2 (3)		1 (3)	2 (4
Medical n(%)	8 (10)	1 (4)	7 (11)		4 (12)	4 (8
Cardiac n(%)	4 (5)	1 (4)	3 (5)		1 (3)	3 (6
Infections n(%)	4 (5)	0 (0)	4 (7)		0 (0)	4 (8
Substance Abuse n(%)	8 (10)	3 (13)	5 (8)		4 (12)	4 (8
Physiologic State						
Neurology n(%)	52 (62)	9 (39)	43 (70)	**0.008**	16 (47)	36 (
Nephrology n(%)	14 (17)	4 (17)	10(16)	0.999	5 (15)	9 (1
Hepatic n(%)	6 (7)	2 (9)	4 (7)	0.663	3 (9)	3 (6
Infection n(%)	29 (35)	6 (26)	23 (38)	0.318	8 (24)	21 (

Variable	*Overall*	*SA on Day 1 to 2*	*No SA on Day 1 to 2*	*P value*	*SA on Day 1 to 5*	*No S 1 to*
N	*84*	*23*	*61*		*34*	*50*
Sepsis n(%)	11 (13)	1 (4)	10 (16)	0.275	2 (6)	9 (1
Anoxia n(%)	7 (8)	0 (0)	7 (11)	0.182	0 (0)	7 (1
Alcohol Abuse n(%)	11 (13)	4 (17)	7 (11)	0.483	4 (12)	7 (1
Drug Abuse n(%)	4 (5)	1 (4)	3 (5)	0.999	2 (6)	2 (4
Dementia n(%)	5 (6)	0 (0)	5 (8)	0.316	1 (3)	4 (8
Cancer n(%)	12 (14)	2 (9)	10 (16)	0.497	4 (12)	8 (1
Encephalopathy n(%)	28 (33)	5 (22)	23 (38)	0.166	7 (21)	21 (
Development Disability n(%)	8 (10)	0 (0)	8 (13)	0.100	1 (3)	7 (1
Seizure n(%)	2 (2)	1 (4)	1(2)	0.475	1 (3)	1 (2
Lab Values						
WBC n(%)	62(74)	15 (65)	47 (77)	0.271	24 (71)	38 (
Abnormal Creatinine n(%)	39 (46)	5 (22)	34 (56)	**0.007**	12 (35)	27 (
Potassium n(%)	30(36)	7 (30)	23 (38)	0.535	11 (32)	19 (
Sodium n(%)	21 (25)	4 (17)	17 (28)	0.323	6 (18)	15 (

SA=Sleep Architecture; SD=Standard Deviation; WBC=White Cell Blood Count.

*N for APACHE III was different: Only 76 or 84 had score

Characteristics of patients with sleep architecture Days 1 and 2. Patients were grouped into exhibiting the presence or absence of sleep architecture over Days 1 to 2 of cEEG monitoring. Sleep architecture was present for 23 patients (27%) over Days 1 to 2 of cEEG monitoring. Sleep architecture was not detected for 61 patients (73%) during the same time period. During Days 1 to 2, there were few differences in characteristics between patients with and without sleep architecture. Neurology was the only physiological state that was statistically significant ($p=0.008$). An abnormal serum creatinine was the only lab value associated with no sleep ($p=0.007$). (See Table 4.1).

Characteristics of patients with sleep architecture Days 1 to 5. Patients were also grouped by the presence or absence of sleep architecture in the group Days 1 to 5 of cEEG monitoring, including patients who had sleep data in the time frame of 1 to 5 days. Sleep architecture was present for 34 patients. Using this grouping criterion, 34 patients (40%) has sleep architecture compared to 50 (60%) with no sleep architecture. There were few differences in characteristics between groups. The APACHE III score was significantly higher in the no sleep architecture group ($p<0.004$). Neurology ($p=0.021$), anoxia (0.038), and encephalopathy ($p=0.041$) were the only physiological states that were observed more often in the group without sleep architecture. (Table 4.1).

Medication Dosing

As shown in Table 4.2, propofol was the only medication in which the dosage group was statistically significant ($p=0.025$) for the group Days 1-2. Of the patients who had sleep architecture, the majority (61%) had no propofol administered. For patients who had no sleep architecture, 24 (39%) received dosage of <2500 mcg and 18 (30%) received ≥2500 mcg. In Days 1 to 5, there were no significant differences in medication administration between groups with or without sleep architecture.

Table 4.2

Medication Dosing Overall and by Presence or Absence of Sleep Architecture Grouped Days 1 to 2 and Days 1 to 5

Variable	Overall n(%) N=84	SA Days 1 to 2 n(%) N=23 (27)	No SA Days 1 to 2 n(%) N=61 (73)	P value	Overall n(%) N=84	SA Days 1 to 5 n(%) N=34 (40)	No Da N=
Morphine Equivalents				0.95			
Dose None	24(29)	7(30)	17(28)		21(25)	7(21)	14
Dose <40mg	25(30)	7(30)	18(30)		29(35)	14(41)	15
Dose ≥40mg	35(42)	9(39)	26(43)		34(40)	13(38)	21
Benzodiazepine Equivalents				0.84			
Dose None	41(49)	11(48)	30(49)		33(39)	12(35)	21
Dose <2mg	22(26)	7(30)	15(25)		30(36)	14(41)	16
Dose ≥2mg	21(25)	5(22)	16(26)		21(25)	8(24)	13
Propofol				**0.025**			
Dose None	33(39)	14(61)	19(31)		32(38)	15(44)	17
Dose <2500mcg	27(32)	3(13)	24(39)		34(40)	12(35)	22
Dose ≥2500mcg	24(29)	6(26)	18(30)		18(21)	7(21)	11
Dexmedetomidine				0.65			
None or any (%)	25(30)	6(26)	19(31)			12(35)	18

