Top 10 Myths Regarding Sedation and Delirium in the ICU

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Abstract: The management of pain, agitation, and delirium in critically ill patients can be complicated by multiple factors. Decisions to administer opioids, sedatives, and antipsychotic medications are frequently driven by a desire to facilitate patients' comfort and their tolerance of invasive procedures or other interventions within the ICU. Despite accumulating evidence supporting new strategies to optimize pain, sedation, and delirium practices in the ICU, many critical care practitioners continue to embrace false perceptions regarding appropriate management in these critically ill patients. This article explores these perceptions in more detail and offers new evidence-based strategies to help critical care practitioners better manage sedation and delirium, particularly in ICU patients. (*Crit Care Med* 2013; 41:S46–S56)

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Sedation and analgesia practices in conjunction with delirium reduction measures in critically ill patients have been evolving processes. Over the last two decades, therapeutic interventions have changed coinciding with new trials and published evidence. The positive benefits of spontaneous awakening trials (SATs), spontaneous breathing trials (SBTs), and the implementation of early mobility in critically ill patients have all been demonstrated (1–3). In addition, investigators and clinicians have further defined the prevalence and consequences of ICU-induced delirium (4–7).

In January 2013, the American College of Critical Care Medicine/Society of Critical Care Medicine (SCCM) released the pain, agitation, and delirium (PAD) guidelines that provide a broad synopsis of PAD interventions aimed at improving short- and long-term outcomes in ICU patients (8). Traditional approaches to managing pain, sedation, and delirium in ICU patients may be at odds with several of the PAD guideline recommendations and can lead to poor ICU patient outcomes. Widespread adoption of the PAD guidelines will require significant efforts to overcome these perceptions or "myths" with intensive provider education and retooling of ICU PAD practice patterns. The primary objective of this article is to explore the basis of these myths regarding sedation and delirium in ICU patients and to provide alternative evidence-based strategies in order to help ICU clinicians improve the management of pain, sedation, and delirium in critically ill patients in an integrated and interdisciplinary fashion, based on the recommendations included in the 2013 ICU PAD guidelines.

SEDATION AND ANALGESIA MANAGEMENT IN THE ICU

Myth 1: All Mechanically Ventilated ICU Patients Require Sedatives

A common perception concerning the critically ill is that all patients who require mechanical ventilation should receive sedative medications. Sedatives, including benzodiazepines, propofol, and dexmedetomidine, are routinely administered to ICU patients in conjunction with opioids in order to allay patients' anxiety, reduce recall of unpleasant ICU experiences, improve patient tolerance of mechanical ventilation,

suppress hyperadrenergic responses, and provide treatment for substance withdrawal (8–10). Additionally, sedatives may also be indicated for treating patients with status epilepticus, increased intracranial pressure, acute psychiatric illness, or for patients receiving neuromuscular blocking agents for any reason (9). But the administration of sedative agents is also associated with undesirable short- and long-term outcomes in these patients. Short-term side effects include respiratory depression, hemodynamic instability, or metabolic acidosis and vary with the type and dose of sedative used. Sustained use of sedatives can prolong mechanical ventilation, increase ICU length of stay (LOS), and increase the likelihood of ICU patients developing acute delirium (11, 12). A meta-analysis investigating outcomes related to ICU sedation showed that benzodiazepines (i.e., midazolam and lorazepam) are associated with a longer ICU LOS than nonbenzodiazepines (i.e., propofol and dexmedetomidine). An updated version of this meta-analysis, published by Fraser et al (13) in this supplement, confirmed this finding, while simultaneously showing that benzodiazepines are associated with a prolonged duration of mechanical ventilation compared to nonbenzodiazepines when used for sedation. Benzodiazepine-based sedation in ICU patients has also been linked to long-lasting psychiatric comorbidities, including posttraumatic stress disorder (PTSD) and depression. A study of 157 adult ICU patients found that the strongest clinical risk factor for developing PTSD after hospital discharge was the prolonged administration of sedative medications (14). Patients who received benzodiazepines for sedation in particular were also more likely to experience depression at 3 months after they were discharged from the ICU. Given the risks associated with sedative medications in the ICU population, clinicians must carefully assess the risk/benefit ratio of their use in these patients.

The question that this issue raises is: Can an ICU patient receiving mechanical ventilation be safely managed primarily using opioids with little, if any, sedative medications (i.e., an analgesia-first strategy)? Perhaps the best-known study designed to address this question was published by Strøm et al (15), who randomly assigned 140 medical and surgical ICU patients undergoing mechanical ventilation to receive either a protocol of no sedation (primarily IV morphine boluses of 2.5–5 mg, with allowances for either IV haloperidol boluses or rescue propofol infusions for 6-hr periods) or a regimen of sedation (IV propofol infusion titrated to a Ramsay score of 3–4 for a maximum of 48 hr, followed by an IV midazolam infusion thereafter, with IV morphine boluses of 2.5–5 mg as needed), with daily sedation interruptions until patients awoke. Patients in the no-sedation group had significantly more days without mechanical ventilation than patients in the sedation cohort (mean difference = 4.2 d; 95% CI, 0.3–8.1; $p = 0.02$). Patients in the no-sedation group also experienced a significantly shorter ICU LOS (hazard ratio, 1.86; 95% CI, 1.05–3.23; $p = 0.03$), but they also experienced higher rates of hyperactive delirium (20% vs 7%; $p = 0.04$) than patients in the sedation arm. There was no difference in the prevalence of accidental extubation or ventilator-associated pneumonia between the two groups.

