CHEST Postgraduate Education Corner

CONTEMPORARY REVIEWS IN SLEEP MEDICINE

Sleep in the ICU

Potential Mechanisms and Clinical Implications

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Patients in the ICU are known to have severely disrupted sleep with disturbed circadian pattern, decreased nocturnal sleep time, abnormally increased stages 1 and 2 sleep, and reduced or absent deep sleep. Recent data reveal that a subpopulation of critically ill patients manifests unique EEG sleep patterns. The etiology of sleep disruption in the ICU includes the inherent nature of the environment, medications, ventilator-patient interaction, and the effect of acute illness. How sleep disruption contributes to outcomes in critically ill patients, such as recovery time and weaning from mechanical ventilation, is unknown. This article reviews the literature describing sleep in ICU patients, including recent investigations in patients who require mechanical ventilation, factors that affect sleep in critically ill patients, and the potential mechanisms and clinical implications of disturbed sleep in the ICU setting with directions to consider for future investigations. ***(CHEST 2009; 136:284–294)***

Abbreviations: ACV = assist-control ventilation; CS = continuous sedation; DEX = dexmedetomidine; GABA = γ-aminobutyric acid; HPA = hypothalamic-pituitary-adrenal; IL = interleukin; IS = intermittent sedation; NIPPV = nasal intermittent positive-pressure ventilation; NREM = non-rapid eye movement; PAV = proportional assist ventilation; PSG = polysomnography; PSV = pressure support ventilation; REM = rapid eye movement; SSRI = selective serotonin reuptake inhibitor; SWS = slow-wave sleep; TNF = tumor necrosis factor; TST = total sleep time

For > 30 years, sleep abnormalities have been well documented problems in patients who are hospitalized in the ICU.[1–9] Quantitative and qualitative deficiencies have been characterized and include decreased total sleep time (TST), decreased deep (or restorative) sleep, fragmented sleep, as well as altered circadian patterns.[1–8] Partial or total sleep deprivation may result. Total sleep deprivation infers complete loss of all sleep for the designated time period. Partial sleep deprivation may be chronic and may constitute insufficient hours of sleep, a reduction or absence of a specific sleep stage, and, often overlooked, the lack of consolidated sleep due to one or more factors that elicit awakening or arousals and impair the normal progression/pattern of sleep stages.

The etiology of sleep perturbation in ICU patients is multifactorial. Moreover, it is noteworthy that sleep duration, architecture, and the sleep-wake cycle are closely associated with many metabolic and regulatory processes that impact critically ill patients by engendering detrimental physiologic and psychological sequelae.[7,9–13] However, high-level evidence regarding the effect of sleep deprivation on recovery from acute illness or the morbidity and mortality in ICU patients remains to be described.

This article provides a review of the literature describing relevant features of sleep physiology and highlighting current knowledge of sleep in adult ICU patients, including recent investigations addressing issues related to individuals who require mechanical ventilation, factors that affect sleep in critically ill patients, as well as the potential mechanisms and clinical implications of disturbed sleep in the ICU environment with direction for future investigations.

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Normal Sleep Architecture and Regulation

Sleep is characterized by a variety of physiologic, behavioral, and EEG changes and is necessary for restoration of cognitive, mood, and physiologic functions.[12,14] Normal sleep architecture, measured by polysomnography (PSG) is divided into the following two distinct states: non-rapid eye movement (NREM) sleep and rapid eye movement (REM) sleep.[14–16] NREM is composed of three distinct stages based on EEG criteria. Stage 1 and 2 are considered to reflect light sleep followed by deep slow-wave sleep (SWS). SWS is an anabolic state and considered the most restorative stage of sleep for physiologic repair.[16]

REM sleep is thought to be necessary for memory consolidation. REM sleep resembles wakefulness by EEG characteristics with bursts of REMs, and it is a catabolic state. However, motor neurons are inhibited, resulting in inhibition of major muscles, except the diaphragm and ocular muscles. Breathing and heart rate are often irregular.[14,16]

Many of the agents used in treating critically ill patients are also directly relevant to the sleep process. Regulation of the sleep-wake cycle is complex and controlled by a balance among the homeostatic need for sleep, circadian rhythm, and interaction between neurotransmitters.[14,16] Neurotransmitters that promote wakefulness include catecholamines (norepinephrine and dopamine) glutamate, histamine, hypocretin (orexin), and acetylcholine. Acetylcholine is also a major REM-promoting neurotransmitter, whereas noradrenergic and serotonergic neurons inhibit REM sleep.[16]

Neurotransmitters predominantly associated with promoting SWS are serotonin and γ-aminobutyric acid (GABA), whereas certain cholinergic neurons inhibit SWS.[14,16] Various inflammatory factors that are involved in acute illness, such as interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF)-α also promote SWS and participate in sleep regulation.[17] Adenosine, a ubiquitous nucleoside and by-product of energy metabolism, promotes sleep by inhibiting wake-active neurons and is thought to be a homeostatic regulator of energy in the brain during sleep. Caffeine and theophylline are adenosine antagonists.

