Promoting Sleep to Improve Delirium in the ICU*

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A night in the ICU is often characterized by a chaotic whirlwind of beeping machines, staff conversations, bright lights, medical interventions, and visits from care providers. Mix in mind-altering drugs, uncomfortable medical devices, an unfamiliar environment and pain, and sleep becomes markedly fragmented and devoid of the restorative stages considered vital for repair and recovery (1). A recent study demonstrated that critically ill patients obtained only 5 hours of sleep per 24-hour period, which was broken into 38 discrete episodes, each lasting a median of 3 minutes (2). Understandably, sleep loss contributes significantly to stress during the ICU stay (1).

Recently, sleep within the ICU setting has gained attention. There is an intriguing, yet poorly understood, relationship between sleep and delirium, a common ICU syndrome affecting up to 80% of mechanically ventilated patients and associated with negative outcomes, such as prolonged length of stay and long-lasting neurocognitive impairments (3). In a recent global survey, 97% of 1,223 ICU physicians and nurses agreed that poor sleep in the ICU is a risk factor for delirium (4). Additionally, in the 2013 Clinical Practice Guidelines for Pain, Agitation, and Delirium (PAD), the Society of Critical Care Medicine recommended "promoting sleep in adult ICU patients by optimizing patients' environments, using strategies to control light and noise, clustering patient care activities, and decreasing stimuli at night to protect patient's sleep cycles" (3). This ICU sleep-delirium relationship has even been highlighted in major news outlets (5, 6) and a bestselling book (7), and motivated a highly viewed YouTube video (8).

In this issue of *Critical Care Medicine*, Flannery et al (9) perform a synthesis of sleep-delirium research within the ICU setting. They conducted a systematic review of ICU studies involving sleep-promoting interventions to improve delirium. Using a comprehensive search strategy, they identify 10 relevant articles (excluding a large randomized controlled trial [RCT] [10], published after the January 2016 search date, demonstrating no effect of bright light therapy on delirium in the ICU). Overall, the studies occurred in six countries, including both medical and postoperative ICU patients, with four studies enrolling less than or equal to 40 patients, and two enrolling only men. Interventions varied markedly, including earplugs, bright light therapy, medications, and sleep/delirium intervention "bundles." Due to substantial heterogeneity, the authors do not perform a meta-analysis, and conclude too many confounders were present to derive a "firm conclusion" regarding the best ICU-based methods to improve sleep.

Notably, eight of 10 studies demonstrated significant improvements in delirium or confusion—albeit using unadjusted analyses in six studies. Furthermore, all four studies evaluating sleep "bundles" demonstrated improvements in delirium. Given the PAD guideline recommendation for use of bundled sleep-promoting interventions (3), and the feasibility of bundled intervention implementation as part of clinical care (11), future studies could evaluate the dissemination, sustainability, and benefit of these interventions across broad ICU settings and populations.

Additionally, RCTs evaluating melatonin supplementation prior to cardiac surgery and daily ramelteon (a melatonin receptor agonist) in elderly ICU patients demonstrated substantial

*See also p. 2231.

Key Words: critical illness; delirium; intensive care unit; sleep

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reductions in delirium in the intervention arms (9). Given melatonin's role in circadian entrainment and the absence of "circadian cues" in the ICU environment (1), these medications might be viable pharmacologic options for improving sleep and delirium; additional trials are completed or planned (clinicaltrials.gov identifiers: NCT00470821, NCT02691013, NCT02588742, and NCT02615340). Notably, improvements in delirium were also observed in pre-post studies involving minimization of sleep-disrupting and deliriogenic medications, suggesting that withholding harmful medications may be a key starting point for any ICU-based pharmacologic sleep guideline.

As an important limitation, only four of 10 studies measured sleep itself, all using subjective tools. In the ICU, sleep measurement is a challenging barrier to research, with no clear solution. Polysomnography, the gold standard for sleep measurement, is challenging to use and interpret in critically ill patients (1). Alternatively, self-report instruments, such as the Richards-Campbell Sleep Questionnaire, are easy and feasible to implement on a large-scale but are impossible to collect from delirious patients; additionally, proxy raters may overestimate patients' sleep duration and quality (12). Finally, actigraphy and bispectral index may be promising tools, but need rigorous validation in the ICU. Hence, future research on sleep promotion for improving delirium may advance the field by simultaneously embedding substudies evaluating sleep measurement techniques (12, 13).

Finally, the authors highlight the importance of using rigorous research methods in future studies, including consideration of both frequency and duration of delirium as outcome measures. In terms of measuring delirium, three different instruments were used within this systematic review, of which only one is recommended in PAD guidelines (3). Notably, 46 intervention studies were excluded from the systematic review since they did not assess for delirium as an outcome, perhaps a missed opportunity for advancing knowledge in ICU sleep research. Importantly, future ICU-based sleep promotion research should be conducted using delirium instruments that have been validated for use in the ICU setting. Furthermore, in the ICU, there are statistical challenges with evaluating delirium as an outcome, including its time-varying nature and the competing risks of mortality and ICU discharge. Notably, recent publications have recommended against using delirium-free days as an outcome measure (14, 15) and instead, recommend employing modern statistical methods, such as a joint modelling approach combining two survival models for a repeated daily delirium outcome and for the competing risk of ICU discharge or death (15, 16).

