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Causes, Consequences, and Treatments of Sleep and Circadian Disruption in the ICU

An Official American Thoracic Society Research Statement

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This official research statement of the American Thoracic Society was approved December 2022

Abstract

Background: Sleep and circadian disruption (SCD) is common and severe in the ICU. On the basis of rigorous evidence in non-ICU populations and emerging evidence in ICU populations, SCD is likely to have a profound negative impact on patient outcomes. Thus, it is urgent that we establish research priorities to advance understanding of ICU SCD.

Methods: We convened a multidisciplinary group with relevant expertise to participate in an American Thoracic Society Workshop. Workshop objectives included identifying ICU SCD subtopics of interest, key knowledge gaps, and research priorities. Members attended remote sessions from March to November 2021. Recorded presentations were prepared and viewed by members before Workshop sessions. Workshop discussion focused on key gaps and related research priorities. The priorities listed herein were selected on the basis of rank as established by a series of anonymous surveys.

Results: We identified the following research priorities: establish an ICU SCD definition, further develop rigorous and feasible ICU SCD measures, test associations between ICU SCD domains and outcomes, promote the inclusion of mechanistic and patient-centered outcomes within large clinical studies, leverage implementation science strategies to maximize intervention fidelity and sustainability, and collaborate among investigators to harmonize methods and promote multisite investigation.

Conclusions: ICU SCD is a complex and compelling potential target for improving ICU outcomes. Given the influence on all other research priorities, further development of rigorous, feasible ICU SCD measurement is a key next step in advancing the field.

Keywords: sleep deficiency; circadian rhythm; delirium; critical illness; research priority

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Contents

Overview

Sleep and circadian function are fundamental to human health. Thus, ICU sleep and circadian disruption (SCD) is an important potential target for improving critical illness outcomes. Herein, we report ICU SCD research priorities as determined during a Workshop of the American Thoracic Society (ATS). During Workshop discussions, there were notable themes regarding research knowledge gaps, challenges, and key next steps. Importantly, technical limitations and feasibility issues have profoundly limited ICU SCD studies in terms of size, duration, and quality. Furthermore, variability in ICU SCD definitions, uncertainty regarding the domains of ICU SCD that are most closely related to patient outcomes, a lack of clarity regarding the natural history of ICU SCD during critical illness and recovery, and inconsistent approaches to ICU SCD risk factor identification remain substantial challenges in the field. Although multicomponent ICU SCD interventions have succeeded in decreasing environmental disturbance and delirium, these heterogeneous studies have largely failed to demonstrate improvements in sleep or circadian function. It remains unclear if this discrepancy is due to a failure of the interventions *per se*, a failure to adequately implement these (usually) complex interventions, an inability to accurately measure the intended ICU SCD domains, inappropriate patient selection, or incorrect timing of intervention or measures.

To improve the quality of evidence and to characterize the relative benefit of sleep and circadian interventions, the following six research priorities were identified:

- Define the natural history of ICU SCD to determine the optimal timing of ICU SCD interventions across the entire trajectory of acute critical illness through recovery.
- Advance the development of ICU SCD measures that are rigorous, feasible, and able to support longitudinal monitoring of SCD in the ICU.
- Define associations between individual ICU SCD domains and patient outcomes.
- Maximize research efforts by embedding mechanistic outcomes within larger clinical studies focused on clinically important patient-centered outcomes.
- Leverage implementation science strategies to maximize intervention fidelity and sustainability of multicomponent sleep and circadian interventions.
- Increase collaboration among interprofessional and clinical–translational investigators to harmonize research methods and promote multisite investigation.

Introduction

This paper reports the proceedings of an ATS Workshop on the causes, consequences, and treatments of SCD in the ICU designed to achieve the following objectives: *1*) delineate a list of priority ICU SCD subtopics; *2*) identify, discuss, and critically evaluate current knowledge and knowledge gaps within these subtopics; and *3*) establish a prioritized research agenda. In this research statement, we briefly review the importance of sleep and circadian function to human health. We next discuss our methods and provide definitions of key terms. Thereafter we discuss each of four identified ICU SCD subtopics: *1*) risk factors, prevalence, and incidence; *2*) ICU sleep and circadian measurement; *3*) ICU and post-ICU outcomes; and *4*) nonpharmacologic and pharmacologic treatment. Within each topic, we summarize the state of knowledge and share Workshop discussion content focused on the identification of key gaps and next steps (Table 1).

Sleep, Circadian Rhythms, and Health

Sleep is an important determinant of physical and mental health, and sleep deficiency is common in modern society (1, 2). Even short-term sleep loss negatively influences cognition (3), alertness (4, 5), mood (6, 7), glucose control (8–10), cardiovascular health (11–15), immune system function (16, 17), and respiratory physiology (18–21). Sleep deficiency includes multiple domains of sleep and circadian functions: sleep duration, timing, architecture, continuity, and regularity; internal and external circadian alignment; circadian amplitude;

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Table 1. High-Priority Next Steps to Meet Existing Knowledge Gaps

Subtopic	Next Steps
Scope	• Define the natural history of ICU SCD to determine the optimal timing of ICU SCD interventions across the entire trajectory of acute critical illness through recovery. • Increase collaboration among interprofessional and clinical–translational investigators to harmonize research methods and promote multisite investigation. • Define distinct study populations that account for the heterogeneity of ICU patients. • Investigate if changes in sleep and circadian domains during acute illness are adaptive vs. maladaptive. • Identify baseline, acute illness, and ICU-based risk factors for ICU SCD. • Include and test the significance of preadmission sleep history in the diagnosis and treatment of maladaptive domains of ICU SCD.
Measures	• Advance the development of ICU SCD measures that are rigorous, feasible, and able to support longitudinal monitoring of SCD in the ICU. This includes circadian measures that are robust against masking in the ICU environment. • Pursue automated, real-time objective sleep and circadian measures that would allow clinical translation of ICU SCD diagnosis and treatment to the bedside. • Maximize the use of patient-perceived sleep measures whenever possible; implement these measures as soon as cognitive and communication barriers resolve.
Outcomes	• Define associations between individual ICU SCD domains and patient outcomes. This includes but is not limited to cognitive, respiratory, metabolic, cardiac, and immune-related outcomes as well as patient-centered outcomes. • Maximize research efforts by embedding mechanistic outcomes within larger clinical studies focused on clinically important patient-centered outcomes. Areas of special interest include the bidirectional interactions of respiratory failure, invasive and noninvasive ventilation, and ICU SCD, and the bidirectional interaction of delirium and ICU SCD. • Identify posthospital outcomes related to ICU SCD.
Treatment	• Leverage implementation science strategies to maximize intervention fidelity and sustainability of multicomponent ICU SCD interventions. • Personalize inpatient sleep and circadian promotion; when possible, continue treatment of preexisting sleep disorders. • Translate circadian biology principles to the ICU to promote internal and external synchrony. • Explore daytime wake promotion as a component of ICU SCD interventions. • Advance current knowledge of pharmacologic sleep and circadian promotion while avoiding excessive sedation or increased delirium.

Definition of abbreviation: SCD = sleep and circadian disruption.

self-perception of sleep; quality of wakefulness; and daytime function (Figure 1).

Circadian rhythms, generated by central and peripheral biological clocks, are integral to directing the proper timing of sleep and a broad array of physiologic processes (e.g., promotion of consolidated sleep during the night and effective metabolic processing during the day). Under normal circumstances, cues such as light and dark, feeding, exercise, sleep, and social interaction promote alignment between solar day and night, the central clock, and the multitude of peripheral clocks located in every tissue of the human body. Misalignment leading to organ dysfunction can occur between the external environment and the central clock (i.e., external misalignment) and/or among clocks in the body (i.e., internal misalignment) (Figure 2) (22).

Methods

Committee Composition

We convened an international multidisciplinary group with expertise in ICU SCD, critical illness, and related outcomes as well as a person who had experienced an ICU admission and had prior involvement in developing ICU practice guidelines. Workshop members then conducted two full-group and several subgroup planning sessions to identify priority topics for discussion. Potential conflicts of interest were disclosed and managed in accordance with the policies and procedures of the ATS.

