Special Article

Executive Summary: Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU

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The American College of Critical Care Medicine (ACCM), which honors individuals for their achievements and contributions to multidisciplinary critical care medicine, is the consultative body of the Society of Critical Care Medicine (SCCM) that possesses recognized expertise in the practice of critical care. The College has developed administrative guidelines and clinical practice parameters for the critical care practitioner. New guidelines and practice parameters are continually developed, and current ones are systematically reviewed and revised.

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Clinical practice guidelines are published and promoted, often by professional societies, because they provide a current and transparently analyzed review of relevant research and are written with the aim to guide clinical practice. The 2018 Pain, Agitation/sedation, Delirium, Immobility (rehabilitation/mobilization), and Sleep (disruption) (PADIS) guidelines (1) first 1) builds on this mission by updating the 2013 PAD guidelines (2); 2) by adding two inextricably related clinical care topics (immobility and sleep); 3) by including patients as collaborators and coauthors; and 4) by inviting panelists from high-income countries as an early step toward incorporating more diverse practices and expertise from the global critical care community.

Readers will find rationales for 37 recommendations (derived from actionable Patient Intervention Comparison Outcome questions), two good practice statements, and 32 statements (derived from nonactionable, descriptive questions for which the Grading of Recommendations Assessment, Development and Evaluation methodology was not used)

across the five guideline sections. Only two of the 37 recommendations are strong; most are conditional. Compared with a strong recommendation (most desirable to clinicians), conditional recommendations apply to most, but not all critically ill adults, and are made when evidence is conflicting, low quality, insufficient and/or applicable to just one patient subgroup, and/or when potential benefits require weighing almost equal risks. The supplemental digital figures and tables linked to the full guideline provide background on how the questions were established, profiles of the evidence, the "evidence to decision" tables used to develop recommendations, and voting results. We also describe the evidence gaps that prevented us from fully addressing all clinical priority questions.

The five sections of this guideline are interrelated, and thus, the guideline should be considered in its entirety rather than as discrete or distinct recommendations. A separate PADIS guideline implementation and integration article (3) and a detailed description of the methodologic innovations that characterize these guidelines (4) have been published separately. This executive summary highlights the 18 recommendations the section leaders and guideline chair/vice-chair felt would be of greatest interest to ICU clinicians. All PADIS recommendations (including those highlighted in this executive summary) are found in **Table 1**. All descriptive questions and ungraded statements are found in **Table 2**.

RECOMMENDATIONS

Pain

Pain management is complex and has many origins. A consistent approach to pain assessment and management is paramount, particularly given the unique features inherent to critically ill adults. In this population, whose reference standard measure of pain is the patient's self-report, the inability to communicate clearly does not negate a patient's pain experience or the need for appropriate pain management (5). Severe pain negatively affects critically ill adults (6) beyond its unpleasant experience dimension. Implementation of assessment-driven and standardized pain management protocols improves ICU outcomes and clinical practice (5, 6). Carefully titrated analgesic dosing is important in balancing the benefits versus risks of opioid exposure (7–10).

Protocol-Based Pain Assessment and Management

Question. Should we use a protocol-based (analgesia/analgosedation) pain assessment and management programs in the care of adult ICU patients when compared with usual care?

Good practice statement. Management of pain for adult ICU patients should be guided by routine pain assessment and pain should be treated before a sedative agent is considered.

Recommendation. We suggest using an assessment-driven, protocol-based, stepwise approach for pain and sedation management in critically ill adults (conditional recommendation, moderate quality of evidence).

Remarks. For this recommendation, analgosedation is defined as either analgesia-first sedation (i.e., an analgesic [usually an opioid] is used before a sedative to reach the sedative goal) or analgesia-based sedation (i.e., an analgesic [usually an opioid] is used instead of a sedative to reach the sedative goal). The implementation of this recommendation infers that institutions should have an assessment-driven protocol that mandates regular pain and sedation assessment using validated tools, provides clear guidance on medication choice and dosing, and makes treating pain a priority over providing sedatives.

Our pooled analysis suggests that protocol-based (analgesia/analgosedation) pain and sedation assessment and management programs compared with usual therapy reduce sedative requirements, duration of mechanical ventilation, ICU length of stay (LOS), and pain intensity (5, 11–31). Panel members issued a conditional recommendation because the benefits of a protocol-based approach were not observed across all critical outcomes.

Pharmacologic Adjuvants to Opioid Therapy. Opioids remain a mainstay for pain management in most ICU settings; however, their side effects preoccupy clinicians because important safety concerns, such as sedation, delirium, respiratory depression, ileus, and immunosuppression, may increase ICU LOS and worsen post-ICU patient outcome. The panel generally supports the use of multimodal pharmacotherapy as a component of an analgesia-first approach to spare/minimize opioid and sedative use and optimize analgesia and rehabilitation (32), as described below.

Acetaminophen

Question. Should acetaminophen be used as an adjunct to an opioid (vs an opioid alone) for pain management in critically ill adults?

Recommendation. We suggest using acetaminophen as an adjunct to an opioid to decrease pain intensity and opioid consumption for pain management in critically ill adults (conditional recommendation, very low quality of evidence).

When compared with placebo in the perioperative period, use of IV acetaminophen 1 g every 6 hours was associated with reduced pain intensity and opioid consumption 24 hours after surgery (33, 34). The risk for IV acetaminophen-associated hypotension may preclude its use in some patients (35). Given these findings, the panel suggests using acetaminophen (IV, oral, or rectal) to decrease pain intensity and opioid consumption when treating pain in critically ill patients, particularly in patients at higher risk for opioid-associated safety concerns.

Nefopam

Question. Should nefopam be used either as an adjunct or a replacement for an opioid (vs an opioid alone) for pain management in critically ill adults?

Recommendation. We suggest using nefopam (if feasible) either as an adjunct or replacement for an opioid to reduce opioid use and their safety concerns when treating pain in critically ill adults (conditional recommendation, very low quality of evidence).