In summary, this systematic review is a timely synthesis of the expanding research evaluating sleep and delirium in the ICU. This review reminds us of the limitations of prior research and provides valuable guidance for investigations moving forward. Although it may be difficult to ascertain whether poor sleep is casually related to delirium, or to determine unequivocally whether interventions actually improve objective sleep quality, it is well known that patients experience poor quality sleep in the ICU and that sleep promotion represents a low-risk intervention with potential to improve patient outcomes. We look forward to more rigorous studies in this area, and anticipate that improving sleep may become a cornerstone in preventing ICU delirium and improving patient outcomes.

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The Impact of Interventions to Improve Sleep on Delirium in the ICU: A Systematic Review and Research Framework*

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Objective : This study aimed to assess whether interventions targeted at improving sleep in the ICU were associated with reductions in ICU delirium. Secondary outcomes include duration of delirium and ICU length of stay.

Data Sources: MEDLINE, CINAHL, Web of Science, Scopus, WorldCat, and International Pharmaceutical Abstracts were searched from inception to January 2016.

Study Selection: Studies investigating any type of sleep intervention (nonpharmacologic or pharmacologic) and assessing the impact on ICU delirium were included. Any type of study design was permitted so long as the delirium assessment was made at least daily with a validated delirium assessment tool.

Data Extraction: The following data were extracted: first author, year of publication, study design, ICU type, components of sleep intervention, use of sleep assessment tool, patient age, sex, severity of illness, sleep measures, delirium assessment tool, incidence of delirium, duration of delirium, and ICU length of stay. The incidence of delirium was used to compare rates of ICU delirium across studies. Methodologic quality of included studies was evaluated using the Effective Public Health Practice Project quality assessment tool.

Data Synthesis: Of 488 citations screened, 10 studies were identified for inclusion in the final review; six of which demonstrated a statistically significant reduction in the incidence of ICU delirium associated with sleep intervention. Four studies assessed duration of delirium; of which, three reported a shorter duration of delirium with sleep intervention. Two studies associated sleep intervention with a reduced ICU length of stay. In regard to quality assessment and risk of bias, only one study was assessed as strong. Multiple identified confounders and the significant qualitative assessment of heterogeneity limit both the conclusions that can be drawn from these findings and the quantitative pooling of data.

Conclusions: Although sleep interventions seem to be a promising approach for improving delirium-related outcomes, studies are limited by bias issues, varying methodologies, and multiple confounders, making the evidence base for this conclusion limited at best. Future studies would benefit from a systematic approach to studying the link between sleep intervention and delirium-related outcomes, which is outlined in the context of reviewing the existing literature. (*Crit Care Med* 2016; 44:2231–2240)

Key Words: critical illness; delirium; intensive care; sleep; systematic review

Delirium is a frequent complication encountered in the ICU and is associated with substantial morbidity and mortality (1–4). Evidence exists that delirium may be minimized by a limited number of interventions, including early mobilization and possibly the choice of sedative (5–7).

Although the relationship between poor sleep in the ICU and delirium has not been definitively established, many practitioners have come to believe that such a relationship exists. A number of findings support such belief. Six decades of research exist on the effects of sleep deprivation, demonstrating that sleep disturbance can cause all features of delirium (8). Physiologic studies show that sleep is important to brain health. For example, it is primarily during sleep that metabolic waste from the CNS is removed (9). An electrophysiologic relationship exists between altered sleep architecture and delirium, with delirium occurring in those with the greatest loss of rapid eye movement sleep and in those with "atypical" sleep characterized by electroencephalogram findings with

*See also p. 2290.

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behavioral signs of wakefulness (10, 11). An imbalance in neurotransmitters, particularly acetylcholine, as well as alteration of melatonin production, may contribute to the pathogenesis of both altered sleep and delirium (8, 12, 13). Sleep deprivation has been shown to precede delirium in postsurgical cardiac patients (14). Other studies have found that ICU patients who were sleep deprived were more likely to develop delirium than those without sleep deprivation (15). As a reflection of a growing consensus of opinion, the Society of Critical Care Medicine has recommended sleep promotion as part of its delirium prevention strategy (16).

A primary focus of delirium management has involved sedative and preventative strategies as a component of bundled care models (17). Interventions specifically targeted to improve sleep remain relatively natural and safe; however, their effect on the occurrence or duration of delirium requires confirmatory research. The past decade has seen an explosion of research articles and reviews involving sleep in the ICU and, in particular, a renewed interest in sleep-promoting activities in efforts to prevent or reduce the impact of delirium. Although systematic reviews have assessed the overall impact of various sleep-promoting interventions on sleep-related outcomes in the ICU (18, 19), no such work has assessed the fundamental question: does the concept of sleep promotion in the ICU, via nonpharmacologic or pharmacologic approaches, have any impact on delirium-related outcomes? In other words, does the available evidence actually support the premise that these proposed sleep-promoting efforts demonstrate any impact on ICU delirium as a growing consensus and valid theory would seem to suggest?