Literature Search and Evidence Appraisal

Targeted literature reviews were conducted, discussed, and summarized within each subgroup. Articles were restricted to adult patients admitted to ICUs, though in some cases evidence from experiments in healthy control subjects were included. Selected speakers then presented a summary of the literature by subtopic as a prerecorded lecture that was watched by all Workshop members in advance of each Workshop session.

Workshop Discussions and Research Recommendations

The in-person Workshop was converted to a series of shorter remote video conference sessions (rather than a single full day) because of the coronavirus disease (COVID-19) pandemic. Each Workshop session focused on one of the subtopics identified during planning. Discussion was moderated by the chair and co-chair and focused on the key research gaps and high-priority next steps. These gaps and next steps were first proposed by the relevant subtopic presenter and then refined during the session by Workshop participants. After each Workshop session (i.e., subtopic), meeting notes were circulated, and all identified themes (i.e., gaps or priorities) were confirmed. Subsequently, the Workshop chair developed and distributed an anonymous survey for the ranking of themes from the relevant session. After the completion of all sessions and surveys, the top three themes from each session (i.e., subtopic) were included in a final anonymous survey and ranked. The listed priorities were selected on the basis of ranking in the final survey, but in a consensus decision among Workshop members, the included research priorities were not listed in rank order.

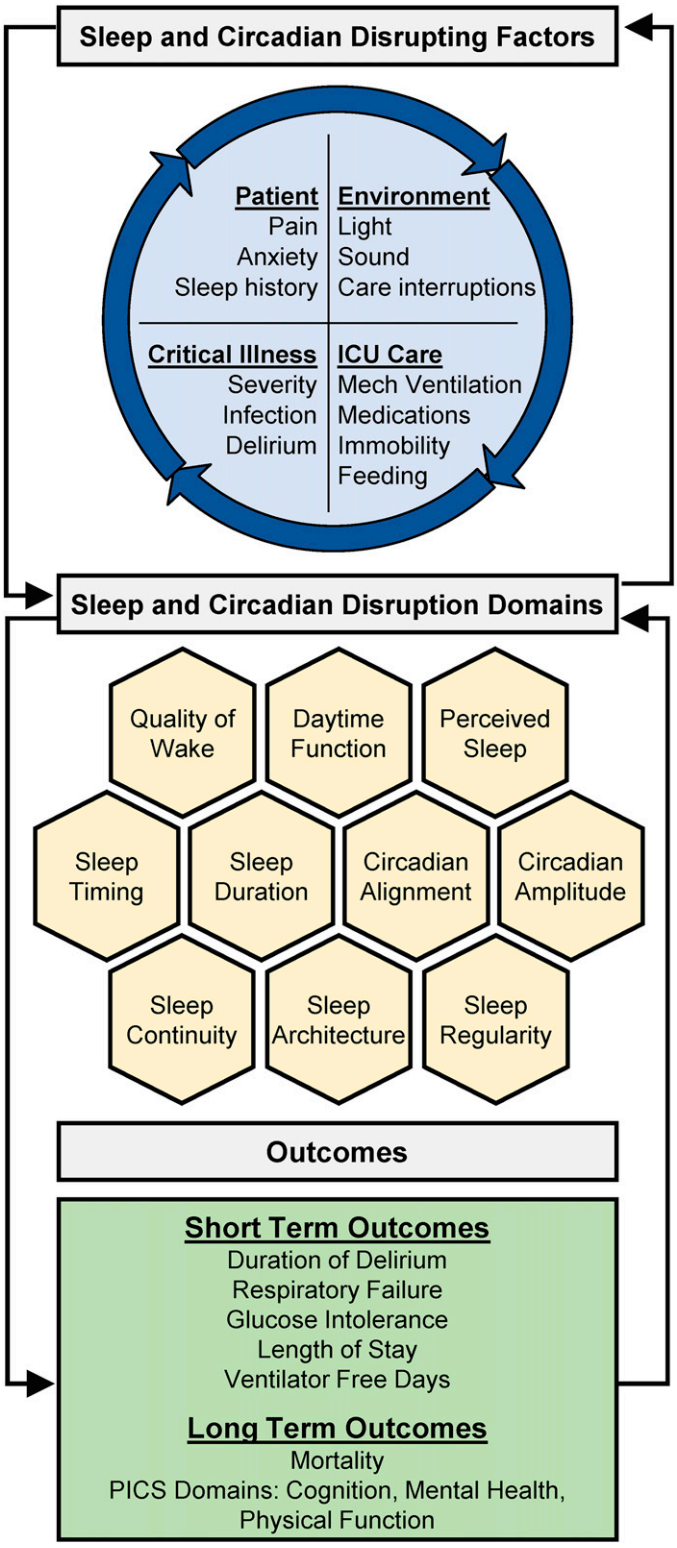

Figure 1. Conceptual model of ICU sleep and circadian disruption (SCD). Factors that disrupt sleep are presented in blue, with arrows indicating interactions among disruptive factors. Proposed domains of ICU SCD are presented in yellow; we hypothesize that patients may experience changes in some or all domains. Proven and hypothesized patient-centered outcomes are presented in green; delirium and respiratory failure have the best established association with ICU SCD to date. Mech = mechanical; PICS = post–intensive care syndrome.

Document Development

The research statement was drafted in parts by each subtopic working group and then assembled and revised for cohesion by the Workshop chair and co-chair. Elements of the statement not directly related to subtopics were written by the chair and co-chair. Completed statement drafts were circulated to each member and discussed via video conference in several rounds before final submission.

Definitions

Several definitions were agreed on by the group for the purpose of this research statement. An ICU was defined as any environment capable of providing mechanical ventilation and/or invasive hemodynamic monitoring that is not a postoperative recovery unit. The target population of interest was defined as any patient admitted to the ICU. In establishing this definition, it was acknowledged that ICU patients are tremendously heterogeneous and may be cared for in diverse locations. Relatedly, and perhaps applicable to the design of particular studies, some Workshop participants expressed an interest in limiting studies to patients admitted to ICUs with at least one qualifying organ failure or implementing other measures to homogenize study populations.

Notably, the group agreed that there are no established definitions of ICU sleep deficiency or circadian disruption. This lack of definition poses a major challenge for the ICU SCD field. Given the multiple potential domains of SCD, it is likely that ICU SCD will ultimately be defined as a multicomponent syndrome, with patients experiencing some or all aspects of ICU SCD. There was consensus among the Workshop members that the ICU SCD definition(s) should be focused on elements of SCD that are most closely associated with ICU outcomes. Furthermore, it was noted that alterations in the multiple domains of sleep and circadian function (e.g., sleep duration, timing, architecture, continuity, and regularity; internal and external circadian alignment; circadian amplitude; self-perception of sleep; quality of wakefulness; and daytime function) that occur during acute critical illness and/or during admission to the ICU may include changes in some domains that are in fact adaptive and should thus not necessarily be reversed.

