Australian Critical Care xxx (xxxx) xxx

Contents lists available at ScienceDirect

Australian Critical Care

journal homepage: www.elsevier.com/locate/aucc

Review paper

A systematic review and critical appraisal of guidelines and their recommendations for sedation interruptions in adult mechanically ventilated patients

Nicole D. Graham, RN [a, *], Ian D. Graham, PhD [b, c, a], Brandi Vanderspank-Wright, PhD [a], Melissa Demery Varin, MScN [a], Letitia Nadalin Penno, PhD [a], Dean A. Fergusson, PhD [b, d], Janet E. Squires, PhD [a, b]

[a] University of Ottawa, Faculty of Health Sciences, School of Nursing, 451 Smyth Road, Ottawa, ON, K1H 8M5, Canada; [b] Clinical Epidemiology Program, Ottawa Hospital Research Institute, 501 Smyth Road, P.O. Box 711, Ottawa ON, K1H 8L6, Canada; [c] Faculty of Medicine, School of Epidemiology and Public Health, University of Ottawa, Ottawa, ON, Canada; [d] Department of Medicine, University of Ottawa, Clinical Epidemiology Program, Ottawa Hospital Research Institute, 501 Smyth Road, P.O. Box 711, Ottawa ON, K1H 8L6, Canada

ARTICLE INFORMATION

Article history:
Received 25 January 2022
Received in revised form
3 October 2022
Accepted 9 October 2022

Keywords:
AGREE-II
AGREE-REX
Guideline quality
Best practice
Critical care
Intensive care
Sedation interruption
Mechanical ventilation
Nurses

ABSTRACT

Objective: The objectives of the review were to (i) assess the methodological quality of all accessible and published guidelines and care bundles that offer a recommendation related to sedation interruptions, using the AGREE-II instrument, to (ii) determine what is the recommended best practice for sedation interruptions from the available guidelines, and then to have (iii) a closer inspection of the overall credibility and applicability of the recommendations using the AGREE-REX instrument. This review will benefit the outcomes of critically ill patients and the multidisciplinary team responsible for the care of mechanically ventilated adults with continuous medication infusions by providing a synthesis of the recommended action(s), actor(s), contextual information, target(s), and timing related to sedation interruptions from current best practice.

Review method used: We conducted a systematic review.

Data sources: We applied a peer-reviewed search strategy to four electronic databases from 2010 to November 2021—MEDLINE, CINAHL, Embase, and The Cochrane Database of Systematic Reviews—and included grey literature.

Review method: Findings are reported in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analyses checklist. We assessed overall quality using the validated Appraisal of Guidelines for Research and Evaluation II and AGREE Recommendation Excellence tools.

Results: We identified 11 clinical practice guidelines and care bundles comprising 15 recommendations related to sedation interruption. There are three key findings: (i) deficiencies exist with the methodological quality of included guidelines, (ii) sedation interruption is recommended practice for the care of adult mechanically ventilated patients, and (iii) the current evidence is of low quality, which impacts overall credibility and applicability of the recommendations.

Conclusions: Sedation interruptions are currently best practice for adult mechanically ventilated patients; however, the available guidelines and recommendations have several deficiencies. Future research is needed to further understand the role of the nurse and other actors to enact this practice.

1. Introduction

Continuous sedation infusions are often necessary for patients that are mechanically ventilated to help mitigate anxiety associated with being intubated and on a ventilator, to assist with physical compliance with the ventilator, and to facilitate nursing care.[1] To

* Corresponding author.
E-mail addresses: ndaig058@uottawa.ca (N.D. Graham), igraham@ohri.ca (I.D. Graham), Brandi.vanderspank@uottawa.ca (B. Vanderspank-Wright), mdeme048@uottawa.ca (M.D. Varin), lnadalinpenno@hotmail.com (L. Nadalin Penno), dafergusson@ohri.ca (D.A. Fergusson), janet.squires@uottawa.ca (J.E. Squires).

https://doi.org/10.1016/j.aucc.2022.10.011

avoid the adverse effects and risk of over sedation, a more recent philosophical approach to care adopts 'less is best' strategies for the use of continuous intravenous sedation in mechanically ventilated patients.[2] Oversedation is known to cause negative sequelae during the acute and recovery phases of critical illness.[3,4] For example, altered mentation is a likely occurrence from the sedation and analgesic infusions, which make the identification of delirium more challenging.[5] Intensive care unit delirium is only one example of adverse events that are linked to worse outcomes in this patient population; other negative sequelae include post-traumatic stress disorder[6] and an increased risk of having no recall which was associated with a longer stay in intensive care.[7]

In response to concerns about prolonged exposure to sedative infusions, recommendations related to sedation interruption (SI) continue to surface in many clinical practice guidelines (CPG)[8] and care bundles.[9] Despite some well-documented benefits of SI, with the practice now recommended by national (e.g., Institute for Health Improvement) and international (e.g., Society of Critical Care Medicine) associations, the reported and observed uptake of SI are inconsistent and suboptimal at best.[10–13] There are multifaceted clinician and guideline factors that influence uptake of recommendations in practice. For example, studies suggest it is more difficult for clinicians to adopt a guideline when there are several different guidelines to choose from,[14] and when they address the same condition, guidelines can confuse healthcare providers and confound implementation of best practices.[15,16]

Currently, the number of available recommendations related to SI is unknown, as is the methodological quality of these guidelines. Providing greater transparency and accessibility to the quality and content of the recommendations is relevant to all clinicians involved in implementing sedation strategies in critical care, especially nurses and physicians,[17] and will improve consensus amongst critical care clinicians about the impetus and approach for SI.[18] The purpose of this systematic review was to identify and appraise recommended best practice for SI. The objectives of this review were to (i) assess the methodological quality of all CPGs and care bundles that offer a recommendation related to SI, using the Appraisal of Guidelines for Research & Evaluation II (AGREE-II) instrument, then to (ii) determine recommended best practice for SI from the available guidelines, and then to 3) have a closer inspection of the overall credibility and applicability of the recommendations using the Appraisal of Guidelines for Research and Evaluation – Recommendations Excellence (AGREE-REX) instrument.

2. Methods and materials

2.1. Design

We conducted a systematic review of the published literature. The protocol was registered with The International Prospective Register of Systematic Reviews (PROSPERO), registration number: CRD42021239699. We used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[19] statement to guide reporting of the findings in the PRISMA checklist (Supplemental Table 1)

2.2. Data sources and searches

We developed a search strategy in consultation with a librarian from the University of Ottawa. The PICAR framework, defined as P: population, clinical indication(s), and conditions(s); I: intervention(s); C: comparator(s), comparison(s), and content; A: attributes of eligible guidelines; and R: recommendation characteristics,[20] illustrates the search strategy: P- mechanically ventilated adults (18 years of age or older) in a critical care environment with a continuous sedative infusion; I- sedation interruption; C- none; A- guidelines published from 2010 to November 2021, written in English, regional, national, or international scope; R- recommendations must discuss sedation interruption. The following four electronic databases were searched: MEDLINE, CINAHL, Embase, and The Cochrane Database of Systematic Reviews. Known grey literature sources including 11 guideline repository websites and 15 professional association websites were also searched. Reference lists of all included CPGs and care bundles were hand searched. Only open-access guidelines or guidelines published in journals requiring subscription were included. If a guideline required payment to a company/organisation, it was excluded. Specific search terms, search strings, the full search strategy, as well as a list of the searched repositories and professional organisations are in Supplemental File 2.

2.3. Inclusion/exclusion criteria

All accessible CPGs and care bundles published between January 2010 and November 2021 that provided at least one explicit recommendation related to SI for mechanically ventilated adult patients, over the age of 18 years, in the ICU, and written in English were included. We only included guidelines and/or care bundles that were published within the past 10 years as best practice should be determined from the best and most recent research evidence. Reviews, letters, editorials, commentaries, reports of all studies, institutional recommendations/policies, and recommendations resulting from a single study were excluded.

2.4. Screening and data extraction

Covidence evidence synthesis software[21] was used to facilitate title and abstract screening, as well as full-text screening, data extraction, and the quality appraisal phases of the review. All phases were conducted in duplicate by two independent reviewers with any disagreements resolved through discussion. A third investigator was consulted to adjudicate unresolved discrepancies. When necessary, the corresponding author was emailed for supplemental material.

