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A systematic meta-review of interventions to prevent and manage delirium in the Intensive Care Unit: Part 1 – Pharmacological interventions

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Abstract

Background Intensive Care Unit (ICU) delirium is a multifactorial syndrome associated with prolonged hospitalization, increased morbidity and mortality, cognitive decline, and higher healthcare costs. Many randomised controlled trials of interventions to prevent or manage ICU delirium have been combined in systematic reviews. We aimed to collate and map the meta-analysed evidence for pharmacological interventions.

Methods Eligible reviews included RCTs of any pharmacological intervention designed to prevent or manage critically ill adults with, or at risk of, ICU delirium. We searched 8 databases from inception to 26 September 2023. Two reviewers independently screened search results and confirmed eligibility of full texts. We then mapped the effects for pharmacological interventions (single or combined drugs and sedation strategies) along with the certainty of the evidence for outcomes in the Del-CorS core outcome set, ICU and hospital length of stay.

Results Of 3,381 studies, we identified 56 relevant systematic reviews reporting our outcomes (17 included in mapping). Thirteen reviews with GRADE assessments were mapped for delirium outcomes (occurrence, duration or severity), six for ICU or hospital mortality, and 15 for ICU or hospital length of stay. The α2-adrenoceptor agonist drug class (primarily dexmedetomidine) had the largest evidence base and was probably favourable over placebo for preventing or reducing delirium occurrence (moderate to high-certainty evidence; 2 systematic reviews). The α2-adrenoceptor agonist drug class (primarily dexmedetomidine) was also probably favourable over placebo for reducing ICU and hospital length of stay (moderate-certainty evidence; one systematic review). The evidence was more variable for other pharmacological comparisons. For ICU mortality, there may have been little or no difference between dexmedetomidine and a non-dexmedetomidine comparator (low certainty), while the evidence was very uncertain on hospital mortality (one systematic review). No meta-analyses reported outcomes for cognition

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or emotional distress. Co-interventions, in particular non-pharmacological interventions, were often incompletely reported.

Conclusions Mapped evidence suggests the α2-adrenoceptor agonist drug class (primarily dexmedetomidine), is most likely to be effective at managing delirium in the ICU. However, underlying conditions indicating or precluding intervention, and the impact of loss to follow-up, remain unclear. We found a lack of synthesised evidence for important core outcomes of cognition and emotional distress, and for deprescribing sedatives/analgesia as part of optimising sedation strategies.

Keywords Delirium, Adult intensive and critical care, Review

Introduction

Delirium is an acute, fluctuating, and reversible syndrome resulting in impaired cognition and/or consciousness [1]. People with delirium have trouble maintaining attention and may have visual and auditory hallucinations [2]. While prevalence estimates vary, up to 7 in 10 patients admitted to intensive care units (ICUs) are anticipated to develop delirium, with estimates higher among mechanically ventilated patients [2, 3]. Patient risk factors for delirium include the severity of the acute illness, older age, and other comorbidities (cardiovascular risk factors, plus pre-existing impaired cognition, withdrawal from alcohol and nicotine) [4]. Risk factors relating to the management of critical illness include drugs (and dose) specific to the ICU e.g. sedatives and analgesia. The incidence of ICU delirium is expected to increase further with increasing admissions of older people living with multiple long-term conditions.

ICU delirium is associated with a higher risk of mortality, morbidity, and prolonged need for mechanical ventilation, extending ICU and hospital lengths of stay and increasing healthcare costs [2, 5–10]. There are also costs associated with longer-term sequelae, which may include dementia, other cognitive or functional decline, and increased need for long-term care [11, 12]. Multiple pharmacological and non-pharmacological interventions have been used to prevent and manage delirium in the ICU setting. Randomised controlled trials of interventions have been combined in multiple systematic reviews, meta-analyses, and network meta-analyses. However, there is a lack of overarching mapping of evidence syntheses and assessment of comprehensiveness to support future research and practice. We aimed to scope and map out the meta-analysed evidence for interventions used for prevention and management of ICU delirium. This review (Part 1) specifically addresses pharmacological interventions. Part 2 addresses non-pharmacological and multicomponent interventions. Together, these reviews are anticipated to inform future critical care research and delivery of complex interventions in the ICU setting.

Methods

The full protocol for this meta-review was published [13] and registered previously with PROSPERO (CRD42023473260). The evidence for pharmacological and non-pharmacological studies was conceptualised as a single meta review. However, given the volume of the evidence identified, we chose to split the review into two parts: Part 1, pharmacological interventions (including sedation strategies) and Part 2, non-pharmacological interventions (including care bundles). We applied guidance from Cochrane overviews [14], the Preferred Reporting Items for Overviews of Reviews (PRIOR [15] and PRISMA Extension for Scoping Reviews (PRISMA-ScR [16] to support standardised evidence synthesis methods in the conduct and the reporting of the meta-review. We also sought input on aspects of the methodology from a Patient and Public Involvement group of people with lived experience of ICU delirium.

Literature search

Our search included any type of pharmacological or non-pharmacological intervention and comprised a combination of subject headings and text words to represent the concepts of delirium AND intensive care AND systematic reviews. The search was performed in MEDLINE (Ovid), Embase (Elsevier), Cochrane Database of Systematic Reviews, Scopus, Cumulative Index to Nursing and Allied Health Literature (CINAHL), PsycINFO and Web of Science (from inception to 26 September 2023), as well as in initial scoping search of Epistemonikos (from inception to 19 July 2023), with manual deduplication of records.

Although we pre-specified in our inclusion criteria that we would only include studies from the year 2000 onwards, most reviews we identified were published after this date, with only a minority of included trials published before 2000. Searches were unrestricted by language but limited to English at study selection. See Additional file 1 for full details.

Study selection and data extraction

Two of three reviewers (KLJ, BK, and AB) independently screened search results. Dual screening was completed

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Table 1 Meta-review eligibility criteria

Criteria	Types of review	Participants and setting	Interventions
Inclusion	o Systematic review* of RCTs or mixed study designs including RCTs where separate analyses reported	o Critically ill adults (aged ≥ 18 years). Mixed patient group or single subgroup (e.g. sepsis, mechanically ventilated) o Mixed or single critical care (HDU/ICU setting e.g. burn, cardiac, medical, surgical, trauma) o Mixed critical and non-critical settings only if ≥ 80% of included studies conducted in ICU	o Any drug or combination of drugs used to prevent, treat or manage ICU delirium o Any sedation strategy used to prevent, treat or manage ICU delirium (e.g. awakening trials, deprescribing or avoidance of benzodiazepines) o Any comparator
Exclusion	o Not in English o Protocol only o Overview of reviews (references checked only) o Review with no systematic search strategy/planned synthesis	o Alcohol withdrawal o POD if not ICU o Intermediate care units (e.g. coronary care units)	o Non-pharmacological intervention o Care bundle (excluding any sedation strategy, classified here as pharmacological intervention)

RCT: randomised controlled trial; ICU: Intensive care unit; HDU: High dependency unit; POD: post-operative delirium.*Systematic reviews included literature reviews with a systematic search strategy and planned synthesis reported

for a subset of at least 20% of records at title/abstract and full text. One reviewer (KLJ) confirmed the eligibility of included studies based on review-level reporting, with discussion among the review team and agreement of exclusion reasons. Standardised data extraction fields included demographics, review methods, and effect estimates (Additional file 2a). One reviewer (KLJ) extracted data, and a second member of the author team (BG) crosschecked a random 10% of included reviews for data entry as well as all mapped outcomes against the extracted results, with any queries resolved by discussion. The main consideration requiring consensus related to how interventions were classified.