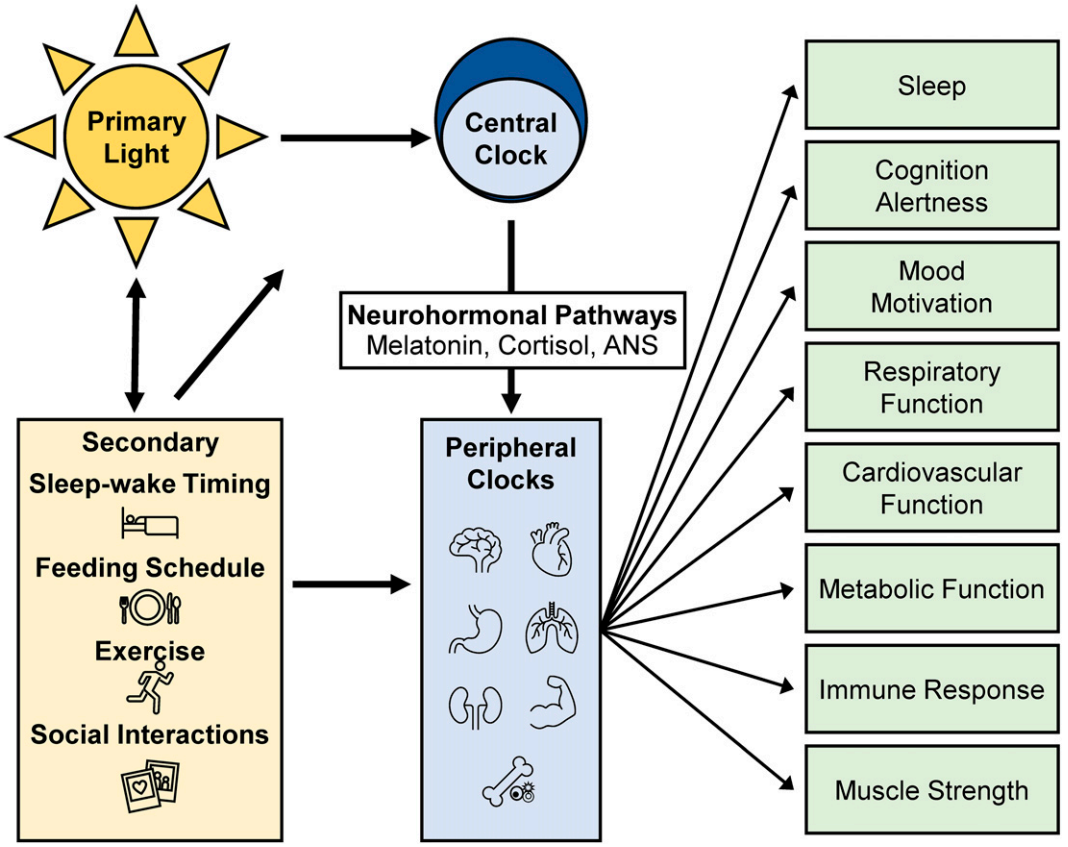

Figure 2. Connections among primary and secondary zeitgebers, central and peripheral clocks, and body functions. Light is the primary zeitgeber, with direct input to the central clock located in the suprachiasmatic nucleus and indirect input into peripheral clocks via neurohormonal pathways. Sleep–wake timing, feeding schedule, exercise, and social interaction are secondary nonphotic zeitgebers that have input into central and peripheral clocks and influence light exposure (e.g., low light exposure while sleeping). Internal and external misalignment contribute to an array of organ dysfunction. ANS = autonomic nervous system.

Subtopic 1: Prevalence, Incidence, and Risk Factors

Prevalence and Incidence

The magnitude of ICU SCD has been difficult to quantify because of study heterogeneity, difficulty in measuring sleep (*see* subtopic 2), and related limitations in crafting a clinically meaningful ICU SCD definition. Nevertheless, the amount, timing, architecture, and quality of sleep in the ICU are highly abnormal (23–29). For example, observational polysomnography (PSG) studies show shortened sleep duration over 24 hours and a high proportion of daytime sleep (23, 24). Sleep is also highly fragmented, with frequent arousals and sleep episodes of short duration (e.g., lasting only 3 min). Finally, there is a paucity of stage REM and non-REM 3 sleep (23, 24).

Circadian rhythms are similarly disrupted in critical illness. Studies have demonstrated that critically ill patients often have misaligned (usually delayed-type) or absent circadian rhythms as defined by melatonin (or its urinary metabolite, 6-sulfatoxymelatonin) concentrations and other circadian phase markers. This finding has been described in multiple critical illness cohorts, including patients with sepsis, those with intracerebral hemorrhage, and those requiring mechanical ventilation (30–41).

Notably, ICU SCD may differ substantially among individual patients and subgroups and may change over time as patients recover from acute illness. This raises key questions of ICU SCD definition and timing including when to measure and when to intervene in ICU SCD. These questions were rediscussed several times during ensuing subtopic discussions.

In addition, the group discussed whether acute changes in sleep and circadian rhythms during critical illness are adaptive or harmful. For example, infection-related illness and other proinflammatory states are known to increase sleepiness and extend sleep timing in non-ICU patients (42). Thus, biological plausibility suggests that sleep duration should be extended during infection-related critical illness rather than shortened, as observed in many ICU studies. Similarly, it does not seem likely that the high degree of sleep fragmentation observed in the ICU, due to light, sound, pain, anxiety, mechanical ventilation, overnight bedside care, and many unnamed factors, is adaptive, however, other aspects of ICU SCD may be. In terms of circadian disruption, limited data on circadian alignment and amplitude during acute infection suggest that acute infection can alter peripheral clock alignment (43), but it remains unclear if this is harmful or beneficial. Given the high relevance of infection and immune function in critically ill adults, this may be an area of particular interest for future research. In addition to parsing which domains of ICU SCD may be

Table 2. Advantages and Disadvantages of Selected ICU Sleep and Circadian Measures

Measure	Advantages	Disadvantages	Sample Studies
Objective sleep measures			
Polysomnography	• Gold standard for sleep/wake and sleep architecture including stages, timing, and continuity	• Resource intensive • Poor patient tolerance • Standard scoring limited	Cooper *et al.* (2000) (25) Bosma *et al.* (2007) (26) Roche Campo *et al.* (2010) (27) Drouot *et al.* (2012) (28) Watson *et al.* (2013) (29) Elliot *et al.* (2013) (23) Knauert *et al.* (2014) (24)
Multichannel EEG Bispectral Index SedLine	• Automated • Feasible and tolerable • Familiar to ICU providers • Longitudinal monitoring possible	• Limited accuracy identifying sleep • Poor accuracy identifying sleep stages	Gimenez *et al.* (2017) (101) Vacas *et al.* (2016) (104) Nieuwenhuijs *et al.* (2020) (103) Pedrão *et al.* (2020) (102)
Automated EEG Odds ratio product	• Automated • Feasible and tolerable • Longitudinal monitoring possible • Measures alertness	• Limited accuracy identifying sleep • Poor accuracy identifying sleep stages	Dres *et al.* (2019) (86)
Actigraphy	• Feasible and tolerable • Longitudinal monitoring possible	• Limited accuracy identifying sleep • No identification sleep stages • Limited in immobile ICU patients	Kamdar *et al.* (2017) (131) Wilcox *et al.* (2021) (109)
Patient-perceived sleep measures			
Richards Campbell Sleep Questionnaire	• Validated in ICU patients • Feasible and tolerable • Longitudinal monitoring possible • Patient centered • Includes five sleep domains	• Restricted to patients with cognitive and communication ability	Richards *et al.* (2000) (110) Kamdar *et al.* (2012) (120) Aitken *et al.* (2017) (113) Menear *et al.* (2017) (112)
Pittsburgh Sleep Quality Index	• Validated in non-ICU patients • Feasible and tolerable • Longitudinal monitoring possible • Seven sleep domains • Allows assessment of pre– and post–acute illness sleep	• Restricted to patients with cognitive and communication ability • High patient burden because of length • Not for inpatient use	Buysse *et al.* (1989) (123) McKinley *et al.* (2013) (124) Wang *et al.* (2019) (125)
Insomnia Severity Index	• Validated for patients and proxy • Detailed insight into insomnia • Feasible and tolerable • Longitudinal monitoring possible • Allows assessment of pre- and postillness insomnia	• Restricted to patients with cognitive and communication ability • Not for inpatient use	Bastien *et al.* (2001) (126) McKinley *et al.* (2013) (124) Elliot *et al.* (2013) (23)
Circadian measures			
Melatonin Serum 6-Sulfatoxymelatonin Urine	• Gold standard	• Frequent sampling • Masking by ICU environment • Anemia/risk anemia for serum samples • Oliguria/anuria limit urine samples; indwelling catheter needed for urine samples	Mundigler *et al.* (2002) (31) Frisk *et al.* (2004) (40) Gehlbach *et al.* (2012) (34) Verceles *et al.* (2012) (33) Li *et al.* (2013) (41) Maas *et al.* (2020) (39)
Heart rate	• Feasible and tolerable • Longitudinal monitoring possible	• Need for specialized data management • Critical illness confounds measure	Knauert *et al.* (2020) (37)
Core temperature	• Longitudinal monitoring possible	• Invasive • Fever/antipyretics confound	Gazendam *et al.* (2013) (35)
Actigraphy	• Feasible and tolerable • Longitudinal monitoring possible	• Indirect behavioral reflection of circadian measures • Limited in immobile ICU patients	Duclos *et al.* (2014) (36) Knauert *et al.* (2021) (129)

adaptive during critical illness, there is considerable interindividual vulnerability to sleep loss, which may influence the associations between ICU SCD and critical illness outcomes (44, 45).