Accordingly, we conducted a systematic review to assess whether interventions targeting sleep in the ICU via nonpharmacologic or pharmacologic means are associated with reductions in ICU delirium. Secondarily, we assessed the impact of these interventions on duration of delirium and ICU length of stay. This analysis is not intended to support or refute the connection between poor sleep and delirium; rather, it is an analysis of the effects of the interventions on the occurrence of delirium. Anticipating marked heterogeneity due to the way sleep and delirium have been costudied, we have also suggested a framework for future studies investigating the link between sleep interventions and delirium. These suggestions draw on our analysis of the previous literature and encourage the critical care community to become objective and systematic in how we study the intricate relationship between sleep and delirium.

METHODS

The procedure and reporting structure of this systematic review are in concordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (20).

Data Sources and Searches

With the assistance of an experienced medical librarian, we systematically searched MEDLINE, CINAHL, Web of Science, Scopus, WorldCat, and International Pharmaceutical Abstracts databases. The following core terms were used in the search: (sleep* or night* or circadian or insomni*) and (*delirium or delirious* or agitat* or manic) and ("intensive care" or ICU or "critical care"). The use of both controlled vocabulary, such as MeSH terminology, and text words was used in the search strategy when applicable. A related citation function and citation-tracing feature were also used as available. Reference lists of potentially included studies and review articles, as well as personal files, were reviewed for additional citations pertinent to this search. Only English-language studies and studies published in the peer-reviewed literature were eligible for inclusion. No date restriction was imposed on the search strategy, which concluded in January 2016.

Study Selection and Eligibility Criteria

Citations were independently assessed by two reviewers and were preliminarily screened at the title and abstract level, assessing full text if needed with manual searches for "sleep" and "delirium." Disagreement between reviewers was resolved by discussion and consensus, seeking the input of a third reviewer.

We included any type of study design (e.g., historical control, prospective trial) investigating any interventions aimed at improving sleep, including nonpharmacologic, pharmacologic, or mixed interventions in adult patients. Included patients must have been admitted to the ICU at the time of study intervention. Delirium was required to be assessed at least daily using a validated delirium screening assessment tool, including Confusion Assessment Method for the ICU (CAM-ICU), Intensive Care Delirium Screening Checklist (ICDSC), or assessment by a psychiatrist using Diagnostic and Statistical Manual, Fourth Edition (DSM-IV) criteria (21–23). In order to increase the scope of our review, the Neelon and Champagne (NEECHAM) Confusion Scale was also allowed given that NEECHAM has been shown to perform as well as CAM-ICU in nonintubated patients (24). Trials must have reported the occurrence rate of delirium in the treatment and comparator groups to be included. For studies investigating interventions among a cohort of mixed ICU and non-ICU patients, corresponding authors were contacted to obtain data for the ICU-specific patient populations. Authors were also contacted for any clarifications regarding assessment of delirium or methods for reporting occurrence rates.

Data Abstraction and Quality Assessment

Using a prespecified data abstraction form, two reviewers abstracted and checked data from eligible studies, including study design, ICU population, specific details regarding the sleep intervention and any associated interventions studied, sleep assessment tool, sleep measures, delirium assessment instrument, delirium occurrence, and other outcomes, including duration of delirium and ICU length of stay, if available.

Two reviewers independently assessed study quality and risk of bias using the validated Effective Public Health Practice Project quality assessment tool (25). Each study was rated by the reviewers with regard to selection bias, study design,

confounders, blinding, data collection methods, and withdrawals and dropouts. Based on the scores of these various components, each study was assigned an overall methodological quality of strong, moderate, or weak. Any disagreement among the reviewers was resolved with discussion and input from the third reviewer if necessary.

RESULTS

Study Selection

Using our initial search strategy combined with reference list searches and personal files, we identified 488 citations, which were narrowed to 372 after duplicates were removed (**Fig. 1**). Of these, 292 articles were excluded on initial review. Of the 80 articles remaining, 46 did not evaluate delirium as an outcome measure and 19 were performed outside of the ICU, leaving 14 studies for inclusion in the preliminary analysis. Of those 14, four were excluded for the following reasons: enrolled only delirious patients (26), delirium was only evaluated at the beginning and end of study as opposed to daily (27), evaluated occurrence rate per number of delirium assessments as opposed to per number of patients (28), and used chart review for delirium diagnosis rather than a validated scale (29). Taken together, we included 10 studies enrolling 1,639 patients for this systematic review (30–39).

