Title

Sleep in the Intensive Care Unit: Strategies for Improvement

Journal

Seminars in Respiratory and Critical Care Medicine, 40(05)

ISSN

1069-3424

Authors

Dorsch, Jennifer J

Martin, Jennifer L

Malhotra, Atul

et al.

Publication Date

2019-10-01

DOI

10.1055/s-0039-1698378

Peer reviewed

HHS Public Access

Author manuscript

Semin Respir Crit Care Med. Author manuscript; available in PMC 2022 March 13.

Published in final edited form as:

Semin Respir Crit Care Med. 2019 October ; 40(5): 614–628. doi:10.1055/s-0039-1698378.

Sleep in the Intensive Care Unit: Strategies for Improvement

Jennifer J. Dorsch, MD[1], **Jennifer L. Martin, PhD**[2,3], **Atul Malhotra, MD**[4], **Robert L. Owens, MD**[4], **Biren B. Kamdar, MD, MBA, MHS**[4]

[1]Department of Medicine, Division of Pulmonary and Critical Care, University of Maryland School of Medicine, Baltimore, Maryland

[2]Department of Medicine, David Geffen School of Medicine at UCLA, University of California, Los Angeles

[3]Geriatric Research, Education and Clinical Center, VA Greater Los, Angeles Healthcare System, Los Angeles, California

[4]Division of Pulmonary, Critical Care and Sleep Medicine, University of California, San Diego

Abstract

Sleep in the intensive care unit (ICU) is considered to be subjectively poor, highly fragmented, and sometimes referred to as “atypical.”Although sleep is felt to be crucial for patient recovery, little is known about the association of sleep with physiologic function among critically ill patients, or those with clinically important outcomes in the ICU. Research involving ICU-based sleep disturbance is challenging due to the lack of objective, practical, reliable, and scalable methods to measure sleep and the multifactorial etiologies of its disruption. Despite these challenges, research into sleep-promoting techniques is growing and has demonstrated a variety of causes leading to ICU-related sleep loss, thereby motivating multifaceted intervention efforts. Through a focused review of (1) sleep measurement in the ICU; (2) outcomes related to poor sleep in the ICU; and (3) ICU-based sleep promotion efforts including environmental, nonpharmacological, and pharmacological interventions, this paper examines research regarding sleep in the ICU and highlights the need for future investigation into this complex and dynamic field.

Keywords

sleep; intensive care; critical care; delirium

Sleep in the intensive care unit (ICU) is subjectively poor, highly fragmented, and sometimes referred to as “atypical.”[1–3] Sleep deprivation is linked to impaired immune function,[4] hyperalgesia,[5] and neurocognitive dysfunction including delirium.[6,7] Given the effects of sleep loss, one could assume that poor sleep would adversely impact critically ill patient outcomes. Hence, sleep promotion is gaining popularity as a method to improve ICU outcomes.

Address for correspondence Jennifer J. Dorsch, MD, Division of Pulmonary and Critical Care Medicine, University of Maryland School of Medicine, 110 South Paca Street, 2nd Floor Pulmonary Division, Baltimore, MD 21201 (Jennifer.J.Dorsch@gmail.com).

Conflicts of Interest

None declared.

Despite advances in design and technology, the ICU is not conducive to sleep. Poor sleep in the ICU has been attributed to sound pollution, inappropriate lighting, patient interactions, medications, and critical illness itself.[8,9] Rising awareness regarding sleep quality has prompted ICUs to develop multifaceted interventions to promote sleep. This interest in sleep has also motivated research focused on novel modes of sleep measurement, the impact of medications and mechanical ventilation on sleep, short- and long-term consequences of ICU-based sleep disruption, sleep environment design, and implementation of sleep-promoting interventions.

This review aims at providing an update on sleep in the ICU, which is focused on the following three specific topics: (1) sleep measurement in the ICU; (2) outcomes related to poor sleep in the ICU; and (3) ICU-based sleep promotion efforts including environmental, nonpharmacological, and pharmacological interventions.

Measuring Sleep in the ICU

Measurement of sleep in critically ill patients is extremely complex and represents a key barrier to ICU investigations involving sleep. Measurement of ICU sleep on a large scale is not only logistically challenging, but common medications, organ dysfunction, and critical illness itself can also affect sleep classification and quantification. For this reason, there is no widely accepted “gold standard” for sleep measurement in the ICU.

Polysomnography

Polysomnography (PSG), the gold standard for sleep evaluation in noncritically ill patients, utilizes electroencephalography (EEG), electrooculography (EOG), and electromyography (EMG) to characterize sleep. In healthy adults, sleep is divided into rapid eye movement (REM) and non-rapid eye movement (NREM), comprising N1 (transition from wakefulness to sleep), N2 (stable sleep), and N3/slow wave sleep (SWS; restorative deep sleep), which cycle over 90- to 100-minute periods over the course of the night.[10,11] PSG demonstrates that critically ill ICU patients exhibit severely deranged sleep, with a preponderance of N1 and significantly diminished or absent REM and SWS (►Fig. 1).[12–15] However, with application of traditional PSG scoring criteria, atypical EEG patterns, seen in up to 85% of nighttime recordings in critically ill patients,[3] have no clearly assignable sleep stage.[16,17] For example, sleep spindles, which characterize N2 sleep, can be induced by benzodiazepines, making the distinction between sleep and sedation challenging. Similarly, diffuse EEG slowing, which is common in the ICU, can be difficult to distinguish from the slow wave activity of N3 sleep. Recently, Drouot et al used PSG data from 57 conscious, nonsedated ICU patients receiving mechanical or noninvasive ventilation to propose a new ICU-specific PSG scoring algorithm, adding atypical sleep and pathologic wakefulness stages to the preexisting scoring system.[18] In addition, Watson and colleagues observed a dissociation between PSG-derived sleep staging and observed sleep–wake behavior in 37 critically ill, mechanically ventilated ICU patients. In this study, some PSG-derived epochs were scored as sleep despite observed patient movements consistent with wakefulness. This observation led to a proposed algorithm of PSG scoring among the critically ill and further defined subdivisions of atypical sleep.[3]

Complicating PSG further, this mode of measurement is expensive, labor intensive, and not feasible for large-scale use in the ICU setting.[12,19–22] A single-center medical ICU feasibility study found that only 2 of 29 patients were able to complete 24 hours of unattended portable PSG monitoring.[19] Alternatives to PSG have been attempted, including application of EEG alone. However, compared with PSG, differentiation of wake versus N1 and N1 versus N2 is difficult with EEG only, especially in the setting of highly fragmented sleep.[23,24]

Bispectral Index

Bispectral index (BIS) involves forehead placement of a single-multichannel EEG lead, with integrated processed data to produce a single integer ranging from 0 (deep coma) to 100 (wide awake).[25] Traditionally used to monitor sedation depth during general anesthesia, recent studies, involving BIS to measure sleep in critically ill patients observed overlapping values for various sleep stages.[26] In addition, misleading recordings were noticed in the presence of common ICU derangements, such as traumatic brain injury, polypharmacy, delirium, and dementia. Hence, despite its ease of use, BIS is not validated for sleep measurement in critically ill patients.[25,27,28]

Actigraphy

Actigraphy has gained popularity as a minimally invasive, low-cost option for estimating sleep. Utilizing a wristwatch-like accelerometer, actigraphy measures patient activity levels corresponding to wake and rest states. Actigraphy is well tolerated for long-term, unattended use and is validated for measuring sleep in community populations[29–32]; however, its use in critically ill patients is problematic as activity levels are impacted by common ICU factors, such as sedating medications, weakness, delirium, and routine staff interventions (i.e., turning and bathing). Moreover, for mostly sedentary ICU patients, traditional actigraphy scoring algorithms can overestimate total sleep time (TST) and sleep efficiency (SE).[33–35] Despite these limitations, the feasibility and accessibility of actigraphy support its potential use in the ICU setting, both as an objective measure of circadian rest–activity rhythms, and pending the development and validation of ICU-specific scoring algorithms, a surrogate marker of sleep and wake.[36,37]

Questionnaires

Subjectively, sleep questionnaires are easy to complete, low cost, and feasible for large-scale use. In the ICU, the most commonly used questionnaires are the Richards–Campbell Sleep Questionnaire (RCSQ) which was previously validated against PSG, and the Verran and Snyder-Halpern Sleep Scale (VSH).[38–40] While both questionnaires utilize easy-to-administer visual–analogue scales evaluating various sleep domains, they have limited reliability due to recall bias, altered patient cognition, rater fatigue, and inability to capture daytime sleep. In the setting of cognitive impairment (i.e., delirium and dementia), bedside nurses can complete questionnaires on their patients' behalf; however, patient–nurse interrater reliability of the RCSQ is modest at best.[41] Finally, the Sleep in Intensive Care Unit Questionnaire (SICUQ), which involves patient-reported ratings of causes of ICU-related sleep disruption, can be used to highlight areas for improvement and the effectiveness of sleep-promoting interventions.[42–45]

Physiological Effects of ICU-Related Sleep Disruption

Although sleep is felt to be crucial for patient recovery, little is known about the association of sleep with physiologic function in critically ill patients, or those with other clinically important outcomes in the ICU (►Fig. 2). Below is a systems-based review of sleep's potential role in critical illness. Studies involving ICU patients are reviewed, although sleep data in this population are lacking. Additional non-ICU data pertinent to the topics are also included.[46]

Delirium

Delirium, a mental disturbance characterized by acute onset of fluctuating degrees of confusion, inattention, and levels of consciousness, is a common ICU syndrome believed to be closely linked to poor sleep.[47–50] Delirium affects 60 to 80% of mechanically ventilated and 20 to 50% of nonventilated ICU patients,[51–53] and is independently associated with prolonged length of stay, long-term cognitive impairments, and early death.[48,53–58] Sleep deprivation is widely considered to be associated with delirium, given their similar symptoms, and shared characteristics including imbalances in neurotransmitters dopamine and acetylcholine and circadian misalignment, as evidenced by altered diurnal melatonin secretion.[48,59,60] Despite these mechanisms, data supporting a sleep–delirium relationship are lacking. One study involving single-night PSG in 29 mechanically ventilated surgical ICU patients demonstrated higher incidence of delirium among patients experiencing < 6% REM.[61] Furthermore, observational studies describe increased delirium incidence in patients reporting poor sleep following thoracic surgery,[62] as well as in patients, with nurse-described fragmented sleep.[63]

Pulmonary

Of specific concern for critically ill patients is the influence of poor sleep on respiratory muscle function, respiratory drive, and upper airway collapsibility. In a study of mechanically ventilated patients, atypical (vs. more typical) sleep was associated with delayed ventilator liberation, despite a lack of substantial differences between groups in maximal inspiratory pressure and negative airway pressure.[64] A recent study failed to detect differences in pathological wakefulness or atypical sleep between patients who were liberated from the ventilator and those who were not. However, compared with patients who remained intubated, patients liberated from the ventilator demonstrated less right-left hemispheric discordance, and more wakefulness 15 hours prior to extubation.[65] In addition, in patients treated for acute hypercarbic respiratory failure, poor sleep predicted late (>48 hours after initiation) noninvasive ventilation failure.[66] To date, no studies have linked sleep improvement efforts with ventilator or other respiratory outcomes.

Metabolic

Normally, growth hormone (GH), an anabolic hormone synthesized by the anterior pituitary gland, is cyclically secreted in response to sleep or physiologic stress.[67] In acute illness, GH levels rise; however, in chronic illness, levels decrease to normal or subnormal levels signaling "wasting syndrome" in which anabolic activity is impaired.[68] Interestingly, GH secretion is delayed until after sleep onset, which is markedly altered in states of sleep

deprivation. Thus, sleep promotion may be proposed as a method to attenuate ICU-related myopathy.[69]

Cardiovascular

No studies have evaluated the association of ICU-related sleep loss with cardiovascular function. In community-dwelling adults, acute sleep deprivation increases sympathetic tone,[70–73] and the risk of cardiovascular complications including hypertension, tachyarrhythmias, and QT interval prolongation.[74–76] Multiorgan derangements, medications, and stress also contribute to cardiac events and complicate research in this area.