Predicting Sleep Architecture Days 1 to 2

All baseline characteristics other than APACHE III were considered and included in models if they were significant at $p \leq 0.2$ in the bi-variate analysis. While no primary diagnosis was found to be relevant, having a neurologic physiologic state ($p<0.008$) was significantly associated with no sleep. Since medications such as opioids, benzodiazepines, propofol, and dexmedetomidine have known associations with changes in sleep architecture (Weinhouse & Watson, 2003; Kondili et al., 2012; Romagnoli et al., 2018), these variables along with age were used to adjust predictors to determine their association with sleep architecture. Abnormal serum creatinine ($p=0.02$) was significantly associated and neurologic physiologic state trended toward significance ($p=0.051$) with no sleep architecture. (Table 4.3)

Table 4.3

Single Predictor Logistic Regression Models Predicting Absence of Sleep Architecture Days 1 to 2 with Continuous Electroencephalogram Monitoring Adjusted by Age & Medications

Variable	Odds Ratio Estimates	95% Confidence intervals	P Value
Neurology Physiologic State	3.17	0.99-10.08	0.051
Encephalopathy Physiologic State	2.06	0.66-7.28	0.265
Abnormal Serum Creatinine	4.62	1.28-16.69	**0.020**

In multivariate regression, significant variables associated with presence or absence of sleep architecture in previous analyses (Table 4.1) were included as candidates in model testing and development. The final multivariate regression model (entering age, medications, abnormal serum creatinine and neurologic physiologic state) found that abnormal serum creatinine was 4.35 times more likely to be associated with no sleep architecture (CL 1.15-16.45, $p=0.031$) (Table 4.4).

Table 4.4

Multivariate Regression Models Predicting Absence of Sleep Architecture Days 1 to 2 with Continuous Electroencephalogram Monitoring Adjusted by Age & Medications

Variable	Odds Ratio Estimates	95% Confidence Intervals	P Value
Neurology Physiologic State	2.92	0.86-9.87	0.086
Abnormal Serum Creatinine	4.35	1.15-16.45	**0.031**

Both developmental disability (p=0.047) and encephalopathy physiologic state (p=0.05) were associated with no sleep architecture adjusting for age and medications (Table 4.5).

Single Predictor Logistic Regression Models Predicting Absence of Sleep Architecture for Days 1 to 5 with Continuous Electroencephalogram Monitoring Adjusted by Age & Medications

Variable	Odds Ratio Estimates	95% Confidence Intervals	P Value
Neurology Physiologic State	2.60	0.93-7.54	0.071
Infection Physiologic State	2.37	0.85-7.12	0.109
Sepsis Physiologic State	3.62	0.79-26.34	0.132
Encephalopathy Physiologic State	3.14	1.04-10.53	**0.050**
Development Disability Physiologic State	10.63	1.40-227.33	**0.047**
Abnormal Serum Creatinine	2.28	0.82-6.69	0.121

Multivariate regression model including developmental disability and encephalopathy physiologic states, adjusted for age and medications, found that development disability was 18.52 times more likely to be associated with no sleep architecture (CL 1.63-210.04, p=0.019). Encephalopathy was 4.53 times more likely to be associated with no sleep architecture (CL 1.33-15.43, p=0.016) (Table 4.6).

Table 4.6

Multivariate Regression Model Predicting Outcome Absence of Sleep Architecture with Days 1 to 5 of Continuous Electroencephalogram Monitoring Adjusted by Age & Medications

Variable	Odds Ratio Estimates	95% Confidence Intervals	P Value
Development Disability Physiologic State	18.52	1.63-210.04	**0.019**
Encephalopathy Physiologic State	4.53	1.33-15.43	**0.016**

The outcome variables hospital length of stay, ICU length of stay and mechanical ventilation days were all significant in Days 1 to 2 of sleep architecture data. The hospital length of stay overall ranged 2-68 days with a median of 11 days. The median hospital length of stay for subjects with sleep architecture was 7 days ranging from 2 to 27 days. In contrast, the median hospital length of stay for patients with no sleep architecture was 14 days ranging 2 to 68 days (Table 4.7). The overall ICU length of stay ranged 2 to 44 days with a median of 4. For subjects with sleep architecture, the median ICU length of stay was 3 days ranging from 2-16 days. The median ICU length of stay for subjects with no sleep architecture was 8 days ranging from 2-44 days. Mechanical ventilation days for subjects exhibiting sleep architecture Days 1 to 2 ranged from 1-11 days with a median of 2 days. For subjects with no sleep architecture, the median mechanical ventilation days was 6, ranging from 2-32 days (Table 4.7).

Table 4.7

ICU and Hospital Days, Mechanical Ventilation Days and Presence or Absence of Sleep Architecture Overall and by Groups: Days 1 to 2 and Days 1 to 5

Variable	Overall Median (range) N=84	SA Days 1 to 2 Median (range) N=23	No SA Days 1 to 2 Median (range) N=61	P Value	SA Days 1 to 5 Median (range N=34	No SA Days 1 to 5 Median (range) N=50	P Value
ICU days	6.5 (2-44)	3 (2-16)	8 (2-44)	**<.001**	4 (2-44)	8 (2-32)	**0.001**
Hospital days	11 (2-68)	7 (2-27)	14 (2-68)	**<.001**	8.5 (2-68)	15 (2-64)	**0.002**
	N=72	N=16	N=56		N=27	N=45	
Mechanical ventilation days	5 (1-32)	2 (1-11)	6 (2-32)	**0.003**	3 (1-29)	6 (2-32)	**0.006**

SA=Sleep Architecture; ICU=Intensive Care Unit; LOS=Length of Stay. Mann-Whitney U tests

When considering presence or absence of sleep architecture Days 1 to 5 with cEEG monitoring, hospital length of stay, ICU days and Mechanical ventilation days were all significant. For patients in the group having sleep architecture, the median length of stay was 8.5 days ranging 2-68 days. The patients in the group with no sleep architecture had a median 15 days hospital length of stay (range: 2-64 days).