Eligibility

The eligibility criteria for our mapping meta-review (embracing aspects of scoping, overview and mapping methodology) [17] are summarised in Table 1. We included sedation strategies as pharmacological interventions not multicomponent care bundles.

Table 2 Primary and secondary outcome measures for the prevention, treatment or management of ICU delirium

Type of intervention	Primary outcomes	Secondary outcomes
Prevention	Delirium occurrence (including incidence and prevalence)	• Time to delirium resolution/Duration of delirium • Delirium severity • Mortality • Cognition including memory • Emotional distress (including anxiety, depression, acute stress, or post-traumatic stress disorder) • Health-related quality of life • ICU length of stay* • Hospital length of stay* • Adverse events*
Treatment or Management	Time to delirium resolution/Duration of delirium/Delirium recurrence	As above except for primary outcomes

*Additional outcomes not in Del-COrS core-outcome set

Outcome measures

We used the Del-COrS core-outcome set [18] for research evaluating interventions to prevent or treat delirium in critically ill adults, as well as additional outcomes considered important by the research team and patient/carer partners. We assessed outcomes separately for interventions designed to i) prevent, and/or ii) manage delirium (see Table 2).

Classifying review interventions

Reviews were classified as prevention, treatment or management, or unclear. The criteria for classification are shown in the data extraction template (Additional file 2a). Classification was based on review-level reporting and included study descriptions; management reviews (including treatment) required delirium diagnosis in selection criteria, and prevention reviews did not report selection criteria for patients with ICU delirium.

Interpreting review comprehensiveness

Quantitative evidence was reported narratively. We applied guidance on the conduct and reporting of overviews [14], avoiding statistical comparison of effect estimates and subsequent conflation of comparisons from reviews with different eligibility criteria and different approaches to meta-analysis. We considered GRADE assessment [19] and the availability of network meta-analyses as key indicators of review comprehensiveness for outcome mapping of the meta-analysed evidence. Other considerations for review comprehensiveness during data extraction are described in the supplementary material (Additional file 2a).

Mapping the review evidence

A mapping strategy for core outcomes from reviews was developed post-protocol to capture the direction of effect for direct comparisons that had pooled, statistical analyses and GRADE assessment. For a large and heterogenous evidence base, this allowed an overview of the level of review agreement and certainty across core outcomes and pharmacological interventions, reducing dependency on consistent review reporting for included studies (i.e. addressing aspects of review methods rather than included study overlap and volume as an indicator of comprehensiveness). If a review reported results for both pairwise and network meta-analysis, this was recorded with the latter mapped. Cardiac surgical ICU results were mapped only in the absence of ICU results, and neurological ICU results would have been mapped similarly if there had been usable results. For transparency, the maps were supported by supplementary reporting of the effect estimates with 95% confidence or credible intervals. Adverse events were broadly charted by type.

Assessing the quality of the review evidence

Included study or outcome risk of bias and GRADE assessments were collected to inform interpretation and mapping. No further assessment was performed for the meta-review. Reasons for downgrading the mapped evidence certainty were reported narratively.

Results

Study selection

Our search results are summarised in a PRISMA flow diagram (Fig. 1). See also PRIOR [15] and PRISMA-ScR checklists [16] in the Supplementary Information: Additional file 8 and 9. Electronic database searches identified 3381 citations. After removing duplicates there were 1330 unique records. We initially excluded 1233 studies at title/abstract and assessed 97 abstracts/full texts that addressed pharmacological interventions; 3 of these were subsequently excluded because full texts could not be retrieved or there was insufficient information in the abstract. During data extraction, 41 further reports were excluded with reasons given in accordance with meta-review eligibility criteria (Additional file 2b). There were 56 included full texts. These reviews are summarised in Table 3 and individual review characteristics reported in Additional files 3a and b.

  All reviews were published after 2000 and most included RCTs only (71%). Six reviews included a small proportion (≤ 25%) of RCTs published before 2000 [20–25]. There was significant primary study overlap but discrepant reporting between reviews for the same studies (e.g. for ICU setting) precluded meaningful analysis.

Review populations

Thirty-four of 56 reviews included a broad population of critically ill adults. Seventeen reviews focused on mechanically ventilated patients only and five reviews specified other subpopulation criteria. All but one review [26], which included a single RCT of healthy adults in a simulated ICU environment, included studies conducted in ICU/HDU settings. Broadly, the review population consisted of middle-aged to older adults except for the review of a trauma population, who were slightly younger to middle-aged patients [10]. Typically, reviews reported a higher proportion of men than women among other demographics reported (Additional file 3a).

Delirium assessment

Across all included reviews, we identified the use of different delirium or delirium-related detection/diagnostic tools—most commonly the Confusion Assessment Method for the ICU (CAM-ICU) [6, 7, 10, 21–23, 26–55]. Other versions/tools included the Confusion Assessment Method (CAM) [33, 34, 48, 52], Intensive Care Delirium Screening Checklist (ICDSC) [6, 7, 22, 23, 27–29, 35, 37, 39, 44, 45, 50, 53, 55], Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria [26, 28, 35, 37, 40, 42, 45–47], 4-point scale for delirium [38], Delirium Detection Scores [22], Cognitive Test for Delirium [22], Neelon and Champagne Confusion Scale [22], and the Delirium Rating Scale [26, 46]. Over one third of reviews did not report a delirium assessment method.

Classifying review interventions

When we attempted to classify interventions as either prevention or treatment/management we found most reviews did not provide enough information or reported this inconsistently. One review investigated both separately [34]. We cautiously identified eight reviews that referred to intervention as prophylactic or preventative of delirium [26, 27, 34, 35, 44, 46, 53, 54], four reviews of treatment or management [20, 34, 39, 40] and the rest (n = 45; 80%) were interpreted as either/or, based on review-level reporting in accordance with our classification criteria (see Methods). It was unclear if 'prevention' was considered primary, secondary or tertiary. Across all included reviews, the comparator group varied between no intervention, placebo, usual care, and other intervention. Reviews also reported inconsistent usual care between trial arms, cross-over and pre-randomisation drug treatment as trial design limitations [24, 31, 37, 46, 56].

