Sleep and recovery from critical illness and injury: A review of theory, current practice, and future directions*

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LEARNING OBJECTIVES

On completion of this article, the reader should be able to:

1. Explain the consequences of sleep deprivation in the intensive care unit (ICU).
2. Describe the approaches to improve sleep in the ICU.
3. Use this information in a clinical setting.

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Objective: **The objectives of this article were to describe the deleterious effects of sleep deprivation, characterize sleep in patients cared for in an intensive care unit (ICU) environment, and propose an integrated strategy to improve sleep in critical care units.**

Study Selection: **Clinical trials and review articles assessing sleep deprivation, sleep in a critical care setting, and interventions to improve sleep in the critical care environment were identified through an in depth PubMed search.**

Conclusions: **Sleep deprivation and disruption are particularly prevalent in patients cared for in the critical care environment. Although numerous observational studies during the past several decades have demonstrated that sleep in patients cared for in ICUs is highly abnormal, little is known about the effects of poor sleep quality on outcomes from critical illness or injury. Reasons for sleep deprivation during recovery from illness and injury in the ICU are multifactorial. Major contributing factors in this patient population are type and severity of underlying illness, the pathophysiology of acute illness/injury, pain from surgical procedures, and perhaps most importantly, the ICU environment itself. Sleep in ICU patients is characterized by prolonged sleep latencies, sleep fragmentation, decreased sleep efficiency, frequent arousals, a predominance of stage 1 and 2 nonrapid eye movement sleep, decreased or absent stage 3 and 4 nonrapid eye movement sleep, and decreased or absent rapid eye movement sleep. Optimizing patient comfort and ensuring that patients achieve adequate restorative sleep while cared for in the ICU is an arduous task. However, environmental alterations in the ICU may reliably improve sleep quality and subsequently alter outcomes during recovery from critical illness and injury. (Crit Care Med 2008; 36:697–705)**

KEY WORDS: sleep; sleep deprivation; recovery; critical illness; injury; intensive care unit

Sleep deprivation and disruption are particularly prevalent in patients cared for in the critical care environment. The design of most clinical care protocols for use in adult intensive care units (ICUs) routinely and severely deprive critically ill patients of sleep at a time when the need for adequate rest is perhaps most essential. In addition, intensive care professionals frequently do not recognize sleep disturbances as complications secondary to the delivery of care for critical illness but instead consider them as inevitable consequences of the critical illness itself. The truth likely lies somewhere in between, with the acute physiologic changes from critical illness itself and environmental factors in the ICU both contributing to the abnormal sleep patterns seen in this patient population.

***See also p. 988.**

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Although numerous observational studies during the past several decades have demonstrated that sleep in adult patients cared for in the intensive care environment is highly abnormal (1–5), little is known about the effects of poor sleep quality on outcomes from critical illness or injury. The consequences of sleep deprivation, which include immune dysfunction, impaired host defenses, protein catabolism, negative nitrogen balance, and psychopathology, are most commonly studied in normal healthy volunteers. In fact, critically ill or injured patients may be more vulnerable to the effects of sleep deprivation, and the deleterious consequences of poor sleep quality may be more profound in these patients.

This article focuses on a review of 1) the deleterious effects of sleep deprivation, 2) sleep disruption in adult patients cared for in the ICU, 3) an integrated strategy to improve sleep in the critical care environment, and 4) future directions to evaluate the role of sleep promotion in recovery from critical illness and injury.

SLEEP DEPRIVATION

Sleep is an essential biological function, and sleep deprivation can lead to a variety of physiologic and psychological dysfunctions. Disrupted sleep can result from numerous and diverse causes, including primary sleep disorders (insomnia, dyssomnias, and parasomnias), medical conditions (chronic pain, respiratory dysfunction, obesity, and congestive heart failure), environmental factors (excessive noise and lighting), and psychological factors (stress and anxiety). Regardless of cause, sleep deprivation has been associated with several adverse outcomes, including abnormalities in immune function and host defense mechanisms, alterations in metabolism, nitrogen balance, and protein catabolism, and psychological disturbances and changes in quality of life measures. Although most of the research on sleep deprivation has been performed in healthy volunteers and animal models, each of these adverse outcomes after sleep deprivation can be observed in patients cared for in the ICU. The effects of these adverse outcomes on morbidity and mortality during recovery from acute illness or injury remain poorly defined.