3.1. Methodology and required data elements for answering the objectives

3.1.1. Objective 1: methodological quality of the CPGs and care bundles

The Appraisal of Guidelines for Research and Evaluation II (AGREE II) instrument was used to complete the quality appraisal of the methodological development of each included guideline.[22] This instrument has quickly become an internationally accepted standard for evaluation of the methodological quality of guidelines[23] and has good validity and reliability in its application to CPGs.[24] The instrument is designed to assess the quality of guidelines, which is defined "as the confidence that the potential biases of guideline development have been addressed adequately and that the recommendations are both internally and externally valid and are feasible for practice".[25] Two independent reviewers completed the AGREE training prior to conducting the review.[25] AGREE II has six domains: (i) Scope and Purpose (items 1–3), (ii) Stakeholder Involvement (items 4–6), (iii) Rigour of Development (items 7–14), (iv) Clarity of Presentation (items 15–17), (v) Applicability (items 18–21), and (vi) Editorial Independence (items 22–23). Each of the 23 items was scored on a seven-point Likert scale from 1 = strongly disagree to 7 = strongly agree. In addition to the primary guideline, we attempted to locate and retrieve supporting documents to inform our appraisal of the guideline, for example, executive summaries and data summary tables identified as supplemental to

Please cite this article as: Graham ND et al., A systematic review and critical appraisal of guidelines and their recommendations for sedation interruptions in adult mechanically ventilated patients, Australian Critical Care, https://doi.org/10.1016/j.aucc.2022.10.011

the guideline and directly reported on the methodological development of the guideline or recommendation for SI.

The AGREE II domain scores were then calculated by summing the consensus item scores within domains and scaling the total as a percentage of the maximum possible score for that domain,[22] using the following formula:

$$\text{Scaled domain score} = \frac{\text{Obtained consensus score} - \text{Minimum possible score}}{\text{Maximum possible score} - \text{Minimum possible score}} \times 100$$

The scaled domain scores were used to determine which CPGs or care bundles are of high quality. Guidelines were considered to have high methodological quality if they had at least four or more AGREE II domain scores ≥60%, similar to thresholds reported in previous reviews.[26–28]

3.1.2. Objective 2: best practice for SI in CPGs and care bundles

Information was abstracted from all recommendations directly related to SI. Any supplemental documents or live links to material that offered additional explanation about SI were also included. For example, data were abstracted from definitions found in the supporting rationales for the recommendations and also decision aids when available. The Action, Actor, Context, Target, Time (AACTT) framework was used to organise the content across recommendations.[29] This framework outlines common domains that can be used to identify the necessary elements needed to specify a behaviour. Data were extracted and organised according to the domains: the action (clinical practice/behaviour recommended); actor (who is to perform the behavior); context (related to SI); target (to whom the practice is to be done); and timing of sedation interruptions. Similar to how the AACTT framework can be used to uncover evidence–practice gaps in care,[29] we used the framework to identify if the foundational elements for implementation (i.e., someone, somewhere, needs to do something differently) are present in the recommendations for SI.

3.1.3. Objective 3: clinical applicability, values and preferences, and implementability of the recommendation(s) related to SI

The AGREE-REX tool was used in this study to assess the methodological quality of each CPG and care bundle's recommendation(s) related to SI.[30] The AGREE-REX was designed to assess the quality of recommendations and to inform their development and reporting.[25] It differs from the AGREE II instrument in that it is used to assess the quality of the recommendation(s) rather than the overall guideline.[31] A high-quality recommendation, using AGREE-REX, is one that is (i) clinically credible, (ii) trustworthy, and (iii) implementable.[30] The instrument is based on these three high-quality factors which are represented by three domains that contain a total of nine quality items. Each of the recommendations in our study was scored according to these nine items. The three domains are as follows: (i) Clinical Applicability is concerned with the evidence used to formulate the recommendation and its applicability to target users, patients, or populations (1–3 items); (ii) Values and Preferences considers the inclusion of the values and preferences of target users, patients and populations, policymakers and decision-makers, and guideline developers in the formulation of the recommendation (4–7 items); (iii) Implementability examines whether the overall purpose of the guideline was achieved in the development of the recommendation as well as the provision of materials and resources to facilitate local application and adoption by users (8–9 items). Each of the items contains a definition and quality criteria for that item, as well as one question related to quality and another focused on suitability for use in a particular setting. Both questions are scored using a seven-point response scale, where 1 = strongly disagree and 7 = strongly agree.[30] The question about suitability was omitted as we did not implement the recommendations. Studies have been conducted to test the validity, reliability, and usability of the AGREE-REX instrument.[31,32] Three hundred and two individuals applied the AGREE-REX to a CPG and completed the AGREE-REX usability survey; the results indicated the instrument is useful for assessing factors related to CPG credibility and implementability.[32] Another study demonstrated how the instrument produced most favourable scores in items related to the quality of the evidence and clinical relevance.[31]

While using the AGREE-REX Manual,[30] two independent reviewers appraised each guideline, specifically focussing on the recommendation(s) related to SI. When the CPG or care bundle contained more than one recommendation related to SI, the recommendations were clustered and appraised together because each recommendation within a particular guideline or care bundle followed the same development process. Consensus was reached for each question.

Scores are reported for each individual item, and average scores were computed by domain to compare the quality of the recommendation(s) in terms of clinical credibility, trustworthiness, and implementability. Additionally, overall AGREE-REX scores were calculated by adding all item scores for each individual CPG and care bundle. The value was then inputted into the following formula to scale the total as a percentage of the maximum possible score:[30]

$$\text{Scaled overall AGREE} - \text{REX score} = \frac{\text{Obtained consensus score} - \text{Minimum possible score}}{\text{Maximum possible score} - \text{minimum possible score}} \times 100$$

Overall AGREE-REX scores were used to identify the quality of each individual or cluster of recommendations. In this review, recommendations with overall AGREE-REX scores >70% are considered high quality, while those with overall quality scores <30% are lower quality, and all others are moderate quality (approach suggested by AGREE-REX Research Team[30]).

3.2. Data summary and synthesis

To summarise the strength and direction of recommendations across guidelines, a simple narrative account of the grading of evidence reported by the authors is presented. Further synthesis of the strengths was not possible due to the limited number of guidelines that appraised the evidence in formulation of the recommendation. All of the content data pertaining to the SI recommendation(s) are organised using the AACTT framework elements. The data were then synthesised in a recommendation matrix. Matrices are commonly used to group together similar recommendations from various guidelines to ease the comparison of content and use of evidence to develop the recommendations and their clinical relevance.[33]

4. Results

4.1. Literature search

Fig. 1shows the flow of article selection and reasons for exclusion. We screened 6873 titles and abstracts, of which 542 were potentially relevant, and 11 were included in the systematic review.

4.2. Characteristics of the included CPGs and care bundles

The characteristics of the included guidelines are displayed in Table 1. Eight out of the 11 guidelines were open access,[34–40] of which

Please cite this article as: Graham ND et al., A systematic review and critical appraisal of guidelines and their recommendations for sedation interruptions in adult mechanically ventilated patients, Australian Critical Care, https://doi.org/10.1016/j.aucc.2022.10.011

one required registration at no charge[41] and, three were in subscription journals.[8,9,42] The authors reported their documents were a 'consensus"—evidence-informed recommendation (n = 1),[35] a systematic review and evidence-based guideline (n = 1),[36] a CPG (n = 4),[8,37–39] a care bundle of evidence-based interventions (n = 4),[9,34,40,41] or taskforce consensus recommendations developed by an expert panel.[43] Development teams were from the US (n = 3),[34,38,41] North America, Europe, Australia,[37] Italy/United Kingdom/United States of America,[42] Columbia,[8] Germany,[39] Scotland,[40] Spain9, Latin America,[35] and Ethiopia.[36] All were endorsed by a formal institute, organisation, or society, except for one developed by a Pan-European Committee of 12 participants representing different disciplines.[9]

4.3. Objective 1: methodological quality of the CPGs and care bundles

Table 2 depicts the overall AGREE II domain scores by guideline. None of the included CPGs and care bundles scored well on the AGREE-II instrument, indicating there are varying deficiencies in the methodological development of guidelines that contain a recommendation related to SI. For example, four guidelines address domain I (Scope and Purpose) by clearly articulating the health questions addressed by the guideline and to which patient population the guideline applies to (89%;[35] 89%;[8] 78%;[37] 72%[38]). Two guidelines satisfy most of the criteria in domain 5 (Applicability) by providing an a higher amount of guidance for implementing the guideline (79%;[34] 71%[41]). No guidelines addressed both of these domains completely, nor did any of the guidelines score >60% on four or more domains.

