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Sleep during and following critical illness: A Narrative Review

Laurie Showler, Yasmine Ali Abdelhamid, Jeremy Goldin, Adam M Deane

Abstract

Sleep is a complex process influenced by biological and environmental factors. Disturbances of sleep quantity and quality occur frequently in the critically ill and remain prevalent in survivors for at least 12 mo. Sleep disturbances are associated with adverse outcomes across multiple organ systems but are most strongly linked to delirium and cognitive impairment. This review will outline the predisposing and precipitating factors for sleep disturbance, categorised into patient, environmental and treatment-related factors. The objective and subjective methodologies used to quantify sleep during critical illness will be reviewed. While polysomnography remains the gold-standard, its use in the critical care setting still presents many barriers. Other methodologies are needed to better understand the pathophysiology, epidemiology and treatment of sleep disturbance in this population. Subjective outcome measures, including the Richards-Campbell Sleep Questionnaire, are still required for trials involving a greater number of patients and provide valuable insight into patients' experiences of disturbed sleep. Finally, sleep optimisation strategies are reviewed, including intervention bundles, ambient noise and light reduction, quiet time, and the use of ear plugs and eye masks. While drugs to improve sleep are frequently prescribed to patients in the ICU, evidence supporting their effectiveness is lacking.

INTRODUCTION

Sleep is an essential biological process that is frequently disturbed in patients with critical illness[1, 2]. Sleep deprivation in healthy adults is associated with adverse effects on neuropsychiatric, cognitive, cardiovascular, respiratory and endocrine systems and with acute and long-term detrimental effects[3].

There are concerns that an inadequate quantity and quality of sleep during critical illness contributes to increased delirium, depression, and a lesser quality of life in survivors and, potentially, increased mortality, with the detrimental effects of sleep deprivation compounded among those with prolonged admission to the intensive care unit (ICU)[4]. In addition, sleep disturbance is frequently reported as a source of patient distress and has been proposed to have financial implications related to longer ICU admission and increased risk of delirium[5].

Sleep disturbance in the ICU is multifactorial, with pre-morbid diagnoses, acute pathology, treatment and environment all contributing[6, 7]. Given the complex pathophysiology, it should be expected that studied interventions, including pharmacological and non-pharmacological strategies, have had mixed results on sleep[7, 8].

This review aims to describe the current understanding of sleep disruption during and after critical illness, current strategies to measure sleep in the ICU, and provide an overview of interventions to improve the quality and quantity of sleep in this population.

METHODS

A narrative review of the literature was performed. Relevant articles were identified by searching Medline, Embase and the Cochrane database. Search terms included “intensive care unit”, “high dependency unit”, “critical illness”, “sleep”, “sleep disturbance”, “sleep deprivation”, “sleep-wake disorder”, and “sleep fragmentation”.

Searches were limited to human adult subjects and English language articles. No restrictions on the date of publication were imposed. Abstracts were reviewed for relevance, and the reference list of these articles was searched for related articles. The full text of relevant articles was reviewed for inclusion.

OVERVIEW OF NORMAL SLEEP

Sleep is a complex and active process, characterised by reversible perceptual disengagement from, and unresponsiveness to, the environment[9]. The initiation and maintenance of the sleep state are controlled by the coordinated interplay of circadian and homeostatic mechanisms[10-13]. On the basis of polygraphic recordings of brain, muscle and eye activity, normal sleep can be divided into distinct periods, which are categorised as non-rapid eye movement (NREM) and rapid eye movement (REM) sleep[11]. Characteristic features of each sleep stage are described in table 1[14, 15]. NREM sleep is further subdivided into three stages, N1, N2 and N3, reflecting an increasing depth of sleep [16, 17]. The N2 phase has characteristic K-complexes and sleep spindles, electrical features which are believed to represent important functions, including the promotion of deeper sleep and memory consolidation[11, 18, 19]. The N3 phase is synonymous with slow wave sleep, during which many of the physiologically restorative processes of sleep occur[11, 20]. REM sleep is when dreaming occurs and is important for memory consolidation and learning [11, 21, 22]. The brain normally cycles through each phase of sleep over 90-120 minutes, with 4-5 cycles occurring over the course of the night[11, 23]. While the total amount of time spent asleep varies significantly, observational studies indicate that adverse outcomes are associated with sleeping less than seven hours or greater than nine hours per day over the long term[24-26]. In summary, both the architecture, or quality, and duration of sleep are important to mediate its beneficial effects.

EPIDEMIOLOGY OF SLEEP DISTURBANCE DURING AND AFTER CRITICAL ILLNESS

Disturbed sleep in the ICU is a near-universal phenomenon. Subjective perception of poor sleep determined using a variety of questionnaires has been reported by 47-59% of patients[27-30]. Studies using objective measures, including polysomnography and actigraphy, estimate that 67-100% of patients experience abnormal sleep quality[29, 31, 32].

Following discharge from the ICU, sleep disturbances persist in 10-61%[33]. Both objective and subjective measures indicate that sleep disruption improves over time but is still present in up to 61% of ICU survivors 6-12 mo after discharge [34]. In a single-centre, prospective cohort study of 347 patients, Coombes, *et al* [35] identified sleep disturbance as far as three years after ICU discharge. Women appear to be more affected by persistent sleep disturbances than men [36]. Sleep disruption was associated with other adverse features, including persistent post-traumatic stress disorder, depression, weakness, fatigue, pain and reduced quality of life, although these associations are likely bidirectional[37-42].

Studies that assess sleep using objective methodologies report improvements in sleep architecture between one week and six months post-discharge. Sleep fragmentation, with a high number of arousals, was prominent up to three months, and sleep efficiency remained impaired out to six months[39, 43, 44]. Objective sleep disturbances correlated with subjectively measured patient perception.