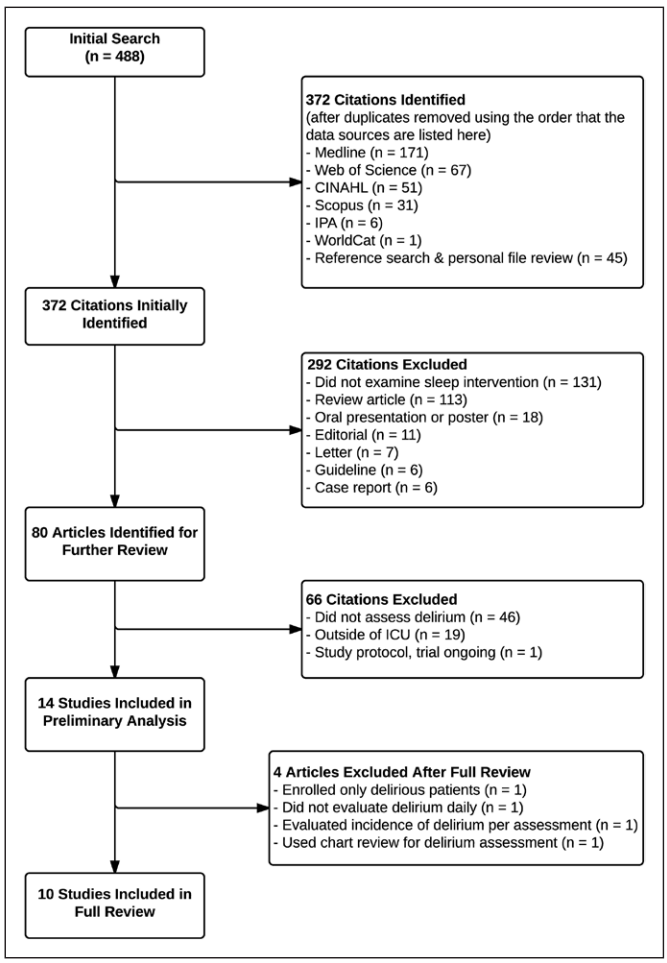

Figure 1. Literature search results and study selection.

Study Characteristics

Of the included studies, four involved multicomponent sleep bundles (31–33, 39), one evaluated earplugs only (34), three evaluated pharmacologic therapy for sleep (30, 36, 38), and two evaluated bright light therapy to optimize the circadian rhythm (35, 37). **Table 1** describes the patient characteristics and study designs of the 10 included studies.

In general, patients included were elderly and spanned a variety of medical and surgical ICUs. The acuity of illness was moderate with none of the studies having an average Acute Physiology and Chronic Health Evaluation II (APACHE II) (40) score above 20. Six of the 10 studies included were randomized controlled trials (30, 34–37, 39), whereas four were pre/post cohort studies following implementation of a new protocol (31–33, 38). Delirium was assessed with CAM-ICU in five studies (31–33, 38, 39), psychiatrist assessment using DSM-IV in three studies (30, 35, 36), and NEECHAM in two studies (34, 37). We rated the methodological quality of the studies as follows: 1 as strong (34), 6 as moderate (30–33, 36, 39), and 3 as weak (35, 37, 38). The most common limitations identified in trial assessment included the lack of blinding followed by selection bias (**Supplemental Table 1**, Supplemental Digital Content 1, http://links.lww.com/CCM/B951).

Study Outcomes

All 10 trials reported the occurrence rate of delirium. Data on duration of delirium were available for four of the 10 studies (31–33, 39). Data on ICU length of stay were available for five of the 10 studies (31, 33, 35, 36, 38). Of the 10 studies, six reported statistically significant reductions in the occurrence rate of ICU delirium (30, 32, 33, 36, 38, 39), two reported nonstatistically significant reductions in the occurrence rate of ICU delirium (35, 37), and two reported no difference in the occurrence rate of ICU delirium (31, 34). Of the four studies reporting on duration of delirium, three of the studies demonstrated a reduced duration of delirium with the sleep intervention (31, 32, 39). Sleep interventions were associated with a reduction in ICU length of stay in two of the five studies reporting on this outcome (31, 38). Outcome data for included studies are presented in **Table 2**.

Sleep assessments were clearly described in four of the 10 identified studies (30, 32–34). Only one study demonstrated a concomitant improvement in sleep indices and corresponding reduction in delirium (32). One study improved measured sleep indices without reduction in delirium (34), whereas two studies demonstrated no documented improvement in measured sleep indices but did find an association between the sleep intervention and a reduction in delirium (30, 33).

DISCUSSION

On review of the totality of the evidence, sleep interventions seem to be associated with improved neurocognitive ICU outcomes, notably a reduction in the occurrence rate and duration of delirium. For those studies suggesting a benefit of sleep interventions, the reduction in the occurrence rate of delirium