Reporting of meta-review primary outcomes

Review outcomes are described in Additional file 3b. Delirium occurrence (incidence and prevalence) was the most reported outcome although this was inconsistently
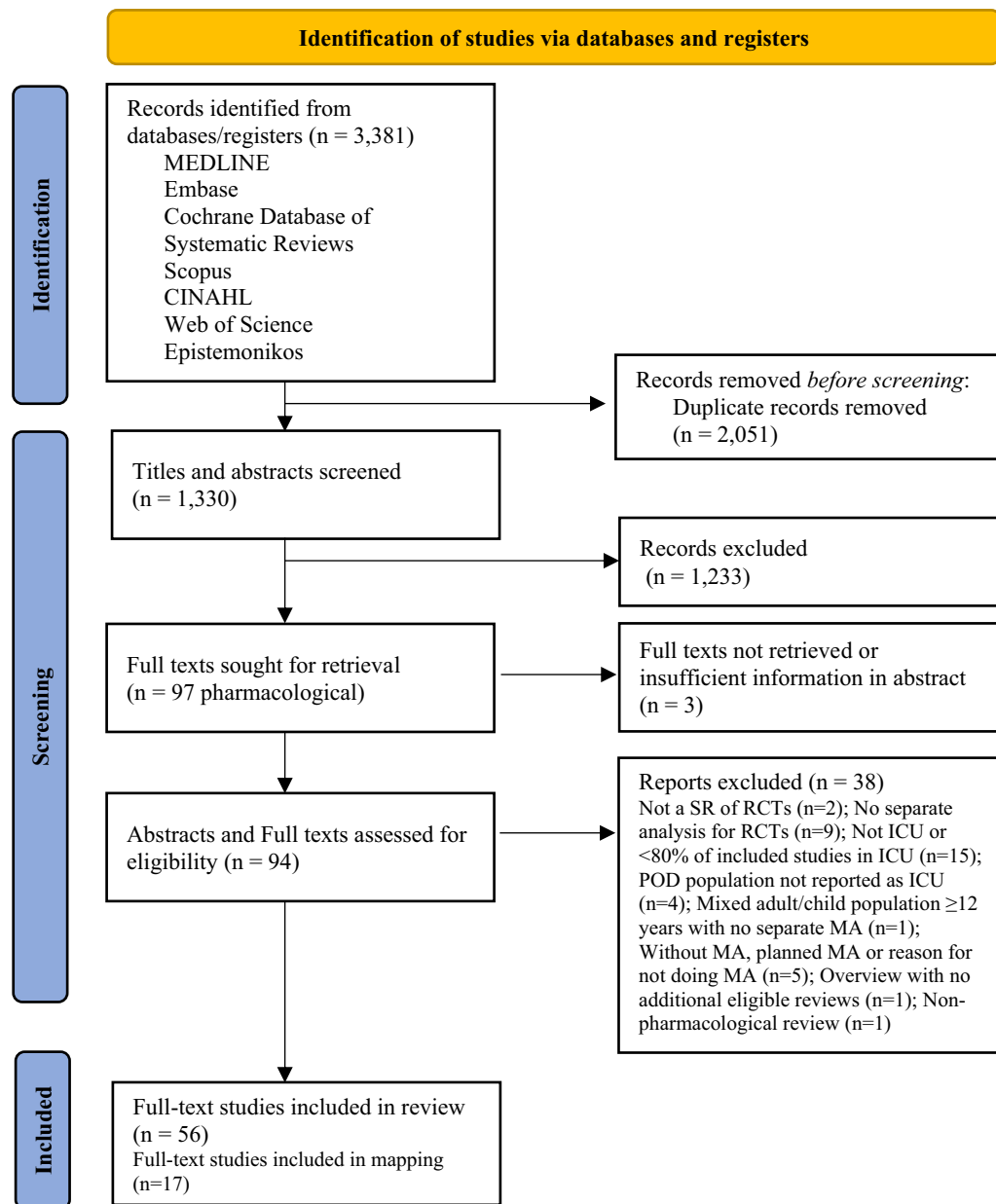
Fig. 1 PRISMA flow diagram

defined and incompletely reported for timing. Several reviews reported composite delirium outcomes, primarily of delirium-free and coma-free days [6, 7, 35, 41, 44, 47, 55].

Single and multiple interventions

Commonly investigated drug classes included α2-adrenoceptor agonists (e.g. dexmedetomidine), typical and atypical antipsychotics, and melatonergics. No included review investigated the effect of deprescribing a specific drug as the intervention. However, the avoidance of benzodiazepines was explored through comparison of non-benzodiazepines (dexmedetomidine or propofol)

with benzodiazepines (lorazepam or midazolam) [21]. Several reviews investigated different strategies to optimise sedation. For example, daily sedation interruption, protocolized sedation and comparisons of different depths of sedation [29, 35, 57].

ICU delirium outcome mapping

Thirteen reviews were included in mapping delirium outcomes (Table 4; effect estimates in Additional file 4) [6, 7, 20, 22, 23, 27, 35, 36, 45, 52, 57–59]. Evidence for reducing delirium occurrence was mostly favourable for the α2-adrenoceptor agonist class (primarily dexmedetomidine) as compared with placebo (moderate to

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Table 3 Summary of included reviews

Review characteristics	No. of reviews, *n* (%)
Total number of included reviews	56 (100)
Reviews of RCTs only	40 (71)
Reviews of RCTs and other study designs	16 (29)
Review populations	
Critical illness (with/without mechanical ventilation)	34 (61)
Mechanical ventilation	17 (30)
Other*	5 (9)
Methodological design	
Network meta-analysis	5 (9)
Pairwise meta-analysis	47 (84)
Planned meta-analysis but not done/Reason given for not doing meta-analysis	4 (7)
Included RCTs published since 2000	
100%	50 (89)
75–99%	6 (11)
<75%	0 (0)

RCT: randomised controlled trial; ICU: Intensive care unit; HDU: High dependency unit.*Post-surgery with/without mechanical ventilation (3) or trauma patients (1) (ICU/HDU), or mechanically ventilated patients in a review of hospitalised patients (1)

high-certainty evidence; 2 systematic reviews) [7, 23] or other intervention (low to high certainty; 4 systematic reviews) [7, 22, 36, 58]. However, the evidence was very uncertain in one comparison of dexmedetomidine versus mixed sedation types [52], and there may have been little or no difference between dexmedetomidine and mixed sedation types in another review [59]. All other pharmacological interventions had low- to high-certainty evidence of little or no difference in delirium occurrence compared with placebo or another intervention (3 systematic reviews) [7, 45, 57] or the evidence was very uncertain (one systematic review) [27]. Fewer reviews reported delirium duration and severity; these had moderate- to high-certainty evidence of little or no difference between interventions (one systematic review) [6] or the evidence was very uncertain (two systematic reviews) [36, 52]. No review compared (modified) intention-to-treat with available case or as-treated analyses.

ICU and hospital mortality outcome mapping

Six included reviews reported analyses with GRADE assessment for ICU and/or hospital mortality (Table 5; effect estimates in Additional file 5) [21, 29, 35, 45, 52, 57]. The results indicated little or no difference between any pharmacological intervention for ICU mortality (low- to high-certainty evidence; 4 systematic reviews) [29, 45, 52, 57]; for hospital mortality, there was moderate-certainty evidence of little or no difference between interventions (three systematic reviews) [21, 35, 57] or the evidence was very uncertain for dexmedetomidine

versus non-dexmedetomidine (one systematic review) [52].

