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Sleep in the Intensive Care Unit Setting

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Sleep is essential to human life. Sleep patterns are significantly disrupted in patients who are hospitalized, particularly those in the intensive care unit. Sleep deprivation is pervasive in this patient population and impacts health and recovery from illness. Immune system dysfunction, impaired wound healing, and changes in behavior are all observed in patients who are sleep deprived. Various factors including anxiety, fear, and pain are responsible for the sleep deprivation. Noise, light exposure, and frequent awakenings from caregivers also add to these effects. Underlying medical illnesses and medications can also dramatically affect a patient's ability to sleep efficiently. Therapy with attempts to minimize sleep disruption should be integrated among all of the caregivers. Minimization of analgesics and other medications known to adversely affect sleep should also be ensured. Although further research in the area of sleep deprivation in the intensive care unit setting needs to be conducted, effective protocols can be developed to minimize sleep deprivation in these settings. **Key words:** *critical care*, *deprivation*, *disruption*, *immune dysfunction*, *sleep*

SLEEP is vital for basic survival in humans. One third of each person's life is spent asleep. All body systems require an adequate amount of sleep to maintain proper function and any disruption in the sleep cycle can dramatically impair any or all of the body systems. Animal studies have shown that rats deprived of sleep for 3 weeks died as a result of the sleep deprivation.[1] Current evidence is increasing regarding the effects of critical illness and its surrounding environs on sleep. This article reviews the effects of acute illness on sleep and reviews an integrated approach to the treatment of sleep deprivation in patients who have acute illness and are being cared for in the intensive care unit (ICU) setting.

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NORMAL SLEEP

Normal sleep architecture is divided into 2 phases, nonrapid eye movement (NREM) and rapid eye movement (REM) (Fig 1). *Nonrapid eye movement* sleep is divided into 3 stages (stages 1, 2, and *N*). Stage 1 sleep is a drowsy state characterized with high muscle tonus and the presence of slow rolling eye movements. Stage 2 sleep is characterized by a decrease in muscle tone and usually occupies 50% of the sleep period. Stage N (formerly known as delta or stage 3/4 sleep or slow-wave sleep) is thought to be the most restful part of sleep and during this stage an increase in growth hormone secretion and a decrease of body metabolism and cortisol secretion occur.[2,3] Rapid eye movement sleep is characterized by an active brain activity with absent muscle activity and is the stage where most dreaming is believed to take place.[2]

The sleep and wake states are generated by 2 general and separate processes (circadian C and homeostatic S processes [Fig 2]). The circadian rhythm is based on a daily internal body clock, which promotes wakefulness during the day and consolidation of sleep during

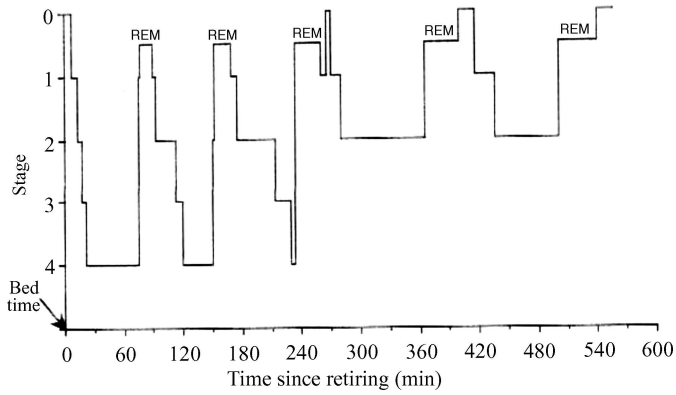

Figure 1. Hypnogram sleep-wake cycle. Normal sleep. Rapid eye movement onset usually occurs between 90 and 120 minutes and increases in duration as sleep continues. The majority of delta sleep (slow-wave sleep) occurs during the first half of the night. Adapted from the *Journal of Internal Medicine*.[2]

the night. The homeostatic process (process S) relates the amount and intensity of sleep to the duration of prior wakefulness. This latter process promotes sleep and builds during wakefulness, thus increasing the drive for sleep as the day progresses.[4,5]