There is a high prevalence of sleep disturbances among ICU patients and survivors that persists for at least 12 mo following discharge and appear to be associated with other long-term, adverse patient outcomes and reduced quality of life.

CAUSES OF SLEEP DISTURBANCE IN THE CRITICALLY ILL

The cause of sleep disruption in the critically ill is multi-factorial and can be divided into environmental, therapy-related and patient factors.

Patient Factors

Patient factors, including increasing age, male sex, and poor sleep quality at home, have been associated with worse ICU sleep parameters[36, 45]. The relationship between acute illness severity and sleep disruption is biologically plausible but has been inconsistently demonstrated. Two small studies, including a total of 35 patients, found a correlation between greater illness severity, determined by Acute Physiology and Chronic Health Evaluation (APACHE III) score and Simplified Acute Physiology Score (SAPS II) respectively, and greater sleep disruption[46, 47]. In contrast, illness severity, as measured by the patient's Acute Physiology and Chronic Health Evaluation (APACHE III) score, was not found to be correlated with total sleep time, sleep fragmentation or subjective perception of sleep quality from four studies involving 264 patients[31, 36, 45, 48].

Patients report that distress, anxiety, and pain are factors that impair their ability to sleep[49-53]. Sleep deprivation has, in turn, been identified as a stressor contributing to patient anxiety and distress and creating a positive feedback loop[51, 54-56].

Environmental Factors

Loss of Diurnal Variation and Circadian Entrainment

Critically ill patients have been shown to have temporally disorganised circadian rhythmicity, likely due to the absence or disruption of normal external entraining cues, such as light exposure, changes in ambient temperature and eating patterns[13, 42, 57, 58]. In health, circadian rhythms are crucial for sleep regulation, and disrupted sleep during critical illness is likely to be part of the circadian dysfunction that occurs in these patients[13, 58, 59].

Ambient Light

Diurnal variation in light is an important entrainer of the circadian rhythm. Light intensity, wavelength and spectral distribution all affect the physiological response to light exposure[60]. ICU patients rate ambient light as a common contributing factor to

poor sleep[30, 61-63]. Both low levels of daytime light and peak light levels in the early evening have been reported, which pose a risk to circadian rhythms and maintenance of normal sleep-wake patterns[6]. Prolonged light exposures have been documented to occur frequently during the nocturnal sleep period[64].

Noise

Patients perceive noise as a significant factor leading to poor sleep in the ICU, with talking, equipment alarms, the television, and use of the bedside phone by staff being common causes[36, 46, 65]. The World Health Organisation recommends that noise levels within hospital environments should not exceed 35 decibels (dB) during the day and 30 dB at night[66]. Multiple studies report noise levels are frequently greater than this, with equivalent continuous sound levels of 50-75 dB and peaks up to 96 dB[67-69]. This noise level is associated with sleep disruption[45, 70]. Polysomnography detected sleep disturbances were observed when sound thresholds exceeded 63 and 59 dB during daytime and nighttime, respectively. Estimates of noise-related sleep disturbance in the ICU vary from 11% to 58%[31, 46, 62, 63, 71-74].

Patient-Care Related

Critically ill patients require intensive monitoring and care 24 h a day. Nursing and medical interventions, including mouth and eye care, decubitus ulcer care, change of dressings, medication administration, blood sampling, endotracheal tube suctioning, clinical examination, and procedures may interfere with patient sleep[46, 75]. Patients perceive these care activities as a substantial contributor to sleep disruption[30, 62, 74]. It has been reported that over the course of a night, patients were subjected to an average of 42.6 to 51 care interactions, with approximately 20% of these resulting in a clinically evident sleep disruption[46, 75, 76]. One study even identified increased care activities occurring between 02:00 and 05:00[75].

A proportion of nocturnal care activities are essential in the ICU. Whether the frequency and intrusiveness of nocturnal care activities are excessive and lead to harm due to sleep fragmentation and sleep deprivation, such as neurological observations performed and recorded at one-hourly intervals, remains uncertain[77, 78].

Treatment-Related

Mode of Mechanical Ventilation

Critically ill patients frequently require respiratory support, and mechanical ventilation contributes to sleep disruption. Patient-ventilator dyssynchrony, abnormal gas exchange, and mechanical ventilation-related central apnoeas are all considered contributory[6, 79, 80]. Mechanically ventilated patients experience disturbed sleep architecture with frequent arousals and decreased amounts of slow wave and REM sleep[48, 57, 81]. The effect of the mode of ventilation on sleep has been studied, but due to the limited number of patients observed and methodological limitations, the impact of ventilator mode remains to be determined.

Studies comparing pressure support ventilation (PSV) to assist-control ventilation (ACV) report point estimates suggesting assist-control decreases fragmentation, increases total sleep time, slow wave sleep and REM sleep, and reduces central apneas, but the wide confidence intervals are indicative of considerable uncertainty about this effect[79, 81, 82].

A single study comparing pressure control ventilation to pressure support ventilation reported statistically significant improvements in sleep efficiency and proportion of time in N2, N3 and REM sleep with a pressure control mode[83]. Notably, all 26 patients included in the study had chronic respiratory disease, which limits the application of these findings to a broader patient population, and whether nocturnal pressure control ventilation delays liberation from ventilation is also unknown.

Several proportional assist ventilatory modes have been compared to pressure support ventilation with mixed results[84], [85, 86].

Details of these studies have been summarised in table 2.

The association between non-invasive ventilation use and sleep quality has also been evaluated. Using an ICU ventilator, rather than a dedicated non-invasive ventilator, to provide non-invasive respiratory support is associated with reduced patient-ventilator dyssynchrony and number of arousals[87]. In addition, detection of early abnormal sleep architecture in patients with hypercapnoeic respiratory failure was associated with late NIV failure[88].