Although this study provided evidence of potential benefits of a no-sedation (i.e., analgesia-first or analgosedation) approach, it had significant limitations. The study site located in Denmark was already accustomed to a standard of care of providing no sedation to ICU patients. Patients admitted to this ICU were historically treated with as-needed IV morphine boluses, with little utilization of continuous sedative or analgesic infusions. The ICU nurse-to-patient ratio in this institution was also 1:1, and physical restraints were never used in ICU patients. In those patients who displayed signs of discomfort, all potential causes (i.e., pain, hypoxia, and tube obstruction) were systematically addressed. When an ICU patient became delirious, a staff person was assigned to verbally comfort and reassure the patient until the was delirium resolved. Although all of these confounding factors may limit the generalizability of this study's findings to other institutions with less rigorous delirium management methods and varying staffing levels, all of these points are important contextual factors that may influence sedative administration practices elsewhere. Other studies using analgesia-first strategies have also demonstrated improvements in ICU outcomes, particularly reducing the duration of mechanical ventilation and ICU LOS, resulting in a PAD guideline recommendation that "analgesia-first sedation be used in mechanically ventilated adult ICU patients (2B)" (8, 16, 17).

Myth 2: It Is Easier to Care for Deeply Sedated ICU Patients

Sedatives are often administered to critically ill patients in order to facilitate patient care activities by ICU staff (18). In a survey of 423 critical care nurses, nearly one third of respondents agreed or strongly agreed with the statement that all mechanically ventilated patients should be sedated. Additionally, 48% of those surveyed indicated their intention to sedate all of their mechanically ventilated patients (18). Coinciding to these attitudes, the prevalence of mechanically ventilated patients receiving IV sedative infusions in the United States has doubled over the period 2001–2007 (19). These findings suggest a widespread culture of keeping mechanically ventilated ICU patients at deep levels of sedation in order to facilitate ICU patient care activities. To address this notion that deeply sedating ICU patients facilitates easier patient care, one should first address the question, "easier for whom?"

Survey data have identified a number of factors that influence ICU nurses' decisions to administer sedative medications to critically ill patients. The primary indications listed by nurses for administering sedation are to provide patient comfort, induce amnesia, and prevent self-injurious behaviors by patients. Many nurses also believe that the overstimulation of patients by family members is a valid rationale for administering additional sedative doses (9). Other potential benefits of deep sedation include enabling ICU nurses to be "more efficient" by facilitating their ability to safely multitask without having to closely watch individual patients and to better manage nurse-to-patient staffing ratio (18).

From ICU patients' perspective, they might believe that it would be "easier" for caregivers to care for them if they were

awake, alert, comfortable, and able to communicate effectively with ICU staff. Presumably, unsedated or lightly sedated ICU patients would be able to express their acute needs, leading to a more positive experience for them during their ICU stay. Additionally, being alert and interactive would also allow patients to participate in their own care decisions, including making end-of-life decisions for themselves. ICU patients who are able to interact in a meaningful way with ICU staff and actively participate in their own care are also more able to participate in activities such as SBTs and early mobility activities that will likely shorten their duration of mechanical ventilation and ICU LOS.

A growing body of evidence demonstrates that deep sedation of ICU patients is more harmful to patients than maintaining them at light levels of sedation. Shehabi et al (20, 21) reported that early deep sedation resulted in longer mechanical ventilation times and increased 6-month mortality. Furthermore, because sedative medications are associated with the development of delirium, it is logical to assume that if these medications were targeted to maintain patients at lighter levels of sedation, both the prevalence and duration of delirium may be reduced. One recent study investigated the effects of maintaining mechanically ventilated patients with acute lung injury at a lighter level of sedation (i.e., a target Richmond Agitation-Sedation Scale [RASS] score of 0 [alert and calm]) using as-needed IV sedative boluses as first line, with continuous sedative infusions used only if patients failed the bolus treatment regimen (22). In addition, the trial implemented a twice-daily delirium screening into routine practice using the Confusion Assessment Method for the ICU (CAM-ICU). This integrated approach resulted in: 1) a reduced use of continuous opioid and sedative infusions in ICU patients (median proportion of medical ICU days per patient: 33% vs 74% and 22% vs 70%, respectively, both $p < 0.001$); 2) an increase in ICU patient wakefulness (i.e., median RASS score per patient: –1.5 vs –4.0, $p < 0.001$); and 3) an increase in the number of days that ICU patients were awake and not delirious (i.e., median proportion of medical ICU days per patient: 19% vs 0%, $p < 0.001$). Since delirious patients can be very difficult to care for and lead to increased healthcare costs (6), the prevention of delirium by sedation reduction may actually make ICU patients easier to care for in this instance. Perceived difficulty in taking care of lightly sedated patients notwithstanding, the evidence outlined in the new PAD guidelines clearly favors keeping ICU patients less sedated and more interactive, resulting in a strong recommendation that "sedative medications be titrated to maintain a light rather than a deep level of sedation in adult ICU patients, unless clinically contraindicated (1B)."