Immunologic

Both innate and humoral immune systems are negatively impacted by sleep deprivation; however, longitudinal ICU studies involving clinically important endpoints are lacking. In healthy adults, sleep loss is associated with decreased natural killer cell activity and suppressed interleukin (IL)-2 levels.[77] In addition, sleep deprivation impairs normal humoral responses to vaccination.[78,79] Taken together, in states of critical illness such as sepsis where host defense is vital to recovery, sleep loss and promotion may play an important role.

Strategies for ICU-Based Sleep Promotion

The variety of causes of ICU-related sleep loss have motivated numerous sleep-promoting intervention efforts (►Table 1). In the ICU setting, sound and light reduction, behavioral modification, bundles, and pharmacologic interventions are becoming increasingly utilized.

Nonpharmacological Interventions

Sound in the ICU—Excessive environmental sound is associated with 17 to 20% of awakenings in ICU patients.[9,15] The World Health Organization (WHO) recommends that continuous background sound in patient treatment areas not exceed 30 dB (dB), and peak nocturnal sounds remain below 40 dB.[121] Notably, ventilator (51 dB), suction (53 dB), and syringe pump alarms (63 dB) breach these sound limits.[8] Unsurprisingly, all ICU studies involving sound report levels exceeded recommended limits [8,122,123] without diurnal variation.[9,15,124,125] Studies have proposed that characteristics of sound, including sources (i.e., electronic vs. environmental), timing and levels, affect sleep.[126] In addition, the degree of sound level variation, as compared with peak and average sound levels, may be particularly disruptive to sleep.[123,127]

In the ICU, sound attenuation can be accomplished by (1) behavioral interventions, that is, minimizing conversations, reducing unnecessary alarms; (2) sound masking, that is, white noise; and (3) sound blocking, that is, earplugs. Behavior-based sound reduction studies comparing staff education, education with sound monitoring, and education with environmental modifications had mixed results, with no improvement in sound levels in some studies[128] and a reduction in others (►Table 1).[80,129] Notably, sound reduction interventions did not evaluate sustainability, and decibel levels commonly remained above recommended limits.[80,130]

While sound masking with white noise has been demonstrated to improve sleep quality,[105–107] sound blocking via earplugs has received particular attention due to recent research suggesting improved sleep perception, satisfaction, and delirium in ICU patients wearing earplugs.[86,88] However, patients offered earplugs usually declined them[45] or found them uncomfortable.[131] More recently, sound blocking via noise cancelling headphones has gained popularity. A recent study involving mannequins exposed to simulated cardiac ICU sounds found that noise cancelling headphones were associated with significant reductions in sound exposure.[132] Investigations on noise cancelling headphones in critically ill patients included one study yielding uninterpretable results due to highly atypical EEG patterns,[101] and another focused on anxiety and sedation levels rather than sleep effects.[102] More research is required to determine the best methods for noise reduction in critically ill patients.

Light in the ICU—It is widely believed that abnormal light levels, whether elevated throughout the night, delivered as bright bursts interrupting nighttime darkness or inappropriately low during the daytime, contribute to sleep–wake rhythm disturbance in the ICU. Although there are no guidelines for light levels in the ICU, nocturnal light levels in this setting are, on average, below the arbitrary maximum value of 20 lux.[133,134] However, severe illness is associated with increased high-lux light exposure, which may contribute to sleep fragmentation.[135] Studies support improved subjective sleep with the use of eye masks in cardiac ICU patients.[98,100]

Recently, inadequate daytime light has gained attention for its disruption of circadian sleep–wake cycles. One study evaluating natural light in the ICU found that, although 84% of patient rooms had windows, almost 100% of this natural light degraded before reaching the patients.[136] Other studies demonstrated ICU daytime light levels ranging from 42 to 158 lux, corresponding to insufficient daytime light.[123,133,134] Finally, the application of daytime bright light therapy is gaining attention, albeit mostly in the context of delirium prevention and circadian rhythm maintenance.[137,138]

Alternative Therapies—Alternative therapies for sleep promotion including music, massage, reflexology, aromatherapy, implementation of relaxation techniques, and therapeutic touch have been shown to reduce stress and improve subjective sleep quality (►Table 1).[139–141] Despite favorable effects on sleep in critically ill patients, the 2018 Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption (PADIS) in adult patients in the ICU do not recommend the individual use of aromatherapy, massage, or music for the promotion of sleep in the ICU due to limited availability and potential respiratory complications from aromatherapy.[142]

Bundled Interventions—Bundling is a practical approach involving implementation of multiple simple interventions at once. The 2018 PADIS guidelines conditionally recommend sleep promoting “bundles,” based on evidence suggesting that bundles involving sound and light reduction and clustering of care may improve sleep quality, [89,91–94,96,142–144] while the addition of music, earplugs, eye masks, pharmacological sleep aid guidelines, room modifications (see section Emerging Interventions) and daytime mobilization practices may

improve outcomes further.[44,45,90,97,142,143] While use of established quality improvement methods have been shown to aid in implementation of such bundles,[145] few studies have evaluated strategies to optimize bundle sustainability.[146]

Ventilators and Sleep

Given that up to 40% of ICU patients are mechanically ventilated,[147] optimizing ventilator settings is vital to prevent nocturnal sleep disruptions and facilitate sedation minimization necessary for daytime wakefulness. Controlled modes of mechanical ventilation such as pressure-controlled ventilation (PCV), assist-control ventilation (ACV), or proportional assist ventilation (PAV) are associated with improved sleep quality compared with spontaneous modes such as pressure support ventilation (PSV).[148–151] Additionally, in tracheostomized patients undergoing ventilator weaning, controlled (vs. spontaneous) modes of ventilation are associated with improved sleep quality.[152] However, despite this evidence, studies of ventilator modes and sleep have revealed inconsistent findings.[153] The 2018 PADIS guidelines conditionally recommend assist control ventilation for nocturnal sleep;[142] however, further research is required, including ventilator settings needed to limit sleep-altering sedative medications and promote consolidative sleep.

Emerging Interventions

Staffing models, unit layout, and visitation policies have the potential to impact sleep in critically ill patients. While ICU patients can experience up to 40 interactions each night,[154,155] it is estimated that up to 14% of interruptions can safely be omitted.[156] Thus, clustering of care and quiet hours are becoming commonplace, but further evaluation of staffing and workflow patterns is needed.

Hospital layout can affect sound and light in the ICU, thus impacting patient sleep. Closely spaced beds facing a central nurse station strongly contribute to sound pollution, which may guide future ICU layout decisions.[157] Furthermore, windows and natural light are associated with decreased pain, agitation, depressive symptoms, and improved circadian rhythmicity, but have yet to be evaluated in the context of sleep.[158]

Finally, as ICUs liberalize their visitation policies, there is potential for sleep disruption due to nighttime visitors; however, family visitation can reduce patient and visitor stress and anxiety,[159] and did not negatively impact patients' ability to rest.[160] Some have proposed using family members to engage patients during the day and protect their loved ones' sleep at night.[161] To date, no studies have evaluated the association of visitation policies, or specific visitors, with sleep in the ICU.

Pharmacologic Interventions

Initial pharmacologic management of poor sleep in the ICU involves deprescribing of medications known to perturb sleep. Medications commonly prescribed for sleep are often accompanied by untoward side effects, particularly in older and critically ill patients. The Beers criteria for inappropriate medications in older adults, updated in 2015 by the American Geriatrics Society, discourage the use of most sleep-promoting medications in the aged population.[162] Nevertheless, medications are often administered in the ICU to

promote sleep. The most commonly prescribed ICU medications associated with sleep are summarized below and in ►Table 2. Notably, studies involving medication effects on sleep were generally small in size, involved non-ICU based populations, and limited to single night sleep evaluation; therefore, they should be interpreted with caution.

Dexmedetomidine—Dexmedetomidine, an α−2-adrenergic agonist, is a hypnotic medication commonly used in the setting of mechanical ventilation, agitation, or alcohol withdrawal. Studies involving dexmedetomidine for sleep promotion uniformly demonstrate increased N2,[163–165] with inconsistent findings regarding SE and N3/SWS.[163,164,166,167] Furthermore, one study demonstrated presence of sleep spindles in patients receiving dexmedetomidine, arguing for its role in approximating "natural sleep."[165] To our knowledge, no study has demonstrated improvement in REM with dexmedetomidine.[166] The 2018 PADIS guidelines make no recommendation on dexmedetomidine for sleep promotion in the ICU; however, it is recommended when agitation precludes ventilator liberation.[142] Notably, two recent randomized controlled trials (RCTs) were performed involving dexmedetomidine in patients requiring sedation; one demonstrating no difference in 90-day mortality with a dexmedetomidine-only (with additional as-needed sedative medications, versus usual care) sedation strategy,[168] and a second demonstrating reduced ICU delirium, but no difference in subjective sleep, when comparing low-dose nocturnal dexmedetomidine with placebo.[169] Larger studies involving dexmedetomidine and its impact on sleep in the ICU are needed.

Propofol—Propofol is a rapidly titratable $GABA_A$ receptor potentiator frequently used fordeep sedation and anesthesia. Although it may produce a clinical state of unconsciousness, propofol has been associated with decreased REM when compared with the same critically ill patients who did not receive propofol[170] as well as when compared with nocturnal sedation with benzodiazepine flunitrazepam.[171] Upon an examination of four studies evaluating propofol for sleep promotion in the ICU, a Cochrane review found insufficient evidence to determine whether propofol improved sleep quality or quantity in critically ill patients.[172] The 2018 PADIS guidelines do not recommend propofol for sleep in critically ill patients.[142]

Melatonin and Melatonin Receptor Agonists—Melatonin and melatonin receptor agonists such as ramelteon are gaining popularity for sleep promotion in the ICU (►Tables 2 and 3). Studies demonstrate reduced delirium in ICU patients receiving melatonin or ramelteon.[173,174] Further studies are needed to evaluate melatonin and melatonin receptor agonists for their role in sleep promotion in the ICU, along with its link to delirium prevention. Due to insufficient evidence, a recent Cochrane review was unable to determine whether melatonin improved sleep quality or quantity in critically ill patients,[175] and the 2018 PADIS guidelines make no recommendation regarding their use in sleep.[142]

Atypical Antipsychotics—The sedative–hypnotic properties of atypical antipsychotic medications appear to be dose-dependent and related to histamine 1 receptor blockade.[180] The use of atypical antipsychotic agents for sleep alone is not Food and Drug Administration (FDA) approved; however, their use is common in the ICU in the setting of delirium or

agitation. Olanzapine and quetiapine are the most studied and efficacious sleep-promoting atypical antipsychotics due to their moderate sedative properties.[180,181]

No studies have evaluated atypical antipsychotics for sleep in critically ill patients. In healthy subjects, quetiapine increased TST, SE, and subjective sleep quality when compared with placebo.[182,183] In addition, N2 and REM sleep increased when quetiapine (25 mg) was administered, but REM subsequently decreased at higher doses (100 mg).[182] Olanzapine increased nocturnal TST, SE, and SWS.[184–186] Olanzapine's effect on REM is unclear, with some studies showing increased REM[184] and others showing decreased REM and increased REM latency.[185,186] Despite improvements in PSG and subjective sleep, the use of atypical antipsychotics for sleep remains off-label and requires further investigation.