In the immediate period following discharge from ICU and at both 6 and 12 mo following discharge, exposure to mechanical ventilation during a patient's ICU stay does not seem to be associated with subsequent sleep disturbance[34, 47].

In summary, there appears to be some effect of ventilatory mode on sleep quality and quantity, however, a consistent physiological rationale remains elusive. In addition, the included studies are hindered by small sample sizes, and further larger-scale studies are required to elaborate on the relationship between ventilation mode and sleep.

Feeding and Nutrition

Nutritional support is an essential ICU treatment and would commonly be administered as a continuous infusion over 24 h in those that cannot eat[89]. The timing of meals and the associated release of nutritional hormones is an important entraining cue for circadian rhythms. Continuous delivery of nutrition may contribute to circadian rhythm and sleep disruption, and intermittent feeding may reduce this effect[90]. However, intermittent feeding regimens have not been shown to improve patient outcomes, possibly because of delayed gastric emptying[91, 92]. Hitherto, there have been

no trials evaluating intermittent enteral nutrition on circadian rhythm and sleep parameters, but a randomised clinical trial will soon be completed (ClinicalTrials.gov Identifier: NCT04737200).

Pharmacological

Critically ill patients are exposed to multiple drug classes that may affect sleep quantity and quality. However, very little published research directly quantifies this, and much of the information below is extrapolated from drug effects in other patient populations.

Sedatives and Analgesics

Several studies have demonstrated that mechanically ventilated patients receiving sedation have longer total sleep time and higher sleep efficiency but more atypical sleep than patients who are not intubated and sedated[57, 93, 94]. Propofol is one of the most frequently used sedative agents in the ICU, but there is conflicting evidence of its effect on sleep. Propofol is reported to disrupt REM sleep and delay sleep onset latency, however, in animal models there is evidence that propofol-induced sedation may confer some of sleep's restorative effects[95, 96]. A single-centre, prospective cohort study of 50 intubated patients found that sedation with propofol as a single agent was associated with increased sleep duration and decreased fragmentation when compared to fentanyl, propofol and fentanyl, or no sedation[97]. In contrast, a small crossover study of 12 mechanically ventilated patients reported that propofol, compared to no sedation, did not significantly affect total sleep duration or fragmentation, but adversely impacted the duration of REM sleep[98].

Benzodiazepine use is associated with increased total sleep time, resulting from decreased sleep latency and prolongation of the N2 sleep phase, at the cost of reduced slow wave and REM sleep[99]. Opioids, even as a single dose, have been shown to reduce the duration of slow wave and REM sleep[100-102]. The central alpha-2

adrenoreceptor agonist, dexmedetomidine, is associated with increased sleep efficiency and proportions of N3 sleep but decreased REM sleep[96, 103, 104].

Cardiovascular Medications

Adrenergic catecholamines can cause suppression of REM and slow wave sleep[105, 106]. Both amiodarone and lipid soluble beta-blockers may theoretically have adverse effects on sleep that include decreased REM sleep and nightmares[99]; however, whether these drugs have any effect during critical illness has not been evaluated.

Antidepressants and Antipsychotics

In other patient groups, sedating tricyclic antidepressants such as amitriptyline decrease sleep latency, increase the proportion of slow wave sleep and decrease the proportion of REM[99, 107]. Venlafaxine is recognised to suppress REM sleep and cause nightmares, while selective serotonin inhibitors can cause increase wakefulness, reduce total sleep time and decrease REM sleep[99, 107, 108]. Antipsychotic medications are of particular interest due to their use in the management of delirium and have been observed to have variable effects on sleep architecture. Haloperidol has been shown to increase sleep efficiency, whereas the atypical agents, olanzapine and risperidone, have the additional effect of promoting slow wave sleep[99, 109-111].

Miscellaneous

Corticosteroid use is associated with multiple neurocognitive, behavioural and circadian changes that may contribute to poor sleep[99, 112]. Exogenous steroid use may cause misalignment of the hypopituitary adrenal axis with adverse effects on the circadian rhythm, which may be further exacerbated by steroid-induced suppression of melatonin secretion[112].

Multiple pharmacological agents may diminish sleep in the ICU. Sedation is frequently necessary to facilitate treatment and reduce patient distress. The true impact of current

sedative regimes on sleep quantity and quality remains incompletely defined. Multiple pharmacological agents suppress slow wave and REM sleep, which may contribute to sleep deficit-related morbidity.

SLEEP DISTURBANCE IN THE CRITICALLY ILL

Sleep disturbance may be characterised by abnormalities, including difficulties falling asleep (sleep initiation), staying asleep (sleep maintenance), frequent awakenings or arousals (fragmentation), and atypical sleep architecture. Patients with critical illness largely preserve their total time asleep, or total sleep time (TST), however, this sleep is highly fragmented and spread over 24-hours[63, 113-118]. Instead of being consolidated in a single nocturnal sleep period, approximately 50% of sleep in critically ill patients occurs during daytime hours[63, 114, 115].

Sleep architecture during critical illness is frequently abnormal[31, 32]. Polysomnographic studies demonstrate a lack of variability in the electroencephalogram (EEG), with a predominance of the 'lighter' N1 and N2 phases, paucity or absence of N3 and REM sleep, and frequent arousals[119, 120]. Additional features of atypical sleep include the relative absence of K-complexes and sleep spindles, as well as dissociation of the EEG from behavioural fin and. Such dissociations manifest as either pathologic wakefulness, characterised by an EEG frequency consistent with sleep in awake patients or unresponsive patients with EEG frequencies associated with being awake[119]. These EEG abnormalities mean that 16-85% of polysomnographic data in observational studies were not able to be qualified using standard scoring systems[113-115, 117, 121]. Amended criteria have been proposed that recognise this atypical sleep pattern[113, 115]. Watson, *et al* [115] proposed an additional seven criteria for sleep scoring in the critically ill with robust reported interrater reliability (weighted kappa 0.80; bootstrapped 95% confidence interval 0.48, 0.89) but this has not been externally validated (table 3). Notably, the development of an atypical sleep pattern was strongly

associated with the subsequent development of delirium, a longer ICU length of stay, and higher odds of death[116].