4.4. Objective 2: best practice recommendation for sedation interruptions

The 15 recommendations identified across the 11 guidelines, along with their respective strength and level of evidence as reported by the authors, are displayed in Table 3. Thirteen recommendations support the use of SI, and two recommendations are against performing SI specifically in patients with intracranial hypertension. All 15 recommendations were deconstructed using the

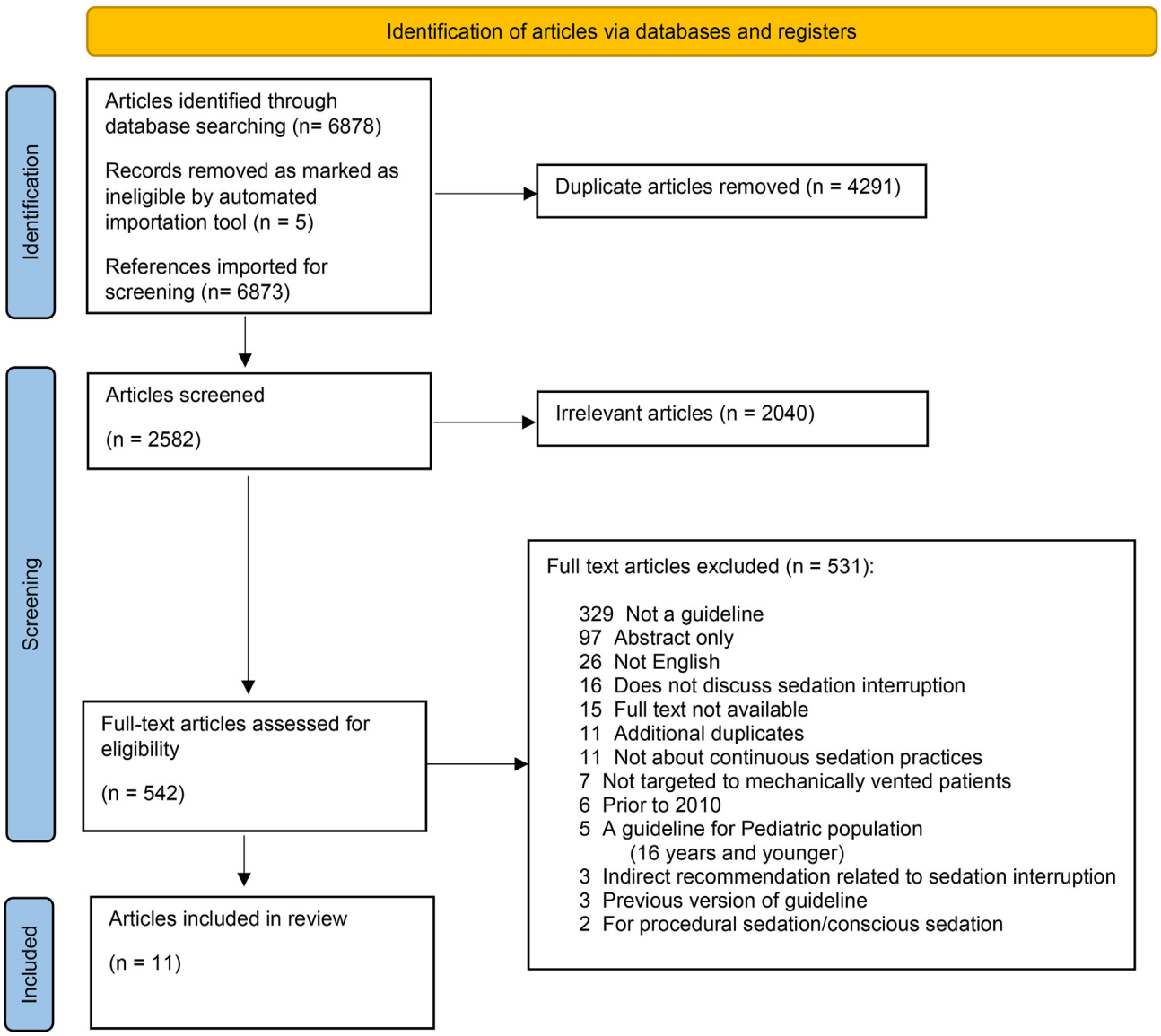

Figure 1. PRISMA flow diagram for the selection of the guidelines and care bundles. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Please cite this article as: Graham ND et al., A systematic review and critical appraisal of guidelines and their recommendations for sedation interruptions in adult mechanically ventilated patients, Australian Critical Care, https://doi.org/10.1016/j.aucc.2022.10.011

Table 1
Characteristics of included guidelines and care bundles.

Author (year) guideline title *Guideline type*	Country	Institution/guideline development group *Composition of development group*	Guideline health outcome	Target population	Intended users	Method used to collect or select the evidence	Method used for quality appraisal of the evidence	Method used to formulate and/or select the recommendations
Donato et al. (2021) Consensus for the management of analgesia, sedation and delirium in adults with COVID-19-associated acute respiratory distress syndrome *'Consensus' - evidence informed recommendations*	Argentina – Latin America	On behalf of the Committee for Analgesia, Sedation and Delirium of the Sociedad Argentina de Terapia Intensiva *Intensivist physicians, pharmacists and kinesiologists who addressed a protocol for managing ASD in adults with ARDS caused by COVID-19.*	Initial approach to the airway, to mechanical ventilation approaches in the different phases and to the withdrawal process	Critical patients that require systematic assessment of analgesia, sedation and delirium (ASD) in adults with ARDS caused by COVID-19	Argentinian health professionals caring for critical patients with ARDS caused by COVID-19	Non-systematic review of the scientific evidence, added to the judgement and clinical experience of the group of participating experts and other groups throughout the world	Not reported	For each stage, the mentioned sources of bibliographic information were analysed, and recommendations were established through nominal group consensus
Temesgena et al. (2021) Adult sedation and analgesia in a resource limited intensive care unit – A systematic review and evidence based guideline *Systematic review and evidence based guideline*	Ethiopia	Netsanet Temesgen, Bsazinew Chekol, Tadesse Tamirie, Denberu Eshetie, Nigussie Simeneh, Abatneh Feleke *Unknown*	Up-to-date perspective on procedures for the treatment of mechanically ventilated adult ICU patients in terms of sedation and analgesia	Mechanically ventilated patients in ICU	Not clear	Systematically reviewed 16 SR and MA, 8 RCTs, 3 evidence-based recommendations, 11 cohort studies, 5 cross-sectional studies, and 1 case report	LoE and SoR determined using criteria from WHO Evidence of Good Clinical Practice (GCP)	Finally conclusions and recommendations are made by balancing the benefits and drawbacks of alternative treatment options for sedation and analgesia protocols in ICU. WHO Evidence of Good Clinical Practice (GCP) used to categorise the recommendations based on level of evidence
Celis-Rodríguez et al. (2019) Evidence-based clinical practice guidelines for the management of sedoanalgesia and delirium in critically ill adult patients *Clinical practice guideline*	9 countries in the Americas and the Iberian Peninsula	Pan-American and Iberian Federation of Societies of Critical Medicine and Intensive Therapy *24 specialists in critical care medicine, with epidemiological and literature research support*	Management of sedation, analgesia, and delirium in the intensive care units	Critically ill adult patients	Physicians, nurses, clinical pharmacologists and professionals in the numerous disciplines that form part of the multidisciplinary team in the ICUs	Systematic search of all relevant studies related to the proposed topic	GRADE	Those recommendations with a voting rate of over 80% were included by consensus
Devlin et al. (2018) Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult *Clinical practice guideline*	North America, Europe, Australia	Society of Critical Care Medicine *Thirty-two experts from five countries, across five topic-specific sections; four methodologists, two medical librarians, four critical illness survivors, and two Society of Critical Care Medicine support staff.*	Assessment, prevention, and treatment of pain, agitation/sedation, delirium, immobility (mobilisation/ rehabilitation), and sleep (disruption) in critically ill adults	Critically ill, intubated adults/adult patients in the ICU	1) clinicians who provide patient care; 2) critically ill patients (and their families); 3) methodologists and other CPG developers; and 4) researchers	Systematic search of five databases	GRADE	Evidence and consensus based; graded recommendations and ungraded statements derived from actionable PICO questions and nonactionable descriptive ungraded statements
AHRQ (2017) Daily Care Processes Guide for Reducing Ventilator-Associated Events in Mechanically Ventilated Patients *Care bundle*	US	Prepared by Johns Hopkins Medicine/Armstrong Institute for Patient Safety and Quality *VAP Prevention committee of 155 healthcare experts in the care of patients on mechanical ventilation.*	Eliminates VAEs, including VAP.	Mechanically ventilated patients in intensive care units (ICUs)	Staff in intensive care units	Unclear	Unclear	Committee members participated in a modified Delphi process to determine the most important interventions

(*continued on next page*)

Table 1 (*continued*)