The presence or absence of sleep architecture was associated with outcomes of post hospital discharge placements or death. In looking at sleep up to two days monitoring, the association between sleep architecture and hospital outcome/discharge placement was significant (p=0.006). (Table 4.8).

Table 4.8

Hospital Outcome or Placement of Patients in Groups with and without Sleep Architecture (Days 1 to 2 and Days 1 to 5)

Variables	Overall n(%) N=84	SA Days 1 to 2 n(%) N=23(27)	No SA Days 1 to 2 n(%) N=61(73)	P value	SA Days 1 to 5 n(%) N=34(40)	No SA Days 1 to 5 n(%) N=50(60)	P value
ICU Outcome				0.420			0.330
Death	8 (10)	1 (4)	7 (11)		1(3)	7(14)	
Home	6 (7)	17 (13)	3 (5)		3(9)	3(6)	
LTACH	9 (11)	1 (4)	8 (13)		4(12)	5(10)	
Rehab	1 (1)	0 (0)	1 (2)		1(3)	0(0)	
Hospital	60 (71)	18 (78)	42 (69)		25(74)	35(70)	
Unit							
Hospital				**0.006**			**0.003**
Outcome	10 (12)	1 (4)	9 (15)		1(3)	9(18)	
Death	31 (37)	17 (74)	14 (23)		21(62)	10(20)	
Home	12 (14)	1 (4)	11 (18)		3(9)	9(18)	
Nursing	11 (13)	2 (9)	9 (15)		5(15)	6(12)	
Home	12 (14)	2 (9)	10 (16)		4(12)	8(16)	
LTACH	4 (5)	0 (0)	4 (7)		0(0)	4(8)	
Rehab	1 (1)	0 (0)	1 (2)		0(0)	1(2)	
Inpatient	3 (4)	0 (0)	3 (5)		0(0)	3(6)	
Psych							
Group							
Home							
Hospice							

SA=Sleep Architecture; LTACH=Long term acute care hospital; Psych=Psychiatric unit

Across groups overall, ten subjects died. However, death was not associated with the presence or absence of sleep architecture. Thirty-one subjects were discharged home from the hospital. Because the Hospital Outcome/Placement variable was significant, analysis was done to determine whether there were differences in presence or absence of sleep architecture and discharge home. Significantly, seventeen subjects with sleep architecture in the Days 1 to 2 group were discharged to home ($p<0.001$; test not in table). ICU outcome or discharge location was not found to be associated with sleep architecture. Adjusting for age and medications, the presence of

sleep architecture was 8.76 times more likely to result in a discharge to home (CL 2.35-38.89, p=0.002) (Table 4.9).

Table 4.9

Multivariate Regression Model Predicting Discharge Home Adjusted by Age & Medications

Variable	*Odds ratio*	*95% Confidence Intervals*	P value
Creatinine	0.43	0.10-1.66	0.229
Sleep Architecture Day 1 to 2	8.76	2.35-38.89	**0.002**

In patient group Day 1 to 5, ICU discharge outcome was also not significant. In this group, hospital discharge location was found to be associated with the presence or absence of sleep. Nine out of ten subjects who died out of this group did not have sleep architecture. Disposition to home from the hospital adjusting for age, medications, developmental disability and encephalopathy physiologic states was 15.92 (CL 3.94-86.13, p<0.001) times more likely to be associated with the presence of sleep architecture during days 1-5 of cEEG monitoring (Table 4.10). It is noted that persons with developmental disability may not have resided at home pre-hospitalization, thus contributing to the non-significance of p value (p=0.78).

Table 4.10

Multivariate Regression Model Predicting Discharge Home Adjusted by Age & Medications

Variable	*Odds ratio*	*95% Confidence Intervals*	P value
Developmental Disability	1.42	0.11-17.03	0.78
Encephalopathy	13.85	2.46-109.55	**0.003**
Sleep Architecture Days 1 to 5	15.92	3.94-86.13	**<0.001**

Discussion

This study uniquely examined the presence or absences of sleep architecture and associated short term outcomes. A study showed that at three months post discharge, poor functional outcomes in subarachnoid hemorrhage patients was associated with no sleep architecture over 24 hours per cEEG controlling for age, grade SAH and extent of hemorrhage on CT scan (Claassen et al., 2006). In status epilepticus patients, the only cEEG feature significantly associated with complete functional recovery at discharge was stage 2 sleep architecture (Alvarez et al., 2015). In contrast, this study found more immediate impact on patient outcomes were associated with no sleep architecture during days 1-2 of cEEG monitoring. No sleep architecture in the ICU in patients grouped Days 1 to 2 of cEEG was associated with patient outcomes such as longer mechanical ventilation days, ICU length of stay, and hospital length of stay.

Age. While this study found that age was not significantly associated with the presence or absence of sleep architecture, aging has a known impact on sleep. Growing older results in decreased total sleep time, sleep efficiency and sleep latency. Even in healthy individuals, sleep architecture changes with age showing increased percentage of time in sleep stages 1 and 2 and decreased time in slow wave and REM sleep (Espiritu, 2007; Moraes et al., 2014). Adding a critical illness and the ICU environment, theoretically results in even further sleep disturbances such as no normal sleep architecture.

Disease Severity. Knowledge related to severity of disease and sleep is limited. Severity of disease scores have been associated with mortality in various disease states such as sepsis, kidney disease and pancreatitis (Kamdar, Needhan & Collop, 2012; Talib et al., 2017; Sundararajan et al., 2017). However, in these studies, patients' sleep states were not measured. The findings of this study showed an association with severity of disease measured by APACHE III scores with the absence of sleep in during both the cEEG monitoring over 1-2 or 1-5 days.

Critical illness is thought to be a factor in the difference in sleep architecture to the point that a new classification of sleep analysis for these patients is being explored (Drouot et al., 2011; Watson et al., 2013). It may be that critical illness in itself does not impact sleep but the severity of the critical illness contributes to the presence or absence of sleep architecture.