In summary, critically ill patients display multiple and severe perturbations in their sleep that are not well described by current sleep scoring classifications. Several of these abnormalities are associated with a worse prognosis, yet it remains unclear if these are modifiable endpoints or markers of disease severity.

MEASURING SLEEP IN THE CRITICALLY ILL

Measuring sleep in the critically ill poses many challenges and is frequently confounded by sedation, encephalopathy, primary neurological insults, and prioritisation of more imminently life-threatening issues[6]. Both objective and subjective measurement tools have been used independently or in combination[59].

OBJECTIVE MEASUREMENT OF SLEEP IN THE CRITICALLY ILL

Polysomnography

Polysomnography uses polygraphic recording of electroencephalographic, electromyographic, and electro-oculographic data to measure sleep and is considered the gold-standard technique. There are two predominant systems for scoring polysomnographic sleep data. The Rechtschaffen and Kales (R&K) criteria, first published in 1968, describe five phases of sleep in healthy individuals but were superseded in 2007 by the American Academy of Sleep Medicine's (AASM) sleep scoring rules[16]. The AASM and R&K scoring rules share many similarities (table 4) but show relatively low concordance when scoring NREM phases[15-17, 122, 123]. Moreover, both lack accuracy in quantifying the atypical sleep seen in the critically ill[124]. Logistical, technical, and financial barriers to the use of polysomnography in ICU have been described, including access to specialist equipment and the support of a sleep service for set-up and analysis[119, 125, 126]. The device itself is reported to interfere with the delivery of patient care, is tolerated poorly by up to 25% of patients, and patient

discomfort from the device may worsen sleep[119, 127]. Accordingly, while polysomnography remains the gold-standard technique for ambulant patients, there is a need for other methodologies to quantify sleep during critical illness.

EEG Spectral Analysis

The electroencephalogram used in polysomnography provides invaluable information about sleep stages. Multiple attempts to simplify this element of sleep analysis have been described, using a reduced number of EEG leads, spectral analysis of the EEG frequencies, and automated scoring algorithms. Several studies have attempted to analyse limited EEG leads using different techniques. Bispectral Index (BIS) was developed as a depth of anaesthesia monitor for use in the operating theatre. A limited channel EEG signal is acquired using a single strip of electrodes applied to the forehead. Bispectral and power spectral analysis of the EEG is used to generate a numerical score to indicate depth of sedation[128]. While BIS has been used to investigate sleep in the critically ill, studies of BIS for sleep monitoring in both healthy volunteers and critically ill adults have reported that BIS is inaccurate for the detection of various sleep stages, particularly in differentiating REM from N1/N2 sleep phases, and correlates weakly with multiple domains on the Richards-Campbell Sleep Questionnaire[129, 130].

Alternative attempts to use spectral EEG analysis to monitor sleep in the critically ill, including the odds-ratio product index and ICU depth of sleep index, offer potentially useful alternatives[131]. Spectral EEG analysis using fast Fourier transformation showed perfect inter-observer and intra-observer agreement, however, the sample size of only 14 patients limits the generalizability of this finding[124]. These techniques do not rely on traditional scoring parameters, such as the presence of sleep spindles, and consequently are not affected by the absence or atypia of these features as reported by other authors[113]. The use of spectral analysis has the potential to simplify sleep assessment in the ICU, however, correlation with standard polysomnography parameters, as well as

standardization and external validation, will be necessary before it can be more widely applied.

Limited Lead EEG

To reduce the complexity associated with the use of polysomnography, several 'simplified' proprietary devices have been trialled. The Sedline™ is a portable monitor that is able to acquire limited lead EEG using bifrontal electrodes to derive a Patient State Index, which represents varying levels of consciousness. Vacas, *et al* [132] assessed the feasibility of using the Sedline to monitor sleep in three volunteers and 23 ICU patients and reported that the device was well tolerated but had poor agreement with polysomnography for stages N1 and N3. The Sleep Profiler™ is a wireless device that is applied to the forehead to acquire frontopolar EEG and uses auto-staging software to interpret the data. The Sleep Profiler™ has been evaluated by Jean, *et al*[97] and Romagnoli, *et al*[133] to assess the effects of sedation on sleep architecture in ICU patients. While reported accuracy is comparable to polysomnography in healthy volunteers, this comparison has not been reported in the ICU population[93].

Actigraphy

Actigraphy devices, commonly worn on the wrist or ankle, use omnidirectional accelerometers to detect limb movement; these limb movements are interpreted using automated algorithms to estimate sleep-wake state[125, 134]. These devices are minimally invasive, relatively straightforward to use, and have been used to assess sleep in outpatient settings[135]. Given the frequency and magnitude of critical illness weakness, studies of actigraphy in the critical care setting have identified poor overall accuracy, with over-estimation of total sleep time and sleep efficiency, when compared to polysomnography, nurse observation, or BIS[136]. Actigraphy has been used to evaluate sleep-promoting interventions in ICU, however, the poor correlation with other validated measures of sleep limits inferences from these studies[136, 137].

Novel Devices

The Nemuri SCAN™, an under-bed mattress sensor, has been evaluated to measure sleep in a total of 29 ICU patients in two prospective observational studies[138, 139]. When compared to polysomnography, moderate agreement but poor specificity was reported. In addition, there was no correlation with subjective sleep, quantified using the Richards-Campbell Sleep Questionnaire.