Author (year) guideline title *Guideline type*	Country	Institution/guideline development group *Composition of development group*	Guideline health outcome	Target population	Intended users	Method used to collect or select the evidence	Method used for quality appraisal of the evidence	Method used to formulate and/or select the recommendations
Schmidt et al. (2017) Liberation From Mechanical Ventilation in Critically Ill Adults: An Official American College of Chest Physicians/ American Thoracic Society Clinical Practice Guideline *Clinical practice guideline*	US	American Thoracic Society (ATS) and the American College of Chest Physicians (CHEST) *Six co-chairs, eight pulmonary/critical care physicians, four critical care physicians, one critical nurse, one physical therapist, and one critical care pharmacist. There were also two methodologists, one of whom is also a critical care physician.*	Liberation from the ventilator	For acutely hospitalised patients ventilated more than 24-h	Clinicians	Systematic review that included six unblinded randomised trials	GRADE	Evidence and consensus based; Evidence to Decision (EtD) framework was to facilitate the discussion and to ensure that all important categories were discussed before formulating the recommendation
DAS-Taskforce (2015) Evidence and consensus based guideline for the management of delirium, analgesia, and sedation in intensive care medicine *Clinical practice guideline*	Germany	German Society of Anaesthesiology and Intensive Care Medicine (DGAI) and the German Interdisciplinary Association for Intensive Care and Emergency Medicine (DIVI) *The guideline task-force consisted of 49 voting members nominated by 17 participating national societies.*	Delirium, anxiety, and agitation, as well as for the protocol- based analgesia, sedation, and sleep management	Critically ill patients of all age groups and severity of illness, regardless of comorbidities	All professions working in the intensive care unit (ICU)	Systematic search of the literature; no details in English	LoE determined using the Oxford System approved of by representative from 17 National Societies	Evidence and consensus based using a DELPHI approach
Sharshar et al. (2014) Neurological examination of critically ill patients: a pragmatic approach. Report of an ESICM expert panel *Clinical practice guideline*	Italy, UK, US	European Society of Intensive Care Medicine *The members of the expert panel were nominated at a meeting of the NIC in March 2010. Participants are senior academic intensivists with training in anesthesiology, critical care medicine, and neurology.*	A pragmatic approach to neurological examination (NE) of the critically ill patient	Patients admitted to the intensive care unit (ICU) that have pre-existing or acquired neurological disorders (delirium or coma)	Critical Care providers	Systematic search of the literature using one database	Because of the lack of robust studies, this group elected to not undertake a formal evidence-based consensus process	Pragmatic approach
HPS (2012) VAP Prevention Bundle Guidance for Implementation *Care bundle*	Scotland	Health Protection Scotland (HPS): NHS National Services Scotland *Experts in intensive care and infection control, from around Scotland.*	Prevention of VAP, primarily aimed at the prevention of Healthcare Associated Infections (HAI)	Patients with respiratory failure and especially those who require invasive ventilation	Those who manage patients with respiratory failure and especially those who require invasive ventilation	Initial rapid literature search; main public health websites; followed by a targeted systematic search of the literature	SIGN checklists	Evidence and expert opinion

IHI (2012) How-to Guide: Prevent Ventilator-Associated Pneumonia: Prevent ventilator-associated pneumonia (VAP) by implementing the five components of care called "the ventilator bundle" *Care bundle*	US	Institute for Health Improvement *IHI Faculty in collaboration with VHA in the Idealised Design of the Intensive Care Unit (IDICU), including intensivists and improvement leaders.*	Prevention of ventilator-associated pneumonia (VAP), venous thromboembolism (VTE), and stress-induced gastrointestinal bleeding	No specific exclusion criteria exist, clinical judgement should be exercised	Multidisciplinary team: intensive care physician, intensive care nurses, respiratory therapists, and pharmacists	Unclear	Unclear	Unclear
Rello et al. (2010) A European care bundle for prevention of ventilator-associated pneumonia *Care bundle*	Spain	None *A pan-European committee of 12 participants representing different disciplines (microbiology, infectious diseases, infection control, epidemiology, nursing, pneumology and critical care).*	Reduce the incidence of clinical complications in patients with VAP	Mechanically vented patients	Those who manage care in VAP treatment settings	Evidence derived from European HAP guidelines produced between 2002 and 2006	Unclear (used the multi-criteria decision analysis (MCDA) framework to decide which interventions were most applicable for the care bundle)	Multi-criteria decision analysis (MCDA) following a process of weighting and scoring

IHI, Institute for Health Improvement; GRADE, Grading of Recommendations Assessment, Development and Evaluation; HICPAC, Healthcare Infection Control Practices Advisory Committee; VAP, ventilator-associated pneumonia; PICO, Patient, Intervention, Comparator, Outcome; WHO, World Health Organization.
Composition of the development team is reported here verbatim from the original authors of the paper.

AACTT framework for specifying a sedation interruption. For complete information on how each guideline mapped to the AACTT framework, please see supplemental file 3. All of the foundational requirements were present to varying extents, with the exception of the *Actor* element. None of the recommendations identified which healthcare professional (Actor) should be responsible for completing the action.

None of the recommendations were explicit or detailed about what actions were being recommended. Devlin et al. offered a description of SI but not directly in the recommendation itself, rather it can be found in the remarks associated with the recommendation. The act of performing an SI is when "[p]atients 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 (SAS) score of 4–7 or a Richmond Agitation Sedation Scale (RASS) score of −1 to +1"[37](p. e838). The only other guideline to specify a recommended action was the Institute for Healthcare Improvement's (IHI) (2012) care bundle; their description of SI originated from Kress et al. which defines and speaks to the positive clinical outcomes of SI use: "[i]nterrupt sedation until the patient is awake and follows instructions, or becomes uncomfortable or agitated. The sedative infusions are started again after the patient [is] awake or, if agitation prevents successful waking, at half the previous rates and adjust according to the need for sedation"[43](as cited by IHI, 2012). Only one guideline[39] states to pair SI with a spontaneous breathing trial, and one states to perform a neurological assessment at the time of SI.[41]

There was a significant gap in who (*Actor)* should perform the action (a sedation interruption) across all guidelines. This information can only be deduced by considering the target users of the guideline as a whole, but no details are provided at the level of the SI recommendations. Collectively, the guidelines give a generalised idea of the target users of the guidelines by referring to critical care unit staff, clinicians, and/or physicians, nurses, respiratory therapists, and pharmacists.

Information on *Context* is more common in the recommendations; however, the elements significantly vary in their wording and complexity, yet compliment and at times contradict one another. All 11 included guidelines recommend including SI in the plan of care for critically ill, intubated, and mechanically ventilated adults. Schmidt et al. specify that SI should occur in patients mechanically ventilated for greater than 24 h, a practical inclusion criterion, as SIs are typically completed daily. Four guidelines[9,36,39,41] indicate SI should be included within the context of a weaning protocol. We have assumed that this is in reference to a mechanical ventilation weaning protocol. Three others[8,34,37] conversely recommend that SI should be part of an ABCDEF protocol which is, a wholistic approach to implementing evidence-informed strategies for patients on a mechanical ventilator. The elements of the protocol promote the assessment, prevention and management of pain; both spontaneous awakening and spontaneous breathing trials; choice of analgesia and sedation; delirium assessment, prevention, and management; early mobility and exercise, and; family engagement and empowerment.[37] One guideline in particular addressed implications associated with COVID-19, specifying that SI is to be used only if clinical conditions specific to the patient allow and proper protection by the health team can be ensured.[35]

The *Target* of an SI is directed at critically ill, intubated, and mechanically ventilated adults, a notion shared across 10 guidelines,[8,9,34,36–42] with some important and unique specifications. Firstly, SIs are reported to be performed only in patients that are mechanically ventilated for more than 24 h[38] and only in patients with the RASS less than or equal to −2,[39] and not in patients

Table 2
Overall AGREE-II scores by guideline.

AGREE II domain (scaled % scores)	Guideline author	Donato et al. (2021)	Temesgena et al. (2021)	Celis-Rodríguez et al. (2019)	Devlin et al. (2018)	Schmidt et al. (2017)	AHRQ (2017)	DAS-Taskforce (2015)	Sharshar et al. (2014)	HPS (2012)	IHI (2012)	Rello et al. (2010)
1. Scope and purpose		89	33	89	78	72	39	67	61	44	33	56
2. Stakeholder Involvement		22	0	50	89	44	17	28	17	22	28	11
3. Rigour of Development		38	6	63	69	69	6	58	25	17	10	15
4. Clarity of Presentation		78	11	72	39	50	78	56	56	33	33	22
5. Applicability		58	8	8	25	4	79	4	0	33	71	17
6. Editorial Independence		33	50	50	42	75	50	83	50	0	8	100
High quality (yes/no)		No	No	No	No	No	No	No	No	No	No	No

*High methodological quality (at least four domains with scores ≥60%).

Table 3
Recommendations for sedation interruptions with reported evidence appraisal.

