Better Sleep in the Intensive Care Unit: Blue Pill or Red Pill... or No Pill?

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SLEEP is hard to come by in the intensive care unit (ICU). When quantified, Elliott et al. found that sleep duration was curtailed (mean, 5 h per night) and very fragmented, with a median duration of sleep before waking of just 3 min! Illness may impact sleep, but it is likely that the ICU environment (e.g., noise and light) and customary practices (e.g., lab draws and x-rays for morning rounds) also greatly contribute to the lack of consolidated sleep. Although changing the ICU culture to promote sleep is difficult, attention to sleep has been associated with improved clinical outcomes, specifically a reduction in the major outcome of ICU delirium.

Given the challenges of improving sleep via workflow and environment redesign, might sleep be improved pharmacologically? If so, what might be the best medication to do so? Traditional sleeping pills, such as benzodiazepines, have been associated with delirium. Even newer nonbenzodiazepine hypnotics, such as zolpidem, are associated with altered mental status and in-hospital falls and may lack efficacy even in less acutely ill non-ICU patients. Melatonin or melatonin receptor agonists might be another option, with a single-center randomized controlled trial showing a marked reduction in delirium in a less severely ill (i.e., not mechanically ventilated) elderly ICU population.

But it is not clear if the mechanism of this improvement is based on improved sleep or due to a circadian effect. Another intriguing option is dexmedetomidine, which has been argued to induce "natural" sleep. Indeed, the drug appears to activate most, though not all, of the pathways important for sleep and produces an electroencephalogram pattern consistent with non–rapid eye movement (ReM) sleep, specifically stage N2 sleep. Thus, as dexmedetomidine is already used in the ICU, causes little respiratory depression, and is short-acting, it makes sense to study its impact on sleep and other outcomes. In theory, pharmacologically induced sleep rather than sedation may have benefits from the standpoint of delirium and other clinically important outcomes.

In this issue of Anesthesiology, Wu et al. tested rigorously the hypothesis that dexmedetomidine would improve sleep in elderly patients in the surgical ICU after noncardiac surgery. This was an ambitious randomized, double-blind, placebo-controlled study that involved more than 60 polysomnographic recordings in the ICU. The patients were those greater than or equal to 65 yr old, mostly recovering from abdominal surgery and, of note, were not receiving mechanical ventilation. Unlike previous small studies that had shown more non-REM sleep with moderate doses (≈0.6 mg kg\(^{-1}\) h\(^{-1}\)) of dexmedetomidine titrated according to Richmond Agitation-Sedation Scale (RASS) over the night, these authors used a fixed, low dose of 0.1 mg kg\(^{-1}\) h\(^{-1}\) during the evening and night (5:00 PM to 8:00 AM). This so-called prophylactic dose was chosen to avoid adverse hemodynamic effects and to avoid sedation per se. The percent of time in stage N2 sleep was chosen as the main outcome. Stage N2 sleep is a stable form of non-REM sleep with easily recognizable electroencephalogram morphology, which is thought to be restorative and is a reasonable outcome especially in elderly patients where deeper stage N3 sleep or REM sleep is relatively rare. Incident delirium, length of ICU stay, and hemodynamic safety endpoints were secondary outcomes.

As expected, those who received dexmedetomidine did have more stage N2 sleep than those who received placebo. There was also a small improvement in subjective sleep quality of uncertain significance. Although this patient-centered outcome might be important by itself, there was no change in downstream incident delirium, and there was an increased incidence of hypotension and Bradycardia. These...
latter hemodynamic effects should limit the enthusiasm to investigate higher doses of this medication. Because of these findings, some might consider this a negative study even though the primary outcome was achieved. The authors conclude that future larger studies will be required to verify the risk–benefit ratio and long-term outcomes that accrue from this kind of intervention. However, the study has important immediate implications for both researchers and clinicians.

First, it emphasizes that changes in the electroencephalogram pattern may not be clinically relevant. Not only are electroencephalogram recordings challenging to obtain in ICU patients, the interpretation of electroencephalogram in the ICU is also notoriously difficult and has led to proposed alternate scoring rules. In addition to dexmedetomidine, illness and other medications may mimic patterns seen with sleep—even when patients are clinically awake. That is, separating sleep from sedation/drug effect or illness using electroencephalogram will be extremely difficult. Sleep recordings will be important when considering mechanisms of how a focus on sleep improves outcomes and perhaps can be used in more feasible simulation studies to inform trials planned in the ICU. However, intervention studies in the ICU should be designed for the clinically relevant outcomes of delirium, analgesic/sedative use, length of stay, and so forth.