Myth 3: Only Surgical ICU Patients Experience Pain

ICU patients routinely receive sedatives and analgesics during their care, and yet 27–77% of all ICU patients still experience significant pain (23), with resulting negative alterations in physiologic and neurocognitive functions (24). Acutely ill patients experiencing untreated pain may develop tachycardia, tachypnea, diaphoresis, increased myocardial oxygen consumption, alterations in bowel motility, and increased release of inflammatory mediators, while also suffering from increased anxiety, fatigue, sleep deprivation, and delirium (25). The causes of postoperative pain in surgical ICU patients are easily recognizable (e.g., incisions and drains), but pain in the nonsurgical ICU patients often goes unrecognized. One study of 171 ICU patients, of which 34% were mechanically ventilated, found at least 40% experienced significant pain during their ICU care (26). Another study examined mechanically ventilated patients' physiologic responses to endotracheal suction by measuring hemodynamic and respiratory variables, pupillary responses, facial expressions, muscle tone, body movements, and patients' RASS score (27). The responses were assessed after endotracheal suction in ICU patients who were initially sedated, then following the discontinuation of sedation, and once again following opioid administration. Endotracheal suctioning induced signs of pain that included changes in hemodynamic and respiratory variables, muscle tone, and body movements in all three groups, including those that received an opioid dose after suctioning. The authors concluded that endotracheal suctioning is a major source of physical discomfort in ICU patients, and despite analgesic therapy, standard ICU doses of opioids were inadequate to attenuate the pain response associated with endotracheal suctioning. Numerous other sources of painful stimuli in ICU patients have been identified including mechanical ventilation and other routine ICU procedures (e.g., needle sticks, urinary catheter insertions, central venous and arterial catheter placements, and bronchoscopies) (8).

In heavily sedated mechanically ventilated patients, it is often very difficult to adequately assess pain control, particularly if validated pain score instruments are not used in patients who cannot self-report their pain (28). A multicenter study of 44 ICUs in France and Luxembourg examined pain and sedation practices in 1,381 mixed ICU patients (29). Despite over 90% of patients receiving opioid analgesics, only 42% received a documented pain assessment within 48 hours of ICU admission. In this study, adequate pain recognition was important because the subsequent secondary analysis showed that for those ICU patients who did receive pain assessment within 48 hours, they were more likely to receive targeted pain treatment and had a shorter duration of mechanical ventilation (i.e., 8 d vs 11 d; $p < 0.01$) and a significant reductions in ICU LOS (13 d vs 18 d; $p < 0.01$) (30). These assessments held true regardless of underlying diagnosis, including those patients with nonoperative pain. In a separate study, 21 patients from various diagnostic groups were assessed for recollection of painful experiences if they regained consciousness prior to discharge from the ICU. Nearly 50% of these patients recalled experiencing moderate to severe pain along with anxiety, fear, and sleep fragmentation during their ICU stay (31). From these data we conclude that significant pain commonly occurs in both nonsurgical and surgical ICU patients. Painful experiences often go unrecognized and untreated in these patients, due to a lack of ICU provider recognition because patients are too sedated to be able to self-report their pain, and because valid and

reliable behavioral pain assessment tools are not widely used in most ICUs. The undertreatment of pain in these patients also increases the risk of them developing acute delirium during their ICU stay and for developing symptoms of PTSD after ICU discharge (32, 33). An analgesia-first strategy can improve pain management and reduce the need for sedatives in critically ill patients and is one of the key recommendations of the 2013 ICU PAD guidelines (8).

Myth 4: Sedatives Help to Facilitate Sleep in ICU Patients

One of the perceived benefits of sedative therapy is the provision of sleep in ICU patients. Sleep deprivation is associated with a higher risk of ICU patients developing delirium (31, 34, 35). Risk factors for sleep fragmentation in ICU patients include mechanical ventilation, untreated pain, ambient noise and light during nighttime hours, prior alcohol use, drug therapy before admission, and concurrent medication therapy (34). The "traditional" approach to overcome discordant ICU sleep patterns was to heavily sedate critically ill patients with continuous sedative and opioid infusions, a practice previously endorsed in the 2002 version of the SCCM's ICU sedation and analgesia guidelines (36). But this practice of using sedatives to facilitate sleep in ICU patients warrants further scrutiny (34, 37).

ICU patients typically experience only level I and II sleep patterns, with extended periods of wakefulness juxtaposed with brief periods of light sleep (34, 35). Rarely do ICU patients progress to level III or IV (rapid eye movement [REM] or non-REM) sleep patterns for prolonged periods of time, thereby depriving themselves of the physiologic and immunologic benefits of deep sleep (34, 35). Similar patterns of sleep deprivation and fragmentation in ICU patients or healthy subjects result in similar patterns of cognitive impairment, disassociated thought processes, and psychotic behaviors (34).