Sedation and Sleep. Sedation and sleep share similar characteristics such as a decreased response to external stimuli, decreased muscle tone and respiratory depression. Sedation medication affect the same neuro pathways used in the transition from wakefulness to sleep. However, sleep is subjected to circadian rhythms and progresses through stages, while sedation does not. The impact of sedation is drug and dose dependent (Weinhouse & Watson, 2009). Sedation may have both positive and negative impact on sleep. Benzodiazepines have been found to increase sleep duration and the light sleep stages 1 and 2 (Engelmann et al., 2014). Stage 2 sleep has increased sleep spindles and there is a considerable suppression of slow wave sleep (Weinhouse & Watson, 2009). Opioids are analgesics but can have a sedative effect. Opioids increase stage 2 and REM sleep while decreasing SWS (Weinhouse & Watson, 2009). Pain can cause sleep disturbances and sleep disturbances can increase the perception of pain (Fu et al., 2018). Therefore, opioids can also have a positive impact on sleep. Propofol suppresses SWS and seems to have no appreciable effect on REM sleep. Propofol seems to enhance sleep and patients have stated they felt rested after low dose propofol. High dose propofol and benzodiazepines can result in burst suppression per EEG leading to no sleep architecture being observed (Kondili et al, 2012; Weinhouse & Watson, 2009). Dexmedetomidine can increase stage 2 and decrease the percentage of REM sleep (Rigmagnoli et al., 2018). In this study during 1-2 days cEEG monitoring (Days 1 to 2), only propofol was found to have a significant association with the presence or absence of sleep architecture. Sedating medications may have a positive impact on sleep by increasing sleep time. However, negative consequences on sleep may also occur leading

to less time in the restorative sleep stages. These negative consequences appear to be dose dependent. This study attempted to address different dosages of all medication except Dexmedetomidine, but what constitutes a lower dose that is less likely to negatively impact sleep architecture has not been explored. The study data also does not provide the opportunity for investigators to distinguish between continuous and intermittent administration. The consequences related to sedation medications' method of administration on sleep is unknown.

Abnormal Creatinine. Abnormal serum creatinine levels were found to be significantly related to no sleep architecture Days 1 to 2 group but not in Days 1 to 5 group. Even though serum creatinine levels were significant, nephrology physiologic state was not. Creatinine levels are related to muscle metabolism. An abnormal creatinine level may be lower or higher than the standard norms. Low creatinine levels may be related to spinal cord injuries, cachexia, neuromuscular blocking agents or a sudden decrease in activity as can occur with a critical illness. High creatinine levels can occur with preeclampsia, dehydration, renal issues, rhabdomyolysis, blocked urinary tract, myasthenia gravis, hyperthyroidism and muscular dystrophy (Renal Function Tests, n.d.). No evidence is available that any of these conditions in themselves have a direct impact on sleep architecture.

Physiologic state neurology. While a primary neurologic diagnosis was not significantly associated with the presence or absence of sleep architecture, a neurologic physiologic state was per bivariate analysis. Continuous EEG monitoring is usually implemented in the presence of seizures or to rule out non-clinical seizure activity evidenced by an unexplained change in level of consciousness. Non-clinical seizure activity is associated with neurosurgical procedures, metabolic derangements, acute neurologic injury, drug related neurotoxicity and transplant patients (Friedman, Claassen, Hirsch, 2009). Thus, sleep disturbances resulting in no sleep architecture related to neurology diagnoses or comorbidities would expect to be present. In fact,

many studies utilizing polysomnography in critically ill patients excluded patients with neurologic diagnoses. However, after adjusting for age, medications and abnormal creatinine where appropriate, a neurology physiologic state was no longer associated with no sleep architecture. Other studies have found that severe neurologic diagnoses do not preclude sleep architecture. Sandsmark and colleagues (2016) showed that 19 of 64 severe traumatic brain injury patients had sleep architecture in the acute phase per cEEG. Neurologic patients are still capable of exhibiting sleep architecture even in the presence of severe disease and exploring the impact of the presence or absence of sleep architecture in these patients is a research opportunity.

Physiological state encephalopathy. Encephalopathy is a medical term for any condition resulting in altered brain function or structure leading to a maladjusted mental state (National Institute of Neurological Disorders and Stroke, 2018). Encephalopathy may be caused by infection, metabolic or mitochondrial dysfunction, brain tumor, increase intracranial pressure, toxins, progressive trauma, poor nutrition, hypoxia, or poor cerebral blood flow (National Institute of Neurological Disorders and Stroke, 2018). This study found encephalopathy was associated with no sleep architecture after accounting for age, medications and developmental disability during the cEEG period of patients in group Days 1 to 5. Other research found patients with hepatic encephalopathy to have disturbed sleep architecture with decreased REM but in these non-critically ill patients sleep architecture was still present. Further information related to encephalopathy and the state of sleep architecture is needed. Encephalopathy is a broad term and it is currently unknown whether certain triggers of the disease are more likely to impact sleep.

Physiologic state developmental disability. Eight subjects had a developmental disability. In the Days 1 to 2 group, no developmentally disabled patients had sleep architecture, so a statistical model could not be developed. Looking at the presence or absence of sleep architecture in the group having monitoring Days 1-5, developmental disability was found to have

a likelihood of no sleep architecture. However, the model had an extremely large confidence interval [CI 1.4-227.3] indicating that more research is needed in this area. In fact, no studies were found exploring sleep in patients with developmental disabilities in the hospital setting let alone in the ICU environment. However, experts indicate that the ICU environment is particularly difficult, unfamiliar and stressful for these subjects (Hsieh et al., 2012; Iacomo et al., 2014). Standards of care for the developmentally disabled indicate that routines, lighting, noise levels and the number of people coming into the room should be controlled to ease the stress for these patients-a sometimes difficult prospect in the ICU (Ailey, Ulmali, & Uyen, 2012). More research is needed to determine if the critical illness, the ICU setting, or both are mainly responsible for the likelihood of no sleep in this patient population.