Typical Antipsychotics—Haloperidol, a typical antipsychotic medication commonly used in the ICU for treatment of hyperactive delirium and agitation, has sedating properties. Few studies evaluating its efficacy as a sleep aid in this population exist; however, one study evaluating haloperidol in pediatric burn patients found increased TST and N2 compared with control, with no effect on SWS or REM.[187] For delirium treatment and prevention, haloperidol does not decrease incidence or duration of delirium when compared with placebo.[188–192]

Trazodone—Trazodone, a selective serotonin reuptake inhibitor and histamine receptor type-1 channel blocker, is an antidepressant–hypnotic. Despite its off-label use, trazodone remains among the most commonly prescribed sleep aids in the United States.[193,194] Trazodone's effect on sleep in critically ill patients has not been studied. Various small studies demonstrate increased SWS following administration of trazodone in healthy[195–198] and depressed populations.[199–203] One systematic review supported the use of trazodone for insomnia,[204] while another felt the benefits did not outweigh the risks.[205] Trazodone is generally well tolerated; however, side effects of arrhythmias, orthostatic hypotension and anticholinergic syndrome have been reported, especially in older patients.[204]

Benzodiazepines—Benzodiazepines bind to gamma-aminobutyric acid $(GABA)_A$ receptors and enhance the effect of GABA, producing anxiolysis and sedation. There are five FDA-approved benzodiazepines used to treat short-term insomnia as follows: estazolam, flurazepam, quazepam, temazepam, and triazolam.[194] While benzodiazepines may improve sleep onset latency (SOL) and TST, and decrease nocturnal arousals in healthy patients, these drugs decrease SWS and REM.[206,207] Additionally, in vulnerable populations including older adults, benzodiazepines are associated with increased delirium.[208,209] Given the detrimental effects of benzodiazepines, including their risk of delirium and dependence, as well as counterproductive effects on sleep, these drugs are not encouraged for sleep promotion in critically ill patients.

Nonbenzodiazepine Hypnotics—Nonbenzodiazepine sedative–hypnotics, commonly known as "z-drugs," such as zolpidem, eszoplicone, and zaleplon are similar to benzodiazepines in that they bind $GABA_A$ receptors and potentiate the effect of GABA. In a meta-analysis of "z-drugs" in community-based insomniacs, SOL was only mildly decreased in the treatment group compared with the control.[210] Recently, the FDA issued a boxed

warning for “z-drugs” due to multiple reports of dangerous side effects.[211] In hospitalized patients, these side effects include dizziness, daytime somnolence, falls, and confusion, particularly in the older population.[212–214] Notably, following hip or knee replacement, postoperative use of zolpidem failed to increase REM or SWS compared with placebo.[215] Such results, combined with safety warnings, raise the question concerning the utility of these drugs for sleep, particularly in at-risk critically ill patients.

Future Directions

Improving our understanding of the ill effects of poor sleep in the ICU and the effects of sleep-promoting interventions on outcomes is an important priority in critical care research. The lack of objective, practical, reliable, and scalable methods to measure sleep poses a major hindrance to large-scale, ICU-based sleep investigations. Novel modes of sleep measurement are needed, in addition to the development of ICU-specific sleep scoring algorithms. Research on sleep in the ICU is growing and has demonstrated a variety of causes leading to ICU-related sleep loss, including common medications, thereby motivating numerous multifaceted intervention efforts. Among these interventions, bundled protocols have been shown to be feasible, and efficacious; however, their generalizability and sustainability require further evaluation.

Funding

B.B.K. is currently supported by a Paul B. Beeson Career Development Award through the National Institutes of Health/National Institute on Aging (K76AG059936). J.L.M. is supported by the National Institutes of Health/National Heart Lung and Blood Institute (K24 HL143055).

References

1. Little A, Ethier C, Ayas N, Thanachayanont T, Jiang D, Mehta S. A patient surveyof sleep quality in the intensive care unit. Minerva Anestesiol 2012;78(04):406–414 [PubMed: 22337154]
2. Pulak LM, Jensen L. Sleep in the intensive care unit: a review. J Intensive Care Med 2016;31(01):14–23 [PubMed: 24916753]
3. Watson PL, Pandharipande P, Gehlbach BK, et al. Atypical sleep in ventilated patients: empirical electroencephalography findings and the path toward revised ICU sleep scoring criteria. Crit Care Med 2013;41(08):1958–1967 [PubMed: 23863228]
4. Irwin M. Why sleep is important for health: a psychoneuroimmunology perspective. Annu Rev Psychol 2015;66:143–172 [PubMed: 25061767]
5. Larson RA, Carter JR. Total sleep deprivation and pain perception during cold noxious stimuli in humans. Scand J Pain 2016;13 (906):12–16 [PubMed: 27867438]
6. Leung JM, Sands LP, Newman S, et al. Preoperative sleep disruption and postoperative delirium. J Clin Sleep Med 2015;11(08): 907–913 [PubMed: 25979094]
7. Lowe CJ, Safati A, Hall PA. The neurocognitive consequences of sleep restriction: A meta-analytic review. Neurosci Biobehav Rev 2017;80(July):586–604 [PubMed: 28757454]
8. Darbyshire JL, Young JD. An investigation of sound levels on intensive care units with reference to the WHO guidelines. Crit Care 2013;17(05):R187 Available at: http://www.biomedcentral.com/content/pdf/cc12870.pdf [PubMed: 24005004]
9. Gabor JY, Cooper AB, Crombach SA, et al. Contribution of the intensive care unit environment to sleep disruption in mechanically ventilated patients and healthy subjects. Am J Respir Crit Care Med 2003;167(05):708–715 [PubMed: 12598213]

10. Carskadon MA, Dement WC. Normal human sleep: an overview. In: Kryger M, Roth T, Dement W, eds. Principles and Practice of Sleep Medicine. 5th ed. St. Louis: Elsevier Saunders; 2011: 16–26
11. Kamdar BB, Collop NA. Sleep issues in the intensive care unit setting. In: Irwin R, Lilly C, Mayo P, Rippe J, eds. Irwin and Rippe's Intensive Care Medicine. 8th ed. Wolters Kluwer; 2018
12. Elliott R, McKinley S, Cistulli P, Fien M. Characterisation of sleep in intensive care using 24-hour polysomnography: an observational study. Crit Care 2013;17(02):R46 [PubMed: 23506782]
13. Elbaz M, Léger D, Sauvet F, et al. Sound level intensity severely disrupts sleep in ventilated ICU patients throughout a 24-h period: a preliminary 24-h study of sleep stages and associated sound levels. Ann Intensive Care 2017;7(01):25 [PubMed: 28255956]
14. Cooper AB, Thornley KS, Young GB, Slutsky AS, Stewart TE, Hanly PJ. Sleep in critically ill patients requiring mechanical ventilation. Chest 2000;117(03):809–818 [PubMed: 10713011]
15. Freedman NS, Gazendam J, Levan L, Pack AI, Schwab RJ. Abnormal sleep/wake cycles and the effect of environmental noise on sleep disruption in the intensive care unit. Am J Respir Crit Care Med 2001;163(02):451–457 [PubMed: 11179121]
16. Silber MH, Ancoli-Israel S, Bonnet MH, et al. The visual scoring of sleep in adults. J Clin Sleep Med 2007;3(02):121–131 [PubMed: 17557422]
17. Berry RB, Budhiraja R, Gottlieb DJ, et al. ; American Academy of Sleep Medicine; Deliberations of the Sleep Apnea Definitions Task Force of the American Academy of Sleep Medicine. Rules for scoring respiratory events in sleep: update of the 2007 AASM Manual for the Scoring of Sleep and Associated Events. J Clin Sleep Med 2012;8(05):597–619 [PubMed: 23066376]
18. Drouot X, Roche-Campo F, Thille AW, et al. A new classification for sleep analysis in critically ill patients. Sleep Med 2012;13 (01):7–14 [PubMed: 22153778]
19. Knauert MP, Yaggi HK, Redeker NS, Murphy TE, Araujo KL, Pisani MA. Feasibility study of unattended polysomnography in medical intensive care unit patients. Heart Lung 2014;43(05):445–452 [PubMed: 25023504]
20. Ambrogio C, Koebnick J, Quan SF, Ranieri M, Parthasarathy S. Assessment of sleep in ventilator-supported critically ill patients. Sleep 2008;31(11):1559–1568 [PubMed: 19014076]
21. Bourne RS, Minelli C, Mills GH, Kandler R. Clinical review: sleep measurement in critical care patients: research and clinical implications. Crit Care 2007;11(04):226 [PubMed: 17764582]
22. Watson PL. Measuring sleep in critically ill patients: beware the pitfalls. Crit Care 2007;11(04):159 [PubMed: 17850679]
23. Vacas S, McInrue E, Gropper MA, et al. The feasibility and utility of continuous sleep monitoring in critically ill patients using a portable electroencephalography monitor. Anesth Analg 2016; 123(01):206–212 [PubMed: 27159066]
24. Lucey BP, Mcleland JS, Toedebusch CD, et al. Comparison of a single-channel EEG sleep study to polysomnography. J Sleep Res 2016;25(06):625–635 [PubMed: 27252090]
25. Nieuwenhuijs DJF. Processed EEG in natural sleep. Best Pract Res Clin Anaesthesiol 2006;20(01):49–56 [PubMed: 16634413]
26. Nieuwenhuijs D, Coleman EL, Douglas NJ, Drummond GB, Dahan A. Bispectral index values and spectral edge frequency at different stages of physiologic sleep. Anesth Analg 2002;94(01): 125–129 [PubMed: 11772814]
27. Nicolás A, Aizpitarte E, Iruarrizaga A, Vázquez M, Margall A, Asiain C. Perception of night-time sleep by surgical patients in an intensive care unit. Nurs Crit Care 2008;13(01):25–33 [PubMed: 18226052]
28. Sleigh JW, Andrzejowski J, Steyn-Ross A, Steyn-Ross M. The bispectral index: a measure of depth of sleep? Anesth Analg 1999;88(03):659–661 [PubMed: 10072023]
29. Sadeh A. The role and validity of actigraphy in sleep medicine: an update. Sleep Med Rev 2011;15(04):259–267 [PubMed: 21237680]
30. Ancoli-Israel S, Cole R, Alessi C, Chambers M, Moorcroft W, Pollak CP. The role of actigraphy in the study of sleep and circadian rhythms. Sleep 2003;26(03):342–392 [PubMed: 12749557]
31. Littner M, Kushida CA, et al. Practice parameters for the role of actigraphy in the study of sleep and circadian rhythms. 2003; 3:337–341