The circadian pacemaker, located in the suprachiasmatic nucleus, is modulated primarily by light and ambient temperature, causing normal sleep to occur at nighttime. Melatonin, secreted by the pineal gland and inhibited by light, has a diurnal variation and thus promotes nocturnal sleep. The physiologic relationship between light exposure and the sleep-wake cycle is an important aspect of sleep in ICU patients because the circadian pattern of light exposure is so unnatural in this setting.

Like melatonin, adrenal secretion of cortisol and body temperature follow a circadian pattern.[16,18,19] The hypothalamic-pituitary-adrenal (HPA) axis modulates the response and release of cortisol to stress. SWS inhibits HPA activity, and reciprocally, glucocorticoids or HPA activation impairs sleep. The HPA axis and disruption to these various regulatory mechanisms is particularly important in ICU patients who are in high-stress states and more vulnerable to sleep disturbance.

Implications of Sleep Deprivation

Studies of sleep-deprived animals and healthy humans reveal many derangements in physiologic parameters that could negatively affect the underlying pathophysiology, treatment, and recovery from acute critical illness in ICU patients.[20–31] Even short-term, partial sleep deprivation (6 nights of 4 to 5 h of sleep per night) results in untoward effects. Studies demonstrate decreased glucose tolerance and increased insulin resistance, which could impact glycemic control in ICU patients. There is increased activation of the HPA axis, resulting in an increased heart rate, BP, and cortisol level, whereas growth hormone peak and melatonin onset are decreased. Thermoregulation is disrupted and gastric acid secretion is increased. Inflammatory cytokines (TNF-α, IL-1, and IL-6) and C-reactive protein, known to cause vascular injury and increase insulin resistance, are also increased and may amplify the impact of sepsis physiology.[21–24]

Additionally, increased anxiety and impaired cognitive performance occur and may contribute to acute delirium. This may adversely impact patient care by necessitating sedation, which is known to prolong mechanical ventilation.[25] In patients with stable moderate to severe COPD, 1 night of sleep loss was associated with a decrease in pulmonary function, which could further prevent the ability to wean from mechanical ventilation.[28–30] Little is known about the clinical ramifications of sleep deprivation during critical illness, and further research is needed to define population characteristics and effect on physiologic parameters and patient outcomes.

Sleep Patterns in ICU Patients

More than 60% of patients surviving ICU admission report poor sleep or being sleep deprived.[32,33] Other studies have shown that patients recall fre-

quent interruptions and memories of pain, anxiety, and fear that impaired their ability to sleep.[33,34] In a study of 464 patients, 51% recalled experiencing dreams and nightmares over the course of their ICU admission; 14% of these patients, 6 months after ICU discharge, believed these dreams continued to negatively impact their quality of life.[35] Additionally, nurses' subjective clinical assessment of patients' sleep correlates poorly with the patient's own perception of sleep quality.[36] Compared with PSG, nurses were inaccurate 26% of the time in determining the presence of sleep and often overestimated sleep time, indicating the need for objective measurement of sleep in this vulnerable population.[4,37,38]

Early PSG investigations in ICU patients revealed sleep deprivation as indicated by decreased TST and disrupted sleep architecture with increased stages 1 and 2 NREM sleep and decreased SWS and REM sleep.[2,3] However, these studies were limited to 8-h nocturnal data collection and usually excluded patients on mechanical ventilation or sedation.

In order to evaluate circadian pattern and the contribution of daytime sleep, 24-h PSG studies in various patient populations were conducted. Studies demonstrated mixed results with mean 24-h TST ranging between 3.2 and 19.4 h and large intersubject variation with some patients sleeping < 1 h. This clearly indicates that some patients were quantitatively sleep deprived.[1,4,7,8,11,39,40] More than 40% of sleep occurred during the daytime.[7,8,39–41] TST over a 24-h period that is "normal" (using nocturnal standard normative values) but is obtained by a combination of short nocturnal sleep plus abnormally timed (daytime) sleep may not achieve the same physiologic benefit as a "normal" TST obtained at night. Consistent with nocturnal studies, 24-h PSG studies also demonstrated abnormal sleep architecture with lack of the normal sequential progression through sleep stages, abnormal distribution of sleep stage quantities, and fragmented sleep with increased arousals and awakenings. Most investigations have shown excessive stages 1 and 2 sleep and reduced to absent SWS and REM sleep.[1,4,8,41]

