Sedation in Critically Ill Patients

Mark Oldham, MD\textsuperscript{a}, Margaret A. Pisani, MD, MPH\textsuperscript{b},* 

KEYWORDS
- Sedation • Critically ill patients • Intensive care unit • Pain • Circadian rhythm
- Delirium

KEY POINTS
- Our understanding of the importance of sleep on recovery of patients who experience critical illness is still in its infancy.
- Although there is biological plausibility regarding the impact and importance of sleep in intensive care unit (ICU) patients especially related to immune dysfunction, infection risk, prolonged length of mechanical ventilation, and delirium development and duration, there are little published data.
- Despite the challenges of caring for critically ill patients, following the recommended guidelines for pain, agitation, and delirium, paying attention to early mobilization and sleep hygiene and individualizing patient care as needed, should lead to the best outcomes for patients.
- Future research studies should continue to inform our practice regarding treatment of pain, agitation, and delirium in the ICU.

INTRODUCTION
Sedation in the intensive care unit (ICU) is a topic that has been frequently researched, and debate still exists as to what are the best sedative agents for critically ill patients. There is increasing interest in sleep and circadian rhythm disturbances in the ICU and how they may impact on outcomes. In addition to patient-related and ICU environmental factors that likely impact sleep and circadian rhythm in the ICU, sedative and analgesic medications may also play a role. This article focuses on
- Current practice guidelines related to pain, sedation, and delirium in the ICU
- Effects of medications used for pain, sedation, and delirium on sleep stages
- Effects of medications used for pain, sedation, and delirium on circadian rhythm
- Conclusions on the interactions between medications, sleep, and circadian rhythm in the ICU

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\textsuperscript{a} Department of Psychiatry, Yale-New Haven Hospital, 15 York Street, New Haven, CT 06510, USA; \textsuperscript{b} Section of Pulmonary, Critical Care & Sleep Medicine, Yale University School of Medicine, PO Box 208057, TAC 5425C, New Haven, CT 06520-8057, USA
* Corresponding author.
E-mail address: margaret.pisani@yale.edu

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BACKGROUND

When patients are critically ill and admitted to an ICU, they are frequently intubated and mechanically ventilated. Historically, when patients were placed on a ventilator, they received large amounts of sedation. Work by Kress and colleagues in 2000 demonstrated that one could safely stop sedation on a daily basis and allow patients to wake up. The benefits of this daily interruption of sedation and awakening have now been studied in several other trials and linked to spontaneous breathing trials in ventilated patients. Several recent reviews have summarized the importance of minimizing the amount of sedation in critically ill patients. Fig. 1 presents a schematic of the inter-relationship between critical illness, ICU care, and long-term outcomes.

Sedation in the Intensive Care Unit: Current Practice and Practice Guidelines

The Society of Critical Care Medicine released updated practice guidelines about the management of pain, agitation, and delirium (PAD) in 2013. These guidelines used the GRADE methodology (Grading of Recommendations, Assessment, Development, and Evaluation) in their development. During the process of guideline development, the task force members posed clinically relevant questions that could be systematically evaluated using evidence in the literature. These questions were then transformed into descriptive clinical statements and actionable items. Each statement and recommendation included an assessment of the strength of the evidence based on the strength of the evidence and the relative risk or benefit of the treatment. Statements were defined as weak or strong; weak recommendations were worded as we suggest, and strong recommendations were worded as we recommend. No recommendation was made when there was a lack of sufficient evidence and consensus opinion was not used to make recommendations. In addition, an anonymous, online, iterative voting schema was used to achieve rapid and transparent consensus regarding the statements and recommendations. Table 1 highlights the recommendations for PAD from the 2013 PAD guidelines.

Pain, agitation, and delirium assessments

The guidelines stress the importance of frequent evaluation of critically ill patients using validated measurement tools. For pain, using a patient self-report with a 1 to 10 numerical rating scale (NRS) is the preferred method for those patients who are able to respond. In those patients who are unable to use an NRS, a Behavioral Pain Scale (BPS) is recommended. Either the BPS or Critical-Care Pain Observation Tool (CPOT) can be used in the evaluation of critically ill patients. Both instruments are valid.

Fig. 1. The interaction between critical illness, ICU care, and patient outcomes. PTSD, posttraumatic stress disorder.
and reliable. The use of observational pain scales that utilize vital signs are not reliable for the assessment of pain.5,6 Pain should be assessed at least 4 times per a 12-hour nursing shift and more frequently if needed.

Assessing sedation in the ICU routinely is important for reducing oversedation and ensuring that patients are comfortable. The Richmond Agitation-Sedation Scale (RASS)7 and the Sedation Agitation Scale8 are the 2 instruments recommended by the PAD guidelines based on studies of their validity and reliability for assessing both the quality and depth of sedation in critically ill patients.9,10 Sedation should also be assessed at least 4 times per a 12-hour nursing shift or more frequently if needed. Patients who are paralyzed with neuromuscular blocking agents cannot be assessed with sedation scales and should be monitored with objective measures of brain function, such as bispectral index or auditory evoked potentials.11,12

Delirium rates have been reported to be as high as 80% in research studies of critically ill patients, but it is frequently undiagnosed clinically.13,14 Delirium has shown to

### Table 1
PAD recommendations

<table>
<thead>
<tr>
<th>Assess</th>
<th>Pain (≥4 Times Per Shift &amp; prn)</th>
<th>Agitation (≥4 Times Per Shift &amp; prn)</th>
<th>Delirium (Once a Shift &amp; prn)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assessment</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>tools</td>
<td></td>
<td></td>
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<tr>
<td>Self-report</td>
<td>use the NRS</td>
<td>RASS</td>
<td>CAM-ICU</td>
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<tr>
<td>Unable to</td>
<td></td>
<td>SAS</td>
<td>ICDSC</td>
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<tr>
<td>self-report</td>
<td>use the BPS or CPOT</td>
<td></td>
<td></td>
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<tr>
<td>With NMB</td>
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<td></td>
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<tr>
<td>use brain</td>
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<tr>
<td>function</td>
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<td></td>
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<tr>
<td>monitoring</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treat</td>
<td>Treat within 30 min</td>
<td>Sedation should be targeted to a</td>
<td>Treat pain if present</td>
</tr>
<tr>
<td>Nonpharmacologic:</td>
<td>relaxation therapy</td>
<td>RASS (−2 to 0) or SAS (3–4) goal</td>
<td>Pharmacologic:</td>
</tr>
<tr>
<td>Pharmacologic:</td>
<td>opioids: non-neuropathic pain</td>
<td></td>
<td>nonpharmacologic:</td>
</tr>
<tr>
<td>Gabapentin</td>
<td></td>
<td>Agitation (RASS &gt;0, SAS &gt;4): treat</td>
<td>Pharmacologic:</td>
</tr>
<tr>
<td>or carbamazepine-neuropathic</td>
<td></td>
<td>pain and with sedatives prn</td>
<td>no recommendation to</td>
</tr>
<tr>
<td>Epidural: postoperatively</td>
<td></td>
<td>(propofol or dexmedetomidine preferred</td>
<td>treat delirium with</td>
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<tr>
<td></td>
<td></td>
<td>over benzodiazepines)</td>
<td>medications</td>
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<td></td>
<td></td>
<td>Suggest: avoiding</td>
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<tr>
<td>Prevent</td>
<td>Provide preprocedural analgesia</td>
<td>Daily SBT, early mobility when at</td>
<td>Identify delirium risk</td>
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<td></td>
<td>and/or nonpharmacologic</td>
<td>goal sedation level, unless</td>
<td>factors</td>
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<tr>
<td>interventions</td>
<td></td>
<td>contraindicated</td>
<td>Early mobilization</td>
</tr>
<tr>
<td>Treat pain</td>
<td>first and then provide sedation</td>
<td>EEG monitoring for those at seizure</td>
<td>Continue/restart baseline</td>
</tr>
<tr>
<td></td>
<td>if needed</td>
<td>risk; treat burst suppression</td>
<td>psychiatric medications</td>
</tr>
<tr>
<td></td>
<td></td>
<td>when there is an increased ICP</td>
<td>if indicated</td>
</tr>
</tbody>
</table>

