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Sleep Deprivation in Critical Illness: Its Role in Physical and Psychological Recovery

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Abstract

Critically ill patients frequently experience poor sleep, characterized by frequent disruptions, loss of circadian rhythms, and a paucity of time spent in restorative sleep stages. Factors that are associated with sleep disruption in the intensive care unit (ICU) include patient-ventilator dysynchrony, medications, patient care interactions, and environmental noise and light. As the field of critical care increasingly focuses on patients' physical and psychological outcomes following critical illness, understanding the potential contribution of ICU-related sleep disruption on patient recovery is an important area of investigation. This review article summarizes the literature regarding sleep architecture and measurement in the critically ill, causes of ICU sleep fragmentation, and potential implications of ICU-related sleep disruption on patients' recovery from critical illness. With this background information, strategies to optimize sleep in the ICU are also discussed.

Keywords

sleep; sleep deprivation; intensive care unit; mental health; outcomes

Introduction

Poor sleep is a frequent occurrence in the intensive care unit (ICU) setting. Despite decades of research describing sleep loss in ICU patients, most ICUs have made few changes to improve patient sleep. This inertia to change clinical practice may be largely due to a lack of research on the negative effects of sleep loss on critical care outcomes, and minimal research regarding the efficacy of sleep-promoting interventions in the ICU. However, such research is beginning to emerge and have growing importance in the ICU. This review provides a broad overview of normal sleep and of sleep in critically ill patients, factors impacting sleep in the ICU, and the consequences of ICU-related sleep disruption on physical and psychological recovery from critical illness.

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Normal Sleep

Sleep is a complex physiologic and behavioral process essential for rest, repair, well-being, and survival.[1,2] Sleep is defined as a periodic, reversible state of cognitive and sensory disengagement from the external environment.[3] While sleep quality and characteristics vary markedly in critically ill patients, an understanding of normal sleep is necessary to fully appreciate sleep abnormalities in the ICU.

Sleep Architecture

Sleep is divided into nonrapid eye movement (NREM) and rapid eye movement (REM), each defined by unique physiologic, electroencephalographic (EEG), and behavioral properties (Figure 1). The normal human sleep period consists of four to six 90- to 100-minute periods during which NREM and REM alternate in a cyclical fashion.[3,4] Nonrapid eye movement sleep is divided into three stages—N1, N2 and N3—which account for 2% to 5%, 45% to 55%, and 15% to 20% of the total sleep period, respectively. Stage N1, or “light sleep”, marks the entry into sleep from the waking state and is characterized by low-voltage theta waves (4–8 Hz) on EEG. Compared to N1, stage N2 is characterized by slower, higher amplitude waves with K-complexes and sleep-spindles on EEG. During stage N3, there is a particularly high threshold for arousal with high amplitude delta waves (0.5–2 Hz) on EEG. For this reason, stage N3 is referred to as “slow wave” or “deep” sleep (and formerly known as stages 3 and 4 under the Rechtschaffen and Kales system).[4] Stage N3 is significant for its role in restorative processes, such as memory consolidation.[5]

Rapid eye movement sleep occupies 20% to 25% of the total sleep period and is composed of tonic REM, which occurs throughout the REM period, and intermittent bursts of phasic REM. Tonic REM is characterized by skeletal muscle atonia and low voltage, high amplitude, mixed frequency beta and “saw-tooth” theta waves on EEG. Phasic REM is characterized by rapid eye movements, along with autonomic variability and somatic muscle twitches. The brain is highly active during REM sleep and is associated with dreaming and perceptual learning.[3,5]

Circadian Rhythms

The sleep-wake cycle is regulated by two finely balanced, opposing processes. The drive for sleep, which includes sleepiness, sleep onset, and sleep promotion is modulated by the sleep homeostat (process S). Process S is primarily driven by the neurotransmitter adenosine, the end-product of ATP (energy) metabolism which increases as a function of wakefulness.[4] The transition from wake to sleep occurs at a certain homeostatic threshold. Diurnal secretion of melatonin by the pineal gland also plays a role in sleep promotion.

Wakefulness, on the other hand, is driven by the circadian pacemaker (process C). Located in the suprachiasmatic nucleus, process C is modulated by neural pathways that inhibit melatonin release via exposure to bright light. Several other clinically relevant neurotransmitters that promote wakefulness include orexin (also known as hypocretin), acetylcholine, serotonin, norepinephrine, dopamine, and histamine.

Physiology During Sleep

The body undergoes a constellation of physiologic changes during sleep that play an important role in growth and homeostasis. These alterations are particularly significant in patients with unstable hemodynamics, impaired defense mechanisms, and limited physiologic reserve; hence, these alterations may be particularly important in critically ill patients who may suffer severe consequences from abrupt physiologic fluctuations.

Thermoregulation—Body temperature and thermoregulation are regulated, in part, by sleep and circadian rhythms. In normal subjects, core body temperature peaks late in the day and declines before sleep onset. Temperature sensitivity decreases during NREM, and REM is characterized by poikilothermia (variation in body temperature based on surroundings) and total loss of compensatory responses, such as shivering and sweating. Body temperature reaches a nadir during the latter part of sleep, following a temperature rise preceding awakening.