Length of Stay Outcome. The presence of sleep architecture and patient outcomes has been studied mainly in the neurological primary diagnosis population. Patients suffering from severe traumatic brain injury with sleep architecture per cEEG had significantly shorter ICU stays and showed a trend towards significantly shorter hospital stays (Sandsmark et al., 2016). In the current study, when an absence of sleep architecture was noted in the group Days 1 to 2 of cEEG monitoring, there was significant association with an increase in ICU and hospital length of stay. Furthermore, increased mechanical ventilation days were also significantly associated with the absence of sleep architecture. Longer mechanical ventilation days intuitively would be related to longer ICU stays. The absence of sleep architecture in patients with monitoring Days 1 to 5 was associated with a longer hospital length of stay but not a longer ICU stay or mechanical ventilation days. Lack of sleep architecture Days 1 to 2 was associated with increased length of stays. However due to the number of patients who obtained sleep architecture during days 3-5 (who were added in the Days 1 to 5 group), an association between mechanical ventilation days and ICU length of stay no longer significant. Implementing interventions to improve sleep as

soon as possible in critically ill patients may potentially decrease mechanical ventilation days, ICU length of stays and hospital days.

Posthospitalization transfer location. An association between the presence of sleep architecture and posthospital transfer location has been found in various studies. Purandare and colleagues (2018) discovered that the presence of stage 2 sleep in critically ill intracranial hemorrhage patients was not associated with death. In severe traumatic brain injury patients, the presence of sleep architecture was associated with the disposition from the hospital to home or acute rehabilitation. The current study found a significant association between the presence or absence of sleep architecture Days 1 to 2 and Days 1 to 5 in persons with cEEG monitoring and hospital disposition such as death, home, nursing home, long term acute care hospital, inpatient psychiatric unit, group home, or hospice. For both monitoring periods, the presence of sleep architecture was associated with the patient being discharged home from the hospital. Assessing for the presence of sleep architecture may give clinicians, families and patients helpful prognostic information.

Conclusion

This study found a number of factors that were associated with the presence or absence of sleep architecture as measured by cEEG monitoring in critically patients. No matter the length of cEEG monitoring, the greater the severity of disease and a neurologic physiologic state was found to be associated with no sleep architecture. In this study, no particular type of primary diagnosis documented in the medical record significantly impacted sleep architecture. However, certain secondary diagnoses or comorbidities did have an association with the state of sleep architecture. However, while an anoxic, encephalopathy and developmental disability physiologic states were associated with no sleep architecture, the actual number of subjects with these conditions was small. In the group having monitoring Days 1 to 2 but not the group having monitoring Days 1 to

5, propofol and creatinine were significant, while there was a trend of an association with increased age and no sleep architecture. Some of the differences could be related to the reasons cEEG monitoring is ordered leading to a decrease use of sedation medications like propofol. Often, sedation is started at admission to the ICU related to various procedures including intubation, but will be weaned to minimal levels to assess level of consciousness and neurologic status. Additional research is needed to explore further associations between patient characteristics and sleep.

Using cEEG monitoring is commonplace in the ICU making it easier to implement compared to polysomnography. Assessing for sleep using cEEG in patients beyond those who have it ordered as part of their plan of care could expand ICU sleep knowledge.

While some research has been conducted to determine the presence of sleep architecture in critically ill patients with neurological disorders and the patients' outcomes, the number of studies is sparse. The finding that no sleep architecture is associated with length of stay in the ICU and hospital, mechanical ventilation days and hospital disposition needs further exploration. This association between sleep and patient outcomes elevates the importance of developing evidenced based sleep interventions and their implementation as early as possible in a patient's admission to the ICU.

Limitations. This study had a number of limitations. This is a retrospective study dependent on chart review data. The cEEG monitoring was ordered as part of the plan of care which may have resulted in the patient population being at the more severe end of the clinical spectrum. The cEEG monitoring was initiated at different points within the ICU stay, but information on when cEEG was initiated per subject was not available. There are other medications than the ones reviewed within this study that may impact sleep architecture such as beta blockers. Sleep is complex and the multiple predictors that may influence sleep were not

explored in this study. For example, the ICU environment with its level of noise and light along with frequent interruptions related to increased monitoring and interventions may impact the ability to sleep. The small sample size limited the number of variables that were able to be studied. Severity of disease was found to be significantly associated with the absence of sleep, but a limited number of subjects were able to have the APACHE III score calculated from the retrospective chart review data. While the knowledge related to patient outcomes of mechanical ventilation days, ICU length of stay, hospital length of stay and disposition is worthwhile, outcomes post discharge would be valuable. It is noted that there were only a few patients with developmental disability, these patients may not have resided at home pre-hospitalization, therefore it may not be and change to not go home after hospital discharge. However, this is unknown. Follow-up of this group in future studies may be warranted.

This study highlights that sleep may be an important part of critically ill patients' recovery and that more research is needed to guide practice and develop evidence-based sleep interventions.

Chapter 5:

Synthesis

This chapter presents the major findings from each manuscript in this dissertation. First, a synthesis of the state of knowledge based on the findings from this dissertation's Chapters 2 and 3 will be given. Second, an overview of the findings from Chapter 4 is provided along with the study's limitations. Finally, implications for future research are discussed.

Chapter 2

Delirium. Delirium is an acute confusional state associated with impaired consciousness (Fleminger, 2002). Delirium is exemplified by the new onset of cerebral dysfunction, change in baseline cognition, inattention, disorganized thinking and/or an altered level of consciousness (Barr & Pandharipanda, 2013; Sendelbach & Guthrie, 2009). Critically ill patients have a high risk for delirium with incidences ranging from 11%-80% (McNicoll, 2003; Van Rompaey et al., 2009).