Second, the current study serves as a reminder that opportunities for wake are likely to be as important as opportunities for sleep. The infusion of study drug in this trial was administered for 15 h, an amount of time that far exceeds normal sleep duration. As in this study and in clinical practice, prolonged sedation is unlikely to help drive natural sleep. Although never directly studied, interventions that have been shown to improve rates of delirium and length of mechanical ventilation, such as daily interruptions of sedation and early physical therapy, may have improved sleep by increasing wake and activity during the day. Future interventions designed to improve sleep should focus not only on changes at night—for example, limiting noise and light, clustering care to reduce interruptions, and retiming blood draws/x-rays—but also on increasing wake and circadian cues during the day, which may include increasing light levels, increasing daytime activity, or bolus feeding to mimic meal times, among others. More broadly, we should also consider an individualized approach to sedation use in the ICU. RASS may be used to track the depth of sedation but does not reflect the rationale or desired goal of sedative use. For example, in patients with acute respiratory distress syndrome, even sedation to induce coma (RASS score −5) may not eliminate patient-ventilator dysynchrony and allow low-tidal volume ventilation. A personalized medicine approach would consider the desired aim of sedation (e.g., ventilatory synchrony) and the physiologic outcome (e.g., transpulmonary pressures) to be monitored for effect. Depending on individual characteristics, effective sedation strategies might range from nearly none to deep sedation with paralysis.

Third, we should consider the possibility that there is no medication that will consistently improve sleep and have the desired downstream effects. For example, while higher doses of dexmedetomidine have shown a greater impact on N2 sleep duration, the drug appears to suppress other stages of sleep, including REM sleep. Or, as in this case, the therapeutic window of all such medications may be exceedingly narrow. While melatonin and melatonin agonists seem safe and may be effective, it may be that the absence of medications for sleep improves patient outcomes. Some studies of sleep interventions that led to reductions in delirium in hospitalized and ICU patients have reduced or proscribed the use of medications for sleep. Indeed, research in the area of “sleep in the ICU” seems split between interventions designed to obviate the need for a sleeping pill and efforts at trying to find the “right” sleeping pill. This study adds to the evidence that such a medication may not exist. Melatonin and related agonists may have benefits but cannot currently be universally recommended without further data.

As of 2016, the optimal choice of sleep aid is not the blue pill or the red pill. Best practice should continue to focus on reducing the need for any pharmacologic sleep aid by adhering to recommended guidelines about care at night and during the day rather than adding on medications for sleep.

Competing Interests
Dr. Owens has received honoraria and travel fees from ResMed (San Diego, California) and Itamar Medical (Franklin, Massachusetts), not related to the content of this manuscript.

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References

How the Fitting of Dentures Led to the Fitting of Anesthetic Facemasks in America

America’s father of “continuous gum” dentures, New York dentist John Allen, M.D., D.D.S. (1810 to 1892, left), taught one of his dental preceptees, Lewis Roper, M.D. (c. 1806 to 1850), of Philadelphia, that aging facial contours could be rejuvenated aesthetically by properly fitted dental work. Allen’s mentoring on facial contouring inspired Dr. Roper to patent an anesthetic inhaler (right) in October of 1848, which included a facemask fitted “directly over the nose and mouth” in order “to administer the vapor of ether through these two organs simultaneously.” Following its inventor’s death from cholera, the Roper Inhaler was mass produced, to the delight of ether pioneer Charles T. Jackson, M.D. In his 1861 Manual of Etherization, Dr. Jackson hailed the Roper Inhaler as “by far the best that has, thus far, been invented.” Two years later, Roper’s mentor, Dr. Allen, would share a Manhattan office with two other dentists and with nitrous oxide pioneer G. Q. Colton. The four had partnered to form the Colton Dental Association, which revived dental use of nitrous oxide anesthesia. (Copyright © the American Society of Anesthesiologists’ Wood Library-Museum of Anesthesiology.)

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