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Devlin, John W
Skrobik, Yoanna
Gélinas, Céline
et al.

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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

John W. Devlin, PharmD, FCCM[1,2]; Yoanna Skrobik, MD, FRCP(c), MSc, FCCM[3,4];
Céline Gélinas, RN, PhD[5]; Dale M. Needham, MD, PhD[6]; Arjen J. C. Slooter, MD, PhD[7];
Pratik P. Pandharipande, MD, MSCI, FCCM[8]; Paula L. Watson, MD[9];
Gerald L. Weinhouse, MD[10]; Mark E. Nunnally, MD, FCCM[11,12,13,14]; Bram Rochwerg, MD, MSc[15,16];
Michele C. Balas, RN, PhD, FCCM, FAAN[17]; Mark van den Boogaard, RN, PhD[18];
Karen J. Bosma, MD[19]; Nathaniel E. Brummel, MD, MSCI[20]; Gerald Chanques, MD, PhD[21,22];
Linda Denehy, PT, PhD[23]; Xavier Drouot, MD, PhD[24,25]; Gilles L. Fraser, PharmD, MCCM[26];
Jocelyn E. Harris, OT, PhD[27]; Aaron M. Joffe, DO, FCCM[28]; Michelle E. Kho, PT, PhD[27];
John P. Kress, MD[29]; Julie A. Lanphere, DO[30]; Sharon McKinley, RN, PhD[31];
Karin J. Neufeld, MD, MPH[32]; Margaret A. Pisani, MD, MPH[33]; Jean-Francois Payen, MD, PhD[34];
Brenda T. Pun, RN, DNP[35]; Kathleen A. Puntillo, RN, PhD, FCCM[36]; Richard R. Riker, MD, FCCM[26];
Bryce R. H. Robinson, MD, MS, FACS, FCCM[37]; Yahya Shehabi, MD, PhD, FCICM[38];
Paul M. Szumita, PharmD, FCCM[39]; Chris Winkelman, RN, PhD, FCCM[40];
John E. Centofanti, MD, MSc[41]; Carrie Price, MLS[42]; Sina Nikayin, MD[43]; Cheryl J. Misak, PhD[44];
Pamela D. Flood, MD[45]; Ken Kiedrowski, MA[46]; Waleed Alhazzani, MD, MSc[16,47]

[1]School of Pharmacy, Northeastern University, Boston, MA.

[2]Division of Pulmonary, Critical Care and Sleep Medicine, Tufts Medical Center, Boston, MA.

[3]Faculty of Medicine, McGill University, Montreal, PQ, Canada.

[4]Regroupement de Soins Critiques Respiratoires, Réseau de Santé Respiratoire, Montreal, PQ, Canada.

[5]Ingram School of Nursing, McGill University, Montreal, PQ, Canada.

[6]Division of Pulmonary and Critical Care Medicine, Department of Physical Medicine and Rehabilitation, School of Medicine, Johns Hopkins University, Baltimore, MD.

[7]Department of Intensive Care Medicine, Brain Center Rudolf Magnus, University Medical Center, Utrecht University, Utrecht, The Netherlands.

[8]Department of Anesthesiology, Division of Anesthesiology Critical Care Medicine, Vanderbilt University Medical Center, Nashville, TN.

[9]Division of Sleep Medicine, Vanderbilt University Medical Center, Nashville, TN.

[10]Division of Pulmonary and Critical Care, Brigham and Women's Hospital and School of Medicine, Harvard University, Boston, MA.

[11]Division of Anesthesiology, Perioperative Care and Pain Medicine, New York University Langone Health, New York, NY.

[12]Division of Medicine, New York University Langone Health, New York, NY.

[13]Division of Neurology, New York University Langone Health, New York, NY.

[14]Division of Surgery, New York University Langone Health, New York, NY.

[15]Department of Medicine (Critical Care), McMaster University, Hamilton, ON, Canada.

[16]Department of Health Research Methods, Impact and Evidence, McMaster University, Hamilton, ON, Canada.

[17]The Ohio State University College of Nursing, Center of Excellence in Critical and Complex Care, The Ohio State University Wexner Medical Center, Columbus, OH.

[18]Department of Intensive Care Medicine, Radboud University Medical Center, Nijmegen, The Netherlands.

[19]Division of Critical Care, London Health Sciences Centre and Schulich School of Medicine and Dentistry, University of Western Ontario, London, ON, Canada.

[20]Department of Medicine, Division of Allergy, Pulmonary and Critical Care Medicine, Center for Quality Aging, and the Center for Health Services Research, Vanderbilt University Medical Center, Nashville, TN.

[21]Department of Anesthesia and Intensive Care, Montpellier University Saint Eloi Hospital, Montpellier, France.