A complex interaction of various neurotransmitters (including norepinephrine, serotonin, acetylcholine, dopamine, histamine, and γ-aminobutyric acid) regulates the sleep and wakefulness.[3] These interactions occur primarily within the suprachiasmatic nucleus within the hypothalamus and the midbrain. One specific substance, melatonin, has undergone a significant degree of investigation over the last decade and is felt to me a major contributor in the sleep-wake cycle.[6,7] The circadian pacemaker from the suprachiasmatic nucleus triggers the pineal gland to produce melatonin at night, thus giving reference to melatonin being the "hormone of darkness." Melatonin levels are usually low during the day and increase at night and are affected by the presence of light.[7]

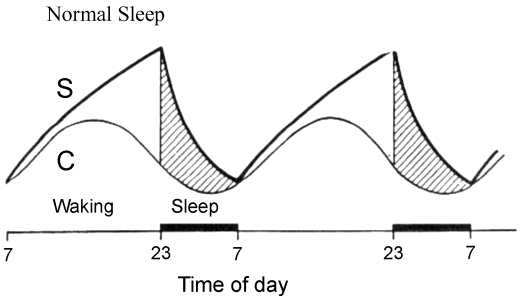

Figure 2. Process C and process S. Adapted from Kryer.

SLEEP DEPRIVATION

Sleep is an essential restorative process, with important circadian variations in protein synthesis and cellular division being present with peak activity during sleep. It can be postulated that this ultimately will impact the healing process.[8–10] Sleep deprivation in rats has been associated with major abnormalities including development of gastric ulcers, internal hemorrhage, pulmonary edema, and systemic bacterial invasion.[10,11] Sleep deprivation in humans has been associated with disruptions in the normal restorative processes. In study with healthy volunteers, immunization with hepatitis A vaccine and influenza vaccine was associated with approximately 50% lower antibody response in those volunteers who were sleep deprived.[12,13] Sleep deprivation can promote negative nitrogen balance and increase energy expenditure in healthy volunteers.[14–16] Chronic sleep loss is detrimental to immune function too.[17]

A number of studies have investigated the link between shift work and cancer. Davis et al

reviewed multiple studies in the Seattle area and found that exposure to light at night and working at night increased the risk of breast cancer.[18] It is presumed that disruption of the circadian rhythm alters nighttime melatonin secretion and thus increases reproductive hormone levels during the day.[19] An increased risk of breast cancer in long-term employees doing shift work (eg, nurses) in comparison with employees who do not work at night has been shown. This is believed to be due to not only melatonin production suppression but also a reduction in cellular immune defense.[20]

SLEEP QUALITY IN THE ICU

Several studies have focused on the poor quality of sleep observed in hospitalized patients. The effects of sleep deprivation in critically ill patients have been studied largely in the ICU patients. It is well known that critically ill patients experience sleep deprivation, which may contribute, in part, to derangement in patients' moods (eg, "ICU psychosis") that are often observed.[21] Patients who are surveyed following their stay in an ICU identify poor sleep as one of the most frequent complaints.[22,23] In nonventilated patients in the ICU, there was a decreased total sleep time, an increased amount of time in stage 1 sleep, and a decreased amount of time in slow-wave and REM sleep. Although patients are not quantitatively sleep deprived, they sleep for frequent short periods and that 50% of the total sleep time occurs in the daytime.[24–26] In mechanically ventilated patients, similar disruptions have been noted.[21]

The association between the severity of illness and sleep disturbance in patients in the ICU has recently been evaluated. There was a greater disruption in sleep in those patients who died and had a higher disease severity score.[27,28] In another study involving patients with posttraumatic coma, those with organized sleep patterns had a lower mortality than those patients without definable features of sleep.[30]