32. Smith MT, McCrae CS, Cheung J, et al. Use of actigraphy for the evaluation of sleep disorders and circadian rhythm sleep-wake disorders: an american academy of sleep medicine clinical practice guideline. J Clin Sleep Med 2018;14(07):1231–1237 [PubMed: 29991437]
33. van der Kooi AW, Tulen JH, van Eijk MM, et al. Sleep monitoring by actigraphy in short-stay ICU patients. Crit Care Nurs Q 2013; 36(02):169–173 [PubMed: 23470702]
34. Ionita R, Ling F, Hettinger K, Jubran A, Tobin M. Does actigraphy or nurse assessment accurately quantify sleep architecture in patients weaning from prolonged mechanical ventilation? Am J Respir Crit Care Med 2010;181(1 MeetingAbstracts) Available at: http://ajrccm.atsjournals.org/cgi/reprint/181/1_MeetingAbstracts/A6704?sid=b9c096eb-3f4b-4587-9632-0b3e6193c9ac%5Cn. Accessed September 2, 2019
35. Beecroft JM, Ward M, Younes M, Crombach S, Smith O, Hanly PJ. Sleep monitoring in the intensive care unit: comparison of nurse assessment, actigraphy and polysomnography. Intensive Care Med 2008;34(11):2076–2083 [PubMed: 18521566]
36. Schwab KE, Ronish B, Needham DM, et al. Actigraphy to evaluate sleep in the intensive care unit: a systematic review. Ann Am Thorac Soc 2018;15(09):1075–1082 [PubMed: 29944386]
37. Kamdar BB, Kadden DJ, Vangala S, et al. Feasibility of continuous actigraphy in patients in a medical intensive care unit. Am J Crit Care 2017;26(04):329–335 [PubMed: 28668919]
38. Snyder-Halpern R, Verran J. Verran and Snyder-Halpern Sleep Scale (VSH). In: Shahid A, Wilkinson K, Marcu S, Shapiro C, eds. STOP, THAT and One Hundred Other Sleep Scales. New York: Sprinkger -Verlag; 2012:397
39. Shahid A, Wilkinson K. Richards-Campbell Sleep Questionnaire SM. (RCSQ). In: Shahid A, Wilkinson K, Marcu S, eds. STOP, THAT, and OneHundredOtherSleepScales.NewYork:Springer;2012:299–302
40. Richards KC, O'Sullivan PS, Phillips RL. Measurement of sleep in critically ill patients. J Nurs Meas 2000;8(02):131–144 [PubMed: 11227580]
41. Kamdar BB, Shah PA, King LM, et al. Patient-nurse interrater reliability and agreement of the Richards-Campbell Sleep Questionnaire. Am J Crit Care 2012;21(04):261–269 [PubMed: 22751369]
42. Freedman NS, Kotzer N, Schwab RJ. Patient perception of sleep quality and etiology of sleep disruption in the intensive care unit. Am J Respir Crit Care Med 1999;159(4 Pt 1):1155–62 [PubMed: 10194160]
43. Li SY, Wang TJ, Vivienne Wu SF, Liang SY, Tung HH. Efficacy of controlling night-time noise and activities to improve patients' sleep quality in a surgical intensive care unit. J Clin Nurs 2011;20 (3–4):396–407 [PubMed: 21219521]
44. Patel J, Baldwin J, Bunting P, Laha S. The effect of a multicomponent multidisciplinary bundle of interventions on sleep and delirium in medical and surgical intensive care patients. Anaesthesia 2014;69(06):540–549 [PubMed: 24813132]
45. Kamdar BB, King LM, Collop NA, et al. The effect of a quality improvement intervention on perceived sleep quality and cognition in a medical ICU. Crit Care Med 2013;41(03):800–809 [PubMed: 23314584]
46. Kamdar BB, Needham DM, Collop NA. Sleep deprivation in critical illness: its role in physical and psychological recovery. J Intensive Care Med 2012;27(02):97–111 [PubMed: 21220271]
47. Trompeo A, Vidi Y, Ranieri V. Sleep and delirium in the critically ill: cause or effect? In: Vincent J, ed. Yearbook of Intensive Care and Emergency Medicine. New York: Springer; 2006:719–725
48. Weinhouse GL, Schwab RJ, Watson PL, et al. Bench-to-bedside review: delirium in ICU patients - importance of sleep deprivation. Crit Care 2009;13(06):234 [PubMed: 20053301]
49. Kamda, Niessen T, Colantuoni E, et al. . Delirium transitions in the medical ICU: exploring the role of sleep quality and other factors. Crit Care Med 2015;43(01):135–141 [PubMed: 25230376]
50. Mistraletti G, Carloni E, Cigada M, et al. Sleep and delirium in the intensive care unit. Minerva Anestesiol 2008;74(06):329–333 [PubMed: 18500209]
51. Brummel NE, Vasilevskis EE, Han JH, Boehm L, Pun BT, Ely EW. Implementing delirium screening in the ICU: secrets to success. Crit Care Med 2013;41(09):2196–2208 [PubMed: 23896832]

52. Dubois MJ, Bergeron N, Dumont M, Dial S, Skrobik Y. Delirium in an intensive care unit: a study of risk factors. Intensive Care Med 2001;27(08):1297–1304 [PubMed: 11511942]
53. Ely EW, Shintani A, Truman B, et al. Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. JAMA 2004;291(14):1753–1762 [PubMed: 15082703]
54. Salluh JIF, Wang H, Schneider EB, et al. Outcome of delirium in critically ill patients: systematic review and meta-analysis. BMJ 2015;350(03):h2538 [PubMed: 26041151]
55. Balas MC, Happ MB, Yang W, Chelluri L, Richmond T. Outcomes associated with delirium in older patients in surgical ICUs. Chest 2009;135(01):18–25 [PubMed: 19017895]
56. Thomason JWW, Shintani A, Peterson JF, Pun BT, Jackson JC, Ely EW. Intensive care unit delirium is an independent predictor of longer hospital stay: a prospective analysis of 261 non-ventilated patients. Crit Care 2005;9(04):R375–R381 [PubMed: 16137350]
57. Girard TD, Jackson JC, Pandharipande PP, et al. Delirium as a predictor of long-term cognitive impairment in survivors of critical illness. Crit Care Med 2010;38(07):1513–1520 [PubMed: 20473145]
58. Zhang Z, Pan L, Ni H. Impact of delirium on clinical outcome in critically ill patients: a meta-analysis. Gen Hosp Psychiatry 2013;35(02):105–111 [PubMed: 23218845]
59. Figueroa-Ramos MI, Arroyo-Novoa CM, Lee KA, Padilla G, Puntillo KA.SleepanddeliriuminICUpatients:areviewofmechanismsand manifestations. Intensive Care Med 2009;35(05):781–795 [PubMed: 19165463]
60. Krueger JM, Majde JA, Blatteis CM, Endsley J, Ahokas RA, Cady AB. Polyriboinosinic:polyribocytidylic acid enhances rabbit slowwave sleep. Am J Physiol 1988;255(5 Pt 2):R748–R755 [PubMed: 3189588]
61. Trompeo AC, Vidi Y, Locane MD, et al. Sleep disturbances in the critically ill patients: role of delirium and sedative agents. Minerva Anestesiol 2011;77(06):604–612 [PubMed: 21617624]
62. Yildizeli B, Ozyurtkan MO, Batirel HF, Kuşcu K, Bekiroğlu N, Yüksel M. Factors associated with postoperative delirium after thoracic surgery. Ann Thorac Surg 2005;79(03):1004–1009 [PubMed: 15734423]
63. Helton MC, Gordon SH, Nunnery SL. The correlation between sleep deprivation and the intensive care unit syndrome. Heart Lung 1980;9(03):464–468 [PubMed: 6901518]
64. Thille AW, Reynaud F, Marie D, et al. Impact of sleep alterations on weaning duration in mechanically ventilated patients: a prospective study. Eur Respir J 2018;51(04):
65. Dres M, Younes M, Rittayamai N, et al. Sleep and pathological wakefulness at the time of liberation from mechanical ventilation (SLEEWE). A prospective multicenter physiological study. Am J Respir Crit Care Med 2019;199(09):1106–1115 [PubMed: 30818966]
66. Roche Campo F, Drouot X, Thille AW, et al. Poor sleep quality is associated with late noninvasive ventilation failure in patients with acute hypercapnic respiratory failure. Crit Care Med 2010; 38(02):477–485 [PubMed: 19789439]
67. Takahashi Y, Kipnis DM, Daughaday WH. Growth hormone secretion during sleep. J Clin Invest 1968;47(09):2079–2090 [PubMed: 5675428]
68. Van den Berghe G. Dynamic neuroendocrine responses to critical illness. Front Neuroendocrinol 2002;23(04):370–391 [PubMed: 12381331]
69. Redwine L, Hauger RL, Gillin JC, Irwin M. Effects of sleep and sleep deprivation on interleukin-6, growth hormone, cortisol, and melatonin levels in humans. J Clin Endocrinol Metab 2000; 85(10):3597–3603 [PubMed: 11061508]
70. Sauvet F, Leftheriotis G, Gomez-Merino D, et al. Effect of acute sleep deprivation on vascular function in healthy subjects. J Appl Physiol (1985) 2010;108(01):68–75 [PubMed: 19910332]
71. Ogawa Y, Kanbayashi T, Saito Y, et al. Total sleep deprivation elevates blood pressure through arterial baroreflex resetting: a study with microneurographic technique. Sleep 2003;26(08): 986–989 [PubMed: 14746379]
72. Zhong X, Hilton HJ, Gates GJ, et al. Increased sympathetic and decreased parasympathetic cardiovascular modulation in normal humans with acute sleep deprivation. J Appl Physiol (1985) 2005;98(06):2024–2032 [PubMed: 15718408]

73. Stamatakis KA, Punjabi NM. Effects of sleep fragmentation on glucose metabolism in normal subjects. Chest 2010;137(01): 95–101 [PubMed: 19542260]
74. Ozer O, Ozbala B, Sari I, et al. Acute sleep deprivation is associated with increased QT dispersion in healthy young adults. Pacing Clin Electrophysiol 2008;31(08):979–984 [PubMed: 18684254]
75. Annane D, Sébille V, Duboc D, et al. Incidence and prognosis of sustained arrhythmias in critically ill patients. Am J Respir Crit Care Med 2008;178(01):20–25 [PubMed: 18388358]
76. Lampert R, Jain D, Burg MM, Batsford WP, McPherson CA. Destabilizing effects of mental stress on ventricular arrhythmias in patients with implantable cardioverter-defibrillators. Circulation 2000;101(02):158–164 [PubMed: 10637203]
77. Irwin M, McClintick J, Costlow C, Fortner M, White J, Gillin JC. Partial night sleep deprivation reduces natural killer and cellular immune responses in humans. FASEB J 1996;10(05):643–653 [PubMed: 8621064]
78. Lange T, Perras B, Fehm HL, Born J. Sleep enhances the human antibody response to hepatitis A vaccination. Psychosom Med 2003;65(05):831–835 [PubMed: 14508028]
79. Spiegel K, Sheridan JF, Van Cauter E. Effect of sleep deprivation on response to immunization. JAMA 2002;288(12):1471–1472
80. Kahn DM, Cook TE, Carlisle CC, Nelson DL, Kramer NR, Millman RP. Identification and modification of environmental noise in an ICU setting. Chest 1998;114(02):535–540 [PubMed: 9726742]
81. Olson DM, Borel CO, Laskowitz DT, Moore DT, McConnell ES. Quiet time: a nursing intervention to promote sleep in neurocritical care units. Am J Crit Care 2001;10(02):74–78 [PubMed: 11244674]
82. Monsén MG, Edéll-Gustafsson UM. Noise and sleep disturbance factors before and after implementation of a behavioural modification programme. Intensive Crit Care Nurs 2005;21(04): 208–219 [PubMed: 16039958]
83. Walder B, Francioli D, Meyer JJ, Lançon M, Romand J-A. Effects of guidelines implementation in a surgical intensive care unit to control nighttime light and noise levels. Crit Care Med 2000;28 (07):2242–2247 [PubMed: 10921547]
84. Boyko Y, Jennum P, Nikolic M, Holst R, Oerding H, Toft P. Sleep in intensive care unit: the role of environment. J Crit Care 2017; 37:99–105 [PubMed: 27660924]
85. Haddock J. Reducing the effects of noise in hospital. Nurs Stand 1994;8(43):25–28
86. Scotto CJ, McClusky C, Spillan S, Kimmel J. Earplugs improve patients' subjective experience of sleep in critical care. Nurs Crit Care 2009;14(04):180–184 [PubMed: 19531035]
87. Neyse F, Daneshmandi M, Sharme MS, Ebadi A. The effect of earplugs on sleep quality in patients with acute coronary syndrome. Iran J Crit Care Nurs 2011;4(03):127–134
88. Van Rompaey B, Elseviers MM, Van Drom W, Fromont V, Jorens PG. The effect of earplugs during the night on the onset of delirium and sleep perception: a randomized controlled trial in intensive care patients. Crit Care 2012;16(03):R73 [PubMed: 22559080]
89. Richardson A, Allsop M, Coghill E, Turnock C. Earplugs and eye masks: do they improve critical care patients' sleep? Nurs Crit Care 2007;12(06):278–286 [PubMed: 17983362]
90. Ryu MJ, Park JS, Park H. Effect of sleep-inducing music on sleep in persons with percutaneous transluminal coronary angiography in the cardiac care unit. J Clin Nurs 2012;21(5,6):728–735 [PubMed: 22082250]
91. Jones C, Dawson D. Eye masks and earplugs improve patient's perception of sleep. Nurs Crit Care 2012;17(05):247–254 [PubMed: 22897811]
92. Le Guen M, Nicolas-Robin A, Lebard C, Arnulf I, Langeron O. Earplugs and eye masks vs routine care prevent sleep impairment in post-anaesthesia care unit: a randomized study. Br J Anaesth 2014;112(01):89–95 [PubMed: 24172057]
93. Yazdannik AR, Zareie A, Hasanpour M, Kashefi P. The effect of earplugs and eye mask on patients' perceived sleep quality in intensive care unit. Iran J Nurs Midwifery Res 2014;19(06): 673–678 [PubMed: 25558268]
94. Dave K, Qureshi A, Gopichandran L, Kiran U. Effects of earplugs and eye masks on perceived quality of sleep during night among patients in intensive care units. Int J Sci Res (Ahmedabad) 2015;4 (06):2294–2297