Respiratory physiology—During sleep, voluntary control of respiration is lost and hypoxic and hypercapnic ventilatory drives are reduced.[6] Responsiveness to low oxygen and high carbon dioxide levels is lowest during REM compared to NREM sleep.[7–10]

Respiration varies markedly during each stage of sleep. The transition from wakefulness to N1 is marked by a decrease in minute ventilation due to variations in tidal volume and respiratory rate.[11] As NREM sleep progresses, hypoventilation and a 3 to 7 mm Hg increase in arterial PCO_2 levels occurs as a result of several factors, including relaxation of upper respiratory muscles, increased airway resistance, and diminished central respiratory drive.[12] Minute ventilation also decreases across N2 and N3 sleep. During REM sleep, both respiratory rate and tidal volume undergo wide variations, with increased variability during bursts of phasic REM.

Cardiovascular physiology—The cardiovascular system undergoes dramatic alterations during sleep. Dynamic fluctuations in blood flow and electrical activity occur and have been associated with life-threatening arrhythmias and ischemic events in patients with underlying heart disease.[13] Autonomic stability characterizes NREM sleep, where increased parasympathetic tone results in decreased blood pressure, heart rate, and systemic vascular resistance. During NREM, heart rate rises with increased venous return during inspiration, and falls with decreased venous return during expiration.[4]

Rapid eye movement sleep is characterized by autonomic variability. During tonic REM, bursts of vagal activity on the background of decreased sympathetic tone lead to bradyarrhythmias and sinus pauses. In contrast, increased sympathetic activity during phasic REM results in transient increases of up to 35% in heart rate and blood pressure.[14]

Gastrointestinal physiology—During sleep, esophageal motility is reduced and rectal tone is preserved, while gastrointestinal motility remains relatively unchanged. A decrease in swallowing and saliva production also occurs, and the tonic contraction of upper esophageal sphincter prevents aspiration. Gastric acid secretion follows a circadian rhythm, peaking during early sleep.

Endocrine physiology—Growth hormone and prolactin, anabolic hormones necessary for cell differentiation and proliferation, follow the sleep-wake cycle and are suppressed during sleep restriction.[15] Growth hormone (GH) peaks during the early stages of N3, while prolactin (PRL) peaks during the second half of the sleep period. In contrast to GH and PRL, cortisol and thyroid hormone fluctuate with circadian rhythm. Cortisol levels rise in the early morning, peak in the late morning, and decline toward nighttime, reaching a nadir after sleep onset. Thyroid stimulating hormone (TSH) follows a similar circadian rhythm, peaking before sleep onset and declining slowly during sleep. Thyroid stimulating hormone secretion is inhibited by N3 sleep and increases with sleep deprivation.[16]

Sleep in the ICU

Sleep Architecture and Quality in ICU Patients

Critically ill patients experience poor sleep quality and consistently report poor perceived sleep quality in the ICU compared to home.[17,18] Surveys of ICU survivors have shown that sleep deprivation and the inability to sleep rank among the top 3 major sources of anxiety and stress during the ICU stay (along with pain and intubation).[19–21]

The reports of poor sleep quality by ICU patients are supported by numerous 24-hour polysomnographic (PSG) studies.[18,22–28] Critically ill adult patients have markedly fragmented sleep compared to healthy adults, with approximately 50% of sleep occurring during daytime hours.[18,29–31] Freedman et al demonstrated that ICU patients experience 41 ± 28 sleep periods per 24 h, with each sleep period averaging 15 ± 9 min (Figure 2).[30] Polysomnography in ICU patients is characterized by increased arousals and a predominance of stages N1 and N2, with a lack or absence of N3 and REM. Mean total sleep time in critically ill patients is comparable to healthy adults but shows considerable inter-patient variation.[30–33] In summary, ICU patients commonly have broken, light sleep with a lack of restorative N3 and REM sleep.

Measurement of Sleep in the ICU

Sleep measurement in critically ill patients remains an important barrier to large studies on ICU-related sleep disturbances.[34] Polysomnography, the gold standard and widely used mode of sleep measurement, involves simultaneous electroencephalogram (EEG), electromyogram (EMG), and electrooculogram (EOG) recordings, which require cumbersome equipment, skilled technicians, and interpretation by a sleep expert. Consequently, PSG is costly and logistically challenging. In the ICU, interpretation of PSG is especially difficult since common ICU medications and illnesses, such as sepsis, shock, hepatic encephalopathy, and renal failure, are associated with altered EEG patterns.[35,36]

Compared to PSG, actigraphy and the BIS have been investigated as more feasible tools for objective sleep measurement in ICU patients. Actigraphy involves an automated wristwatch device that evaluates patient motion to measure sleep-wake periods and sleep efficiency.[37] Actigraphy is widely regarded as a low-cost, minimally invasive alternative for sleep-wake measurement. However, 24-hour actigraphy in ICU patients has been shown to consistently overestimate total sleep time compared to PSG.[33,37] This discrepancy is likely due to inability of actigraphy to decipher between sleep and motionless wakefulness in mostly inactive, bedridden ICU patients.[33,37].