Nefopam is a nonopioid analgesic; a 20-mg dose has an analgesic effect comparable to 6 mg of IV morphine (36). Nefopam has potential safety advantages over opioids and

TABLE 1. Summary of Actionable Patient Intervention Comparison Outcome Questions and Recommendations

Question	Recommendation	Strength	Quality of Evidence
Pain			
Should a protocol-based (analgesia/analgosedation) pain assessment and management program be used in the care of critically ill adults when compared with usual care?	Management of pain for adult ICU patients should be guided by routine pain assessment and pain should be treated before a sedative agent is considered (Good Practice Statement).	N/A	N/A
	We suggest using an assessment-driven, protocol-based, stepwise approach for pain and sedation management in critically ill adults. Remarks: For this recommendation, analog sedation is defined as either analgesia-first sedation (i.e., an analgesic [usually an opioid] is used before a sedative to reach the sedative goal) or analgesia-based sedation (i.e., an analgesic [usually an opioid] is used instead of a sedative to reach the sedative goal). The implementation of this recommendation infers that institutions should have an assessment-driven protocol that mandates regular pain and sedation assessment using validated tools, provides clear guidance on medication choice and dosing, and makes treating pain a priority over providing sedatives.	Conditional	Moderate
Should acetaminophen be used as an adjunct to an opioid (vs an opioid alone) for pain management in critically ill adults?	We suggest using acetaminophen as an adjunct to an opioid to decrease pain intensity and opioid consumption for pain management in critically ill adults.	Conditional	VL
Should nefopam be used either as an adjunct or a replacement for an opioid (vs an opioid alone) for pain management in critically ill adults?	We suggest using nefopam (if feasible) either as an adjunct or replacement for an opioid to reduce opioid use and their safety concerns for pain management in critically ill adults.	Conditional	VL
Should ketamine be used as an adjunct to an opioid (vs an opioid alone) for pain management in critically ill adults?	We suggest using low-dose ketamine (1–2 μg/kg/hr) as an adjunct to opioid therapy when seeking to reduce opioid consumption in postsurgical adults admitted to the ICU.	Conditional	Low
Should a neuropathic pain medication (e.g., gabapentin, carbamazepine, and pregabalin) be used as an adjunct to an opioid (vs an opioid alone) for pain management in critically ill adults?	We recommend using a neuropathic pain medication (e.g., gabapentin, carbamazepine, and pregabalin) with opioids for neuropathic pain management in critically ill adults.	Strong	Moderate
	We suggest using a neuropathic pain medication (e.g., gabapentin, carbamazepine, and pregabalin) with opioids for pain management in ICU adults after cardiovascular surgery.	Conditional	Low
Should IV lidocaine be used as an adjunct to an opioid (vs an opioid alone) for pain management in critically ill adults?	We suggest not routinely using IV lidocaine as an adjunct to opioid therapy for pain management in critically ill adults.	Conditional	Low
Should a COX-1 selective NSAID be used as an adjunct to an opioid (vs an opioid alone) for pain management in critically ill adults?	We suggest not routinely using a COX-1 selective NSAID as an adjunct to opioid therapy for pain management in critically ill adults.	Conditional	Low
Should an opioid (vs no opioid) be used for critically ill adults undergoing a procedure? Should a high-dose opioid (vs a low-dose opioid) be used for critically ill adults undergoing a procedure?	We suggest using an opioid, at the lowest effective dose, for procedural pain management in critically ill adults. Remarks: The same opioids (i.e., fentanyl, hydromorphone, morphine, and remifentanil) that are recommended in the 2013 guidelines to manage pain should also be considered when an opioid is deemed to be the most appropriate pharmacologic intervention to reduce procedural pain (2).	Conditional	Moderate

(*Continued*)

TABLE 1. (*Continued*). Summary of Actionable Patient Intervention Comparison Outcome Questions and Recommendations

Question	Recommendation	Strength	Quality of Evidence
Should local analgesia (vs an opioid) be used for critically ill adults undergoing a procedure? Should nitrous oxide (vs an opioid) be used for critically ill adults undergoing a procedure?	We suggest not using either local analgesia or nitrous oxide for pain management during chest tube removal in critically ill adults.	Conditional	Low
Should an inhaled volatile anesthetic (vs no use of this agent) be used for critically ill adults undergoing a procedure?	We recommend not using inhaled volatile anesthetics for procedural pain management in critically ill adults.	Strong	VL
Should an NSAID administered IV, orally, or rectally (vs an opioid) be used for critically ill adults undergoing a procedure?	We suggest using an NSAID administered IV, orally, or rectally as an alternative to opioids for pain management during discrete and infrequent procedures in critically ill adults.	Conditional	Low
Should an NSAID topical gel (vs no use of NSAID gel) be used for critically ill adults undergoing a procedure?	We suggest not using an NSAID topical gel for procedural pain management in critically ill adults	Conditional	Low
Should cybertherapy (i.e., virtual reality) (vs no use of cybertherapy) be used for pain management in critically ill adults? Should hypnosis (vs no use of hypnosis) be used for pain management in critically ill adults?	We suggest not offering cybertherapy (virtual reality) or hypnosis for pain management in critically ill adults	Conditional	VL
Should massage (vs no massage) be used for pain management in critically ill adults?	We suggest offering massage for pain management in critically ill adults. Remarks: Massage interventions varied in session time (10–30 min), frequency (once or bid), duration (for 1–7 d), and body area (back, feet and hands, or only hands).	Conditional	Low
Should music therapy (vs no music therapy) be used for pain management in critically ill adults to relieve both procedural and nonprocedural pain?	We suggest offering music therapy to relieve both nonprocedural and procedural pain in critically ill adults.	Conditional	Low
Should cold therapy (vs no use of cold therapy) be used for critically ill adults undergoing a procedure?	We suggest offering cold therapy for procedural pain management in critically ill adults. Remarks: Cold ice packs were applied for 10 min, and wrapped in dressing gauze, on the area around the chest tube before its removal.	Conditional	Low
Should relaxation techniques (vs no use of relaxation techniques) be used for critically ill adults undergoing a procedure?	We suggest offering relaxation techniques for procedural pain management in critically ill adults. Remarks: The relaxation technique used in each study differed.	Conditional	VL
Agitation/sedation			
Does light sedation (vs deep sedation), regardless of the sedative agent(s) used, significantly affect outcomes in critically ill, mechanically ventilated adults?	We suggest using light sedation (vs deep sedation) in critically ill, mechanically ventilated adults.	Conditional	Low