Delirium Outcomes. ICU delirium is associated with negative short-term and long-term outcomes. Patients with delirium are more apt to face acute respiratory distress syndrome (ARDS), nosocomial pneumonia, cardiopulmonary edema, self-extubation, re-intubation, cardiac arrhythmias, and to be discharged to a skilled nursing facility (Inouye, 2006; Ouimet et al., 2007; Yoo, Nakagawa, & Kim, 2013). Mechanical ventilation days and length of stay in the ICU and hospital may increase in patients diagnosed with delirium (Ely et al., 2004; Lin et al., 2004).

Critically Ill Patient Sleep. More than half of critically ill patients are found to have sleep disturbances as demonstrated by abnormal sleep duration, patterns, and architecture related to critical illness or the ICU environment. Sleep fragmentation, short bursts of sleep resulting in predominant N1 sleep stage with minimal time in the restorative sleep stages SWS or REM, is a common ICU finding (Bijwadia, 2009).

Delirium and Sleep. Slow wave sleep contributes to physiologic repair. Slow wave sleep allows the brain to appropriately process new sensory input during the next wake period. This permits a person to acquire new information. Different aspects of REM and NREM sleep are necessary for learning and memory. Theoretically, sleep disturbances that negatively impact SWS and REM sleep could lead to delirium as memory, learning and the ability to process new situations are impacted. Ongoing sleep interruption and deprivation leads to cognitive impairment (Sanders & Mace, 2010). Delirium etiology is not known; however, the prefrontal cortex and posterior parietal cortex are both impacted by sleep deprivation and delirium (Maldonado, 2013; Weinhouse et al., 2009). Neurotransmitter imbalance may be related to both delirium and sleep disturbances. The exact mechanism by which the impaired neurocognition of delirium occurs is unknown whether by sleep deprivation, neurotransmitter derangement or a combination of both.

Findings. A literature review found seven articles that measured both sleep and delirium in critically ill patients. The findings were mixed in determining if there was an association between sleep disturbances and delirium. Not all instances of a reduction in total sleep time or REM sleep was associated with delirium. Four of the studies used patient questionnaires to measure the quality and quantity of sleep, so an exploration of sleep architecture and delirium was not able to be conducted in more than half the studies. Theoretically sleep and delirium may have a causal relationship. This possible relationship may be related to the absence of slow wave and REM sleep which cannot be measured by questionnaires. Further research is needed to explore the theoretical associations between sleep architecture and delirium particularly using sleep measurement methods that capture the presence or absence of sleep architecture. The presence or absence of sleep architecture may result in delirium, which has been linked to negative patient outcomes. More research is needed to explore the variables related to critically ill patients' sleep architecture disturbances, delirium and patient outcomes.

Chapter 3

Sleep Measurement in the ICU Environment. Critical illness and the ICU environment can interfere in the measure of sleep in critically ill patients. Critical illness effecting level of consciousness and/or memory could impact the accuracy of patient self-report sleep questionnaires (Bourne et al., 2007). Nurses mainly use physical cues to determine patients' sleep status for provider sleep assessment tools. However, critical illness and sedating medications may result in closed eyes and decreased movement resulting in an over report of sleep (Ritmala-Castran et al., 2016; Bourne et al., 2007; Richards, O'Sullivan, & Phillips, 2000). Actigraphy utilizes an algorithm that takes patient movement data to determine sleep/wake cycles. Critical illness can result in muscle weakness and decreased physical movement potentially confounding actigraphy sleep findings actigraphy (Bourne, 2007; Van der Kooi et al., 2012; Schwab et al. et al., 2018). Bispectral index (BIS) monitors brain waves but does not differentiate sleep into its various stages. BIS can give total sleep time information, but neurological trauma, dementia, and delirium can impact BIS values which may falsely be interpreted as adding to total sleep time (Bourne, 2007). Sleep self- reports, nurse sleep assessments, BIS and actigraphy have challenges to reliably measure sleep in critically ill patients.

Polysomnography and Critically Ill Patients. Polysomnography (PSG) is considered the gold standard of sleep measurement. PSG is comprised of EEG electrodes along with electrodes to measure eye and muscle movement. The use of PSG in the ICU environment has challenges related to expense, technical interference and ability to obtain data on recruited subjects. Since 2000, twenty-six articles were found to have used PSG to measure sleep in the ICU environment. Thirteen had less than 24 hours of PSG data per subject even though research has shown that a significant amount of ICU sleep occurs during daytime hours. The expense of

implementing PSG may be the reason for shorter data collection periods. Eighteen of the studies had subjects with missing PSG data. The reasons for missing data include: subject withdrawal, artifact, abnormal PSG, inaccurate PSG, missed ventilator data, respiratory distress, hypoxia, sepsis, poor signal quality or technology limits. However, the standards used to determine what data is used or discarded is not clearly articulated. Traditional PSG with multiple potentially uncomfortable scalp electrodes is monitored by technicians for electrode conductivity which adds to PSG expense. Technicians adjusting electrodes during a study can interrupt sleep and lead to subject dissatisfaction. Due to the expense of PSG, difficulty in initiating and obtaining sleep data, many studies use extensive inclusion and exclusion criteria to try to obtain reliable sleep data from every subject. Finally, some critically ill patients have abnormal PSG findings without the presence of normal sleep architecture leading to a theory that these patients have a different sleep architecture (Watson et al., 2013).

Continuous Electroencephalogram (cEEG). Continuous electroencephalogram is a diagnostic procedure that is common in ICUs that measures brain waves including some sleep stages. Since cEEG does not measure eye or muscle movement, it is not able to differentiate between stage 1 and rapid eye movement sleep. However, cEEG can capture stage 2 and slow wave sleep. While some of the same technical issues exists between PSG and cEEG that may result is missing data, cEEG is easier to implement with less expense meaning that larger sample sizes could be enrolled.