Immune Function and Host Defenses

It is a common perception that the loss of sleep increases an individual's risk of infection and disease and, conversely, that sleep is vital for recovery from illness. Several avenues of investigation have been undertaken to ascertain the link between sleep and immune function. Sleep deprivation studies in both animal and human models designed to assess functional biological and physiologic changes in recovery from illness have shed some light on this issue.

Animal Models. Most research examining the influence of infection on sleep patterns and architecture has been performed using animal models. Several pathogens, including viral, bacterial, fungal, and protozoan, have been studied and found to increase either the amplitude or intensity of slow-wave, nonrapid eye movement (NREM) sleep after infection (6–10). Sepsis models induced by exposure to bacterial products have also been shown to alter sleep. Lipopolysaccharide, administered intraperitoneally in rats, leads to fever, decreased rapid eye movement (REM) sleep, and increased NREM sleep. Younger animals exhibit an increase in the intensity and duration of NREM sleep. Older animals exhibit an increase in NREM sleep duration without a concomitant change in slow-wave sleep (SWS) intensity (11, 12). In addition, exposure to muramyl peptides, components of bacterial peptidoglycans, increases NREM sleep while suppressing REM sleep in several animal models (13, 14).

Animal models of sleep deprivation designed to explore the effects of sleep loss on immunity and host defenses have demonstrated that chronic sleep deprivation leads to cachexia and septicemia, with both opportunistic and pathologic organisms, and in fact, can be fatal (15, 16). Some (17), but not all (18, 19), studies of a less extreme sleep deprivation stimuli have shown that viral clearance in mice after influenza challenge is altered and that immunized, sleep-deprived mice responded to viral challenge similar to unimmunized mice. In addition, thermoregulation has been shown to be dysfunctional after sleep deprivation in a rat model. This thermoregulatory dysfunction was also associated with an increased metabolic rate and systemic hormonal changes (16). More recent studies have demonstrated that sleep restriction and deprivation result in reduced antioxidant activity (catalase and glutathione), decreased spleen weight, alterations in leukocyte and lymphocyte counts, and the production of serum antibodies without the experimental administration of antigen (20–22).

Substantial variability can be found in the literature with regard to the effects of sleep deprivation on immune function in an animal model. Findings reported by some authors have not been duplicated by others. This lack of generality of results for sleep deprivation studies likely results from differences in species utilized, variables examined, and in methods and length of the sleep deprivation stimulus (23).

Human Models. Most clinical studies examining the effects of sleep deprivation on immune function in humans have utilized healthy volunteers. It seems logical to assume that any immune dysfunction observed in sleep-deprived healthy subjects is likely to be more pronounced in patients with acute or chronic illnesses. However, a direct relationship between severity of illness and the degree of immune dysfunction resulting from sleep deprivation remains to be established.

Early studies of healthy men demonstrated that sleep deprivation and disruption altered the immunologic functions of peripheral blood lymphocytes, polymorphonucleocytes, and natural killer cells *in vitro* (24–26). In addition, observational studies of patients with severe depression and alcoholism, who are at high risk for sleep abnormalities, found that natural killer cell activity is negatively correlated with severity of insomnia (27, 28). Following these observations, several investigators began to explore the effects of sleep deprivation on cytokine expression, and accumulating data suggest that a robust association among sleep, circadian rhythms, and several cytokines (interleukin-6, interleukin-1, and tumor necrosis factor-α) exists (29, 30). The diverse effects of sleep deprivation on immune function are summarized in Table 1.

Table 1. Sleep deprivation and immune function

	Sleep Deprivation
Metabolic rate	Increased
PMN/lymphocyte counts	Decreased
NK cells	Dysfunctional
PMN	Dysfunctional
Antigen-specific defenses	Impaired
Mortality	Increased

PMN, polymorphonucleocyte; NK, natural killer.