Baseline Risk Factors

Baseline risk factors for ICU SCD have been difficult to establish. However, reporting poor sleep and using sleep medications at home before admission are factors that have been consistently implicated in ICU sleep disruption (46). Concerningly, short sleep duration and poor sleep quality are a serious global health threat (1, 2, 47–51). The use of sleep aids is also common in the adult population, especially elderly individuals and persons with sleep disorders (52). Sleep disruption is more common in some populations on the basis of race, ethnicity, occupation, and social factors such as reduced socioeconomic status (53), substance abuse (54, 55), smoking (1), and psychiatric (47, 56) or medical disorders (including sleep disorders) (57–59). Relatedly, lack of attention to patient sleep history and sleep preferences has been an ICU SCD care gap. For example, obstructive sleep apnea (OSA) is common and often goes untreated during hospital admissions (60–62). Similarly, preexisting sleep problems such as insomnia and restless legs syndrome can be exacerbated or unmasked by factors associated with critical illness, including blood loss, anxiety, immobility, sleep deprivation, provoking drugs, or cessation of therapeutic medications (63). Furthermore, preexisting disrupted sleep and undiagnosed OSA disproportionately affect racial and ethnic minorities (64, 65). Exploration of this health disparity is a key a research gap outside the scope of this document (66).

Discussion during the Workshop highlighted the importance of obtaining a more detailed sleep history to identify patients at highest risk for ICU SCD. The impact of preadmission sleep abnormalities on ICU outcomes and management has not been well studied. At the very least, knowledge of these conditions may help guide care (e.g., presence of severe preexisting OSA, insomnia, or restless legs syndrome). Finally, attention to sleep history may also allow targeted sleep and circadian promotion interventions (e.g., providing a sleep opportunity during a patient's preferred sleep time).

ICU and Acute Illness Risk Factors

In the ICU, contributors to ICU SCD include environmental factors, illness-related factors, medication exposures, and mechanical ventilation. The ICU environment, especially noise, has been consistently reported to be associated with sleep disruption (67). Numerous studies demonstrate that the ICU environment exceeds recommended sound levels around the clock (68–71). PSG studies show that excessive noise contributes to approximately 20% of awakenings in ICU patients (72, 73). Although evidence is more limited, inadequate daytime and excessive nighttime light are also common in the ICU and may significantly disrupt sleep and circadian rhythms (74–76). Frequent bedside care interruptions also contribute to excessive noise and light exposure and induce pain or anxiety, which have been reported by patients as sleep disruptive (67, 77, 78). Associations between sleep disruption and severity of illness, length of stay, admission diagnosis, and/or sedative hypnotic drug therapy have not been supported by most studies (67). Loss of circadian alignment and amplitude has been variably associated with severity of illness, brain injury, and sepsis in diverse ICU cohorts (30–39). Additional hypothesized sources of circadian disruption include abnormal circadian cues such as altered light exposure, disrupted sleep–wake schedule, immobility, and continuous feeding (79–81).

Workshop members noted that studies to date have generally been small and based at single centers. Furthermore, there has been substantial variability in data collection regarding patient characteristics, exposures, ICU SCD measures, and outcomes. Consequently, the lack of consistent associations between proposed risk factors and ICU SCD may be related to study variability rather than a lack of underlying associations.

Subtopic 2: Measurement of Sleep and Circadian Rhythm in the ICU

Although advances in portable, wearable devices have improved measures of sleep and circadian function in the ICU, numerous challenges remain. Sleep and circadian measures must have acceptable cost, feasibility, tolerance, and interpretability to allow longitudinal around-the-clock monitoring. This would, in turn, facilitate meaningful ICU SCD definitions, guide the timing of interventions, and support rigorous outcome evaluation. Circadian measures carry additional challenges of frequent sampling needs (e.g., hourly) and of being vulnerable to masking, a phenomenon in which environmental factors (e.g., light) directly alter the circadian measure at the time of collection (e.g., serum melatonin). Table 2 lists proposed ICU SCD measures.

Objective Sleep Measures

PSG is considered the gold-standard method to objectively measure sleep. PSG studies in the ICU require EEG, electrooculography, and chin EMG to measure sleep–wake cycles, sleep stages, and arousals from sleep; such monitoring in critically ill patients is challenging and resource intensive. Furthermore, the necessary monitors can be uncomfortable for patients and thus poorly tolerated during prolonged monitoring (24). PSG is useful to determine the cause of arousals (26), for pharmacologic or pathophysiological studies (27, 82–86), or to test sleep interventions (87). In non-ICU patients, sleep scoring is based on rules originally established by Rechtschaffen and Kales (88) and later adapted by the American Academy of Sleep Medicine (89). In ICU patients, EEG sleep features may differ from those of non-ICU patients, and atypical patterns have been described. The key EEG features of atypical sleep include loss of sleep spindles and K-complexes, and "pathological wakefulness," in which EEG features of sleep are present during behavioral wakefulness (25, 27–29). These atypical features can make conventional scoring rules unreliable. Atypical EEG patterns have been associated with poor outcomes in many studies (27, 28, 73, 90–95) but not in all studies (86, 96). Alternative rules have been proposed to improve the rigor and reproducibility of PSG scoring in ICU patients but have not been widely adopted (28, 29).

Workshop discussions highlighted the cumbersome nature of PSG-based methodologies in the ICU. Study size and duration have typically been limited by a need for experienced staff members to apply and maintain monitoring leads, a need for epoch-by-epoch scoring by experts in ICU sleep, and poor patient tolerance. These limitations have challenged efforts to monitor sleep longitudinally on a large scale and have made comparison of data among studies difficult, as there is no accepted

standard for scoring. The group did touch on more portable EEG devices (e.g., "dry EEG") that may be easier to apply, but these emerging technologies are not always able to provide EEG of sufficient quality and do not mitigate scoring challenges.

Although not rigorously explored in ICU populations, automated and/or simplified PSG measures such as spectral analysis (97) or the preservation of normal sleep architecture may overcome some of the listed barriers; the latter has been associated favorably with ICU outcomes (93, 98). Similarly, sleep continuity, which requires determination of only two PSG states (sleep and wake), has also been associated with clinically relevant outcomes (99). In addition, automated algorithms that use novel EEG montages have been tried to alleviate the challenges described above. The readily available Bispectral Index (Medtronic) has been studied as a method to assess the depth of sleep (100–102) but with poor results in scoring sleep stages (103); similarly, SedLine (Masimo) was evaluated in a single limited study (104). Other methods using automated EEG algorithms to score sleep depth, such as spectral power and the odds ratio product, have been proposed and studied in a small number of ICU patients (86, 97, 105). These techniques are promising and may provide a rapid and reproducible analysis of sleep quality using a small device that is more comfortable for patients and more practical for research or clinical staff members.

