SYSTEMATIC REVIEW

Pharmacological and non-pharmacological interventions to prevent delirium in critically ill patients: a systematic review and network meta-analysis

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Abstract

Purpose: To compare the effects of prevention interventions on delirium occurrence in critically ill adults.

Methods: MEDLINE, Embase, PsychINFO, CINAHL, Web of Science, Cochrane Library, Prospero, and WHO international clinical trial registry were searched from inception to April 8, 2021. Randomized controlled trials of pharmacological, sedation, non-pharmacological, and multi-component interventions enrolling adult critically ill patients were included. We performed conventional pairwise meta-analyses, NMA within Bayesian random effects modeling, and determined surface under the cumulative ranking curve values and mean rank. Reviewer pairs independently extracted data, assessed bias using Cochrane Risk of Bias tool and evidence certainty with GRADE. The primary outcome was delirium occurrence; secondary outcomes were durations of delirium and mechanical ventilation, length of stay, mortality, and adverse effects.

Results: Eighty trials met eligibility criteria: 67.5% pharmacological, 31.3% non-pharmacological and 1.2% mixed pharmacological and non-pharmacological interventions. For delirium occurrence, 11 pharmacological interventions (38 trials, \(N = 11,993\)) connected to the evidence network. Compared to placebo, only dexmedetomidine (21/22 alpha2 agonist trials were dexmedetomidine) probably reduces delirium occurrence (odds ratio (OR) 0.43, 95% Credible Interval (CrI) 0.21–0.85; moderate certainty). Compared to benzodiazepines, dexmedetomidine (OR 0.21, 95% CrI 0.08–0.51; low certainty), sedation interruption (OR 0.21, 95% CrI 0.06–0.69; very low certainty), opioid plus benzodiazepine (OR 0.27, 95% CrI 0.10–0.76; very low certainty), and protocolized sedation (OR 0.27, 95% CrI 0.09–0.80; very low certainty) may reduce delirium occurrence but the evidence is very uncertain. Dexmedetomidine probably reduces ICU length of stay compared to placebo (Ratio of Means (RoM) 0.78, CrI 0.64–0.95; low certainty) and compared to antipsychotics (RoM 0.76, CrI 0.61–0.98; low certainty). Sedative interruption, protocolized sedation and opioids may reduce hospital length of stay compared to placebo, but the evidence is very uncertain. No intervention influenced mechanical ventilation duration, mortality, or arrhythmia. Single and multi-component non-pharmacological interventions did not connect to any evidence networks to allow for ranking and comparisons as planned; pairwise comparisons did not detect differences compared to standard care.

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Conclusion: Compared to placebo and benzodiazepines, we found dexmedetomidine likely reduced the occurrence of delirium in critically ill adults. Compared to benzodiazepines, sedation-minimization strategies may also reduce delirium occurrence, but the evidence is uncertain.

Keywords: Delirium, Prevention, Pharmacological, Non-pharmacological interventions, Critical care

Introduction

Delirium, a highly prevalent syndrome in critically ill patients, is characterized by acute changes in mental status with inattention, disorganized thinking, and altered level of consciousness not explained by pre-existing conditions [1]. Although delirium is potentially preventable and reversible, it is associated with adverse patient consequences with excess mortality, cognitive impairment, functional decline, and increased healthcare system costs associated with prolonged mechanical ventilation and length of stay [2, 3]. The pathophysiology of delirium is not yet fully understood but is likely multifactorial, although sedatives, especially benzodiazepines, commonly administered for intensive care unit (ICU) sedation, are associated with delirium occurrence [2, 4, 5].

Effective interventions to treat established ICU delirium have not yet been identified [6]. Pharmacological interventions that target known alterations in neurotransmitter pathways, primarily dopaminergic and cholinergic pathways, have failed to demonstrate effect [2, 6]. Antipsychotics are commonly administered to mitigate agitated delirium, but have not yet shown to reduce delirium severity or resolve symptoms in ICU or hospitalized non-ICU patients [6, 7]. Non-pharmacological interventions (e.g., patient orientation, multi-component) shown to be effective in hospitalized non-ICU populations [8] have failed to demonstrate consistent treatment effect in the ICU [9]. In the absence of known effective treatments, it is imperative to identify effective prevention strategies. The current coronavirus disease 2019 (COVID-19) pandemic with the worldwide surge in critical illness has further highlighted the extent of delirium in the ICU and the importance of understanding the best approach to preventing ICU delirium [10, 11].