(*Continued*)

TABLE 1. (*Continued*). Summary of Actionable Patient Intervention Comparison Outcome Questions and Recommendations

Question	Recommendation	Strength	Quality of Evidence
Should propofol, when compared with a benzodiazepine, be used for sedation in mechanically ventilated adults after cardiac surgery?	We suggest using propofol over a benzodiazepine for sedation in mechanically ventilated adults after cardiac surgery.	Conditional	Low
Should propofol, when compared with a benzodiazepine, be used for sedation in critically ill, mechanically ventilated adults?	We suggest using either propofol or dexmedetomidine over benzodiazepines for sedation in critically ill, mechanically ventilated adults.	Conditional	Low
Should dexmedetomidine, when compared with a benzodiazepine, be used for sedation in critically ill, mechanically ventilated adults?			
Should dexmedetomidine, when compared with propofol, be used for sedation in critically ill, mechanically ventilated adults?			
Delirium			
Should we assess for delirium using a valid tool (compared with not performing this assessment with a valid tool) in critically ill adults?	Critically ill adults should be regularly assessed for delirium using a valid tool (Good Practice Statement). Remarks: The 2013 guideline provided psychometric appraisals of pain, sedation, and delirium screening tools. A reevaluation of the psychometrics for available delirium screening psychometrics was not conducted as part of these guidelines. The focus of this question is the effect of using any delirium assessment tool (vs no assessment tool) in clinical practice.	N/A	N/A
Should a pharmacologic agent (vs no use of this agent) be used to "prevent" delirium in critically ill adults?	We suggest not using haloperidol, an atypical antipsychotic, dexmedetomidine, a HMG-CoA reductase inhibitor (i.e., statin), or ketamine to prevent delirium in all critically ill adults.	Conditional	VL to Low
Should a pharmacologic agent (vs no use of this agent) be used to "treat subsyndromal delirium" in all critically ill adults with subsyndromal delirium?	We suggest not using haloperidol or an atypical antipsychotic to treat subsyndromal delirium in critically ill adults.	Conditional	VL to Low
Should a pharmacologic agent (vs no use of this agent) be used to treat delirium in all critically ill adults with delirium?	We suggest not routinely using haloperidol, an atypical antipsychotic, or a HMG-CoA reductase inhibitor (i.e., a statin) to treat delirium. We suggest using dexmedetomidine for delirium in mechanically ventilated adults where agitation is precluding weaning/extubation.	Conditional Conditional	Low Low
Should a single-component, nonpharmacologic strategy not solely focused on sleep improvement or early mobilization (vs no such strategy) be used to reduce delirium in critically ill adults?	We suggest not using bright light therapy to reduce delirium in critically ill adults.	Conditional	Moderate

(*Continued*)

TABLE 1. (*Continued*). Summary of Actionable Patient Intervention Comparison Outcome Questions and Recommendations

Question	Recommendation	Strength	Quality of Evidence
Should a multicomponent, nonpharmacologic strategy (vs no such strategy) be used to reduce delirium in critically ill adults?	We suggest using a multicomponent, nonpharmacologic intervention that is focused on (but not limited to) reducing modifiable risk factors for delirium, improving cognition, and optimizing sleep, mobility, hearing, and vision in critically ill adults. Remarks: These multicomponent interventions include (but are not limited to) strategies to reduce or shorten delirium (e.g., reorientation, cognitive stimulation, use of clocks), improve sleep (e.g., minimizing light and noise), improve wakefulness (i.e., reduced sedation), reduce immobility (e.g., early rehabilitation/mobilization), and reduce hearing and/or visual impairment (e.g., enable use of devices such as hearing aids or eye glasses).	Conditional	Low
Immobility (rehabilitation/mobilization)			
For critically ill adults, is rehabilitation or mobilization (performed either in-bed or out-of-bed) beneficial in improving patient, family, or health system outcomes compared with usual care, a different rehabilitation/mobilization intervention, placebo, or sham intervention?	We suggest performing rehabilitation or mobilization in critically ill adults (conditional recommendation, low quality of evidence). Remarks: Rehabilitation is a "set of interventions designed to optimize functioning and reduce disability in individuals with a health condition." Mobilization is a type of intervention within rehabilitation that facilitates the movement of patients and expends energy with a goal of improving patient outcomes. This recommendation supports performing rehabilitation/mobilization interventions over usual care or similar interventions with a reduced duration, reduced frequency, or later onset. The implementation of this recommendation will be influenced by feasibility-related issues, particularly related to variability in the availability of appropriate staffing and resources to perform rehabilitation/mobilization interventions across ICUs.	Conditional	Low
Sleep			
Should physiologic monitoring be routinely used clinically to evaluate sleep in critically ill adults?	We suggest not routinely using physiologic sleep monitoring clinically in critically ill adults. Remarks: Physiologic monitoring refers to the use of actigraphy, bispectral analysis, electroencephalography, and polysomnography to determine if a patient is asleep or awake. It specifically does "not" include monitoring of patients' perceived sleep by either validated assessment (e.g., the Richards Campbell Sleep Questionnaire) or informal subjective bedside assessment.	Conditional	VL
Should assist-control ventilation be used at night (vs pressure support ventilation) to improve sleep in critically ill adults?	We suggest using assist-control ventilation at night (vs pressure support ventilation) for improving sleep in critically ill adults.	Conditional	Low
Should an adaptive mode of ventilation be used at night (vs pressure support ventilation) to improve sleep in critically ill adults?	We make no recommendation regarding the use of an adaptive mode of ventilation at night (vs pressure support ventilation) for improving sleep in critically ill adults.	None	VL
Among critically ill adults requiring NIV, should an NIV-dedicated ventilator (vs a standard ICU ventilator with NIV capacity) be used to improve sleep?	We suggest using either an NIV-dedicated ventilator or a standard ICU ventilator for critically ill adults requiring NIV to improve sleep.	Conditional	VL

(*Continued*)

TABLE 1. (*Continued*). Summary of Actionable Patient Intervention Comparison Outcome Questions and Recommendations