Workshop members agreed that validation of automated scoring together with the development of more comfortable, miniaturized leads is likely a key path forward. These methods need to be validated against full PSG and visual scoring in a large cohort of ICU patients. Once accomplished, this would mitigate challenges across the field, such as ICU SCD definition and natural history, intervention testing, and assessment of outcomes. Notably, objective sleep measures that are robust despite a patient's inability to communicate or move are necessary in the quest to define the various phases of ICU SCD, especially early in critical illness, when we are most limited in our use of alternative measures (*see* the following discussion of actigraphy and subjective sleep measures). Furthermore, automated real-time sleep measurements could be used at the bedside to guide clinical care. Aspirationally, sleep could be considered a key clinical parameter, like delirium, and would thus be frequently monitored as part of routine care.

Actigraphy is an objective, noninvasive measure of rest and activity that can be used to infer sleep–wake schedule. In healthy subjects, rest–activity cycle, day–night variation of activity, and circadian rhythms can be reliably assessed for a prolonged duration (several consecutive days or weeks) (106). In ICU patients, sedation, induced paralysis, and/or immobilization will decrease movement and thus reduce the validity of actigraphy for sleep detection (107). However, as we trace the trajectory of ICU SCD, actigraphy might be a key component in studying sleep once patients progress beyond their immediate critical illness (108, 109).

Subjective Sleep Measures

Patient perception of sleep quality (i.e., subjective sleep quality) is assessed using questionnaires and is an important domain of sleep (110). Patient perception of sleep quality is correlated with outcomes in non-ICU populations and is pragmatic and cost effective (111–113). The Richards Campbell Sleep Questionnaire (RCSQ) has been validated against PSG and is the most reliable questionnaire for sleep assessment in ICU patients (110). The RCSQ uses visual analogue scales to evaluate five sleep domains of patient-perceived sleep quality from the preceding night. As with other domains of ICU SCD, it is not clear how each of these domains relates to ICU outcomes. Unfortunately, an estimated 50% of patients cannot use the RCSQ, because of communication or cognitive barriers (e.g., sedation or delirium) (114, 115). Other patient questionnaires include the Numerical Rating Scale–Sleep (114), the Sleep in the ICU Questionnaire (116), the Coronary Care Unit Questionnaire (117), and the Verran Snyder-Halpern Sleep Scale (118, 119). Observation by research staff members or bedside caregivers would seem like a possible way to overcome some of these challenges, but observers tend to overestimate sleep time and, by definition, do not include the patient perspective (107, 119–122). During recovery from critical illness, sleep can be longitudinally assessed using established outpatient instruments such as the Pittsburgh Sleep Quality Index or the Insomnia Severity Score (23, 123–126).

The Workshop discussion of patient perception of sleep as measured by questionnaires focused on the tension between the high value of such measures and the logistical limitations of implementing them in the ICU population. Nevertheless, it was agreed that it is important to obtain patients' sleep perceptions whenever possible. Finally, as with actigraphy, questionnaires may be used as soon as possible upon resolution of delirium and/or return of the ability to communicate and then used for longitudinal monitoring during illness recovery.

Circadian Measures

Key domains of assessing circadian function include phase (i.e., alignment) and amplitude. Melatonin concentrations, which rise sharply before habitual bedtime and fall sharply after habitual wake, are considered gold-standard measures of circadian phase and amplitude. In the critically ill population, which may have unpredictable alignment, sampling of blood (melatonin) or urine (6-sulfatoxymelatonin) must be frequent (e.g., hourly) and around the clock, which can be cumbersome and thus limit sample size. Variations in sampling frequency have limited the interpretation of results in some cases. Furthermore, melatonin is vulnerable to masking, as noted above. To avoid, or at least control for, the impact of zeitgebers such as light, feeding, exercise, and sleep, investigators must also track these variables in ICU patients.

Other physiologic signals can help identify circadian phase and have both established norms and known relationships to melatonin onset and offset (127). For example, core body temperature, blood pressure, and heart rate have been used (35, 37, 128); these measures can be problematic in many critically ill patients, as they can be substantially influenced by sleep–wake cycle, disease processes, and/or medications. Actigraphy rest–activity patterns have also been used as a proxy for circadian phase (129, 130) but are limited because rest–activity cycle is a behavioral correlate of circadian phase rather than a direct physiologic measure. As noted above, this disconnect can be exacerbated in the generally immobile ICU population (36, 131). Novel biomarkers of circadian phase that use RNA expression analysis to estimate melatonin onset have been developed in non–critically ill human populations (132, 133). However, preliminary studies suggest that these

measures cannot predict melatonin onset in critically ill patients (38).

After considering existing sleep and circadian measures, Workshop discussion turned to the potential of artificial intelligence and machine learning techniques that could address several of the identified measurement issues. Machine learning techniques could be used to integrate a wide variety of physiologic and environmental monitors at the bedside to identify markers of poor sleep and to identify novel proxies of circadian rhythmicity. Integrated machine learning analyses of the environment in ICU patient rooms are feasible and, as proof of principle, have been used to demonstrate that light, sound, and visitation frequency patterns differ between patients with delirium and those without (134).

Subtopic 3: Outcomes of ICU SCD

Sleep and circadian rhythms are believed to play an important role in recovery from injury and illness. Sleep quality and quantity are linked to mortality in the general population (135–137), and emerging data suggest that acute SCD may be linked to ICU mortality (37, 93). As noted above, even short-term sleep loss and/or circadian disruption in non-ICU study subjects can negatively influence an array of body functions, including cognition (3), alertness (4, 5), mood (6, 7), glucose control (8–10), cardiovascular function (11–15), immune response (16, 17), and respiratory physiology (18–21). Although associations between ICU SCD and functional outcomes are challenging to prove in the complex ICU environment, the promise of broad-ranging benefits related to promotion of normal sleep and circadian function has motivated the field forward. Research to date has focused on the associations between ICU SCD, respiratory function, and delirium; however, impact on cardiovascular, metabolic, and immune functions is also likely. In addition to short-term outcomes, sleep disturbances such as insomnia are common after ICU admission and may influence rehabilitation capacity and quality of life beyond the acute phase of critical illness. Opportunities may therefore exist to improve outcomes by improving sleep and circadian function throughout the trajectory of critical illness and recovery.

Respiratory Failure and Mechanical Ventilation

Sleep deficiency may impair respiratory function in ICU patients. Several studies in healthy volunteers have shown that respiratory and peripheral muscle endurance is reduced after sleep deprivation and that changes in the chemoreflex control system can occur (18–21). In addition, the subjective experience of dyspnea, especially air hunger, can be intensified by sleep deprivation (21, 138). ICU studies have shown that sleep disturbances are associated with failure to liberate from noninvasive (27) and invasive mechanical ventilation (83). Interestingly, a recent study demonstrated that the degree of wakefulness, as assessed by the odds ratio product, was significantly higher in patients with a successful spontaneous breathing trial (86).

Relatedly, mechanical ventilation is associated with sleep disruption. Contributing factors to sleep disruption relevant to mechanical ventilation include increased work of breathing (139), ineffective triggering of the ventilator (i.e., patient–ventilator asynchronies) (26, 85), and ventilatory over-assistance (140) (Figure 3). Several studies describe sleep improvements attributable to the optimization of ventilator settings. In patients with acute hypercapnic respiratory failure, sleep quality was improved when patients were supported by noninvasive ventilatory support at night (85). Respiratory muscle rest using pressure control ventilation titrated to achieve passive ventilation was found to improve sleep quality, efficiency, and REM sleep compared with low-pressure support (139). However, ventilatory support in excess of a patient's metabolic need can result in hyperventilation, decreased carbon dioxide concentrations, and central apneas (141); central apneas can in turn result in frequent awakenings and arousals, leading to sleep fragmentation (140, 142, 143). Proportional modes of ventilation (e.g., proportional assist ventilation and neurally adjusted ventilatory assist) can be used to deliver pressure proportional to the patient's instantaneous efforts in terms of amplitude and timing, which avoids over- and under-assistance and improves synchrony (144–146). Proportional assist ventilation has been shown to decrease patient–ventilator dyssynchrony and improve sleep quality because of the combined effects of fewer arousal per hour, fewer awakenings per hour, and greater proportion of REM sleep (26), though this result is not consistent across studies (147). Neurally adjusted ventilatory assist has been shown to be superior to pressure support ventilation, resulting in increased REM and lesser sleep fragmentation, possibly because of a lack of ineffective efforts or central apnea events (148).