[22]PhyMedExp, INSERM, CNRS, University of Montpellier, Montpellier, France.

[23]Melbourne School of Health Sciences, The University of Melbourne, Melbourne, VIC, Australia.

[24]Faculte de Medecine Pharmacie, University of Poitiers, Poitiers, France.

[25]Service de Neurophysiologie, CHU de Poitiers, Poitiers, France.

[26]Department of Critical Care, Maine Medical Center and School of Medicine, Tufts University, Portland, ME.

[27]School of Rehabilitation Science, McMaster University, Hamilton, ON, Canada.

[28]Department of Anesthesiology and Pain Medicine, Harborview Medical Center, University of Washington, Seattle, WA.

[29]Division of Pulmonary and Critical Care Medicine, University of Chicago, Chicago, IL.

[30]Department of Physical Medicine and Rehabilitation, Intermountain Health, Salt Lake City, UT.

[31]School of Nursing and Midwifery, Deakin University, Geelong, VIC, Australia.

[32]Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, MD.

[33]Division of Pulmonary, Critical Care and Sleep Medicine, School of Medicine, Yale University, New Haven, CT.

[34]Department of Anesthesiology and Critical Care, Grenoble Alpes University Hospital, Grenoble, France.

[35]Center for Health Services Research, Vanderbilt University Medical Center, Nashville, TN.

[36]School of Nursing, University of California San Francisco, San Francisco, CA.

[37]Department of Surgery, University of Washington, Seattle, WA.

[38]Department of Critical Care and Perioperative Medicine, School of Clinical Sciences, Monash University, Melbourne, VIC, Australia.

[39]Department of Pharmacy, Brigham and Women's Hospital, Boston, MA.

[40]Frances Payne Bolton School of Nursing, Case Western Reserve University, Cleveland, OH.

[41]Department of Anesthesia and Critical Care, McMaster University, Hamilton, ON, Canada.

[42]Welch Medical Library, Johns Hopkins University, Baltimore, MD.

[43]Department of Psychiatry and Behavioral Sciences, New York Medical College, Valhalla, NY.

[44]Department of Philosophy, University of Toronto, Toronto, CA.

[45]Division of Anesthesiology, Stanford University Hospital, Palo Alto, CA.

[46]Patient and Family Advisory Committee, Johns Hopkins Hospital, Baltimore, MD.

[47]Department of Medicine (Critical Care and Gastroenterology), McMaster University, Hamilton, ON, Canada.

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 1g 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.	Conditional	Moderate
	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.		
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?	We suggest using an opioid, at the lowest effective dose, for procedural pain management in critically ill adults.	Conditional	Moderate
Should a high-dose opioid (vs a low-dose opioid) be used for critically ill adults undergoing a procedure?	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).		

(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?	We suggest not using either local analgesia or nitrous oxide for pain management during chest tube removal in critically ill adults.	Conditional	Low
Should nitrous oxide (vs an opioid) be used for critically ill adults undergoing a procedure?			
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?	We suggest not offering cybertherapy (virtual reality) or hypnosis for pain management in critically ill adults	Conditional	VL
Should hypnosis (vs no use of hypnosis) be used for pain management in critically ill adults?			
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 non-procedural 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

Question	Recommendation	Strength	Quality of Evidence
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 co-enzyme 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.

REFERENCES

1. Devlin JW, Skrobik Y, Gelinas C, et al: Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU. *Crit Care Med* 2018; 46:e825–e873

2. Barr J, Fraser GL, Puntillo K, et al; American College of Critical Care Medicine: Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. *Crit Care Med* 2013; 41:263–306

3. Balas MC, Weinhouse GL, Denehy L, et al: Interpreting and Implementing the 2018 Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption Clinical Practice Guideline. *Crit Care Med* 2018; 46:1464–1470

4. Devlin JW, Skrobik Y, Rochwerg B, et al: Methodological Innovation in Creating Clinical Practice Guidelines: Insights From the 2018 Society of Critical Care Medicine Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption Guideline Effort. *Crit Care Med* 2018; 46:1457–1463

5. Skrobik Y, Ahern S, Leblanc M, et al: Protocolized intensive care unit management of analgesia, sedation, and delirium improves analgesia and subsyndromal delirium rates. *Anesth Analg* 2010; 111:451–463

6. Vervest AC, Schimmel GH: Taxonomy of pain of the IASP. *Pain* 1988; 34:318–321

7. de Jong A, Molinari N, de Lattre S, et al: Decreasing severe pain and serious adverse events while moving intensive care unit patients: A prospective interventional study (the NURSE-DO project). *Crit Care* 2013; 17:R74