Studies examining the effects of infection on human sleep patterns and those examining the effects of sleep deprivation on immunity in humans are more difficult to conduct than those using animal models. Data on experimentally induced human infections are limited. Experimental infection with influenza virus has been found to cause reduced sleep during the incubation period and increased sleep during the symptomatic period (31). Similar to the findings in animals, exposure to bacterial products has also been found to affect sleep in humans. High doses of lipopolysaccharide disrupt sleep by causing an initial decrease in SWS, stage 3 and 4 NREM duration, followed a short time later by an increase in SWS duration, with a concomitant decrease in REM sleep (32). Low doses of lipopolysaccharide, however, result in an increase in SWS duration and intensity (32, 33). Some studies of human viral infection, however, indicate that sleep duration is decreased. Overall, the most common finding after infection is an increase in total sleep duration. Although REM sleep is decreased, this is offset by an increase in the intensity and duration of SWS (34).

Further evidence that sleep has an effect on immune function in humans comes from a study of healthy patients examining antibody response after vaccination for hepatitis A virus. Patients were vaccinated and either allowed to sleep normally on the evening after vaccination or were deprived of sleep. Those who were sleep deprived had lower antibody titers at 4 wks, demonstrating that sleep deprivation soon after immunization impairs the formation of antigen-specific immune defenses (35). Additional work examining cellular adhesion molecule expression also suggests that sleep and immune function are interrelated. In one study, healthy subjects exposed to partial night sleep deprivation exhibited alterations in the expression of cellular adhesion molecules, L selectin, and macrophage-associated antigen. These alterations indicate that sleep deprivation and disruption may interfere with the regulation of immune cell trafficking (36). Other evidence that sleep has an effect on immune function in humans comes from recent work examining levels of cellular and genomic markers of inflammation after sleep deprivation. In this study, 30 healthy adults were observed. Monocyte intracellular proinflammatory cytokine production was followed over a baseline period and after partial night sleep deprivation. An increase in monocyte interleukin-6 and tumor necrosis factor-α production was noted after sleep deprivation. In addition, this study found a three-fold increase in the transcription of interleukin-6 messenger RNA and a two-fold increase in tumor necrosis factor-α messenger RNA transcription after sleep deprivation (37).

Lastly, the association between sleep abnormalities and mortality in humans merits consideration. Patients with fatal familial insomnia, a genetically transmitted prion disease, die within 6–24 months of the onset of the disease (38, 39). In addition, several recent observational studies have shown strong associations between sleep hygiene and longevity. Several authors have found that either a shorter or longer than normal duration of sleep may be related to mortality (40, 41).

Metabolism, Nitrogen Balance, and Protein Catabolism

The effects of sleep deprivation on metabolism, nitrogen balance, and protein catabolism have been studied for decades. Fundamental early human studies have documented that urinary nitrogen secretion increases markedly with sleep reversal (change in diurnal activity) and sleep deprivation. In addition, these studies found that urinary cortisol, glucose, and electrolytes (sodium and chloride) were decreased with sleep deprivation and disruption (42, 43). These findings remain significant in that they identify an elementary difference in the body's metabolic response to sleep deprivation and stress. The body requires more energy during periods of stress and during periods of sleep deprivation. Thus, under both conditions, protein stores are mobilized, resulting in an increase in nitrogen excretion. However, whereas cortisol excretion is unchanged or mildly decreased during sleep deprivation, it is markedly increased during periods of stress (43). Other authors have described an increase in serum cortisol level on the evening after a period of sleep deprivation but not during the deprivation stimulus itself (44). This disparate metabolic management of steroids may be secondary to a disruption of baseline circadian rhythms caused by sleep deprivation, which likely does not occur under brief periods of stress. More recently, secretion of other hormones has been shown to be linked to sleep and sleep deprivation. Growth hormone secretion is increased during sleep and growth hormone–releasing hormone has been found to potentiate sleep in sleep-deprived subjects (45, 46).

Psychological Disturbances and Quality of Life Measures

Loss of sleep in the critical care setting has been associated with a decrease in subjective quality of life measures (47, 48). Long-term complications of prolonged critical illness, which include depression, continued sleep disruption, and posttraumatic stress disorder, are being more readily recognized. Sleep loss, both acute and chronic, may contribute to these persistent complications after prolonged critical illness (49, 50). Other groups of patients with sleep disorders, specifically sleep apnea, have also been shown to have neurocognitive dysfunction that can persist for months after the initiation of treatment (51, 52).