The above studies, like others in the ICU SCD field, are small and have produced inconsistent findings. Key questions remain, such as whether the mode of mechanical ventilation versus the achievement of physiologic principles (e.g., synchrony, respiratory muscle rest, avoidance of hyperventilation, comfort or relief of dyspnea) is most important in preventing ventilator-related sleep disruption. Furthermore, though there are associations between sleep disruption and poor respiratory outcomes, it remains to be proven that promoting sleep will positively affect these outcomes. Barriers related to ICU SCD measurement have also affected outcome studies. To provide detailed, mechanistic information, many of the described studies have included PSG with its limitations as discussed above. It may ultimately prove beneficial to nest small mechanistic studies of sleep promotion via ventilator strategies within larger, randomized studies focused on clinical outcomes. Additional design concerns for future studies include selecting the phase of critical illness for sleep promotion, analytic plans that accommodate the likely bidirectional nature of the sleep and respiratory function, and integration of alternative ventilator modes with recommended parameters such as low-V_T ventilation (149).

Delirium

Delirium is defined by the presence of inattention, fluctuating mental status, disorganized thinking, and an altered level of consciousness. These findings are also often found in severe sleep deprivation. Although sleep and circadian rhythm disturbances are regarded as potentially modifiable risk factors for the development of delirium, delirium itself may contribute to sleep disturbances. Studies conducted mainly in cardiac surgical patients indicate that sleep deprivation can cause (150), be a result of (151), or simply lower the threshold for transitioning to delirium. A prospective cohort study of surgical ICU patients demonstrated an association between delirium and severe REM sleep reduction

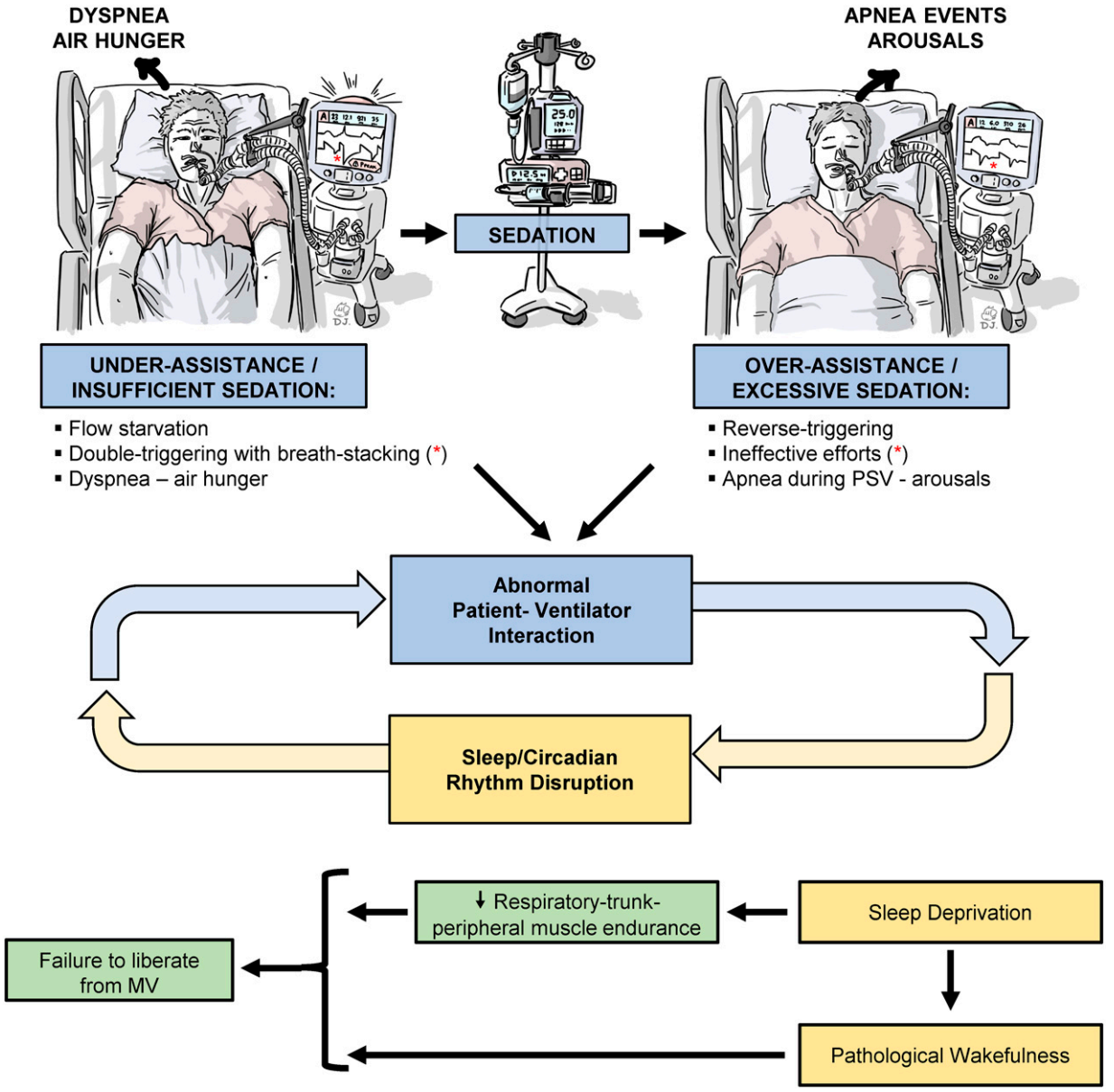

Figure 3. Proposed mechanisms for the bidirectional relationship between respiratory dysfunction and sleep and circadian disruption (SCD) in the ICU. Abnormal patient–ventilator interactions illustrated at the top of the figure (blue) contribute to ICU SCD (yellow). In turn, ICU SCD contributes to respiratory ability and outcomes illustrated at the bottom of the figure (green). MV = mechanical ventilation; PSV = pressure support ventilation. * = that part of the drawing in the image that depicts the listed abnormality.

(<6% of total sleep time) (82). Similarly, in a single-center case–control study, critically ill patients who developed delirium during their stays experienced less REM sleep compared with those who did not experience delirium (152). Furthermore, peripheral melatonin and cortisol concentrations were lower in the delirious compared with the nondelirious group, suggesting an association between ICU SCD and delirium (152).

Sleep promotion has been tested as a mitigation strategy for ICU delirium. In a systematic review (153), 6 of the 10 identified studies demonstrated statistically significant reductions in the incidence of ICU delirium associated with a sleep intervention (154–159). Similar results were seen in a randomized clinical trial (RCT) in which delirium-free patients ($N = 100$) receiving sedatives were given either nocturnal dexmedetomidine or placebo until ICU discharge; nocturnal dexmedetomidine was associated with a greater proportion of patients who remained delirium free, but patient-reported sleep quality was unchanged (160). In contrast, changes in sleep were seen in two RCTs ($N = 61$ and $N = 30$) in which patients were randomized to either nocturnal dexmedetomidine or placebo; in these studies, sleep parameters as determined by PSG were improved under the dexmedetomidine condition, whereas delirium was not (161, 162).

During the Workshop, we highlighted that the mechanisms linking individual domains of ICU SCD and delirium remain

unclear. Furthermore, there appears, at this relatively early stage, to be a bidirectional relationship between ICU SCD and delirium; however, the details of causality need to be clarified in appropriately designed studies. Finally, although sleep interventions seem to be a promising approach for improving delirium and related outcomes, as noted throughout this statement, conclusions are limited by small study sizes, confounding, and variable methodology.