The most frequently used research methods to objectively measure sleep in the critically ill have been summarised in table 5. There is no methodology available that provides clinicians with real-time objective information each morning regarding the quantity and quality of a patient's sleep the night before. Such information has the capacity to transform clinical care.

SUBJECTIVE MEASUREMENT OF SLEEP IN THE CRITICALLY ILL

Understanding the subjective quality of patients' sleep is an important component of a holistic assessment. Direct patient self-report is of greatest interest, however, due to factors such as delirium and administration of sedation and analgesic drugs, it is estimated that only around 50% of the ICU population can participate in such efforts[73].

Thirteen different questionnaires have been used to quantify sleep in the ICU, of which 10 were reported by patients and three reported by ICU nurses[119, 140]. Several tools allow for either the patient or nurse to complete them, although accuracy is inconsistent[140].

Of the 13 sleep questionnaires used, the most rigorously studied is the Richards-Campbell Sleep Questionnaire (RCSQ). The RCSQ was specifically designed for use in the ICU population and uses five visual analogue scales to assess the domains of sleep latency, sleep efficiency, sleep depth, number of awakenings and overall sleep quality (figure 1)[141]. Individual domain scores can be interpreted respectively or combined

into a global score, with a score of ≥ 63 out of 100 reported as the optimal cut-off for self-reported 'good sleep'[142]. Both content and criterion validity have been established against polysomnography[143]. While the RCSQ was designed as a patient self-assessment tool, it may also be completed by clinical staff. The accuracy of clinician-completed RCSQ remains unclear with a reported strength of agreement including slight to moderate, moderate, and strong [73, 144]. The use of the RCSQ in the outpatient setting has also been established, allowing serial assessments to be continued following ICU discharge[145]. The RCSQ has been translated and validated in multiple languages[146].

The Verran Snyder-Halpern (VSH) sleep scale is an 8-15 visual analogue scale, self-reported sleep questionnaire that assesses similar domains to the RCSQ but, due to its higher number of questions, is considered more labour intensive[125]. The VSH sleep scale was designed to assess sleep in hospitalised patients without known sleep disorder[125, 147, 148]. The VSH has been validated for use in the ICU in several studies, but the association between patient and clinician-reported sleep was low [120, 149-152].

The Pittsburgh Sleep Quality Index (PSQI) is a nine-item, self-reported sleep questionnaire initially developed for use in the psychiatric population[153]. However, the use of the PSQI in critical care has mainly been to assess sleep following ICU discharge and has no association with objective sleep parameters [154].

Integrating sleep assessment into a daily patient assessment is hindered by the complexity of current tools. The Numeric Rating Scale for sleep (NRS-Sleep) is a single-item assessment tool that requires patients to rank their sleep on a scale of 0 to 10. It was developed in a prospective, multicentre study of 456 ICU patients and using receiver operator curves, a score greater than five was determined as the threshold for good sleep. The NRS-sleep is significantly correlated with mean RCSQ score (Pearson's correlation coefficient 0.88, $p < 0.01$)[155].

The Sleep Observation Tool (SOT) requires an observer to assess and document the patient's sleep or wake status every 15 minutes and has been found to correctly identify sleep 81.9% of the time compared to polysomnography. It has been used in its standard format to assess the effect of therapeutic interventions and in an amended format that uses 30-minute intervals[156-158].

The use of subjective measurement tools alongside objective measures is vital to ensure that future research maintains a patient-focused outcome. The RCSQ is promising as a tool for the measurement of sleep both during and after ICU admission. It may be beneficial for researchers to use a core subjective methodology to facilitate comparisons between studies.

EFFECTS OF SLEEP DISTURBANCE DURING CRITICAL ILLNESS

The effects of disrupted sleep in the critically ill remain poorly understood. In healthy adults, short-term sleep deprivation is associated with multi-system physiologic disturbances, and longer term is associated with increased risks of obesity, type 2 diabetes, malignancy and death[3].

Neurological

Delirium occurs in up to 80% of mechanically ventilated patients and is independently associated with increased mortality[159]. There are suggestions of a bidirectional relationship with sleep deprivation contributing to the development of delirium, and delirium worsening sleep disturbances[160]. A causal link between sleep deprivation and delirium has not been established, but several studies support an association. The detection of atypical sleep on EEG, commonly seen in critically ill patients, was associated with a significantly increased risk of developing delirium in the following 48 h[113]. A prospective observational before and after study of the introduction of a quality improvement intervention to promote sleep in 300 ICU patients reported a marked

reduction in the incidence of delirium (odds ratio 0.46; 95% confidence intervals, 0.23-0.89), however, improvements in RCSQ measured sleep did not reach statistical significance[161]. A similar study on the introduction of a multicomponent, multidisciplinary bundle of interventions in 338 ICU patients reported improved sleep efficiency, decreased daytime sleepiness, and reduced incidence and duration of delirium[162]. The results of meta-regression conducted by Kakar, *et al*[94] reported a somewhat unexpected relationship between total sleep time and delirium, where each hour increase in total sleep time per night was associated with a 5.8% increase in the risk of delirium. This counterintuitive result may be due to confounders, such as duration of mechanical ventilation, depth of sedation or disease severity.

Seizures are exacerbated by sleep deprivation and in focal epilepsy, the risk of seizure has been shown to correlate with day-to-day variations in daily sleep[163, 164]. In animal models, REM sleep seems to play an important role in enhancing the seizure threshold [165]. However, the impact of sleep deprivation on seizures during critical illness is yet to be described or quantified.