The mechanisms that lead to normal sleep patterns are thought to involve circadian rhythms and the activation of gamma-aminobutyric acid (GABA) and galananin inhibitory neurons (34, 35, 37). Benzodiazepines and propofol, the most commonly used sedatives in ICU patients, interact with the GABA receptor to promote inhibitory effects that lead to central nervous system depression, followed by hypnotic effects (38). These agents promote level I and II non-REM sleep but suppress level III and IV sleep. Furthermore, benzodiazepines reduce cerebral blood flow after just a single IV dose, and propofol reduces cerebral glucose metabolism (35). In a small study of healthy subjects receiving propofol, whole brain glucose metabolic rates were depressed by 48–58% in subcortical and cortical regions, respectively (39). Opioids also impact sleep by inducing a dose-dependent effect on mu receptors, resulting in a suppression of REM sleep. Thus, the combination of sedatives as GABA receptor inhibitors administered in conjunction with opioids may produce a multifactorial effect on sleep and sleep patterns in ICU patients. Likewise, when these medications are rapidly withdrawn, a rebound surge in REM activity occurs that has been linked to nightmares in healthy subjects (40, 41). Based on currently available evidence, sleep disturbances in the ICU are poorly understood and may lead to grave consequences including a higher mortality (34). Equally important, the use of continuous sedative infusions for sleep promotion is also associated with higher delirium rates, which is also associated with a higher risk of mortality in ICU patients. So the question must be asked: Does drug-induced sedation really benefit ICU patients in terms of facilitating sleep, or merely appear to mimic sleep? Due to potential undesirable side effects of sedation, promotion of sleep in ICU patients should focus more on environmental sleep hygiene programs to facilitate natural sleep rather than drug-induced sedation that paradoxically impairs sleep in critically ill patients. This would include strategies to control ICU light and noise at night, clustering ICU patient care activities to be at specific times, and decreasing nighttime stimuli to protect patients' sleep cycle (8, 42).

DELIRIUM MANAGEMENT IN ICU PATIENTS

Myth 5: Delirium Is a Benign and Expected Side Effect of Being in the ICU

Delirium is defined as an acute change in mental status accompanied by inattention (43). It can manifest as one of three subtypes: hyperactive (e.g., restless, agitated, or combative), hypoactive (e.g., lethargic, slow responses), or mixed (i.e., a fluctuation between hyperactive and hypoactive subtypes). Historically, these types of mental status changes, especially hyperactive delirium, were labeled as "ICU psychosis" and considered to be an ICU experience that would eventually resolve when the patient was transferred with minimal impact on short- or long-term patient outcomes. A 2004 survey by Ely et al (44) reported that only 23.7% of providers agreed or strongly agreed that delirium was "normal" in the ICU, but more than 45% of the same respondents disagreed or strongly disagreed that delirium caused long-term neurologic or psychological defects. However, with the development of valid and reliable tools to detect delirium in ICU patients, we have gained a greater understanding of the epidemiology of delirium in ICU patients over the past decade. We now know that acute delirium affects up to 80% of critically ill patients and 10% of these patients remain delirious at the time of their hospital discharge (7, 45–47). ICU delirium is associated with a longer duration of mechanical ventilation, longer ICU and hospital length of stay, and increases in-hospital mortality (4, 5, 7). Pisani et al (48) determined that each day that a patient is delirious in the ICU increases the risk of death by 10%. There are also significant long-term consequences of ICU delirium, affecting patients long after their ICU and hospital discharge. Delirium is associated with a three-fold increased risk of death up to 6 months after hospital discharge (5). Delirium is also linked to the development of long-term, dementia-like cognitive impairment. Girard et al (49) reported that an increase in delirium duration in the ICU from 1 day to 5 days was associated with nearly a five-point decline in cognitive battery scores 6 months after discharge. One ICU survivor describes

her experience, "One quite literally loses one's grip on what is true and what is false because the true and the false are mixed together in a mess of experience" (50). The economic costs of ICU delirium are also considerable, resulting in an additional expenditure of $4–$16 billion in United States healthcare dollars annually (6).

Given these significant risks and costs associated with the development of delirium in critically ill patients, ICU teams should view delirium as a form of acute brain dysfunction and give it the same attention as other organ system failures in ICU patients (45), beginning with accurate delirium detection. Without using a standardized delirium assessment tool, ICU clinicians may underestimate the presence of delirium in critically ill patients (51–53). For this reason, the ICU PAD guidelines (8) recommend that all ICU patients be routinely screened for delirium using a valid and reliable assessment tool, such as the Confusion Assessment Method for the ICU (CAM-ICU) (47, 54) or the Intensive Care Delirium Screening Checklist (ICDSC) (55). All ICU patients should be systematically evaluated for delirium with institutional strategies implemented to prevent and reduce the occurrence and impact of delirium, such as ICU early mobility, sleep hygiene programs, and the minimization of benzodiazepine use in patients who are at risk for delirium (3, 12, 56, 57).