Bispectral index integrates EEG data to provide a scaled numerical value from 0 to 100, with a larger value representing a higher degree of consciousness. Bispectral index utilizes a single foam sensor containing several EEG electrodes and is sometimes used in monitoring the depth of anesthesia in the operating room. Unlike actigraphy, BIS has the potential to estimate sleep depth, although significant overlap and variability in inter-rater cutoffs for sleep stages can lead to inaccurate characterization of sleep architecture.[38–41] Further-more, studies employing BIS in the ICU have been complicated by detachment of electrodes and artifact due to patient movement.[38] Bispectral index has not yet shown clinical benefit in ICU care.[42,43]

Subjective survey instruments also may be used for sleep measurement.[33] Probably the most widely used instrument[44–47] is the Richards-Campbell Sleep Questionnaire (RCSQ), a 5-question survey validated against PSG in 70 critically ill patients.[44] The RCSQ uses a visual analog scale to rate perceived sleep depth, efficiency, and quality.[48] As a patient self-report measure, use of RCSQ in ICU patients may be limited by cognitive impairment, such as

delirium.[46] However, the survey does allow for nurse-reported sleep quality ratings on behalf of patients unable to complete the survey, with high rates of agreement between nurses and patients ($r = .869$; $P < .001$).[44,46,47] The RCSQ may be a feasible option for large scale, ICU-wide perceived sleep measurement as part of routine clinical care and quality improvement efforts.

Causes of Sleep Disruption in the ICU

There are several common causes of disrupted sleep in hospitalized patients, including underlying sleep disorders, medical conditions, and psychological problems. There are also several modifiable factors causing sleep disruption in critically ill patients, such as noise, light, patient care interactions, and medications (Figure 3).[49] Other factors such as severity of illness and mechanical ventilation also contribute to sleep disruption.

Noise—High levels of noise are common in ICUs. Noise is commonly reported by ICU patients as a significant disruptor of sleep and most often is due to staff conversations, alarms, overhead pages, telephones, and televisions.[26,50,51] The Environmental Protection Agency recommends maximum hospital noise levels of 45 decibels (dB) during the day and 35 dB at night.[52]In the ICU setting, peak daytime and nighttime noise levels routinely exceed 80 dB, the threshold associated with sleep disruption in critically ill patients.[22,30,32,53–56] However, 18 to 24 hour PSG recordings in ICU patients have attributed only 11% to 18% of arousals and 17% to 24% of awakenings to environmental noise.[30,32,55] Interestingly, healthy participants experienced more arousals due to noise when exposed to an ICU setting, suggesting that critically ill patients may be more sensitive to environmental noise as they are recovering.[32,57]

Patient care activities—ICU patients may experience 40 to 60 interruptions each night due to patient care activities.[32,58] These activities include patient assessments, vital sign measurement, equipment adjustment, medication administration, phlebotomy, radiographs, wound care, transportation, and bathing. In 1 study, patient care interactions accounted for 7% of sleep arousals in the ICU, while 18% of all interactions resulted in sleep disruption.[32] This data is supported by a survey of 203 patients awaiting discharge from 4 ICUs revealing that 2 patient care activities—vital signs and phlebotomy—were more disruptive to sleep than noise.[51]

Indeed, frequent patient interactions are necessary for physiologically unstable ICU patients. However, nurses have reported that modifiable factors, such as visitation times, bathing, patient turning, and linen changes, often prevent ICU patients from obtaining consolidated sleep.[59]

Light—Light plays a vital role in synchronization of the circadian rhythm. Light levels of 1500 lux are necessary to disrupt sleep and 100 to 500 lux are needed to suppress melatonin release (normal indoor light ~180 lux).[60,61] While light may disrupt sleep in ICU patients, ICU survivors have reported that light is less disruptive to sleep than noise and patient care activities.[51] These reports are supported by continuous light measurements in 4 ICUs, where the mean maximum nocturnal level of 128 to 1445 lux is high enough to suppress melatonin, but below the threshold necessary to disturb sleep.[61] Independent of light levels, nocturnal melatonin secretion in ICU patients is perturbed or suppressed, suggesting that other factors in addition to light and dark affect circadian rhythms in this population.[62,63]

Mechanical ventilation—Multiple studies have demonstrated that mechanical ventilation contributes to sleep disruption.[30,64–66] Compared to their nonventilated counterparts, mechanically ventilated patients exhibit more fragmented sleep, reduced sleep efficiency,

and increased sleep during daytime hours (up to 50% of total sleep time).[64] Patients receiving mechanical ventilation report significantly increased levels of perceived daytime sleepiness.[51]

The aspects of mechanical ventilation that contribute to sleep fragmentation include increased ventilatory effort, abnormal gas exchange, and patient-ventilator dysynchrony.[67–71] Noxious factors associated with mechanical ventilation, such as endotracheal tube discomfort, ventilator alarms, suctioning, positioning, and frequent assessments likely contribute to sleep disruption as well; however, these associations have not been studied.

