



# Optimizing Sleep and Circadian Health in the NeuroICU

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Published online: 15 July 2022

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This article is part of the Topical Collection on *Critical Care Neurology*

**Keywords** Sleep · Circadian · Intensive care · Neurointensive

## Abstract

**Purpose of Review** This article introduces fundamental concepts in circadian biology and the neuroscience of sleep, reviews recent studies characterizing circadian rhythm and sleep disruption among critically ill patients and potentially links to functional outcomes, and draws upon existing literature to propose therapeutic strategies to mitigate those harms. Particular attention is given to patients with critical neurologic conditions and the unique environment of the neuro-intensive care unit.

**Recent Findings** Circadian rhythm disruption is widespread among critically ill patients and sleep time is reduced and abnormally fragmented. There is a strong association between the degree of arousal suppression observed at the bedside and the extent of circadian disruption at the system (e.g., melatonin concentration rhythms) and cellular levels (e.g., core clock gene transcription rhythms). There is a paucity of electrographically normal sleep, and rest-activity rhythms are severely disturbed. Common care interventions such as

neurochecks introduce unique disruptions in neurologic patients. There are no pharmacologic interventions proven to normalize circadian rhythms or restore physiologically normal sleep. Instead, interventions are focused on reducing pharmacologic and environmental factors that perpetuate disruption.

*Summary* The intensive care environment introduces numerous potent disruptors to sleep and circadian rhythms. Direct neurologic injury and neuro-monitoring practices likely compound those factors to further derange circadian and sleep functions. In the absence of direct interventions to induce normalized rhythms and sleep, current therapy depends upon normalizing external stimuli.

## Circadian Rhythms and Sleep – a Brief Introduction

### Biological Rhythms and Circadian Physiology

Most organisms exhibit recurring physiologic processes that constitute biological rhythms. These rhythms occur in an extensive range of frequencies from infradian processes like annual hibernation and menstrual (i.e., monthly) ovulation, circadian or diurnal (i.e., daily) rhythms like sleep and wake, to ultradian (i.e., cyclical processes happening many times per day). Daily shifts between daytime and nighttime create marked changes in the environment. Most multicellular organisms have evolved physiologic processes to adapt to those predictable fluctuations. Circadian rhythms—those organized around the cycle of one day—are among the most complex and prominent. Many well-known biological rhythms, from sleep and wake cycles to blood pressure dipping and morning cortisol surges, result from entrainment to the circadian rhythm.

The suprachiasmatic nucleus (SCN) is often described as a central pacemaker for the circadian rhythm, but because all cells contain molecular clocks, body tissues are not “pacemaker-dependent” over short time intervals. The principal role of the SCN is to integrate relevant internal and external influences on circadian rhythm timing and to function as a central synchronizer. Individual cells maintain an internal clock comprised of a transcriptional feedback loop involving at least ten gene products [1]. Each cell therefore needs to be maintained in alignment with respect to timing (phase) in order to function in concert. This is accomplished by the SCN communicating signals to the peripheral circadian clocks in brain and other body tissues through hormonal rhythms and autonomic signals [2, 3]. The process of influencing the timing of the circadian rhythms is called entrainment, and factors that entrain rhythms are called *zeitgebers* (“time-givers”).

It is the rhythmic activity of the transcriptome that directly effectuates much of the physiology of the circadian rhythm. Nearly half of our protein-encoding genes demonstrate circadian transcription rhythms, mostly in an organ-specific pattern [4]. Brain arousal, sympathetic tone, cardiovascular function, coagulation, immune system activity, glycemic control and metabolism all exhibit circadian variability [5].

The most prominent natural phenomenon in the environment to direct daily rhythms is the cycling from light to dark. Light exposure on the retina is the most potent environmental zeitgeber in humans. Other known zeitgebers include enteral nutrient intake, physical exertion/exercise and activity rhythms, all of which reinforce rhythms in groups of social animals like human beings. Modern living conditions have overcome much of our need to be constrained by the natural environment, but these conditions have also introduced environmental and biochemical exposures that now confound the natural entrainment of the circadian rhythm. Artificial light at night, irregular rest, eating and activity patterns and substances that interfere with circadian signaling—from caffeine to medications like beta blockers—all introduce destabilizing signals to the body's clocks.