A wide-ranging list of prevention strategies evaluated to date include pharmacological, sedation, and non-pharmacological single or multi-component interventions that can be commenced during or immediately prior to (e.g., peri-operative) an ICU admission. Non-pharmacologic multi-component interventions have been studied extensively in hospitalized older non-ICU adults with evidence suggesting these are the most effective method to prevent delirium [12]. Previous systematic reviews investigating the effect of delirium prevention have either focused on direct evidence from head-to-head comparisons for a single intervention (versus placebo or alternative drug class) or have mixed critically ill patients with hospitalized non-ICU patient populations [2, 7, 13]. Given the numerous interventions to choose from, the abundance of trials, and the inconsistent findings reported, we believed a network meta-analysis (NMA) would provide clinicians with additional information to further support bedside decision-making. A NMA is a statistical approach that enables synthesis of both direct and indirect evidence in a multi-treatment comparison analytical framework, allowing assessment and ranking of relative efficacy and safety of multiple interventions that clinicians might consider at the bedside that may or may not have been directly compared in the published trials [14].

Our primary objective was to synthesize data from trials comparing any intervention for preventing delirium in critically ill adults using NMA. Our secondary objectives were to compare the effects of these interventions on the numbers of delirium-free and coma-free days, delirium duration, delirium severity, incidence of sub-syndromal delirium, duration of mechanical ventilation, length of stay, mortality, long-term outcomes (cognitive, discharge disposition, health-related quality of life), and adverse events.

Methods

We registered this review prospectively in PROSPERO (CRD42016036313) and published the protocol [15]. Institutional review board approval was not required as this study did not include individual patient data. Reporting of findings was guided by the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) Extension Statement for NMA (eTable 1) [16].
Eligibility criteria, search, and study selection
Using a search strategy developed in consultation with a Medical Information Specialist and peer reviewed by a second using the PRESS framework (search strategy previously published [6]), we searched the following databases from respective inception dates to April 8, 2021: Ovid MEDLINE ALL, Embase Classic + Embase, PsychINFO, CINAHL and Web of Science. We searched the grey literature using sources listed in the Canadian Agency for Drugs and Technologies in Health (CADTH) Grey Matters, the Cochrane Library and Prospero for relevant reviews, and the WHO international clinical trial registry for unpublished and ongoing trials.

We sought randomized and quasi-randomized controlled trials that examined any non-pharmacologic, pharmacologic, or multi-component for prevention of delirium in critically ill adults (≥16 years of age in an ICU of any type or high-acuity unit) as well as sedation strategy (e.g., protocolized sedation). We included studies that reported delirium incidence or prevalence and grouped them under the outcome delirium occurrence. We excluded trials using a crossover design, those focused on delirium treatment, and those with interventions applied in the pre- or intra-operative period only. We did not apply restrictions based on publication language, sex, or race. Two authors (LB, LR) independently screened citations against pre-set inclusion–exclusion criteria.

Outcomes
The selection of outcomes was informed by the core outcome sets for effectiveness trials of interventions to prevent and/or treat delirium [17, 18]. The primary outcome was delirium occurrence; secondary outcomes were numbers of delirium-free and coma-free days, delirium duration, delirium severity, incidence of sub-syndromal delirium, duration of mechanical ventilation, length of stay, mortality, long-term outcomes (cognitive, discharge disposition, health-related quality of life), and adverse events. For outcomes reported at multiple time intervals, such as mortality, we used the longest time point available [19].

Data extraction, risk of bias, and GRADE certainty assessment
Working in pairs, two authors independently abstracted data on study characteristics, interventions, outcomes, and risk of bias. Risk of bias was assessed as recommended by the Cochrane Collaboration (version 1), judging the overall risk of bias as the worst score of six domains (random sequence generation, allocation concealment, blinding, attrition, selective reporting, and other biases) [20]. A third author (LB) confirmed extraction, adjudicated inconsistencies, and another (WC) entered data into Review Manager (version 5.3, The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). We used the GRADE approach (Grading of Recommendations Assessment, Development and Evaluation, https//gradpro.org) to assess and report the certainty of each NMA estimate as either high, moderate, low, or very low certainty [21, 22]. The authors (WC, LB) assessed the certainty of each direct, indirect, and network meta-analysis estimate using the four-step GRADE approach (i.e., risk of bias, inconsistency, indirectness, and publication bias) with limitations in any of these domains resulting in a downgrade of the certainty. Imprecision was assessed for the NMA estimate. If differences were detected between direct and indirect evidence (i.e., incoherence), we selected the lower certainty of the assessments.

Statistical analysis
For continuous outcomes, we transformed means and standard deviations (SDs) to the log scale due to their skewed nature [23]; medians and interquartile ranges (IQRs) were converted to means and SDs using established methods [24]. We performed DerSimonian–Laird random effects pairwise meta-analyses for all continuous and binary outcomes [25]. We performed NMA for interventions that connected to an evidence network by data available from ≥2 studies. For outcomes without adequate network structure, we performed pairwise meta-analyses only. Using established procedures, we assessed validity of assumptions of homogeneity, similarity, and consistency, and performed NMAs using Bayesian fixed and random effect models with normal likelihood and the identify link, accounting for correlations in multi-arm studies [26], with comparisons reported as ratio of means (RoM) with 95% credible intervals (Crl). We addressed transitivity or exchangeability within the network, such that treatment effects in direct comparisons that informed indirect estimates of effect would not be biased by study characteristics. To do so, clinical experts and methodologists reviewed the extracted key clinical and methodological factors (i.e., age, severity of illness, mechanical ventilation, assessment tools for delirium and sedation, and control for analgesia, sedation, agitation, and non-pharmacological interventions) and determined that there was reasonable balance across studies to proceed. For binary outcomes, we fitted both fixed and random effects NMA models with binomial likelihood, with comparisons reported as odds ratios (OR) (95% Crl). If a trial reported multiple mortality outcomes, we prioritized selection of analyzed data as follows: 90-day, hospital, 28/30-day, and ICU mortality. We used a vague prior
distribution for the common between-study variance parameter in random effects NMAs [specifically, Uniform (0, 3)], and vague prior distribution for log RoM for each intervention compared with placebo [specifically, Normal (0, 100)].