Guideline and recommendation	Strength of the recommendation and level of evidence as reported by the author
Donato et al. (2021)	
1. We recommend daily sedation "breaks" or interruptions in adults with COVID-19 ARDS only if clinical conditions specific to the patient allow and proper protection by the health team can be ensured.	1. Not reported
Temesgen et al. (2021)	
2. Light sedation is recommended so that patients are responsive and able to communicate and daily interruption of sedation is stimulated.	2. Level 1 a.
3. Protocolised sedation or daily sedation interruption is recommended.	
Celis-Rodríguez et al. (2019)	
4. The recommendation is to apply the ABCDEF protocol in critically ill patients to increase the number of days without delirium and the days without coma, and to reduce the duration of ventilatory support, intensive care stay and mortality.	4. SoR = Strong; LoE = Low 5. SoR = Conditional; LoE = Low 6. SoR = Conditional; LoE = Low
5. If needed, continue sedation with dexmedetomidine as maintenance for over 7days, since there is not enough evidence to recommend a maximum time. It is advisable to alternate with periods of drug suspension and to monitor the appearance of adverse effects.	
6. The daily interruption of sedation in patients with intracranial hypertension is not recommended.	
Devlin et al. (2018)	7. Ungraded Statement
7. In critically ill, intubated adults, DSI protocols and NP-targeted sedation can achieve and maintain a light level of sedation.	
AHRQ (2017)	8. Not reported
8. Minimise sedative use and perform a daily sedation interruption or vacation, or SAT.	
Schmidt et al. (2017)	9. Conditional Recommendation, Low Quality of Evidence
9. For acutely hospitalised patients ventilated for more than 24 h, we suggest protocols attempting to minimise sedation. Example of protocols is provided in rationale (eg, bedside nursing sedation algorithms, daily sedative interruption).	
DAS-Taskforce (2015)	10 LOE = [a] 1a, [b] 1b; GoR = A (strong recommendation (we recommend/one shall))
10. If there are no contraindications, we recommend daily SAT and SBT only in patients with a RASS less than or equal to −2.	
Sharshar et al. (2014)	11. Moderate evidence, strong recommendation
11. Daily interruption or reduction of sedation is recommended in mechanically ventilated patients to enhance NE and improve short- and long-term outcomes.	12. Moderate evidence, strong recommendation
12. Sedation interruption is not recommended in patients with intracranial hypertension.	
HPS (2012)	13. Category 1B: strong recommendation based on low quality of evidence which suggest net clinical benefits or harms or an accepted practice.
13. Sedation is reviewed and, if appropriate, stopped each day.	
IHI (2012)	14. Not reported
14. Include a sedative interruption strategy in your overall plan to wean the patient from the ventilator; if you have a weaning protocol, add sedative interruption to that strategy.	
Rello et al. (2010)	
15. The incorporation of sedation vacation and weaning protocols into patient care.	15. Not reported

SoR, strength of recommendation; LoE, level of evidence; Level 1 a., strongly recommended and directly applicable; DAS, Delirium, Analgesia, and Sedation; AHRQ, Agency for Healthcare Research and Quality; DSI, daily sedation interruption; SAT, spontaneous awakening trial; SBT, spontaneous breathing trial; RASS, Richmond Agitation Sedation Scale; NE, neurological evaluation.

DAS -Taskforce LoE using the Oxford System: [a] - Burry L, Rose L, McCullagh IJ, Fergusson DA, Ferguson ND, Mehta S. Daily sedation interruption versus no daily sedation interruption for critically ill adult patients requiring invasive mechanical ventilation. Cochrane Database Syst Rev. 2014 Jul 9;7:CD009176. https://doi.org/10.1002/14651858.CD009176.pub2. [b] - Mehta S, Burry L, Cook D, Fergusson D, Steinberg M, Granton J, Herridge M, Ferguson N, Devlin J, Tanios M, Dodek P, Fowler R, Burns K, Jacka M, Olafson K, Skrobik Y, Hébert P, Sabri E, Meade M; SLEAP Investigators. Canadian Critical Care Trials Group. Daily sedation interruption in mechanically ventilated critically ill patients cared for with a sedation protocol: a randomised controlled trial. JAMA. 2012 Nov;308(19):1985-92. https://doi.org/10.1001/jama.2012.13872.

Please cite this article as: Graham ND et al., A systematic review and critical appraisal of guidelines and their recommendations for sedation interruptions in adult mechanically ventilated patients, Australian Critical Care, https://doi.org/10.1016/j.aucc.2022.10.011

with intracranial hypertension.[8,42] Finally, 10 out of 11 guidelines recommend that SI should be performed daily (*Time*).[8,34–42]

4.4. Objective 3: clinical applicability, values and preferences, and implementability of the recommendation(s) related to SI

Table 4 illustrates the results of the AGREE-REX individual item consensus scores, the scores by domain, as well as a final overall score by guideline for the specific recommendation related to SI. The overall AGREE-REX scores range from 9%[42] to 76%.[37] We identified that most SI-related recommendations are formulated using poor to moderate guideline development methods. Only one recommendation was considered to be of high methodological quality[37](overall AGREE-REX score = 76%). Four guidelines contained recommendations of moderate quality (44%;[8] 41%;[35] 37%;[34] and 33%[38]), and six were of low quality (24%;[39] 22%;[41] 20%;[36] 19%;[9] 11%;[40] and 9%[42]).

A closer inspection of the individual AGREE-REX domains illustrates the strengths and inadequacies of the available recommendations:

4.4.1. Domain 1. Clinical Applicability

The average score across guidelines ranged from 11%[34] to 94%.[37] Overall, the evidence base reportedly used in the formulation of the recommendations for SI was derived from low-quality trials,[8,38–40] with the exception of Sharshar et al. who reported a moderate evidence base. Notably, one guideline offered an ungraded statement,[37] despite having considered the evidence base available for SI. Five others did not report having undertaken a formal evidence appraisal.[9,34–36,41] Only two guidelines, Celis-Rodriguez et al. (83%) and Devlin et al. (94%), provided a comprehensive report of the analysis of evidence and how the anticipated outcomes of SI are relevant to *target patients*. Although, these same two guidelines could be more transparent about the target user's scope and role in performing an SI.

4.4.2. Domain 2. Values and preferences

The average score across guidelines ranged from a low of zero[39,40,42] to only a modest 54%.[37] Overall, most of the guidelines do not provide a detailed description of the methods or approaches used to address the values and preferences of target users, patients, policymakers and decision-makers, or guideline developers in the formulation of the recommendation. The notable exception is Devlin et al. which described having critical illness survivors along with the 32 experts from five countries, four methodologists, and two librarians having participated in the development of the recommendations. This guideline received only moderate scores because the target users or Actor(s) needed to complete an SI were not well described.

4.4.3. Domain 3. Implementability

The average scores ranged from 0%[42] to 92%.[31] Devlin et al. (92%) and the Agency for Healthcare Research and Quality (AHRQ) (2017) (75%) scored the highest for achieving the purpose of the guideline with provision of advice and tools for implementation. This domain is focused on whether or not the guideline addresses implementation factors, such as system level changes, resources, and strategies needed for uptake of SI at the bedside. Both Devlin et al.'s

Table 4
AGREE-REX Clinical Applicability, Values and Preferences, and Implementatbility of the Recommendation(s) related to SI.

	Donato et al. (2021)	Temesgena et al. (2021)	Celis-Rodríguez et al. (2019)	Devlin et al. (2018)	AHRQ (2017)	Schmidt et al. (2017)	DAS-Taskforce (2015)	Sharshar et al. (2014)	HPS (2012)	IHI (2012)	Rello et al. (2010)
AGREE-REX items clustered by domain	Consensus scores by recommendation cluster for each guideline										
Domain 1 Clinical Applicability (% out of 100)	*67*	*28*	*83*	*94*	*11*	*67*	*56*	*33*	*28*	*22*	*22*
1 Evidence	2	2	6	7	1	7	4	2	3	2	2
2 Clinical Relevance/ Applicability to target users	6	3	5	6	2	6	5	3	2	3	3
3 Relevance and Applicability to patients or population	7	3	7	7	2	2	4	3	3	2	2
Domain 2 Values and Preferences (% out of 100)	*13*	*0*	*21*	*54*	*38*	*17*	*0*	*0*	*0*	*8*	*8*
4 Values and Preferences of target users	2	1	2	4	4	2	1	1	1	2	1
5 Values and Preferences of patients or population	1	1	1	6	1	2	1	1	1	1	1
6 Values and Preferences of policymakers and decision-makers	3	1	4	3	6	2	1	1	1	2	3
7 Values and Preferences of guideline developers	1	1	2	4	2	2	1	1	1	1	1
Domain 3 Implementability (% out of 100)	*53*	*50*	*33*	*92*	*75*	*17*	*25*	*0*	*8*	*50*	*33*
8 Purpose	6	6	4	6	6	3	2	1	2	3	3
9 Local application and adoption	3	2	2	7	5	1	3	1	1	5	3
Recommendation for use in appropriate context	No	No	No	Yes	No	No	No	No	No	No	No
Overall AGREE-REX score (% out of 100)	*41*	*20*	*44*	*76*	*37*	*33*	*24*	*9*	*11*	*22*	*19*

Each of the items contain a definition of that item, quality criteria for that item, one question related to quality, as well as one question that focused on suitability for use in a particular clinical setting. Both questions are scored using a seven-point response scale, 1 = strongly disagree and 7 = strongly agree.[25] In this review, recommendations with overall AGREE-REX scores >70% are considered high quality, while those with overall quality scores <30% are lower quality, and all others are moderate quality (approach suggested by AGREE-REX Research Team, 2019).