Question	Recommendation	Strength	Quality of Evidence
Should aromatherapy, acupressure, or music be used at night (vs not using it) to improve sleep in critically ill adults?	We suggest not using aromatherapy, acupressure, or music at night to improve sleep in critically ill adults	Conditional	Low, VL
Should noise and light reduction strategies (vs not using these strategies) be used at night to improve sleep in critically ill adults?	We suggest using noise and light reduction strategies to improve sleep in critically ill adults.	Conditional	Low
Should a sleep-promoting medication (i.e., melatonin, dexmedetomidine, or propofol) (vs no use of medication) be used to improve sleep in critically ill adults?	We make no recommendation regarding the use of melatonin to improve sleep in critically ill adults.	None	VL
	We make no recommendation regarding the use of dexmedetomidine at night to improve sleep.	None	Low
	We suggest not using propofol to improve sleep in critically ill adults.	Conditional	Low
Should a sleep-promoting protocol be used to improve sleep in critically ill adults?	We suggest using a sleep-promoting, multicomponent protocol in critically ill adults.	Conditional	VL

COX-1 = cyclooxygenase 1, HMG-CoA =3-hydroxy-3-methylglutaryl coenzyme A reductase, N/A = not applicable, NIV = noninvasive ventilation, NSAID = nonsteroidal anti-inflammatory drug, VL, very low.

other nonopioid analgesics (e.g., cyclooxygenase 1 selective nonsteroidal anti-inflammatory drugs) because it has no detrimental effects on hemostasis, gastric mucosal integrity, renal function, vigilance, ventilatory drive, and intestinal motility. However, nefopam use can be associated with tachycardia, glaucoma, seizure, and delirium. Although not available in the United States or Canada, nefopam is a low-cost drug that is used in nearly 30 countries. In cardiac surgery patients, nefopam's analgesic effect resembles IV fentanyl when delivered as patient-controlled analgesia, with less nausea (37).

Ketamine

Question. Should ketamine be used as an adjunct to an opioid (vs an opioid alone) for pain management in critically ill adults?

Recommendation.We suggest using low-dose ketamine (1–2 μg/kg/hr) as an adjunct to opioid therapy when seeking to reduce opioid consumption in postsurgical adults admitted to the ICU (conditional recommendation, very low quality of evidence).

IV ketamine, although shown to reduce opioid requirements among abdominal surgery patients admitted to the ICU, was not shown to improve patients' self-reported pain intensity (38). Reduced opioid consumption is only a surrogate for better patient-centered outcomes. The frequency of side effects (i.e., nausea, delirium, hallucinations, hypoventilation, pruritus, and sedation) was similar between the ketamine and control groups. Although indirect evidence from randomized controlled trials (RCTs) in non-ICU patients supports a role for ketamine as an analgesic adjuvant to opioid therapy, evidence evaluating its role in the ICU for this indication currently remains limited.

Neuropathic pain medications

Question. Should a neuropathic pain medication (e.g., gabapentin, carbamazepine, and pregabalin) be used as an adjunct to an opioid (vs an opioid alone) for pain management in critically ill adults?

Recommendations. We recommend using a neuropathic pain medication (e.g., gabapentin, carbamazepine, and pregabalin) with opioids for neuropathic pain management in critically ill adults (strong recommendation, moderate quality of evidence).

We suggest using a neuropathic pain medication (e.g., gabapentin, carbamazepine, and pregabalin) with opioids for pain management in ICU adults after cardiovascular surgery (conditional recommendation, low quality of evidence).

Neuropathic pain medications as an adjuvant to opioid therapy have been evaluated in critically ill adults with Guillain-Barré syndrome or who have recently undergone cardiac surgery (39–42). Across both populations, their use significantly reduced opioid consumption within 24 hours of their initiation. Among cardiac surgery patients, neuropathic pain medication use did not affect time to extubation or ICU LOS (41, 42). Panel members estimated that neuropathic agents had negligible costs and were widely available although the possible sedative and cognitive effects of these agents could preclude their use in some patients. These drugs require the ability for patients to swallow or have enteral access.

Agitation/Sedation

Sedatives are frequently administered to critically ill patients to relieve anxiety and prevent agitation-related harm (2).

TABLE 2. Summary of Descriptive Questions and Ungraded Statements

Descriptive Question	Ungraded Statement
Pain	
What factors influence pain in critically ill adults during both rest and during procedures?	Pain at rest is influenced by both psychologic (e.g., anxiety, depression) and demographic (e.g., young age, one or more comorbidities, history of surgery) factors. Pain during a procedure is influenced by preprocedural pain intensity, the type of procedure, underlying surgical or trauma diagnoses, and demographic factors (younger age, female sex, and non-white ethnicity).
What are the most reliable and valid pain assessment methods to use in critically ill adults?	Self-report scales: A patient's self-report of pain is the reference standard for pain assessment in patients who can communicate reliably. Among critically ill adults who are able to self-report pain, the 0–10 numeric rating scale administered either verbally or visually is a valid and feasible pain scale. Behavioral pain assessment tools: Among critically ill adults unable to self-report pain and in whom behaviors are observable, the BPS and BPS-NI patients and the CPOT demonstrate the greatest validity and reliability for monitoring pain. Proxy reporters: When appropriate, and when the patient is unable to self-report, family can be involved in their loved one's pain assessment process. Physiologic measures: Vital signs (i.e., heart rate, blood pressure, respiratory rate, oxygen saturation, and end-tidal CO_2) are not valid indicators for pain in critically ill adults and should only be used as cues to initiate further assessment using appropriate and validated methods such as the patient's self-report of pain (whenever possible) or a behavioral scale (i.e., BPS, BPS-NI, CPOT).
Agitation/sedation	
In critically ill intubated adults, is there a difference between DSIs vs NP-targeted sedation in the ability to achieve and maintain a light level of sedation?	In critically ill intubated adults, DSIs and NP-targeted sedation can achieve and maintain a light level of sedation. Remarks: A DSI or a spontaneous awakening trial is defined as a period of time, each day, during which a patient's sedative medication is discontinued and patients can wake up and achieve arousal and/or alertness, defined by objective actions such as opening eyes in response to a voice, following simple commands, and/or having a Sedation-Agitation Scale score of 4–7 or a Richmond Agitation-Sedation Scale score −1 to +1. NP-targeted sedation is defined as an established sedation protocol implemented by nurses at the bedside to determine sedative choices and to titrate these medications to achieve prescription-targeted sedation scores.
Are objective sedation monitoring tools (electroencephalogram-based tools or tools such as heart rate variability, actigraphy, and evoked potentials) useful in managing sedation in adult critically ill intubated adults?	BIS monitoring appears best suited for sedative titration during deep sedation or neuromuscular blockade, although observational data suggest potential benefit with lighter sedation as well. Sedation that is monitored with BIS compared with subjective scales may improve sedative titration when a sedative scale cannot be used.
What are the prevalence rates, rationale, and outcomes (harm and benefit) associated with physical restraint use in intubated or nonintubated critically ill adults?	Physical restraints are frequently used for critically ill adults although prevalence rates vary greatly by country. Critical care providers report using restraints to prevent self-extubation and medical device removal, avoid falls, and to protect staff from combative patients despite a lack of studies demonstrating efficacy and the safety concerns associated with physical restraints (e.g., unplanned extubations, greater agitation).
Delirium	
Which predisposing and precipitating risk factors are associated with delirium occurrence (i.e., incidence, prevalence, or daily transition), delirium duration, or severity in critically ill adults?	For the following risk factors, strong evidence indicates that these are associated with delirium in critically ill adults: 1) Modifiable: benzodiazepine use and blood transfusions b) Nonmodifiable: greater age, dementia, prior coma, pre-ICU emergency surgery or trauma, and increasing Acute Physiology and Chronic Health Evaluation and American Society of Anesthesiology scores
Can delirium be predicted in critically ill adults?	Predictive models that include delirium risk factors at both the time of ICU admission and in the first 24 hr of ICU admission have been validated and shown to be capable of predicting delirium in critically ill adults.