Over the past decade, the impact of ventilation mode on sleep has received particular attention. Parthasarathy and Tobin were among the first to study the association between sleep architecture and ventilator mode.[65] Their study was based on the theory that pressure support ventilation (PSV) leads to hyperventilation and decreased PCO_2 levels, thus potentiating central apneas and sleep arousals. The investigators performed overnight PSG on 11 critically ill patients receiving mechanical ventilation, alternating 2 hours each of PSV, assist control ventilation (ACV), and PSV plus dead space ventilation. As predicted, PSV resulted in significantly more arousals and awakenings per hour than ACV (79 ± 7 vs. 54 ± 7, $P < .05$). The addition of dead space (maintaining higher levels of PCO_2) significantly reduced sleep disruptions ($P < .01$) and central apneas ($P < .01$). Toublanc et al added to these findings, showing that patients receiving PSV at lower levels of pressure (6 cm H_2O) also experienced significantly disrupted sleep compared to those receiving ACV.[72] However, sleep quality did not differ when Cabello and colleagues compared clinician-adjusted PSV, automatically adjusted PSV, and ACV, likely due to appropriate matching of ventilator settings with patient mechanics.[55] Hence, adjusting a ventilator to maximize patient comfort may depend more on ventilator settings and not ventilator mode, but the final answer remains uncertain.

More recent research has focused on sleep disruption and patient-ventilator dysynchrony with studies of proportional-assist ventilation (PAV).[66,73] Unlike PSV, where the same pressure is applied with each breath, PAV adjusts flow and volume based on respiratory resistance, elastance, and inspiratory effort. In a crossover study comparing PSV and PAV, PAV was associated with improved patient-ventilator synchrony, tidal volume, and minute ventilation, resulting in decreased sleep arousals and increased REM and N3 sleep.[66] However, when applied only to those with good patient-ventilator synchrony, PAV did not result in significant improvements in sleep quality compared to PSV.[73]

There is little data describing sleep in ICU patients receiving non-invasive positive pressure ventilation (NPPV). Preliminary 24-hour PSG in 4 patients receiving NPPV demonstrated frequent arousals and nearly absent REM and N3 sleep.[74] However, in patients with hypoventilation (eg obesity hypoventilation syndrome, neuromuscular disease, COPD), nocturnal NPPV may improve sleep quality while preventing worsening hypoventilation.[75]

In summary, evaluation of ventilation mode and sleep quality is still an emerging field, and decisions should be individualized to optimize patient-ventilator mechanics.

Medications—Several commonly used ICU medications have profound effects on sleep quantity and quality (Table 1).[76,77] These agents act through a variety of neurotransmitter pathways, receptors, and modulators. Although the interplay of these medications with sleep is difficult to study in ICU patients, their effects in normal participants has been well described. Drug withdrawal can also alter sleep architecture and precipitate delirium and must be appreciated in any patient using long-term medications that influence sleep.

Sedation is used in many ICU patients, particularly in those requiring mechanical ventilation. Despite their sedative, anxiolytic, and analgesic properties, benzodiazepines and opiates are potentially disruptive to sleep. Benzodiazepines provide sedation through GABA-ergic pathways but increase stage N2 and reduce N3 sleep at low doses in healthy participants.[78,79] Opiates such as fentanyl and morphine promote sleep onset in healthy adults, but inhibit REM, profoundly suppress N3, provoke nocturnal awakenings, and can precipitate central apneas.[80–84] Both benzodiazepines and opiates are associated with delirium in critically ill patients, even at low doses.[1,85].

Propofol, a GABA receptor agonist, is associated with suppressed N3 sleep in human studies.[86] However, in a rat model, a continuous propofol infusion did not result in sleep deprivation[87] and suggested rebound sleep (based on EEG analysis) following prolonged sleep deprivation.[88] Dexmedetomidine, a newer α2-agonist with both sedative and analgesic properties, enhances N3 sleep in a rat model, and is associated with lower incidence of delirium compared to benzodiazepines in ICU patients.[85,89] Further investigation is needed to examine the effects on sleep architecture in both healthy and ICU populations receiving these sedative agents.

Finally, off-label use of medications with sedating side effects to treat insomnia in ICU patients can also compromise sleep quality.[90] Medications such as diphenhydramine are deliriogenic.[91] Additionally, sedating antidepressants such as trazodone (the most commonly prescribed sleep aid in the United States[91]), amitryptyline, and mirtazapine have not been studied for use in insomnia and have important potential side effects including hypotension, arrhythmias, and anticholinergic syndrome. Use of these medications to promote sleep has been discouraged by an NIH consensus panel on chronic insomnia.[91] Given the common use of sedatives in the ICU, little data exists regarding the use of medications to treat insomnia. However, given the effect of medications commonly used in the ICU (eg, benzodiazepines, narcotics, and propofol) on delirium, these medications should not be used to treat insomnia. Further studies are needed to understand the potential risks and benefits of newer sleep-promoting medications in the ICU setting.

