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

RATIONALE: Critically ill adults are at risk for a variety of distressing and consequential symptoms both during and after an ICU stay. Management of these symptoms can directly influence outcomes.

OBJECTIVES: The objective was to update and expand the Society of Critical Care Medicine's 2018 Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU.

PANEL DESIGN: The interprofessional inclusive guidelines task force was composed of 24 individuals including nurses, physicians, pharmacists, physiotherapists, psychologists, and ICU survivors. The task force developed evidence-based recommendations using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach. Conflict-of-interest policies were strictly followed in all phases of the guidelines, including task force selection and voting.

METHODS: The task force focused on five main content areas as they pertain to adult ICU patients: anxiety (new topic), agitation/sedation, delirium, immobility, and sleep disruption. Using the GRADE approach, we conducted a rigorous systematic review for each population, intervention, control, and outcome question to identify the best available evidence, statistically summarized the evidence, assessed the quality of evidence, and then performed the evidence-to-decision framework to formulate recommendations.

RESULTS: The task force issued five statements related to the management of anxiety, agitation/sedation, delirium, immobility, and sleep disruption in adults admitted to the ICU. In adult patients admitted to the ICU, the task force issued conditional recommendations to use dexmedetomidine over propofol for sedation, provide enhanced mobilization/rehabilitation over usual mobilization/rehabilitation, and administer melatonin. The task force was unable to issue recommendations on the administration of benzodiazepines to treat anxiety, and the use of antipsychotics to treat delirium.

CONCLUSIONS: The guidelines task force provided recommendations for pharmacologic management of agitation/sedation and sleep, and nonpharmacologic management of immobility in critically ill adults. These recommendations are intended for consideration along with the patient's clinical status.

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

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Most critically ill patients experience pain, anxiety, agitation, delirium, immobility, and sleep disruption at some point during their ICU stay (1–3). If these symptoms are not appropriately managed, they can lead to increased morbidity and mortality. 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 for adult patients admitted to the ICU. 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 the release of the 2018 PADIS guidelines, several relevant high-quality studies have been published, prompting the SCCM to reconvene another panel of international experts, ICU survivors, and methodologists to provide a brief guidelines update, with a specific focus on anxiety (a new domain), agitation/sedation, delirium, immobility, and sleep disruption in adult patients admitted to the ICU. The results are presented herein.

METHODOLOGY

Committee Membership and Conflict of Interest

SCCM appointed two co-chairs (J.M.A., M.C.B.) and two vice co-chairs (J.L.S., M.M.) who then assembled a diverse group of 20 additional members including subject matter experts, physicians, nurses, pharmacists, physiotherapists, a psychologist, three ICU survivors (R.J., A.H., C.R.), and two methodologists from the Guidelines in Intensive Care, Development, and Evaluation Group (K.L., K.L.C.) to update the PADIS guidelines (**Supplemental Digital Content 1**, http://links.lww.com/CCM/H667). Intellectual and financial conflicts of interest (COIs) were reviewed and addressed according to the SCCM Standard Operating Procedures (**Supplemental Digital Content 2**, http://links.lww.com/CCM/H667).

Guidelines Scope and Population, Intervention, Comparison, and Outcome Development

The Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach was used throughout all aspects of guidelines development (6). Population, Intervention, Comparison, and Outcome (PICO) questions were developed for the guidelines through panel discussions (**Table 1**). Each PICO had a dedicated subpanel assigned (**Supplemental Digital Content 3**, http://links.lww.com/CCM/H667). The objective was to update elements of the 2018 PADIS guidelines that had new evidence published, address clinically relevant topics not addressed in previous guidelines versions, and include both pharmacologic and nonpharmacologic interventions. Possible topics that would be important to patients, their families, and clinicians were listed, and the final selection was made through discussion and consensus. Of note, the 2018 PADIS guidelines did not specifically address the management of anxiety, a common symptom in adult ICU patients. In these guidelines update, members of the "Pain" subpanel focused on anxiety to address this gap in the previous guidelines version. A list of all possible outcomes was created and then voted upon using an online survey (Survey Monkey, Palo Alto, CA, www.surveymonkey.com). Committee members rated outcomes according to patient importance, and only those that were deemed critical or important were examined (**Supplemental Digital Content 4**, http://links.lww.com/CCM/H667). The ICU survivors provided input on the final outcomes.