(*Continued*)

TABLE 2. (*Continued*). Summary of Descriptive Questions and Ungraded Statements

Descriptive Question	Ungraded Statement
Does the level of arousal influence delirium assessments with a validated screening tool?	Level of arousal may influence delirium assessments with a validated screening tool.
What are the short- and long-term outcomes of delirium in critically ill adults and are these causally related?	Positive delirium screening in critically ill adults is strongly associated with cognitive impairment at 3 and 12 mo after ICU discharge and may be associated with a longer hospital stay. Delirium in critically ill adults has consistently been shown not to be associated with posttraumatic stress disorder or post-ICU distress. Delirium in critically ill adults has not been consistently shown to be associated with ICU length of stay, discharge disposition to a place other than home, depression, functionality/dependence, or mortality.
What are the short- and long-term outcomes of rapidly reversible delirium?	Rapidly reversible delirium is associated with outcomes that are similar to patients who never experience delirium.
Immobility (rehabilitation and mobility)	
For critically ill adults, is receiving rehabilitation/mobilization (performed either in-bed or out-of-bed) commonly associated with patient-related safety events or harm?	Serious safety events or harms do not occur commonly during physical rehabilitation or mobilization.
For critically ill adults, what aspects of patient clinical status are indicators for the safe initiation of rehabilitation/mobilization (performed either in-bed or out-of-bed)?	Major indicators for safely initiating rehabilitation/mobilization include stability in cardiovascular, respiratory, and neurologic status. Vasoactive infusions or mechanical ventilation are not barriers to initiating rehabilitation/mobilization, assuming patients are otherwise stable with the use of these therapies.
For adult critically ill patients, what aspects of patient clinical status are indicators that rehabilitation/mobilization (performed either in-bed or out-of-bed) should be stopped?	Major indicators for stopping rehabilitation/mobilization include development of new cardiovascular, respiratory, or neurologic instability. Other events, such as a fall or medical device removal/malfunction, and patient distress are also indications for stopping.
Sleep (disruption)	
How does sleep in critically ill adults differ from normal sleep in healthy adults?	Total sleep time and sleep efficiency are often normal. Sleep fragmentation, the proportion of time spent in light sleep (stages N1 + N2), and time spent sleeping during the day (vs night) are higher. The proportion of time spent in deep sleep (stage N3 sleep and REM) is lower. Subjective sleep quality is reduced.
Is sleep different in critically ill adults if delirium (vs no delirium) is present?	The presence of delirium may not affect total sleep time, sleep efficiency, or sleep fragmentation. The influence of delirium on the proportion of time spent in light (N1 + N2) vs deeper (N3) sleep is unknown. REM sleep is lower if delirium is present. Delirium is associated with greater circadian sleep-cycle disruption and increased daytime sleep. Whether delirium affects reported subjective sleep quality remains unclear.
Is sleep different in critically ill adults who are mechanically ventilated (vs not mechanically ventilated)?	The use of mechanical ventilation in critically ill adults may worsen sleep fragmentation, architecture, and circadian rhythm (daytime sleep) compared with normal sleep, but these effects are often variable and have not yet been fully investigated. The use of mechanical ventilation (vs periods without mechanical ventilation) in patients with respiratory failure may improve sleep efficiency and reduce fragmentation, but data are limited.
What is the prevalence of unusual or dissociative sleep patterns in critically ill adults?	The prevalence of unusual or dissociated sleep patterns is highly variable and depends on patient characteristics.

(*Continued*)

TABLE 2. (*Continued*). Summary of Descriptive Questions and Ungraded Statements

Descriptive Question	Ungraded Statement
What risk factors that exist prior to the onset of critical illness affect sleep quality in critically ill adults in the ICU?	Patients who report poor-quality sleep and/or use of a pharmacologic sleep aid at home are more likely to report poor-quality sleep in the ICU.
Which ICU-acquired risk factors affect sleep quality in critically ill adults?	Pain, environmental stimuli, healthcare-related interruptions, psychologic factors, respiratory factors, and medications each affect sleep quality in the ICU.
Do sleep and circadian rhythm alterations "during" an ICU admission affect outcomes during and/or after the ICU stay in critically ill adults?	Although an association between sleep quality and delirium occurrence exists in critically ill adults, a cause-effect relationship has not been established.
	An association among sleep quality and duration of mechanical ventilation, length of ICU stay, and ICU mortality in critically ill adults remains unclear.
	The effects of sleep quality and circadian rhythm alterations on outcomes in critically ill patients after ICU discharge are unknown.