Other causes of ICU-related sleep disruption—Sleep deprivation in the ICU can be exacerbated by factors inherent to critical illness. Pain, a very common symptom in critically ill patients, contributes to awakenings during sleep.[92–95] Anxiety and stress due to unfamiliarity with the ICU environment, inability to speak, or illness can also contribute to sleep loss.[93,94,96]

Data on the association of severity of illness and sleep quality are limited.[97] Critically ill patients with sepsis have more pronounced perturbations in melatonin excretion than nonseptic ICU patients, suggesting worse sleep quality with sepsis.[98] Sleep evaluation is challenging, however, since septic patients have slowed EEG activity resembling an altered state of consciousness different from both sleep and wakefulness.[37]

Preexisting disease can also contribute to poor sleep quality in the ICU. Chronic obstructive pulmonary disease (COPD), for instance, is a common comorbidity in mechanically ventilated ICU patients and associated with prolonged sleep latency and decreased total sleep time.[99] Sleep-related hypoventilation and hypoxia in COPD trigger sleep arousals and disrupt REM and N3 sleep.[99–105] Stroke patients and congestive heart failure (CHF) patients with depressed left ventricular systolic function often exhibit nocturnal Cheyne-Stokes respiration, which markedly disrupts sleep.[106,107] Finally, sleep disorders such as obstructive sleep apnea and obesity hypoventilation syndrome are increasing in prevalence in ICU populations and can cause severe sleep fragmentation.[108,109]

Physical Consequences of Sleep Deprivation in Critically Ill Patients

Ventilatory Disturbances

There is little data regarding the effect of sleep deprivation on the respiratory system in the critically ill. However, studies in non-ICU patients have shown that altered respiration can occur after small amounts of sleep loss.[110] For example, after 1 night without sleep, COPD patients have a significant decline in FEV1 and FVC, and a decrease in maximal inspiratory pressure.[111] Additionally, healthy participants with 24 to 30 hours of sleep deprivation have shown significantly increased respiratory muscle fatigue[112] and a 17% to 24% decrease in ventilatory response to hypercapnea, suggesting a potential role of sleep deprivation in ventilatory chemoreceptor mechanisms;[113–116] however, these results are not universally supported.[117] Finally, disrupted sleep leads to greater upper airway collapsibility, which can precipitate obstructive apnea and potentiate problems following extubation.[118,119] Although not yet investigated, these data may indicate that the typical prolonged and sustained sleep disruption in ICU patients may have a detrimental effect on respiration, particularly in those patients with preexisting pulmonary morbidity and difficulty weaning from mechanical ventilation.

Cardiovascular Disturbances

A relationship between sleep deprivation and cardiovascular morbidity is well established but poorly understood.[120] Studies have shown that normal participants with insufficient sleep have increased sympathetic and decreased parasympathetic tone, and elevated catecholamines, resulting in blood pressure and heart rate lability and increased risk of acute myocardial infarction.[121–123] Sleep restriction, even over 1 night, triggers the release of inflammatory cytokines (see “Immunologic disturbances” below) that foster endothelial disruptions associated with atherosclerosis, hypertension, and coronary artery disease.[124,125] Despite this evidence, it remains unknown whether sleep deprivation or ICU-related sleep disruption contribute to cardiovascular mortality.

Immunologic Disturbances

Common perception holds that adequate sleep is necessary to prevent and combat infection. The notion that sleep reinforces host defense mechanisms is supported by murine models demonstrating that prolonged sleep deprivation produced a catabolic state, opportunistic infection, and death from septicemia within 27 days.[126] Rats undergoing prolonged sleep restriction also had decreased lymphocytes, total leukocytes, and spleen weight, possible early signs of immune compromise.[127]

The relationship between immunity and sleep in humans is less clear and more complex.[128,129] Numerous studies have demonstrated attenuated response to vaccination[130,131] and disruption in markers and modulators of immunity following sleep deprivation; however, the findings have questionable clinical relevance due to inconsistent data and/or lack of microbiological or morbidity correlates. Two nights of sleep deprivation (63 hours awake) in normal participants produces a linear decline in T-helper cells and an increase in leukocytes, monocytes, and natural killer cell activity,[132] but neither 1 night of partial sleep deprivation, selective slow-wave sleep restriction, nor prolonged sleep restriction produces similar results.[127,133] Similarly, natural killer cells reach a nadir after 1 night without sleep but increase substantially during a second night of sleep loss.[132] While partial sleep deprivation suppresses release of IL-2,[133] other pro-inflammatory cytokines such as intercellular adhesion molecule 1 (ICAM-1), E-selectin, interleukin (IL)-1β, IL-6, and TNF-α are stimulated following 1 night without sleep.[125,134] These data suggest that duration of sleep deprivation affects cellular immunity and cytokine function, but the exact mechanism and clinical implications are not known. Clearly, significant knowledge gaps

remain to be filled on sleep and immune physiology before similar mechanisms can be studied in the critically ill.

Hormonal and Metabolic Disturbances

Sleep loss profoundly effects metabolism and endocrine function.[135] During sleep deprivation, cortisol and catecholamine levels increase[136–138] along with indices of energy expenditure, such as oxygen consumption (VO_2) and carbon dioxide production (VCO_2).[139,140] Similar hormonal and metabolic disturbances are observed in critically ill patients, especially in sepsis,[141,142] which may suggest that sleep deprivation intensifies the stress response. Thyroid stimulating hormone, T_3, and T_4 also increase during sleep deprivation[137] but are inhibited during critical illness,[143] suggesting potential antagonism between the 2 processes.