Findings. Measuring sleep in critically ill patients has challenges. Researchers need to be sure of what knowledge they wish to explore about sleep to determine the best sleep measurement. PSG gives the most detailed sleep information, but at a higher cost and potential for missed data for a variety of reasons. Additionally, extensive inclusion and exclusion criteria limits the critically ill patient population from which sleep knowledge is gathered. Sleep

measured by cEEG can give information about the presence or absence of sleep architecture and including the restorative SWS. Exploring the presence and amount of state 2 and SWS from larger sample sizes would add to the state of sleep knowledge in the critically ill patient. This knowledge can be used to determine sleep barriers, sleep interventions and patient outcomes related to sleep.

Chapter 4

Predictors of Sleep Architecture. The retrospective chart review of 84 patients looked at predictors associated with the presence or absence of sleep architecture Days 1 to 2 and Days 1 to 5 of cEEG monitoring. Severity of disease was by bivariate analysis significantly associated with the absence of sleep architecture for both groups. Abnormal creatinine and propofol were both associated with the absence of sleep architecture during days 1-2 of cEEG monitoring. No primary diagnosis was associated with the presence or absence of sleep architecture. However, a neurologic physiological state was associated with no sleep Days 1 to 2 and Days 1 to 5 of having cEEG. The neurologic physiological state when adjusted for age, medications and abnormal serum creatinine no longer remained significant. Days 1 to 5 cEEG, no sleep architecture was significantly associated with the physiologic states of anoxia, encephalopathy, and developmental disability. No subjects with anoxia had sleep architecture so anoxia was excluded as a predictor variable in models. A multivariate regression model with encephalopathy, developmental disability, age and medications as predictors resulted in both physiological states remaining significantly associated with no sleep architecture.

Sleep Architecture and Patient Outcomes. The presence or absence of sleep architecture was associated with various patient outcomes. No sleep architecture during days 1-2 cEEG was associated with longer mechanical ventilation days, ICU length of stay and hospital length of stay. In contrast to days 1-2 cEEG to days 1-5 cEEG, eleven more subjects had sleep

architecture. No sleep architecture during days 1-5 was significantly associated with a longer hospital length of stay, but mechanical ventilation days and ICU length of stay is no longer significant.

Hospital disposition was found to be significantly associated with no sleep architecture for both groups, Days 1 to 2 cEEG and Days 1 to 5 cEEG. Discharge to home was the most common posthospitalization discharge location. After adjusting for age, medications and abnormal serum creatinine, the presence of sleep architecture during Days 1 to 2 group having cEEG was associated with a discharge home from the hospital. In the Days 1 to 5 group having cEEG, the presence of sleep architecture adjusting for age, medications, encephalopathy and developmental disability physiological state was significantly associated with discharge to home.

Limitations. This study had a number of limitations. This is a retrospective study dependent on chart review data. The cEEG monitoring was ordered as part of the plan of care which may have resulted in the patient population being at the more severe end of the clinical spectrum. Continuous EEG is usually ordered in the presence of unexplained decreased level of consciousness with a concern for subclinical seizures. Additionally, the cEEG monitoring was initiated at different points within the ICU stay. There are other medications than the ones reviewed within this study that may impact sleep architecture such as beta blockers. Sleep is complex and the multiple predictors that may influence were not all explored in this study. For example, the ICU environment with its level of noise and light along with frequent interruptions may impact the ability of patients to sleep. These variables were not included in this study. However, the small sample size limited the number of variables that were able to be studied. Severity of disease was found to be significantly associated with the absence of sleep but a limited number of subjects were able to have the APACHE III score calculated from the retrospective chart review. Therefore, in view of the small sample size, APACHEIII scores were

not included in statistical models. While the outcomes of mechanical ventilation days, ICU length of stay, hospital length of stay and disposition have value, outcomes post discharge would be valuable.

Synthesis. The exploratory retrospective study found associations between sleep architecture and patient outcomes. Longer mechanical ventilation days, ICU and hospital length of stays were all associated with the absence of sleep architecture as measured by no stage 2 or slow wave sleep per cEEG. The absence of sleep architecture was associated with propofol, abnormal serum creatinine and physiological state of a neurologic nature, encephalopathy, and developmental disability. Delirium has also been found to be related to negative patient outcomes (Ely et al., 2004; Van Rompaey et al., 2009). Delirium is theoretically associated with sleep disturbances, but minimal research has been conducted to support this theory. No or minimal restorative slow wave or rapid eye movement sleep may result in delirium possibly due to impaired memory consolidation or the brain's inability to process new information. Even so, delirium prevention and interventions include promoting sleep (Barr et al., 2013). This exploratory retrospective study did not include delirium as a possible predictor.

The research study of this dissertation explored the presence or absence of sleep architecture. Measuring sleep in the critically ill can be challenging. As an exploratory study, an overview of the presence or absence sleep architecture was chosen, but the presence of certain sleep architecture stages can be determined by cEEG. Polysomnography can capture all sleep stages and may be the appropriate choice to answer certain research questions. However, PSG is expensive and is rarely implemented in the ICU environment. The less expensive and the frequently implemented in the ICU cEEG is able to recognize stage 2 and slow wave sleep which could be an appropriate sleep architecture measurement tool that allows for larger sample sizes than normally seen with PSG.

This dissertation has identified areas where there is a deficit of scientific knowledge and would benefit from further research. The possible relationship between sleep architecture and delirium is a gap in knowledge. Sleep disturbances and deprivation are known to exist in the critically ill. However, the factors that interfere with sleep architecture is not fully known. Acute hospital outcomes related to sleep disturbances and deprivations that occur in the critically ill needs to be explored further. Post discharge long term outcomes related to critically ill sleep disturbances should also be explored. Methods of critically ill sleep measurement need to be developed or refined. Actigraphy may be refined to capture the presence or absence of sleep in the critically ill and as this tool evolves research will be needed to validate its accuracy and reliability. Using cEEG possibly with less electrodes may give enough detailed sleep information with less expense and missing data that larger sample sizes would be available increasing the power of critically ill sleep research.