However, Gabor and colleagues[11] found REM sleep to be 2.5 times higher (14.3% of TST) than previously reported in ICU patients. The authors did not speculate about why their patients had more REM sleep than in prior studies. This discrepancy may reflect different patient profiles where previous patients received REM-suppressing medications or patients were studied at various points in the course of illness such that the latter patients were experiencing REM rebound. In postsurgical patients, REM sleep has been described as biphasic with severely diminished or no REM sleep for the first few nights followed by REM rebound on day 3 with peak levels higher than preoperatively.[4,42–44] Surgery is known to disrupt the circadian regulation of cortisol, melatonin, core body temperature, and the autonomic nervous system with increased norepinephrine levels, which could suppress REM sleep.[44]

Until recently, studies have excluded patients who were receiving continuous sedation (CS) or required aggressive hemodynamic support. Cooper and colleagues[39] were the first to investigate 24-h sleep patterns in 20 critically ill mechanically ventilated patients who received CS/narcotics. Patients were retrospectively categorized into three patient groups based on the following EEG features: disrupted sleep (all stages of sleep were present), atypical sleep (absent stage 2 sleep), or the presence of "coma" (> 50% delta or slow frequency waves). Twelve of the 20 patients were considered to have "unidentifiable electrophysiologic sleep." Seven of these patients had > 50% delta activity believed to be consistent with encephalopathy or coma (four patients had pathologic wakefulness where the patient has behavioral correlates of wakefulness, but with slow-frequency EEG), and the other five patients had atypical EEG patterns (no stage 2). Severity of illness scores, sedatives and narcotic doses were higher among these patients, although no specific source for encephalopathy could be determined to explain the increase in delta activity.

Similar to Cooper's study, Hardin and coworkers[40] prospectively evaluated three groups of mechanically ventilated patients (18 patients) receiving either CS with and without neuromuscular blocking agents or intermittent sedation (IS). All three groups demonstrated increased delta activity. Patients who received CS had a greater percentage of delta activity and with slower frequency than patients who received only IS (Fig 1). Of particular note, patients receiving neuromuscular blocking agents were scored as awake 20% of the time. Severity of illness scores, sedatives, and narcotic doses were higher among the patients receiving CS, but no specific source for encephalopathy could be determined to explain the increase in delta activity.[39,40] However, all patients receiving CS demonstrated appropriate EEG response to external stimuli. This implies intact brain reactivity and is less supportive of "coma" as the etiology. Importantly, patients in the IS group who were completely awake and responsive also had more slow-wave activity than previously reported. This may indicate pathologic wakefulness (behavioral correlates of wakefulness but with slow frequency EEG) as in the study by Cooper et al,[39] or the slow waves may be reflective of other mechanisms, such as medications or recovery from illness. The pattern of sleep-wake organization and its resemblance to normal sleep-wake encephalographic characteristics

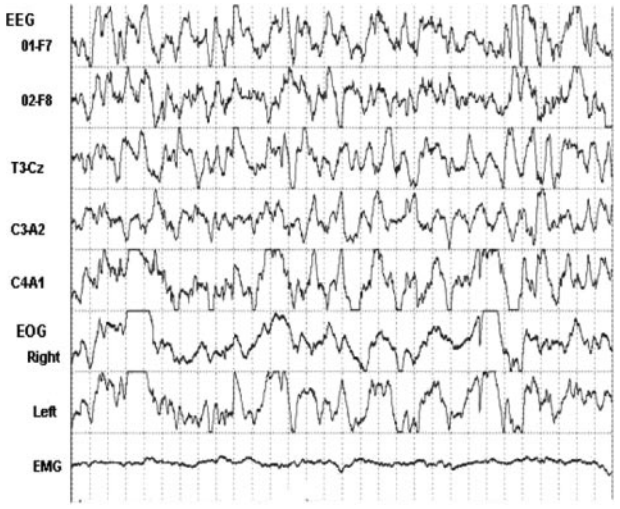

FIGURE 1. Low-voltage delta waves: nonphysiologic sleep. Shown are 30-s polysomnographic epoch representations of low-voltage, low-frequency delta activity scored as SWS. Each box represents 80 μV. From Hardin et al.[40]

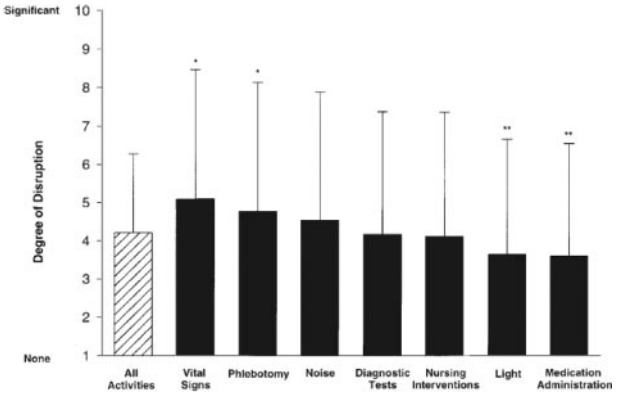

FIGURE 2. Patient's perception of factors disrupting sleep. Reprinted with permission from Freedman et al.[32]

based on 24-h PSG is a reliable prognostic marker for survival and functional recovery in the subacute phase (> 24 h off any sedative medication) of post-traumatic head injury coma.[45] Whether a similar process may be present in patients with acute illness needs to be determined.