**Abbreviations:** BPS, Behavioral Pain Scale; CAM-ICU, Confusion Assessment Method for the ICU; CPOT, Critical, Care Pain Observation Tool; EEG, electroencephalography; ICDSC, Intensive Care Unit Delirium Screening Checklist; ICP, intracranial pressure; IV, intravenous; NMB, neuromuscular blockade; NRS, numeric rating scale; prn, as needed; RASS, Richmond Agitation Sedation Scale; SAS, Sedation Agitation Scale; SBT, spontaneous breathing trial.

increase length of mechanical ventilation, ICU and hospital length of stay, and mortality as well as increasing the risk for long-term cognitive dysfunction.\textsuperscript{15–19} The PAD guidelines make a strong recommendation for delirium screening once each nursing shift and more frequently depending on patient status. The 2 recommended instruments for delirium screening are the Confusion Assessment Method for the ICU\textsuperscript{20,21} and the Intensive Care Delirium Screening Checklist.\textsuperscript{22}

Management of pain, agitation, and delirium

The PAD guidelines make several strong recommendations for treating pain in ICU patients. These recommendations include administering pain medications in the presence of significant pain determined by an NRS of 4 or greater, a BPS greater than 5, or a CPOT of 3 or greater and before performing any painful invasive procedure. Parenteral opioids should be the first-line treatment of non-neuropathic pain, and either gabapentin or carbamazepine can be given enterally for neuropathic pain either alone or in addition to opioids. Acetaminophen, nonsteroidal antiinflammatory drugs, or ketamine can be used as adjunctive pain medications in select patient populations to reduce dosing requirements and side effects from opioids.

Based on randomized controlled trials, the 2013 PAD guidelines emphasize the importance of minimizing sedation use that includes targeted sedation and daily sedative interruption.\textsuperscript{2} The guidelines recommend treating pain first, that is, using analgesia first and then the sedative medication approach. Based on a meta-analysis performed during the development of the PAD guidelines that compared ICU outcomes in patients who received benzodiazepines versus nonbenzodiazepines (propofol or dexmedetomidine), there is a weak recommendation for preferential use of nonbenzodiazepines for sedation in critically ill patients.\textsuperscript{2} Clearly the choice of a sedative agent needs to be tailored to the individual patient’s clinical presentation; there is a role of benzodiazepines in patients with alcohol withdrawal, seizures, or severe anxiety and when there is a need for deep sedation.\textsuperscript{23,24}

In a change from the 2002 guidelines, the 2013 PAD guidelines do not include a specific medication recommendation for treating delirium. Although haloperidol has been recommended to treat delirium in numerous reviews and guidelines, this is secondary to extrapolated data in its use for treating psychosis. There are no randomized controlled trials (RCTs) that have examined the use of haloperidol for treating delirium in critically ill patients. There are some small studies that have suggested that atypical antipsychotics may reduce delirium duration in critically ill patients, but they are not definitive.\textsuperscript{25–27} Currently there is an ongoing multicenter RCT examining the use of haloperidol versus ziprasidone versus placebo, the MIND-USA (Modifying the Incidence of Neurologic Dysfunction-USA) study, which should answer questions regarding the use of these medications for delirium treatment. The one specific recommendation the PAD guidelines make regarding delirium treatment is against the use of rivastigmine secondary to high mortality rates observed during its use in ICU patients.\textsuperscript{28} Two large RCTs demonstrated that the prevalence of delirium was lower in patients who were sedated with dexmedetomidine versus benzodiazepines.\textsuperscript{29,30} Based on these two studies, the PAD guidelines recommend the avoidance of benzodiazepines in patients with delirium.

Although the PAD guidelines do not make any strong recommendations regarding the use of medications for delirium prevention in the ICU, they strongly recommend the use of early and progressive mobilization and the promotion of sleep hygiene. Sleep hygiene recommendations include reduction of noise and light at night and clustering of patient care activities to prevent sleep disruption. Both mobilization and sleep hygiene should help to maintain a normal circadian rhythm for ICU patients.
In summary, a key message of the PAD guidelines is the importance of integrated and patient-centered care for PAD in the ICU.

**Sleep Physiology**

**Physiologic sleep architecture**

Sleep is critical for health and well-being, particularly among the critically ill. From the late 1960s until just recently, the pioneering work of Rechtschaffen and Kales\(^3\) has served as the standard for classifying sleep architecture. In this system, sleep stages are divided into rapid eye movement (REM) sleep and non-REM (NREM) sleep, with NREM being further subdivided into 4 stages numbered NREM 1 through NREM 4. More recently, the American Academy of Sleep Medicine (AASM) published new scoring criteria in which NREM is subdivided into 3 stages (N1, N2, N3). Effectively, NREM 3 and 4 are condensed into N3.\(^3\) Polysomnography (PSG), which principally includes electroencephalography (EEG), electrooculography (EOG), and electromyography (EMG), is required for classification of sleep architecture with sleep/wake stages scored based on 30-second periods known as epochs.