TABLE 1. Description of Study Characteristics Included in the Systematic Review

Study Design and ICU Type		Age (yr)[a]	Men (%)	Severity of Illness[b]	Intervention[c]	Components of Sleep Bundle Intervention (If Applicable)[d]	Sleep Assessment Performed	Delirium Assessment	Risk of Bias Assessment[e]
Guo et al (39)									
RCT Surgical ICU *n* = 160	Intervention Control	73.3 ± 6.1 73.7 ± 5.2	38 43	NR NR	E, N, S	1–7	NP	CAM-ICU	Moderate
Artemiou et al (38)									
Pre/post cohort Cardiovascular Surgery ICU *n* = 500	Intervention Control	64.3 ± 10.1 65.2 ± 10.3	72 68	NR NR	P[f]	N/A	NP	CAM-ICU	Weak
Hatta et al (30)									
RCT All ICU *n* = 24 (ICU subgroup)	Intervention Control	78.2 ± 6.6 78.3 ± 6.8	48 32	13.5 ± 2.8 14.6 ± 2.9	P[g]	N/A	Patient report Nurse assessment Rater observation	DSM-IV[h]	Moderate
Bryczkowski et al (31)									
Pre/post cohort Surgical ICU *n* = 123	Intervention Control	67 (64–69)[i] 66 (63–69)[i]	53 63	18[j] 15[j]	E,[k,l] P,[m] S	1, 2, 4, 5, 8, 9	NP	CAM-ICU	Moderate
Patel et al (32)									
Pre/post cohort Mixed ICU *n* = 338	Intervention Control	60.6 ± 16.3 60.0 ± 13.7	53 51	14.2 ± 6.6 15.0 ± 7.6	E,[k] S	1, 2, 3, 5, 6	Nurse assessment RCSQ Sleep in intensive care questionnaire	CAM-ICU	Moderate
Kamdar et al (33)									
Pre/post cohort Medical ICU *n* = 285	Intervention Control	54 (44–66)[n] 54 (43–63)[n]	48 56	NR NR	S	1st phase: 1, 2, 5, 7, 10 2nd phase: above+ 3, 4, 6 3rd phase: above + 9, 11	RCSQ	CAM-ICU	Moderate
Van Rompaey et al (34)									
RCT Mixed ICU *n* = 136	Intervention Control	57 (19–81)[o] 62 (18–84)[o]	68 64	42.5 (0–78)[o,p] 42.1 (0–78)[o,p]	N	N/A	Patient report	NEECHAM	Strong
Ono et al (35)									
RCT Surgical ICU *n* = 22	Intervention Control	63.4 ± 9.7 63.8 ± 7.8	100 100	7.6 ± 2.5 8.8 ± 2.2	L	N/A	Not specified	Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition), Text Revision	Weak
Taguchi et al (37)									
RCT Surgical ICU *n* = 11	Intervention Control	56.3 ± 14.1 59.2 ± 14.1	100 100	NR NR	L	N/A	NP	NEECHAM (Japanese version)	Weak

(*Continued*)

TABLE 1. (*Continued*). Description of Study Characteristics Included in the Systematic Review

Study Design and ICU Type		Age (yr)[a]	Men (%)	Severity of Illness[b]	Intervention[c]	Components of Sleep Bundle Intervention (If Applicable)[d]	Sleep Assessment Performed	Delirium Assessment	Risk of Bias Assessment[e]
Aizawa et al (36)									
RCT	Intervention	75.9 ± 4.5	75	8.3 ± 1.4	P[q]	N/A	NP	DSM-IV[h]	Moderate
Surgical ICU *n* = 40	Control	76.2 ± 4.1	55	7.6 ± 1.7					

CAM-ICU = Confusion Assessment Method for the ICU, DSM-IV = Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition), N/A = not applicable, NEECHAM = Neelon and Champagne Confusion Scale, NP = not performed, NR = not reported, RCSQ = Richards-Campbell Sleep Questionnaire, RCT = randomized controlled trial.

[a]Reported as mean ± SD unless otherwise indicated.

[b]Acute Physiology and Chronic Health Evaluation II unless otherwise indicated.

[c]Key: E = education, L = light therapy, N = noise reduction, P = pharmacologic, and S = sleep bundle.

[d]Key: 1 = minimize nighttime interventions, 2 = noise reduction, 3 = earplugs, 4 = soothing music, 5 = dim lights, 6 = eye masks, 7 = raise blinds during daytimelight exposure during daytime, 8 = artificial light exposure during daytime, 9 = avoid deliriogenic medications, 10 = minimize napping, and 11 = pharmacologic measures (zolpidem or antipsychotic).

[e]As assessed by the Effective Public Health Practice Project quality assessment tool (25).

[f]Melatonin 5 mg at bedtime.

[g]Ramelteon 8 mg oral at bedtime.

[h]Performed by a psychiatrist.

[i]Reported as mean (95% CI).

[j]Injury Severity Score.

[k]Education to providers and staff.

[l]Education provided to family.

[m]Limit deliriogenic medications.

[n]Reported as median (interquartile range).

[o]Provided as mean (range).

[p]Simplified Acute Physiology Score III score.

[q]Diazepam, flunitrazepam, and pethidine (meperidine) nightly for three consecutive nights.

ranged from 12% to 43% for the pharmacologic sleep interventions tested in randomized controlled trials to a 16–20% reduction in the pre/post studies (30, 33, 38, 39). However, too many identified confounders in the included studies cloud the picture to make a firm conclusion. The heterogeneity of the existing body of literature (in terms of patient populations and concomitant interventions that confound results) and quality of data (only one study rated strong) makes the evidence base for this conclusion weak at best and precludes quantitative pooling in a meta-analysis.

Although the studies in this review have laid the groundwork, in the following, we review the limitations in the existing literature with the intent to provide recommendations on a research framework for future study designs investigating the link between sleep interventions and delirium in the ICU. In order to evaluate which, if any, particular sleep interventions have neurocognitive benefits in the ICU, the critical care community must embrace a systematic approach to study sleep interventions in critical care and their impact on patient-centered outcomes. Only in this way, can the speculation on the importance of sleep in critical illness be confirmed with more robust data.

Recommendation 1–The Link Between Sleep Intervention, Improved Sleep, and Outcome Must Be Clearly and Objectively Demonstrated

The future successful landmark study involving sleep and delirium incorporates a sleep intervention linked to an objective measurement of improved sleep, which in turn is linked to assessed clinical outcomes, including occurrence rate of ICU delirium.

The studies identified in our review used a variety of sleep assessment tools, including patient self-reported sleep quality/questionnaires, nursing observations, and rater observations. Several studies included used subjective measurements of sleep assessment, including arguably flawed assessments, such as hourly awake/asleep assessments, which are of little utility as they offer no assessment of sleep quality. Furthermore, some studies analyzed did not assess sleep at all.