FACTORS CONTRIBUTING TO SLEEP DISRUPTION

Many factors can disturb sleep in ICU patients. These include the environment with disruptions due to noise, lighting, and patient care activities; disruption due to medical illness itself; and sleep disturbance due to medical treatments, such as respiratory care, drug therapies, and mechanical ventilation.[7,9–11]

The ICU Environment

Noise: The Environmental Protection Agency recommends hospital noise levels be < 40 dB.[9] Noise levels in ICUs have been found to be elevated with average daytime sound peaks of 150 to 200 dB and nighttime peaks > 80 dB (for reference, sitting in front-row seats of a rock concert reflects exposure to approximately 110 dB).[9] Surprisingly, PSG studies in ICU patients show that only 10 to 30% of arousals/awakenings could be attributed to noise.[7,11,46] Patients also subjectively report that noise was not the most disruptive factor[32] (Fig 2). Nonetheless, of specific sources of noise (staff talking, various alarms, ventilator sounds, suctioning sounds, physician beepers, telephone, and television), staff talking accounted for 26% of the noise, had the highest peak decibel level, and was perceived to be the most disruptive.[11,32,46] Additionally, when healthy subjects slept in the ICU, noise caused even more (57%) arousals and awakenings, and staff conversations and alarms were rated to be the most disruptive.[11] This suggests that as patients recover from illness or become more cognitive, noise may be perceived as a more substantially disruptive sleep factor. Studies have shown that implementing guidelines and education of staff regarding noise can effectively change staff behavior and reduce peak noise levels.[46–48] Decreasing noise with ear plugs improves sleep efficiency and REM sleep in normal subjects in a simulated ICU environment and has subjectively improved sleep in ICU patients.[49,50] But when healthy subjects have slept in open vs private ICU rooms, there was no change in sleep architecture or fragmentation despite lower peak noise levels in private rooms.[11] Stanchina and colleagues[51] speculated that it was not the peak noise levels that created disruption but rather the change in noise level. They found that adding white noise to background ICU noise substantially reduced patients' arousals from 48.4/h back to baseline no-noise level of 13.3/h. Table 1 suggests strategies that may optimize sleep in the ICU.

Patient Care Activities: Despite the use of new technologies to monitor patients, frequent hands-on manipulation of sleeping patients continues to be the norm in critical care units. Studies have documented a mean range of 40 to 60 direct patient contacts during the night for activities such as wound dressings, medication administration, and nightly baths.[52,53] Approximately 10% of arousals and awakenings over a 24-h period are due to patient-care activities.[11] Other studies show that patients are interrupted so often that only 5 to 30 min of

Table 1—*Strategies to Improve Sleep in ICU Patients*

Barriers to Sleep	Strategies to Optimize Sleep in the ICU
Noise	Limit unnecessary noise, such as televisions and phones in the ICU
	Consider liberalizing the monitor alarm setting, if appropriate, and have central monitoring personnel
	Keep patients' doors closed, if possible
	Post signs to remind staff and visitors to minimize conversations at or near the bedside
	Adhere to visiting hours
	Encourage staff to switch their beepers and other electronic devices to "vibrate" at night
	Limit the number of visitors at a time and/or if appropriate consider ear plugs
	Add background low-level white noise
	Consider monitoring decibel level in the ICU, particularly at night
Patient-care activities	Minimize bathing, dressing changes, room switches, and other activities at night
	Regularly review nighttime orders to see whether to decrease the frequency of overnight monitoring (*eg*, fingersticks, draws for laboratory testing, or checking of vital signs)
Circadian rhythm	Encourage exposure to brighter light during the day (turn on the lights, open the curtains), and turn off the lights by 10:00 PM
Medications and substances	Minimize use of benzodiazepines for sleep; consider melatonin
	Consider short-acting IV agents, such as propofol
	Avoid starting multiple medications at one time; minimize use of sleep-disrupting medications
Discomfort	Maximize pain management, particularly with procedures
	Evaluate patient for anxiety as source of sleep disruption and treat accordingly with reorientation to environment, nightmares, dyssynchrony with the ventilator, effect from medications
Ventilator	Adjust settings and mode of ventilator to maximize patient-ventilator synchrony, avoid hyperinflation
	Provide nocturnal O_2, NIPPV as appropriate; if patient is receiving NIPPV, assess the mask's fit and comfort, and maximize synchrony with ventilator

undisrupted time may be available for sleep.[3,9] Despite attempts to optimize the environment, studies have shown that patients continue to exhibit disrupted sleep, indicating there are other factors more intrinsic to the patient that may be the source.[4,47] Nonetheless, longer periods to allow sleep consolidation should be fostered. Although it may be cumbersome to implement, staff need to coordinate with the patient's nurse all activities of ICU care; this may require changing routine schedules to facilitate nighttime sleep (Table 1).