Myth 6: Delirium Assessment and Recognition Is Consistent and Uniform

Given that delirium is a common problem in the ICU and associated with worse clinical outcomes (4–6, 48), it is imperative to reliably detect delirium in order to minimize risk factors or initiate appropriate treatment interventions. Of the screening tools available for delirium, the most reliable scoring indicators are the previously mentioned CAM-ICU and the ICDSC (47, 55), both of which are recommended by the PAD guidelines (8). Despite the endorsement for the use of these tools, available literature suggests suboptimal compliance and reliability with the performance of delirium screenings.

Survey data demonstrate a wide range of delirium screening practices, perceptions, and attitudes across multiple healthcare disciplines, with low adherence and familiarity with ICU delirium screening. In a survey of 912 healthcare professionals including 753 physicians, only 32% of the survey respondents believed that the routine monitoring of delirium was supported by evidence, and only 40% of those surveyed routinely assessed for delirium (44). Additionally, these same survey participants estimated that they had properly diagnosed delirium only 22% of the time. The survey also identified that a wide variety of delirium screening tools were being used. Only 7% of the respondents indicated using CAM-ICU for their observatory method, whereas none listed the ICDSC. In a similar study (53), surveys were specifically disseminated to ICU nurses to determine their perceptions of delirium in the ICU. All of the 331 nurses surveyed practiced in ICUs that used a sedation protocol that instituted a delirium assessment component. Interestingly, respondents indicated that even though ICU nurses frequently assessed patients' sedation status (98% of the time), less than half of the same respondents (47%) would simultaneously perform a delirium assessment, despite this step being mandated by their own sedation protocol. Some of this low compliance with delirium assessments may stem from the fact that only 63% of respondents had ever received formal training in delirium assessments, and more than 40% of all respondents indicated that neither the CAM-ICU nor ICDSC tools were ever mentioned or employed at their institution. Other studies illustrate similar findings, describing both low prevalences of delirium screening and low confidence in the ability to accurately recognize delirium in ICU patients (58, 59). This question of caregivers' ability to appropriately identify delirium when present was studied in more detail by Spronk et al (7). Using CAM-ICU scores performed by a group of independent study-specific nurses to verify actual caregivers' assessment of delirium status, the study's results demonstrated that there is an identification deficit pertaining to accurate delirium diagnosis. The study's observations concluded that only 28% of delirium days were correctly identified by intensivists; ICU nurses faired slightly better in this study with a delirium detection rate of only 35%.

The aforementioned misunderstanding and poor recognition of delirium prompts investigation into the rationale for low compliance with delirium assessments. Several barriers to performing appropriate delirium screening may currently exist for healthcare providers. Potential limitations to using delirium assessment tools include difficulty in assessing delirium in intubated or sedated patients, assessment tool complexity, and caregivers' perception of unimportant results (53, 60). Despite these barriers, institutionally driven educational programs have been shown to improve delirium screening accuracy and compliance rates, while maintaining them for several years (61–64). These studies support the PAD guidelines' claim that systematic ICU delirium screening is feasible and promote efforts to boost staff education and the monitoring of delirium screening implementation programs. As efforts to improve outcomes related to delirium in intensive care patients become more widely accepted, it is important that delirium monitoring be performed regularly in the ICU, as early detection of delirium could lead to faster resolution in these patients.

Myth 7: All ICU Delirium Is Similar and Can Be Managed Effectively by Medications

Risk factors for delirium have been described as the manifestation of an acute illness, a preexisting patient specific factor, or exposure to a modifiable risk factor such as medications or environmental components (8, 65). Specific risk factors for delirium include baseline dementia, increased age, hypertension, sepsis, hypoalbuminemia, prior alcohol abuse, and benzodiazepines (46, 56, 66). These factors and others trigger complex interacting neurotransmitter systems and pathologic processes leading to the fluctuating mental status or disorganized thinking accompanied by the acute onset of delirium. Although hyperactive delirium is more easily recognized due to outward symptoms of restlessness, agitation, combativeness, and sometimes hallucinations and delusions, hypoactive

delirium is frequently missed by caregivers, especially in those patients who are heavily sedated. Hypoactive delirium, which presents as inattentiveness or a disorganized thought process, is prevalent in 43–60% of all delirium cases and is associated with greater mortality than hyperactive delirium (67). Regardless of delirium classification, practitioners are often eager to implement both pharmacologic and nonpharmacologic interventions to treat delirious patients, given the negative consequences of the disorder in the ICU (44, 53, 58, 59, 68).