8. Georgiou E, Hadjibalassi M, Lambrinou E, et al: The impact of pain assessment on critically ill patients' outcomes: A systematic review. *Biomed Res Int* 2015; 2015:503830

9. Puntillo KA, Naidu R: Chronic pain disorders after critical illness and ICU-acquired opioid dependence: Two clinical conundra. *Curr Opin Crit Care* 2016; 22:506–512

10. Macintyre PE, Huxtable CA, Flint SL, et al: Costs and consequences: A review of discharge opioid prescribing for ongoing management of acute pain. *Anaesth Intensive Care* 2014; 42:558–574

11. Payen JF, Bosson JL, Chanques G, et al; DOLOREA Investigators: Pain assessment is associated with decreased duration of mechanical ventilation in the intensive care unit: A post hoc analysis of the DOLOREA study. *Anesthesiology* 2009; 111:1308–1316

12. Brook AD, Ahrens TS, Schaiff R, et al: Effect of a nursing-implemented sedation protocol on the duration of mechanical ventilation. *Crit Care Med* 1999; 27:2609–2615

13. Quenot JP, Ladoire S, Devoucoux F, et al: Effect of a nurse-implemented sedation protocol on the incidence of ventilator-associated pneumonia. *Crit Care Med* 2007; 35:2031–2036

14. Robinson BR, Mueller EW, Henson K, et al: An analgesia-delirium-sedation protocol for critically ill trauma patients reduces ventilator days and hospital length of stay. *J Trauma* 2008; 65:517–526

15. Chanques G, Jaber S, Barbotte E, et al: Impact of systematic evaluation of pain and agitation in an intensive care unit. *Crit Care Med* 2006; 34:1691–1699

16. Berger MM, Davadant M, Marin C, et al: Impact of a pain protocol including hypnosis in major burns. *Burns* 2010; 36:639–646

17. Aday AW, Dell'orfano H, Hirning BA, et al: Evaluation of a clinical pathway for sedation and analgesia of mechanically ventilated patients in a cardiac intensive care unit (CICU): The Brigham and Women's Hospital Levine CICU sedation pathways. *Eur Heart J Acute Cardiovasc Care* 2013; 2:299–305

18. Awissi DK, Bégin C, Moisan J, et al: I-SAVE study: Impact of sedation, analgesia, and delirium protocols evaluated in the intensive care unit: An economic evaluation. *Ann Pharmacother* 2012; 46:21–28

19. Diby M, Romand JA, Frick S, et al: Reducing pain in patients undergoing cardiac surgery after implementation of a quality improvement postoperative pain treatment program. *J Crit Care* 2008; 23:359–371

20. Egerod I, Jensen MB, Herling SF, et al: Effect of an analgo-sedation protocol for neurointensive patients: A two-phase interventional non-randomized pilot study. *Crit Care* 2010; 14:R71

21. Erdek MA, Pronovost PJ: Improving assessment and treatment of pain in the critically ill. *Int J Qual Health Care* 2004; 16:59–64

22. Faust AC, Rajan P, Sheperd LA, et al: Impact of an analgesia-based sedation protocol on mechanically ventilated patients in a medical intensive care unit. *Anesth Analg* 2016; 123:903–909

23. MacLaren R, Plamondon JM, Ramsay KB, et al: A prospective evaluation of empiric versus protocol-based sedation and analgesia. *Pharmacotherapy* 2000; 20:662–672

24. Park G, Lane M, Rogers S, et al: A comparison of hypnotic and analgesic based sedation in a general intensive care unit. *Br J Anaesth* 2007; 98:76–82

25. Tedders KM, McNorton KN, Edwin SB: Efficacy and safety of analgosedation with fentanyl compared with traditional sedation with propofol. *Pharmacotherapy* 2014; 34:643–647

26. van Gulik L, Ahlers SJ, Brkić Z, et al: Improved analgesia after the realisation of a pain management programme in ICU patients after cardiac surgery. *Eur J Anaesthesiol* 2010; 27:900–905

27. van Valen R, van Vuuren H, van Domburg RT, et al: Pain management after cardiac surgery: Experience with a nurse-driven pain protocol. *Eur J Cardiovasc Nurs* 2012; 11:62–69

28. Breen D, Karabinis A, Malbrain M, et al: Decreased duration of mechanical ventilation when comparing analgesia-based sedation using remifentanil with standard hypnotic-based sedation for up to 10 days in intensive care unit patients: A randomised trial [ISRCTN47583497]. *Crit Care* 2005; 9:R200–R210

29. Karabinis A, Mandragos K, Stergiopoulos S, et al: Safety and efficacy of analgesia-based sedation with remifentanil versus standard hypnotic-based regimens in intensive care unit patients with brain injuries: A randomised, controlled trial [ISRCTN50308308]. *Crit Care* 2004; 8:R268–R280