An association between delirium, mental status changes, and other psychological disturbances with care in the ICU is well established. Medical causes of delirium and psychological symptoms include metabolic and electrolyte imbalances, withdrawal syndromes, acute infection, hypoxia, dehydration, seizure disorder, head trauma, and vascular disorders. Additional contributing factors include pharmacologic agents, advanced age, stress/anxiety induced by the ICU environment, apolipoprotein E4 phenotype, and sleep deprivation (53–55). Some authors, however, have suggested that lack of sleep is not a causative factor for ICU delirium but is, in fact, a result of delirium (56).

Regardless of cause, delirium remains a significant complication of critical illness and injury. Recent evidence suggests that delirium develops in 20–50% of patients with low severity of illness cared for in the ICU and in up to 80% of patients requiring mechanical ventilation (54). The significance of ICU delirium becomes most apparent when outcome is evaluated. ICU delirium is predictive of a three-fold higher reintubation rate, a prolonged hospital length of stay (57), and increased mortality (58).

SLEEP AND RECOVERY FROM ILLNESS/INJURY

Sleep abnormalities are common in the ICU setting. These abnormalities, including sleep deprivation, sleep disrup-

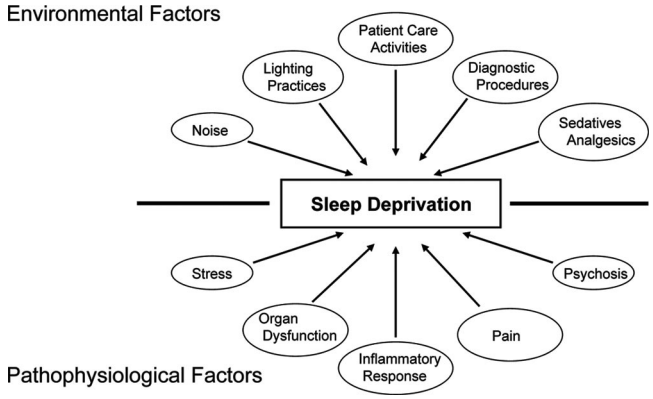

Figure 1. Causes of sleep deprivation in the intensive care unit. Both environmental and pathophysiological factors contribute to sleep deprivation in the intensive care unit.

Table 2. Sleep abnormalities in intensive care unit patients

Total sleep time	Unchanged/decreased
Sleep latency	Unchanged/increased
Sleep efficiency	Decreased
NREM stage 1	Increased
NREM stage 2	Increased
Sleep fragmentation	Increased
NREM stage 3	Decreased
NREM stage 4	Decreased
REM	Decreased

NREM, nonrapid eye movement; REM, rapid eye movement.

tion, and abnormal sleep architecture, have become more apparent with the advent of the specialty of critical care medicine. Reasons for sleep deprivation during recovery from illness and injury in the ICU are multifactorial. Major contributing factors in this patient population are type and severity of underlying illness, the pathophysiology of acute illness/injury, pain from surgical procedures, and perhaps most importantly, the ICU environment itself (Fig. 1).

Environmental factors contributing to sleep disruption in the ICU include lack of diurnal cues (lighting practices, excessive noise), patient care activities (vital sign measurements, therapeutic interventions, mechanical ventilation), diagnostic procedures (lab draws, radiographs), and medications (sedatives, analgesics) (59, 60). However, the respective influence of the illness itself vs. the ICU environment on sleep deprivation is not entirely clear. In addition, there is substantial evidence that disrupted sleep is an added stressor to the acutely ill/injured patient and may be a potential impediment to successful recovery (61).

Several studies have documented sleep disturbances in ICU patients utilizing polysomnography. Sleep in ICU patients has been characterized by prolonged sleep latencies, sleep fragmentation, decreased sleep efficiency, frequent arousals, a predominance of stage 1 and 2 NREM sleep, decreased or absent stage 3 and 4 NREM sleep, and decreased or absent REM sleep (2, 4, 62–64). These findings have been demonstrated in a variety of ICU settings (medical, surgical, and cardiac) and have shown remarkable consistency. In addition, surveys taken of patients surviving critical illness indicate that sleep disturbances are one of the most frequent complaints noted. This poor sleep, which manifests during the acute illness, often persists for an extended period of time after discharge from the ICU (60, 65–67). A summary of the sleep abnormalities noted in critically ill patients managed in the ICU setting is presented in Table 2.