The first stage of sleep is almost always N1, which represents the transition from wakefulness to other sleep stages. It comprises less than 5% of total sleep time (TST) and is characterized by EEG waves in the theta range (4–7 Hz). Additional features include slow, conjugate eye movements and vertex sharp waves.\(^3\) N2 comprises roughly a half of TST and is defined by the presence of either K complexes (specifically those unassociated with arousals) or sleep spindles. A person is said to have entered N3, perhaps more commonly known as slow wave sleep, once slow, high-amplitude waves in the delta frequency (0.5–2.0 Hz) are seen over the frontal regions for at least 20% of an epoch. N3 seldom comprises more than 20% TST. REM sleep is characterized by an EEG similar to wakefulness (low amplitude, mixed frequency tracings), with the additional findings of REM on EOG and low tone on chin EMG. REM accounts for roughly a quarter of TST in healthy individuals.\(^3\)

Physiologic sleep involves recurring 1- to 2-hour cycles of varying sleep depth. Initially, a person passes from wakefulness to N1 en route to N2. From here, sleep deepens to N3 then returns to N2 before entering REM. Most NREM sleep is achieved during the first few hours of a sleep period, with REM predominating toward the end of the sleep period. In the ICU, however, altered states of consciousness have been proposed because traditional sleep classification does not encompass findings from PSG among the critically ill.\(^3\) Broadly, these proposals have included states of pathologic wakefulness and atypical sleep. In fact, in a recent PSG study of 37 ICU patients, 85% of all around-the-clock PSG data obtained could not be classified as either traditional wake or sleep based on AASM criteria.\(^3\)

**Two-process model of sleep**

Borbély’s\(^3\) proposed 2-process model of sleep, which consists of a sleep-dependent homeostatic drive and a sleep-independent circadian component (Process S & C, respectively), remains the predominant model to explain sleep coordination. With prolonged sleep restriction, homeostatic drive (Process S) builds to create greater sleep propensity and ultimately deeper sleep: Process S may explain why deeper sleep occurs during the first third of the night. An independent circadian rhythm (Process C) is much more closely allied with the generation and timing of REM sleep.

In the following 2 sections, the authors take these two processes, S and C, in turn. First the effects of sedative agents on traditional sleep stages with an emphasis on NREM are discussed (see Table 1). Next the potential effects of sedatives on circadian rhythm with a broader consideration of 24-hour patterns of psychomotor activity are addressed.
Effects of Sedatives on Sleep Stages

Benzodiazepines
Since the introduction of chlordiazepoxide in 1957, the benzodiazepines have all but entirely supplanted the forerunning barbiturates and have found diverse utility in both inpatient and outpatient settings. Although often incorrectly described as γ-aminobutyric acid (GABA) agonists, benzodiazepines bind at a site distinct from GABA on a ligand-gated chloride ion channel. They serve as positive allosteric modulators of GABA<sub>A</sub> receptors because their binding facilitates the binding of GABA to GABA<sub>A</sub> receptors by way of a conformational change. Indications for benzodiazepines include anxiety, panic disorder, alcohol withdrawal, preoperative apprehension, acute treatment of seizures, muscle spasms, short-term use for insomnia, and, in the case of midazolam, parenteral use for sedation. Common off-label uses include general sedation, acute management of agitation, adjunctive administration for mania, and treatment of acute catatonia. In particular, caution should be exercised in children, older patients, and those with acquired brain injury given the risk of delirium and paradoxical agitation. Later the authors discuss the 3 most common benzodiazepines used in the ICU: lorazepam, midazolam, and diazepam.

Class effects on sleep stages
In general, benzodiazepines increase sleep efficiency (SE; ie, time asleep divided by time in bed), shorten sleep latency (SL; ie, time to fall asleep), suppress REM and N3, and cause a respective increase in percent of TST spent in N2. Benzodiazepines constrict sleep to the theta-frequency range (4–7 Hz) at the expense of restorative slow wave (N3) sleep and memory-consolidating REM sleep. In fact, N3 suppression has been documented on drug-free nights even after one dose of midazolam, triazolam, or flurazepam the night prior. Cerebral blood flow during benzodiazepine sedation differs from that seen with physiologic sleep.

Benzodiazepines may also alter sleep in withdrawal. Sleep fragmentation is a common feature of benzodiazepine withdrawal that may persist for months after the last use. A retrospective review of 28 mechanically ventilated ICU patients demonstrated that after only a few weeks of ICU-level care, patients may be at risk of developing acute withdrawal from sedatives, including benzodiazepines and opioids.

Most deliria are characterized by diffuse slowing of brain waves on EEG, with triphasic waves and spindle comas perhaps representing unique clinical entities. However, benzodiazepines, although deliriogenic, tend to increase the prevalence of fast, β waves and decrease the amplitude of the EEG tracing. Such findings are consistent with their suppression of slow wave sleep.

Midazolam
Although available as an oral formulation outside the US, midazolam is restricted in the US to parenteral use for sedation of intubated or mechanically ventilated patients in the ICU, anesthesia induction, premedication before surgery, or procedural sedation. Studies of midazolam use for sedation in the ICU have uniformly revealed abnormal sleep architecture. In particular, the effects of midazolam on sleep stages in mechanically ventilated patients has been studied comparing 2 different protocols: constant sedation (CS; n = 11) versus daily sedative interruption (DSI; n = 11). In

1 Although alprazolam is sometimes used in critical care settings, its short half-life and potent binding affinity mean that rebound anxiety, abuse liability, and potential for complicated withdrawal including seizures are all increased with this agent. It does not seem to offer significant benefits over the 3 agents discussed here.
this study, midazolam was titrated to achieve a RASS score of –4 to –5 during infusion. All subjects had abnormal sleep architecture, but 24-hour PSG revealed the DSI subjects had greater total duration of N3 (54 vs 0 minutes) and REM (6 vs 0 minutes) relative to CS subjects. The absence of any N3 or REM sleep among CS subjects is striking. Similarly, reportedly optimized midazolam infusion for sleep among 5 ICU subjects resulted in a median of 10-minute REM, no N3 sleep, and a median of 16 awakenings per hour.50 Clearly, midazolam does not promote physiologic sleep.

Lorazepam
As with other benzodiazepines, lorazepam causes a shift toward N2 sleep and suppresses REM. Its sedative effects occur 10 to 40 minutes after peak plasma concentration because of the time required for entrance into the central nervous system,52 and its half-life of 8 to 15 hours precludes minute-to-minute dose titration to achieve a narrowly defined sedation level. Although most of the evidence for lorazepam’s effects on sleep is derived from outpatient settings, bolus lorazepam followed by infusion has been shown to increase $\beta$ frequency on EEG.53 In particular, cumulative daily lorazepam dose equivalents were found to be an independent predictor of severe REM reduction, defined as REM comprising less than 6% of TST, in a cohort of surgical ICU patients.54

In contradistinction to the division between REM and NREM sleep—collectively known as sleep macrostructure—studies have investigated subtle changes in brain wave patterns known as sleep microstructure. One such microstructural parameter, cyclic alternating pattern (CAP), seems to reflect instability of arousal and may detect the effects of ambient noise in situational insomnia.55 In an outpatient study of healthy volunteers, lorazepam was only partly effective at blunting the effects of ambient noise on sleep disruption as reflected in CAP rate. Perhaps studies of sleep microstructure in the ICU would provide valuable information on how sedatives mediate the relationship between ambient stimuli in the ICU and sleep disruption.