## Sleep and Sleep Impairment

The daily rhythm of sleep and active wakefulness is one of the many phenomena entrained by the circadian rhythm. In turn, brain functions such as memory consolidation and attention are secondarily influenced by sleep [6]. The initiation of sleep is principally regulated by two processes: the circadian rhythm and a sleep homeostat that increases sleep pressure as the duration of wake time increases. It is crucial to recognize that sleep is not simply the absence of wakefulness, but rather, a set of complex central nervous system processes that can be recognized in healthy subjects by physical manifestations (e.g., rapid eye movements) or electrographic biomarkers (e.g., sleep spindles, slow waves). Unconsciousness due to medications or severe systemic derangements is predominantly mediated by neuronal dysfunction or gamma-aminobutyric acid (GABA) receptor agonists, which do not stimulate the neural mechanisms for sleep induction. Therefore, the normal physiological processes that occur during healthy sleep are likely also impaired during this abnormal absence of wakefulness.

In otherwise healthy subjects, sleep timing and duration are more straightforward to measure than molecular rhythms. Much of the pathology that occurs from disrupting normal rhythms has been attributed to sleep disruption even if the pathophysiologic pathway mediating the abnormalities may not directly involve sleep. For example, glymphatic flow that clears metabolic waste from the brain has been described as a function linked to sleep; more recently, however, carefully structured experiments indicate that glymphatic flow is tightly regulated by the circadian rhythm but independent of arousal state (sleep/wake status) [7]. Sleep itself exerts little entrainment back on the circadian rhythm, but the behaviors that coincide with wakefulness (lights on, physical activity, eating) do, so sleep disruption can cause rhythm disruption. Consequently, it is reasonable to interpret literature identifying associations between sleep disruption and morbidity as likely mediated by circadian rhythm disruption. Optimizing sleep, therefore, should be understood broadly to mean optimizing sleep as well as all exposures that influence the circadian rhythm in order to maximize healthy function of the brain and body.

## Circadian Rhythm and Sleep Disruption during Critical Illness

The consequences of sleep deprivation and circadian rhythm disruption have been extensively studied and are understood to be detrimental to health. Circadian and sleep health have been explored extensively in patients with chronic sleep disorders (e.g., obstructive sleep apnea) or under conditions of persistent rhythm disruptions (e.g., irregular shift work schedules). More recent research has evaluated sleep and rhythms in patients with critical illness and found that the circadian rhythm is rapidly disrupted with onset of critical illness [8•].

Polysomnography, which incorporates scalp electroencephalography with measurements of breathing and muscle tone, has been a preferred method for measuring sleep. Encephalopathy in the context of acute illness alters brain function in a way that makes usual sleep patterns unrecognizable, so alternative methods are often needed to assess sleep in acutely ill subjects, especially those with critical illness [9–11]. Activity quantification is the standard method for evaluating sleep and wake in animal models of circadian research [12]. Measurement of rest and activity by wrist actigraphy, often used as an alternative to polysomnography as a biomarker for sleep and wake, can be analyzed for rhythmicity characteristics [13]. Moreover, actigraphy can be analyzed with methods that are minimally confounded by bedrest, intravenous catheters and other physical constraints of hospitalization and is feasible and interpretable in critically ill patients [14••]. Analysis of wrist actigraphy in patients with sepsis and intracerebral hemorrhage has found that critically ill humans rapidly enter a state of behavioral quiescence with rest-activity rhythms that are suppressed or abolished in proportion to the degree of encephalopathy that is measurable at the bedside [14]. This phenomenon has previously been described in animal models with experimental injury or chemical physiologic stress, and there is evidence that the quiescence state is mediated by a dedicated neural pathway as part of a protective response [15, 16].

Melatonin, an endogenous hormone secreted primarily by the pineal gland after conversion from precursor serotonin, is the most commonly used and robust marker of circadian phase in humans and an important signal of circadian phase to peripheral tissues [17]. Melatonin secretion rapidly becomes abnormal in patients with neurologic or multisystem critical illnesses. As the degree of encephalopathy worsens into coma, melatonin secretion dampens [18]. Another major factor influencing melatonin secretion patterns is exposure to catecholamine vasopressors, which are commonly used in multiorgan failure cases and can induce severely supraphysiologic melatonin levels [18]. Melatonin is released by  $\beta$ -adrenergic stimulation on pineal cell membranes, and is thus sensitive to abnormal release from medications such as norepinephrine, or suppression from exposure to beta-adrenergic receptor antagonists (beta blockers) [19].