BIS = bispectral analysis, BPS = Behavioral Pain Scale in intubated, BPS-NI = Behavioral Pain Scale in nonintubated, CPOT = Critical Care Pain Observation Tool, DSI = daily sedative interruption, NP = nursing protocolized, REM = rapid eye movement.

These medications may predispose patients to increased morbidity (43–46). In addition to the healthcare provider determining the specific indication for the sedative use, the patient's current and subsequent sedation status should be continuously assessed using valid and reliable scales (47–49). The 2013 guidelines (2) suggested targeting light levels of sedation or using daily awakening trials (44, 50–52), and minimizing benzodiazepines (53), to improve short-term outcomes (e.g., duration of mechanical ventilation and ICU LOS). In addition, sedation delivery paradigms and specific sedative medications can have an important effect on post-ICU outcomes including 90-day mortality, physical functioning, and neurocognitive and psychologic outcomes.

Light Sedation

Question. Does light sedation (vs deep sedation), regardless of the sedative agent(s) used, significantly affect outcomes in critically ill mechanically ventilated adults?

Recommendation. We suggest using light sedation (vs deep sedation) in critically ill, mechanically ventilated adults (conditional recommendation, low quality of evidence).

The 2013 guidelines' ungraded statement associated maintaining a light level of sedation with shortened time to extubation and ICU LOS (2). Although the previous guideline defined light sedation as a Richmond Agitation-Sedation Scale (RASS) scale score of greater than or equal to –2 and eye opening of at least 10 seconds (50), this level of sedation is probably deeper than that required for mechanically ventilated patient management in an ICU. No universally accepted definition of light sedation exists. For studies that used scales, such as the RASS (48), a RASS score of –2 to +1 (or its equivalent using other scales) was defined as light sedation in the studies evaluated by this panel.

The outcomes evaluated differ from the short-term outcomes assessed in the 2013 guidelines (2) in their consideration of post-ICU discharge measurements. Light sedation was associated with a shorter time to extubation (51, 54, 55) and a reduced tracheostomy rate (50). Light sedation was not associated with a reduction in 90-day mortality (44, 50, 53), delirium prevalence (44, 54), posttraumatic stress disorder incidence (31, 50), or self-extubation (44, 50, 53, 55). No RCTs evaluated the impact of light versus deep sedation on cognitive or physical functioning.

Choice of Sedative. Sedation indication, goal, clinical pharmacology, and acquisition cost are important determinants in choosing a sedative agent. The 2013 guidelines suggest (conditionally) that nonbenzodiazepine sedatives (either propofol or dexmedetomidine) are preferable to benzodiazepine sedatives (either midazolam or lorazepam) in critically ill, mechanically ventilated adults because of improved short-term outcomes, such as ICU LOS, duration of mechanical ventilation, and delirium (2). For the 2018 guidelines (1), we considered both short- and long-term outcomes as critical in our evaluation.

Questions. Should propofol, when compared with a benzodiazepine, be used for sedation in critically ill, mechanically ventilated adults?

Should dexmedetomidine, when compared with a benzodiazepine, be used for sedation in critically ill, mechanically ventilated adults?

Should dexmedetomidine, when compared with propofol, be used for sedation in critically ill, mechanically ventilated adults?

Recommendation. We suggest using either propofol or dexmedetomidine over benzodiazepines for sedation in critically ill, mechanically ventilated adults (conditional recommendation, low quality of evidence).

We evaluated the effect of propofol versus a benzodiazepine, dexmedetomidine versus a benzodiazepine, and propofol versus dexmedetomidine in three separate analyses for the outcomes deemed critical. In most studies, benzodiazepines were administered as continuous infusions and not intermittent boluses. We combined studies using midazolam and lorazepam. A shortened time to light sedation of at least 4 hours and time to extubation of at least 8–12 hours (one nursing shift) were deemed clinically significant.

Compared with a benzodiazepine, propofol use was associated with a shorter time to light sedation in seven

RCTs (56–62) and a shorter time to extubation in nine RCTs (56, 57, 61, 67). Only one RCT assessed delirium and found no difference (61). No data were available for other critical outcomes. Although propofol was associated with a higher risk of self-extubation, the CI for this outcome was wide and it remains unclear if harm resulted (i.e., need for reintubation).

Dexmedetomidine, when compared with a benzodiazepine infusion (one study used intermittent boluses), was associated with a shorter duration of mechanical ventilation in five RCTs (53, 67–70) and ICU of stay in three RCTs (53, 68, 71). Delirium prevalence was evaluated in four RCTs (53, 68, 69, 71); the Midazolam versus Dexmedetomidine (MIDEX) (69) trial data could not be pooled as delirium was assessed only once, 48 hours after sedation discontinuation. Dexmedetomidine was associated with a significant reduction in delirium in the three remaining pooled RCTs that evaluated delirium bid throughout the ICU stay (53, 68, 71). The Safety and Efficacy of Dexmedetomidine Compared With Midazolam (53) and Maximizing Efficacy of Targeted Sedation and Reducing Neurological Dysfunction (MENDS) (68) studies both demonstrated a greater incidence of bradycardia in the dexmedetomidine group; neither study found that intervention was required for the bradycardia.

We evaluated three RCTs comparing dexmedetomidine and propofol; none of the three demonstrated any difference in time to extubation (67, 69, 72). No data were available for other critical outcomes. A single RCT, the Propofol versus Dexmedetomidine (PRODEX) study, showed that delirium incidence was decreased with dexmedetomidine at the single time point of 48 hours after sedation cessation (69). Patients could communicate more effectively if sedated with dexmedetomidine when compared with propofol (69). No differences were reported in bradycardia or hypotension between patients sedated with propofol versus dexmedetomidine (69).