30. Rozendaal FW, Spronk PE, Snellen FF, et al; UltiSAFE Investigators: Remifentanil-propofol analgo-sedation shortens duration of ventilation and length of ICU stay compared to a conventional regimen: A centre randomised, cross-over, open-label study in the Netherlands. *Intensive Care Med* 2009; 35:291–298

31. Strøm T, Martinussen T, Toft P: A protocol of no sedation for critically ill patients receiving mechanical ventilation: A randomised trial. *Lancet* 2010; 375:475–480

32. White PF, Kehlet H, Neal JM, et al; Fast-Track Surgery Study Group: The role of the anesthesiologist in fast-track surgery: From multimodal analgesia to perioperative medical care. *Anesth Analg* 2007; 104:1380–1396

33. Cattabriga I, Pacini D, Lamazza G, et al: Intravenous paracetamol as adjunctive treatment for postoperative pain after cardiac surgery: A double blind randomized controlled trial. *Eur J Cardiothorac Surg* 2007; 32:527–531

34. Memis D, Inal MT, Kavalci G, et al: Intravenous paracetamol reduced the use of opioids, extubation time, and opioid-related adverse effects after major surgery in intensive care unit. *J Crit Care* 2010; 25:458–462

35. Cantais A, Schnell D, Vincent F, et al: Acetaminophen-induced changes in systemic blood pressure in critically ill patients: Results of a multicenter cohort study. *Crit Care Med* 2016; 44:2192–2198

36. Beloeil H, Delage N, Nègre I, et al: The median effective dose of nefopam and morphine administered intravenously for postoperative pain after minor surgery: A prospective randomized double-blinded isobolographic study of their analgesic action. *Anesth Analg* 2004; 98:395–400

37. Kim K, Kim WJ, Choi DK, et al: The analgesic efficacy and safety of nefopam in patient-controlled analgesia after cardiac surgery: A randomized, double-blind, prospective study. *J Int Med Res* 2014; 42:684–692

38. Guillou N, Tanguy M, Seguin P, et al: The effects of small-dose ketamine on morphine consumption in surgical intensive care unit patients after major abdominal surgery. *Anesth Analg* 2003; 97:843–847

39. Pandey CK, Bose N, Garg G, et al: Gabapentin for the treatment of pain in Guillain-Barré syndrome: A double-blinded, placebo-controlled, crossover study. *Anesth Analg* 2002; 95:1719–1723

40. Pandey CK, Raza M, Tripathi M, et al: The comparative evaluation of gabapentin and carbamazepine for pain management in Guillain-Barré syndrome patients in the intensive care unit. *Anesth Analg* 2005; 101:220–225

41. Pesonen A, Suojaranta-Ylinen R, Hammarén E, et al: Pregabalin has an opioid-sparing effect in elderly patients after cardiac surgery: A randomized placebo-controlled trial. *Br J Anaesth* 2011; 106:873–881

42. Joshi SS, Jagadeesh AM: Efficacy of perioperative pregabalin in acute and chronic post-operative pain after off-pump coronary artery bypass surgery: A randomized, double-blind placebo controlled trial. *Ann Card Anaesth* 2013; 16:180–185

43. Ouimet S, Kavanagh BP, Gottfried SB, et al: Incidence, risk factors and consequences of ICU delirium. *Intensive Care Med* 2007; 33:66–73

44. Shehabi Y, Bellomo R, Reade MC, et al; Sedation Practice in Intensive Care Evaluation (SPICE) Study Investigators; ANZICS Clinical Trials Group: Early intensive care sedation predicts long-term mortality in ventilated critically ill patients. *Am J Respir Crit Care Med* 2012; 186:724–731

45. Pandharipande P, Shintani A, Peterson J, et al: Lorazepam is an independent risk factor for transitioning to delirium in intensive care unit patients. *Anesthesiology* 2006; 104:21–26

46. Zaal IJ, Devlin JW, Hazelbag M, et al: Benzodiazepine-associated delirium in critically ill adults. *Intensive Care Med* 2015; 41:2130–2137

47. Brattebø G, Hofoss D, Flaatten H, et al: Effect of a scoring system and protocol for sedation on duration of patients' need for ventilator support in a surgical intensive care unit. *BMJ* 2002; 324:1386–1389

48. Sessler CN, Gosnell MS, Grap MJ, et al: The Richmond Agitation-Sedation Scale: Validity and reliability in adult intensive care unit patients. *Am J Respir Crit Care Med* 2002; 166:1338–1344