Data have emerged indicating that peripheral clocks — the cellular system of rhythmic transcriptome regulation — rapidly become disorganized during critical illness. Peripheral blood samples have shown that RNA transcripts of core clock gene products (most of which exhibit overt rhythmicity in healthy

individuals) show diminished rhythmicity in critically ill patients [20••, 21, 22]. Those core clock genes regulate transcription of many other genes, and methods have been developed to characterize rhythmicity and phase of the broader transcriptome [23]. Applying those methods to critically ill patients found abnormally diminished organization of the whole transcriptome compared to healthy subjects [14].

Finally, there are characteristics of the neurologic critical illness that merit particular attention. Projections between the retina, SCN, hypothalamus, pineal gland and autonomic pathways relay afferent information about zeitgeber exposures to the central clock and disseminate timing signals to peripheral clocks; direct injury to any of those neurological structures can produce sleep and circadian dysregulation. The rapid onset of transcriptomic dysrhythmia in peripheral clocks suggests that abnormal autonomic signals and inflammatory mediators quickly disrupt rhythms [20]. Second, monitoring strategies and specific therapies pose unique risks for disruption. For example, the potential role of neurochecks as mediators of harm through forced awakenings has received particular attention. Neurochecks are brief, standardized neurologic exams that are used ubiquitously in neurologic ICUs (neuroICUs) to monitor the evolution of symptoms and assess response to therapies in patients with brain and spinal cord injury [24]. The implementation of neurochecks in ICUs is variable, but prolonged exposure to many days of hourly awakening is fairly common [25•].

## Effect of Circadian Rhythm and Sleep Disruption on ICU Outcomes

Confirming causality in critically ill patients is challenging in the context of myriad physiologic perturbations and medication exposures. There are no large randomized trials that specifically target a sleep or circadian therapy and demonstrate clear improvement in mortality or long-term functional outcomes. In the absence of high-level evidence, our understanding about the relationship between sleep and circadian pathology and post-intensive care outcomes is based on two sources: mechanistic research in other populations, and uncontrolled, observational studies identifying associations between sleep/circadian disruption and outcomes.

An episode of critical illness markedly worsens the trajectory of older adults' functional status, causing new disability mediated by acquired symptoms in mood, sleep, cognition impairment, and physical function [26–29]. Post-Intensive Care Syndrome (PICS) describes a set of comorbidities affecting cognition, mental health and physical function that develop in the majority of patients after severe illnesses, often persisting as chronic disability [27]. Depending on the method of measurement and diagnostic threshold used, physical disability, cognitive impairment, depression, anxiety and sleep disturbance each occur in around 30–70% of ICU survivors, with substantial comorbid overlap [27, 30–33••]. These symptoms, in turn, are associated with worse health-related quality of life [34, 35]. The symptoms of PICS overlap

substantially with the neurocognitive effects of sleep and circadian disorders, so interventions to minimize the extent of sleep and circadian disruption that develops during acute illness and to maximize the re-establishment of healthy sleep and rhythms are plausible strategies to prevent or mitigate PICS [36]. Prolonged sleep deprivation is an established source of physical and cognitive impairment—even in healthy study volunteers—which raises concern for round-the-clock care interventions that occur in the ICU.

Given the importance of peripheral clocks in homeostasis and normal function of other organ systems, rhythm disruptions may influence non-neurologic outcomes as well. For example, many immune functions are regulated by circadian rhythms. Circadian disruption may contribute to the development of acquired immunodeficiency that is observed to develop after several days of critical illness and leaves patients vulnerable to nosocomial infectious complications [37]. Drawing upon studies in other populations, circadian disruption likely impairs the function of many other systems, including endocrine-regulated processes, glycemic control and other metabolic pathways, autonomic and cardiac stability, lung function, renal clearance and liver function, the basis for which has been reviewed in details elsewhere [38]. In the remainder of this article, we will discuss the rationale for specific pharmacologic and environmental interventions that may attenuate sleep and circadian disruption in the ICU, with special attention to the neurologic population.

## Pharmacological Strategies

Many medications used during intensive care management can directly or indirectly impact the central nervous system, as well as sleep (see Table 1). The first point to make regarding pharmacological strategies for optimizing sleep is that sedation (the absence of wakefulness) and sleep are not equivalent and likely involve different areas and networks within the brain [39]. Although there are many sedating medications that induce a clinical state resembling sleep, the relationship between sedation and sleep is complex and not fully understood, and patient sedation likely does not achieve restorative sleep.