Sleep deprivation in healthy adults is associated with cognitive dysfunction, including impaired attention, memory and situational awareness[166]. Critical illness survivors frequently report troublesome short- and long-term impairments of cognitive function[167]. For example, a multicentre observational study of 102 ICU survivors reported that sleep fragmentation was associated with cognitive impairment at seven days post discharge from ICU in patients who had been mechanically ventilated[168]. No measured sleep parameters were associated with cognitive outcomes at 6 or 12 mo.

Endocrine Function

Sleep and circadian disruption during critical illness have been proposed to result in endocrine abnormalities, including decreased secretion of anabolic hormones, including testosterone, growth hormone and insulin-like growth factor, as well as increased

secretion of catabolic hormones that results in reduced protein synthesis and increased protein breakdown[169]. This net loss of protein contributes to muscle atrophy and critical illness weakness, which may be more marked in older populations and contribute to adverse outcomes, including increased frailty and functional decline in ICU survivors[169, 170].

A single night of sleep deprivation in healthy adults causes impaired glucagon secretion, elevated evening cortisol, and insulin resistance[171, 172]. In the critically ill, these endocrine disturbances may conceivably contribute to the development of impaired glucose tolerance and hyperglycaemia[173].

Melatonin is a circadian regulating hormone produced by the pineal gland[174]. Critically ill patients may experience reduced plasma melatonin concentrations due to loss of light-related physiological regulation of melatonin secretion and lack of normal diurnal variation[175-177]. These abnormalities likely contribute to sleep disturbances in the ICU population and have been associated with increased morbidity and mortality in animal models[178].

Immune Function

Immune upregulation, including immune cell proliferation and production of pro-inflammatory cytokines, is typical during the early phases of sleep[179]. Natural killer cell activity is reduced by 28% after one night of sleep deprivation, and a significant increase in total white blood cell count is seen after 3-5 days of sleep restriction[180, 181]. A reduced response to influenza and hepatitis A vaccination is seen with sleep deprivation, which does not improve with catch-up sleep[182, 183]. A retrospective cohort study of 135 patients with COVID-19 reported that poor sleep was linked to more severe lymphopaenia and a more frequent need for ICU admission[184].

Respiratory Function

Sleep deprivation is associated with an impaired ventilatory response to hypercapnia and hypoxaemia, reduced cortical respiratory motor output, and decreased inspiratory muscle endurance[185]. In addition, sleep fragmentation, but not sleep deprivation, has been found to increase the risk of upper airway collapsibility, which may predispose to extubation failure[186].

A prospective observational study of 45 patients evaluating sleep alterations and duration of mechanical ventilation, reported that the detection of atypical sleep on polysomnography was associated with a longer period of invasive respiratory support[187]. This relationship remained after multivariate logistic regression. Furthermore, a separate study reported that each percentage increase in slow wave sleep was associated with 0.58 day increase in the duration of mechanical ventilation[94]. Slow wave sleep is usually considered a deeper, restorative sleep phase and is typically reduced or absent during critical illness. Consequently, confounding variables, such as sedation, are influencing these associations.

Psychological

The relationship between sleep deprivation and psychiatric disorders may be bidirectional[188]. Total sleep deprivation in healthy adults disrupts affective functioning[189]. In contrast, one night of total sleep deprivation has been shown to improve depressive symptoms in up to 60% of depressed patients. However, this improvement is not evident in the majority after recovery sleep[190]. Anxiety and depression frequently occur in ICU survivors, occurring in up to 43% and 48% respectively[191]. ICU survivors with depressive symptoms three months after discharge were observed to have a higher likelihood of sleep disturbance, yet the direction of causality is unclear[161].

SLEEP OPTIMISATION STRATEGIES

Given the prevalence, persistence and impact of sleep disturbance during critical illness, there is considerable interest in improving patients' sleep duration and quality. In 2018, the Society of Critical Care Medicine published its clinical practice guidelines for the prevention and management of pain, agitation, delirium, immobility and sleep disruption (PADIS) to summarise the contemporary evidence on this subject[192]. Sleep optimisation strategies can be categorised into non-pharmacological and pharmacological interventions.

Non-pharmacological Management of Sleep Disturbances

Intervention bundles

Several authors have reported on implementing nurse-led or multi-disciplinary, multi-component, intervention bundles to improve patient sleep. Eight domains that could be included in an intervention bundle were described by Beck Edvardsen, *et al.*[193] including noise reduction; use of earplugs and eye masks; use of music; promotion of natural circadian rhythms; managing pain; use of "quiet time"; clustering of nursing activities, and optimising mechanical ventilation. However, evidence regarding such sleep-promoting intervention bundles is mixed. Improved objective and subjective measures of sleep have been reported in two studies[162, 194]. Bundles from each study were implemented by a multi-disciplinary team and contained over 10 interventions, including the offer of eye masks and ear plugs. In contrast, no significant benefit of a sleep promotion bundle was reported in two further studies that had fewer interventions and did not include the provision of ear plugs and eye masks[195, 196]. Studies of bundled care assess the net effect of multiple interventions, obscuring the magnitude and direction of effect from the individual components. Consequently, it is unclear which interventions contained in the reported studies are mediating the benefit[197].

Noise Reduction

Several strategies have been described to reduce the effect of noise disturbance on sleep. For example, Walder, *et al*. [198] reported the implementation of five policy steps, including the closure of doors, reducing monitor alarm volumes and, between 23:00 and 05:00, limiting nursing care, conversational noise and direct light in patients' rooms. These interventions successfully reduced nocturnal noise and light. The implementation of a behavioural modification program for nursing staff reported similar results that such measures could reduce ambient noise and light in the ICU to provide a better sleeping environment[199]. However, neither study measured patients' sleep, making it impossible to assess the impact of these environmental interventions on sleep outcomes.