Circadian Rhythm Disruption: Daytime sleep represents 40 to 50% of TST in ICU patients.[7,8,39,40] Nighttime patient-care activities often disrupt the sleep-wake cycle. Variation in the light-dark pattern also disrupt the normal sleep-wake cycle. Although light levels have been adjusted to simulate a circadian variation with higher mean peak levels during the daytime (1,602 to 5,089 lux) and lower levels at nighttime (127.6 to 318.5 lux),[9] the normal circadian variation in melatonin measured by urinary and serum levels was lost in critically ill patients and may impact sleep regulation.[18,54–58] Avoiding high nocturnal light levels and intermittent bursts of bright light, such as with nursing activities, could be important for sleep consolidation.

Mechanical Ventilation

Approximately 60% of patients complain of disturbed sleep related to being on a ventilator; 30% stated they felt panic and anxiety, which directly inhibited their ability to rest and sleep.[59] Only recently has mechanical ventilation been investigated as a direct mechanism causing sleep disruption. Potential factors that may contribute to sleep disruption due to mechanical ventilation include mode of ventilation, patient-ventilator asynchrony, and improper ventilator settings.[10,60]

Parthasarathy and Tobin[10] compared 11 patients on mechanical ventilation in a randomized crossover study who received assist-control ventilation (ACV) and pressure support ventilation (PSV). Six of the 11 patients developed central apneas with increased sleep fragmentation while on PSV but not during ACV. Five of these six patients had a history of congestive heart failure. The other five patients did not have central apneas, and in four of these five patients, there was no difference in sleep fragmentation between modes of mechanical ventilation. Adding dead space to those patients with central events increased end-tidal P_{CO_2} and decreased central apneas along with arousals and awakenings and improved sleep efficiency.

When low level (6 cm H_2O) PSV was compared to ACV in patients with acute or chronic respiratory failure who were near extubation, ACV was associated with improved sleep architecture with increased SWS and REM sleep.[61] However, when Cabello and coworkers[62] compared automatically adjusted PSV to clinician-adjusted PSV and ACV in nonsedated patients, there was no difference in sleep between the groups. This may be due to clinicians adequately

matching ventilator settings with the patient's underlying pulmonary mechanics or a different population with less carbon dioxide retention.

Switching modes of ventilation during sleep may be unnecessary as long as overventilation and ineffective patient effort are prevented. When PSV settings are congruent with the patient's effort, sleep improved and requirements for pressure support and positive end-expiratory pressure actually decreased.[63] This was further supported when proportional assist ventilation (PAV) was compared with PSV in sedated patients; PAV was associated with better patient-ventilator synchrony, less arousals and awakenings, and improved sleep architecture than in the PSV group.[64,65]

Instituting management strategies based more closely on patient-ventilator mechanics, rather than tidal volume or respiratory rate, may improve sleep quality. Further studies are needed in various patient populations to confirm that PAV may be a superior mode of ventilation for decreasing arousals related to ventilator asynchrony, as well as comparison studies in the ICU with nasal intermittent positive-pressure ventilation (NIPPV).

Medications

Any agent that acts on or through sleep regulatory neurotransmitters, modulators, or their receptors can impact sleep architecture. Abrupt withdrawal from chronic medications, including recreational drugs, can cause severe sleep disruption and delirium. In critically ill patients, it is difficult to ascertain a single drug's effect on sleep architecture. Pharmacokinetics may be altered due to variable volume of distribution, renal and hepatic clearance/metabolism, and the confounding adrenergic effects from acute stress.[66,67] Table 2 summarizes the effect on sleep architecture and mechanism of action of drugs that are frequently used in ICU patients.