Diazepam
Diazepam is seldom used as an infusion for continuous sedation because of its pharmacokinetic properties.56 The parent compound diazepam has a half-life of roughly a day, but its principal metabolite nordiazepam (also known as desmethyldiazepam) has a half-life of more than 120 hours in some individuals. Nordiazepam accrues with repeated dosing, which precludes a reliable steady state. However, for the purposes of its intermittent use in the ICU, intravenous diazepam does exhibit rapid onset of sedative effects.53 Although diazepam causes sleep architecture changes similar to other benzodiazepines, ICU studies of its influence on sleep when used for sedation are lacking.

Opioids
Opioids serve as agonists at the $\mu$, $\delta$, and/or $\kappa$ opioid receptors; however, their principal mechanism for sedation and analgesia occurs via $\mu$ opioid agonism. A fairly limited literature describes the effects of opioids on sleep architecture,57 and much of this literature has been conducted in prisoners with heroin addiction or in patients with chronic pain with an emphasis on cancer-related pain.58 Studies of opioid-induced sleep changes generally do not attempt to disentangle intrinsic physiologic effects versus sleep changes effected by analgesia.

Studies before 1990 identified REM suppression as the most consistent effect of morphine, methadone, and heroin on sleep architecture.57 Additional findings have included increased REM latency, decreased TST, and suppression of N3. However, these findings are difficult to interpret given that standardized Rechtschaffen and
Kales\textsuperscript{31} sleep scoring was not performed in these studies, and all but one of these small studies was conducted in prisoners. Beyond direct effects on sleep architecture, opioids may cause central sleep apnea (CSA) by way of respiratory suppression. Opioids cause dose-dependent reductions in central respiratory drive, which leads to hypoxia and hypercapnia,\textsuperscript{59} an effect additive with benzodiazepines. It is unclear how clinically relevant CSA is in the ICU given the ready availability of ventilatory support; however, CSA may influence ventilator settings.

**Morphine**

In a rare placebo-controlled sleep study of opioids, Dimsdale and colleagues\textsuperscript{60} investigated the PSG effects of single-dose sustained-release morphine and methadone in healthy subjects. In this 3-night crossover trial (\(n = 46\)), both sustained-release morphine 15 mg and methadone 5 mg at bedtime reduced N3 (7.6 minutes, 7.1 minutes, 11.7 minutes, respectively) and increased N2 (61.3 minutes, 63.8 minutes, 58.5 minutes, respectively) relative to placebo. This study did not reveal REM suppression or changes in either TST or wake after sleep onset.\textsuperscript{60} An additional modern crossover placebo-controlled trial of 7 nonaddicted, pain-free subjects found that intravenous morphine 0.1 mg/kg reduced N3 and REM sleep while increasing the total time spent in NREM.\textsuperscript{61} Data on whether morphine exerts significant effects on REM sleep remain equivocal.

**Fentanyl**

Fentanyl’s lipophilic properties can lead to accumulation in fat stores with sustained use. Fentanyl may exert a more pronounced effect on consciousness than morphine, particularly at higher doses.\textsuperscript{62} Clear conclusions on fentanyl’s sleep-related effects in the ICU are typically confounded by coadministration of numerous other compounds. For instance, postoperative REM rebound has been documented in patients who received fentanyl in combination with thiopental, nitrous oxide, and isoflurane as anesthesia,\textsuperscript{63} although the relative contribution of each anesthetic agent is difficult to differentiate. Additional analysis of postoperative nights supports an inverse relationship between morphine dose and REM sleep time.\textsuperscript{65} Some studies convert fentanyl doses into morphine equivalents,\textsuperscript{64} and others are unable to attribute independent effects of fentanyl given limited power.\textsuperscript{65} Of note, a randomized study of fentanyl patient-controlled analgesia (PCA) versus alfentanil/morphine PCA found the latter regimen was better for analgesia only during the first 24 postoperative hours; but subjective reports of pain-related sleep disturbance was not statistically different between groups.\textsuperscript{66}

**Hydromorphone**

Discussion of hydromorphone’s effects on sleep is very limited in the literature. Like fentanyl, hydromorphone is often one of several sedatives included in a study of critical care patients\textsuperscript{67}; but such studies do not allow for conclusions regarding its independent effects on sleep.

**Propofol**

Only recently was the propofol binding site on \(\beta_3\) subunits of GABA\(_A\) receptor-complexes described,\textsuperscript{68} but additional findings suggest ancillary roles for glutamate modulation and cannabinoid activity in propofol’s unique sedative properties.\textsuperscript{69} Propofol may rarely cause a potentially fatal condition known as propofol infusion syndrome, characterized by refractory bradycardia plus at least one of the following: metabolic acidosis, rhabdomyolysis, hyperlipidemia, or hepatomegaly.\textsuperscript{70}
Propofol causes regional, dose-dependent EEG effects. Unique among sedatives, it induces γ waves (35–55 Hz) on EEG, which are faster than the β waves strengthened by benzodiazepines. Enhanced gamma power originating from the cingulate cortex seems to occur with low- and high-dose propofol, but dose-dependent emergence of slow wave activity resembling NREM sleep has been documented. With escalating doses, propofol causes a burst-suppression pattern. Propofol sedation to loss of consciousness is associated with a greater than 50% reduction in cerebral glucose metabolism, a metabolic change roughly twice as pronounced as seen in physiologic sleep.

The effect of propofol on sleep has been studied using overnight EEG among the critically ill. In this 2-night crossover study, 12 patients on assisted ventilation were administered either propofol titrated to a Ramsay scale score of 3 or no overnight sedation. During propofol nights, EEG revealed decreased REM sleep; but no differences were identified in SE, sleep fragmentation, or NREM sleep distribution. Although its applicability to critical care settings is unclear, 2-hour propofol infusions for 5 nights has been demonstrated to aid in normalization of sleep in patients with chronic primary insomnia. Both on the first night following a 5-night propofol protocol and 6 months after therapy, subjects randomized to propofol had a greater proportion of N3 and REM than those who had received saline infusion.

**Dexmedetomidine**

The only α2 agonist approved for parenteral use in the United States, dexmedetomidine has been of interest to intensivists because it causes sedation, anxiolysis, and analgesia, though not as effective as opioids, without respiratory suppression. It binds α2-adrenergic receptors in the locus ceruleus, inhibiting norepinephrine release. This sympatholysis disinhibits the arousal-suppressing neurons in the ventrolateral preoptic area ultimately leading to sedation. Its 2-hour half-life allows for effective dose titration, and its absence of active metabolites prevents accumulation with extended use. Devoid of GABAergic activity, dexmedetomidine is associated with less delirium risk than midazolam or propofol.

