CLINICAL RESEARCH STUDY

THE AMERICAN JOURNAL of MEDICINE®

# A Meta-analysis of Sleep-promoting Interventions During Critical Illness

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## ABSTRACT

**BACKGROUND:** Sleep quality and quantity are severely reduced in critically ill patients receiving mechanical ventilation with a potential for adverse consequences. Our objective was to synthesize the randomized controlled trials (RCTs) that measured the efficacy of sleep-promoting interventions on sleep quality and quantity in critically ill patients.

**METHODS:** We included RCTs that objectively measured sleep with electroencephalography or its derivatives and excluded observational studies and those that measured sleep by subjective reports. The research was performed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

**RESULTS:** Of 6022 studies identified, 13 met eligibility criteria involving 296 critically ill patients. Eight trials looked at different modes of mechanical ventilation as sleep interventions, and the remaining 5 involved pharmacologic, nonpharmacologic, or environmental interventions. Meta-analysis of the studies revealed that sleep-promoting interventions improved sleep quantity (pooled standardized mean difference [SMD], 0.37; 95% confidence interval [CI], 0.05-0.69; $P = .02$) and sleep quality through reduction in sleep fragmentation (SMD, −0.31; 95% CI, −0.60 to −0.01; $P = .04$). Subgroup analysis revealed that timed modes of ventilation improved sleep quantity when compared with spontaneous modes of ventilation (SMD, 0.45; 95% CI, 0.10-0.81; $P = .01$). Nonmechanical ventilation interventions tended to improve sleep quantity (SMD, 0.65; 95% CI, −0.03 to 1.33; $P = .06$) and to reduce sleep fragmentation (SMD, −0.29; 95% CI, −0.61 to 0.03; $P = .07$).

**CONCLUSIONS:** The synthesized evidence suggests that both mechanical ventilation- and nonmechanical ventilation-based therapies improve sleep quantity and quality in critically ill patients, but the clinical significance is unclear. In the future, adequately powered multicenter RCTs involving pharmacologic interventions to promote sleep in critically ill patients are warranted.

 • *The American Journal of Medicine (2015)* ■, ■-■

**KEYWORDS:** Artificial respiration; Critical care; Critical illness; Hypnotics and sedatives; Polysomnography; Positive-pressure respiration; Sleep

Sleep quality and quantity are severely reduced in critically ill patients, with the potential for adverse consequences.[1-5] Lack of sleep may contribute to delirium and agitation in critically ill patients and cause immune dysregulation and negative nitrogen balance in healthy volunteers.[4,6-8] In community-dwelling participants, lack of sleep has been associated with all-cause mortality.[9-15] Although abnormalities of sleep are extremely common in critically ill patients, the mechanisms are not well understood.[4] Intervention-based studies in critically ill patients can elucidate the mechanistic basis of sleep derangements and are direly needed. However, there is a paucity of such intervention-based mechanistic studies for sleep promotion in critically ill patients because of the arduous nature of conducting such intervention-based experiments and

**Funding:** See last page of article.

**Conflict of Interest:** See last page of article.

**Authorship:** See last page of article.

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0002-9343/$ -see front matter 
http://dx.doi.org/10.1016/j.amjmed.2015.05.026

difficulties in surrogate consenting and collecting electroencephalography signals in an artefact-ridden intensive care unit environment.[4] Even the few randomized controlled trials (RCTs) of sleep in the intensive care unit are limited by small sample size. Nevertheless, they were rigorous in study design and conduct while exploring the effect of mechanical ventilation, pharmacologic, environmental, and other nonpharmacologic interventions on sleep in critically ill patients.[16-19] A meta-analysis by combining such smaller RCTs could increase the overall power to estimate the efficacy of sleep-promoting interventions during critical illness. Such an undertaking could help us better understand the mechanistic underpinnings of sleep derangements during critical illness and ultimately inform future adequately powered trials aimed at improving sleep and consequent outcomes in critically ill patients.

**CLINICAL SIGNIFICANCE**

- Sleep-promoting interventions improved sleep quantity in critically ill patients.
- Timed modes improved sleep quantity when compared with spontaneous modes of ventilation.
- Effect size of sleep promotion interventions was small and heterogeneous in the critically ill.
- Effect size of nonmechanical ventilation was larger than mechanical ventilation-based interventions.

Our primary objective was to synthesize the RCTs that measured the efficacy of sleep-promoting interventions on sleep quality and quantity in critically ill patients. Our secondary objective was to understand the treatment effects of sleep-promoting interventions that were categorized by mechanical ventilation vs other interventions.

## MATERIALS AND METHODS

### Data Source and Searches

We conducted an electronic search of the literature in Medline, Cochrane Central, and DynaMed from 1966 to August 2014. We then updated the search in October 2014. We used a combination of Medical Subject Headings (MESH) subheadings and keywords (sleep, sleep interventions, critical illness, mechanical ventilation, randomized controlled trials). We used "sleep AND critical illness," "sleep AND mechanical ventilation," "sleep interventions AND mechanical ventilation," "sleep interventions AND critical illness," and these 4 combinations with "OR randomized controlled trials" with exploded search terms. We limited the entire list to studies published until October 2014, but there were no limits to the age of the studies. We reviewed the bibliographies of the included studies and previous reviews to identify additional citations. The research was guided by an extraction protocol that followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[20]

### Definitions

Operational definitions of outcome variables were as follows: (a) Sleep quantity was defined as sleep efficiency, which is time spent asleep expressed as a percentage of total recording time. (b) Sleep quality was defined as sleep fragmentation measured as arousals and awakenings per hour of sleep. (c) Information on proportion of time spent in various sleep stages was also extracted when available and proportioned into various non-rapid eye movement (stage N1, N2, slow wave sleep) and rapid eye movement sleep. Explanatory variables were interventions that were categorized into changes (or intervention) made to mechanical ventilation (mode of ventilation), pharmacologic therapy (sedatives type or infusion method), and environmental (noise reduction or music) and nonpharmacologic (eg, massage) interventions.

### Eligibility Criteria

We included intervention-based studies if they were RCTs and objectively measured sleep in critically ill patients. We excluded observational studies and those that measured sleep without electroencephalography or its derivatives. A priori, we decided not to include articles that measured sleep through subjective reports, nursing assessments, or actigraphy because of known reservations about their test characteristics.[21] We included Bispectral Index or fast Fourier transformation of electroencephalography signals because such automatically processed signals have good reproducibility characteristics and there was a paucity of RCTs in this area of study identified through an iterative process.[22] The search was limited to RCTs that were published in English and studied human subjects.

### Data Extraction and Quality Assessment

One study team member (CP) reviewed all included articles (n = 13) and abstracted all of the relevant data from them into a formatted Windows Excel database (Microsoft Corp, Redmond, Wash). To validate the abstraction process, the other 2 study team members (SGJ, ASK) each reviewed a randomly selected sample so that at least 2 study members had abstracted each included article. A third study member (SP) reviewed extracted data from all of the articles to identify differences in the abstraction between previous abstractions and resolve discrepancies by consensus. Data were extracted from each selected article using a formatted Windows Excel database. Disagreement between the extracting investigators was resolved by consensus. We rated the study quality using US Preventive Services Task Force criteria (**Table 1**).[23]

### Data Synthesis and Analysis

We conducted a meta-analysis assuming random effects on sleep quantity and quality that provided enough detail to