Quiet Time

'Quiet time' protocols designate a 1–2-hour period during the day during which ambient noise and light are reduced to facilitate patient sleep. Three prospective studies of quiet time, involving 361 patients and using once or twice daily two hour sessions, report that patients are more likely to be reported as asleep during quiet time than during the control period[156, 157, 200]. Sleep was determined using a novel subjective nurse assessment or the Sleep Observation Tool[201]. Given the short available sleep period, the highly subjective nature of the assessments, and the inability to interpret reported sleep in the context of total sleep time, the inferences are limited. A quasi-experimental, non-randomised, post-test-only study of a once-daily session of quiet time in 129 patients did not detect a significant improvement in sleep measured by RCSQ with increasing numbers of quiet time sessions[202].

While quiet time is a simple, safe and low-cost intervention, methodological issues in the few available studies mean the impact of quiet time on sleep in the ICU remains uncertain.

Ear Plugs and Eye Masks

Earplugs and eye masks offer an inexpensive and potentially low-risk intervention to reduce or diminish the impact of nocturnal ambient noise and light. Despite the intuitive appeal, the available literature reports mixed results (Supplementary table 1).

Studies evaluating earplugs as a single intervention include a total of 276 patients but are methodologically heterogeneous with respect to duration of the intervention, inclusion of intubated patients, use of sedation, and choice of sleep measurement tool [152, 203, 204]. One study reported a statistically significant improvement in sleep satisfaction with earplugs but had a 12% dropout rate[152]. Van Rompaey, *et al*.[204] reported that earplugs were associated with improved sleep on the first study night, but this improvement lessened on the second night and reported sleep was worse than the intervention group by the third night. Litton, *et al*.[203] proved that using earplugs for noise abatement in the ICU setting was feasible but did not demonstrate a statistically significant benefit to sleep quality.

The combination of ear plugs and eye masks has been assessed together. Several single-centre studies report an improved subjective perception of sleep compared to usual care[195, 205-214]. Earplugs and eye masks have also been reported to significantly improve sleep compared to relaxing ocean sounds played for 30 minutes around the onset of the sleep period[215].

Within the methodological limitations (single centre and lack of blinding), there is increasing evidence that combined eye masks and ear plugs improve self-reported sleep. In contrast, the available literature does not support using earplugs alone.

Music

The use of non-commercial music as a sleep-promoting therapy has been evaluated. In a prospective, quasi-experimental, randomised study, 96 patients who were post-op following coronary artery bypass grafting were exposed to either a daily 30 minute

session of music or a rest period[216]. Patients receiving the music intervention were reported to have significantly improved sleep, as measured by RCSQ, on postoperative day three. Further studies on music to improve sleep in the ICU were unable to identify clear evidence of benefit. A small, randomised, controlled trial of 28 ICU patients receiving either 45 minutes of music prior to sleep or usual care did not identify a difference in total sleep time or subjective sleep assessment[120]. An increased duration of N3 sleep was reported in the first two hours, however, the polysomnogram was not assessed beyond this window and the significance of this finding is obscured by this methodological choice. A cross-over, randomised, experimental study evaluated the effect of 20 minutes of music therapy against uninterrupted rest on the bispectral index (BIS)[217]. The bispectral index was reduced during the music session; however, no assessment of nocturnal sleep quantity or quality was made, obfuscating any association with improved sleep.

The use of music therapy to improve sleep is not well supported by the published literature. Factors including the type, volume, duration and timing of the intervention are likely all important but have not been well explored to date.

Massage

Studies of massage or therapeutic touch to aid sleep in the ICU have conflicting results. A case series of 53 patients receiving therapeutic touch from a trained nurse could not identify any statistically significant change in physiologic variables [218]. Patients were reported to fall asleep frequently during treatments, but no effect on nocturnal sleep was reported. A quasi-experimental study in 60 patients compared the efficacy of a 10-minute back massage on three consecutive days against usual care and reported improvements in self-reported sleep and actigraphy-determined total sleep on the second and third days of the intervention.

Acupressure

A randomised controlled trial of acupressure for three hours on two consecutive nights was compared to usual care and reported a statistically significant difference in actigraphy-derived total sleep time and sleep quality, as per the Stanford Sleepiness Scale[137]. However, the use of actigraphy, which overestimates total sleep time and is not accurate in the ICU setting, and the Stanford Sleepiness Scale, which has not been validated for use in the ICU, raises questions about the internal validity of this result.

PHARMACOLOGICAL MANAGEMENT OF SLEEP DISTURBANCES

About half of the ICU survivors asked about their sleep believe a sleeping pill would have improved their sleep, but there is scant evidence to support the use of pharmacological sleep aids in this setting[30]. Cohort studies indicate that pharmacological sleep aids are frequently administered to ICU patients[219, 220].

Melatonin

Because of the disturbed secretion of melatonin (described above), there is a biologically plausible rationale to support the use of exogenous melatonin. However, a meta-analysis of four studies reported that melatonin, at doses of between 3 and 10mg per day, had uncertain effects on objective and subjective measures of sleep quantity and quality (table 6)[136, 158, 221-223].

More recently, a blinded, parallel-group, placebo-controlled, randomised clinical trial compared 10 mg melatonin to placebo in 203 ICU patients reported a statistically significant improvement in sleep with melatonin represented by an increase in RCSQ by nine points, but no difference in nurse-observed total sleep time[224]. Finally, the Pro-MEDIC study was a multicenter, parallel-group, placebo-controlled randomised clinical trial that included 841 patients and assessed a 4mg dose of melatonin[225]. While the primary outcome was the incidence of delirium, sleep was recorded using RSCQ. The investigators identified no effect of melatonin on sleep and, as the largest trial to date, provides the greatest certainty as to the effect of melatonin on sleep in the ICU.