Systematic Review and Meta-Analyses

An experienced medical librarian developed a peer-reviewed search strategy and conducted a literature review of five electronic databases from inception to April 2024 (**Supplement Digital Content 5**, http://links.lww.com/CCM/H667). Citations of all potentially eligible studies were screened independently and in duplicate (**Supplemental Digital Content 6**, http://links.lww.com/CCM/H667). Relevant baseline and outcome data for all eligible trials was extracted independently and in duplicate. Authors were contacted for missing data. The Cochrane Modified Risk of Bias tool (7) was applied to evaluate the risk of bias of each included study. Statistical analyses were conducted using RevMan software, Version 5.4 (The Cochrane Collaboration, 2020; revman.cochrane.org). The DerSimonian and Laird (8) random-effects model was used to pool the weighted effect of estimates across studies. Pooled binary outcomes are presented as relative risks (RRs) and 95% CIs while

TABLE 1.
Population, Intervention, Control, and Outcomes Questions

Topic	Question	Population	Intervention	Comparator	Outcomes
Anxiety	In adults admitted to the ICU, do benzodiazepines administered for anxiety, when compared with no benzodiazepines, impact patient outcomes?	Adults admitted to the ICU who are anxious	A benzodiazepine of any dose, route, duration, or frequency	No benzodiazepine	1) Occurrence of anxiety 2) Occurrence of agitation 3) Occurrence of delirium 4) Duration of mechanical ventilation 5) Occurrence of post-ICU PTSD 6) Occurrence of post-ICU anxiety 7) Mortality 8) Quality of life post-ICU/functional/cognitive abilities 9) Adverse events
Agitation & Sedation	In mechanically ventilated adults admitted to the ICU, should dexmedetomidine, when compared with propofol, be used for sedation?	Adults admitted to the ICU who are mechanically ventilated and require sedation	Dexmedetomidine of any dose, route, duration, and frequency	Propofol of any dose, duration, frequency	1) Occurrence of delirium 2) Duration of delirium 3) % of Richmond Agitation-Sedation Scale measurements inside target range 4) Duration of mechanical ventilation 5) ICU LOS 6) Use of additional rescue medications while in ICU 7) Mortality 8) Quality of life post-ICU/functional/cognitive abilities 9) Adverse events
Delirium	In adults admitted to the ICU, do antipsychotics administered for delirium compared with no antipsychotics, impact patient outcomes?	Adults with delirium who are admitted to the ICU	Any antipsychotic medication, of any dose, route, duration, or frequency	No antipsychotics	1) Mortality 2) Duration of mechanical ventilation 3) Occurrence of delirium 4) Duration of delirium 5) ICU LOS 6) Hospital LOS 7) Quality of life post-ICU/functional/cognitive abilities 8) Occurrence of post-ICU anxiety/PTSD 9) Adverse events

(*Continued*)

TABLE 1. (*Continued*)
Population, Intervention, Control, and Outcomes Questions

Topic	Question	Population	Intervention	Comparator	Outcomes
Immobility	In adults admitted to the ICU, does enhanced mobilization/rehabilitation, compared with usual care mobilization/rehabilitation, impact patient outcomes?	Adults admitted to the ICU	Enhanced mobilization/rehabilitation	Usual care mobilization/rehabilitation	1) Occurrence of delirium 2) Duration of delirium 3) Occurrence of agitation 4) Duration of mechanical ventilation 5) Adverse events 6) ICU LOS 7) Quality of life post-ICU/functional/cognitive abilities 8) Mortality
Sleep	In adults admitted to the ICU, does melatonin compared with placebo, impact patient outcomes?	Adults admitted to the ICU	Melatonin at any dose, duration or frequency	No melatonin	1) Occurrence of delirium 2) Duration of delirium 3) Sleep quality/quantity 4) Occurrence of anxiety 5) Occurrence of agitation 6) ICU LOS 7) Duration of mechanical ventilation 8) Quality of life post-ICU/functional/cognitive abilities 9) Occurrence of post-ICU PTSD 10) Mortality 11) Adverse events

LOS = length of stay, PTSD = posttraumatic stress disorder.

continuous outcomes are presented as mean differences (MDs) and 95% CIs.

