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Crit Care Med. Author manuscript; available in PMC 2017 September 14.

Published in final edited form as:

Crit Care Med. 2016 December ; 44(12): 2290–2291. doi:10.1097/CCM.0000000000001982.

Promoting Sleep to Improve Delirium in the ICU

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Keywords

critical illness; delirium; intensive care unit; sleep

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

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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 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).

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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.

Acknowledgments

Dr. Kamdar received support for article research (He is currently supported by a grant through the UCLA Clinical Translational Research Institute [CTSI] and the National Institutes of Health/National Center for Advancing Translational Sciences [UL1TR000124]). Dr. Martin served as a board member for the American Academy of Sleep Medicine, consulted for Equinox Fitness, lectured for Equinox Fitness, received support for development of educational presentations from Equinox fitness, received support for travel from the American Academy of Sleep Medicine, and disclosed government work. Her institution received funding from the American Sleep Medicine Foundation. Dr. Needham disclosed other support (he is a current member of the Society of Critical Care Medicine committee for creating an updated Clinical Practice Guideline for delirium and sleep in the ICU). Dr. Ong disclosed government work.

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