ICU and hospital length of stay mapping

Fifteen reviews were included in mapping ICU or hospital length of stay (Table 6; effect estimates in Additional file 6) [6, 7, 21, 22, 27, 29, 30, 35, 36, 45, 52, 57–60]. Effect estimates from four systematic reviews were favourable for α2-adrenoceptor agonists (primarily dexmedetomidine) reducing ICU length of stay compared to placebo (moderate-certainty evidence; one systematic review) [7] or other intervention (low- to moderate-certainty evidence) [21, 22, 58] although the evidence was very uncertain in several systematic reviews, and there was high-certainty evidence of no difference in ICU length of stay in one comparison of dexmedetomidine versus other, mixed sedatives [59]. There was also low- to high-certainty evidence (six systematic reviews) [6, 7, 29, 35, 45, 57] of little or no difference for ICU length of stay between other pharmacological comparisons or the evidence was very uncertain (one systematic review) [27]. However, remifentanil may have reduced ICU length of stay compared to other opioids (low-certainty evidence) [60]. There was very uncertain evidence for reduced hospital length of stay in one comparison of dexmedetomidine versus non-dexmedetomidine intervention [52]. In one review, an α2-adrenoceptor agonist class probably reduced hospital length of stay compared to placebo (moderate certainty) [7] but there was probably little or no difference between dexmedetomidine and other sedatives in another review (moderate certainty) [22]. The results for other pharmacological comparisons suggested low- to moderate-certainty evidence of little or no difference in hospital length of stay or the evidence was very uncertain.

Quality of the mapped evidence for delirium outcomes

Where reported, the reasons for downgrading the certainty of evidence in reviews of dexmedetomidine included imprecision, inconsistency, risk of bias and publication bias [7, 36, 52]. Evidence for all other pharmacological interventions was downgraded for reasons including imprecision, inconsistency and indirectness [6, 7, 27, 35].

Network Meta-Analyses (NMA)

Delirium occurrence: Three NMAs reported delirium occurrence [7, 10, 25]. One NMA reported GRADE assessment [7]. This NMA considered direct and indirect evidence and found moderate-certainty evidence of the α2-adrenoceptor agonist drug class (primarily dexmedetomidine) probably reducing delirium occurrence compared to placebo and low-certainty evidence in favour of dexmedetomidine compared to benzodiazepines, while

Table 4 Effects of pharmacological interventions on delirium outcomes (pooled analyses of direct comparisons with GRADE assessment)

Review	Drug / Drug class / Sedation strategy	Comparator	Delirium occurrence	Delirium duration	Delirium severity
Alpha-2 adrenoceptor agonists / Dexmedetomidine					
Burry 2021	**'Alpha-2 adrenoceptor agonists'**	**Placebo**	⊕⊕⊕◯		
Burry 2021	**Dexmedetomidine**	**Benzodiazepine**	⊕⊕◯◯		
Ng 2019	Dexmedetomidine	Placebo	⊕⊕⊕⊕		
Heybati 2022*	Dexmedetomidine	Propofol	⊕⊕⊕⊕		
Heybati 2022*	Dexmedetomidine	Propofol		⊕◯◯◯	
Lewis 2021	Dexmedetomidine	Mixed (other sedation strategies)	⊕⊕⊕◯		
Lewis 2022	Dexmedetomidine	Mixed (other sedatives)	⊕⊕⊕◯		
Zhang 2022	Dexmedetomidine	Mixed (other sedation types)	⊕⊕◯◯		
Wang 2021	Dexmedetomidine	Mixed (non-dexmedetomidine)	⊕◯◯◯	⊕◯◯◯	
Antipsychotics					
Burry 2021	**All**	**Placebo**	⊕⊕◯◯		
Burry 2019	**Typical**	**Placebo**		⊕⊕⊕⊕	
Burry 2019	**Atypical**	**Placebo**		⊕⊕⊕◯	
Barbateskovic 2020	Haloperidol	Mixed (chlorpromazine, lorazepam, risperidone or ondansetron)			⊕◯◯◯
Melatonergics					
Mukundarajan 2023	Melatonin / Ramelteon	Placebo / Standard	⊕⊕⊕⊕		⊕⊕⊕⊕
Burry 2021	**Melatonin / MRA**	**Placebo**	⊕⊕◯◯		
Aiello 2023	Melatonin / Ramelteon	Placebo	⊕◯◯◯		
Other drugs					
Burry 2019	**Statin (HMG-CoA)**	**Placebo**		⊕⊕⊕◯	
Sedation strategies					
Herling 2018	Protocolized sedation	Daily sedation interruption	⊕◯◯◯		
Aitken 2021	Light sedation	Deep sedation	⊕⊕⊕◯		

Green: Benefit (in favour of index intervention)
Grey: Favours neither the index intervention or comparator
Bold: Effect estimate from NMA
Blank cell: Outcome not assessed

⊕⊕⊕⊕ High-certainty evidence (GRADE by review)
⊕⊕⊕◯ Moderate-certainty evidence (GRADE by review)
⊕⊕◯◯ Low-certainty evidence (GRADE by review)
⊕◯◯◯ Very low-certainty evidence (GRADE by review)

Abbreviations. MRA: Melatonin Receptor Agonist. NMA: Network-Meta-Analysis. ICU: Intensive care unit.*Cardiac surgical ICU

other comparisons were too uncertain to draw conclusions [7].

Duration of delirium: Two NMAs reported duration of delirium [5, 6]. One NMA reported GRADE assessment [6] and found the 95% credible interval was wide and included the possibility of little or no difference for all pharmacological interventions, including evidence from one study of dexmedetomidine, compared to placebo (low- to moderate-certainty evidence).

Delirium severity: There were no complete network maps reported for delirium severity.

Other core outcomes: quality of life, cognition and emotional distress

One review performed pairwise meta-analysis of health-related quality of life at six months or more post-discharge. The review population involved ICU survivors who had been critically ill and required invasive mechanical ventilation [29]. They received either daily sedation interruption or no daily sedation interruption. Results included the possibility of an effect in either direction; there was no GRADE assessment of the certainty of the evidence. No meta-analyses were found for endpoint

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Table 5 Effects of pharmacological interventions on ICU and hospital mortality (pooled analyses of direct comparisons with GRADE assessment)

Review	Drug / Drug class / Sedation strategy	Comparator	ICU mortality	Hospital mortality
Alpha-2 adrenoceptor agonists / Dexmedetomidine				
Wang 2021	Dexmedetomidine	Non-dexmedetomidine	⊕⊕◯◯	⊕◯◯◯
Antipsychotics				
Herling 2018*	Haloperidol	Placebo		⊕⊕⊕◯
Melatonergics				
Mukundarajan 2023	Melatonin / Ramelteon	Placebo / Standard	⊕⊕⊕⊕	
Sedation strategies				
Aitken 2021	Light sedation	Deep sedation	⊕⊕⊕◯	⊕⊕⊕◯
Burry 2014	Daily sedation interruption	No daily sedation interruption	⊕⊕⊕◯	
Other				
Fraser 2013#	Non-benzodiazepine (dexmedetomidine or propofol)	Benzodiazepine (lorazepam or midazolam)		⊕⊕⊕◯

Grey: Favours neither the index intervention or comparator
Blank cell: Outcome not assessed

⊕⊕⊕⊕ High-certainty evidence (GRADE by review)
⊕⊕⊕◯ Moderate-certainty evidence (GRADE by review)
⊕⊕◯◯ Low-certainty evidence (GRADE by review)
⊕◯◯◯ Very low-certainty evidence (GRADE by review)

* In-hospital mortality within 28 days; # In-hospital or up to 45 days after randomisation ('short-term mortality')

or change outcomes in cognition or emotional distress within ICU and/or post-discharge.