Economic considerations surrounding sedative choice were not assessed as both propofol and dexmedetomidine acquisition costs are now lower than when they were initially studied. Incorporating both propofol and dexmedetomidine into practice was considered likely acceptable and feasible, whereas recognizing dexmedetomidine may not be the preferred unique sedative when deep sedation (with or without neuromuscular blockade) is required. Panel members judged that the desirable and undesirable consequences of propofol (vs dexmedetomidine) were balanced; therefore, they issued a conditional recommendation to use either agent for sedation of critically ill adults.

Delirium

Delirium is common in critically ill adults. Delirium is a clinical diagnosis; most studies detect its presence using screening tools such as the Confusion Assessment Method for the ICU (CAM-ICU) or the Intensive Care Delirium Screening Checklist (73, 74). Delirium can be disturbing for affected patients and relatives and is associated with worse cognitive outcome, increased ICU and hospital LOS, and greater costs (75).

Multicomponent Nonpharmacologic Prevention and Treatment

Question. Should a multicomponent, nonpharmacologic strategy (vs no such strategy) be used to reduce delirium in critically ill adults?

Recommendation. We suggest using a multicomponent, nonpharmacologic intervention that is focused on (but not limited to) reducing modifiable risk factors for delirium, improving cognition, and optimizing sleep, mobility, hearing, and vision in critically ill adults (conditional recommendation, low quality of evidence).

Remarks. These multicomponent interventions include (but are not limited to) strategies to reduce or shorten delirium (e.g., reorientation, cognitive stimulation, use of clocks), improve sleep (e.g., minimizing light and noise), improve wakefulness (i.e., reduced sedation), reduce immobility (e.g., early rehabilitation/mobilization), and reduce hearing and/or visual impairment (e.g., enable use of devices such as hearing aids or eye glasses).

The multicomponent intervention studies, many of which were not randomized, evaluated a bundle of interventions. Overall, the use of such strategies significantly reduced delirium (76, 80). Further, ICU duration of delirium in patients who developed it (79), ICU LOS (76), and hospital mortality all decreased (77). Another multiple intervention approach, the Awakening and Breathing Coordination, Delirium monitoring/management, and Early exercise/mobility (ABCDE) bundle, was significantly associated with less delirium in a before-after study (81). When a revised and expanded ABCDEF bundle (which included a focus on "A," assessment and treatment of pain, and "F," family engagement) was evaluated in a larger, multicenter, before-after, cohort study, and where delirium was also assessed using the CAM-ICU, an adjusted analysis showed that improvements in bundle compliance were significantly associated with reduced mortality and more ICU days without coma or delirium (82). Adverse effects were not reported in the nonpharmacologic interventions studies.

Delirium Treatment

Question. Should a pharmacologic agent (vs no use of this agent) be used to "treat" delirium in all critically ill adults with delirium?

Antipsychotic/Statin

Recommendation. We suggest not routinely using haloperidol, an atypical antipsychotic, or a 3-hydroxy-3-methylglutaryl coenzyme A reductase reductase inhibitor (i.e., a statin) to treat delirium (conditional recommendation, low quality of evidence).

A total of six RCTs, haloperidol ($n = 2$) (83, 84), atypical antipsychotics (quetiapine [$n = 1$] [83], ziprasidone [$n = 1$] [81], and olanzapine [$n = 1$] [84]), a statin (rosuvastatin) ($n = 1$) (87), informed this question. This evidence suggests that the use of the typical antipsychotic, haloperidol, an atypical antipsychotic, or a statin was not associated with a shorter duration of delirium, mechanical ventilation or ICU LOS, or decreased mortality.

Although this recommendation discourages the "routine" use of antipsychotic agents in the treatment of delirium, the short-term use of haloperidol or an atypical antipsychotic in patients may be warranted, despite a lack of evidence, for those patients

who experience significant distress secondary to the symptoms of a delirium, such as hallucination and/or delusion-associated fearfulness or who are delirious and have agitation that may be physically harmful to themselves or others (88). However, all antipsychotic agents should be discontinued immediately following the resolution of the patient's distressful symptoms.

Dexmedetomidine

Recommendation. We suggest using dexmedetomidine for delirium in mechanically ventilated adults where agitation is precluding weaning/extubation (conditional recommendation, low quality of evidence).

A single randomized trial evaluated dexmedetomidine's role as a treatment for agitation precluding ventilator liberation (89). It screened 21,500 intubated patients from 15 ICUs to enroll the 71 study patients and was terminated early because the allocated funding (from dexmedetomidine's manufacturer) was expended (89). Although dexmedetomidine (vs placebo) was associated with a small, but statistically significant, increase in ventilator-free hours within 7 days of randomization, its use did not affect either ICU or hospital LOS, or patients' disposition location at hospital discharge.

Immobility (Rehabilitation and Mobility)

Survivors of critical illness frequently experience many long-term sequelae, including ICU-acquired muscle weakness (ICUAW). ICUAW can occur in 25–50% of critically ill patients (90) and is associated with impairments in patients' long-term survival, physical functioning, and quality of life (91–93). One important risk factor for ICUAW is bed rest (91, 94). The safety, feasibility, and benefits of rehabilitation and mobilization delivered in the ICU setting have been evaluated as potential means to mitigate ICUAW and impaired physical functioning. As highlighted in the 2013 guidelines (2), rehabilitation/mobilization may be beneficial as a delirium management strategy. Furthermore, important associations exist between analgesic and sedation practices, and pain and sedation status with whether patients participate in rehabilitation/mobilization in the ICU (95).

Question. For critically ill adults, is rehabilitation or mobilization (performed either in-bed or out-of-bed) beneficial in improving patient, family, or health system outcomes compared with usual care, a different rehabilitation/mobilization intervention, placebo, or sham intervention?

Recommendation. We suggest performing rehabilitation or mobilization in critically ill adults (conditional recommendation, low quality of evidence).

Remarks. Rehabilitation is a "set of interventions designed to optimize functioning and reduce disability in individuals with a health condition." Mobilization is a type of intervention within rehabilitation that facilitates the movement of patients and expends energy with a goal of improving patient outcomes. This recommendation supports performing rehabilitation/mobilization interventions over usual care or similar interventions with a reduced duration, reduced frequency, or later onset. The implementation of this recommendation will be influenced by feasibility-related issues, particularly related to variability in the availability of appropriate staffing and resources to perform rehabilitation/mobilization interventions across ICUs.