For a detailed explanation of sleep measurement in the ICU, readers are referred to an excellent review by Bourne et al (41). Polysomnography is well recognized as the gold standard for assessing sleep outside of the ICU although its use poses significant challenges in the ICU, including labor, cost, and skill in interpretation of electroencephalogram findings distinguishing sleep from alterations secondary to critical illness (e.g., electroencephalogram slowing) (42). In fact, some critically ill patients have been shown to have uninterpretable polysomnography based on applying the standard Rechtschaffen and Kales' criteria (10, 43). Investigations are currently underway to better characterize sleep in the ICU. For example, Watson et al (43) have proposed a revised sleep scoring system using polysomnography criteria that account for the atypical polysomnography findings noted in critically ill patients.

Simpler objective methods, such as bispectral index (BIS) monitoring, have been considered as a potentially

TABLE 2. Outcomes Reported From Studies Included in the Systematic Review

References	Effectiveness of Sleep Intervention	Incidence of Delirium			Duration of Delirium (d)			ICU Length of Stay (d)		
		Intervention, *n* (%)	Control, *n* (%)	*p*	Intervention (Mean ± SD)	Control (Mean ± SD)	*p*	Intervention (Mean ± SD)	Control, (Mean ± SD)	*p*
Guo et al (39)	NA	10/67 (15)	25/80 (31)	0.006	1.2 ± 0.4	2.5 ± 0.7	< 0.001	NR	NR	NR
Artemiou et al (38)	NA	21/250 (8.4)	52/250 (20.8)	0.001	NR	NR	NR	4.2 ± 3.0	4.6 ± 3.5	0.001
Hatta et al (30)	No difference in any measured sleep parameters	0/10 (0)	6/14 (43)	0.024	NR	NR	NR	NR	NR	NA
Bryczkowski et al (31)	NA	38/66 (58)	27/57 (47)	0.26	3 (2–5)[a]	6 (4–8)[a]	0.002	6 (4–8)[a,b]	9 (6–11)[a,b]	0.04
Patel et al (32)	Improvement in all components of RCSQ ($p < 0.05$); improved sleep time ($p < 0.001$) and > 3 hr of sleep window ($p = 0.029$); improved sleep efficiency index ($p < 0.001$); improved sleep quality (< 0.001); reduced daytime sleepiness (0.042)	24/171 (14)	55/167 (33)	< 0.001	1.2 ± 0.9	3.4 ± 1.4	0.021	NR	NR	NR
Kamdar et al (33)	No difference in RCSQ ratings for overall sleep quality ($p = 0.46$)	86/175 (49)	76/110 (69)	0.02	2.2 ± 4.5	2.8 ± 6.7	0.37	4.3 ± 6.8	5.4 ± 9.5	0.26
Van Rompaey et al (34)	Improved patient-reported sleep on night 1 ($p = 0.042$)	14/69 (20)	13/67 (19)	0.9	NR	NR	NR	NR	NR	NR
Ono et al (35)	No difference in daily sleeping hours	1/10 (10)	5/12 (42)	0.16	NR	NR	NR	5.0 ± 1.3	4.1 ± 1.9	0.22
Taguchi et al (37)	NA	1/6 (17)	2/5 (40)	0.55	NR	NR	NR	NR	NR	NR
Aizawa et al (36)	NA	1/20 (5)	7/20 (35)	0.023	NR	NR	NR	1.3 ± 0.6	1.9 ± 1.7	0.314

NA = not assessed, NR = not reported, RCSQ = Richards-Campbell Sleep Questionnaire.

[a]Reported as mean (95% CI).

[b]For ICU length of stay, median value was 4 d (intervention) and 5 d (control).

reasonable, more practical alternative to polysomnography (44). Unfortunately, BIS monitoring has a number of its own limitations, including sensor removal and hardware failure. Furthermore, it is likely that critical illness may alter the effectiveness of BIS monitoring in the same way that critical illness may impact the polysomnography via the electroencephalogram interpretation. Available data are limited regarding the clinical utility of BIS for assessment of sleep quality in the ICU (45–47).

Actigraphy initially seems to be a simple, user friendly means of assessing sleep in the ICU. However, when compared with simultaneous polysomnography in 12 critically ill patients, agreement between actigraphy and polysomnography was noted to be poor (48). Appropriate use of this tool is limited by somewhat common occurrences in the ICU, including sedatives, restraints, and neuromuscular blockers (42). Although actigraphy deserves further exploration as a tool for sleep assessment, we suggest other tools be used first line at this time in future research design.

Many patient-reported assessment methods are available, including the Verran and Snyder-Halpern Sleep Scale, the Sleep in the ICU Questionnaire, the Richards-Campbell Sleep Questionnaire (RCSQ), and the St Mary's Hospital Sleep Questionnaire (49). Of these, the RCSQ seems to be the most reliable and has been validated against polysomnography in a small, prospective study of 70 alert and oriented critically ill men (50). Kamdar et al (51) recently reported on a secondary analysis of their original study data, suggesting that patients' perceived sleep-quality ratings using the RCSQ were not associated with the transition to delirium. These questionnaires, however, have not been validated for use with delirious

patients. In one study identified from our review analyzing patient-completed RCSQ scores, only one questionnaire per patient was selected at random for the analysis rather than an aggregate of the scores (32). Although repeated patient assessments of the RCSQ have been suggested to introduce bias, an aggregate measure of the patient's total perception of sleep during each night in the ICU is more likely to be informative in assessing sleep interventions.