In the neuroICU, we commonly use infusions for patient sedation, anxiolysis and analgesia, particularly in intubated patients. The most common of these include opioids, midazolam, propofol, dexmedetomidine, and ketamine. There are limited data describing the impact of opioids on sleep architecture, but in general, restorative sleep and the total sleep time are decreased [40]. Benzodiazepines are also known to reduce restorative sleep and REM, as well as decrease total sleep time. Additionally, benzodiazepine and opioid use are known risk factors for development of delirium [41, 42]. Dexmedetomidine studies are inconsistent in their effect on restorative sleep and sleep efficiency, though sleep spindles have been reported [43]. Given its alpha-2 activity and endogenous activity in non-REM sleep pathways, dexmedetomidine has been studied extensively as an agent to promote sleep. Early evaluations of dexmedetomidine in critically ill patients demonstrated increase sleep efficiency and improvement in sleep architecture [44, 45].

**Table 1 Summary of pharmacological impact of common CNS medications on sleep architecture as measured by electroencephalography or polysomnography**

Medication class	REM	Restorative sleep	Sleep time, sleep efficiency, and sleep latency
Opioids	↑ REM latency	↓ N3 (suppression)	↓ TST
Benzodiazepines	↓ REM	↓ N3 and SWS	↓ TST ?↑ SE ↓ Sleep latency
Dexmedetomidine	No change in REM	Inconsistent effect on restorative sleep	Inconsistent effect on SE (some studies with improvement, some no change) No change in SE ↑ TST
Propofol	↓ REM	↑ SWS	
Ketamine	↓ REM	No change in N3	
Typical antipsychotics	↓ REM latency		
Atypical antipsychotics	Quetiapine: low-dose (25mg) ↑ REM, high-dose (100mg) ↓ REM	Olanzapine: ↑ SWS Trazodone: ↑ SWS	Quetiapine: ↑ TST, ↑ SE Olanzapine: ↑ TST, ↑ SE
Anti-epileptic medications	PHT: ↓ REM PHB: ↓ REM VPA: ↓ REM LEV: ↓ REM	PHT: ↑ or unchanged SWS VPA: increased light sleep relative to SWS LEV: ↓ SWS	PHT: ↓ SE, ↓ Sleep latency PHB: ↓ Sleep latency
Melatonin receptor agonists			Melatonin: ↓ Sleep latency Ramelteon: ↓ Sleep latency, ↑ TST, ↑ SE ↓ Sleep latency
Non-benzodiazepine hypnotics		No change	

CNS central nervous system, LEV levetiracetam, PHB phenobarbital, PHT phenytoin, REM rapid eye movement, SE sleep efficiency, SWS slow wave sleep, TST total sleep time, VPA valproic acid

Unfortunately, these effects on sleep quality were not borne out in additional double-blind, randomized trials, though delirium may be decreased in patients receiving protocolized dexmedetomidine when compared with placebo [46, 47]. Specifically in comparison with propofol, major clinical trials have not shown a difference in measured clinical outcomes such as mortality and delirium, though sleep was not assessed in either the SPICE III or Mends study [48, 49]. Dexmedetomidine—like propofol—can be limited by bradycardia and hypotension [49]. Propofol's impact on sleep has been studied extensively, but there is insufficient evidence to determine whether it improves sleep, and many studies show no differences in sleep efficiency or sleep fragmentation [40, 43, 50]. Lastly, ketamine may promote restorative slow wave sleep via the NMDA inhibitory pathway at higher doses, but also produces unconsciousness [51].

In terms of enteral pharmacologic agents, antipsychotic and antiepileptic medications both impact sleep. Typical antipsychotics such as haloperidol have been reported to decrease both REM latency and sleep fragmentation without noticeable suppression of REM or restorative sleep. Atypical antipsychotics increase total sleep time and sleep efficiency, and quetiapine may improve subjective sleep quality [40]. Epilepsy itself is known to alter sleep architecture, and anti-epileptic medications including phenytoin, phenobarbital, valproic acid, and levetiracetam all alter sleep architecture with most decreasing REM sleep without a reciprocal increase in slow wave restorative sleep [52].