We identified a total of 16 RCTs (96–111) that met our eligibility criteria and reported on five critical outcomes. Rehabilitation/mobilization significantly improved muscle strength at ICU discharge (99–101, 103, 105, 111) and significantly reduced duration of mechanical ventilation (96–100, 102, 104, 107). A moderate, but not significant, improvement in health-related quality of life measured using the short form 36 instrument within 2 months of discharge was observed across four RCTs (103, 107–109).

Rehabilitation/mobilization had no effect on hospital mortality (96, 98–109, 112) or short-term physical functioning measures (96, 102, 105, 107, 110). The incidence of adverse events for patients was very low based on five trials and eight observational studies. Three additional outcomes (cognitive function, mental health, and timing of return to work and related economic outcomes) could not be evaluated due to insufficient data.

Rehabilitation/mobilization was assessed as feasible, acceptable to key stakeholders, and likely to be cost-effective based on preliminary data. In addition, indirect evidence (112), along with a discussion with panel members (including an ICU patient representative), suggests that patients value rehabilitation/mobilization benefits (113). Given the small benefit of rehabilitation/mobilization interventions (performed either in-bed or out-of-bed) and the low overall quality of evidence, panel members agreed that the desirable consequences for patients probably outweigh the undesirable consequences.

Sleep Disruption

Poor sleep is a common complaint and a source of distress for many critically ill patients (114, 115). Sleep disruption in the ICU can be severe and is characterized by sleep fragmentation, abnormal circadian rhythms, increased light sleep (stage N1), and decreased slow-wave (stage N3) and rapid eye movement (REM) sleep (116). The interplay of medications, critical illness, delirium, cerebral perfusion, and sleep is complex, but it is important and is an increasing focus of research. In addition to emotional distress, sleep deprivation has been hypothesized to contribute to ICU delirium (117), prolonged duration of mechanical ventilation (116), deranged immune function (118), and neurocognitive dysfunction.

Pharmacologic Interventions

Question. Should a sleep-promoting medication (i.e., melatonin, dexmedetomidine, or propofol) (vs no use of a medication) be used to improve sleep in critically ill adults?

Melatonin

Recommendation.We make no recommendation regarding the use of melatonin to improve sleep in critically ill adults (no recommendation, very low quality of evidence).

Three small, placebo-controlled, randomized trials ($n = 60$) evaluating the night-time administration of melatonin were reviewed (119–121). Two of the studies (120, 121) reported a small improvement in sleep quality, but the panel determined

that the data were insufficient to warrant a recommendation. The manufacture of melatonin in the United States is not Food and Drug Administration regulated; concerns as to the quality and consistency of the product have prevented many hospitals from adding it to their formulary. Melatonin is, however, associated with relatively few adverse effects (e.g., mild sedation and headache) and inexpensive.

Dexmedetomidine

Recommendation.We make no recommendation regarding the use of dexmedetomidine at night to improve sleep (no recommendation, low quality of evidence).

Two randomized trials ($n = 74$) compared dexmedetomidine to placebo in critically ill mechanically ventilated (122) and in critically ill, nonmechanically ventilated patients not requiring a continuous sedative infusion (123). Dexmedetomidine (vs placebo) increased stage 2 sleep and decreased stage 1 sleep in both studies; however, neither demonstrated a decrease in sleep fragmentation or an increase in deep or REM sleep. A third, observational trial, not included in our analysis, corroborated these findings with regard to sleep architecture and noted preserved day-night cycling when dexmedetomidine was administered overnight in mechanically ventilated ICU patients (124). If a sedative infusion is indicated for a hemodynamically stable critically ill adult overnight, dexmedetomidine may be a reasonable option because of its potential to improve sleep architecture.

Propofol

Recommendation. We suggest not using propofol to improve sleep in critically ill adults (conditional recommendation, low quality of evidence).

Two RCTs compared propofol to benzodiazepines (125, 126), and one compared propofol to placebo (127). No demonstrable improvement in sleep occurred with propofol compared with placebo. Further, propofol was associated with REM suppression, hemodynamic side effects, and respiratory depression, sometimes necessitating mechanical ventilation. Although we recommend against using propofol for the sole purpose of improving sleep in the critically ill, this recommendation does not intend to address its use in patients requiring procedural or continuous sedation.

Sleep-Promoting Protocol

Question. Should a sleep-promoting protocol be used to improve sleep in critically ill adults?

Recommendation. We suggest using a sleep-promoting, multicomponent protocol in critically ill adults (conditional recommendation, very low quality of evidence).

The sleep-promoting protocols eligible for inclusion varied in their components: all included offering earplugs and eyeshades to patients (128–131) and two included use of relaxing music (128, 130). Among the two compromising a more complex combination of interventions (128, 131), one specified a pharmacologic guideline that discouraged the use of sedating medications known to alter sleep and/or precipitate delirium and introduced interventions in stages over a 5-month period (128). In all studies, protocols were applied to all ICU patients and did not target a subset of patients known to have poor sleep quality.

One small RCT in open-heart surgery patients demonstrated that earplugs, eyeshades, and relaxing music improved self-reported sleep quality (129). Of the three observational before-and-after studies, one found an improvement in sleep in a mixed ICU population (131), whereas the other two did not (128, 130). Pooled analysis of the three studies demonstrated an overall reduction in the prevalence of delirium with a sleep-promoting protocol. Which of the interventions, or combinations of interventions, are effective in improving sleep and reducing delirium cannot be discerned from the above studies.

SUMMARY

Under the auspices of the Society of Critical Care Medicine, this executive summary aims to provide the most clinically meaningful and novel aspects, by section, of the PADIS guidelines that clinicians, stakeholders, and decision makers should consider using when improving care for critically ill adults. The recommendation rationales, fueled by rigorous data evaluation, debate, and discussion, circled back to the bedside experience—and the perspective of what was best for patient—held by the panelists and patients involved in producing the guidelines. We believe that the 2018 PADIS guideline (1) will foster the delivery of excellent care regarding pain, agitation/sedation, delirium, immobility, and sleep disruption and stimulate the completion of pragmatic, patient-centered research across each of these important critical care domains.

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