Nurse assessment of sleep using direct observation may overestimate sleep time, and the use of the Patient's Sleep Behavioral Observation Tool, although reasonable to use in the study environment, requires extensive nurse involvement with only modest correlation with polysomnography (52, 53). The use of the nurse-completed RCSQ may be the most promising subjective assessment available as it is reliable and generally correlates well with patient-completed RCSQ in critically ill patients (54, 55). However, nurse-completed RCSQ may overestimate sleep depth when compared with patient-completed RCSQ, particularly in more severely ill patients (56).

The following question still remains: do sleep interventions improve sleep quality, subsequently reducing the development of delirium? Or are patients simply exposed to calmer environments, thereby reducing the number of positive delirium screening tests? Indeed, our review identified multiple disparities in the change in assessed sleep indices and occurrence rate of ICU delirium. Only one single study improved both sleepindices and delirium occurrence. This begs the question: is sleep not involved in the development of delirium or are we simply using insensitive measures of sleep? Future research that incorporates a clinical intervention with a physiologic assessment of sleep quality or biomarker of circadian rhythmicity may come closer to answering whether sleep itself improves these outcomes. Objective measurements of sleep further allow us to discern which particular aspect of sleep is most important and prioritize interventions: increase sleep duration (e.g., quiet time), reduce sleep fragmentation (e.g., ear plugs), reduce circadian misalignment (e.g., melatonin and bright light therapy), minimize medication-induced alteration in sleep architecture (e.g., avoid benzodiazepines), or any combination of the above.

Although additional research involving sleep measurement in critically ill patients continues to evolve, we suggest that future studies evaluating the ability of sleep improvement interventions to reduce delirium should use validated, consistent, and objective sleep measurement tools in conjunction with subjective assessment tools, such as a patient- or nurse-completed RCSQ. For those patients who are neither sedated nor delirious and perhaps have a lower severity of illness, polysomnography or actigraphy alone or in combination with a subjective assessment tool may be an acceptable way to measure sleep as it is for noncritically ill patients. For patients experiencing delirium or are under the influence of sedation and have a higher severity of illness, there may in fact be no current "gold standard" regarding objective measurement of sleep. In these cases, perhaps a combination of measurements (e.g., polysomnography combined with actigraphy and nurse-completed RCSQ) may offer the most insight regarding objective measurement at this time. Ultimately, it may require additional physiologic measures, such as neuroimaging in combination with electrophysiology to define sleep in these patients. Until better ways to accurately measure sleep in the critically ill are elucidated and considering the limitations of the existing assessments, a combination approach is most advised at this time.

Recommendation 2–Prospective Studies of Sleep Intervention Should Be Undertaken in Environments With Guideline-Recommended and Consistent Practices Regarding the Prevention and Treatment of Delirium to Allow the Testing of a Single Intervention on the Impact of Delirium

The most significant limitation of the three largest studies identified in our review was their pre/post design (32, 33, 38). Although these studies offer hope that sleep intervention mayreduce delirium, their single center, pre/post nature introduces the opportunity for differences in patient characteristics and assessor bias. In particular, the interventions were tiered in one of the studies (33). This further complicates the study analysis on which of the sleep interventions precisely may have been responsible for any observed benefits. In future prospective studies, many challenges exist to minimize the bias and confounding observed in our systematic review. By their very nature, "sleep bundle" activities are difficult to blind from bedside clinicians. Although pharmacologic sleep interventions may be studied in a blinded fashion, studying other sleep-promoting behaviors in a blinded way remains extremely challenging. One study identified was able to successfully blind ear plugs from researchers although blinding an entire bundle of sleep-promoting activities likely remains almost impossible (34). Randomizing patients by individual ICUs, or a cluster randomized approach, to a "sleep bundle" or control may minimize the amount of bias introduced into these study designs.

Equally important, the existing literature makes a firm conclusion difficult because of the number of confounding interventions studied simultaneously with sleep-promoting activities. These cointerventions studied with sleep-promoting activities make it difficult to assess whether any benefits can be attributed to sleep promotion or are a reflection of the other activities. These other cointerventions from our review include provider, patient, and family education regarding delirium and formal recommendations to medical staff to limit deliriogenic medications, including benzodiazepines (31, 32, 39). All of these are logical interventions for delirium prevention but limit the conclusion that sleep is responsible for the improved outcomes related to delirium and not one of these other measures. Ensuring that avoidance of coma, minimization of deliriogenic medications, and early mobilization are consistent throughout the study period is also critical. Ideally, future studies should be conducted at centers with guideline-recommended and consistent practices regarding the prevention and treatment of delirium in place, including education of patients, family, and providers on delirium. In this way, the study intervention of sleep promotion can be tested by itself rather than confounded

by other concurrent interventions in a prospective fashion. We recognize that many centers are continually improving their delirium practices in pursuit of best practice; however, consistent practices with regard to delirium prevention and treatment across the study period are paramount in future studies to minimize the confounding observed from this review.