There is little published data on the effect of ICU-related sleep disruption on growth hormone (GH) or prolactin (PRL) levels. Studies have shown that GH and PRL levels rise early in critical illness.[144] Days after the onset of critical illness, however, both GH and PRL levels fall and may play a role in ICU muscle wasting and impaired immunity, respectively.[144] The potent inhibitory effect of sleep deprivation on release of GH and PRL may influence this process, particularly during prolonged critical illness and associated sleep fragmentation, which provides an interesting avenue for future research.[137]

Recent research has focused on sleep deprivation and glucose metabolism. Following slow wave sleep restriction[145] and 2 to 6 consecutive nights of restricted sleep,[138,146] previously healthy participants had blunted insulin secretion, decreased sensitivity to insulin, and impaired glucose regulation.[135] These findings are particularly relevant in the critically ill, where hyperglycemia is common and associated with adverse outcomes.[147–149] Whether ICU-related sleep disruption contributes to or amplifies glucose abnormalities in critical illness is unknown, but provides another compelling area for investigation.

Physical Activity

Sleep loss leads to significant reductions in energy and activity levels,[150–152] which may impact physical recovery from critically illness. A large body of research demonstrates a variety of complications from bed rest,[153] and increasing research is evaluating these specific harms in critically ill patients. Emerging evidence demonstrates that early and intensive physical rehabilitation in the ICU improves physical function, ICU delirium, and ICU length of stay.[154–158] As we learn more about the feasibility, efficacy, and outcomes of early physical medicine and rehabilitation for ICU patients, it is conceivable that fatigue from ICU-related sleep deprivation may impair mobilization efforts, stimulating much-needed initiatives to improve ICU sleep quality.[156,159,160]

Psychological Consequences of Sleep Deprivation in Critically Ill Patients

Delirium

The connection between sleep deprivation and delirium has particular importance in the ICU setting. The vast majority of ICU patients may experience both sleep deprivation and delirium, especially among those who are elderly and/or mechanically ventilated.[161] Delirium is independently associated with patient mortality, increased cost and length of stay, and long-term cognitive impairment.[161–165]

Whether sleep deprivation directly contributes to ICU delirium has not been investigated. However, both conditions share a number of important mechanisms, risk factors, and symptoms.[1,26,161,162,166–168] Circadian rhythm disturbance has been described in delirious

ICU patients.[169] Sedating medications such as benzodiazepines[85,170] and opiates[171] also contribute to both delirium and sleep disruption. Additionally, both inattention and hallucinations can occur with both sleep deprivation and delirium.[166] Given these overlapping factors, and the deleterious short- and long-term consequences of ICU delirium, evaluation of sleep is a logical next step in ICU delirium research.

Disturbances to Mental Health and Quality of Life

A growing body of literature has highlighted a variety of disabling psychiatric and neurocognitive impairments affecting survivors of critical illness. Several similar mood and cognitive derangements are observed following inadequate sleep, suggesting a potential influence of ICU-related sleep disruption on post-ICU mental health.

Psychiatric disturbances—Intensive care is associated with many traumatic stressors, such as respiratory distress, endotracheal intubation, pain, inability to speak, feelings of helplessness, and confusion and hallucinations associated with delirium. As a result, survivors of critical illness often experience frightening flashbacks, nightmares, anxiety, and mood disturbances related to their ICU stay.[172,173]

Posttraumatic stress disorder (PTSD), one of the most prevalent psychiatric disorders following critical illness, is characterized by disabling symptoms of re-experiencing, avoidance, numbing, and hyperarousability regarding a traumatic event.[174] A systematic review of 12 studies of ICU-associated PTSD confirmed that 10% to 39% (median 19%) of 1104 ICU survivors suffered from clinically significant PTSD symptoms during their first year after the ICU.[175] The prevalence of ICU-related PTSD symptoms is up to 45% at ICU discharge and 24% at 8 years after ICU discharge.[176] Predictors of PTSD include ICU length of stay, duration of mechanical ventilation, preexisting psychiatric disorders, delirium, neuromuscular blockade, and the use of sedation, particularly benzodiazepines.[175]

Depression is also common following critical illness and associated with impaired quality of life and delay in returning to work.[177] A systematic review of 14 studies of post-ICU depression revealed clinically significant depression in 28% of patients within the first year of ICU discharge.[177] In ARDS survivors, the prevalence of depression is as high as 46% at 1 year[178] and 23% at 2 years[179] after ICU discharge. Preliminary studies suggest that preexisting depression[180] and poor physical functioning,[180] along with ICU-related hypoglycemia,[181] excessive sedation,[182] and delirium,[183] may be associated with depression following ICU discharge.

Nonspecific anxiety symptoms have been reported in 23% to 48% of ARDS survivors up to 28 months following ICU discharge.[184] While post-ICU anxiety shares many risk factors with depression, the inability of a patient to recall their ICU experience is an additional potentially important risk factor that commonly occurs in the setting of delirium.[185]

The potent effect of sleep quantity and quality on mood is supported by decades of research.[186] Multiple studies have demonstrated depressive symptoms[120] and increased levels of fatigue, anxiety, and stress[187] in healthy participants undergoing total or partial sleep restriction. The underlying mechanism between sleep loss and depression is not well understood; however, it is theorized that sympathetic activation during sleep arousals potentiates stress responses underlying PTSD and nonspecific anxiety disorders.[188] Likewise, sleep disruptions in the critically ill may contribute to post-ICU psychiatric disorders, but the exact association may be challenging to understand in patients with multiple comorbidities and ICU-related stressors. Research may instead focus on the effects of ICU sleep promotion on post-ICU psychological outcomes.