Although illness, pain, and sedatives/analgesics contribute to sleep abnormalities in ICU patients, the ICU environment itself is likely a major contributor. Noise from multiple sources in the ICU, such as alarms, conversations, mechanical ventilation, telephones, pagers, and televisions, has been implicated as a cause of sleep disruption in the ICU. Several studies have documented peak noise levels in excess of those recommended by the Environmental Protection Agency for ICUs (45 dB during the day and >35 dB at night). Mean noise levels in ICU environments have been shown to be as high as 55–65 dB during a 24-hr period, with peaks as high as 80 dB (5, 68). The effect of noise reduction on sleep quality in the ICU remains controversial. Some studies have demonstrated improvements in sleep quality, fewer arousals and increased REM duration, with use of earplugs (69, 70). However, another study showed that the effect of noise reduction (door closure) was to increase sleep quantity without any change in sleep architecture or arousal index (68). Patients treated in an ICU are frequently exposed to light 24 hrs/day. Nocturnal light levels in the ICU also contribute to an environment less conducive to sleep. Nocturnal light levels as low as 100–500 lux are known to affect melatonin secretion, and nocturnal levels between 300 and 500 lux may have an effect on the circadian pacemaker (71, 72). Other factors related to patient care, such as nursing procedures, lab draws, vital signs, radiographs, pain medications and sedation, and physician interventions, all contribute meaningfully to sleep deprivation in the ICU.

Two other important factors for consideration are the influence of mechanical ventilation and pharmacologic interventions on sleep disruption in the ICU. Sleep in mechanically ventilated patients has been reported to be highly fragmented (4). In addition, ventilated patients may experience dyssynchrony with the ventilator, especially during periods of NREM sleep when the range of respiratory frequencies to which the patient can entrain (phenomenon in which neuronal impulses that normally initiate inspiration adjust to the presence of mechanical breaths) is narrower (73, 74). The ventilatory mode utilized may also contribute to sleep disruption. Although pressure support ventilation allows the patient to determine his or her own tidal volume and respiratory rate, some authors have described central apneas on this mode of ventilation. One potential modification to prevent these central apneas involves increasing dead space with a resultant increase in the arterial partial pressure of CO_2 (75). A recent study found that nocturnal proportional assist ventilation resulted in fewer patient–ventilator dyssynchronies and was superior to pressure support ventilation in allowing improved sleep quality (76).

Several pharmacologic agents, including cardiovascular pressors, antibiotics, chemical paralytic agents, and sedatives and analgesics, have been found to have a negative effect on patient sleep quality and architecture in the ICU. Although benzodiazepines increase total sleep time, they result in abnormal sleep architecture by prolonging stage 2 NREM and decreasing SWS and REM sleep. Analgesics have also been associated with abnormal sleep architecture at doses of >10 mg/hr (morphine equivalent) (4, 77, 78).

Similar to benzodiazepines, propofol, another commonly used sedative in the ICU, increases total sleep time without enhancing REM sleep or SWS (72). In a recent study of patients receiving paralytic agents in addition to sedation, REM sleep was completely absent; however, total sleep time was adequate (79). Cardiovascular pressors, specifically inotropic agents, affect sleep quality through their effects on adrenergic receptors. Other cardiovascular agents, such as beta blockers, can also negatively affect sleep in the ICU and may result in insomnia and nightmares secondary to suppressed REM sleep (80). Quinolone antimicrobial agents have been reported to cause sleep disturbances via γ-aminobutyric acid type A receptor inhibition (81).

Lastly, although the relationship between sleep and severity of illness remains controversial, it is likely important and should not be overlooked. Several groups have tried to more thoroughly define this relationship. One group noted an increase in sleep disruptions, as defined by arousals and awakenings per hour, in those patients with higher disease severity scores and in nonsurvivors when compared with survivors of critical illness (82). Another group described an association between increasing severity of illness and frequency of sleep disturbances, as defined by increased sleep fragmentation, in coronary care unit patients (83). Finally, a study comparing ICU patients with healthy volunteers who were exposed to the same ICU environment found that the ICU patients had decreased total sleep time and a lower proportion of time spent in SWS (68). These data are preliminary, and the relationship between sleep disturbances and severity of illness may be influenced by many factors. This relationship is likely highly complex and would be best explored by a randomized controlled trial that could control for the many potential factors involved.