Development of Consensus and Clinical Recommendations

The subpanels and ICU survivors used the GRADE evidence-to-decision framework to generate recommendations and evidence summary tables (**Supplemental Digital Content 7**, http://links.lww.com/CCM/H667). For each PICO, a subpanel issued a Strong Recommendation or a Conditional Recommendation, either for or against the intervention (**Table 2**). Once preliminary recommendations were established, the recommendations and evidence summaries were distributed to the full panel and ICU survivors. Panel members who were free of overt or potential COIs and ICU survivors were invited to vote on their agreement (or disagreement) for each recommendation. A minimum 70% response rate was required for each question and consensus was defined as 80% agreement (**Supplement Digital Content 8**, http://links.lww.com/CCM/H667).

RECOMMENDATIONS

The panel generated recommendations which are summarized in **Table 3** (**Supplemental Digital Content 9**, http://links.lww.com/CCM/H667).

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.

Evidence Summary

Anxiety is one of the most distressing symptoms identified by adult ICU patients, both in terms of occurrence and intensity (3, 9). This holds true whether the assessment is conducted during the ICU stay (10–12) or among survivors based on their recollections of the ICU experience (13, 14). Benzodiazepines are commonly used for the treatment of acute anxiety in the ICU. A systematic literature search was conducted to identify trials that answered 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 (15).

Evidence to Recommendation

Due to a lack of evidence, the panel cannot currently make a recommendation regarding the use of benzodiazepines for the treatment of anxiety in ICU patients.

Special Considerations

Severe anxiety is experienced by more than one quarter of intubated patients 6 hours after the interruption of midazolam or propofol (16), while ten of 16 patients reported anxiety about the endotracheal tube at hospital discharge regardless of sedation (17). Given the potential magnitude of this issue, there is an urgent need for standardization of anxiety assessments in ICU patients (18), and investigation of diverse therapeutic options for anxiety, including pharmacologic and nonpharmacologic interventions. In patients able to respond, the Faces Anxiety Scale, which has been validated for both intubated (19) and nonintubated patients (20), presents a viable option for assessing anxiety in adult ICU patients. In addition, unidimensional self-assessment scales (e.g., Visual Analogue Scale, Numeric Rating Scale) could serve as pragmatic alternatives (9) for assessing anxiety (21, 22), and other distressing symptoms such as pain, dyspnea (23), and thirst (24). Nonpharmacological treatment approaches, such as music listening (21, 25) or virtual reality (22), have shown promise. A patient-centered approach to care, research, and quality improvement that encompasses all sources of discomfort and distress in the ICU is essential to providing comprehensive management of anxiety.

Of note, abrupt cessation of benzodiazepines prescribed for baseline chronic anxiety may precipitate acute withdrawal; hence, continuation of the chronic benzodiazepines upon admission to the ICU should be considered.

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

TABLE 2.
Grading of Recommendation Assessment, Development, and Evaluation Classification of Strengths of Recommendations and Their Implications

Implications for	Strong Recommendation "We Recommend…"	Conditional Recommendation "We Suggest…"
	Desirable effects of intervention clearly outweigh undesirable effects, or clearly do not	Trade-offs are less certain, either because of low-quality evidence or because evidence suggests desirable and undesirable effects are closely balanced
Patients	Most individuals in this situation would want the recommended course of action, and only a small proportion would not	The majority of individuals in this situation would want the suggested course of action, but many would not
Clinicians	Most individuals should receive the recommended course of action. Adherence to this recommendation according to the guidelines could be used as a quality criterion or performance indicator. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences	Different choices are likely to be appropriate for different patients, and therapy should be tailored to the individual patient's circumstances. Those circumstances may include the patient or family's values and preferences
Policymakers	The recommendation can be adapted as policy in most situations, including for use as performance indicators	Policymaking will require substantial debates and involvement of many stakeholders. Policies are also more likely to vary between regions. Performance indicators would have to focus on the fact that adequate deliberation about the management options has taken place

reduction in delirium are of highest priorities (conditional recommendation; for intervention; moderate certainty of evidence).