Cognitive dysfunction—Numerous investigations describe a variety of short- and long-term neurocognitive deficits following critical illness, including impairment of memory, attention, concentration, language, mental processing speed, visuospatial abilities, and executive function (eg, decision making, organization, and planning).[189] The pathophysiology of these deficits is not fully elucidated, but several mechanisms have been proposed, including hypoxemia, hypotension, delirium, sedating medications, and hyperglycemia.[173]

An early study of post-ICU neurocognitive function examined 55 survivors of ARDS. At hospital discharge, 100% of these patients exhibited some level of cognitive impairment; 1-year later, 78% had impaired memory, attention, and/or concentration, 48% had decreased processing speed, and 30% had global cognitive decline, compared to population norms.[190] Two-year follow-up revealed persistent neurocognitive deficits in 46% of this study population, with minimal improvement between years 1 and 2 posthospitalization.[179] Even 6 years after ICU discharge, 24% of patients in a separate ARDS cohort had persistent problems with attention.[191] At least 10 studies have demonstrated similar neurocognitive impairments, both in ARDS and general ICU populations.[192,193]

Sleep deprivation elicits neurocognitive impairments, some of which have similarity to critical illness. Such cognitive impairments have been described since 1896, when deficits in memory, attention, and reaction time were described in 3 healthy participants following 90 hours of sustained wakefulness.[194] Since then, hundreds of studies have detailed a myriad of neurocognitive impairments following short-term, long-term, and partial sleep deprivation, including inattention, short-term memory loss, decreased reaction time, and altered executive function.[186,195]

Based on the current knowledge—that sleep fragmentation is common in the ICU, and that sleep loss and critical illness both impair cognition—ICU-related sleep disruption may causally influence post-ICU neurocognitive impairment. However, sleep loss has yet to receive significant attention as a potential contributor to cognitive outcomes in ICU survivors,[173] since the effects of sleep deprivation in healthy participants are considered short-lived and reversed with adequate recovery sleep. However, whether this positive prognosis can be extrapolated to patients who are critically ill, with concomitant neurological insults, is unclear. Given that the consequences of post-ICU neurocognitive dysfunction pose a significant burden to ICU survivors, who experience challenges with daily functioning, social isolation, and difficulties returning to work,[173,179,191] further investigation of the role of improving sleep in the ICU is a novel potential intervention.

Quality of life measures—Health-related quality of life (HRQOL) broadly captures one's perception of their overall well-being and incorporates measures of physical, mental, emotional, and social functioning.[196] Not surprisingly, critical illness is associated with long-term impairments in HRQOL, regardless of pre-ICU functional capacity.[197,198] Survivors of critical illness have statistically significant decrements in the Medical Outcome Study 36-Item Short Form Health Survey (SF-36) HRQOL instrument for years after ICU discharge.[197,198] Moreover, post-ICU depression and PTSD are associated with substantial reductions in HRQOL.[173] Chronically reduced sleep also leads to substantial decrements in HRQOL,[199,200] suggesting that ICU-related sleep disruption may contribute to post-ICU quality of life measures.

Promotion of Sleep in the ICU

Developing a strategy to improve ICU sleep quality is a challenging proposition. Existing evidence supports ICU sleep promotion via multi-faceted interventions focused on

minimization of nighttime sleep disruptions and maintenance of the homeostatic sleep-wake cycle. While specific interventions will differ based on ICU staffing, equipment, and facilities, any effective sleep intervention will require elimination of unnecessary noise and light, consolidation of patient care interactions, and consideration of nonpharmacologic sleep aids such as earplugs, eye masks, white noise, and relaxation techniques (eg, calming music, biofeedback, and massage).[57,201–203] A guideline for judicious use of medications that disrupt sleep (eg, benzodiazepines and opiates) and use, when necessary, of medications that promote restorative sleep (eg, zolpidem) should also be considered. Finally, daytime wakefulness should be promoted with ambient daylight and regular mobilization.

Effective implementation of any ICU sleep guideline will involve a significant change in culture. Education and engagement of all involved ICU physicians, nurses, and staff will be paramount to achieve buy-in, and frequent performance measurement will be a vital tool for feedback and motivation.[204] Monitored outcomes will vary based on available resources but may include objective sleep measurement such as polysomnography and validated sleep quality instruments such as the Richards-Campbell Sleep Questionnaire. Success and sustainability of sleep interventions also will be dictated by secondary outcomes, such as ICU length of stay and post-ICU psychological and cognitive functioning.

Conclusion

Critical illness is characterized by markedly abnormal sleep, with frequent disruptions, altered circadian rhythms, and reduction in restorative N3 and REM sleep. These perturbations are caused by factors inherent to critical illness, such as disease severity and mechanical ventilation, sedating medications, and environmental factors such as noise, light, and patient care interactions. Despite decades of research in healthy participants demonstrating numerous physiologic and psychological derangements following sleep loss, data remain scarce regarding the relative contribution of ICU-related sleep disruption on recovery from critical illness, including weaning from mechanical ventilation, cardiovascular disturbances, host-defense mechanisms, and post-ICU cognition and physical and mental health. Given our current knowledge regarding poor sleep quality in the critically ill, and its potential implications, optimization of sleep in the ICU is a logical next step in critical care outcomes research.