INTEGRATED STRATEGY FOR SLEEP PROMOTION IN THE ICU

Optimizing patient comfort and ensuring that patients achieve adequate restorative sleep while cared for in the ICU is an arduous task. Due to the advanced technological equipment available in ICUs for monitoring and patient support and the need for rapid aggressive intervention at any time, the ICU environment is frequently not conducive to ensuring adequate undisturbed time for patient rest. It is unlikely that addressing one or two ICU environmental factors contributing to sleep disruption would have a profound effect on correcting ICU-related sleep deprivation. Accordingly, several issues should be considered when developing strategies for sleep promotion in the ICU. These issues include controlling noise levels, use of diurnal lighting practices, appropriate pharmacologic interventions, providing adequate uninterrupted time for sleep, appropriate physiologic support, obtaining patient–ventilator synchrony, effective pain therapy, relaxation techniques, music therapy, minimization of staff conversation near patient bedside, and individual patient rooms (Table 3).

Table 3. Considerations for an integrated strategy to promote sleep in the intensive care unit

- Noise reduction
- Diurnal lighting practices
- Use of sleep-promoting pharmacologic agent
- Minimizing use of pharmacologic agents inhibiting sleep
- Uninterrupted time for adequate sleep
- Appropriate physiologic support
- Active promotion of patient orientation
- Patient-ventilator synchrony
- Relaxation techniques

Noise Reduction

Noise reduction can be readily achieved with a few straightforward interventions. Individual patient rooms contribute to noise reduction, as do liberalizing monitor alarm settings and the use of earplugs, white noise, or music therapy. Another essential component involves collaboration with the nursing and support staff to minimize conversations at or near the patient bedside. Staff education and training will need to be an important part of instituting any integrated strategy designed to improve sleep in ICU patients.

Lighting Practices

Patients cared for in the ICU are frequently exposed to light 24 hrs/day. This continued exposure to light can disrupt the patient's naturally occurring circadian rhythms. Melatonin secretion has been shown to be influenced by retinal exposure to light during periods of darkness. During periods of darkness, melatonin secretion is increased; however, an immediate drop in melatonin secretion occurs when the retina is exposed to light (84). A strategy to promote sleep requires significant modifications in lighting practices. Daytime natural light or fluorescent lighting is preferred. During the nighttime, light should be dimmed significantly in the entire unit not simply in individual patient rooms. Decreased lighting could be coupled with shielding of each patient's eyes (blindfold) to allow for a sufficiently lit environment for ICU staff to carry out necessary nighttime activities and minimizing retinal stimulation for the patients. The adoption of this practice will again require the cooperation of the nursing and hospital staff. Staff education highlighting the importance of adequate rest during recovery from illness and the possible effects of diurnal lighting practices should be vigorously pursued.

Pharmacologic Interventions

Pharmacologic agents that induce sleep and sedation have been used in the ICU setting for decades. However, not all of these agents are suited for a sleep-promotion strategy. In addition, many other medications interfere with the patient's ability to achieve normal sleep. Most critically ill or injured patients cared for in an ICU are receiving multiple different medications. In fact, polypharmacy is the norm rather than the exception in most ICUs. To devise an adequate sleep-promotion strategy, one must carefully choose an agent to induce sleep and minimize the use of agents that inhibit or hinder the patient's ability to achieve normal sleep.

Sleep-Promoting Agents. Nonbenzodiazepine hypnotic agents, such as zolpidem and zopiclone, which interact with the γ-aminobutyric acid receptor complex at domains close or allosterically coupled to benzodiazepine receptors, do not suppress SWS, whereas benzodiazepines do. In addition, these γ-aminobutyric acid type A receptor agonists have a less suppressive effect on REM sleep than benzodiazepines (85). An additional selective γ-aminobutyric acid type A receptor agonist, gaboxadol, has been shown to increase sleep efficiency and the total amount of SWS. This agent may in fact result in improved SWS rather than simply a lack of suppression of SWS, as seen with zolpidem and zopiclone (86, 87). The effects of decreased disordered sleep with the use of these newer γ-aminobu-

tyric acid type A receptor agonist hypnotic agents on the outcomes of critically ill and injured patients cared for in the ICU remain unknown.