95. Mashayekhi F, Rafiei H, Arab M, Abazari F, Ranjbar H. The effect of sleep quality on patients in a coronary care unit. Br J Card Nurs 2013;8(09):443–448
96. Bajwa N, Saini P, Kaur H, Kalra S, Kaur J. Effect of ear plugs & eye maskon sleep among icu patients: a randomized control trial. Int J Curr Res 2015;7(12):23741–23745
97. Hu R-F, Jiang XY, Hegadoren KM, Zhang Y-H. Effects of earplugs and eye masks combined with relaxing music on sleep, melatonin and cortisol levels in ICU patients: a randomized controlled trial. Crit Care 2015;19:115 [PubMed: 25881268]
98. Babaii A, Adib-Hajbaghery M, Hajibagheri A. Effect of using eye mask on sleep quality in cardiac patients: a randomized controlled trial. Nurs Midwifery Stud 2015;4(04):e28332
99. Mashayekhi F, Mansour A, Motahhareh P, Amiri M, Rafiei H. The effect of eye mask on sleep quality in patients of coronary care unit. Sleep Sci 2012;6(03):75–78
100. Daneshmandi M, Neiseh F, SadeghiShermeh M, Ebadi A. Effect of eye mask on sleep quality in patients with acute coronary syndrome. J Caring Sci 2012;1(03):135–143 [PubMed: 25276688]
101. Foreman B, Westwood AJ, Claassen J, Bazil CW. Sleep in the neurological intensive care unit: feasibility of quantifying sleep after melatonin supplementation with environmental light and noise reduction. J Clin Neurophysiol 2015;32(01):66–74 [PubMed: 25647773]
102. Chlan LL, Weinert CR, Heiderscheit A, et al. Effects of patientdirected music intervention on anxiety and sedative exposure in critically ill patients receiving mechanical ventilatory support: a randomized clinical trial. JAMA 2013;309(22):2335–2344 [PubMed: 23689789]
103. Hansen IP, Langhorn L, Dreyer P. Effects of music during daytime restintheintensivecareunit. NursCritCare 2018;23(04):207–213
104. Su C-P, Lai H-L, Chang E-T, Yiin L-M, Perng S-J, Chen P-W. A randomized controlled trial of the effects of listening to noncommercial music on quality of nocturnal sleep and relaxation indices in patients in medical intensive care unit. J Adv Nurs 2013;69(06):1377–1389 [PubMed: 22931483]
105. Gragert MD. The use of a masking signal to enhance the sleep of men and women 65years of age and older in the critical care environment. PhD Thesis. The University of Texas at Austin; 1990
106. Williamson JW. The effects of ocean sounds on sleep after coronary artery bypass graft surgery. Am J Crit Care 1992;1 (01):91–97
107. Farokhnezhad Afshar P, Bahramnezhad F, Asgari P, Shiri M. Effect of white noise on sleep in patients admitted to a coronary care. J Caring Sci 2016;5(02):103–109 [PubMed: 27354974]
108. Richards KC. Effect of a back massage and relaxation intervention on sleep in critically ill patients. Am J Crit Care 1998;7(04): 288–299 [PubMed: 9656043]
109. Nerbass FB, Feltrim MIZ, Souza SA, Ykeda DS, Lorenzi-Filho G. Effects of massage therapy on sleep quality after coronary artery bypass graft surgery. Clinics (São Paulo) 2010;65(11):1105–1110 [PubMed: 21243280]
110. Oshvandi K, Abdi S, Karampourian A, Moghimbaghi A, Homayonfar S. The effect of foot massage on quality of sleep in ischemic heart disease patients hospitalized in CCU. Iran J Crit Care Nurse 2014;7(02):66–73
111. Shinde MB, Anjum S. Effectiveness of slow back massage on quality of sleep among ICU patients. Int J Sci Res (Ahmedabad) 2014;3(03):292–298
112. Hsu WC, Guo SE, Chang CH. Back massage intervention for improving health and sleep quality among intensive care unit patients. Nurs Crit Care 2019 (e-pub ahead of print). Doi: 10.1111/nicc.12428
113. Moeini M, Khadibi M, Bekhradi R, Mahmoudian SA, Nazari F. Effect of aromatherapy on the quality of sleep in ischemic heart disease patients hospitalized in intensive care units of heart hospitals of the Isfahan University of Medical Sciences. Iran J Nurs Midwifery Res 2010;15(04):234–239 [PubMed: 22049287]
114. Cho M-Y, Min ES, Hur M-H, Lee MS. Effects of aromatherapy on the anxiety, vital signs, and sleep quality of percutaneous coronary intervention patients in intensive care units. EvidenceBased Complement Altern Med 2013;2013:381381
115. Hajibagheri A, Babaii A, Adib-Hajbaghery M. Effect of Rosa damascene aromatherapy on sleep quality in cardiac patients: a randomized controlled trial. Complement Ther Clin Pract 2014;20(03):159–163 [PubMed: 25129884]

116. Karadag E, Samancioglu S, Ozden D, Bakir E. Effects of aromatherapy on sleep quality and anxiety of patients. Nurs Crit Care 2017;22(02):105–112 [PubMed: 26211735]
117. Cho EH, Lee MY, Hur MH. The effects of aromatherapy on intensive care unit patients' stress and sleep quality: a nonrandomised controlled trial. Evid Based Complement Alternat Med 2017;2017:2856592
118. Chen JH, Chao YH, Lu SF, Shiung TF, Chao YF. The effectiveness of valerian acupressure on the sleep of ICU patients: a randomized clinical trial. Int J Nurs Stud 2012;49(08):913–920 [PubMed: 22391336]
119. Bagheri-Nesami M, Gorji MAH, Rezaie S, Pouresmail Z, Cherati JY. Effect of acupressure with valerian oil 2.5% on the quality and quantity of sleep in patients with acute coronary syndrome in a cardiac intensive care unit. J Tradit Complement Med 2015;5 (04):241–247 [PubMed: 26587395]
120. Rahmani A, Naseri M, Salaree MM, Nehrir B. Comparing the effect of foot reflexology massage, foot bath and their combination on quality of sleep in patients with acute coronary syndrome. J Caring Sci 2016;5(04):299–306 [PubMed: 28032074]
121. Berglund B, Lindvall T, eds. Guidelines for Community Noise. Geneva: World Health Organization; 1999
122. Johansson L, Bergbom I, Waye KP, Ryherd E, Lindahl B. The sound environment in an ICU patient room–a content analysis of sound levels and patient experiences. Intensive Crit Care Nurs 2012;28 (05):269–279 [PubMed: 22537478]
123. Jaiswal SJ, Garcia S, Owens RL. Sound and light levels are similarly disruptive in ICU and non-ICU Wards. J Hosp Med 2017;12(10): 798–804 [PubMed: 28991944]
124. White BL, Zomorodi M. Perceived and actual noise levels in critical care units. Intensive Crit Care Nurs 2017;38:18–23 [PubMed: 27567305]
125. Hilton BA. Quantity and quality of patients' sleep and sleep-disturbing factors in a respiratory intensive care unit. J Adv Nurs 1976;1(06):453–468 [PubMed: 1050357]
126. Buxton OM, Ellenbogen JM, Wang W, et al. Sleep disruption due to hospital noises: a prospective evaluation. Ann Intern Med 2012;157(03):170–179 [PubMed: 22868834]
127. Stanchina ML, Abu-Hijleh M, Chaudhry BK, Carlisle CC, Millman RP. The influence of white noise on sleep in subjects exposed to ICU noise. Sleep Med 2005;6(05):423–428 [PubMed: 16139772]
128. Konkani A, Oakley B, Penprase B. Reducing hospital ICU noise: a behavior-based approach. J Healthc Eng 2014;5(02): 229–246 [PubMed: 24918185]
129. Kol E, Demircan A, Erdoğan A, Gencer Z, Erengin H. The effectiveness of measures aimed at noise reduction in an intensive care unit. Workplace Health Saf 2015;63(12):539–545 [PubMed: 26493219]
130. Luetz A, Weiss B, Penzel T, et al. Feasibility of noise reduction by a modification in ICU environment. Physiol Meas 2016;37(07): 1041–1055 [PubMed: 27243942]
131. Huang HW, Zheng BL, Jiang L, et al. Effect of oral melatonin and wearing earplugs and eye masks on nocturnal sleep in healthy subjects in a simulated intensive care unit environment: which might be a more promising strategy for ICU sleep deprivation? Crit Care 2015;19:124 [PubMed: 25887528]
132. Gallacher S, Enki D, Stevens S, Bennett MJ. An experimental model to measure the ability of headphones with active noise control to reduce patient's exposure to noise in an intensive care unit. Intensive Care Med Exp 2017;5(01):47 [PubMed: 29043462]
133. Fan EP, Abbott SM, Reid KJ, Zee PC, Maas MB. Abnormal environmental light exposure in the intensive care environment. J Crit Care 2017;40:11–14 [PubMed: 28292665]
134. Durrington HJ, Clark R, Greer R, et al. 'In a dark place, we find ourselves': light intensity in critical care units. Intensive Care Med Exp 2017;5(01):9 [PubMed: 28168516]
135. Craig T, Mathieu S. CANDLE: The critical analysis of the nocturnal distribution of light exposure - A prospective pilot study quantifying the nocturnal light intensity on a critical care unit. J Intensive Care Soc 2018;19(03):196–200 [PubMed: 30159010]
136. Castro RA, Angus DC, Hong SY, et al. Light and the outcome of the critically ill: an observational cohort study. Crit Care 2012;16 (04):R132 [PubMed: 22827924]