Post–Intensive Care Syndrome

ICU SCD likely affects the three domains of post–intensive care syndrome: cognition, mental health, and physical function. There is considerable evidence linking poor sleep quality with cognitive impairment in a variety of patient populations (163–166). Although sleep disturbances improved over time, more than half of ICU survivors (61%) reported persistently poor sleep at 6-month follow-up (167). To date, few studies have rigorously evaluated the prevalence of sleep disruption after critical illness and its potential association with cognitive impairment. For example, a systematic review reported on 22 studies examining sleep after hospital discharge in survivors of critical illness; however, none of these studies reported on cognitive outcomes (167). A more recent study showed that sleep fragmentation is associated with worse cognitive performance shortly after ICU discharge (109), suggesting that sleep remains important to address in the ICU, on hospital wards, and perhaps later in post-ICU recovery.

Anxiety, depression, and post-traumatic stress disorder are also common among ICU survivors (168) and are known to be associated with poor sleep quality (169, 170). Numerous studies have demonstrated an association between depressive symptoms and increased degrees of fatigue, stress, and anxiety in healthy participants subjected to sleep restriction (171, 172). The underlying mechanisms among sleep deficiency, circadian disruption, and mood disturbances are not well understood (173). Further research is needed to understand the contribution of poor post-ICU sleep to the development of anxiety, depression, and post-traumatic stress disorder.

Persistent sleep loss after ICU admission may also affect physical recovery. Sleep loss leads to significant reductions in energy, activity levels, and muscle strength and function (174, 175), which may affect physical recovery from critical illness. Emerging evidence demonstrates that early and intensive physical rehabilitation in the ICU improves physical function, decreases ICU delirium, and shortens ICU length of stay (176, 177). Initiatives to improve ICU sleep quality might enhance mobilization efforts and thus positively affect functional recovery (178).

To extend our understanding of ICU SCD along the entire trajectory of acute critical illness and recovery, Workshop members noted that integration of sleep and circadian outcomes in long-term follow-up studies is needed. As with other aspects of ICU SCD investigation, the establishment of core measures to serve as common building blocks for studies and the development of a collaborative network among investigators in ICU SCD and investigators in related fields such as post–intensive care syndrome is a high priority.

Subtopic 4: Treatment of ICU SCD

Given the multifaceted nature of ICU SCD and the diversity of hypothesized and identified risk factors, interventions to promote sleep or circadian function tend to be complex and include multiple components (Table 3). This can lead to challenges for implementation and sustainability. Furthermore, issues regarding which ICU SCD domains are most closely linked to ICU outcomes and therefore the best targets for intervention when interventions should occur, and how to measure hypothesized changes in sleep and circadian processes have limited intervention testing to date. In this section, we discuss gaps and next steps in the development of nonpharmacologic and pharmacologic interventions for ICU SCD.

Nonpharmacologic Interventions

As noted above, the ability to initiate or maintain sleep is hampered by multiple patient factors, notably anxiety, pain, and preexisting sleep disorders (67). These entities have been key targets for nonpharmacologic interventions that promote sleep by eliminating these patient sources of sleep disruption. Diverse relaxation techniques aimed at reducing stress and thus promoting sleep have been associated with improved subjective sleep quality and, in some studies, an increase in total sleep time (179–181). A systemic review of 11 music therapy studies demonstrated consistent associations between music therapy and reduced anxiety or stress in critically ill patients (182). Data on music's direct impact on sleep are more limited (183, 184). Finally, incorporation of patient sleep preferences may also improve patient sleep, though robust evidence is lacking. A recent pilot project on a general medical ward provided patients with help arranging their rooms comfortably for sleep (e.g., adjustment of temperature, lights, television, blinds) and offering sleep-promoting items from a "comfy cart" (e.g., blankets, tea, snacks); the pilot was associated with subjective sleep improvements (185).

Discussion during the Workshop acknowledged a lack of information regarding a patient's sleep history and preferences. It seems straightforward, barring contraindications, to continue preexisting outpatient treatments for sleep disorders. Personalization of sleep promotion interventions is novel and potentially beneficial but adds complexity to already encumbered protocols. Workshop members agreed, on the basis of anecdotal clinical experience, that asking patients about sleep and showing empathy regarding inadequate sleep is helpful. Doing so may also raise team member awareness of ICU SCD.

ICU Environment

Control of the ICU environment has historically been a major focus when attempting to reduce sleep disruption; more recently, circadian principles have also been applied. Numerous studies have explored interventions to control the environment, cluster bedside care delivery patterns, or combine elements of both (186). In fact, multicomponent sleep promotion bundles are guideline recommended for ICU patients (46, 187). Environmental control interventions reduce disturbances including noise, light, and care interruptions (78, 188–191); however, not all studies have been successful (192, 193), and when reduced, sound levels continue to exceed recommendations (78, 188). Improvements in sleep outcomes have been more difficult to demonstrate. For example, multicomponent protocols that emphasized environmental control demonstrated improvements in delirium but did not show changes in sleep (156, 194). Although not universally tolerated, earplugs and eye masks that block the ICU environment may be a simple, low-cost intervention for ICU SCD.

Table 3. Sleep Promotion Intervention Components

Domain	Strategies	Special Considerations
Zeitgeber optimization	• Bright daytime light • Dim or no light at night • Daytime time-restricted feeding • Mobility	• Light interventions must consider spectra, duration, timing, and light exposure history that reach the angle of gaze. Note that most patients are delayed by Day 1 or 2 of ICU admission, and therefore light exposure should start later than preillness wake times. Providers should mitigate light from screens in the room (e.g., televisions, mobile computers). • Time-restricted feeding should be structured to deliver food during the day and provide a fast during the night. • Providers should minimize daytime sedation to optimize daytime mobility and wakefulness.
Patient comfort	• Pain control • Anxiolysis • Toileting before sleep • Treatment of nausea	• Follow PADIS guideline to optimize nonpharmacologic and pharmacologic analgesic strategies. • Balance pain and anxiety with the need to minimize analgesics and anxiolytics known to disrupt sleep (e.g., narcotics and benzodiazepines).
Personalization	• Treat preexisting sleep disorders • Accommodation of sleep timing preferences • Adjustment of room (e.g., temperature, lights, shades) and bed (e.g., blankets, pillows) per patient preferences	• If patient not able to convey sleep preferences, consider asking surrogate.
Environmental control	• Mitigate noise from both inside and outside room • Offer eye masks • Offer earplugs	• Investigate sources of noise, which can be diverse and highly unique to each unit or room; talking and equipment alarms are common sources of noise, but many other sound sources exist. • Discourage nighttime visitors outside of special circumstances (e.g., end of life).
Clustered care	• Define dedicated overnight sleep period and reschedule nonurgent care, including medications, phlebotomy, radiology, bathing, skin or wound care, room maintenance	• Involve stakeholders for all changed work flows. • Restaffing may be needed to increase tasks during nonsleep times. • Dedicated sleep period may not be feasible on the basis of patient acuity, but care can be reduced to urgent tasks. • Reassure patients that while they are being allowed to rest, remote monitoring (e.g., telemetry) is ongoing.
Mechanical ventilation	• Optimize ventilator synchrony • Avoid ventilator underassistance and overassistance	• It is unclear if the mode of mechanical ventilation vs. the achievement of physiologic principles (e.g., synchrony, respiratory muscle rest, avoidance of hyperventilation, relief of dyspnea) is most important in preventing ventilator-related sleep disruption.
Medication use	• Minimize analgesics and anxiolytics known to disrupt sleep (e.g., narcotics and benzodiazepines) • Avoid polypharmacy • Consider withdrawal effects from abrupt discontinuation of home medications on sleep	• Multidisciplinary review of medications daily with critical care pharmacist; reduce dose or discontinue when possible.
Medication timing	• Revise medication timing to avoid administration during protected sleep periods	• Leverage electronic medical record defaults to preferentially schedule medication administration in the daytime. • Strategize continuous infusion bag volumes, concentrations, and start times such that bag and tubing changes do not occur during protected sleep periods.