Evidence Summary

A total of 3087 mechanically ventilated adults admitted to the ICU were randomized to dexmedetomidine vs. propofol in 29 randomized controlled trials (RCTs) (26–54), the majority of which explicitly stated medications were titrated to achieve light sedation (22 RCTs). Compared with propofol, dexmedetomidine probably reduced the prevalence of delirium (RR, 0.55; 95% CI, 0.37–0.81; absolute risk reduction [ARR], 15 fewer patients per 100; 95% CI, from 20 fewer to 6 fewer; moderate certainty) and may reduce the duration of delirium (MD, −25.58 hr; 95% CI, −43.49 to −7.66 hr; low certainty). Dexmedetomidine may cause a slight reduction in ICU length of stay (MD, −0.19 d; 95% CI, −0.33 to −0.05 d; low certainty) and may result in little to no difference in the duration of mechanical ventilation (MD, −1.6 hr; 95% CI, −2.77 to −0.42 hr; low certainty). It may improve the time spent at target sedation (low certainty) and reduce the proportion that require supplemental analgesics (RR, 0.71; 95% CI, 0.52–0.99; moderate certainty). There may be little to no effect on mortality at longest follow-up (RR, 0.98; 95% CI, 0.86–1.13; ARR, 0 fewer per 100; 95% CI, from 3 fewer to 3 more; low certainty). Dexmedetomidine may improve long-term outcomes such as quality of life and functional status at 6 months (both low certainty). Dexmedetomidine probably increases the risk of bradycardia (RR, 1.65; 95% CI, 1.28–2.12; absolute risk increase [ARI], 6 more per 100; 95% from 2 more to 10 more; moderate certainty) and may result in little to no difference in the risk of hypotension (RR, 1.07; 95% CI, 0.92–1.25; low certainty). Due to a very low certainty of evidence, it is unclear how dexmedetomidine impacts post-ICU cognitive impairment and 28-day mortality.

Evidence to Recommendation

The panel judged the desirable effects of dexmedetomidine to outweigh the possible adverse event of bradycardia in most ICU patients. While dexmedetomidine may be preferable to propofol for light sedation or if the patient

TABLE 3.
Table of Recommendations

No.	Recommendations	Recommendation Strength, Direction, and Certainty of Evidence	Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption 2018 Recommendations
1	There is insufficient evidence to make a recommendation on the use of benzodiazepines to treat anxiety in adult patients admitted to the ICU	No recommendation; no evidence available	No recommendations previously existed
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	We suggest using either propofol or dexmedetomidine over benzodiazepines for sedation in critically ill, mechanically ventilated adults (conditional recommendation, low quality of evidence)
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	We suggest not routinely using haloperidol or an atypical antipsychotic, to treat delirium (conditional recommendation, low quality of evidence)
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	We suggest performing rehabilitation or mobilization in critically ill adults (conditional recommendation, low quality evidence)
5	We suggest administering melatonin over no melatonin in adult patients admitted to the ICU	Conditional recommendation; for intervention; low certainty	We make no recommendation regarding the use of melatonin to improve sleep in critically ill adults (no recommendation, very low quality of evidence)

has delirium, clinical judgment must be used. If a patient requires deep sedation or has a high risk of bradycardia, alternative sedative agents should be considered. The cost of dexmedetomidine acquisition for many hospitals is now lower than when initially marketed, and the cost of propofol and dexmedetomidine are likely comparable in many countries. However, there is significant variability in costs and availability of dexmedetomidine. Therefore, cost and ability to obtain dexmedetomidine may well be prohibitive in some centers and hence our recommendation is conditional rather than strong.

Special Considerations

Currently, there is no definitive evidence of heterogeneity in the safety or efficacy of dexmedetomidine in patients over or under the age of 65. All subgroup findings in prior trials are simply hypothesis-generating at this point and further research is needed (55, 56). The Intensive Care Medicine Rapid Practice Guidelines recommended the use of dexmedetomidine over the use of other sedation medications if the desirable effects of a reduction in delirium were valued over the undesirable effects of hypotension and bradycardia. Similar to us, they did not make a recommendation to avoid use of dexmedetomidine in those under the age of 65 but left it to the practitioner's discretion (57).

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).

Evidence Summary

A total of eight RCTs (58–65) enrolling 1869 adult ICU patients administered antipsychotics compared with no antipsychotic for the treatment of established delirium. Six RCTs administered haloperidol as the antipsychotic, one administered both atypical and typical antipsychotics, and the last RCT had three treatment arms: haloperidol, ziprasidone, and placebo. Overall, antipsychotics may slightly increase the number of delirium-free days (MD, 1.25 d; 95% CI, –0.35 to 2.86 d; low certainty) and may reduce 28-day mortality (RR, 0.87; 95% CI, 0.75–1.01; low certainty) and mortality at longest follow-up (RR, 0.89; 95% CI, 0.79–1.01; low certainty). There was little to no effect on the duration of invasive mechanical ventilation (moderate certainty), ICU length of stay (very low certainty), or hospital length of stay (low certainty). There was uncertainty regarding the effect on post-ICU post-traumatic stress disorder, functional status at 3 months, post-ICU quality of life, post-ICU cognitive impairment, and duration of delirium (all very low certainty). There may be a slight increase in the risk of arrhythmias (RR, 1.57; 95% CI, 0.66–3.74; low certainty), and little to no effect on QT interval prolongation and extrapyramidal symptoms (both low certainty).