We know that many medications used in the ICU negatively impact traditional sleep measures, but what remains unclear is whether there are pharmacological agents available to optimize sleep. Additional agents studied for their potential improvement in sleep are the melatonin receptor agonists, including melatonin and ramelteon. Melatonin reduces sleep latency, but when compared with placebo, there is a lack of effect on total sleep time, sleep efficiency, and sleep fragmentation [51, 53]. Melatonin is regulated in the USA as a dietary supplement rather than a prescription or over-the-counter drug, whereas other jurisdictions regulate melatonin as a prescription medication. As a consequence, melatonin formulation may contain doses that differ from the label or include a substantial quantity of serotonin [54]. A related MT1 and MT2 receptor agonist, ramelteon, is available at most institutions. Ramelteon also decreases sleep latency and may additionally improve sleep efficiency, total sleep time, and subjective sleep quality. When studied in critically ill patients *without* brain injury, ramelteon has been reported to decrease ICU duration, delirium incidence, and increase ventilator-free hours [55–57], though inconsistently across studies [58]. Importantly, ramelteon is a potent CYP1 and 2 inhibitor. Given that melatonin levels may be either abnormally suppressed or severely supraphysiologic in critically ill patients (depending on illness severity, environmental and medication exposures), a simplistic strategy of adding more melatonin at night is unlikely to be effective for all patients [18]. There may be a clearer role for melatonin to support circadian normalization during illness recovery.

Ultimately, there is lack of strong evidence for any pharmacological agent to promote sleep in the ICU. Yet, neuroactive medications are newly initiated in approximately 10% of critically ill patients admitted for greater than 24

h—most commonly melatonin agonists or antipsychotics—and continued for nearly three-quarters of nights that patients spend in the ICU [59]. This trend is concerning, especially because there is no pharmacological agent recommended by the PADAS guidelines to “promote sleep” [60, 61]. Our priority for pharmacological optimization may simply be eliminating polypharmacy and minimizing the use of sedative infusions and opioids.

## Environmental and Zeitgeber Strategies

Strategies discussed herein leverage known zeitgebers that cue a person’s internal body clock. These strategies attempt to optimize sleep by normalizing the circadian rhythm—for instance, by promoting appropriate stimulation/rest environments, improving eating and drinking patterns, clustering care and ultimately, minimizing arousals.

### Light/Dark and Quiet Time

Day-night light patterns are one of the most important circadian entrainment signals, and abnormal light exposure in the hospital is a major source of circadian disruption [62]. Light strongly suppresses melatonin secretion from the pineal gland (which peaks overnight in healthy individuals). Light levels in the hospital during the day are often too low to promote normal entrainment [63, 64]. In the ICU, light levels range from 30 to 165 lux during the day (compared with natural light, >4000 lux), but can also be as high as 1445 lux overnight, further contributing to circadian misalignment [63, 65, 66]. Prolonged intervals of eyelid closure during the day also reduces exposure to daytime light. Existing data suggest that inadequate daytime light is the principal abnormality driving day-night circadian dysregulation, and that efforts to minimize nighttime light without boosting daytime light may be insufficient to promote entrainment.

In addition to suboptimal day-night light levels, noise is also reported to be disruptive to sleep [62, 67]. In the ICU, noises are produced by people (e.g., talking), machines (e.g., alarms), and normal movements (e.g., doors opening and closing). The Environmental Protection Agency recommends hospital noise levels average less than 45 dB during the day and less than 35 dB at night; recorded levels in the ICU exceed these recommendations [68–71]. Unfortunately, there is a large degree of heterogeneity in studies of noise in the ICU, and it is currently impossible to quantify the extent to which noise contributes to sleep disruption and arousals among ICU patients [68]. Perhaps more important than absolute noise levels are changes in noise levels from baseline sound levels [68, 72, 73]. In this way, the sudden pump alarm may be more disturbing to a patient than the constant talking outside the room.

## Feeding

Healthcare professionals should supply adequate nutrition to every patient unless prolongation of life is not in the patient's goals of care [74, 75]. There are several methods for supplying enteral nutrition. In critically ill patients, however, the most common modalities used are continuous and intermittent/bolus feedings. Continuous feeding uses a pump to administer feeding nearly continuously throughout the 24-h period, whereas bolus and intermittent feeding generally supply a small volume of feeds multiple times throughout the day, e.g., every 4–6 h.