In a 24-hour PSG study of ventilated ICU patients (n = 10), dexmedetomidine was associated with relative preservation of gross sleep–wake cycle, as 78% of sleep occurred overnight likely owing to DSI. However, dexmedetomidine-induced sleep exhibited exclusively N1 and N2 stages and revealed significant fragmentation (9 arousals or awakenings an hour). In healthy subjects (n = 11), dexmedetomidine sedation induces a state similar to N2 sleep as evidenced by a similar prevalence of sleep spindles on EEG, a conclusion further supported by functional MRI. Patients sedated with dexmedetomidine are more easily aroused than patients on most other sedatives. In this regard, dexmedetomidine sedation is much more akin to physiologic sleep, which is defined as a state of reversible loss of consciousness. This feature likely explains how patients sedated with dexmedetomidine are more easily weaned off mechanical ventilation. Nevertheless, patient reports seem to favor propofol over dexmedetomidine for sleep quality in critical care settings.

**Neuroleptics**

This class of agents, also described with the terms typical and atypical antipsychotics, is perhaps best described as neuroleptics (from lepsis, Greek “to seize”), particularly because their use extends far beyond the management of psychosis. They are not sedatives in a traditional sense, but their historical designation as major tranquillizers speaks to their ataractic properties. They are commonly used in critical care settings for the management of agitation and hyperactive delirium. Data on the sleep-related
effects of neuroleptics are derived principally from studies including patients with acute mental illness. Previously reviewed, the impact of neuroleptics on the sleep architecture in schizophrenia may provide some insight into their global effects on sleep. They demonstrate relatively consistent improvements in sleep continuity, TST, and SE among patients with primary psychotic illness.

**Haloperidol**

In a 5-day crossover trial of healthy volunteers ($n = 20$), morning haloperidol increased NREM sleep, particularly N2, and enhanced SE; but such findings are difficult to interpret because haloperidol was administered in the morning, more than 15 hours before sleep onset. As previously discussed, studies in patients with schizophrenia suggest that haloperidol may improve the shortened REM latency and sleep fragmentation typically seen in this condition; but the effects of haloperidol on sleep vary with clinical status of psychotic symptoms. Additionally, haloperidol may work synergistically with sleep deprivation in enhancing the phasic generation of saw tooth waves in REM sleep. Overall, haloperidol does not seem to cause pronounced REM or N3 suppression.

**Atypical neuroleptics**

Atypical (or second generation) neuroleptics commonly used in critical care settings include risperidone, quetiapine, and olanzapine. Subjective sleep quality is generally more improved on atypical neuroleptics than on typicals, and somnolence is a common feature of quetiapine and olanzapine in particular because of histamine (H1) receptor antagonism.

Olanzapine is often used in acute medical settings for its ability to mollify agitation. Because sleepiness is a common side effect, it is often given at bedtime. In healthy male volunteers, bedtime olanzapine at 5 and 10 mg has been shown to increase N3 while suppressing REM sleep and increasing REM latency. In a separate study of healthy volunteers, a single bedtime dose of olanzapine 10 mg increased N3 and prolonged REM latency, findings more pronounced in women ($n = 6$) than in men ($n = 7$), but caused insignificant effects on REM duration. Additionally, in the crossover study of morning-dosed haloperidol cited earlier, subjects were also assigned to receive olanzapine and risperidone in random order on separate nights. Morning olanzapine was associated with increased TST, SE, N3 sleep, and REM sleep on the night of administration, whereas risperidone led to decreased wake time, REM suppression, and a shift toward greater N2 sleep. Studies in patients with schizophrenia and bipolar disorder who are manic also attest to olanzapine’s enhancement of NREM and overall sleep maintenance. Olanzapine seems to have a unique profile on sleep in that it enhances N3, and inconsistent data suggest that it may have limited effects on REM sleep.

Quetiapine is used in critical care settings for the management of agitation and delirium. Like olanzapine, quetiapine also tends to cause sleep as a side effect. In a double-blind placebo-controlled study of healthy subjects, bedtime quetiapine at 25 or 100 mg increased TST, SE, percent in N2 sleep, and subjective sleep quality; however, the 100-mg dose was noted to worsen periodic leg movements during sleep. Studies of quetiapine for the management of major depression, bipolar depression, and primary insomnia have found quetiapine to also have hypnotic properties.

**EFFECTS OF SEDATIVES ON CIRCADIAN RHYTHMS**

Circadian rhythms describe recurring 24-hour cycles of psychomotor and physiologic activity; dozens of studies have investigated circadian rhythm disturbances among the...
critically ill, for which the authors use the term *circadian arrhythmias*. Common circadian arrhythmias in the ICU include pathologic wakefulness and nonrestorative daytime sleep, atypical sleep and nocturnal sleep fragmentation, near absence of REM or N3 sleep, blunted amplitude of circadian rhythms, and circadian phase delay. Unfortunately, most of these studies are not sufficiently powered or explicitly designed to isolate the effects of sedation, much less the effect of any particular agent on circadian rhythm. Such studies are generally observational and use a variety of sedation strategies: different sedative agents and doses, varying patient populations, and different timing (continuous vs intermittent; daytime sedation interruption or not). In this section, the authors turn to studies of circadian rhythm in critical care settings and extract from a limited evidence base regarding what is known about the effect of sedation on circadian rhythms.

Tables 2 and 3 present real-world observational ICU studies of circadian markers, such as core body temperature, blood pressure, actigraphy, cortisol, serum melatonin, and its metabolite 6-sulftatoxymelatonin (6-SMT), in which sedatives are at the very least listed. A surprising proportion of studies on circadian rhythm fail to provide any information on current medications despite the fact that many agents, sedatives in particular, not only influence sleep parameters (see earlier section) but also directly alter melatonin and other physiologic parameters often used to study circadian rhythms, such as core body temperature.

### Effects of Sedatives on Melatonin

Both opioids and benzodiazepines influence melatonin release. Opioids are generally understood to increase melatonin perhaps by way of opioid receptors in the pineal gland.121 In particular, studies of diazepam,122 alprazolam,123 and flunitrazepam124 suggest that benzodiazepines decrease melatonin levels. The differential effects of opioids and benzodiazepines on melatonin levels leaves one to wonder what the resultant effect of concurrent opioids and benzodiazepines on melatonin release is, particularly because they are often used concurrently in the ICU. Further, one is left to speculate about the potential for a melatonin rebound after benzodiazepine washout or whether melatonin levels may dip after opioid use because of temporary pineal depletion. An additional pharmacologic consideration in studies of melatonin and 6-SMT derives from the fact that melatonin is released via β-agonism. Vasopressors, positive inotropes, and aerosolized β-agonists, such as albuterol, tend to increase melatonin levels; conversely, β-blockers may decrease melatonin secretion. All future ICU studies of circadian rhythm should report medications being used in study subjects.

### Isolating the Effect of Sedatives on Circadian Rhythm

Even conscious, nonsedated ICU patients demonstrate very significant disruption in rest–activity cycles. In an observational study of using 24-hour actigraphy and urinary 6-SMT as an outcome measure, 14 conscious ICU subjects were found to be restless around the clock.109 Subjects exhibited dramatic fragmentation of physiologic rest patterns: no subject experienced an hour of sustained rest over a period of up to 72 hours. Shilo and colleagues109 specified that subjects were not on opioids, β-blockers, or other “drugs known to affect melatonin secretion.”109 Presuming that this includes benzodiazepines, these subjects reveal that even nonsedated ICU patients may often experience a circadian arrhythmia. Therefore, being able to isolate the effects of sedatives on circadian rhythm requires dedicated analysis.