DISTURBANCE OF SLEEP IN THE ICU

Many factors are related to the effects of disrupted sleep on the health of patients who are residing in an ICU. Fragmented sleep has been associated with dysfunction of the immune system, interference with wound healing, and neurological and behavioral changes. Quality of life has also been affected significantly.[23,28,29] Extensive research has examined the factors contributing to poor sleep in critically ill patients.[23,26–29] Sleep is disturbed in the ICU for many reasons—anxiety, fear, illness, and pain—but many other factors contribute to sleep disruption in this setting. The ICU environment is filled with 24-hour noise, light exposure, and frequent awakenings from medical personnel.[28,29] Freedman et al studied the effects of environmental noise on sleep disruption in the ICU. Their research concluded that the ICU noise level was consistently above the Environmental Protection Agency noise recommendations at a mean level of 59.1 dB during the day and 56.8 dB at night and contributed to more than 25% of the awakenings per subject during the nighttime hours.[26] The Environmental Protection Agency recommends that noise levels in the hospital should not exceed 45 dB during the day and 35 dB at night.[31]

Light levels in the ICU have been shown to disrupt sleep in patients by altering melatonin levels, thus altering circadian rhythms. Light is usually measured by a lux meter, and its unit is called lux. For comparison purposes, moonlight is 0.5 to 1 lux, a bright office is 400 lux, and a sunny day in spring is 32 000 to 60 000 lux.[32,33] Nocturnal light levels vary among ICUs with mean maximum levels ranging from 1 to 1400 lux.[16,32] Low light intensities (100–500 lux) have been shown to affect melatonin secretion and moderate light intensities (300–500 lux) have been reported to affect the circadian pacemaker.[33] Thus, even low levels of light can contribute to the sleep disturbances noted in the ICU setting.

Patient care interventions such as measurement of blood pressure, pulse, and temperature can also result in sleep fragmentation.[27]

Physical examinations by the medical staff at various times throughout the evening, night, and early morning hours can significantly disrupt sleep patterns and physiology. All of the factors noted can contribute in a significant manner to the disruption in sleep that patient experiences.

SLEEP DEPRIVATION IN ICU AND ASSOCIATED HORMONAL CHANGES

Various types of hormonal changes are also affected by sleep deprivation. Growth hormone is normally secreted during delta sleep and aids in protein synthesis, tissue repair, bone growth, and red blood cell production. Reduction in the levels of growth hormone, insulin growth factor—I (the active form of growth hormone), prolactin, thyroid hormone, and leptin is induced by sleep deprivation in a rat model.[34] Most of the study involving such hormonal changes in patients who are critically ill has involved the general influence of the critically ill state on the hormone release/production. During the initial phases of the acute illness, critically ill patients have been found to have high levels of catecholamines, growth hormone, and prolactin. However, prolonged critical illness is associated with impairment of the normal pulsatile secretion of growth hormone, thyroid stimulating hormone, and prolactin.[35] The loss of the circadian rhythmicity of cortisol secretion is also noted in critically ill patients.[36,37] The overall influence of sleep deprivation, however, and its influence on hormone production and release need further study in the critically ill adult.

SLEEP DEPRIVATION AND COGNITION

Loss of memory and of communication skills with impaired word generation and decreased verbal fluency can result following 36 hours of sleep deprivation.[38,39] Studies have shown positive correlation between the sleep deprivation and mental status changes in an ICU.[11,25] Sleep loss has been associated with irritability, memory loss, inattention, delusions, hallucinations, slurred speech, incoordination, and blurred vision, which fits the criteria for delirium.[40] However, there are many confounding factors in ICU, such as age, medications, and others, which can contribute to delirium. It is not known at present whether sleep deprivation is a direct cause or contributor of delirium in the ICU.[14,28,29] Evidence exists to suggest that the development of delirium in the ICU is an independent predictor of higher mortality and morbidity, increased length of stay, disposition to an institutional setting from the hospital, and cognitive impairment at hospital discharge.[41–43] Sleep deprivation also affects mood with increased sadness and irritability and decreased vigor.[44]

SLEEP IN THE MECHANICALLY VENTILATED PATIENT

Mechanically ventilated patients have severely fragmented sleep in relation to many of the factors mentioned above. In addition, they have other problems that may worsen sleep including dyssynchronous breathing, mode of ventilation, endotracheal tube discomfort, and stress resulting from the inability to easily communicate with caregivers and family members.[21,45] Severe sleep fragmentation has been described in 20 mechanically ventilated patients with lung injury and the subsequent effects on daytime function. Up to 74 arousals and awakenings per hour were noted in this group of patients.[21]