Please cite this article as: Graham ND et al., A systematic review and critical appraisal of guidelines and their recommendations for sedation interruptions in adult mechanically ventilated patients, Australian Critical Care, https://doi.org/10.1016/j.aucc.2022.10.011

guideline and AHRQ's care bundle offered generalised guidance for implementing the guideline in its entirety or as appropriate portions of the guideline/care bundle. Devlin et al.'s guideline did get more specific about SI implementation and aligned this practice with other recommendations that should be bundled together as part of the ABCDEF protocol.

Although there are significant methodological deficiencies noted in this review, even within the highest scoring guideline, one guideline does meet a quality threshold that has been commonly used in other reviews. The guideline that met most of the criteria for guideline development was from Devlin et al., which has moderately addressed the values and preferences of key stakeholders, and is the most applicable and implementable of the nine included guidelines. The Devlin guideline offers a 'good practice statement' related to SI, "In critically ill, intubated adults, [daily sedation interruption] (DSI) protocols and [nursing-protocolised] NP-targeted sedation can achieve and maintain a light level of sedation" (2018, p. e838). As the highest overall AGREE-REX scoring guideline, the recommendations were based on a thorough review and analysis of the available evidence related to SI; however, the recommendation was not graded. The recommendation is defined by the authors to be a 'good practice statement' because "… there is an unequivocal belie[f] that the benefit of the intervention outweighs the risk but no available direct evidence that could be summarised or evaluated"[37](Supplemental Digital Content 1, http://links.lww.com/CCM/D733, p. 10).

5. Discussion

Sedation interruptions are an important component of care that has been identified as necessary for mitigating negative sequelae associated with the treatments received in the critical care environment.[44] In this review, we have systematically identified, appraised, and synthesised 15 recommendations related to SI from 11 published guidelines. We have developed a summary table with current best practices for SI recommendations derived from existing guidelines and present three key findings. (i) There are important deficiencies with the quality of the methodological development of all available guidelines that contain a recommendation related to SI. (ii) Best practice is in favour of performing a SI for adult mechanically ventilated patients, but there are key elements missing in the formulation of the recommendation. (iii) The evidence for the SI recommendations are generally weak.

To the best of our knowledge, our review is the first to appraise CPGs as well as care bundles with recommendations directly related to SI using the AGREE-REX as a compliment to the AGREE II instruments. Prior to this review, the AGREE II instrument has been used to appraise CPGs on pain, agitation, and delirium management in the ICU to identify high-quality guidelines appropriate for clinical use.[27] The use of the AGREE II instrument in this review adds a novel perspective in the literature about the overall quality of the methodological development of the guideline while AGREE REX adds transparency to the quality of the recommendations themselves. Three of the eight included guidelines in Rosenthal et al.'s systematic literature search and quality appraisal of guidelines on pain, agitation, and delirium management are also included in this review.[8,39,44] There were differences in the AGREE-II appraisal scores for Celis-Rodriguez et al. and the Delirium, Analgesia, and Sedation (DAS)-Taskforce. The reason for the discrepancy in scoring may reflect Rosenthal et al.'s inclusion of Celis-Rodriguez past guideline from 2013. The Celis-Rodriguez et al. version included in our review is an update of the 2013 version. The older version from 2013 contains a more detailed account of the methodological approaches which could impact AGREE-II scores. Similarly, Rosenthal et al. also included DAS-Taskforce (2015) extended version published in German only, which again would impact AGREE-II scores. Three of the authors on the Rosenthal et al. review are also contributing members on the DAS-Taskforce (2015) guideline, and they may have had access to additional methodological information for that review.

Clinicians need to be aware of certain considerations when they are trying to decide whether to incorporate guidelines and in particular, recommendations related to SI, into unit-specific policies. Being aware of the methodological quality of the formulation of the guideline and individual recommendation itself is important when trying to weigh the options that are available in the literature. This review provides a synthesised view of the available evidence about recommendations related to SI in all available guidelines written in English and may be of particular interest to the individuals developing polices for the critical care clinicians. This review can also help clinicians and policy developers alike to interpret the available recommendations related to SI.

5.1. Guideline quality

There were 11 guidelines identified in this review, none which were of high methodological quality after applying the AGREE II instrument. None of the included guidelines in this review scored $\geq$60% on at least four AGREE-II domains, which reflects overall poor methodological quality at the level of the guideline as a whole. Clinicians looking to implement the recommendations from these guidelines should be aware that these recommendations are a more practical option for improving the quality of care that this patient population receives rather then being a product of high-quality evidence. The recommendations continue to surface in guidelines despite this lack of high-quality evidence to support their use. This may be because maintaining the ideal minimal level of sedation to keep a patient cooperative enough on the ventilator and also be able to participate in spontaneous breathing trials and early ambulation is not always possible or practical.

Guideline developers would benefit from using more rigorous methodology in guideline development by addressing the domains and criteria detailed by instruments, such as the AGREE II. Despite this finding, the guidelines do offer some valuable information about SI and can serve to inform a clinician or policy developer's knowledge about the elements needed to enact this practice, albeit they do require some modifications. Optimistically, researchers have begun to address the issue of needing higher quality clinical trials evaluating the safety and effectiveness of sedation medications used in mechanically ventilated patients.[45]

5.2. Current best practice for SI

Despite the low methodological quality of the guidelines, the foundational elements for SI that are presented are of value to clinicians. Clinicians are faced with the need to make decisions everyday about patient care, one of these decisions is whether or not to perform SI. Thirteen out of 15 recommendations support the use of SI in practice, and the remaining two only recommend not performing SI on patients with intracranial hypertension. This indicates that including a daily SI can generally be considered current best practice. As best practice, it is important for the recommendation to contain enough detail for clinicians to be able to use it in practice. Currently, the existing recommendations provide some instruction about how to perform SI (action) but lack detail about who is responsible for performing SI (actor), the circumstance(s) when SI should or should not be performed (context) (assuming that a patient may not be eligible for a SI for more reasons than intracranial hypertension) and lastly the goal of performing a SI

Please cite this article as: Graham ND et al., A systematic review and critical appraisal of guidelines and their recommendations for sedation interruptions in adult mechanically ventilated patients, Australian Critical Care, https://doi.org/10.1016/j.aucc.2022.10.011

(target); there is, however, agreement across recommendations that SI should be performed daily (time).

Overall, there is agreement from the results of this review that the benefits of including a SI in the plan of care out weigh the potential risks. SIs are recommended for patients that are deeply sedated but not recommended for those with diagnosed intracranial hypertension. Indeed, after having deconstructed the foundational requirements (AACTT) for implementing a SI across all 11 guidelines, we can appreciate why it is challenging for clinicians to understand the what, who, when, and under what circumstances a SI should be performed. Guideline developers can ameliorate the current state of recommended practices related to SI by working together to reach consensus on the precise actions required to complete an SI clarity on who is/are the actor(s) and what is/are their role(s), as well as under what contextual circumstances that SI should be performed.

Nomenclature is also important as, arguably, a weaning protocol for mechanical ventilation can be considered to be different from the ABCDEF protocol.[44] A weaning protocol aims to actively discontinue mechanical ventilation, while the ABCDEF protocol is a holistic approach to patient management.[44] More consistency with terminology and specificity about what actions are required to be taken, under what conditions, when, and will likely improve guideline recommendation adherence and patient outcomes. Clinicians and policy-developers need to come together and look at this synthesis of recommendations related to SI and decide what is most appropriate and implementable for their unique context, given the variability that exists.

5.3. Quality of SI recommendation formulation

According to the thresholds set in this review, only the recommendation from Devlin et al. is considered to be of high methodological quality, although the same guideline failed to meet the quality threshold for overall guideline methodological development. The poorest scoring domains for AGREE-REX in this review were Domains 2 (Values and Preferences) and 3 (Implementability). If guideline developers attend to these items in future recommendation formulation, more detailed recommendations could influence the uptake of SI practice at the bedside. This finding is congruent with a study that appraised 161 CPGs using the prototype of the AGREE-REX (draft) tool and the AGREE II tool.[31] The results suggest the least favourable (defined as ratings below the mid-point of the 7-point Likert scale, < 4.0) are more commonly found for *patients/population values, policy values, alignment of values, local applicability* and *resources, tools, and capacity* items.[31] Furthermore, our results reveal the applicability of SI recommendations has the greatest potential for improvement. This finding is consistent with Rosenthal et al.'s appraisal of similar delirium guidelines. To inform the development of recommendations related to SI, it is plausible that recommendations are intentionally left ambiguous since the quality of the evidence to draw from is generally of low quality.[37,38]

5.4. Practice implications

As a potential consumer of guidelines and recommendations related to SI, caution should be taken when deciding to implement these recommendations in practice. In general, the quality of SI recommendation formulation is low, and furthermore, the evidence base in support of these recommendations is mostly of low quality. The heterogeneity of the small number of studies that examine patient outcomes and SI management can explain the low-quality evidence base. Some of the guidelines in this review cite Burry et al.'s systematic review from 2014 in support of the recommendations. Burry et al.'s review examined SI versus no SI in terms of total duration of invasive mechanical ventilation and the influence on mortality, ICU length of stay, adverse events, the total doses of sedative medication required, as well as quality of life.[46] Burry et al advise caution when interpreting their findings given they are based on a small number of heterogenous RCTs and that these results are unstable rather then negative for SI.[46] Inconsistency in the findings on the effects SI recently spurred Chen et al. to conduct a systematic review and meta-analysis of 45 RCTs (i.e., 49 effect size) from different countries. Conversely, Chen's review revealed there is a need to include SI as routine care to reduce the mechanical ventilation duration, especially in higher disease severity populations.[47] The implications of these inconsistencies are reflected in the current state of recommendations related to SI. Clinicians should be aware, whether they continue to implement SI either as a stand-alone intervention or paired with others, research is ongoing about the benefits and risks of SI, and a recent review[47] has demonstrated favourable results.