Of the studies listed in Table 1, the study by Frisk and colleagues113 may be the most illuminating. In this study of 16 ICU subjects, urinary 6-SMT and cortisol levels
<table>
<thead>
<tr>
<th>Sedative Agent (Proprietary Name)</th>
<th>Dosing</th>
<th>Mechanism of Action</th>
<th>Pharmacokinetics</th>
<th>Effects on Sleep Architecture</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midazolam (Versed)</td>
<td>1–5 mg IVP, 1–5 mg/h gtt</td>
<td>Positive allosteric modulator of GABA&lt;sub&gt;A&lt;/sub&gt; receptor</td>
<td>3–11 h t&lt;sub&gt;1/2&lt;/sub&gt;</td>
<td>↓ REM, ↓ N3, ↑ %N2</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>2- to 5-min onset</td>
<td>Enhances β waves</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Phase I metabolism</td>
<td>May ↑ SE and ↓ SL</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Active metabolite</td>
<td></td>
</tr>
<tr>
<td>Lorazepam (Ativan)</td>
<td>1–4 mg IVP, 1–5 mg/h gtt</td>
<td></td>
<td>8- to 15-h t&lt;sub&gt;1/2&lt;/sub&gt;</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>≥ 10-min onset</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Phase II (including extrahepatic) metabolism</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>No active metabolites</td>
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<td></td>
<td>24- to 120-h t&lt;sub&gt;1/2&lt;/sub&gt;</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>5-min onset</td>
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<td></td>
<td></td>
<td></td>
<td>Phase I metabolism</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Nordazepam accrues</td>
<td></td>
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<tr>
<td>Diazepam (Valium)</td>
<td>1–5 mg IVP</td>
<td></td>
<td>24- to 120-h t&lt;sub&gt;1/2&lt;/sub&gt;</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>5-min onset</td>
<td></td>
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<td></td>
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<td></td>
<td>Phase I metabolism</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Nordazepam accrues</td>
<td></td>
</tr>
<tr>
<td>Morphine (Roxanol; Duramorph)</td>
<td>1–5 mg/h gtt, 2–5 mg IVP (for loading)</td>
<td>μ (κ and δ to lesser extent) opioid receptor agonists</td>
<td>3–7 h t&lt;sub&gt;1/2&lt;/sub&gt;</td>
<td>↓ N3, ↑ %N2</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Slower onset than fentanyl</td>
<td>Likely ↓ REM</td>
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<td></td>
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<td></td>
<td>Phase II metabolism</td>
<td>May ↑ REM latency &amp; ↓ TST</td>
</tr>
<tr>
<td>Fentanyl (Sublimaze)</td>
<td>20–100 μg/h gtt, 50–100 μg IVP (for loading)</td>
<td></td>
<td>1.5- to 6.0-h t&lt;sub&gt;1/2&lt;/sub&gt;</td>
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<td></td>
<td>&lt;5-min onset</td>
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<td>Phase II metabolism</td>
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<td></td>
<td>Lipophilic: accrues in fat</td>
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<tr>
<td>Hydromorphone (Dilaudid)</td>
<td>0.5–2 mg/h gtt, 0.4–1.5 mg IVP (for loading)</td>
<td></td>
<td>1.5- to 3.5-h t&lt;sub&gt;1/2&lt;/sub&gt;</td>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Phase II metabolism</td>
<td></td>
</tr>
<tr>
<td>Drug</td>
<td>Dosage</td>
<td>Effects</td>
<td>Metabolism</td>
<td>Side Effects</td>
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<tr>
<td><strong>Propofol</strong> (Diprivan)</td>
<td>50–200 mg/h gtt</td>
<td>Bind to $\beta_3$ of GABA$_A$; additional effects on glutamate and cannabinoid receptors</td>
<td>30- to 60-min t$_{1/2}$</td>
<td>↓ REM Enhances $\gamma$ waves &amp; dose-dependent burst suppression May not affect SE or NREM</td>
</tr>
<tr>
<td></td>
<td>1–3 mg/kg/h gtt</td>
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<tr>
<td><strong>Dexmedetomidine</strong> (Precedex)</td>
<td>0.2–1.5 $\mu$g/kg/h</td>
<td>$\alpha_2$ agonist</td>
<td>2-h t$_{1/2}$</td>
<td>↓ REM, ↓ N3 Enhances N2 spindle activity</td>
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<tr>
<td><strong>Haloperidol</strong>&lt;sup&gt;a&lt;/sup&gt; (Haldol)</td>
<td>1–10 mg IVP&lt;sup&gt;b&lt;/sup&gt;</td>
<td>D$_2$ receptor antagonist</td>
<td>14- to 30-h t$_{1/2}$</td>
<td>↑ N2, ↑ SE Limited effects on REM or N3</td>
</tr>
<tr>
<td></td>
<td>1–10 PO</td>
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<td></td>
<td>1–10 mg IM</td>
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<tr>
<td><strong>Risperidone</strong>&lt;sup&gt;c&lt;/sup&gt; (Risperdal; Risperdal M-Tab)</td>
<td>1–6 mg PO</td>
<td>D$_2$ and 5-HT$_2$ receptor antagonists</td>
<td>20- to 30-h t$_{1/2}$</td>
<td>↓ REM, ↑ %N2</td>
</tr>
<tr>
<td></td>
<td>1–6 mg ODT</td>
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<td></td>
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<tr>
<td><strong>Olanzapine</strong>&lt;sup&gt;e&lt;/sup&gt; (Zyprexa; Zyprexa Zydis)</td>
<td>2.5–10 mg PO</td>
<td></td>
<td>20- to 50-h t$_{1/2}$</td>
<td>↑ N3, equivocal REM effects May ↑ TST and ↑ SE</td>
</tr>
<tr>
<td></td>
<td>5–10 mg ODT&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.5–10 mg IM&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>Quetiapine</strong>&lt;sup&gt;a&lt;/sup&gt; (Seroquel)</td>
<td>12.5–100 mg PO</td>
<td></td>
<td>6-h t$_{1/2}$</td>
<td>↑ %N2, ↑ SE, ↑ TST</td>
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</tr>
</tbody>
</table>

Abbreviations: %N2, percent of total sleep time spent in N2; gtt (guttae for drops), intravenous infusion; IM, intramuscular; IVP, (intravenous push), intravenous bolus; ODT, orally disintegrating tablet; PO, by mouth; t$_{1/2}$, half-life.

<sup>a</sup> All neuroleptics carry a black box warning for “increased mortality in elderly patients with dementia-related psychosis.” Also, the use of neuroleptics for the management of general agitation, delirium, or sleep disturbances in the ICU is off-label.