Adverse event mapping

Types of adverse events reported in reviews of pharmacological interventions are shown in Additional file 7. These were identified from across all included reviews in the meta-review (with/without meta-analysis). They were classified broadly as any type of adverse event, and subtypes as haemodynamic, cardiac, extrapyramidal or other. Heart rate and blood pressure were among those measures more commonly selected for statistical analysis. However, the evidence highlighted variation in the interpretation of continuous measures as adverse outcomes or not. A minority of included reviews recorded delirium within adverse outcome reporting (see Additional file 3b).

Discussion

We mapped outcomes in the Del-CorS core outcome set, as well as length of stay in the ICU or hospital for 17 of 56 included systematic reviews. The use of an α2-adrenoceptor agonist (primarily dexmedetomidine) had the largest evidence base and was mostly favourable over placebo and other pharmacological interventions for preventing or reducing delirium occurrence and ICU length of stay. There was no evidence to support any pharmacological intervention reducing ICU mortality.

The impact of loss to follow-up, including death, on delirium outcomes is unclear; no review compared intention-to-treat with available case or as-treated analyses for delirium occurrence. Unmapped reviews mostly pooled multiple timepoints (ICU and any) for mortality. Methodological limitations included incomplete reporting of individual agents as part of complex interventions, and their potential for effect modification, not reporting units of measurement for some outcomes (e.g. length of stay in days or hours), and variable approaches to meta-analysis and data transformation (e.g. median to mean number of days for length of stay). There was also variation in how some outcomes were conceptualised, for example delirium severity was measured using both duration (time measurement) and different numerical rating scales. No review reported outcomes for cognition, emotional distress, or change in quality-of-life although one review estimate included the possibility of little or no difference between sedation strategies for health-related quality of life among ICU survivors.

We applied an internationally agreed core outcome set to evaluate ICU delirium [18] but found variation in the meaning and interpretation of ICU delirium, such that it was also sometimes unclear whether the intervention was directed at prevention or management. We focused on meta-analysed evidence (primarily in ICU and hospital) although at least one narrative review with planned meta-analysis decided against pooling due to the

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Table 6 Effects of pharmacological interventions on ICU and hospital length of stay (pooled analyses of direct comparisons with GRADE assessment)

Review	Drug / Drug class / Sedation strategy	Comparator	ICU LOS	Hospital LOS
Alpha-2 adrenoceptor agonists / Dexmedetomidine				
Burry 2021	'Alpha-2 adrenoceptor agonists'	Placebo	⊕⊕⊕◯	⊕⊕⊕◯
Heybati 2022*	Dexmedetomidine	Propofol	⊕◯◯◯	
Chen 2015	Dexmedetomidine	Traditional (benzodiazepine or propofol or standard care (propofol and midazolam))	⊕◯◯◯	
Fraser 2013	Non-benzodiazepine (dexmedetomidine or propofol)	Benzodiazepine (lorazepam or midazolam)	⊕⊕⊕◯	
Lewis 2021	Dexmedetomidine	Mixed (other sedation strategies or placebo)	⊕⊕◯◯	
Lewis 2022	Dexmedetomidine	Mixed (other sedatives)	⊕⊕◯◯	⊕⊕⊕◯
Zhang 2022	Dexmedetomidine	Mixed (other sedatives)	⊕⊕⊕⊕	
Wang 2021	Dexmedetomidine	Mixed (non-dexmedetomidine)	⊕◯◯◯	⊕◯◯◯
Antipsychotics				
Burry 2021	All	Placebo	⊕⊕◯◯	⊕⊕◯◯
Burry 2019	Typical	Placebo	⊕⊕⊕◯	⊕⊕◯◯
Burry 2019	Atypical	Placebo	⊕⊕⊕⊕	⊕⊕⊕◯
Herling 2018	Haloperidol	Placebo	⊕⊕⊕⊕	
Melatonergics				
Mukundarajan 2023	Melatonin / Ramelteon	Placebo / Standard	⊕⊕⊕⊕	⊕⊕⊕◯
Burry 2021	Melatonin / MRA	Placebo	⊕⊕◯◯	⊕⊕⊕◯
Aiello 2023	Melatonin / Ramelteon	Placebo	⊕◯◯◯	
Opioids				
Yang 2021	Remifentanil	Other opioids	⊕⊕◯◯	⊕◯◯◯
Other drugs				
Burry 2019	Statin	Placebo		⊕⊕⊕◯
Sedation strategies				
Aitken 2021	Light sedation	Deep sedation	⊕⊕⊕◯	⊕◯◯◯
Burry 2014	Daily sedation interruption	No daily sedation interruption (usual care or other protocolized sedation strategies)	⊕⊕⊕◯[1]	⊕⊕⊕◯[1]

Green: Benefit (in favour of index intervention)
Grey: Favours neither the index intervention or comparator
Bold: Effect estimate from NMA

⊕⊕⊕⊕ High-certainty evidence (GRADE by review)
⊕⊕⊕◯ Moderate-certainty evidence (GRADE by review)
⊕⊕◯◯ Low-certainty evidence (GRADE by review)
⊕◯◯◯ Very low-certainty evidence (GRADE by review)

Abbreviations. LOS: length of stay; MRA: Melatonin Receptor Agonist; NMA: Network-Meta-Analysis; ICU: intensive care unit.
*Cardiac surgical ICU. [1]Note mismatch in a GRADE symbol used / missing reasons for downgrading

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heterogeneity of the population, interventions, comparators and outcomes [46]. We had to amend the protocol and proposed mapping strategy because reviews reported the study setting and some interventions differently; for example, study settings were not always reported as "ICU" and sedation strategies were reported as pharmacological interventions or multicomponent bundles. One excluded review [61] addressed non-pharmacological interventions and included two studies focused on protocolized sedation or awakening and breathing although neither intervention was meta-analysed. It was beyond the current meta-review to explore all potentially relevant subgroup and sensitivity analyses (e.g. for subgroup populations, individual agents or drug dose). However, among the mixed critically ill population, approximately 30% of included reviews focused on mechanically ventilated patients only.

An earlier overview of pharmacological interventions [2] found several hundred narrative reviews but only one systematic review and eight partially systematic reviews. Findings were broadly consistent with our meta-review although they found reviews classified only as prevention not management and did not map the certainty of the evidence across core outcomes. The overview did not report potential effects of interventions on outcomes including delirium severity, emotional distress, and ICU and hospital length of stay, and there was a lack of synthesised evidence found on quality-of-life and cognitive function.

