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

KEYWORDS: antipsychotics; anxiety; deliriuim; dexmedetomidine; melatonin; mobility

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Patients admitted to the ICU often experience distressing symptoms and issues such as pain, anxiety, agitation, delirium, immobility, and sleep disruption related to both their critical illness, and the discomfort involved with the provision of life support. If not appropriately managed, these symptoms and issues may result in both short and long-term morbidity and mortality (1–3). The Society of Critical Care Medicine (SCCM) has previously published two sets of evidence-based clinical practice guidelines with specific recommendations across these domains to improve care and outcomes in adult ICU patients. These include the 2013 Pain, Agitation, and Delirium guidelines, and the 2018 Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption (PADIS) guidelines (4, 5). Since 2018, several relevant, high-quality randomized clinical trials (RCTs) have been published in the areas of sedation, delirium, immobility, and sleep disruption. In addition, the distressing symptom of anxiety was not addressed in the 2018 guidelines, creating a need to update the previous recommendations.

To address this growing body of evidence, SCCM convened another panel of international experts, ICU survivors, and methodologists to provide a brief PADIS guidelines update, focusing on the domains of anxiety, agitation/sedation, delirium, immobility, and sleep disruption in adult ICU patients. The Grading of Recommendations Assessment, Development, and Evaluation approach was rigorously adhered to. First, the panel developed five Population, Intervention, Control, and Outcome (PICO) questions for this focused update. A systematic review was then conducted to identify the best available evidence to address each question. The panel evaluated the certainty of evidence. From there, recommendations were formulated using the evidence-to-decision framework. The strength of each recommendation could range from strong (indicated by "we recommend") to conditional ("we suggest"). A detailed description of these guidelines is published separately. This executive summary reviews all PICO questions addressed in this focused update (**Table 1**).

DOI: 10.1097/CCM.0000000000006573

TABLE 1.

Summary of Actionable Patient, Intervention, Comparison, and Outcome Questions and Recommendations

Pain, Agitation/ Sedation, Delirium, Immobility, and Sleep Disruption Topic	Question	Recommendation	Strength of Recommendation	Certainty of Evidence
Anxiety	In adults admitted to the ICU, do benzodiazepines administered for anxiety, when compared with no benzodiazepines, impact patient outcomes?	There is insufficient evidence to make a recommendation on the use of benzodiazepines to treat anxiety in adult patients admitted to the ICU.	N/A	N/A
Agitation and sedation	In mechanically ventilated adults admitted to the ICU, should dexmedetomidine, when compared with propofol, be used for sedation?	We suggest using dexmedetomidine over propofol for sedation in mechanically ventilated adult patients admitted to the ICU where light sedation and/or a reduction in delirium are of highest priorities.	Conditional	Moderate
Delirium	In adults admitted to the ICU, do antipsychotics administered for delirium, compared with no antipsychotics, impact patient outcomes?	We are unable to issue a recommendation for or against the use of antipsychotics over usual care for the treatment of delirium in adult patients admitted to the ICU.	Conditional	Low
Immobility	In adults admitted to the ICU, does enhanced mobilization/rehabilitation, compared with usual care mobilization/rehabilitation, impact patient outcomes?	We suggest providing enhanced mobilization/rehabilitation over usual care mobilization/rehabilitation to adult patients admitted to the ICU.	Conditional	Moderate
Sleep	In adults admitted to the ICU, does melatonin compared with placebo, impact patient outcomes?	We suggest administering melatonin over no melatonin in adult patients admitted to the ICU.	Conditional	Low

N/A = not applicable.

RECOMMENDATIONS

Benzodiazepines for Anxiety

Recommendation 1. There is insufficient evidence to make a recommendation on the use of benzodiazepines to treat anxiety in adult patients admitted to the ICU.