Evidence to Recommendation

The panel was unable to issue a recommendation for the use of antipsychotics to treat delirium, despite a possible reduction in mortality and increase in delirium-free days. First, all potential benefits were of low certainty evidence, in part due to imprecision. Second, it is not understood how antipsychotics may result in a reduction in mortality when the only change we detected was a slight improvement in the number of delirium-free days, but no change in other outcomes such as duration of mechanical ventilation, ICU length of stay, etc. Last, a delirium-free outcome does not account for coma, that is, a patient can be delirium-free because they have a normal mental status, or they are comatose.

Special Considerations

Most RCTs enrolled a mix of patients with either hypoactive and/or hyperactive delirium and, therefore, it is unclear if there is a single patient population that would benefit most from an antipsychotic. In addition, if used, one must be prudent to discontinue antipsychotics that were newly initiated in the ICU upon discharge if no longer clinically required (66).

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

Rehabilitation and mobilization in the ICU aim to mitigate the long-term effects of ICU-acquired weakness (e.g., survival and quality of life) (67), yet the appropriate frequency, intensity, duration, or delivery of these interventions is not established. We adopted a previously established definition of mobilization: "the process of moving oneself and of changing and maintaining postures," excluding pulmonary rehabilitation (68). We defined enhanced to be anything more than a unit's usual mobilization/rehabilitation (e.g., enhanced may include one of: cycling, stepping, early, twice daily, protocolized, or extended durations of mobilization/rehabilitation).

Evidence Summary

The final evidence summary included 58 RCTs and 8038 patients (69–126).

Enhanced mobilization/rehabilitation compared with usual care mobilization/rehabilitation reduces the proportion of patients that develop ICU-acquired weakness (RR, 0.77; 95% CI, 0.64–0.93; ARR, 9 fewer per 100 patients; 95% CI, 14 fewer to 3 fewer; high certainty). It may slightly reduce the duration of delirium (MD, –1.34 d; 95% CI, –1.85 to –0.83 d; low certainty), duration of invasive mechanical ventilation (MD, –1.1 d; 95% CI, –1.69 to –0.51 d; moderate certainty), ICU length of stay (MD, –1.01 d; 95% CI, –1.75 to –0.27 d; low certainty), and hospital length of stay (MD, –1.16 d; 95% CI, –2.94 to –0.62 d; low certainty). Enhanced mobilization/rehabilitation probably improves functional outcomes and quality of life after discharge (both moderate certainty) and may increase the number of patients discharged home (RR, 1.15; 95% CI, 1.00–1.33; low certainty). There was little to no effect on mortality at longest follow-up (low certainty). There is uncertainty surrounding the effect of enhanced mobilization/rehabilitation on delirium occurrence and ICU mortality (both very low certainty).

Enhanced mobilization/rehabilitation may result in a slight increase in adverse events such as arrhythmias (RR, 2.27; 95% CI, 0.73–7.08; ARI, one more per 100; 95% CI, 0 fewer to 3 more), but likely causes little to no difference in the risk of accidental line removal (RR, 1.28; 95% CI, 0.25–6.58; ARI, 0 fewer per 100; 95% CI, from 0 fewer to 1 more), unplanned extubation (RR, 0.93; 95% CI, 0.49–1.75; ARI, 0 fewer per 100; 95% CI, from 0 fewer to 1 more), and hypotension (RR, 1.32; 95% CI, 0.47–3.75; ARI, 1 more per 100, 95% CI, from 2 fewer to 9 more) (all moderate certainty).

Evidence to Recommendation

The evidence suggests that the benefits of enhanced mobilization/rehabilitation in adult ICU patients outweigh the marginally increased risk of an adverse event, such as arrhythmias, which occur infrequently. As no RCTs reported the required resources for an ICU enhanced mobilization/rehabilitation program, the panel issued a conditional recommendation, recognizing that resource limitations can be a significant barrier to implementing such a program. However, implementing enhanced mobilization/rehabilitation could introduce important savings in the healthcare system. In addition, the RCTs tended to primarily include patients that were previously functionally independent at baseline; hence, a recommendation may not apply to all patients. Finally, 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 studies.