Nonpharmacologic interventions that are effective in treating and preventing delirium include minimizing risk factors and initiating early progressive mobility in ICU patients (3, 8, 69). But pharmacologic intervention is often the first therapy initiated in these patients. Survey data indicate consistent attitudes among ICU clinicians that pharmacologic treatment is an appropriate strategy for the management of delirium, with antipsychotic drugs frequently administered to treat ICU patients with delirium (44, 59, 68). One particular survey of U.S. pharmacists from 45 hospitals in eight states illustrates that 85% of respondents believe that delirium should be pharmacologically managed, with 65% of responses indicating the need for dual medication regimens. Haloperidol was the treatment of choice by 85% of those surveyed (68). Results from another survey also demonstrate that antipsychotics are frequently administered for treatment of delirium, with haloperidol again being the drug of choice in these patients (44). Given these survey results, it is no surprise then that haloperidol utilization increases in institutions as ICU delirium screening increases (70). However, despite the perceived benefit of giving an antipsychotic to treat delirium, there is a paucity of evidence to support the safety and effectiveness of this practice. Studies evaluating haloperidol use in the management of delirious patients lack uniformity, have mixed efficacy results, mixed safety results, and include few, if any, ICU patients. Although recent studies suggest the value of low-dose haloperidol for delirium prophylaxis, each trial employed a nonrigorous study design and screened for and treated only high-risk patients (71, 72). The evidence for using other atypical antipsychotic medications to both treat and prevent delirium in ICU patients is also sparse. In one randomized placebo-controlled pilot trial comparing quetiapine versus placebo given in conjunction with haloperidol for the treatment of delirium in ICU patients, there was a reduction in duration of delirium and shortened time to delirium resolution, but the sample size in this study was small ($n = 36$) (73). A larger study is needed to validate these results. Given the limited data regarding the safety and efficacy of administering antipsychotics for the treatment of delirium in ICU patients, the current ICU PAD guidelines provide no recommendation on their use in this instance (8). Nevertheless, antipsychotics are likely to continue to be used commonly for the treatment of delirium in these patients, and providers should be familiar with the inherent risks and lack of evidence when administering antipsychotics. Both traditional antipsychotics (e.g., haloperidol) and atypical antipsychotics (e.g., quetiapine) pose a significant cardiac risk and should be avoided in patients with underlying QTc prolongation and should be used cautiously when administered in conjunction with other QC interval corrected for heart rate prolonging medications (e.g., methadone, moxifloxacin, and amiodarone). Antipsychotics can also cause significant extrapyramidal symptoms in these patients, even in small doses (74). Since data remain sparse on the use of antipsychotics for the treatment of delirium, modifiable risk factors should first be minimized, and nonpharmacologic interventions should be implemented before any pharmacologic treatment of delirium is considered.

The choice of sedative used in ICU patients may also decrease the prevalence of delirium. In one large multicenter trial (Safety and Efficacy of Dexmedetomidine Compared with Midazolam [SEDCOM] study), there was a lower prevalence of delirium in mechanically ventilated ICU patients receiving dexmedetomidine compared with those who received midazolam for sedation (12). In a subgroup analysis of the Maximizing Efficacy of Targeted Sedation and Reducing Neurological Dysfunction (MENDS) study, delirium outcomes were compared in 103 mechanically ventilated ICU patients with sepsis ($n = 63$) or without sepsis ($n = 40$), who received either IV dexmedetomidine or lorazepam for sedation (75). Septic patients receiving dexmedetomidine had more delirium/coma-free days, more delirium-free days, and more ventilator-free days than patients receiving lorazepam for sedation. Across all patients evaluated, those sedated with dexmedetomidine had a 70% lower likelihood of having delirium on any given treatment day compared with patients sedated with lorazepam. To date, however, there are no published studies demonstrating that dexmedetomidine reduces either the duration or severity of delirium in ICU patients. The PAD guidelines include a weak recommendation for avoiding benzodiazepines in ICU patients who are at risk for delirium, and those who are diagnosed with delirium should receive dexmedetomidine for sedation rather than a benzodiazepine. But the PAD guidelines do not recommend avoiding the use of benzodiazepines as sedative agents in ICU patients altogether. In fact, benzodiazepines remain the sedative of choice for treatment of drug and alcohol withdrawal symptoms in ICU patients (76). Benzodiazepines may also be indicated for sedation of critically ill patients with intractable seizures and can provide synergistic sedative effects in ICU patients who cannot otherwise be effectively sedated with propofol and/or dexmedetomidine (19, 77). There are no large, well-designed studies comparing the prevalence and duration of delirium in ICU patients receiving propofol versus dexmedetomidine. More study is needed to address these issues related to sedative choice and delirium in critically ill patients.

UNTOWARD EFFECTS OF ICU SEDATION STRATEGIES

Myth 8: Daily Interruptions of Sedative Medications Are Unsafe

Sedative and opioid analgesic medications are intermittently or continuously administered to facilitate patients' comfort and improve mechanical ventilation synchrony (29, 78). However, these agents do not come without undesirable adverse effects.