Accordingly, while there is a physiological rationale that melatonin should be an effective pharmacological sleep aid in the critically ill, there is a lack of clinical trial data to support its use.

Melatonin Receptor Agonists

The melatonin receptor agonist, Ramelteon, has been assessed in a single centre, blinded, randomised, placebo-controlled trial using 8mg ramelteon per day in 88 ICU patients[226]. While the primary outcome was delirium, the use of ramelteon was associated with fewer awakenings and a higher proportion of nights without awakenings but no difference in mean hours of sleep. Determination of sleep status was performed by non-validated, retrospective means, creating uncertainty regarding this tertiary outcome.

Temazepam

There is no clinical trial data to guide the use of temazepam in the critically ill. A single-centre, placebo-controlled, blinded, randomised trial evaluating temazepam is currently recruiting (ANZCTR registration number: ACTRN12621000742875).

Nocturnal Propofol

Propofol is an intravenous anaesthetic agent that enhances GABA-ergic inhibition in the brain and is frequently administered in the ICU for patient sedation[227]. Engelmann, *et al.*[228] conducted a single-centre, blinded trial comparing an intravenous infusion of 2 mg/kg/hr propofol against a single bolus of intravenous 0.015 mg/kg flunitrazepam for a single night. Sleep quantity was measured using BIS, and the investigators reported a statistically significant improvement in the propofol group. However, the comparison of a continuously infused agent against a single bolus, and the use of BIS to monitor sleep undermine the validity of this result. A randomised cross-over trial of nocturnal propofol infusion in 12 mechanically ventilated ICU patients reported no

difference in total sleep time or NREM sleep distribution using polysomnography[98]. A prospective clinical study of 30 mechanically ventilated patients sedated with propofol and morphine evaluated additional doses of propofol to achieve a diurnal sedation pattern[229]. The authors report that 60% of patients receiving additional nocturnal propofol developed a diurnal rhythmicity, which they attributed to natural sleep, rather than deeper anaesthesia, despite using increased sedation in this group. An open-label, randomised, comparative study of 0.3-3 mg/hr propofol infusion compared to 0.03-0.2 mg/hr midazolam infusion was performed in 40 conscious ICU patients overnight to assess sleep quality, anxiety and depression[230]. Using the Hospital Anxiety and Depression Scale, no significant difference in sleep quality could be detected. Notably, the Hospital Anxiety and Depression scale is not validated for sleep assessment and is likely to be insufficiently sensitive or specific to measure this outcome accurately.

Overall, there is no convincing published evidence that propofol is able to improve sleep quality or quantity in critically ill patients.

Dexmedetomidine

Two, small pilot experimental studies have assessed the effect of dexmedetomidine on sleep quality and polysomnographic appearances in critically ill patients[85, 231]. Subsequent randomised trials have shown that when compared to placebo, dexmedetomidine increases sleep efficiency, total sleep time and percentage of N2 sleep phase in intubated and non-intubated patients[103, 133, 232]. Subjective measures of sleep have infrequently been assessed but have not reached statistical significance when reported[103]. A single, non-randomised clinical trial of non-intubated, post-abdominal surgery ICU patients compared dexmedetomidine and sufentanil infusion against sufentanil infusion alone[104]. BIS monitoring showed increased total sleep time in the dexmedetomidine group. Although this result is consistent with prior data, the outcome must be interpreted in the context of the significant limitations created by non-random allocation, small sample size and use of BIS monitoring. A blinded, parallel-group,

placebo-controlled clinical trial evaluated the effect of nocturnal dexmedetomidine in 100 delirium-free, critically ill patients[233]. The secondary outcome of sleep quality, measured by the Leeds Sleep Evaluation Questionnaire, reported no significant difference in sleep quality with dexmedetomidine.

Studies of dexmedetomidine report objective improvements in sleep duration and architecture. However, many of the studies of dexmedetomidine do not have sleep as a primary outcome; therefore, interpreting these findings should be undertaken with cautious curiosity.

Orexin Receptor Antagonists

Suvorexant is an orexin receptor antagonist used as a novel hypnotic agent[234]. A single randomised, placebo-controlled trial of 15 mg/day of suvorexant for the prevention of delirium reported a significantly decreased incidence of delirium in the suvorexant group[235]. No other measured parameters, including time to sleep onset, number of awakenings, subjective quality of sleep, or total sleep time, were statistically different.

There are no currently available pharmacological sleep aids that have a robust evidence base to support their use in the ICU population.

CONCLUSION

Sleep is an important issue for the critically ill. Observational studies report that sleep disturbance is common during critical illness, and a growing body of evidence reports that this is subjectively distressing for the patient, causes physiological derangements and is associated with adverse outcomes. The causes for disrupted sleep in this population are multifactorial and, while not unique to the ICU, may be exacerbated by the treatment modalities, the intensity of care delivery, and the severity of illness that is synonymous with the management of critical illness in this setting.

Measuring sleep in the ICU for clinical and research purposes poses many issues. Polysomnography remains the gold-standard technique but is hindered by logistical issues and the frequent occurrence of atypical electroencephalographic findings. Other objective modalities, including actigraphy and BIS, have not proven sufficiently accurate and do not have a clear role in the ICU setting. Validated, subjective measures of sleep provide an important, patient-centred perspective. However, future research may benefit from adopting a core subjective methodology that would facilitate comparisons between studies.

Many interventions have been assessed to improve sleep during critical illness. When used together, earplugs and eye masks seem to improve sleep. However, a clear and reproducible benefit from other non-pharmacologic strategies has been hard to demonstrate. The use of pharmacological sleep aids to improve sleep is common, yet the currently available evidence does not demonstrate consistent, patient-oriented benefits from any agent. Sleep is a complex physiological process, and successful management of sleep disturbance will likely require a multimodal approach to benefit this vulnerable patient group.

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