Continuous feeding may be well tolerated in brain injured patients when focusing on residual volumes and glucose variability, but poorly tolerated from a circadian standpoint [76]. Continuous feeding violates the body's biological rhythm. When food availability is disconnected from the master clock (the SCN), metabolic processes regulated by nutritional inputs are also dysregulated and discordant [77, 78]. Therefore, intensivists should consider bolus or intermittent feeding, which more closely resembles "meal-time" feeds. Even so, bolus feeds are alone not the solution to circadian realignment; these feeds should also be given at appropriate times of the day (daytime-restricted feeds) while still meeting caloric requirements [79]. In addition to its potential role in re-aligning the circadian rhythm, feeding at the physiologically correct time also promotes improved glycemic control and reduced inflammation, though there is a potential risk for aspiration debated in the literature [78, 80]. There is current controversy about the best methods for determining metabolic demands in the neuroICU, and further research is required to understand better nutritional initiation, advancement and metabolic monitoring in the neuroICU [81].

## Clustered Care

Although vigilant monitoring of our critically ill patients is paramount, excessive or frequent patient interruptions can be detrimental. Some of these interruptions include lab draws, medication administration, vital sign checks, nursing care such as bathing and wound care, and radiographs. Critically ill patients can experience up to 8 care-related interruptions each hour during usual sleep time—with up to 50 throughout the nightshift hours—and one in five of these interactions results in an arousal or awakening when assessed by polysomnography [82–84]. Changes in ICU workflow to cluster care can be difficult to accomplish [85]. Recently, though, clustered care in the ICU has become more common-place and necessary since the COVID-19 pandemic began, and this bundling of care interventions may improve sleep and reduce delirium, with studies actively underway [43, 86–88].

## Neurologic Assessments

Guidelines for care of patients with acute brain injury recommend “frequent” neuromonitoring, though stop short of defining a frequency or duration of neurochecks [89–91]. This has resulted in variation in neuromonitoring practices across the country, with a general adoption of hourly (Q1) or every-other-hour (Q2) neurochecks as “frequent” monitoring [92]. The extent to which frequent neuroassessments contribute to circadian derangement and sleep impairment is uncertain.

Although the link between disruptions in the abnormal sleep seen in brain-injured patients and poor outcomes is much more tenuous than the clear link between secondary brain injury and poor outcomes, frequent neurochecks may have negative consequences, particularly when prolonged. In an evaluation of approximately 9500 hourly neurocheck orders in nearly 9000 patients with acute brain injury at a tertiary academic medical center, it was noted that a substantial proportion of patients are maintained on continuous hourly neurochecks for >3 days (20%) and >7 days (7%) [25]. A smaller but still non-trivial number of patients (3%) were maintained on hourly neurochecks continuously for >14 days. Additionally, one-quarter of hourly neurochecks were transitioned to no neurochecks at the time of discontinuation, suggesting that they were likely unnecessary for the full duration that they were ordered.

Taken together, the implication is that there is room for improvement in our serial examinations, and we must be more mindful about the frequency we choose and the duration for which they are ordered. Generally, we have an appreciation for the disease- and severity-specific risks of neurodeterioration, and we must focus on how we can monitor the complexity of the brain perhaps more intelligently [24, 93, 94]. The ideal monitoring system is likely one that balances risk and need in a personalized and individualized manner rather than strict adherence to protocols, tapering neurocheck frequency as the risk of acute deterioration wanes.

## Conclusion

Circadian rhythms organize a vast array of biological processes that must remain synchronized to function effectively. Nearly all tissues are regulated by a cellular-level molecular clock and demonstrate unique patterns of gene transcription rhythms that effect biological rhythms. Wake and sleep describe brain states comprising the sets of complex processes of the central nervous system’s circadian rhythm expression, and disruption of the sleep versus wake pattern both causes and reflects brain dysfunction. Abnormal exposures in the ICU environment including medications, feeding strategies, light, noise and arousals disrupt the central circadian rhythm and the hormonal and autonomic signals that entrain the peripheral clocks into synchrony. Strategies to reduce harm from sleep and circadian disruption begin with reducing mistimed stimuli with simple steps, such as: minimizing nighttime light and

arousals and increasing daytime light, restricting enteral nutrition to daytime and preferably blousing feeds to simulate meals, and minimizing medications that interfere with rhythms. Sedating medications do not activate physiologically normal sleep and are unlikely to be restorative. It is more promising to reduce disruptive factors and promote circadian therapies aimed at entraining a normal rhythm during illness recovery.

## Declarations

### Conflict of Interest

Jamie Nicole LaBuzetta declares that she has no conflict of interest. Atul Malhotra declares that he has no conflict of interest. Phyllis C. Zee declares that she has no conflict of interest. Matthew B. Maas declares that he has no conflict of interest.

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