One of the challenges for outcome reporting in this meta-review is that most primary studies of ICU delirium do not collect baseline data at ICU admission to evaluate change in ICU delirium and other core outcomes. In a clinically heterogenous population, this missing information could confound our understanding of causal relationships between interventions and outcomes.

Specific subgroups, such as patients with chronic pain or common psychiatric disorders, might benefit from pharmacological interventions that are not indicated for the general ICU population. However, our meta-review suggests that patients with psychiatric disorders are widely excluded from trials, so the benefits or harms of pharmacological intervention in this population are unknown. While some care bundles attempt to integrate the assessment, identification and management of pain, our meta-review has shown inconsistent use of rescue treatment, such as pain medication, that is not fully captured by the analysis of intervention effect. Our meta-review also highlights variation in how interventions are classified and that, despite greater confidence in the use of dexmedetomidine (and sparse evidence for other α2-adrenoceptor agonist drugs), the certainty of evidence is judged differently by different evidence syntheses (i.e. research teams) and across different core outcomes.

Our findings did not uncover possible variations in implementation or drug response by patient age, comorbidity and pharmacokinetics, such as potential hepatic impairment and interaction effects with other medications. Dexmedetomidine has been associated with an increased risk of mortality among ventilated critically ill patients under 65 years, possibly related to different infusion rates [62], although the mechanism remains uncertain. Dexmedetomidine causes limited respiratory depression and less impairment of consciousness compared to other sedatives (e.g. propofol). This could allow for better patient engagement in assessment of delirium (delirium cannot be diagnosed in coma/deep anaesthesia), and therefore some bias may exist if delirium alone is used as an outcome (i.e. not considering delirium and coma together).

Our meta-review highlighted the possibility of publication bias, emphasising the importance of independent research into interventions for ICU delirium. More research is needed that controls for the baseline population admitted to an ICU, addressing the underlying conditions indicating or precluding intervention, pharmacokinetics, and how these relate to core ICU outcomes that are important to patients. Baseline assessment at study randomisation may be feasible within a subset of patients who are risk-stratified (e.g. for age and comorbidities), and loss to follow-up investigated to support further analysis.

Conclusions

This meta-review has shown that the α2-adrenoceptor agonist drug class (primarily dexmedetomidine) had the largest evidence base of the pharmacological interventions and is probably favourable over placebo for preventing/reducing the occurrence of ICU delirium. However, the evidence base for this ranged from very uncertain to high certainty in favour of dexmedetomidine compared to other interventions. The evidence across ICU and hospital length of stay outcomes was variable for dexmedetomidine. There may have been little or no difference between dexmedetomidine and a non-dexmedetomidine comparator for ICU mortality and the evidence was too uncertain to draw conclusions on hospital mortality. We found the distinction between prevention and treatment/management was sometimes unclear in reviews and there was a lack of certainty or assessment of the certainty of the evidence to support the use of interventions other than dexmedetomidine (including sedation strategies) for either prevention or treatment/management of ICU delirium. We found no evidence for the effects of pharmacological interventions on either follow-up or change in cognition and emotional distress. As the evidence remains unclear on an optimal combination of interventions for preventing or managing ICU delirium, there is a

critical need for a well-designed RCT testing a multicomponent intervention that includes the most promising elements identified in this review, as well as those identified in the non-pharmacological review (Part 2 [63]). This type of rigorous evaluation would establish a stronger evidence base for clinical practice guidelines.

Abbreviations

CAM	Confusion Assessment Method
CAM-ICU	Confusion Assessment Method for the ICU
Del-COrS	Development of a Core Outcome Set for effectiveness trials of interventions to prevent and/or treat delirium
DSM	Diagnostic and Statistical Manual for mental disorders
GRADE	Grading of Recommendations, Assessment, Development, and Evaluations
HDU	High Dependency care Unit
ICDSC	Intensive Care Delirium Screening Checklist
ICU	Intensive Care Unit
LOS	Length Of Stay
MA	Meta-Analysis
MRA	Melatonin Receptor Agonist
NMA	Network Meta-Analysis
POD	Post-Operative Delirium
PRIOR	Preferred Reporting Items for Overviews of Reviews
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-ScR	Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews
RCT	Randomised Controlled Trial
SR	Systematic Review

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13054-025-05615-0.

> Additional file 1: Databases, search results and search strings.
>
> Additional file 2a: Data extraction template.
>
> Additional file 2b: Exclusion reasons and references.
>
> Additional file 3a: Included review characteristics - population.
>
> Additional file 3b: Included review characteristics - interventions, comparators and outcomes.
>
> Additional file 4: Pharmacological effect estimates for mapped ICU delirium outcomes.
>
> Additional file 5: Pharmacological effect estimates for mapped ICU and hospital mortality outcomes.
>
> Additional file 6: Pharmacological effect estimates for mapped ICU and hospital length of stay outcomes.
>
> Additional file 7: Types of adverse events reported in pharmacological reviews of ICU delirium.
>
> Additional file 8: PRISMA ScR Checklist.
>
> Additional file 9: PRIOR Checklist.

Data Availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

No ethical approval was required for the completion of this meta-review. Consent to participate was not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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References

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 5th ed. Arlington: American Psychiatric Association; 2013.
2. Barbateskovic M, Krauss SR, Collet MO, Larsen LK, Jakobsen JC, Perner A, et al. Pharmacological interventions for prevention and management of delirium in intensive care patients: a systematic overview of reviews and meta-analyses. BMJ Open. 2019;9(2):e024562.
3. Salluh JI, Soares M, Teles JM, Ceraso D, Raimondi N, Nava VS, et al. Delirium epidemiology in critical care (DECCA): an international study. Crit Care. 2010;14(6):R210.
4. Tilouche N, Hassen MF, Ali HBS, Jaoued O, Gharbi R, El Atrous SS. Delirium in the intensive care unit: incidence, risk factors, and impact on outcome. Indian J Crit Care Med. 2018;22(3):144–9.
5. Afzal MS, Atunde FJ, Yousaf RA, Ali S, Nasir N, Medarametla GD, et al. Pharmacologic management of intensive care unit delirium and the impact on the duration of delirium, length of intensive care unit stay and 30-day mortality: a network meta-analysis of randomized-control trials. Cureus. 2023;15(3): e35843.
6. Burry L, Hutton B, Williamson DR, Mehta S, Adhikari NK, Cheng W, et al. Pharmacological interventions for the treatment of delirium in critically ill adults. Cochrane Database Syst Rev. 2019;9(9):CD011749.
7. Burry LD, Cheng W, Williamson DR, Adhikari NK, Egerod I, Kanji S, et al. Pharmacological and non-pharmacological interventions to prevent delirium in

critically ill patients: a systematic review and network meta-analysis. Intensive Care Med. 2021;47(9):943–60.

8. Ely EW, Shintani A, Truman B, Speroff T, Gordon SM, Harrell FE Jr, et al. Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. JAMA. 2004;291(14):1753–62.