The mode of ventilation may affect sleep and there may be an "optimal" mode of ventilation that helps facilitate sleep. Pressure support ventilation was shown in one study to disrupt sleep more significantly than assisted ventilation.[9] In patients with congestive heart failure (CHF) or a left ventricular ejection fraction of less than 50%, 5 of 6 patients with pressure support ventilation were associated with the development of central sleep apnea and resultant awakenings. The inspiratory assistance from pressure support was suspected to cause hypocapnia below the apnea threshold,

thus resulting in central sleep apnea. Addition of dead space increased the end-tidal CO_2 and caused a decrease in the frequency of central apneas and reduction in sleep disruption.[9] The overall effects of mechanical ventilation on sleep (eg, endotracheal tube discomfort, inability to communicate) needs further study.

SLEEP IN SURGICAL PATIENTS

Surgical procedures itself will cause disturbances in the normal sleep pattern. In general, changes in sleep include decrease in total sleep time, elimination of REM sleep, a marked reduction in the amount of slow-wave sleep (SWS) and increased amount of non-REM sleep stage 2.[25]

Postoperative sleep disturbance can be involved in the mental status changes, development of episodic hypoxemia, and hemodynamic instability. These effects are result of the rebound in the amount of REM sleep that is noted beginning several days following the surgery. In most patients, REM sleep subsequently reappears with increased density and duration, and REM-associated hypoxemic episodes increase about 3-fold on the second and third postoperative nights than the night before surgery.[25] The patient can present with confusion and episodes of oxyhemoglobin desaturation. Because REM sleep is characterized by unstable breathing patterns and sympathetic-parasympathetic imbalances, the increase in REM sleep in early postoperative period may increase the risk of postoperative atelectasis, pneumonia, hypoxemia, and cardiovascular morbidity including myocardial infarction.[45]

SLEEP AND MEDICATIONS COMMONLY USED IN THE INTENSIVE CARE SETTING

Critically ill patients are often sedated in the ICU. There is very little evidence that sedation serves a restorative function compared with natural sleep. However, there are many similarities between sedation and sleep. Both involves similar neurophysiological pathways, muscle hypotonia, altered mentation, and respiratory depression. However, sleep is spontaneous, reversible with external stimuli, regulated by homeostatic and circadian processes, associated with decreased release of norepinephrine, cyclic progression of electroencephalographic stages, and essential for biological function.[25,28,29] Tung et al reviewed the literature on anesthesia and sleep and their findings were somewhat contradictory to the belief that anesthesia is different from naturally occurring sleep. Studies suggest that anesthesia and natural sleep share similar neuronal pathways for brain activity. In rat studies, sleep deprivation imposed on rats seemed to resolve during anesthesia.[50] This research raises important questions whether sleep and anesthesia share a molecular basis for homeostatic control.

A new medication, dexmedetomidine, is an α-2 agonist approved for initial sedation in mechanically ventilated patients and has been shown to inhibit norepinephrine release and increase SWS. In a recent study, dexmedetomidine infusion resulted in more days without delirium or coma and more time at the targeted level of sedation than with a lorazepam infusion.[51] Sedatives such as benzodiazepines, opioids, and propofol continue to allow release of norepinephrine decreasing SWS and REM.

Many of the medications used in the ICU for sedation, pain control, heart rate control, blood pressure, gastric prophylaxis, and seizures interfere with sleep-wake cycle (Table 1). Medications such as benzodiazepines, opiates, antipsychotics, and corticosteroids decrease REM sleep. Some medications such as benzodiazepines, opiates, and epinephrine can decrease SWS. The changes in SWS and REM sleep by these medications lead to poor sleep quality. The pressor agents, epinephrine and dopamine, usually do not cross the blood-brain barrier, but when used with propofol they have increased penetration into the brain decreasing SWS and REM sleep. Amiodarone and β-blockers used in atrial fibrillation generally cause insomnia and nightmares. Commonly used H_2 receptor antagonist medications for

Table 1. Common drugs in the intensive care unit and their effects on sleep patterns[a]