Benzodiazepines and opiates are commonly used in the ICU, particularly in patients on mechanical ventilation. However, sedation does not imply normal or quality sleep and can have negative effects. Although intermittent low doses of benzodiazepines decrease sleep latency and increase TST, they also increase spindle activity (stage 2 sleep) and cortical arousals and decrease SWS.[14] At higher doses, a dose-dependent suppression of cerebral function occurs manifested by diffuse slowing or delta waves followed by a reduction in EEG amplitude and ultimately a lack of electrical activity and death.[68,69] Benzodiazepines activate CNS GABA type A receptors and are thought to cause acute brain dysfunction by altering other CNS neurotransmitters, such as norepinephrine and glutamate that potentially induce delirium and impair sleep.[70–72]

Although there are clear indications for sedation in the ICU, further exploration is required to determine if prolonged sedative-induced sleep facilitates or impairs recovery and which agent is optimum.[73] Excessive sedation is known to increase days on mechanical ventilation and prolong ICU stay.[74,75] Short-acting agents, such as propofol (Diprivan; AstraZeneca; Wilmington, DE), do not induce better sleep quality in ICU patients than lorazepam (Ativan; Wyeth/Baxter; Deerfield, IL).[76,77] Although studies have not evaluated the direct affect on sleep, dexmedetomidine (DEX) [Precedex; Abbott; Abbott Park, IL], a novel α_2-specific agent, produces better anxiolytic effect plus analgesia while maintaining a higher degree of arousability without respiratory impairment or hypotension when compared to propofol or lorazepam.[78,79] Randomized trials are needed to evaluate whether DEX may be a better agent to use in critically ill patients to promote sleep and more effective sedation.

Reduction in REM sleep can occur with several medications (Table 2), particularly narcotics, selective serotonin reuptake inhibitor (SSRI) antidepressants, and/or vasopressor agents.[19,66] Although REM sleep is thought to be necessary for mental well-being, patients most frequently complain of vivid disturbing dreams, confusion, and anxiety (delirium) during the 3rd to 5th days postoperatively coinciding with the resurgence of REM sleep.[42] Interestingly, cardiovascular complications (including stroke) also occur most frequently during this time and may be related to the respiratory and autonomic instability associated with REM sleep. The etiology of REM rebound during this time is most likely due to the withdrawal of narcotics. A linear relationship has been demonstrated between decreasing dosage of morphine and increasing REM sleep (Fig 3). The duration before REM sleep returns to normal after prolonged administration of narcotics is unknown.

Melatonin, a naturally occurring hormone, can now be provided as a supplement. Melatonin promotes sleep without inducing daytime sedation or respiratory depression and maintains normal sleep architecture.[66,80,81] Shilo and coworkers[58] investigated the effect of exogenous melatonin on the sleep in ICU patients with COPD. In a double-blind, placebo-controlled study, eight patients were given 3 mg of melatonin or placebo tablets at 10:00 PM on 2 consecutive nights. Investigators reported that melatonin increased TST and decreased sleep fragmentation. The placebo data were not shown; therefore it is difficult to establish what change occurred from baseline. A recent study by Bourne and coworkers[82] indicated melatonin improved sleep efficiency in patients on mechanical ventilation. They conducted a randomized double-blind, placebo-controlled trial

Table 2—*Common Drugs in ICU Patients and Effect on Sleep Architecture*

Drug Class	Examples of Drugs	Effect on Sleep Architecture	Potential Mechanism
CNS			
AED	Phenobarbital, carbamazepine, phenytoin	Very sedating. AEDs tend to ↑ TST, ↓ sleep latency. May ↑ SWS	Action on neuronal sodium influx in glutamate channels or GABA type A
TCA	Amitriptyline, imipramine, nortriptyline, desipramine, doxepin, clomipramine	Very sedating; suppresses REM sleep, ↑ TST, ↑ stage 2 sleep	Antimuscarinic activity, α_1-receptor stimulation
Anxiolytic BzRA	Alprazolam, lorazepam, diazepam, oxazepam, propofol	Very sedating; ↑ TST, ↓ sleep latency, ↓ SWS duration, ↓ REM, ↑ stage 2 sleep same	GABA type A receptor stimulation; may also affect endocannabinoid
SSRI	Sedating: paroxetine, fluvoxamine; "activating": fluoxetine, sertraline, citalopram	In general, SSRIs tend to ↑ TST; less sedating than TCAs and MAOIs; ↓ REM, ↓ SWS ↑ TST, ↓ SE	↑ 5HT activity
SNRI	Venlafaxine	TST	↑ 5HT and NE activity
Mood stabilizer	Lithium	↑ TST, ↑ SWS, ↑ stage 2 sleep, ↓ REM, ↓ REM latency	Neuronal sodium channels
Anti-Parkinson	Bromocriptine, levodopa	Sedating; nightmares, ↓ SWS	Dopamine
Cardiovascular			
Stimulant	Norepinephrine, epinephrine dopamine	Activating; ↓ REM, ↓ SWS	α_1-, α_2-, β−Receptor stimulation; D_2 α_1-receptor stimulation
Lipophilic β-blocker	Propranolol, pindolol, metoprolol, timolol	Activating; ↑ awakenings, ↑ TWT, ↓ REM, nightmares	CNS β-blockade
α_2-Receptor agonist	Clonidine, DEX	↑ Stage 1, ↓ REM, nightmares	α_2-Receptor stimulation
α_1-Receptor blocker	Doxazosin, prazosin, terazosin	↑ TST	α_1-Receptor inhibition
Analgesic			
Opioid	Codeine, morphine, hydrocodone	Sedating; ↓ SWS, ↓ REM	μ-Receptor stimulation
NSAID	Ibuprofen, indomethacin, celecoxib	↓ TST, ↓ SE	Prostaglandin synthesis inhibition
Other			
Methylxanthine	Theophylline	Activating; ↓ TST, ↓ SE, ↑ stage 1, ↓ REM	Inhibits adenosine
Antihistamine	Diphenhydramine, promethazine	Sedating	Histamine 1 receptor blockade and can have Ach effect
Corticosteroid	Dexamethasone, prednisone	Activating; ↓ REM, ↓ SWS, nightmares	↓ Melatonin secretion