<sup>b</sup> Haloperidol is not approved by the Food and Drug Administration for intravenous use; however, this route of administration is commonly used off-label in hospitals across the United States.

<sup>c</sup> Olanzapine is available as an orally disintegrating tablet under the brand name Zyprexa Zydis. The traditional 5-mg tablet can be broken in half to administer 2.5 mg, but the 5 mg ODT is too fragile for this purpose.

<sup>d</sup> Intramuscular olanzapine causes significant respiratory suppression and in general should not be administered with parenteral benzodiazepines unless a patient is on mechanical ventilation.
### Table 3
**Observational studies of circadian rhythms in the ICU in which sedative use is described**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Population</th>
<th>Sedation</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dauch &amp; Bauer, 1990</td>
<td>31 ICU subjects with severe cerebral lesions</td>
<td>20 On sedation (no further description provided) 8 Received muscle relaxants</td>
<td>Nonexistence of physiologic CR measured by core body temperature associated with acute lesion, decreased level of consciousness, and neurologic findings No analysis of sedative effects on outcomes</td>
</tr>
<tr>
<td>Nuttall et al, 1998</td>
<td>137 ICU subjects after thoracic or vascular operation: 17 with ICU psychosis and 120 without</td>
<td>All subjects: fentanyl epidural (plus midazolam during intubation for surgery) Specific sedatives listed only for ICU psychosis subjects</td>
<td>Cosinar rhythmometry of temperature and urinary output nadir randomly distributed around the clock for up to postoperative d 3 in most patients; no statistically significant difference between groups No analysis of sedative effects on outcomes</td>
</tr>
<tr>
<td>Shilo et al, 1999</td>
<td>14 Conscious ICU subjects</td>
<td>No β-blockers, opiates, or other “drugs known to affect melatonin secretion”</td>
<td>24-h Actigraphy revealed no quiescent period longer than an h, and urine 6-SMT lacked physiologic nocturnal peak relative to non-ICU controls</td>
</tr>
<tr>
<td>Shiihara et al, 2001</td>
<td>1 ICU subject</td>
<td>Midazolam and fentanyl over discrete period</td>
<td>Continuous monitoring of skin potentials; reduced skin conductance concurrent with sedation</td>
</tr>
<tr>
<td>Mundigler et al, 2002</td>
<td>24 ICU subjects: 17 septic 7 nonseptic 23 rehab subjects</td>
<td>17 of 17 septic and 1 of 7 nonseptic subjects on sufentanil and midazolam No subject on β-blocker 17 of 17 septic and 3 of 7 nonseptic ICU subjects MV</td>
<td>Preserved CR (q4 h urinary 6-SMT): 1 of 17 septic ICU, 6 of 7 nonseptic ICU, and 18 of 23 controls</td>
</tr>
<tr>
<td>Olofsson et al, 2004</td>
<td>8 ICU subjects: 5 of 8 septic</td>
<td>All sedated: most on midazolam/fentanyl; remainder on propofol/fentanyl</td>
<td>7 of 8 Without discernible CR of q4 h serum MT over 72 h No association of serum MT with sedation level</td>
</tr>
<tr>
<td>Frisk et al, 2004</td>
<td>16 ICU subjects: 16 of 16 intubated</td>
<td>Use of benzodiazepines, propofol, opioids, cortisol,</td>
<td>75% Subjects lost CR (urinary 6-SMT and cortisol) periodically; 65% lost CR consistently</td>
</tr>
</tbody>
</table>
Multiple regression analysis of factors on CR:
MV (F = 66): decrease urinary 6-SMT
Benzodiazepine (F = 18): increase urinary 6-SMT
Adrenergic (F = 10): increase urinary 6-SMT
Cortisone (F = 39): increase urinary cortisol
Propofol (F = 5): decrease urinary cortisol

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Study Population</th>
<th>Interventions</th>
<th>CR (measured by Chronos-Fit program), including serum MT, serum cortisol, diurnal blood pressure &amp; heart rate variation, actigraphy, and core body temperature, severely degraded, worse in cerebral injury group</th>
<th>Unable to isolate independent effect of sedation as all subjects sedated and ventilated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paul &amp; Lemmer</td>
<td>2007</td>
<td>24 ICU subjects: 11 cerebral injury, 13 without</td>
<td>All: benzodiazepine/fentanyl, inotropic support, 23 of 24 MV, 1 of 24 assisted ventilation, No β-blockers or corticosteroids</td>
<td>CR (measured by Chronos-Fit program), including serum MT, serum cortisol, diurnal blood pressure &amp; heart rate variation, actigraphy, and core body temperature, severely degraded, worse in cerebral injury group</td>
<td>Unable to isolate independent effect of sedation as all subjects sedated and ventilated</td>
</tr>
<tr>
<td>Perras et al</td>
<td>2007</td>
<td>15 ICU subjects: 5 high MT, 15 low MT</td>
<td>Opioid: 5 of 5, 9 of 15 Benzo-diazepine: 2 of 5, 7 of 15 Norepinephrine: 2 of 5, 8 of 15 Steroid: 4 of 5, 5 of 15</td>
<td>An h of 10,000 lux light overnight had limited effect on serum MT</td>
<td>Sample size precludes conclusions on medication effect</td>
</tr>
<tr>
<td>Riutta et al</td>
<td>2009</td>
<td>40 ICU nonseptic subjects</td>
<td>25 of 40: benzodiazepines, 14 of 40: other sedatives (mostly haloperidol), 20 of 40: opioids, 12 of 40: β-blockers, 20 of 40: MV</td>
<td>Urinary 6-SMT q6 h were higher at night than during the day and serum cortisol at noon greater than at midnight, both suggesting gross CR preservation</td>
<td>Gross CR preservation (urinary 6-SMT &amp; serum cortisol) among the 25 subjects receiving benzodiazepines, although doses and timing of administration not discussed; effect of other sedatives, opioids, and MV on CR not discussed</td>
</tr>
<tr>
<td>Lazreg et al</td>
<td>2011</td>
<td>22 ICU subjects: 12 comatose, 10 conscious</td>
<td>Limited information on sedatives, 4 of 12 comatose subjects on phenobarbital</td>
<td>Comatose subjects had greater preservation of CR in core body temperature and blood counts than noncomatose subjects</td>
<td>No analysis of sedative effects on outcomes</td>
</tr>
</tbody>
</table>