49. Riker RR, Fraser GL, Simmons LE, et al: Validating the Sedation-Agitation Scale with the bispectral index and Visual Analog Scale in adult ICU patients after cardiac surgery. *Intensive Care Med* 2001; 27:853–858

50. Kress JP, Pohlman AS, O'Connor MF, et al: Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. *N Engl J Med* 2000; 342:1471–1477

51. Treggiari MM, Romand JA, Yanez ND, et al: Randomized trial of light versus deep sedation on mental health after critical illness. *Crit Care Med* 2009; 37:2527–2534

52. Girard TD, Kress JP, Fuchs BD, et al: Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): A randomised controlled trial. *Lancet* 2008; 371:126–134

53. Riker RR, Shehabi Y, Bokesch PM, et al; SEDCOM (Safety and Efficacy of Dexmedetomidine Compared With Midazolam) Study Group: Dexmedetomidine vs midazolam for sedation of critically ill patients: A randomized trial. *JAMA* 2009; 301:489–499

54. Shehabi Y, Bellomo R, Reade MC, et al; Sedation Practice in Intensive Care Evaluation Study Investigators; Australian and New Zealand Intensive Care Society Clinical Trials Group: Early goal-directed sedation versus standard sedation in mechanically ventilated critically ill patients: A pilot study. *Crit Care Med* 2013; 41:1983–1991

55. Bugedo G, Tobar E, Aguirre M, et al: The implementation of an analgesia-based sedation protocol reduced deep sedation and proved to be safe and feasible in patients on mechanical ventilation. *Rev Bras Ter Intensiva* 2013; 25:188–196

56. Carrasco G, Molina R, Costa J, et al: Propofol vs midazolam in short-, medium-, and long-term sedation of critically ill patients. A cost-benefit analysis. *Chest* 1993; 103:557–564

57. Chamorro C, de Latorre FJ, Montero A, et al: Comparative study of propofol versus midazolam in the sedation of critically ill patients: Results of a prospective, randomized, multicenter trial. *Crit Care Med* 1996; 24:932–939

58. Weinbroum AA, Halpern P, Rudick V, et al: Midazolam versus propofol for long-term sedation in the ICU: A randomized prospective comparison. *Intensive Care Med* 1997; 23:1258–1263

59. Sanchez-Izquierdo-Riera JA, Caballero-Cubedo RE, Perez-Vela JL, et al: Propofol versus midazolam: Safety and efficacy for sedating the severe trauma patient. *Anesth Analg* 1998; 86:1219–1224

60. Sandiumenge Camps A, Sanchez-Izquierdo Riera JA, Toral Vazquez D, et al: Midazolam and 2% propofol in long-term sedation of traumatized critically ill patients: Efficacy and safety comparison. *Crit Care Med* 2000; 28:3612–3619

61. Mesnil M, Capdevila X, Bringuier S, et al: Long-term sedation in intensive care unit: A randomized comparison between inhaled sevoflurane and intravenous propofol or midazolam. *Intensive Care Med* 2011; 37:933–941

62. Zhou Y, Jin X, Kang Y, et al: Midazolam and propofol used alone or sequentially for long-term sedation in critically ill, mechanically ventilated patients: A prospective, randomized study. *Crit Care* 2014; 18:R122

63. Boeke A, Lauwers J, Schurink G: A pilot study to compare the use of propofol and midazolam for long-term sedation. *J Drug Dev* 1989; 2:71–72

64. Barrientos-Vega R, Mar Sánchez-Soria M, Morales-García C, et al: Prolonged sedation of critically ill patients with midazolam or propofol: Impact on weaning and costs. *Crit Care Med* 1997; 25:33–40

65. Costa J, Cabré L, Molina R, et al: Cost of ICU sedation: Comparison of empirical and controlled sedation methods. *Clin Intensive Care* 1994; 5:17–21

66. Hall RI, Sandham D, Cardinal P, et al; Study Investigators: Propofol vs midazolam for ICU sedation: A Canadian multicenter randomized trial. *Chest* 2001; 119:1151–1159

67. Srivastava VK, Agrawal S, Kumar S, et al: Comparison of dexmedetomidine, propofol and midazolam for short-term sedation in postoperatively mechanically ventilated neurosurgical patients. *J Clin Diagn Res* 2014; 8:GC04–GC07

68. Pandharipande PP, Pun BT, Herr DL, et al: Effect of sedation with dexmedetomidine vs lorazepam on acute brain dysfunction in mechanically ventilated patients: The MENDS randomized controlled trial. *JAMA* 2007; 298:2644–2653

69. Jakob SM, Ruokonen E, Grounds RM, et al; Dexmedetomidine for Long-Term Sedation Investigators: Dexmedetomidine vs midazolam or propofol for sedation during prolonged mechanical ventilation: Two randomized controlled trials. *JAMA* 2012; 307:1151–1160