Continuous sedative regimens have resulted in prolonged mechanical ventilation times, increased LOS, greater organ failure, and increased likelihood of reintubation (79). In 2000, Kress et al (1) first introduced the concept of daily interruption of sedation (DIS), otherwise referred as *SATs*, as a means of reducing sedative use and improving patient outcomes in the ICU. Although the use of DIS is one strategy recommended by the PAD guidelines to improve ICU outcomes, widespread reluctance on the part of ICU practitioners to routinely suspend sedative medications in critically ill patients still persists. A 2009 survey of 1,384 healthcare professionals found that only 44% of respondents believed that DISs (SATs) were performed at least 50% of the time in their mechanically ventilated ICU patients despite simultaneously reporting that 71% of the respective institutions used sedation protocols that included SATs (59). Furthermore, many clinicians believe that lightening sedation predisposes critically ill patients to hemodynamic instability, increased oxygen requirements, increased risk of self-extubation, or untoward long-term psychological defects (18, 80). Similarly, ICU nurses are more likely to perform an SAT in ICU patients with favorable respiratory variables (e.g., F_{IO_2} < 50% or positive end-expiratory pressure < 5 mm Hg), who are receiving propofol rather than a benzodiazepine, or if the nurse had prior favorable experiences performing SATs (81, 82). The presence or absence of interdisciplinary communication may also play a role as SATs are more likely to happen for ICU patients whose multidisciplinary care team incorporates sedation goals in its daily discussions on ICU rounds (81).

Since the goal of SATs is to reduce sedative use and to facilitate ventilator weaning, it is intuitive to think that by stopping these medications in conjunction with SBTs that outcomes could be improved. This hypothesis was tested in the Awakening and Breathing Controlled (ABC) (2) trial, where the linking of daily SATs with SBTs shortened mechanical ventilation time by more than 3 days, and reduced ICU and hospital LOS by 3.8 days and 4.3 days, respectively, when compared to performing daily SBTs alone. The study also demonstrated that the SAT + SBT group had a significantly reduced mortality risk at 1 year (HR, 0.68; 95% CI, 0.5–0.92; $p = 0.01$). Despite safety concerns for ICU patients awakening from sedation, the implementation of a daily DIS does not have untoward consequences in the cardiac patient (83), nor does it lead to long-term neurocognitive effects (84, 85). In the ABC trial, though the combination of an SAT with an SBT resulted in more self-extubations, there was no statistical difference in reintubation rates between the intervention and control groups. Despite similar mechanical ventilation times and LOS between those patients receiving lighter targeted sedation and patients receiving DIS, a recent trial has shown no difference in adverse events between the cohorts (86). These results provide additional evidence that performing DIS in appropriate patients is safe.

The implementation of DIS should include a safety screen with clear exclusion criteria for performing DIS to avoid possible adverse events (e.g., avoid in patients receiving neuromuscular blocking agents, patients about to undergo invasive procedures or transports outside the ICU, or in those patients receiving benzodiazepines for alcohol withdrawal or intractable seizures). Broad educational efforts among ICU staff and family members regarding the safety and efficacy of performing DIS/SATs will be necessary in order to get widespread buy-in and support for DIS/SATs (81, 82). Finally, DIS/SAT protocols should include careful coordination of sedative suspension by nursing staff in order to synchronize this with efforts by respiratory therapists to conduct SBTs and physical therapists to perform mobility exercises in order to maximize the benefits of DIS/SATs. Thoughtfully implemented, DIS can be performed safely in most ICU patients and is one of the key strategies recommended for minimizing the use of sedatives and maintaining light levels of sedation in critically ill patients in the new PAD guidelines (the other being to continuously target a light level of sedation) (8).

Myth 9: Sedative and Analgesic Medications Do Not Accumulate With Prolonged Use

Opioids and sedative hypnotics commonly administered to ICU patients each have their own unique pharmacologic profile and vary considerably in terms of their volumes of distribution, elimination half-lives, potencies, onset and offset of action, and side effects. These differences should influence the choice of agent(s) used for each patient rather than having a "one-size-fits-all approach" (38). All of these drugs can accumulate in tissues when administered over extended periods, resulting in prolonged emergence from sedation when these drugs are discontinued (29, 38, 78, 87–90). Some drugs, such as midazolam and morphine, have active metabolites (i.e., α-hydroxymidazolam and morphine-6-glucoronide, respectively) that are excreted by the kidneys and can accumulate in ICU patients with renal insufficiency (91, 92). Emergence from sedation is also dependent on the baseline depth of sedation, such that patients who are sedated more deeply will take longer to regain consciousness than those who are maintained at lighter levels of sedation (88, 89, 93). Finally, larger volumes of distribution and/or reduced clearance of medications may further delay emergence from sedation in critically ill patients. It is therefore important to use analgesia and sedation strategies that minimize the total dose of opioids and sedatives administered to critically ill patients, in order to reduce the likelihood of delayed emergence from sedation and perhaps resulting in failed attempts at DIS/SATs (18, 59, 82).

Myth 10: Deep Sedation and Amnesia Derived From Sedative Administration in ICU Patients Result in Improved Psychological Outcomes, Especially PTSD

For decades, the treatment and management of critically ill patients has focused primarily on ensuring patient survival. Advancements in therapies, technology, and novel medications have all resulted in improved survival, thus compelling critical care staff to look beyond hospital discharge data and consider the long-term impact of therapies and treatments administered to these patients during their ICU stay (94). There has been a recent explosion in research focused on identifying and describing the long-term complications following critical

illness, including long-term impacts on physical and psychological recovery, cognition, and quality of life. The foundation for understanding these relationships between in-hospital management strategies and long-term patient outcomes is to be able to identify modifiable risk factors that can be influenced during each patient's ICU stay.