(continued on next page)
<table>
<thead>
<tr>
<th>Reference</th>
<th>Population</th>
<th>Sedation</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verceles et al,118 2012</td>
<td>7 ICU subjects with severe sepsis</td>
<td>Medications that influence MT noted</td>
<td>Urinary 6-SMT revealed degradation of CR in all subjects</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 of 7: propofol</td>
<td>No analysis of sedative effects on outcomes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 of 7: dexmedetomidine</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 of 7: β-blocker</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>2 of 7: corticosteroid</td>
<td></td>
</tr>
<tr>
<td>Gehlbach et al,119 2012</td>
<td>22 ICU subjects</td>
<td>All sedated(^a) on MV</td>
<td>Urinary 6-SMT (16 subjects with data): grossly preserved CR in 13 of 16</td>
</tr>
<tr>
<td></td>
<td></td>
<td>All: opioid</td>
<td>but generally exhibited phase delay</td>
</tr>
<tr>
<td></td>
<td></td>
<td>18 of 22: propofol</td>
<td>PSG (21 subjects with data): REM sleep in 2 of 21; slow wave sleep lack</td>
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<td>5 of 22: benzodiazepine</td>
<td>physiologic variation; spectral edge frequency 95% consistently low</td>
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<td></td>
<td>without diurnal variation (ie, around-the-clock low level of consciousness)</td>
</tr>
<tr>
<td>Yoshitaka et al,120 2013</td>
<td>40 Postoperative ICU subjects:</td>
<td>Delirium: 9 of 13 (69%) on MV (with continuous propofol)</td>
<td>Change in MT 1 h after surgery predicted postoperative delirium</td>
</tr>
<tr>
<td></td>
<td>13 with delirium</td>
<td>(with continuous propofol)</td>
<td>(OR 0.5 [0.26, 0.99]).</td>
</tr>
<tr>
<td></td>
<td>27 no delirium</td>
<td>No delirium: 10 of 27 (37%) on MV (also with propofol)</td>
<td>The point estimate OR of MV (hence, also of sedation) for postop</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Non-MV subjects received morphine PCA</td>
<td>delirium was 14.1, but a wide confidence interval (0.38, 519.2) precludes</td>
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<td></td>
<td></td>
<td></td>
<td>statistical significance</td>
</tr>
</tbody>
</table>

**Abbreviations:** CR, circadian rhythm; Benzo, benzodiazepines; MT, melatonin; MV, mechanical ventilation; OR, odds ratio; postop, postoperative; rehab, rehabilitation; 6-SMT, 6-sulftatoxymelatonin.

\(^a\) Daytime sedation interruption.
were obtained every 4 hours to evaluate for circadian rhythmicity. At the time of each measurement, researchers recorded whether that subject had received benzodiazepines, propofol, opioids, cortisone, adrenergic agents, or were on mechanical ventilation (MV) over the preceding 4 hours. These 342 data points served as the basis for a multiple regression analysis of factors affecting urinary 6-SMT or cortisol. They revealed that the single-most significant feature associated with 6-SMT level was MV, which was associated with decreased 6-SMT. Consistent with data in healthy subjects, benzodiazepines were independently associated with suppressed 6-SMT excretion; propofol was associated with a fairly weak but still statistically significant decrease in urinary cortisol. Opioids were not associated with significant alteration in urinary 6-SMT or cortisol (Frisk and colleagues,113 2004).

REM sleep is closely allied with circadian rhythms or the process C of sleep,125 and as discussed previously benzodiazepines suppress REM sleep in healthy individuals. In fact, a dose-dependent relationship between benzodiazepine use and REM reduction has been documented in a surgical ICU.54 In this study of overnight PSG, Trompeo and colleagues54 stratified subjects into REM reduction or severe REM reduction based on whether REM sleep comprised greater or less than 6% of TST, respectively. REM sleep accounted for an average of 44 minutes in the REM reduction group (n = 14) versus a mean of 2.5 minutes in the severe REM reduction group (n = 15). A statistically significant, 10-fold difference in average daily lorazepam equivalents was identified between groups: 0.001 mg/kg/h (~1.8 mg in 24 hours presuming 70-kg subjects) among REM reduction subjects and 0.01 mg/kg/h among those with severe REM reduction.

Limitations of the Literature and Future Considerations

Although all ICU studies of circadian rhythms should include data regarding all potentially contributory factors (eg, medications, medical conditions, lighting and sound conditions, number of care interruptions, and so forth), enrollment of fairly small cohorts precludes statistically significant conclusions regarding the effects of sedatives on circadian rhythm.107,108,110,117,120,126 For instance, an observational study of 40 nonseptic ICU subjects, half of whom were intubated, found that overnight urinary 6-SMT were generally higher than daytime values (Riutta and colleagues,116 2009), which is the expected circadian pattern. The authors further described that this pattern of elevated nightly urinary 6-SMT was seen among the 25 subjects on benzodiazepines concluding that “benzodiazepine treatment did not abolish the diurnal periodicity of [6-SMT] excretion.”116 However, in the absence of power calculations and appropriate statistical considerations of significance, such conclusions seem premature. Further, given that the effects of sedatives on circadian rhythm are likely to be dose related, correlational analysis that accounts for sedative dosing or sedation level on circadian rhythm outcomes would likely serve as meaningful outcomes.

On the other end of the spectrum are studies wherein all subjects are on continuous sedation with both opioids and GABAergic agents, that is, either benzodiazepines or propofol.114 In such studies, providing information on cumulative doses and the timing of dose adjustments would further elucidate the effect of sedation on circadian rhythm. Finally, where sedatives are being administered, perhaps their administration based on categorical time blocks may be meaningful (eg, medications administered from 12–4 AM, 4–8 AM, 8 AM to 12 PM, and so forth). Such information would help to create correlations between medication administration and circadian rhythm outcomes because the timing of these outcomes is an inherently meaningful aspect of the assessment, namely, circadian rhythm.
The use of DSI deserves particular mention, particularly because its influence on circadian rhythms is at once both clinically apparent (patients are more alert and can be more participatory in care during the day and more restful at night) and likely confounding. For instance, Gehlbach and colleagues\textsuperscript{119} conducted a study of 22 intubated ICU subjects who were all sedated using a DSI protocol. Gross preservation of circadian excretion of 6-SMT was observed in the 16 subjects for whom data were available; however, the degree to which a DSI protocol is directly responsible for circadian rhythm preservation remains unclear in the absence of a comparator group.

**SUMMARY**

Our understanding of the importance of sleep on recovery of patients who experience critical illness is still in its infancy. Although there is biological plausibility regarding the impact and importance of sleep in ICU patients, especially related to immune dysfunction, infection risk, prolonged length of MV, and delirium development and duration, there are little published data. Our understanding of how the medications we use in the ICU for pain, sedation, or delirium impact circadian rhythm is limited by several factors. The first challenge is our ability to easily and accurately measure circadian rhythm in an ICU setting. The second challenge is determining the impact of critical illness itself on circadian rhythm alterations. The third challenge is determining the impact various medications may have on circadian rhythm after adjusting for the multitude of confounding factors.

Despite the challenges of caring for critically ill patients, following the recommended guidelines for PAD, paying attention to early mobilization and sleep hygiene and individualizing patient care as needed, should lead to the best outcomes for patients. In addition future research studies should continue to inform our practice regarding treatment of PAD in the ICU.

**REFERENCES**