Furthermore, there is a lack of consensus across recommendations about the *actors*, the *action*, and the *context* by which SI is best performed, with notable absence of specificity about the actor. Although not specified in recommendations related to SI, nurses are primarily responsible for the management of sedative infusions and have self-reported using SI in practice.[17,48] The lack of specificity in recommendations about how to perform SI likely led to variation in SI practice. In 2012, Millller et al. conducted focus groups with intensive care unit physicians, nurses, and respiratory therapists and found a pervasive lack of consensus within and across disciplines about the reason for performing an SI and, most importantly, confusion about the end-points or goals of the intervention.[18]

The recommendation matrix presented in this review can be used by clinicians, policymakers, and guideline developers to make decisions about adopting one of the guidelines or recommendations for local use. The matrix can serve as a starting point for refinement of existing local protocols that include SI. This review also brings increased awareness of two appraisal instruments that can be used during guideline development and/or recommendation formulation. More trustworthy and implementable recommendations alongside structured and multifaceted knowledge translation interventions will increase the likelihood of SI uptake at the bedside. Notably, there is a global need for strengthened guideline quality that is not unique to this field of research.[49]

5.5. Limitations

This study has limitations. It is possible that some CPGs and care bundles were missed during the search. Four databases and 15 critical care associations from around the world and all 11 guideline repositories were hand searched to find guidelines. A selection bias may exist from inadvertently neglecting to include search terms that may result in additional relevant guidelines or ignorantly missing relevant associations or repositories. Also, the authors accept the possibility of a language bias considering only articles published in English were considered for full-text review. Despite the possibility of a selection and/or language biases, countries from around the world are represented here. We had originally planned, as noted in our protocol, to assess the quality of the evidence supporting each guideline recommendations using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system.[50] The GRADE system differs from the AGREE instruments, which do not specifically rate and categorise the quality of evidence and the strength of the recommendations. We were unable to undertake the GRADE analysis because some guidelines

Please cite this article as: Graham ND et al., A systematic review and critical appraisal of guidelines and their recommendations for sedation interruptions in adult mechanically ventilated patients, Australian Critical Care, https://doi.org/10.1016/j.aucc.2022.10.011

did not assess the evidence in support of their recommendations or reported on this.

6. Conclusion

In this review, we identified 11 CPGs and/or care bundles with a total of 15 recommendations related to SI for adult mechanically ventilated patients in the critical care setting. Thirteen recommendations are in favour of SI, and two recommend not performing SI in patients with intracranial hypertension. This review provides greater transparency of the quality and formulation of recommendations related to SI for clinicians policy-, and guideline developers. Nurses and other critical care clinicians can compare the recommendations related to SI to better facilitate application in their local context. Future research should focus on understanding the more technical aspects of completing a SI (e.g., explicating recommended procedural steps) to better assist nurses and other clinicians with the implementation of this practice.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CRediT authorship contribution statement

Nicole Graham: conceptualisation, methodology, formal analysis, investigation, writing - original draft preparation. **Ian Graham:** conceptualisation, methodology, writing - review and editing, supervision. **Brandi Vanderspank-Wright:** conceptualisation, review and editing, supervision. **Melissa Demery Varin:** investigation, validation, writing - review and editing. **Letitia Nadalin Penno:** investigation, validation, writing - review and editing. **Dean Fergusson:** methodology, writing - review and editing, supervision. **Janet Squires:** conceptualisation, methodology, writing - review and editing, supervision.

Conflict of interest

The authors declare that they have no competing interests.

Acknowledgements

Thank you to Lindsey Sikora, the Health Sciences Research Librarian at the University of Ottawa for the peer review of the search strategy in the current study. IDG is a recipient of a Canadian Institutes of Health Research Foundation Grant (FDN# 143237).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.aucc.2022.10.011.

References

[1] Kress JP, Hall JB. Sedation in the mechanically ventilated patient. Crit Care Med 2006 Oct;34(10):2541–6.
[2] Ely EW. The ABCDEF bundle: science and philosophy of how ICU liberation serves patients and families. Crit Care Med [Internet] 2017;45(2). Available from: https://journals.lww.com/ccmjournal/Fulltext/2017/02000/The_ABCDEF_Bundle__Science_and_Philosophy_of_How.21.aspx.
[3] Pandharipande PP, Ely EW, Arora RC, Balas MC, Boustani MA, La Calle GH, et al. The intensive care delirium research agenda: a multinational, interprofessional perspective. Intensive Care Med 2017;43(9):1329–39.
[4] Pandharipande PP, Girard TD, Ely EW. Long-term cognitive impairment after critical illness. N Engl J Med 2014 Jan 9;370(2):185–6.
[5] Krewulak KD, Stelfox HT, Ely EW, Fiest KM. Risk factors and outcomes among delirium subtypes in adult ICUs: a systematic review. J Crit Care 2020 Apr;56:257–64.
[6] Girard TD, Shintani AK, Jackson JC, Gordon SM, Pun BT, Henderson MS, et al. Risk factors for post-traumatic stress disorder symptoms following critical illness requiring mechanical ventilation: a prospective cohort study. Crit Care 2007;11(1):R28.
[7] Samuelson K, Lundberg D, Fridlund B. Memory in relation to depth of sedation in adult mechanically ventilated intensive care patients. Intensive Care Med 2006 May;32(5):660–7.
[8] Celis-Rodriguez E, Diaz Cortes JC, Cardenas Bolivar YR, Carrizosa Gonzalez JA, Pinilla D-I, Ferrer Zaccaro LE, et al. Evidence-based clinical practice guidelines for the management of sedoanalgesia and delirium in critically ill adult patients. Med Intensiva 2020;44(3):171–84.
[9] The VAP Care Bundle Contributors, Rello J, Lode H, Cornaglia G, Masterton R. A European care bundle for prevention of ventilator-associated pneumonia. Intensive Care Med 2010 May;36(5):773–80.
[10] Balas MC, Vasilevskis EE, Olsen KM, Schmid KK, Shostrom V, Cohen MZ, et al. Effectiveness and safety of the awakening and breathing coordination, delirium monitoring/management, and early exercise/mobility bundle. Crit Care Med 2014 May;42(5):1024–36.
[11] Burry LD, Williamson DR, Perreault MM, Rose L, Cook DJ, Ferguson ND, et al. Analgesic, sedative, antipsychotic, and neuromuscular blocker use in Canadian intensive care units: a prospective, multicentre, observational study. Can J Anesth/J Can Anesth. 2014 Jul;61(7):619–30.
[12] Carrothers KM, Barr J, Spurlock B, Ridgely MS, Damberg CL, Ely EW. Contextual issues influencing implementation and outcomes associated with an integrated approach to managing pain, agitation, and delirium in adult ICUs. Crit Care Med 2013 Sep 2:S128–35.
[13] Klompas M, Anderson D, Trick W, Babcock H, Kerlin MP, Li L, et al. The preventability of ventilator-associated events. The CDC prevention epicenters wake up and breathe collaborative. Am J Respir Crit Care Med 2015 2/1/2015;191(3):292–301.
[14] Jiang V, Brooks EM, Tong ST, Heintzman J, Krist AH. Factors influencing uptake of changes to clinical preventive guidelines. J Am Board Fam Med 2020 Mar;33(2):271–8.
[15] Fong JJ, Cecere K, Unterborn J, Garpestad E, Klee M, Devlin JW. Factors influencing variability in compliance rates and clinical outcomes among three different severe sepsis bundles. Ann Pharmacother 2007 May 8;41(6):929–36.
[16] Hawe CS, Ellis KS, Cairns CJS, Longmate A. Reduction of ventilator-associated pneumonia: active versus passive guideline implementation. Intensive Care Med 2009 Jul;35(7):1180–6.
[17] Sneyers B, Laterre P-F, Perreault MM, Wouters D, Spinewine A. Current practices and barriers impairing physicians' and nurses' adherence to analgosedation recommendations in the intensive care unit - a national survey. Crit Care 2014;18(1):655.
[18] Miller MA, Bosk EA, Iwashyna TJ, Krein SL. Implementation challenges in the intensive care unit: the why, who, and how of daily interruption of sedation. J Crit Care 2012;27(2):218.e1–7.
[19] Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Int J Surg 2021 Apr;88:105906.
[20] Johnston A, Kelly SE, Hsieh SC, Skidmore B, Wells GA. Systematic reviews of clinical practice guidelines: a methodological guide. J Clin Epidemiol 2019 Apr;108:64–76.
[21] Operated by Veritas Health Innovation Ltd. Covidence [Internet]. Melbourne, Australia: Covidence.org; Available from: https://www.covidence.org/.
[22] Brouwers MC, Kho ME, Browman GP, Burgers JS, Cluzeau F, Feder G, et al. AGREE II: advancing guideline development, reporting, and evaluation in health care. Prev Med 2010 Nov;51(5):421–4.
[23] The AGREE Reporting Checklist. A tool to improve reporting of clinical practice guidelines. BMJ 2016 Sep 6:i4852.
[24] MacDermid JC, Brooks D, Solway S, Switzer-McIntyre S, Brosseau L, Graham ID. Reliability and validity of the AGREE instrument used by physical therapists in assessment of clinical practice guidelines. BMC Health Serv Res 2005 Dec;5(1):18.
[25] 47. ANSC. The AGREE II Instrument [Electronic version] [Internet]. AGREE Scientific Office; 2017. Available from: http://www.agreetrust.org/.
[26] Altokhais TI, Al-Obaid OA, Kattan AE, Amer YS, CPG Collaborative Groups. Assessment of implementability of an adapted clinical practice guideline for surgical antimicrobial prophylaxis at a tertiary care university hospital. J Eval Clin Pract 2017 Feb;23(1):156–64.
[27] Rosenthal M, Grunow JJ, Spies CD, Mörgeli R, Paul N, Deffland M, et al. Critical care guidelines on pain, agitation and delirium management: which one to use? A systematic literature search and quality appraisal with AGREE II. J Crit Care 2020 May 29;59:124–9.
[28] Adamiec A, Ambrożej D, Ryczaj K, Ruszczynski M, Elenius V, Cavkaytar O, et al. Preschool wheezing diagnosis and management-Survey of physicians' and caregivers' perspective. Pediatr Allergy Immunol 2020 Feb;31(2):206–9.
[29] Presseau J, McCleary N, Lorencatto F, Patey AM, Grimshaw JM, Francis JJ. Action, actor, context, target, time (AACTT): a framework for specifying behaviour. Implement Sci 2019 Dec;14(1):102.
[30] 25. ARRT. The appraisal of guidelines research & evaluation—recommendation EXcellence (AGREE-REX) [Electronic version]