Ach = acetylcholine; AED = antiepileptic drug; BzRA = benzodiazepine; DOPA = dopamine; 5HT = serotonin, serotonergic; MAOI = monoamine oxidase inhibitor; NE = norepinephrine; NSAID = nonsteroidal antiinflammatory drug; SE = sleep efficiency; SNRI = serotonin norepinephrine reuptake inhibitor; TCA = tricyclic and tetracyclic antidepressant; ↓ = decrease or reduce; ↑ = increase.

in 24 patients who had undergone a tracheostomy to assist in weaning from mechanical ventilation. Patients did not receive narcotics or sedatives for > 48 h, and attempts were made to control the ICU environment. Enteral melatonin, 10 mg, or placebo was administered at 9:00 PM for 4 nights. Nocturnal sleep was monitored using the Bispectral Index Sensor. All patients had severely restricted sleep time. Those who received melatonin had a 1-h increase in sleep, although the improvement in sleep efficiency did not reach statistical significance. The effect of melatonin on sleep architecture is unknown because PSG was not used. The 10-mg dose resulted in sustained supranormal plasma levels, and the effect on daytime sleep was not measured.

Side effects of melatonin are uncommon. However, drug–drug interactions may occur, particularly with immunosuppressive agents due to its proimmunologic actions.[83,84] Although promising, there is insufficient data to warrant routine administration of melatonin in critically ill patients. Further studies are needed using PSG to evaluate the sleep efficacy of melatonin and dosage in larger randomized trials with various populations of critically ill patients.

Inherent Effect of Critical Illness

Patients with chronic medical problems, such as COPD and obstructive sleep apnea, often have less deep sleep with increased arousals or awakenings.[19]

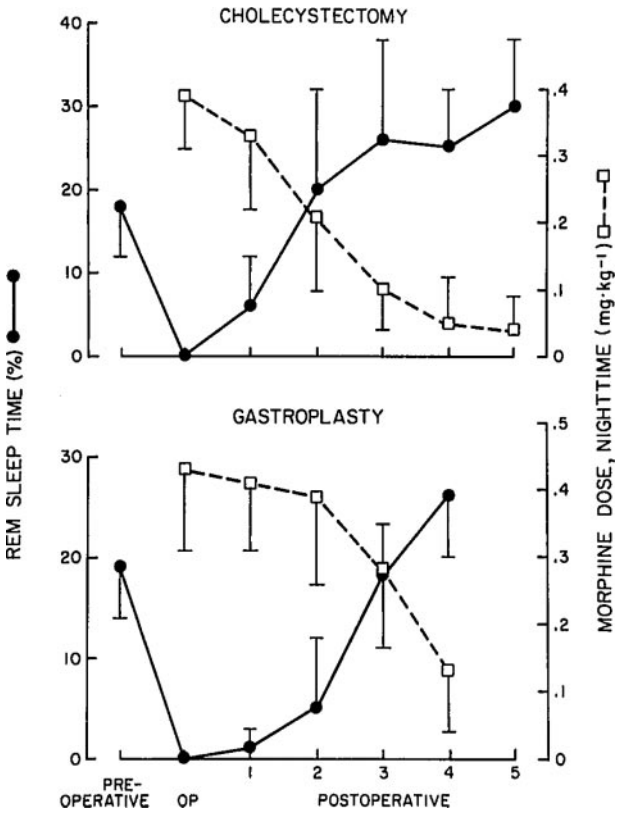

FIGURE 3. Relationship between REM sleep, morphine, and perioperative period. Reprinted with permission from Knill et al.[42]

Acute illness can exacerbate sleep disruption due to symptoms such as pain, nausea and vomiting, and fever.[85] In humans and animals, acute illness is associated with an increased need to sleep.[17,19] Data suggest that critically ill patients with higher severity of illness scores have greater sleep disturbance, as well as abnormal electrophysiologic sleep patterns with absent sleep stages and increased low amplitude slow waves.[39,40,86] However, the mechanism of this altered pattern is poorly understood. It is difficult to determine from these small studies whether the abnormal electrophysiologic patterns are due to sedation, the inherent effect of acute illness, or a normal adaptive process related to acute illness, particularly during sepsis or acute inflammation.