Special Considerations

Mobilization is a multifaceted, team-based intervention conducted in a complex environment. Based on clinical team expertise, the frequency, intensity, timing, and type of mobility/rehabilitation activities may differ by ICU. Of note, there was insufficient data to perform a subgroup analysis of post-cardiac surgery patients; therefore, this recommendation applies to the general medical-surgical patients.

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).

Evidence Summary

The final evidence summary includes 30 RCTs (127–156) that enrolled 3739 adults ICU patients. In total, 24 RCTs compared melatonin with either no melatonin or placebo, two RCTs compared melatonin with dexmedetomidine, and one with benzodiazepines. The other three RCTs compared ramelteon to placebo.

Melatonin may reduce the prevalence of delirium (RR, 0.70; 95% CI, 0.57–0.87; low certainty), although melatonin made little to no difference in delirium duration (MD, –0.16 d; 95% CI, –1.0 to 0.68 d; low certainty). Melatonin may increase patients' perceived sleep quality (low certainty) but showed little to no difference in total nocturnal sleep duration (MD, 0.04 hr; 95% CI, –0.18 to 0.26 hr; moderate certainty). Use of melatonin may slightly reduce the ICU length of stay (MD, –0.5 d; 95% CI, –0.89 to –0.1 d; low certainty) but has little to no difference in duration of mechanical ventilation or hospital length of stay (both low certainty). Evidence was uncertain related to the number of awakenings, anxiety, the proportion of patients with agitation, post-ICU cognitive function, and post-traumatic stress disorder (all very low certainty), as well as ICU mortality and functional status post-ICU (both low certainty). There may be a slight reduction in adverse events (as defined by study authors) when melatonin is administered compared with no melatonin (low certainty).

Evidence to Recommendation

Melatonin is commonly used in practice to mitigate the adverse effects of sleep and circadian disruption in critically ill adults (157). Endogenous melatonin suppression and circadian disturbances have been found in critically ill patients (158), which provides a rationale for replacement therapy. The conditional recommendation favoring melatonin is based on the reduction of delirium prevalence and perceived improvement in sleep quality balanced against the low risk of adverse events. These data have limitations which is why a strong recommendation was not provided. Sleep/circadian outcomes were not assessed in many included RCTs. Most RCTs that included sleep as an outcome used subjective measurement tools, which may introduce recall bias, includes only those who can respond, and does not measure sleep architecture.

Special Considerations

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 significant heterogeneity of included trials in terms of dose, duration, and frequency of melatonin which limits specific recommendations for administration. Furthermore, cost may vary by country.

RESEARCH AGENDA FOR PADIS AND PATIENT-IMPORTANT OUTCOMES

Anxiety

- Further development and testing of instruments to detect and quantify anxiety in critically ill adults.
- RCTs aimed at testing the safety and effectiveness of using benzodiazepines and other medications to treat anxiety in critically ill adults.
- RCTs examining nonpharmacologic and/or multimodal approaches to treat anxiety in the critically ill.

Sedation

- The role of dexmedetomidine in alcohol withdrawal.
- The role of sedative medications in the context of an analgesia-first approach or to supplement analgesia-sedation needs to be better studied.
- Studies evaluating the value of patient communication with family members during ICU care and the perceptions of patients while on propofol vs. dexmedetomidine (may include patients who can participate in their own care).
- The role of dexmedetomidine in patients who require treatment with deep sedation.
- RCTs definitively addressing a possible heterogeneity of dexmedetomidine treatment effect by age (over or under 65 yr old).

Delirium

- RCTs examining the use of an antipsychotic in hypoactive delirium, hyperactive delirium (as independent populations), and other delirium subtypes.
- RCTs examining long-term cognitive effects of antipsychotics in patients admitted to the ICU with delirium.
- RCTs examining the use of antipsychotics in progressive delirium severities.

Immobility

- Determining the impact of enhanced mobilization/rehabilitation as prevention vs. treatment of delirium.
- Determining the possibility of having other stakeholders (e.g., family members) assist with rehabilitation/mobilization in light of the current resource shortages.
- Determining the optimal modality of enhanced mobilization/rehabilitation, including frequency, duration, and time to initiation from ICU admission.
- Implementing an enhanced mobilization/rehabilitation program in the ICU in limited resource settings.

Sleep

- RCTs examining melatonin with nocturnal dosing and a rigorous assessment of sleep quality and quantity.
- RCTs on appropriate dosing of melatonin.

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