[Internet]. AGREE Scientific office; 2019 [cited 2021 May 7]. Available from: https://www.agreetrust.org/wp-content/uploads/2019/04/AGREE-REX-2019.pdf.

[31] Florez ID, Brouwers MC, Kerkvliet K, Spithoff K, Alonso-Coello P, Burgers J, et al. Assessment of the quality of recommendations from 161 clinical practice guidelines using the Appraisal of Guidelines for Research and Evaluation–Recommendations Excellence (AGREE-REX) instrument shows there is room for improvement. Implement Sci 2020 Dec;15(1):79.

[32] Brouwers MC, Spithoff K, Kerkvliet K, Alonso-Coello P, Burgers J, Cluzeau F, et al. Development and validation of a tool to assess the quality of clinical practice guideline recommendations. JAMA Netw Open 2020 May 27;3(5):e205535.

[33] ADAPTE Collaboration. The ADAPTE process: resource toolkit for guideline adaptation. Version 2.0. [Internet]. Guideline International Network; 2009. p. 1–95. Available from: http://www.g-i-n.net.

[34] Agency for Healthcare Research and Quality. Daily care processes guide for reducing ventilator-associated events in mechanically ventilated patients [Internet]. AHRQ Pub.; 2017. Available from: https://www.ahrq.gov/sites/default/files/wysiwyg/professionals/quality-patient-safety/hais/tools/mvp/modules/technical/daily-care-processes-guide.pdf.

[35] Donato M, Carini FC, Meschini MJ, Saubidet IL, Goldberg A, Sarubio MG, et al. Consensus for the management of analgesia, sedation and delirium in adults with COVID-19-associated acute respiratory distress syndrome. Rev bras ter intensiva 2021;33(1):48–67.

[36] Temesgen N, Chekol B, Tamirie T, Eshetie D, Simeneh N, Feleke A. Adult sedation and analgesia in a resource limited intensive care unit - a Systematic Review and evidence based guideline. Ann Med Surg (Lond). 2021;66(101616869):102356.

[37] Devlin JW, Skrobik Y, Gelinas C, Needham DM, Slooter AJC, Pandharipande PP, 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(9):e825–73.

[38] Ouellette DR, Patel S, Girard TD, Morris PE, Schmidt GA, Truwit JD, et al. Liberation from mechanical ventilation in critically ill adults: an official American college of chest physicians/American thoracic society clinical practice guideline: inspiratory pressure augmentation during spontaneous breathing trials, protocols minimizing sedation, and noninvasive ventilation immediately after extubation. Chest 2017 Jan;151(1):166–80.

[39] Baron R, Binder A, Biniek R, Braune S, Buerkle H, Dall P, et al., DAS -Taskforce 2015. Evidence and consensus based guideline for the management of delirium, analgesia, and sedation in intensive care medicine. Revision 2015 (DAS-Guideline 2015) - short version. Ger Med Sci 2015;13 (101227686): Doc19.

[40] 34. HPS. VAP prevention bundle guidance for implementation [Internet]. National Services Scotland; 2012. Available from:, Version 2.0. https://www.sicsag.scot.nhs.uk/hai/VAP-Prevention-Bundle-web.pdf.

[41] Institute for Healthcare Improvement. How-to guide: prevent ventilator-associated pneumonia [Internet]. Cambridge, MA: Institute for Healthcare Improvement; 2012. Available from, www.ihi.org.

[42] Sharshar T, Citerio G, Andrews PJD, Chieregato A, Latronico N, Menon DK, et al. Neurological examination of critically ill patients: a pragmatic approach. Report of an ESICM expert panel. Intensive Care Med 2014;40(4):484–95.

[43] Kress JP, Pohlman AS, O'Connor MF, Hall JB. Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. N Engl J Med 2000 May 18;342(20):1471–7.

[44] Pun BT, Balas MC, Barnes-Daly MA, Thompson JL, Aldrich JM, Barr J, et al. Caring for critically ill patients with the ABCDEF bundle: results of the ICU liberation collaborative in over 15,000 adults. Crit Care Med 2019 Jan;47(1):3–14.

[45] Ward DS, Absalom AR, Aitken LM, Balas MC, Brown DL, Burry L, et al. Design of clinical trials evaluating sedation in critically ill adults undergoing mechanical ventilation: recommendations from sedation consortium on endpoints and procedures for treatment, education, and research (SCEPTER) recommendation III. Crit Care Med 2021 Oct;49(10):1684–93.

[46] Burry L, Rose L, McCullagh IJ, Fergusson DA, Ferguson ND, Mehta S. Daily sedation interruption versus no daily sedation interruption for critically ill adult patients requiring invasive mechanical ventilation. Cochrane Emergency and Critical Care Group. In: Cochrane database of systematic reviews [Internet]; 2014 Jul 9 [cited 2022 Oct 3];2018(12). Available from: https://doi.org/10.1002/14651858.CD009176.pub2.

[47] Chen T, Chung Y, Chen P, Hu SH, Chang C, Hsieh S, et al. Effects of daily sedation interruption in intensive care unit patients undergoing mechanical ventilation: a meta-analysis of randomized controlled trials. Int J Nurs Pract [Internet] 2022 Apr;28(2):e12948. Available from: https://onlinelibrary.wiley.com/doi/10.1111/ijn.12948.

[48] Hetland B, Guttormson J, Tracy MF, Chlan L. “Sedation is tricky”: a qualitative content analysis of nurses' perceptions of sedation administration in mechanically ventilated intensive care unit patients. Aust Crit Care 2018;31(3):153–8.

[49] McCormack JP, Loewen P. Adding “value” to clinical practice guidelines. Can Fam Physician 2007 Aug;53(8):1326–7.

[50] Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008 Apr 26;336(7650):924–6.

Please cite this article as: Graham ND et al., A systematic review and critical appraisal of guidelines and their recommendations for sedation interruptions in adult mechanically ventilated patients, Australian Critical Care, https://doi.org/10.1016/j.aucc.2022.10.011