Rationale. Anxiety is one of the most distressing symptoms, both in terms of occurence and intensity, identified by ICU patients (3, 6). Benzodiazepines are commonly used for the treatment of anxiety in the ICU. A systematic literature search was conducted to identify studies that assessed the effect of benzodiazepines on patients' anxiety in the ICU to answer the question: "In adults admitted to the ICU, do benzodiazepines administered for anxiety, when compared with no benzodiazepines, impact patient outcomes?" Unfortunately, no studies directly answered our PICO, with the exception of one before-and-after cohort study conducted in burn patients, which presented limited evidence (7). Due to the lack of evidence, the panel cannot currently make a recommendation regarding the use of benzodiazepines for the treatment of anxiety in ICU patients. This led to a call-to-action for further attention and research on this important topic.

Dexmedetomidine for Sedation

Recommendation 2. We suggest using dexmedetomidine over propofol for sedation in mechanically ventilated adult patients admitted to the ICU where light sedation and/or a reduction in delirium are of highest priorities (conditional recommendation; for intervention; moderate certainty of evidence).

Rationale. Moderate certainty evidence supports that dexmedetomidine, compared with propofol, probably reduces the prevalence of delirium and improves the proportion of time spent at target sedation. Of note, the majority of RCTs included in our meta-analysis targeted light sedation. This is a change from the 2018 PADIS guidelines where either propofol or dexmedetomidine were recommended to be used over benzodiazepines for sedation (4), except it was suggested that dexmedetomidine should be used to treat delirium that was precluding weaning/extubation. This change reflects the fact that only three RCTs comparing the effects of dexmedetomidine to propofol for sedation in the ICU were available in 2018, compared with the 29 RCTs (8–36) that we identified.

The panel judged the desirable effects to outweigh the possible adverse event of bradycardia or small possibility of hypotension for most patients. Note that this is a conditional recommendation, and clinical judgment must be used if a patient requires deep sedation or has a high risk of bradycardia, in which case, alternative sedative agents should be considered. Finally, the panel acknowledged that propofol is a reasonable alternative if the cost and ability to obtain dexmedetomidine is prohibitive.

Antipsychotics for Delirium

Recommendation 3. We are unable to issue a recommendation for or against the use of antipsychotics over usual care for the treatment of delirium in adult patients admitted to the ICU (conditional recommendation; for intervention or comparison; low certainty of evidence).

Rationale. A total of eight RCTs (37–44) treated adult patients admitted to the ICU with either established hypoactive or hyperactive delirium with antipsychotics vs. usual care. The panel was unable to issue a recommendation for the use of antipsychotics compared with usual care to treat delirium, despite a possible reduction in mortality and increase in delirium-free days in those who were administered antipsychotics. The panel arrived at this decision, as it is not understood how antipsychotics may result in a reduction in mortality when the only change detected was a slight improvement in the number of delirium-free days, but no change was seen in other outcomes such as duration of mechanical ventilation, ICU length of stay, or hospital length of stay. There may be a slight increase in the risk of arrhythmias, and little to no effect on QT interval prolongation and extrapyramidal symptoms (both low certainty) associated with antipsychotic administration. This is a change from the 2018 PADIS guidelines (4) where a suggestion was made against using antipsychotics to treat delirium, as antipsychotics were not found to change delirium or mortality.

Enhanced Mobilization for Immobility

Recommendation 4. We suggest providing enhanced mobilization/rehabilitation over usual care mobilization/rehabilitation to adult patients admitted to the

ICU (conditional recommendation; for intervention; moderate certainty of evidence).

Remark. The 2018 PADIS guidelines issued a conditional recommendation to mobilize patients over no mobilization. However, the appropriate frequency, intensity, duration, or delivery of ICU mobilization and rehabilitation was not established. We adopted a previously established definition of mobilization: the process of moving oneself and of changing and maintaining postures (45). We then defined enhanced mobilization to be anything more than a unit's usual mobilization/rehabilitation (i.e., enhanced may include one of: cycling, stepping, early interventions, twice daily, protocolized, or extended durations of mobilization/rehabilitation). For an RCT to be included in our systematic review, some amount of mobilization/rehabilitation was required in the control groups to be considered usual care (i.e., RCTs that compare no mobilization were excluded as a complete lack of mobilization is not standard of care).