Definition of abbreviation: PADIS = pain, agitation and sedation, delirium, immobility, and sleep disruption.

Meta-analyses suggest that the use of earplugs and eye masks is associated with increased total sleep time as well as lower incidence of delirium in ICU patients (195, 196).

At several points in the Workshop, participants highlighted the importance of using established implementation frameworks (197–199) when designing and testing interventions to promote sleep and circadian rhythms in the ICU. From a research perspective, such approaches are necessary to support the fidelity of the interventions being evaluated. From a clinical perspective, these frameworks are vital for adapting, scaling, and sustaining such efforts within complex, dynamic ICU settings (200). Applying such principles to the design of ICU-based sleep and circadian promotion would involve engaging relevant departments (e.g., nursing, respiratory therapy, physical therapy, pharmacy, laboratory medicine, diagnostic imaging, information services, facilities) to identify environmental, nonpharmacologic, and pharmacologic interventions and to iteratively adopt, evaluate, and redesign these interventions to meet the unique, changing needs of involved ICUs.

Circadian Cues as Treatment

More recently, some ICU SCD interventions have focused on reestablishing normal diurnal light variation. Effective circadian entrainment depends on exposure to light that has sufficient intensity and duration and has the correct spectral characteristics (i.e., mimicking natural sunlight) (201, 202). Although sample sizes are small, daytime light interventions have demonstrated benefits (203), including increased subjective patient satisfaction (204), improved early postoperative mobility (205), reduced perioperative delirium (205–207), and normalization of circadian phase as determined by urine 6-sulfatoxymelatonin acrophase (208). Other daytime light studies have failed to show a benefit. However, high lighting levels in the control group (209) and inappropriate timing, duration, and spectral characteristics of the light intervention (210) may have limited findings in these studies.

There are limited investigations of nonphotic circadian cues such as exercise and modifications of feeding schedules. The timing of nutrition is an influential circadian time cue, particularly for peripheral clocks in the gut, liver, and pancreas. Misalignment of peripheral clocks (i.e., internal misalignment) is associated with circadian disruption, poor sleep, and poor glucose tolerance (81, 211, 212). Thus, feeding during the day in a time-restricted manner may be more optimal than a continuous feeding schedule. Recent studies have shown that time-restricted daytime feeding is feasible (213) and will improve metabolic parameters (214). Further studies investigating the impact of time-restricted feeding on circadian phase alignment and additional clinical outcomes are ongoing (NCT 04437264, NCT 04870554).

Similarly, critical illness–related immobility interrupts normal entrainment and may be an important target for ICU SCD interventions. However, in the setting of a multicomponent sleep promotion intervention, patient engagement in physical therapy was not associated with any change in subjective sleep quality (215). Further study of early mobility in this population and related effects on sleep and circadian outcomes may provide evidence for novel, mobility-related methods to promote sleep in the ICU.

Workshop discussion focused on means of improving the implementation of zeitgeber-based interventions to improve circadian alignment in the ICU. Although investigators are familiar with the two-process model of homeostatic and circadian drives, specialized understanding of entrainment and leveraging of circadian cues is not widespread. Photic zeitgebers are the most potent stimuli for entraining the central circadian clock, while a variety of nonphotic zeitgebers are known to entrain peripheral clocks. Improving circadian alignment may significantly affect important sleep domains such as timing, duration, architecture, and continuity. Translating fundamental circadian knowledge to bedside clinical care poses logistical challenges. The many abnormal circadian signals present in the ICU environment must be carefully tracked (e.g., light, feeding, sleep, and immobility). Furthermore, the timing of interventions is critically important, as incorrectly timed environmental cues for circadian rhythms (i.e., zeitgebers) can fail to produce the desired change in alignment or, more concerningly, may cause a change in the directionality that was not intended. Although outside the scope of this document, we also note that lighting adjustments such as low overnight light affect the alertness and sleepiness of overnight workers in the hospital environment, and considerations such as appropriate spectra bright lighting in work and break rooms are needed. Further research is needed to define optimal circadian intervention protocols in the ICU, including appropriate timing, duration, and intensity of zeitgeber exposures. We note as well that formalization of light recommendations for circadian entrainment is just emerging (201, 202).

Pharmacologic Treatment

To date, there are no ICU guideline recommendations supporting the use of a pharmacologic treatment to improve ICU SCD (46). Nevertheless, medications are frequently prescribed for sleep in the ICU (216). Melatonin is the most commonly prescribed medication, followed by ramelteon and quetiapine (216). Among studies of sleep bundles in the ICU, only two allowed use of pharmacologic sleep aids to promote sleep (156, 217); despite inclusion in the protocol, sleep aid use was relatively uncommon in study subjects (16% in Kamdar and colleagues [156], 7% in Andrews and colleagues [217]), and therefore the impact of pharmacologic sleep aids on sleep was not established by these studies.

More recent studies involving sleep promotion through pharmacotherapy have primarily involved melatonin agonists, α-2-agonists, and orexin antagonists. Two recent large RCTs of melatonin in ICU patients showed no association between melatonin use and improvement in delirium and conflicting results regarding sleep outcomes as measured by the RCSQ and nursing observation (218, 219). The melatonin agonist ramelteon has been reported to improve both sleep-related (nursing observation) and delirium (220) endpoints. Results are mixed in studies evaluating nocturnal dexmedetomidine for promoting sleep (160–162), though this may be related to sleep measurement methodology (e.g., no change in patient-reported sleep outcomes [160] vs. improvement in PSG measures of sleep [161, 162]). Finally, a retrospective cohort study demonstrated the administration of the orexin antagonist suvorexant to be associated with a lower incidence of delirium but no difference in any sleep-related endpoints compared with no suvorexant, after adjustment of confounders (221).

Workshop members noted the high demand for sleep medications from caregivers, surrogates, and patients together with the common misperception that

sedation is equivalent to sleep. Bedside clinicians express a strong desire for a safe and effective sleep aid, particularly in patients with concomitant delirium. However, the study of pharmacologic options to promote nighttime sleepiness is limited by small trial sizes, the failure to enroll mechanically ventilated adults with a high severity of illness, and an overreliance on delirium reduction and/or patient-reported sleep quality to define efficacy. In addition, RCTs to date have involved prescribing of pharmacologic agents upon ICU admission or timed in relation to specific clinical events (e.g., surgical procedure) (222–224). However, in practice, clinicians are frequently seeking options to promote sleep after patients report sleep disruption or have already presented with delirium. This discrepancy raises important questions regarding the timing and patient selection for pharmaceutical interventions. Interestingly, pharmacologic therapies to promote daytime wakefulness in the ICU have not been rigorously studied, and this may be a novel and effective approach to sleep promotion in the ICU. Finally, we should continue to consider the sleep and circadian implications of medications routinely used in the ICU (e.g., corticosteroids, benzodiazepines, narcotics, antipsychotics).

Conclusions

ICU SCD is a complex and compelling potential target for improving critical illness outcomes. Herein, we have reported the findings, discussions, and conclusions of the ATS Workshop on causes, consequences, and treatments of SCD in the ICU, which had the following three objectives: *1*) delineate a prioritized list of ICU SCD subtopics; *2*) identify, discuss, and critically evaluate existing knowledge gaps within these subtopics; and *3*) establish a prioritized ICU SCD research agenda. We note that challenges in defining and measuring ICU SCD have led to a set of related limitations hampering the field's progress. Specifically, study size, brevity in monitoring periods, and heterogeneity in study exposures and outcomes have limited evidence to date. However, emerging technologies that have improved longitudinal wearability and the potential for automation of sleep measures hold promise as a means of moving the field forward. Investigators are eager to increase collaborative infrastructure, foster multisite study design, test individual domains of ICU SCD for associations with ICU outcomes, and clarify the natural history of ICU SCD. Opportunities such as this ATS Workshop have and will continue to support a rich exchange of information and foster collaboration among investigators. ■

This official document was prepared by an *ad hoc* subcommittee of the Assembly on Sleep and Respiratory Neurobiology.

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