137. Yang J, Choi W, Ko YH, Joe SH, Han C, Kim YK. Bright light therapy as an adjunctive treatment with risperidone in patients with delirium: a randomized, open, parallel group study. Gen Hosp Psychiatry 2012;34(05):546–551: [PubMed: 22717090]
138. Simons KS, Laheij RJ, van den Boogaard M, et al. Dynamic light application therapy to reduce the incidence and duration of delirium in intensive-care patients: a randomised controlled trial. Lancet Respir Med 2016;4(03):194–202 [PubMed: 26895652]
139. Erdoğan Z, Atik D. Complementary health approaches used in the intensive care unit. Holist Nurs Pract 2017;31(05):325–342 [PubMed: 28786890]
140. DuBose JR, Hadi K. Improving inpatient environments to support patient sleep. Int J Qual Health Care 2016;28(05):540–553 [PubMed: 27512130]
141. Richards K, Nagel C, Markie M, Elwell J, Barone C. Use of complementary and alternative therapies to promote sleep in critically ill patients. Crit Care Nurs Clin North Am 2003;15(03): 329–340 [PubMed: 12943139]
142. Devlin JW, Skrobik Y, Gélinas C, et al. Executive summary: clinical practice guidelines for the prevention and management of pain, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the ICU. Crit Care Med 2018;46 (09):1532–1548 [PubMed: 30113371]
143. Locihová H, Axmann K, Padyšáková H, Fejfar J. Effect of the use of earplugs and eye mask on the quality of sleep in intensive care patients: a systematic review. J Sleep Res 2018;27(03):e12607
144. Hu RF, Jiang XY, Zeng YM, Chen XY, Zhang YH. Effects of earplugs and eye masks on nocturnal sleep, melatonin and cortisol in a simulated intensive care unit environment. Crit Care 2010;14 (02):R66 [PubMed: 20398302]
145. Kamdar BB, Kamdar BB, Needham DM. Bundling sleep promotion with delirium prevention: ready for prime time? Anaesthesia 2014;69(06):527–531 [PubMed: 24813131]
146. Kamdar BB, Yang J, King LM, et al. Developing, implementing, and evaluating a multifaceted quality improvement intervention to promote sleep in an ICU. Am J Med Qual 2014;29(06):546–554 [PubMed: 24270169]
147. Esteban A, Anzueto A, Alía I, et al. How is mechanical ventilation employed in the intensive care unit? An international utilization review. Am J Respir Crit Care Med 2000;161(05):1450–1458 [PubMed: 10806138]
148. Andréjak C, Monconduit J, Rose D, et al. Does using pressure-controlled ventilation to rest respiratory muscles improve sleep in ICU patients? Respir Med 2013;107(04):534–541 [PubMed: 23391488]
149. Toublanc B, Rose D, Glérant J-C, et al. Assist-control ventilation vs. low levels of pressure support ventilation on sleep quality in intubated ICU patients. Intensive Care Med 2007;33(07): 1148–1154 [PubMed: 17492431]
150. Bosma K, Ferreyra G, Ambrogio C, et al. Patient-ventilator interaction and sleep in mechanically ventilated patients: pressure support versus proportional assist ventilation. Crit Care Med 2007;35(04):1048–1054 [PubMed: 17334259]
151. Parthasarathy S, Tobin MJ. Effect of ventilator mode on sleep quality in critically ill patients. Am J Respir Crit Care Med 2002; 166(11):1423–1429 [PubMed: 12406837]
152. Roche-Campo F, Thille AW, Drouot X, et al. Comparison of sleep quality with mechanical versus spontaneous ventilation during weaning of critically ill tracheostomized patients. Crit Care Med 2013;41(07):1637–1644 [PubMed: 23507721]
153. Cabello B, Thille AW, Drouot X, et al. Sleep quality in mechanically ventilated patients: comparison of threeventilatory modes. Crit Care Med 2008;36(06):1749–1755 [PubMed: 18496373]
154. Celik S, Oztekin D, Akyolcu N, Işsever H. Sleep disturbance: the patient care activities applied at the night shift in the intensive care unit. J Clin Nurs 2005;14(01):102–106 [PubMed: 15656854]
155. Tamburri LM, DiBrienza R, Zozula R, Redeker NS. Nocturnal care interactions with patients in critical care units. Am J Crit Care 2004;13(02):102–112, quiz 114–115 [PubMed: 15043238]

156. Le A, Friese RS, Hsu CH, Wynne JL, Rhee P, O'Keeffe T. Sleep disruptions and nocturnal nursing interactions in the intensive care unit. J Surg Res 2012;177(02):310–314 [PubMed: 22683076]

157. Christensen M. Noise levels in a general intensive care unit: a descriptive study. Nurs Crit Care 2007;12(04):188–197 [PubMed: 17883600]

158. Joseph A. The Impact of Light on Outcomes in Healthcare. Concord, CA: The Center for Health Design; 2006

159. Simon SK, Phillips K, Badalamenti S, Ohlert J, Krumberger J. Current practices regarding visitation policies in critical care units. Am J Crit Care 1997;6(03):210–217 [PubMed: 9131200]

160. Gonzalez CE, Carroll DL, Elliott JS,Fitzgerald PA, Vallent HJ.Visiting preferences of patients in the intensive care unit and in a complex care medical unit. Am J Crit Care 2004;13(03):194–198 [PubMed: 15149052]

161. Owens RL, Huynh T-G, Netzer G. Sleep in the intensive care unit in a model of family-centered care. AACN Adv Crit Care 2017;28 (02):171–178 [PubMed: 28592477]

162. Panel AGS; By the American Geriatrics Society 2015 Beers Criteria Update Expert Panel. American Geriatrics Society 2015 Updated Beers criteria for potentially inappropriate medication use in older adults. J Am Geriatr Soc 2015;63(11):2227–2246 [PubMed: 26446832]

163. Alexopoulou C, Kondili E, Diamantaki E, et al. Effects of dexmedetomidine on sleep quality in critically ill patients: a pilot study. Anesthesiology 2014;121(04):801–807 [PubMed: 24988068]

164. Wu X-H, Cui F, Zhang C, et al. Low-dose dexmedetomidine improves sleep quality pattern in elderly patients after noncardiac surgery in the intensive care unit: a pilot randomized controlled trial. Anesthesiology 2016;125(05):979–991 [PubMed: 27571256]

165. Huupponen E, Maksimow A, Lapinlampi P, et al. Electroencephalogram spindle activity during dexmedetomidine sedation and physiological sleep. Acta Anaesthesiol Scand 2008;52(02): 289–294 [PubMed: 18005372]

166. Akeju O, Hobbs LE, Gao L, et al. Dexmedetomidine promotes biomimetic non-rapid eye movement stage 3 sleep in humans: A pilot study. Clin Neurophysiol 2018;129(01):69–78 [PubMed: 29154132]

167. Oto J, Yamamoto K, Koike S, Onodera M, Imanaka H, Nishimura M. Sleep quality of mechanically ventilated patients sedated with dexmedetomidine. Intensive Care Med 2012;38(12):1982–1989 [PubMed: 22961436]

168. Shehabi Y, Howe BD, Bellomo R, et al. ; ANZICS Clinical Trials Group and the SPICE III Investigators. Early Sedation with dexmedetomidine in critically ill patients. N Engl J Med 2019; 380(26):2506–2517 [PubMed: 31112380]

169. Skrobik Y, Duprey MS, Hill NS, Devlin JW. Low-dose nocturnal dexmedetomidine prevents icu delirium. a randomized, placebo-controlled trial. Am J Respir Crit Care Med 2018;197(09): 1147–1156 [PubMed: 29498534]

170. Kondili E, Alexopoulou C, Xirouchaki N, Georgopoulos D. Effects of propofol on sleep quality in mechanically ventilated critically ill patients: a physiological study. Intensive Care Med 2012;38 (10):1640–1646 [PubMed: 22752356]

171. Engelmann C, Wallenborn J, Olthoff D, Kaisers UX, Rüffert H. Propofol versus flunitrazepam for inducing and maintaining sleep in postoperative ICU patients. Indian J Crit Care Med 2014;18(04):212–219 [PubMed: 24872650]

172. Lewis SR, Schofield-Robinson OJ, Alderson P, Smith AF. Propofol for the promotion of sleep in adults in the intensive care unit. Cochrane Database Syst Rev 2018;1(01):CD012454

173. Hatta K, Kishi Y, Wada K, et al. l; DELIRIA-J Group. Preventive effects of ramelteon on delirium: a randomized placebo-controlled trial. JAMA Psychiatry 2014;71(04):397–403 [PubMed: 24554232]

174. Nishikimi M, Numaguchi A, Takahashi K, et al. Effect of administration of ramelteon, a melatonin receptor agonist, on the duration of stay in the ICU: a single-center randomized placebo-controlled trial. Crit Care Med 2018;46(07):1099–1105 [PubMed: 29595562]

175. Lewis SR, Pritchard MW, Schofield-Robinson OJ, Alderson P, Smith AF. Melatonin for the promotion of sleep in adults in the intensive care unit. Cochrane Database Syst Rev 2018;5(05):CD012455

176. Shilo L, Dagan Y, Smorjik Y, et al. Effect of melatonin on sleep quality of COPD intensive care patients: a pilot study. Chronobiol Int 2000;17(01):71–76 [PubMed: 10672435]

177. Ibrahim MG, Bellomo R, Hart GK, et al. A double-blind placebocontrolled randomised pilot study of nocturnal melatonin in tracheostomised patients. Crit Care Resusc 2006;8(03):187–191. [PubMed: 16930101]

178. Bourne RS, Mills GH, Minelli C. Melatonin therapy to improve nocturnal sleep in critically ill patients: encouraging results from a small randomised controlled trial. Crit Care 2008;12 (02):R52 [PubMed: 18423009]

179. Mistraletti G, Sabbatini G, Taverna M, et al. Pharmacokinetics of orally administered melatonin in critically ill patients. J Pineal Res 2010;48(02):142–147 [PubMed: 20070489]

180. Kane JM, Sharif ZA. Atypical antipsychotics: sedation versus efficacy. J Clin Psychiatry 2008;69(Suppl 1):18–31 [PubMed: 18484805]

181. Miller DD. Atypical antipsychotics: sleep, sedation, and efficacy. Prim Care Companion J Clin Psychiatry 2004;6(Suppl 2):3–7

182. Cohrs S, Rodenbeck A, Guan Z, et al. Sleep-promoting properties of quetiapine in healthy subjects. Psychopharmacology (Berl) 2004;174(03):421–429 [PubMed: 15029469]

183. Wiegand MH, Landry F, Brückner T, Pohl C, Veselý Z, Jahn T. Quetiapine in primary insomnia: a pilot study. Psychopharmacology (Berl) 2008;196(02):337–338 [PubMed: 17922110]

184. Giménez S, Clos S, Romero S, Grasa E, Morte A, Barbanoj MJ. Effects of olanzapine, risperidone and haloperidol on sleep after a single oral morning dose in healthy volunteers. Psychopharmacology (Berl) 2007;190(04):507–516 [PubMed: 17205319]

185. Sharpley AL, Vassallo CM, Cowen PJ. Olanzapine increases slowwave sleep: evidence for blockade of central 5-HT(2C) receptors in vivo. Biol Psychiatry 2000;47(05):468–470 [PubMed: 10704958]

186. Sharpley AL, Attenburrow ME, Hafizi S, Cowen PJ. Olanzapine increases slow wave sleep and sleep continuity in SSRI-resistant depressed patients. J Clin Psychiatry 2005;66(04):450–454 [PubMed: 15816787]

187. Armour A, Gottschlich MM, Khoury J, Warden GD, Kagan RJA. A randomized, controlled prospective trial of zolpidem and haloperidol for use as sleeping agents in pediatric burn patients. J Burn Care Res 2008;29(01):238–247 [PubMed: 18182928]

188. Girard TD, Exline MC, Carson SS, et al. ; MIND-USA Investigators. Haloperidol and ziprasidone for treatment of delirium in critical illness. N Engl J Med 2018;379(26):2506–2516 [PubMed: 30346242]

189. Page VJ, Ely EW, Gates S, et al. Effect of intravenous haloperidol on the duration of delirium and coma in critically ill patients (Hope-ICU): a randomised, double-blind, placebo-controlled trial. Lancet Respir Med 2013;1(07):515–523 [PubMed: 24461612]

190. van den Boogaard M, Slooter AJ, Brüggemann RJ, et al. Prevention of ICU delirium and delirium-related outcome with haloperidol: a study protocol for a multicenter randomized controlled trial. Trials 2013;14:400 [PubMed: 24261644]

191. van den Boogaard M, Slooter AJC, Brüggemann RJM. Effect of haloperidol on survival among critically ill adults with a high risk of delirium. JAMA 2018;319(07):680–690 [PubMed: 29466591]