Dexmedetomidine, an α_2-agonist, has sedative–analgesic properties and is approved for use in the ICU. Dexmedetomidine has been shown to inhibit the release of norepinephrine from the locus ceruleus and enhance SWS (88). This agent is currently approved for use in mechanically ventilated patients. Its lack of respiratory depression, however, makes it a good candidate for a broad spectrum of ICU patients (72).

The cyclic (circadian) secretion of melatonin acts as a robust hormonal signal indicating times of environmental darkness. In humans, the circadian rhythm of melatonin secretion contributes to the initiation and consolidation of sleep and the regulation of the circadian rhythm of core body temperature (89). The master clock controlling circadian rhythms is located in the suprachiasmatic nucleus of the hypothalamus. The suprachiasmatic nucleus receives information about the environment from the retina during daylight hours and the pineal gland, via melatonin secretion, in times of darkness. During daylight hours, suprachiasmatic nucleus activity promotes arousal. At nighttime and during periods of darkness, melatonin secretion from the pineal gland increases and suprachiasmatic nucleus activity is attenuated, resulting in a diminished arousal (85, 90).

In addition to its effects on the circadian clock, melatonin may have sleep-promoting properties. In several studies of human subjects, melatonin has been shown to induce sedation, lower core body temperature, and induce other changes associated with sleep (91, 92). In addition, melatonin secretion is disturbed in both postoperative and long-term, chronic ICU patients. One small trial demonstrated improved sleep in medical ICU patients with chronic obstructive pulmonary disease and pneumonia when melatonin supplementation was used (93–95).

Agents Inhibiting Sleep. Frequently in the ICU, a combination of a benzodiazepine and an opioid is used to address pain and anxiety and facilitate mechanical ventilation or tolerance of other uncomfortable methods of physiologic support. The critical care provider must recognize that although patients may appear to be sleeping, benzodiazepines and opioids alter the normal sleep pattern significantly. Benzodiazepines may result in an increased total sleep time; however, their use causes a prolongation in stage 2 sleep and a decrease in SWS and REM sleep. A tolerance to the anxiolytic effects of benzodiazepines occurs within a few days, requiring dose escalation to maintain desired sedation levels. In addition, paradoxic effects such as insomnia, hallucinations, and agitation can occur. Opioid use has been shown to decrease REM sleep and SWS in the postoperative period (77, 80). There is little evidence to suggest that sedation achieves the restorative function within the brain and central nervous system that results from natural sleep. Further exploration into sleep promotion during recovery from illness and injury is needed to demonstrate whether enhancement of natural sleep improves outcome.

Several other medications commonly used in the care of ICU patients can also affect sleep architecture. Most patients in the ICU are on many different types of medications for a variety of reasons. A careful review of the patient's medications with elimination of those that are not essential is warranted to increase the likelihood that restful sleep occurs.

Cardiovascular inotropic agents can affect sleep quality through stimulation of the adrenergic receptor. Although most of these pressors do not normally cross the blood brain barrier, there is evidence to suggest that in sedated or anesthetized patients, these agents can enter the central nervous system and result in increased cerebral blood flow. One study documented an epinephrine-induced increase in sedation scores and bispectral index values in patients sedated with propofol (80, 96). Lipid-soluble beta blockers have also been associated with insomnia and reduced REM sleep (97). H_2-receptor antagonists and the proton pump inhibitors can cause insomnia. Corticosteroids, specifically high-dose therapy, are known to cause decreased SWS and REM sleep. Certain antimicrobial agents, specifically the beta-lactams and quinolones, have been linked to sleep disturbances (80).

Because the therapeutic need for sedation and the biological need for restful sleep coexist in critically ill and injured patients, the use of sedatives, analgesics, and other medications that cause sleep disruption cannot be completely eliminated in the ICU. However, these medications should be used judiciously, and when their use is no longer required, rapid discontinuation should occur.