Rationale. The final evidence summary included 58 RCTs and 8038 patients (46–103). Enhanced mobilization/rehabilitation compared with usual care mobilization/rehabilitation reduces the incidence of ICU-acquired weakness (high certainty), probably improves functional outcomes and quality of life after discharge (both moderate certainty), and may increase the number of patients discharged home (low certainty). Enhanced mobilization/rehabilitation compared with usual care mobilization/rehabilitation slightly reduces the duration of delirium (low certainty), duration of invasive mechanical ventilation (moderate certainty), ICU length of stay (low certainty), and hospital length of stay (low certainty). Consistent with the 2018 PADIS guidelines (4), there was little to no effect on mortality (low certainty).

The evidence suggests that the benefits likely outweigh the marginally higher risk of adverse events, of which the incidence rates were low. As no RCTs reported the required resources for an ICU enhanced mobilization/rehabilitation program, the panel issued a conditional recommendation, recognizing that resource limitation can be a significant barrier to implementing such a program. This acknowledged the fact that many ICUs are likely doing the most they can with limited resources. In addition, the RCTs tended to primarily include patients that were previously functionally independent at baseline; hence, the recommendations may not apply to all patients. The panel was not able to issue a recommendation on the ideal mobilization/rehabilitation dose, timing, duration, or method due to the heterogeneity of included RCTs.

Melatonin for Patient Outcomes

Recommendation 5. We suggest administering melatonin over no melatonin in adult patients admitted to the ICU (conditional recommendation; for intervention; low certainty of evidence).

Rationale. Endogenous melatonin suppression and circadian disturbances have been found in critically ill patients (104), which provides a rationale for replacement therapy. We identified 30 RCTs (105–134) that enrolled 3739 adults admitted to the ICU. The pooled result of 15 RCTs demonstrated that melatonin may reduce the prevalence of delirium (low certainty). Three RCTs concluded that the patient's perceived sleep quality may be improved (low certainty). Given the low certainty of effect on both delirium and perceived sleep quality, balanced against the low risk of adverse events, the panel issued a conditional recommendation for the use of melatonin in these patients. These data have limitations; hence, a strong recommendation was not provided. Sleep/circadian outcomes were not assessed in many included studies. Most studies that included sleep as an outcome used subjective measurement tools, which may introduce recall bias, include only those who can respond, and do not measure sleep architecture. In addition, melatonin is not U.S. Food and Drug Administration (FDA)-regulated so quality may vary. Ramelteon, an FDA-approved melatonin receptor agonist, could be considered a melatonin alternative in countries where it is available. There was also significant heterogeneity of included trials in terms of melatonin dose, duration, and frequency, which limits the panel's ability to issue specific recommendations for administration.

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Mr. Jennings, Ms. Hines, and Dr. Ross are patient partners.

Drs. Balas and Girard received funding from Ceribell. Dr. Balas received funding from the National Heart, Lung, and Blood Institute (NHLBI), the National Institute of Nursing Research, and the National Institute of Child Health and Human Development. Drs. McNett and Girard received funding from the National Institutes of Health (NIH). Dr. McNett received funding from Dexcom and the Patient-Centered Outcomes Research Institute. Dr. Girard received funding from Liberate Medical, Lungpacer, and the Department of Defense. Dr. Kho received funding from Restorative Therapies, the Canada Research Chair in Critical Care Rehabilitation and Knowledge Translation, the Canadian Institutes of Health Research (CIHR), and the Canada Foundation for Innovation. Dr. Weinhouse received funding from UpToDate. Dr. Chlan received funding from the NHLBI (1R01 HL 130881-01), the National Institutes on Aging, and the National Eye Institute (NIH R01AG067631). Dr. Gélinas received funding from the Society of Critical Care Medicine and the SAMDOC Medical Technologies; their institution received funding from the CIHR. Dr. Krupp disclosed she was an invited speaker for Fall 2022 American Association of Nurse Practitioners. Dr. Young received funding from the Southeastern Pennsylvania Chapter of American Association of Critical-Care Nurses. The remaining authors have disclosed that they do not have any potential conflicts of interest.

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The Society of Critical Care Medicine guidelines are intended for general information only, are not medical advice, and do not replace medical professional advice, which should be sought for any medical condition. The full disclaimer for guidelines can be accessed at: https://sccm.org/Clinical-Resources/Guidelines/Guidelines.

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