192. Girard TD, Pandharipande PP, Carson SS, et al. ; MIND Trial Investigators. Feasibility, efficacy, and safety of antipsychotics for intensive care unit delirium: the MIND randomized, placebocontrolled trial. Crit Care Med 2010;38(02):428–437 [PubMed: 20095068]

193. NIH state of the science conference statement on manifestations and management of chronic insomnia in adults statement. J Clin Sleep Med 2005;1(04):412–421 [PubMed: 17564412]

194. Morin AK, Jarvis CI, Lynch AM. Therapeutic options for sleepmaintenance and sleep-onset insomnia. Pharmacotherapy 2007; 27(01):89–110 [PubMed: 17192164]

195. Roth AJ, McCall WV, Liguori A. Cognitive, psychomotor and polysomnographic effects of trazodone in primary insomniacs. J Sleep Res 2011;20(04):552–558 [PubMed: 21623982]

196. Yamadera H, Nakamura S, Suzuki H, Endo S. Effects of trazodone hydrochloride and imipramine on polysomnography in healthy subjects. Psychiatry Clin Neurosci 1998;52(04):439–443 [PubMed: 9766695]

197. Yamadera H, Suzuki H, Nakamura S, Endo S. Effects of trazodone on polysomnography, blood concentration and core body temperature in healthy volunteers. Psychiatry Clin Neurosci 1999;53 (02):189–191 [PubMed: 10459685]

198. Ware JC, Pittard JT. Increased deep sleep after trazodone use: a double-blind placebo-controlled study in healthy young adults. J Clin Psychiatry 1990;51(Suppl):18–22

199. Saletu-Zyhlarz GM, Abu-Bakr MH, Anderer P, et al. Insomnia in depression: differences in objective and subjective sleep and awakening quality to normal controls and acute effects of trazodone. Prog Neuropsychopharmacol Biol Psychiatry 2002; 26(02):249–260 [PubMed: 11817501]

200. Mouret J, Lemoine P, Minuit MP, Benkelfat C, Renardet M. Effects of trazodone on the sleep of depressed subjects–a polygraphic study. Psychopharmacology (Berl) 1988;95(Suppl):S37–S43 [PubMed: 3133713]

201. Parrino L, Spaggiari MC, Boselli M, Di Giovanni G, Terzano MG. Clinical and polysomnographic effects of trazodone CR in chronic insomnia associated with dysthymia. Psychopharmacology (Berl) 1994;116(04):389–395 [PubMed: 7701038]

202. Saletu-Zyhlarz GM, Abu-Bakr MH, Anderer P, et al. Insomnia related to dysthymia: polysomnographic and psychometric comparison with normal controls and acute therapeutic trials with trazodone. Neuropsychobiology 2001;44(03):139–149 [PubMed: 11586054]

203. Scharf MB, Sachais BA. Sleep laboratory evaluation of the effects and efficacy of trazodone in depressed insomniac patients. J Clin Psychiatry 1990;51(9, Suppl):13–17

204. Jaffer KY, Chang T, Vanle B, et al. Trazodone for insomnia: a systematic review. Innov Clin Neurosci 2017;14(7,8):24–34

205. Mendelson WB. A review of the evidence for the efficacy and safety of trazodone in insomnia. J Clin Psychiatry 2005;66(04): 469–476 [PubMed: 15816789]

206. Borbély AA, Mattmann P, Loepfe M, Strauch I, Lehmann D. Effect of benzodiazepine hypnotics on all-night sleep EEG spectra. Hum Neurobiol 1986;4(03):189–194

207. Achermann P, Borbély AA. Dynamics of EEG slow wave activity during physiological sleep and after administration of benzodiazepine hypnotics. Hum Neurobiol 1987;6(03):203–210 [PubMed: 2896653]

208. Clegg A, Young JB. Which medications to avoid in people at risk of delirium: a systematic review. Age Ageing 2011;40(01): 23–29 [PubMed: 21068014]

209. Pandharipande P, Shintani A, Peterson J, et al. Lorazepam is an independent risk factor for transitioning to delirium in intensive care unit patients. Anesthesiology 2006;104(01):21–26 [PubMed: 16394685]

210. Huedo-Medina TB, Kirsch I, Middlemass J, Klonizakis M, Siriwardena AN. Effectiveness of non-benzodiazepine hypnotics in treatment of adult insomnia: meta-analysis of data submitted to the Food and Drug Administration. BMJ 2012;345(December):e8343 [PubMed: 23248080]

211. FDA Drug Safety Communication. FDA adds boxed warning for risk of serious injuries caused by sleepwalking with certain prescription insomnia medicines. U.S. Food and Drug Administration. Available at: https://www.fda.gov/drugs/drug-safety-and-availability/fda-adds-boxed-warning-risk-serious-injuries-caused-sleepwalking-certain-prescription-insomnia. Accessed August 3, 2019

212. Mahoney JE, Webb MJ, Gray SL. Zolpidem prescribing and adverse drug reactions in hospitalized general medicine patients at a Veterans Affairs hospital. Am J Geriatr Pharmacother 2004;2 (01):66–74 [PubMed: 15555480]

213. Edwards BJ, Reilly T, Waterhouse J. Zeitgeber-effects of exercise on human circadian rhythms: What are alternative approaches to investigating the existence of a phase-response curve to exercise? Biol Rhythm Res 2009;40(01):53–69

214. Kolla BP, Lovely JK, Mansukhani MP, Morgenthaler TI. Zolpidem is independently associated with increased risk of inpatient falls. J Hosp Med 2013;8(01):1–6 [PubMed: 23165956]

215. Krenk L, Jennum P, Kehlet H. Postoperative sleep disturbances after zolpidem treatment in fast-track hip and knee replacement. J Clin Sleep Med 2014;10(03):321–326 [PubMed: 24634631]

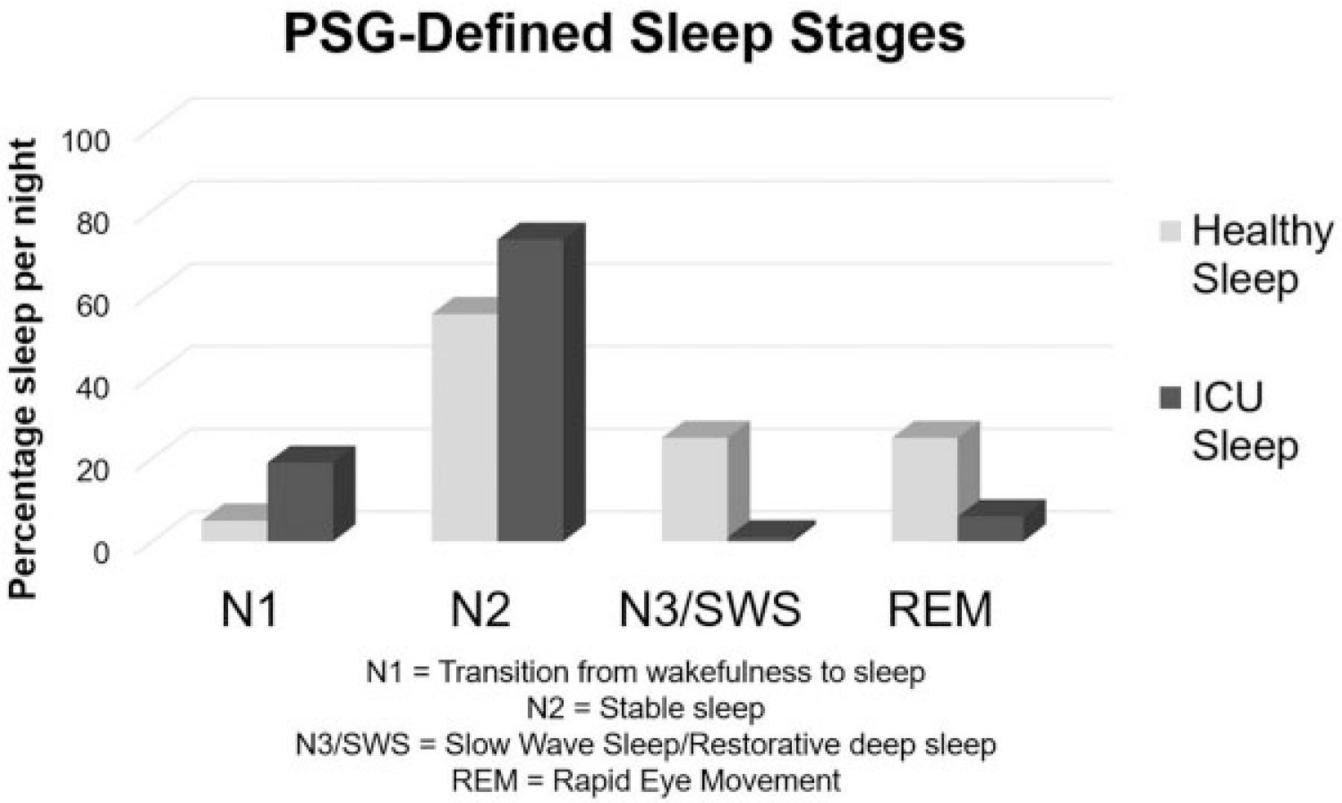

Fig. 1.

Polysomnography-defined sleep stages. Total sleep time in prototypical healthy[10] versus critically ill adults.[12] Percentages based on nocturnal PSG in healthy adults and 24-hour PSG in ICU patients. ICU, intensive care unit; PSG, polysomnography; REM. rapid eye movement; SWS, slow wave sleep.

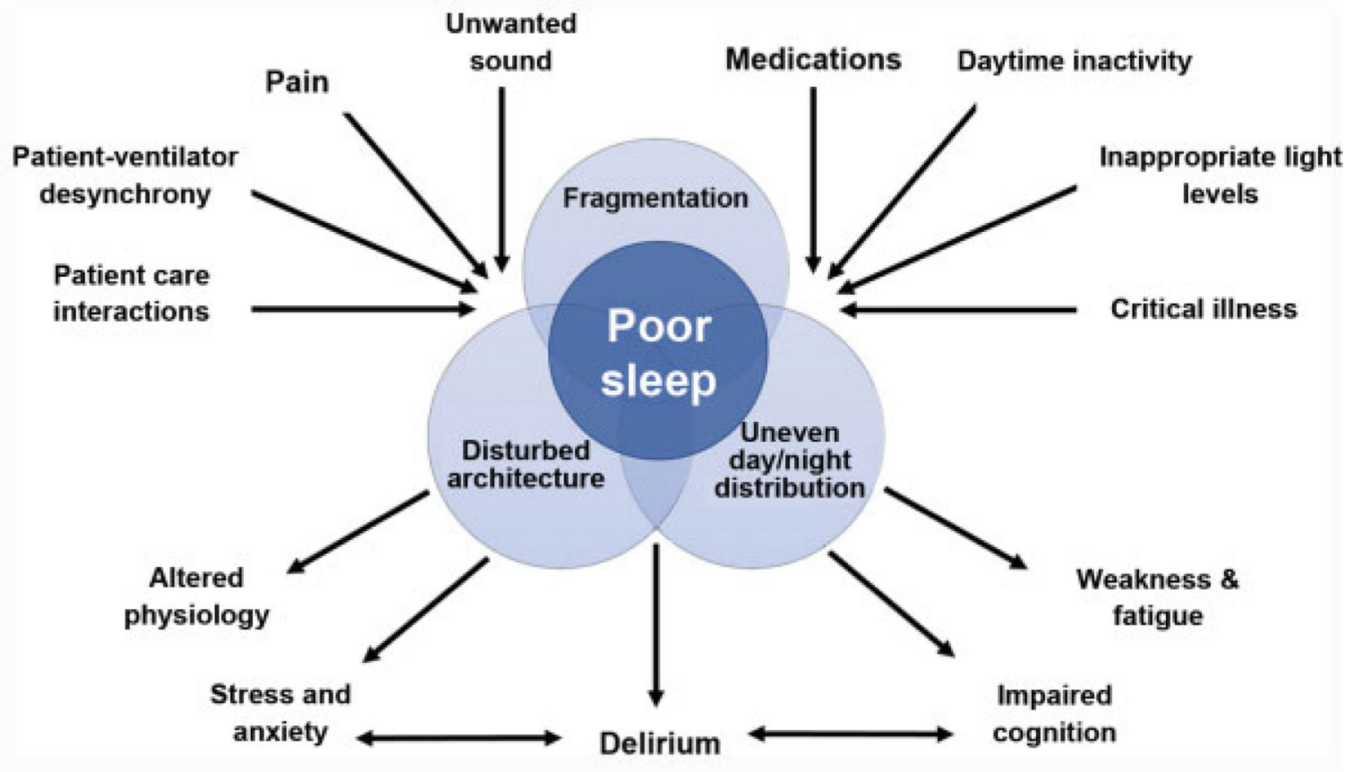

Fig. 2.