70. MacLaren R, Preslaski CR, Mueller SW, et al: A randomized, double-blind pilot study of dexmedetomidine versus midazolam for intensive

care unit sedation: Patient recall of their experiences and short-term psychological outcomes. *J Intensive Care Med* 2015; 30:167–175

71. Xu JB, Wang YZ, Shi QS: A combined protocol for dexmedetomidine used in prolonged sedation in intensive care unit. *Mod Med J Chin* 2012; 14:20–22

72. Herr DL, Sum-Ping ST, England M: ICU sedation after coronary artery bypass graft surgery: Dexmedetomidine-based versus propofol-based sedation regimens. *J Cardiothorac Vasc Anesth* 2003; 17:576–584

73. Ely EW, Margolin R, Francis J, et al: Evaluation of delirium in critically ill patients: Validation of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). *Crit Care Med* 2001; 29: 1370–1379

74. Bergeron N, Dubois MJ, Dumont M, et al: Intensive Care Delirium Screening Checklist: Evaluation of a new screening tool. *Intensive Care Med* 2001; 27:859–864

75. Slooter AJ, Van De Leur RR, Zaal IJ: Delirium in critically ill patients. *Handb Clin Neurol* 2017; 141:449–466

76. Foster J, Kelly M: A pilot study to test the feasibility of a nonpharmacologic intervention for the prevention of delirium in the medical intensive care unit. *Clin Nurse Spec* 2013; 27:231–238

77. Moon KJ, Lee SM: The effects of a tailored intensive care unit delirium prevention protocol: A randomized controlled trial. *Int J Nurs Stud* 2015; 52:1423–1432

78. Colombo R, Corona A, Praga F, et al: A reorientation strategy for reducing delirium in the critically ill. Results of an interventional study. *Minerva Anestesiol* 2012; 78:1026–1033

79. Hanison J, Conway D: A multifaceted approach to prevention of delirium on intensive care. *BMJ Qual Improv Rep* 2015; 11:4

80. Rivosecchi RM, Kane-Gill SL, Svec S, et al: The implementation of a nonpharmacologic protocol to prevent intensive care delirium. *J Crit Care* 2016; 31:206–211

81. Balas MC, Burke WJ, Gannon D, et al: Implementing the awakening and breathing coordination, delirium monitoring/management, and early exercise/mobility bundle into everyday care: Opportunities, challenges, and lessons learned for implementing the ICU Pain, Agitation, and Delirium Guidelines. *Crit Care Med* 2013; 41:S116–S127

82. Barnes-Daly MA, Phillips G, Ely EW: Improving hospital survival and reducing brain dysfunction at seven California community hospitals: Implementing PAD guidelines via the ABCDEF bundle in 6,064 patients. *Crit Care Med* 2017; 45:171–178

83. Girard TD, Pandharipande PP, Carson SS, et al; MIND Trial Investigators: Feasibility, efficacy, and safety of antipsychotics for intensive care unit delirium: The MIND randomized, placebo-controlled trial. *Crit Care Med* 2010; 38:428–437

84. Page VJ, Ely EW, Gates S, et al: Effect of intravenous haloperidol on the duration of delirium and coma in critically ill patients (Hope-ICU): A randomised, double-blind, placebo-controlled trial. *Lancet Respir Med* 2013; 1:515–523

85. Devlin JW, Roberts RJ, Fong JJ, et al: Efficacy and safety of quetiapine in critically ill patients with delirium: A prospective, multicenter, randomized, double-blind, placebo-controlled pilot study. *Crit Care Med* 2010; 38:419–427

86. Skrobik YK, Bergeron N, Dumont M, et al: Olanzapine vs haloperidol: Treating delirium in a critical care setting. *Intensive Care Med* 2004; 30:444–449

87. Needham DM, Colantuoni E, Dinglas VD, et al: Rosuvastatin versus placebo for delirium in intensive care and subsequent cognitive impairment in patients with sepsis-associated acute respiratory distress syndrome: An ancillary study to a randomised controlled trial. *Lancet Respir Med* 2016; 4:203–212

88. Devlin JW, Smithburger P, Kane JM, et al: Intended and unintended consequences of constraining clinician prescribing: The case of antipsychotics. *Crit Care Med* 2016; 44:1805–1807

89. Reade MC, Eastwood GM, Bellomo R, et al; DahLIA Investigators; Australian and New Zealand Intensive Care Society Clinical Trials Group: Effect of dexmedetomidine added to standard care on ventilator-free time in patients with agitated delirium: A randomized clinical trial. *JAMA* 2016; 315:1460–1468