9. Klein Klouwenberg PM, Zaal IJ, Spitoni C, Ong DS, van der Kooi AW, Bonten MJ, et al. The attributable mortality of delirium in critically ill patients: prospective cohort study. BMJ. 2014;349: g6652.

10. Zitikyte G, Roy DC, Tran A, Fernando SM, Rosenberg E, Kanji S, et al. Pharmacologic interventions to prevent delirium in trauma patients: a systematic review and network meta-analysis of randomized controlled trials. Crit Care Explor. 2023;5(3):e0875.

11. Girard TD, Thompson JL, Pandharipande PP, Brummel NE, Jackson JC, Patel MB, et al. Clinical phenotypes of delirium during critical illness and severity of subsequent long-term cognitive impairment: a prospective cohort study. Lancet Respir Med. 2018;6(3):213–22.

12. Pandharipande P, Cotton BA, Shintani A, Thompson J, Costabile S, Truman Pun B, et al. Motoric subtypes of delirium in mechanically ventilated surgical and trauma intensive care unit patients. Intensive Care Med. 2007;33(10):1726–31.

13. Jones KL, Kundakci B, Booth A, Pufulete M, Gibbison B. Protocol for a metareview of interventions to prevent and manage ICU delirium. BMJ Open. 2025. https://doi.org/10.1136/bmjopen-2024-090815.

14. Pollock M, Fernandes RM, Becker LA, Pieper D, Hartling L. Chapter V: Overviews of Reviews. In: Higgins JPT, Chandler J, Cumpston M, Li T, Page MJ, et al., editors. Cochrane Handbook for Systematic Reviews of Interventions. version 6.5. ed: Cochrane; 2023.

15. Gates M, Gates A, Pieper D, Fernandes RM, Tricco AC, Moher D, et al. Reporting guideline for overviews of reviews of healthcare interventions: development of the PRIOR statement. BMJ. 2022;378: e070849.

16. Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA extension for scoping reviews (PRISMA-ScR): checklist and explanation. Ann Intern Med. 2018;169(7):467–73.

17. Campbell F, Tricco AC, Munn Z, Pollock D, Saran A, Sutton A, et al. Mapping reviews, scoping reviews, and evidence and gap maps (EGMs): the same but different- the "Big Picture" review family. Syst Rev. 2023. https://doi.org/10.1186/s13643-023-02178-5.

18. Rose L, Burry L, Agar M, Campbell NL, Clarke M, Lee J, et al. A core outcome set for research evaluating interventions to prevent and/or treat delirium in critically ill adults: an international consensus study (Del-COrS). Crit Care Med. 2021;49(9):1535–46.

19. Schünemann H, Brożek J, Guyatt G, Oxman A, editors. GRADE handbook for grading quality of evidence and strength of recommendations. The GRADE Working Group; 2013.

20. Barbateskovic M, Krauss SR, Collet MO, Andersen-Ranberg NC, Mathiesen O, Jakobsen JC, et al. Haloperidol for the treatment of delirium in critically ill patients: a systematic review with meta-analysis and trial sequential analysis. Acta Anaesthesiol Scand. 2020;64(2):254–66.

21. Fraser GL, Devlin JW, Worby CP, Alhazzani W, Barr J, Dasta JF, et al. Benzodiazepine Versus Nonbenzodiazepine-Based Sedation for Mechanically Ventilated, Critically Ill Adults: A Systematic Review and Meta-Analysis of Randomized Trials. Crit Care Med. 2013;41(9):S30–8.

22. Lewis K, Alshamsi F, Carayannopoulos KL, Granholm A, Piticaru J, Al Duhailib Z, et al. Dexmedetomidine vs other sedatives in critically ill mechanically ventilated adults: a systematic review and meta-analysis of randomized trials. Intensive Care Med. 2022;48(7):811–40.

23. Ng KT, Shubash CJ, Chong JS. The effect of dexmedetomidine on delirium and agitation in patients in intensive care: systematic review and meta-analysis with trial sequential analysis. Anaesthesia. 2019;74(3):380–92.

24. Tan JA, Ho KM. Use of dexmedetomidine as a sedative and analgesic agent in critically ill adult patients: a meta-analysis. Intensive Care Med. 2010;36(6):926–39.

25. Wang H, Wang C, Wang Y, Tong H, Feng Y, Li M, et al. Sedative drugs used for mechanically ventilated patients in intensive care units: a systematic review and network meta-analysis. Curr Med Res Opin. 2019;35(3):435–46.

26. Zhang Q, Gao F, Zhang S, Sun W, Li Z. Prophylactic use of exogenous melatonin and melatonin receptor agonists to improve sleep and delirium in the intensive care units: a systematic review and meta-analysis of randomized controlled trials. Sleep Breath. 2019;23(4):1059–70.

27. Aiello G, Cuocina M, La Via L, Messina S, Attaguile GA, Cantarella G, et al. Melatonin or ramelteon for delirium prevention in the intensive care unit: a

28. Al-Qadheeb NS, Balk EM, Fraser GL, Skrobik Y, Riker RR, Kress JP, et al. Randomized ICU trials do not demonstrate an association between interventions that reduce delirium duration and short-term mortality: a systematic review and meta-analysis. Crit Care Med. 2014;42(6):1442–54.

29. 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;7:CD009176.

30. Chen K, Lu Z, Xin YC, Cai Y, Chen Y, Pan SM. Alpha-2 agonists for long-term sedation during mechanical ventilation in critically ill patients. Cochrane Database Syst Rev. 2015;1(1): CD010269.

31. Constantin JM, Momon A, Mantz J, Payen JF, De Jonghe B, Perbet S, et al. Efficacy and safety of sedation with dexmedetomidine in critical care patients: a meta-analysis of randomized controlled trials. Anaesth Crit Care Pain Med. 2016;35(1):7–15.

32. Cuninghame S, Jerath A, Gorsky K, Sivajohan A, Francoeur C, Withington D, et al. Effect of inhaled anaesthetics on cognitive and psychiatric outcomes in critically ill adults: a systematic review and meta-analysis. Br J Anaesth. 2023;131(2):314–27.

33. Duan YS, Yang Y, Zhu WH, Wan LJ, Wang G, Yue JX, et al. Melatonin intervention to prevent delirium in the intensive care units: a systematic review and meta-analysis of randomized controlled trials. Front Endocrinol (Lausanne). 2023;14:1191830.

34. Flükiger J, Hollinger A, Speich B, Meier V, Tontsch J, Zehnder T, et al. Dexmedetomidine in prevention and treatment of postoperative and intensive care unit delirium: a systematic review and meta-analysis. Ann Intensive Care. 2018;8(1):92.

35. Herling SF, Greve IE, Vasilevskis EE, Egerod I, Bekker Mortensen C, Moller AM, et al. Interventions for preventing intensive care unit delirium in adults. Cochrane Database Syst Rev. 2018;11(11):CD009783.