Melatonin and melatonin receptor agonists seem to be promising pharmacologic targets to improve sleep in the ICU setting (27, 30). Studies investigating pharmacologic therapy should logically only be studied in individual units already promoting good sleep hygiene practices, in addition to minimizing deliriogenic medication exposure, promoting early mobility, and offering patient and family education. For example, providing a pharmacologic agent without the coexistence of a "sleep bundle" to minimize laboratory draws, noise, bathing, and other common interruptions during the night is likely setting any particular pharmacologic agent studied up for failure in future clinical trials.

Recommendation 3–Delirium Should Be Carefully and Appropriately Assessed With a Validated Screening Tool

In our review, 46 studies investigating a sleep intervention in the ICU were excluded because of no assessment of delirium status. Although we included NEECHAM in this analysis to complete our synthesis of the literature, we suggest CAM-ICU or ICDSC be used at least once per nursing shift, which is consistent with current recommendations and practice standards (16). Given the advances in knowledge regarding the potential for sedative artifact in the delirium screening process, efforts should be taken to minimize sedation prior to delirium screening (57). Sedative exposure may also be a risk factor for impacting the composite outcome of delirium/coma, an outcome measure used in one of the included studies in this review (33).

There may also be benefits of sleep intervention on cognitive disturbances and delirium not formally detected in this review based on the measures analyzed. For example, one study that did not formally evaluate delirium demonstrated in a randomized, controlled trial that melatonin significantly reduced sedation requirements compared with placebo (58). In the study by Bryczkowski et al (31), the use of the bundle involving sleep interventions was not associated with a reduction in the occurrence rate of delirium per se. It was, however, associated with a statistically significant increase in delirium-free days (27 vs 24; $p = 0.002$) (31). This may reflect the decrease in the duration of delirium observed in the study or simply reflect the sensitivity of the delirium measurement (occurrence rate vs delirium-free days). To this end, it is reasonable that study endpoints for sleep interventions include the occurrence rate of delirium and the duration of delirium and delirium-free days as outcomes to determine if improving sleep can prevent delirium from occurring, help with resolution of existing delirium, or both.

Similarly in the study by Van Rompaey et al (34) assessing ear plugs in the ICU, the intervention did not reduce the occurrence rate of delirium as defined on the NEECHAM scale; it was, however, associated with a significant reduction in mild confusion (14.5% vs 40.3%). Further Cox regression in the analysis revealed that ear plugs decreased the risk of delirium or mild confusion by 53% (hazard ratio, 0.47; CI, 0.27–0.82) (34). In an ideal situation, additional measures, such as cognitive performance in the ICU and at follow up after discharge, would be assessed in future landmark studies. A recent meta-analysis draws doubt that interventions decreasing delirium translate to meaningful outcomes post ICU discharge (59). Assessing the impact of sleep interventions during critical illness on these short- and long-term cognitive performance metrics remains arguably as important as, if not more important than, the actual delirium status as a study endpoint.

Recommendation 4–Efforts Must Be Taken to Minimize Selection Bias and Use Study Populations That Are Generalizable to a Large Majority of Critically Ill Patients

Perhaps one of the major limitations of the existing literature is that it has poor generalizability to the critical care community as a whole. The lack of external validity is exemplified by the ramelteon study identified in this review, which excluded more than 90% of patients assessed for eligibility (30). The majority of the studies consisted of elderly patients, particularly in the postoperative setting. Across the range of studies, severity of illness was generally low to moderate (APACHE II score range, 7.6–15.0) (32, 36) with relatively short lengths of stay. The impact of sleep interventions on the most critically ill, including those requiring sedation for more than 24–48 hours, remains poorly studied. Whether promoting sleep is beneficial or even possible in the face of the adverse effects of sedative-induced changes on sleep architecture remains an unknown yet important question. It is critical that these patient populations are included in future studies, as their risk of delirium and associated complications is high. Considerations to address at the time of enrollment in future studies include the delirium status of the patient at that time, severity of illness, and requirement for sedation. Stratification at enrollment or preplanned subgroup analyses in these important subgroups may assist with the generalizability of the findings.

The Need for a Research Framework

The physiologic rationale for promoting sleep to reduce delirium is sound, but the link needs to be evaluated definitively for it to be embraced by the critical care community. Although the costs of sleep interventions at face value may seem to be limited, implementing them comes with considerable effort and potentially low compliance (60). Sleep efforts require cross-departmental coordination across multiple disciplines for quiet times and workflow changes that may ultimately cost immense amounts of time, effort, and resources. However, if shown to improve delirium-related and other cognitive outcomes, sleep interventions may be one of the most natural remedies available to offer ICU patients and one with a very favorable benefit-to-risk ratio. Careful further study using the lessons learned from existing literature will help determine if

sleep plays as much a role as we theorize and specifically which interventions are worth the investment in our ICUs.

CONCLUSIONS

Although studies evaluating interventions targeting sleep optimization in the ICU, including nonpharmacologic sleep bundles, earplugs, bright light therapy, and pharmacologic therapy, are promising, the methodologies are varied and moderate-significant biases exist. A systematic approach is necessary to evaluate the complex link between sleep interventions and delirium. Lessons learned from the existing literature provide a research framework for answering these important questions in future studies.

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