Patient Care Interventions

Adequate Uninterrupted Time for Sleep. Patients in the ICU often undergo frequent evaluations at the bedside, including physician rounds, nursing assessments, patient care activities, respiratory therapist interventions, and bedside procedures. These frequent evaluations result in little undisturbed time for the patient to obtain adequate rest. In establishing an integrated strategy for sleep promotion in the ICU, these interruptions should be minimized. Certainly, necessary assessments and patient care activities cannot be eliminated. However, nighttime assessments can be minimized or omitted in patients with continuous monitors in place, such as arterial catheters and arterial saturation monitors. In addition, nighttime routine patient care activities such as chest radiography, bedding changes, bathing, medication delivery, and laboratory blood draws can be rescheduled for daylight hours to ensure uninterrupted sleep time for the patient. Lastly, careful attention should be paid to monitor alarms. Noncritical alarms should be set to sound at a centralized station, and these alarms should be set to sound at reasonable thresholds. The alarm limits should be broadened at night to allow for maximal safe variation. Critical alarms should still sound at the bedside to allow for rapid staff response and evaluation.

Actively Prompt Patient Orientation. Acute delirium is a common complication of receiving care in an ICU environment. Delirium will also inhibit a patient's ability to achieve restful sleep. The treatment and prevention of acute delirium must be addressed in any sleep-promotion strategy. All metabolic and electrolyte disturbances must be corrected. Appropriate therapy for infections should be initiated in a timely fashion. The use of medications that promote confusion and disorientation and reduce consciousness must be minimized. In addition, careful prevention and treatment of withdrawal from alcohol and anxiolytic/hypnotic agents is required. Lastly, prompting and actively orienting the patient on a regular basis will help to prevent acute delirium. Placing clocks and calendars in direct view of patients and engaging patients in frequent conversa-

tion are useful tools to promote orientation (61).

Obtain Patient–Ventilator Synchrony. Mechanical ventilation is an important tool frequently utilized in the ICU for pulmonary support, and data demonstrate that mechanically ventilated patients experience 20–60 arousals and awakenings per hour of sleep (98). Several studies have suggested that the mode of mechanical ventilation can influence sleep quality. Pressure support ventilation has been associated with increased central apneas, which may result in sleep fragmentation (75). Another more recent study identified proportional assist ventilation as an efficacious means of matching patient ventilatory requirements with ventilatory assistance (76).

To ensure the least amount of patient–ventilator dyssynchrony, the critical care provider must carefully assess the ventilatory requirements of each critically ill patient individually and choose the most appropriate mode of ventilation. This may require an assessment of the P_{CO_2} at resting ventilation and each patient's apnea threshold. Central apneas are more likely to occur when the P_{CO_2} approaches the apnea threshold. To prevent central apneas and the associated sleep disturbance, the addition of increased dead-space ventilation may be required (98).

Other Methods. Behavioral interventions as a means of enhancing sleep quality have also been utilized, including relaxation techniques, massage, biofeedback, music therapy, and hypnosis. Deep breathing exercises and relaxation techniques were studied in a cohort of cardiac surgical patients (99). The authors found that these patients had decreased heart rate, blood pressure, and respiratory rate, and they also had less pain. These outcomes would likely result in improved sleep quality. A 6-min back massage before dimming the lights for the evening has been shown to improve sleep efficiency and sleep duration in ICU patients (100). Music therapy may give some relief from the noisy ICU environment. Listening to white noise (taped ocean sounds) at night may improve sleep quality in postoperative cardiac surgical patients (101).

If sleep promotion is to be effective in the ICU, a paradigm shift must occur at all levels of the healthcare team. Although there is a paucity of information supporting the idea that environmental alterations in the ICU and other interventions can reliably improve sleep quality, it is apparent that a less hostile ICU environment would increase patient comfort and decrease patient anxiety, which in turn may lead to better sleep.

FUTURE DIRECTIONS FOR RESEARCH ON SLEEP AND RECOVERY FROM ILLNESS

Research on the effects of protocols that enhance the quantity and quality of sleep during recovery from critical illness or injury are lacking. Specifically, randomized controlled trials evaluating the effects of strategies to improve sleep quantity and quality during recovery are needed. These trials should be designed to identify differences in outcomes, such as hospital length of stay, ICU length of stay, ventilator days, infectious complications, nutritional markers, and mortality. In addition, such trials should be designed to search for a possible mechanism of potential outcome differences by examining the effects of improved sleep on circulating markers of inflammation.

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