Causes and consequences of sleep-wake rhythm disturbance in the ICU. ICU, intensive care unit (adapted from Kamdar et al[46]).

Table 1

Nonpharmacological sleep-promoting interventions

Intervention	First author	Year	Study type	Sample size	ICU Type	Measurement tool	Outcome
Behavior modification	Kahn et al[80]	1998	Pre–post	All medical ICU staff	Medical	Sound levels	↓ Mean peak sound
	Olson et al[81]	2001	CCT	843	Neuro	Nurse observation	↑ Sleep quantity
	Monsén and Edéll-Gustafsson[82]	2005	CCT	23	Neuro	Sound Levels	↓ mean peak sound
Behavior modification + noise/light reduction + clustering of care	Walder et al[83]	2000	Pre–post	17	Surgical	Sound levels Light levels	↓ peak sound No change in light
Behavioral modification + earplugs + eye mask	Kamdar et al[45]	2013	Pre–post	300	Medical	RCSQ	No difference in sleep quality ↓ subjective sound ↓ delirium
	Patel et al[44]	2014	Pre–post	59	Mixed	RCSQ Sound levels Light levels	↑ Sleep quality ↓ mean nocturnal sound + light ↓ delirium
	Boyko et al[84]	2017	RCT	17	Mixed	PSG Sound levels	No differences in sleep or mean sound level
Earplugs	Haddock[85]	1994	RCT	18	Gynecology	Custom questionnaire	↑ Sleep quality
	Scotto et al[86]	2009	Quasi-experimental	88	Mixed	VHS	
	Neyse et al[87]	2011	CCT	60	Cardiac	PSQI	
	Van Rompaey et al[88]	2012	RCT	136	Unspecified	Custom questionnaire	
Earplugs + eye mask	Richardson et al[89]	2007	Quasi-experimental	64	CT Surgery	Custom questionnaire	↑ Sleep quality in some patients
	Ryu et al[90]	2011	Quasi-experimental	58	Cardiac	VHS	↑ Sleep quality
	Jones and Dawson[91]	2012	Pre–post	100	Surgical	Custom questionnaire	
	Le Guen et al[92]	2014	RCT	41	PACU	SSQ MOSS Actigraphy	
	Yazdannik et al[93]	2014	CCT	50	Unspecified	VHS	
	Dave et al[94]	2015	Crossover	50	Cardiac	RCSQ	
	Mashayekhi et al[95]	2013	Crossover	90	Cardiac	VHS	
	Bajwa et al[96]	2015	RCT	100	Unspecified	VHS	
Earplug + eye mask + music	Hu et al[97]	2015	RCT	45	CT Surgery	RCSQ	↑ Sleep quality

Intervention	First author	Year	Study type	Sample size	ICU Type	Measurement tool	Outcome
Eye mask	Babaii[98]	2015	RTC	60	Cardiac	PSQI	
	Mashayekhi et al[99]	2012	Crossover	60	Cardiac	VHS	
	Daneshmandi et al[100]	2012	CCT	60	Cardiac	PSQI	
Eye mask + headphones + melatonin	Foreman et al[101]	2015	RCT	12	Neuro	PSG	UTD due to abnormal EEG
Music versus noise cancelling headphones	Chlan et al[102]	2013	RCT	373	Unspecified	VAS-A Sedative dosage and frequency	↓ Anxiety and sedative use in music group only
Music + daytime rest period	Hansen et al[103]	2017	RCT	37	Mixed	RCSQ	↑ Subjective sleep
Music	Su et al[104]	2012	RCT	28	Medical	PSG VSH	↑ SWS ↑ subjective sleep
White noise	Gragert[105]	1990	CCT	40	Elderly cardiac	RCSQ	↑ Subjective sleep
	Williamson[106]	1992	CCT	60	General ward postCABG	RCSQ	
	Afshar et al[107]	2016	Quasi-experimental	60	Cardiac	PSQI	
Massage	Richards[108]	1998	RCT	71	Unspecified	PSG	↑ Sleep efficiency in older men
	Nerbass et al[109]	2010	RCT	57	Cardiac	VAS sleep	↑ Sleep quality
	Oshvandi et al[110]	2014	RCT	60	Cardiac	SMHSQ	
	Shinde and Anjum[111]	2014	Prepost	60	Unspecified	Modified GSQS Observation	
	Hsu et al[112]	2019	Quasi-experimental	60	Unspecified	VHS Actigraphy Observation	
Aromatherapy	Moeini et al[113]	2010	RCT	64	Cardiac	SMHSQ	
	Cho et al[114]	2013	Prepost	56	Cardiac	VHS	
	Hajibagheri et al[115]	2014	RCT	60	Cardiac	PSQI	
	Karadag et al[116]	2015	RCT	60	Cardiac	PSQI	
	Cho et al[117]	2017	CCT	60	Unspecified	VHS	
Valerian acupressure	Chen et al[118]	2012	RCT	85	Unspecified	Actigraphy SSS Nurse Observation	↑ Actigraphic sleep ↓ waking frequency
Valerian acupressure oil versus massage	Bagheri-Nesami et al[119]	2015	RCT	90	Cardiac	SMHSQ	↑ Sleep quality w/valerian acupressure oil
Foot reflexology massage ± foot bath versus control	Rahmani et al[120]	2016	Quasi-experimental	140	Cardiac	VSH	↑ Subjective sleep with foot reflexology massage foot bath

Abbreviations: CCT, controlled clinical trial; CT, cardiothoracic; EEG, electroencephalogram; GSQS, Groningen's sleep quality scale; MOSS, Michigan opiate safety score; PACU, postanesthesia care unit; PSG, polysomnography; PSQI, Pittsburgh sleep question index; RCSQ, Richards-Campbell sleep questionnaire; RCT, randomized control trial; REM, rapid eye movement; SMHSQ, St. Mary's Hospital sleep questionnaire; SSQ, Spiegel sleep questionnaire; SSS, stanford sleepiness scale; UTD, unable to determine; VAS-A, visual analog scale for anxiety; VHS, Verran and Snyder-Halpern sleep scale.

[a] Excludes studies performed in simulated ICU environments.

Table 2

Medications commonly used to promote sleep

Medication	Mechanism of action	Route of administration	Side effects	Sleep effects
Dexmedetomidine	*a2*-agonist	Intravenous	Bradycardia, hypotension	↑N2 with sleep spindles, ?↑N3/SWS, ↓REM, ↑SE, ↓SL
Propofol	GABA receptor agonist	Intravenous	Bradycardia, hypotension, propofol infusion syndrome, respiratory depression	↓REM, ↓SL, ↑TST, ↓W
Opiates	CNS opioid receptor agonist	Oral or Intravenous	Dependency, delirium-inducing, hypotension, respiratory depression, withdrawal	↓N3, ↓REM, ↓TST, ↑W
Melatonin and melatonin receptor agonists	Melatonin 1 and 2 receptor agonist	Oral	Dizziness, hallucinations, nausea, vivid dreams	↑SE, ↓SL, ↑TST
Atypical antipsychotics	$5HT_2$, D_2–receptor antagonist	Oral	Dizziness, extrapyramidal Symptoms, neuroleptic malignant syndrome, orthostatic hypotension	↑N3, ↑REM, ↑SE, ↓SL, ↑TST, ↓W
Typical antipsychotics	Dopamine receptor antagonist	Oral or intravenous	Anticholinergic effects, extrapyramidal symptoms, neuroleptic malignant syndrome, QT prolongation, tardive dyskinesia	↑N2, ↑N3, ↑SE, ↓SL, ↑TST, ↓W
Trazodone	Serotonin reuptake inhibitor, 5-HT1A,1C,2, H1 receptor antagonist	Oral	Anticholinergic syndrome, arrhythmias, orthostatic hypotension	↑N3, ↑↓REM, ?↑SE, ↓SL
Antihistamines	H1-receptor antagonist	Oral or intravenous	Anticholinergic syndrome, dizziness, impaired coordination	?↑N3, ↓REM, ?↑SE, ↓SL
Benzodiazepines	GABA receptor agonist	Oral or intravenous	Dependency, delirium-inducing, dizziness, hypotension, withdrawal	↓N3, ↓REM, ↓SL, ↑TST, ↓W
Nonbenzodiazepine hypnotics	GABA receptor agonist	Oral	Daytime somnolence, dizziness, confusion	↓N2, ↓N3, ↑↓REM, ↓SL ↑TST, ↓W

Abbreviations: CNS, central nervous system; GABA, gamma-aminobutyric acid; N2, deeper sleep; N3/SWS, restorative, slow wave sleep; REM, rapid eye movement; SE, sleep efficiency; SL, sleep latency; TST, total sleep time; W, wake;↓, decreased; ↑, increased; ↑↓, equivocal; ?↑, may increase; ?↓, may decrease.

Table 3

Trials of melatonin and ramelteon (melatonin-receptor agonist) in critically ill patients

Medication	First author year	Study type	Sample size	Population	Dose (mg)	Medication timing	Assessment	Results
Melatonin	Shilo[176] 2000	RCT	8	ICU	3	22:00	Actigraphy	↑ Sleep quality ↑ sleep time
	Ibrahim[177] 2006	RCT	32	ICU tracheostomy	3	20:00	Nurse observation	No change in nocturnal sleep duration
	Bourne[178] 2008	RCT	24	ICU tracheostomy	10	21:00	BIS	↓ BIS AUC ↑ sleep quality ↑ sleep time
	Mistraletti[179] 2010	RCT	82	Mixed ICU mechanically ventilated	3 and 3	20:00 and 00:00	Nurse observation	↑ Nocturnal TST
	Huang[131] 2015	NR	40	Healthy volunteers subjected to ICU environment	1	21:00	PSG	↑ REM ↑ TST ↓ SOL ↓ awakenings
	Foreman[101] 2015	RCT	12	Neuro ICU	3	20:00	EEG	UTD; only one patient in each group had scorable sleep
Ramelteon	Hatta[173] 2014	RCT	67	Elderly patients ICU and general wards	8	21:00	DRS-R-98	↓ Delirium
	Nishikimi[174] 2018	RCT	88	ICU	8	20:00	CAM-ICU nurse observation	↓ Delirium ↓ nocturnal awakenings Trend toward ↓ ICU LOS

Abbreviations: BIS, bispectral index area; CAM-ICU, confusion assessment method-ICU; DRS-R-98, delirium rating scale-revised-98; EEG, electroencephalogram; ICU, intensive care unit; LOS, length of stay; NR, nonrandomized; PSG, polysomnography; RCT, randomized control trial; SE, sleep efficiency; SOL, sleep onset latency; TST, total sleep time; WASO, wake after sleep onset.