90. Denehy L, Lanphere J, Needham DM: Ten reasons why ICU patients should be mobilized early. *Intensive Care Med* 2017; 43:86–90

91. Fan E, Dowdy DW, Colantuoni E, et al: Physical complications in acute lung injury survivors: A two-year longitudinal prospective study. *Crit Care Med* 2014; 42:849–859

92. Hermans G, Van Mechelen H, Clerckx B, et al: Acute outcomes and 1-year mortality of intensive care unit-acquired weakness. A cohort study and propensity-matched analysis. *Am J Respir Crit Care Med* 2014; 190:410–420

93. Dinglas VD, Aronson Friedman L, Colantuoni E, et al: Muscle weakness and 5-year survival in acute respiratory distress syndrome survivors. *Crit Care Med* 2017; 45:446–453

94. Needham DM, Wozniak AW, Hough CL, et al; National Institutes of Health NHLBI ARDS Network: Risk factors for physical impairment after acute lung injury in a national, multicenter study. *Am J Respir Crit Care Med* 2014; 189:1214–1224

95. Kamdar BB, Combs MP, Colantuoni E, et al: The association of sleep quality, delirium, and sedation status with daily participation in physical therapy in the ICU. *Crit Care* 2016; 19:261

96. Brummel NE, Girard TD, Ely EW, et al: Feasibility and safety of early combined cognitive and physical therapy for critically ill medical and surgical patients: The Activity and Cognitive Therapy in ICU (ACT-ICU) trial. *Intensive Care Med* 2014; 40:370–379

97. Patman S, Sanderson D, Blackmore M: Physiotherapy following cardiac surgery: Is it necessary during the intubation period? *Aust J Physiother* 2001; 47:7–16

98. Morris PE, Goad A, Thompson C, et al: Early intensive care unit mobility therapy in the treatment of acute respiratory failure. *Crit Care Med* 2008; 36:2238–2243

99. Schweickert WD, Pohlman MC, Pohlman AS, et al: Early physical and occupational therapy in mechanically ventilated, critically ill patients: A randomised controlled trial. *Lancet* 2009; 373:1874–1882

100. Routsi C, Gerovasili V, Vasileiadis I, et al: Electrical muscle stimulation prevents critical illness polyneuromyopathy: A randomized parallel intervention trial. *Crit Care* 2010; 14:R74

101. Dantas CM, Silva PF, Siqueira FH, et al: Influence of early mobilization on respiratory and peripheral muscle strength in critically ill patients. *Rev Bras Ter Intensiva* 2012; 24:173–178

102. Denehy L, Skinner EH, Edbrooke L, et al: Exercise rehabilitation for patients with critical illness: A randomized controlled trial with 12 months of follow-up. *Crit Care* 2013; 17:R156

103. Ali MS, Talwar D, Jain SK: The effect of a short-term pulmonary rehabilitation on exercise capacity and quality of life in patients hospitalised with acute exacerbation of chronic obstructive pulmonary disease. *Indian J Chest Dis Allied Sci* 2014; 56:13–19

104. Dong ZH, Yu BX, Sun YB, et al: Effects of early rehabilitation therapy on patients with mechanical ventilation. *World J Emerg Med* 2014; 5:48–52

105. Kayambu G, Boots R, Paratz J: Early physical rehabilitation in intensive care patients with sepsis syndromes: A pilot randomised controlled trial. *Intensive Care Med* 2015; 41:865–874

106. Kho ME, Truong AD, Zanni JM, et al: Neuromuscular electrical stimulation in mechanically ventilated patients: A randomized, sham-controlled pilot trial with blinded outcome assessment. *J Crit Care* 2015; 30:32–39

107. Moss M, Nordon-Craft A, Malone D, et al: A randomized trial of an intensive physical therapy program for patients with acute respiratory failure. *Am J Respir Crit Care Med* 2016; 193:1101–1110

108. Morris PE, Berry MJ, Files DC, et al: Standardized rehabilitation and hospital length of stay among patients with acute respiratory failure: A randomized clinical trial. *JAMA* 2016; 315:2694–2702

109. Burtin C, Clerckx B, Robbeets C, et al: Early exercise in critically ill patients enhances short-term functional recovery. *Crit Care Med* 2009; 37:2499–2505

110. Yosef-Brauner O, Adi N, Ben Shahar T, et al: Effect of physical therapy on muscle strength, respiratory muscles and functional parameters in patients with intensive care unit-acquired weakness. *Clin Respir J* 2015; 9:1–6

111. Hodgson CL, Bailey M, Bellomo R, et al; Trial of Early Activity and Mobilization Study Investigators: A binational multicenter pilot feasibility randomized controlled trial of early goal-directed mobilization in the ICU. *Crit Care Med* 2016; 44:1145–1152