Drug	Sleep disorder	Mechanism of action
Benzodiazepines	↓ REM, ↓ SWS	γ-Aminobutyric acid type A receptor stimulation
Opioids	↓ REM, ↓ SWS	μ receptor stimulation
NSAIDS	↓ TST, ↓ SE	Prostaglandin synthesis inhibition
Dopamine	Insomnia, ↓ REM, ↓ SWS	D_2 receptor stimulation/α_1 receptor stimulation
β-Blockers	Insomnia, ↓ REM, nightmares	Central nervous system β-blockade by lipophillic agents
Amiodarone	Nightmares	Unknown mechanism
Corticosteroids	Insomnia, ↓ REM, ↓ SWS	Reduced melatonin secretion
Quinolones	Insomnia	γ-Aminobutyric acid type A receptor inhibition
Tricyclic antidepressants	↓ REM	Antimuscarinic activity and α_1 receptor stimulation
SSRI	↓ REM, ↓ TST, ↓ SE	Increased serotonergic activity
Phenytoin	↑ Sleep fragmentation	Inhibition of neuronal calcium influx

Abbreviations: REM, rapid eye movement; SWS, slow-wave sleep; NSAIDS, nonsteroidal anti-inflammatory drugs; TST total sleep time; SE, sleep efficiency SSRI, selective-serotonin reuptake inhibitor.
Adapted from *Anesthesia*.[3]

gastric prophylaxis in the ICU can cause insomnia. Older antiepileptic medications such as phenytoin, carbamazepine, and phenobarbital have been shown to increase sleep fragmentation and decrease REM sleep.[3] Common ICU drugs such as β-blockers, benzodiazepines, corticosteroids, and nonsteroidal anti-inflammatory drugs can decrease melatonin secretion.[7]

Another concern for disturbed sleep in the ICU is medication withdrawal. Abrupt cessation of sedatives, alcohol, barbiturates, and nicotine can lead to insomnia and increase sleep fragmentation. Withdrawing other medications, such as β-blockers and α-agonists, can cause increased sympathetic activity that can worsen sleep continuity[28,29]

SLEEP ASSOCIATED WITH MEDICAL ILLNESS

General medical illness (eg, CHF, chronic obstructive pulmonary disease (COPD), acute myocardial infarction) has been associated with a decrease in the quality of sleep. Sleep-disordered breathing (SDB) is present in up to 60% of patients with CHF.[52,53] These sleep disorders (obstructive sleep apnea [OSA], central sleep apnea, or Cheyne-Stokes respirations) are associated with a decrease in total sleep time and an increased number of arousals. Nocturnal hypoxemia can also occur resulting in a higher morbidity and mortality in those patients who have SDB in comparison with those who do not have SDB.[11,54]

Patients with COPD have a significant decrease in total sleep duration with a significant number of arousals.[11] Although the effects of hypertension on sleep pattern are unclear, it can be expected that in such patients who have an increase in the overall sympathetic activity with increase in their baseline blood pressure, sleep disruption is likely to exist.[55]

Sepsis has been associated with increases in NREM sleep, decreases in REM sleep, altered electroencephalographic stages, and with low-voltage, mixed frequency waves with variable theta and delta (also known as

"septic encephalopathy").[28,29] Sepsis is also associated with the loss of normal circadian melatonin secretion.[56] Disturbed melatonin secretion is also associated with sleep disturbances and delirium in postoperative and long-term ICU patients.[53]

TREATMENT

On the basis of the above discussion, it is clear that priority should be given to patients' need for sleep, which is a basic human necessity. Nurses, physicians, and paramedical staff should be aware of the importance of patients' normal sleep patterns and habits and of the factors which might be disturbing to their sleep or preventing them from sleeping. On the basis of limited clinical data, we suggest following the treatment aspects.