Sepsis is associated with biochemical changes that affect sleep regulation and sleep architecture. Mundigler and coworkers[87] demonstrated that circadian secretion of melatonin is altered in septic vs nonseptic ICU patients. Septic patients maintained a continuous secretion of melatonin, in contrast to normal cyclic variation of melatonin in the nonseptic patients. Melatonin is known to have immunologic properties. In animal models of sepsis, melatonin is necessary for free-radical scavenging, antioxidant properties, and survival from sepsis.[19,83,84] The continuous excretion of melatonin noted in septic patients supports the immunologic role of melatonin and suggests that increased sleep is necessary for recovery from illness.

Acute infection in animal models increases SWS and reduces REM sleep. IL-1 and TNF, both released during sepsis, induce a centrally mediated pyogenic and somnogenic effect, as well as enhance the acute phase response to infection by increasing cortisol, WBC, and other inflammatory cytokines.[88,89] In healthy human subjects, acute inoculation with rhinovirus and low-dose endotoxin elicited a mild increase in quantity and consolidation of SWS.[17,88,89] Additionally, low-voltage mixed frequency or slow waves have been demonstrated in nonsedated critically ill patients who developed sepsis or had positive blood cultures.[7] These EEG changes occurred while the patient's eyes were both open and closed and are thought to be consistent with a "dissociative state" of consciousness reflecting neither normal sleep nor wakefulness.[7,90] Importantly, these EEG changes preceded the onset of clinical signs of sepsis and may be an early indicator of illness. Other studies do not confirm such a direct relationship of EEG changes with positive blood cultures.[11,39,40] In the study by Gabor et al,[11] five of seven patients had positive blood culture findings, but SWS accounted for only 2.7% of TST. Other studies show increased low-amplitude slow waves but without positive blood cultures.[39,40] This may be related to the clinical course of the infection, prior antibiotic administration, or a focal source of infection.

Delta activity in normal subjects is strongly related to prior wakefulness and sleep deprivation (homeostatic need for sleep). It is unknown how much sleep is required during illness and whether increased delta activity may be due to the homeostatic need for restorative sleep.[17] Sepsis may alter sleep by affecting the neurohormonal environment in the CNS or by a more direct affect on electrical activity. REM sleep is the most vulnerable period and associated with more cardiovascular instability. Therefore, it is suggested that during acute illness, the lack of REM sleep may be an adaptive and protective mechanism. Serial PSG or EEG is needed in acutely ill septic patients to determine the changes in sleep patterns related to infection and recovery from illness.[19]

SUMMARY

Sleep in the ICU is perceived by patients to be poor, often associated with fear, anxiety, and nightmares that impair later quality of life. Quantitative and qualitative sleep deprivation occurs and can have

negative consequences on physiologic function, particularly immune mechanisms, as well as psychological well-being. Noise, particularly staff talking and patient-care activities, are clearly contributing factors and represent 40% of the source of sleep disruption. Medications such as vasopressors, benzodiazepines, and narcotics can suppress both SWS and REM sleep. Recent studies also indicate that patient-ventilator discordance contributes to poor sleep. Sleep quality may be enhanced by modifying the ICU environment to decrease staff conversation, decrease nocturnal lighting and routine nursing-care activities, as well as selection of a ventilatory mode that is congruent with the patient's effort and with the goal of preventing overventilation.

Although most studies have shown that patients exhibit increased stage 1 and 2 sleep with diminished SWS, a subgroup of critically ill patients demonstrate unidentifiable electrophysiologic sleep with increased delta or slow-wave activity. Whether the excessive slow-wave activity is secondary to sedation, acute illness, and particularly sepsis, and how it may affect recovery from illness warrants further investigation in ICU patients who have higher severity of illness scores, receive ongoing sedation or narcotics, and who require more aggressive supportive care measures. Larger longitudinal studies in various severely ill populations, with concomitant measures of melatonin, IL, and TNF, are needed to delineate the contribution of each of these factors to sleep architecture and the effect on ICU outcomes. Future interventions that target sleep may be a mechanism to modulate the inflammatory response. Melatonin, a naturally occurring hormone with immunologic properties, may have a future role in facilitating sleep.

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