112. Burns KE, Jacob SK, Aguirre V, et al: Stakeholder engagement in trial design: Survey of visitors to critically ill patients regarding preferences for outcomes and treatment options during weaning from mechanical ventilation. *Ann Am Thorac Soc* 2016; 13:1962–1968

113. Eakin MN, Patel Y, Mendez-Tellez P, et al: Patients' outcomes after acute respiratory failure: A qualitative study with the PROMIS framework. *Am J Crit Care* 2017; 26:456–465

114. Simini B: Patients' perceptions of intensive care. *Lancet* 1999; 354:571–572

115. Helton MC, Gordon SH, Nunnery SL: The correlation between sleep deprivation and the intensive care unit syndrome. *Heart Lung* 1980; 9:464–468

116. White DP, Douglas NJ, Pickett CK, et al: Sleep deprivation and the control of ventilation. *Am Rev Respir Dis* 1983; 128:984–986

117. Trompeo AC, Vidi Y, Locane MD, et al: Sleep disturbances in the critically ill patients: Role of delirium and sedative agents. *Minerva Anestesiol* 2011; 77:604–612

118. Benca RM, Quintas J: Sleep and host defenses: A review. *Sleep* 1997; 20:1027–1037

119. Bourne RS, Mills GH, Minelli C: Melatonin therapy to improve nocturnal sleep in critically ill patients: Encouraging results from a small randomised controlled trial. *Crit Care* 2008; 12:R52

120. Shilo L, Dagan Y, Smorjik Y, et al: Effect of melatonin on sleep quality of COPD intensive care patients: A pilot study. *Chronobiol Int* 2000; 17:71–76

121. Ibrahim MG, Bellomo R, Hart GK, et al: A double-blind placebo-controlled randomised pilot study of nocturnal melatonin in tracheostomised patients. *Crit Care Resusc* 2006; 8:187–191

122. Alexopoulou C, Kondili E, Diamantaki E, et al: Effects of dexmedetomidine on sleep quality in critically ill patients: A pilot study. *Anesthesiology* 2014; 121:801–807

123. Wu XH, Cui F, Zhang C, et al: Low-dose dexmedetomidine improves sleep quality pattern in elderly patients after noncardiac surgery in the intensive care unit: A pilot randomized controlled trial. *Anesthesiology* 2016; 125:979–991

124. Oto J, Yamamoto K, Koike S, et al: Sleep quality of mechanically ventilated patients sedated with dexmedetomidine. *Intensive Care Med* 2012; 38:1982–1989

125. Kondili E, Alexopoulou C, Xirouchaki N, et al: Effects of propofol on sleep quality in mechanically ventilated critically ill patients: A physiological study. *Intensive Care Med* 2012; 38:1640–1646

126. Treggiari-Venzi M, Borgeat A, Fuchs-Buder T, et al: Overnight sedation with midazolam or propofol in the ICU: Effects on sleep quality, anxiety and depression. *Intensive Care Med* 1996; 22:1186–1190

127. Engelmann C, Wallenborn J, Olthoff D, et al: Propofol versus flunitrazepam for inducing and maintaining sleep in postoperative ICU patients. *Indian J Crit Care Med* 2014; 18:212–219

128. Kamdar BB, King LM, Collop NA, et al: The effect of a quality improvement intervention on perceived sleep quality and cognition in a medical ICU. *Crit Care Med* 2013; 41:800–809

129. Hu RF, Jiang XY, Zeng YM, et al: Effects of earplugs and eye masks on nocturnal sleep, melatonin and cortisol in a simulated intensive care unit environment. *Crit Care* 2010; 14:R66

130. Li SY, Wang TJ, Vivienne Wu SF, et al: Efficacy of controlling nighttime noise and activities to improve patients' sleep quality in a surgical intensive care unit. *J Clin Nurs* 2011; 20:396–407

131. Patel J, Baldwin J, Bunting P, et al: The effect of a multicomponent multidisciplinary bundle of interventions on sleep and delirium in medical and surgical intensive care patients. *Anaesthesia* 2014; 69:540–549

132. Muller L, Chanques G, Bourgaux C, et al: Impact of the use of propofol remifentanil goal-directed sedation adapted by nurses on the time to extubation in mechanically ventilated ICU patients: The experience of a French ICU. *Ann Fr Anesth Reanim* 2008; 27:481. e1–481.e8

133. Rotondi AJ, Chelluri L, Sirio C, et al: Patients' recollections of stressful experiences while receiving prolonged mechanical ventilation in an intensive care unit. *Crit Care Med* 2002; 30:746–752