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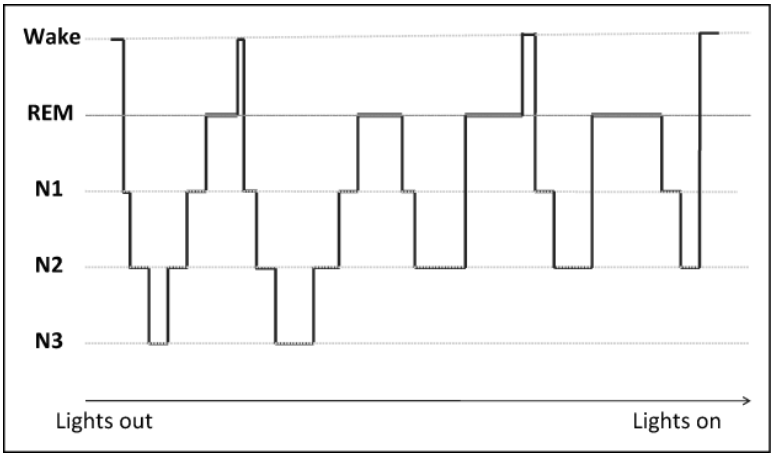

Figure 1.
Normal adult hypnogram demonstrating usual sleep stage transitions. REM indicates rapid eye movement sleep.

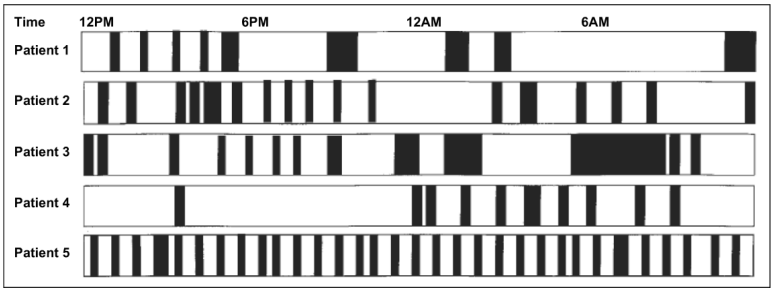

Figure 2.
Sleep fragmentation in 5 critically ill patients. Black areas represent sleep and white areas represent wakefulness. Reprinted with permission of the American Thoracic Society. Copyright © American Thoracic Society. Freedman NS, Gazendam J, Levan L, et al.[30]

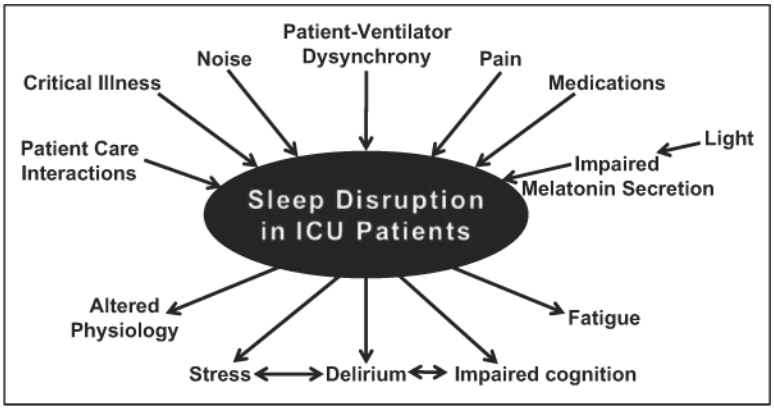

Figure 3.
Etiology and potential outcomes of sleep disruption in the intensive care unit (ICU).

Table 1

Effect of Common ICU Medications on Sleep

Drug Use/Medications	Mechanism of Action	Effect on Sleep
Sedation		
Benzodiazepines	GABA receptor agonist	↑TST, ↓N3, ↓ REM
Dexmedetomidine	α2-agonist	↑N3, ↓SL, ↓REM
Propofol	GABA receptor agonist	↑TST, ↓SL, ↓W
Analgesia		
Opioids	CNS opioid receptor agonist	↓TST, ↓N3, ↓REM, ↑W
Antipsychotic		
Haloperidol	Dopamine-receptor antagonist	↑TST, ↑N3, ↑SE, ↓SL, ↓W
Olanzapine	$5HT_2$-, D_2-receptor antagonist	↑TST, ↑N3, ↑SE, ↓SL, ↓W
Cardiovascular		
β-blockers	CNS β-receptor antagonist	↑W, ↓REM, nightmares
Dopamine	D_2-, β_1-, α_1-receptor agonist	↓N3, ↓REM
Norepinephrine/Epinephrine	α- and β-receptor agonist	↓N3, ↓REM
Phenylephrine	α_1-receptor agonist	↓N3, ↓REM
Other		
Corticosteroids	Decreases melatonin levels	↑W, ↓N3, ↓REM

Abbreviations: CNS, central nervous system; GABA, gamma-aminobutyric acid; N3, deep or slow wave sleep stage; REM, rapid eye movement sleep; SE, sleep efficiency; SL, sleep latency; TST, total sleep time; W, wakefulness after sleep onset