PTSD is one specific long-term outcome that affects a subset of ICU survivors. PTSD is a psychiatric condition that develops from exposure to a traumatic event and is characterized by intrusive recollections (e.g., recurrent dreams, nightmares, or flashbacks), avoidant/numbing symptoms, and hyperarousal symptoms (e.g., sleep disruption, hypervigilance, and exaggerated startle response) (95). Systematic reviews indicate a wide prevalence of PTSD ranging from 2% to 66% following ICU discharge (96, 97). This is likely due to variations in study methodology including poor patient follow-up, selection bias, and heavy reliance on screening questionnaires rather than diagnostics interview, making it difficult to know the true prevalence of PTSD in ICU survivors (96, 97). A systematic review of 15 studies looking at the prevalence and risk factors for PTSD in ICU survivors and its impact on their quality of life concluded that the median point prevalence of questionnaire-ascertained "clinically significant" PTSD symptoms was 22% ($n = 1,104$), and the median point prevalence of clinician-diagnosed PTSD was 19% ($n = 93$). Risk factors for post-ICU PTSD included prior psychopathology, greater ICU benzodiazepine administration, and post-ICU memories of in-ICU experiences which were either frightening and/or psychotic (98). Not surprisingly, post-ICU PTSD was associated with substantially lower health-related quality of life in these patients.

There is a long-held belief that deeply sedated patients will be spared from remembering specific ICU events while protecting them from developing psychological stress (99, 100). In reality, sedation itself is thought to be a significant risk factor for the development of PTSD in ICU survivors. Girard et al (101) found an association between ICU patients receiving high doses of benzodiazepines for sedation and the development of PTSD in ICU survivors. Jones et al (11) hypothesized that depth and length of sedation could result in greater opportunities to form delusional memory and thus be associated with PTSD in ICU survivors. They demonstrated that delusion memory is more strongly associated with the development of PTSD following the ICU rather than factual memory (11, 102).

In a study comparing light sedation with deep sedation, Treggiari et al (103) reported that the patients receiving deep sedation had more trouble remembering important parts of their ICU stay and more disturbing memories of the ICU, but scored similar to the light sedation group on the PTSD questionnaire screen. Two studies investigating potential long-term neurologic consequences from daily sedation interruption and lighter sedation levels found no negative psychological impact. Kress et al (84) reported that ICU patients who received DIS experienced less PTSD and had fewer PTSD symptoms at 6-month follow-up. In a follow-up investigation to the ABC trial, it was found that ICU patients who experienced daily SATs paired with SBTs experienced no difference in cognitive, psychological (including PTSD), or functional outcomes at either 3 or 12 months after hospital discharge (2, 85). These studies provide clear and compelling evidence that maintaining lighter levels of sedation by using either targeted sedation delivery (103) or daily sedative interruption (84, 85) results in improved in-hospital outcomes, such as shorter ICU length of stay and shorter ventilator time, without causing long-term psychological harm in ICU survivors. As a result, the ICU PAD guidelines recommend that most ICU patients should be maintained at a light level of sedation that allows for patients to interact in a meaningful way with the ICU environment and to participate in their ICU care (8).

CONCLUSIONS

A growing body of evidence published over the past decade challenges widely held beliefs regarding the prevalence and management of pain, agitation/sedation, and delirium in adult ICU patients. Several new PAD treatment strategies have emerged in recent years, which have led to significant improvements in both short- and long-term outcomes in these patients and significant reductions in their costs of care. The 2013 ICU PAD guidelines provide a clear, evidence-based road map for optimizing the management of pain, agitation/sedation, and delirium in ICU patients in an integrated and interdisciplinary fashion, based on the most recent evidence. But widespread adoption and implementation of these guidelines is likely to be impeded by long-held beliefs and "myths" that have ingrained existing PAD practice patterns among ICU providers.

Knowledge of the most current evidence behind the best practices recommended in the PAD guidelines will help to debunk these myths, but a single strategy education alone will be ineffective in promoting widespread adoption of the PAD guidelines. Current PAD management habits triggered by the interpretation of existing cues (i.e., *the patient is agitated!*) and followed by traditional routines (*turn up the sedatives!*) lead to perceived rewards (i.e., *the patient is calm now!*). But many of these cue-routine-rewards in managing PAD in ICU patients are based on false assumptions about the risks and benefits of current PAD management strategies. What is needed here is a new set of habits based on new cues (or new interpretations of old cues), new routines, and new rewards (104). Routine assessments of patients to detect significant pain, over- or under-sedation, and delirium using valid and reliable assessment tools will help to form new "cues" to help change clinical practice. ICUs will then need to decide how to incorporate these PAD assessments into the broader framework of their PAD management protocols in such a way that they become part of the everyday workflow in the ICU as new "routines." Finally, regulatory bodies and third-party payers will need to incentivize and reward hospitals in order to encourage widespread adoption of these guidelines in their ICUs in order to create new "rewards." But knowledge is the principle driver of change, and this article attempts to debunk many current beliefs regarding current ICU practices in pain, agitation/sedation, and delirium management and to promote

a greater understanding of the benefits of implementing the 2013 ICU PAD guidelines.

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