36. Heybati K, Zhou FW, Ali S, Deng J, Mohananey D, Villablanca P, et al. Outcomes of dexmedetomidine versus propofol sedation in critically ill adults requiring mechanical ventilation: a systematic review and meta-analysis of randomised controlled trials. Br J Anaesth. 2022;129(4):515–26.

37. Huang J, Zheng H, Zhu X, Zhang K, Ping X. The efficacy and safety of haloperidol for the treatment of delirium in critically ill patients: a systematic review and meta-analysis of randomized controlled trials. Front Med. 2023;10:1200314.

38. Leigh V, Stern C, Elliott R, Tufanaru C. Effectiveness and harms of pharmacological interventions for the treatment of delirium in adults in intensive care units after cardiac surgery: a systematic review. JBI Database Syst Rev Implement Rep. 2019;17(10):2020–74.

39. Liu X, Xiong J, Tang Y, Gong CC, Wang DF. Role of dexmedetomidine in the treatment of delirium in critically ill patients: a systematic review and meta-analysis. Minerva Anestesiol. 2021;87(1):65–76.

40. Liu SB, Liu S, Gao K, Wu GZ, Zu G, Jie LJ. Olanzapine for the treatment of ICU delirium: a systematic review and meta-analysis. Ther Adv Psychopharmacol. 2023;13:20451253231152110.

41. Lonergan E, Luxenberg J, Areosa SA. Benzodiazepines for delirium. Cochrane Database Syst Rev. 2009;2009(4):CD006379.

42. Long L, Ren S, Gong Y, Zhao H, He C, Shen L, et al. Different depths of sedation versus risk of delirium in adult mechanically ventilated patients: a systematic review and meta-analysis. PLoS One. 2020;15(7):e0236014.

43. Luo W, Yang QH, Yu Q, Shi SQ. Effects of statins on short and long-term cognitive impairment in patients with critical illness: a systematic review and meta-analysis. Int J Clin Exp Med. 2019;12(5):4572–9.

44. Marra A, Vargas M, Buonanno P, Iacovazzo C, Kotfis K, Servillo G. Haloperidol for preventing delirium in ICU patients: a systematic review and meta-analysis. Eur Rev Med Pharmacol Sci. 2021;25(3):1582–91.

45. Mukundarajan R, Soni KD, Trikha A. Prophylactic melatonin for delirium in intensive care unit: an updated systematic review and meta-analysis of randomized controlled trials. Indian J Crit Care Med. 2023;27(9):675–85.

46. Nelson S, Muzyk AJ, Bucklin MH, Brudney S, Gagliardi JP. Defining the Role of Dexmedetomidine in the Prevention of Delirium in the Intensive Care Unit. Biomed Res Int. 2015;2015: 635737.

47. Pasin L, Landoni G, Nardelli P, Belletti A, Di Prima AL, Taddeo D, et al. Dexmedetomidine reduces the risk of delirium, agitation and confusion in critically ill patients: a meta-analysis of randomized controlled trials. J Cardiothorac Vasc Anesth. 2014;28(6):1459–66.

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48. Pereira JV, Sanjanwala RM, Mohammed MK, Le ML, Arora RC. Dexmedetomidine versus propofol sedation in reducing delirium among older adults in the ICU: a systematic review and meta-analysis. Eur J Anaesthesiol. 2020;37(2):121–31.

49. Porhomayon J, Joude P, Adlparvar G, El-Solh AA, Nader ND. The impact of high versus low sedation dosing strategy on cognitive dysfunction in survivors of intensive care units: a systematic review and meta-analysis. J Cardiovasc Thorac Res. 2015;7(2):43–8.

50. Serafim RB, Bozza FA, Soares M, do Brasil PE, Tura BR, Ely EW, et al. Pharmacologic prevention and treatment of delirium in intensive care patients: a systematic review. J Crit Care. 2015;30(4):799–807.

51. Tran A, Blinder H, Hutton B, English SW. A systematic review of alpha-2 agonists for sedation in mechanically ventilated neurocritical care patients. Neurocrit Care. 2018;28(1):12–25.

52. Wang S, Hong Y, Li S, Kuriyama A, Zhao Y, Hu J, et al. Effect of dexmedetomidine on delirium during sedation in adult patients in intensive care units: a systematic review and meta-analysis. J Clin Anesth. 2021;69:110157.

53. Yan W, Li C, Song X, Zhou W, Chen Z. Prophylactic melatonin for delirium in critically ill patients: a systematic review and meta-analysis with trial sequential analysis. Medicine (Baltimore). 2022;101(43): e31411.

54. Yiewong T, Corry M, Mooney M. Early sedation with dexmedetomidine in post-operative adult intensive care unit patients. Nurs Crit Care. 2023;28(5):718–26.

55. Zayed Y, Barbarawi M, Kheiri B, Banifadel M, Haykal T, Chahine A, et al. Haloperidol for the management of delirium in adult intensive care unit patients: a systematic review and meta-analysis of randomized controlled trials. J Crit Care. 2019;50:280–6.

56. Sedhai YR, Shrestha DB, Budhathoki P, Jha V, Mandal SK, Karki S, et al. Effect of thiamine supplementation in critically ill patients: a systematic review and meta-analysis. J Crit Care. 2021;65:104–15.

57. Aitken LM, Kydonaki K, Blackwood B, Trahair LG, Pursell E, Sekhon M, et al. Inconsistent relationship between depth of sedation and intensive care outcome: systematic review and meta-analysis. Thorax. 2021;76(11):1089–98.

58. Lewis K, Piticaru J, Chaudhuri D, Basmaji J, Fan E, Moller MH, et al. Safety and Efficacy of Dexmedetomidine in Acutely Ill Adults Requiring Noninvasive Ventilation: A Systematic Review and Meta-analysis of Randomized Trials. Chest. 2021;159(6):2274–88.

59. Zhang T, Mei Q, Dai S, Liu Y, Zhu H. Use of dexmedetomidine in patients with sepsis: a systematic review and meta-analysis of randomized-controlled trials. Ann Intensive Care. 2022;12(1):81.

60. Yang S, Zhao H, Wang H, Zhang H, An Y. Comparison between remifentanil and other opioids in adult critically ill patients: a systematic review and meta-analysis. Medicine (Baltimore). 2021;100(38): e27275.

61. Bannon L, McGaughey J, Verghis R, Clarke M, McAuley DF, Blackwood B. The effectiveness of non-pharmacological interventions in reducing the incidence and duration of delirium in critically ill patients: a systematic review and meta-analysis. Intensive Care Med. 2019;45(1):1–12.

62. Shehabi Y, Serpa Neto A, Bellomo R, Howe BD, Arabi YM, Bailey M, et al. Dexmedetomidine and propofol sedation in critically ill patients and dose-associated 90-day mortality: a secondary cohort analysis of a randomized controlled trial (SPICE III). Am J Respir Crit Care Med. 2023;207(7):876–86.

63. Kundakci B, Jones K, Booth A, et al. A systematic meta-review of interventions to prevent and manage delirium in the Intensive Care Unit: Part 2 – Non-pharmacological and multicomponent interventions. Crit Care 29 2025;501. https://doi.org/10.1186/s13054-025-05726-8.

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