Various types of treatments should be used to reduce the sleep disruption that occurs in the intensive care setting. An integrated approach to the management from the physician, nursing, and respiratory therapist perspectives must be maintained. Environmental issues should be addressed in all patients. Reducing excessive noise levels and providing earplugs can help increase REM sleep onset and duration. Minimizing conversation (especially at night) in close proximity to the patient's room will also help promote and maintain sleep. Dimming the lights during normal sleep hours can help with sleep and scheduling bedside activities of the various caregivers so that the several interventions can be completed in one visit, which will further avoid unnecessary disturbance of sleep.[54]

Continuous control of pain with the use of patient-controlled analgesia or regular dosing should be considered for patients with pain. Avoidance of medications (eg, diphenhydramine, morphine, barbiturates, sedative-hypnotics) that directly interfere with sleep should be a priority. Antidepressants (particularly selective serotonin reuptake inhibitors) have no sleep-promoting effects and in many instances are known to reduce REM sleep and should also be avoided when possible. Whenever analgesics or sedatives are required, the lowest dose for the shortest period of time needed to control the underlying problem(s) should be used. Withdrawal from many of these medications (eg, narcotics, benzodiazepines) may result in and increase, transiently, the sleep disruption in that particular patient. It should also be remembered that patients who are heavy smokers or who are regular consumers of alcohol prior to their acute illness may experience withdrawal effects if suddenly removed from nicotine or alcohol exposure and in such instances significant insomnia can result. In the case of smokers, nicotine replacement therapy should be considered, whereas in the case of patients who used alcohol, benzodiazepine administration should be considered.[3]

Medications (eg, zolpidem, ramelteon, eszopiclone) used to promote sleep under other circumstances could be used in selected cases in the ICU setting; however, there is a lack of evidence to support their use in these situations. Melatonin replacement has been shown to improve the sleep in small number of patients with COPD/pneumonia who were hospitalized in the intensive care unit,[3] but again significant data are lacking in the acute care setting. Further study is needed to determine whether these medications are helpful for patients who are acutely ill.

For those patients who are mechanically ventilated, maintenance of the patient's own respiratory efforts and physiologic baseline is important. Sleep quality is significantly improved when proportional assist ventilation was used in comparison with pressure support ventilation. In this group, less ventilator dyssynchrony, less sleep fragmentation, and increased amount of time spent in REM sleep was noted.[55] With the appropriate adjustments to the level of ventilator support with maintenance of the patient's physiologic baseline, an improvement in the sleep quantity and quality has been observed in patients with neuromuscular disease.[57]

Other types of nonpharmacologic therapy may also help promote sleep in such environments. Relaxing massage lasting 10 minutes helps promote sleep. It also reduces anxiety, heart rate, respiratory rate, and oxygen consumption, and has been shown to increase sleep efficiency and REM sleep in older patients admitted with cardiovascular illness in the ICU.[54]

Music therapy can be used to reduce postoperative pain and improve sleep particularly for patients who have had recent coronary artery bypass graft surgery.[56] The patient's willingness to listen to music and the patient's preference for music type should be determined. Music that is best suited for sleep and promotion of relaxation is that which has a tempo of approximately 60 beats per minute with low tones played predominantly with a stringed instrument.[54] Appropriate infection control measures should be undertaken if music players and headphones are shared among patients.

Aromatherapy (the use of essential oils, such as thyme, rosemary, lavender, and jasmine, extracted from plants to facilitate healing or improve mood) can be potentially used to help promote sleep in patients in the ICU;[54] however, there are limited data supporting its use.

SUMMARY

Awareness of the role that sleep plays in preserving physical and mental health must be recognized by all healthcare providers. Patients perceive their sleep quality to be worse in the ICU and evidence shows that their sleep is abnormal. In addition, sleep deprivation is associated with worse outcomes.

Education about sleep deprivation must be integrated into critical care training and orientation programs. Sleep deprivation should be addressed during the multidisciplinary care plan and in health team conference with subsequent changes then made by the nursing, respiratory therapy, and physician staffs to minimize the extent of sleep deprivation. The use of all medications and their potential effects on sleep should be evaluated for each patient from both the physician and nursing perspective. Integrating this approach with an attempt to minimize sleep disruption for patients who are in the ICU will ultimately help improve overall sleep quantity and quality and potentially reduce morbidity and mortality. Further study is needed, however, to more completely define the effects of sleep loss in patients in the ICU and to develop better methods to avoid and treat sleep deprivation in this setting.

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