This dissertation highlights that the sleep state in the critically ill can be significantly associated with patient outcomes. Sleep architecture knowledge may have prognostic value for clinicians. Evidenced-based sleep promotion interventions based on known predictor variables should be implemented as soon as appropriate in the critically ill patient population.

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Appendix A

Allina Letter

Allina Health
Human Research Protection Program
Institutional Review Board

P.O. Box 43 Mail Route 10105
Minneapolis, MN 55440-0043
Tel: 612-262-4920
Fax: 612-262-4953
www.allinahealth.org

DATE:	June 22, 2018
TO:	Ruth Lindquist, PhD
FROM:	Allina Health IRB Office
PROJECT TITLE:	The relationship between patient outcomes and sleep architecture in critically ill patients
REFERENCE #:	1207736-1
SUBMISSION TYPE:	New Project
SUBMISSION DATE:	June 6, 2018
ACTION:	NOT HUMAN SUBJECT RESEARCH DETERMINATION
ACTION DATE:	June 22, 2018

Thank you for your recent request regarding the above referenced project.

The following items were included in this submission:

- Allina Health - Application Part 1 - Allina Health - Application Part 1 (UPDATED: 06/18/2018)
- Application Form - Application 2 - Request for Exempt Determination v05302017.doc (UPDATED: 06/18/2018)
- Conflict of Interest - Declaration - Lindquist COI.pdf (UPDATED: 06/6/2018)
- Conflict of Interest - Declaration - Mathiason COI.pdf (UPDATED: 06/6/2018)
- Conflict of Interest - Declaration - Genzler COI disclosure form.pdf (UPDATED: 05/7/2018)
- Conflict of Interest - Declaration - Hadidi COI disclosure form April 2018.pdf (UPDATED: 04/30/2018)
- CV/Resume - Lindquist_biosketch_Robin Austin.docx (UPDATED: 06/6/2018)
- CV/Resume - Mathiason_Moore CV 20180604.docx (UPDATED: 06/6/2018)
- CV/Resume - Hadidi CV Updated 1.30.18.pdf (UPDATED: 05/1/2018)
- CV/Resume - CURRICULUM VITAE laura.docx (UPDATED: 04/26/2018)
- Other - Memo of Acknowledgement.pdf (UPDATED: 05/2/2018)
- Protocol - Sleep Architecture & Outcomes Protocol no notes3_4_18.docx (UPDATED: 04/29/2018)
- Training/Certification - Mathiason Moore CITI CompletionReport2 20180605.pdf (UPDATED: 06/6/2018)
- Training/Certification - Ruth Lindquist CITI training Part 2.pdf (UPDATED: 05/7/2018)
- Training/Certification - Genzler COI CITI training Allina.pdf (UPDATED: 05/1/2018)
- Training/Certification - Hadid CITI certificate.pdf (UPDATED: 04/30/2018)

Based on the information provided, it has been determined that this activity does not constitute "human subjects research" as defined by the federal regulations because the protocol is using a limited data set from a closed study with no patient identifiers and no linkage document that can be used to link the patient subject number with the data set. As such, IRB review is not required.

Any alteration to the project that could potentially change this determination (e.g., change in procedures) must be submitted for review prior to implementation, unless such a change is necessary to avoid immediate harm to participants, in which case the IRB must be notified as soon as possible.

If you have any questions, regarding this determination, please contact the Allina Health IRB Office at (612) 262-4920 or irb@allina.com. Please include your project title and IRBNet ID# in all correspondence.

This letter has been electronically signed in accordance with all applicable regulations, and a copy is retained within Allina Health IRB Office's records.

Appendix B

University of Minnesota Letter

UNIVERSITY OF MINNESOTA

Twin Cities Campus

Human Research Protection Program
Office of the Vice President for Research

D528 Mayo Memorial Building
420 Delaware Street S.E.
MMC 820
Minneapolis, MN 55455

Phone: 612-626-5654
Fax: 612-626-6061
Email: irb@umn.edu
http://www.research.umn.edu/subjects/

NOT HUMAN RESEARCH

November 9, 2018

Ruth Lindquist

612-624-5646
lindq002@umn.edu

Dear Ruth Lindquist:

On 11/9/2018, the IRB reviewed the following submission:

Type of Review:	Initial Study
Title of Study:	The relationship between patient outcomes and sleep architecture in critically ill patients
Investigator:	Ruth Lindquist
IRB ID:	STUDY00004889
Sponsored Funding:	None
Grant ID:	None
Internal UMN Funding:	None
Fund Management Outside University:	None
IND, IDE, or HDE:	None
Documents Reviewed with this Submission:	• UMD IRB ICU Sleep.docx, Category: IRB Protocol; • Allina IRB Letter, Category: Other;

The IRB determined that the proposed activity is not research involving human subjects as defined by DHHS and FDA regulations. To arrive at this determination, the IRB used "WORKSHEET: Human Research (HRP-310)." If you have any questions about this determination, please review that Worksheet in the HRPP Toolkit Library and contact the IRB office if needed.

Ongoing IRB review and approval for this activity is not required; however, this determination applies only to the activities described in the IRB submission and does not apply should any changes be made. If changes are made and there are questions about

whether IRB review is required, please submit a Modification to the IRB for a determination.

Sincerely,

Jessica Wright, MA CIP

IRB Analyst

We value feedback from the research community and would like to hear about your experience. The link below will take you to a brief survey that will take a minute or two to complete. The questions are basic, but your responses will help us better understand what we are doing well and areas that may require improvement. Thank you in advance for completing the survey.

Even if you have provided feedback in the past, we want and welcome your evaluation.

https://umn.qualtrics.com/SE/?SID=SV_5BiYrqPNMJRQSBn