Models were evaluated for adequacy of fit by comparing posterior total residual deviance to the number of unconstrained data points (i.e., total number of study arms); fit was considered adequate if these quantities were of similar magnitude. We compared models using the deviance information criterion (DIC), with lower values indicating better model fit [27]. We also fitted unrelated means models to the data and compared DIC values and posterior mean deviance contributions with those from consistency models to detect violations of the consistency assumption. We assessed model convergence with established methods including inspection of the Gelman–Rubin–Brooks diagnostics plots and the potential scale reduction factor (with threshold 1.01) [28].

For each outcome, we estimated secondary measures of effect, including surface under the cumulative ranking curve (SUCRA) values [29]. Methodological heterogeneity was assessed using similarity of point estimates, overlap of confidence intervals (CIs), and statistical tests (χ² test for homogeneity and I² measure for heterogeneity) [30]. All NMAs were performed using Open Bayesian inference Using Gibbs Sampling (BUGS) software version 3.2.3 and the R2WinBUGS package version 3.2–3.2 in R [31–33].

Results
The search strategy resulted in 80 trials that met inclusion criteria (Fig. 1), with a total of 17,140 participants [34–113]. Included trials were comprised of 54 (67.5%) pharmacological or sedation intervention studies [34–36, 38–40, 42–45, 47, 49–51, 55–57, 59–63, 67–69, 71, 73–76, 78, 79, 81, 82, 85–87, 89, 90, 92–94, 97–100, 102, 103, 105–108, 110, 112, 113] with 14,224 participants, 25 (31.3%) studies of non-pharmacological single or multi-component interventions with 2904 participants [37, 41, 46, 48, 52, 53, 57, 58, 64–66, 70, 72, 77, 80, 83, 84, 88, 91, 95, 96, 101, 104, 109, 111], and 1 study (1.2%) included a combination non-pharmacological with a pharmacological intervention with 12 participants [54]. Key features of all included trials are presented in detail in eTable 2. Trials were geographically dispersed but primarily conducted in North America (22.5%), Europe (25.0%) and Asia (26.3%). All trials were published between 2006 and 2021 and 43 (53.8%) were conducted in mixed ICUs. Trials allocated participants to two to four study arms and enrolled between 11 and 4000 ICU participants. The mean or median age at randomization ranged from 34.6 to 77.4 years, and 56 (70%) of trials reported a mean or median age of 60 or greater. Nearly all trials (78 trials, 97.5%) used a validated delirium assessment tools; 72 trials (90.0%) used either the Confusion Assessment Method for the ICU (CAM-ICU) or Intensive Care Delirium Screening Checklist (ICDSC). From the perspective of the primary outcome, 51% (41) trials had high risk of bias, primarily due to lack of blinding and risk of differential co-interventions (eTable 3).

Neither single nor multi-component non-pharmacological intervention trials connected to evidence networks for any outcomes of interest; pairwise comparisons are presented in eFigure 1. In the presentation of results below, we focus on the NMA estimates from random effects models for interventions (pharmacological and sedation strategies) that connected to the network; random effects models were superior to fixed effects. Model fit details including posterior mean deviance contributions plots, DIC, between-study SD and funnel plots are presented in eTable 4 and eFigures 2 and 3.

Delirium occurrence
Eleven pharmacological interventions studied in 38 trials [34–36, 38, 40, 43, 44, 49–51, 56, 59, 61, 67, 69, 71, 73, 74, 76, 79, 81, 82, 85, 86, 89, 90, 93, 94, 97–100, 103, 105–107, 112, 113] (N=11,993) connected to the evidence network (Table 1, Fig. 2A, eTable 5 summarizes node references); 24% (13/55) of the pairwise comparisons included direct evidence. Compared to placebo, only α₁ agonists (all trials but one examined dexmedetomidine) probably reduce delirium occurrence (OR 0.43, 95% CrI 0.21–0.85; moderate certainty) (Fig. 3A, Table 2, eFigure 1). Compared to benzodiazepines, dexmedetomidine (OR 0.21, 95% CrI 0.08–0.51; low certainty), sedation interruption (OR 0.21, 95% CrI 0.06–0.69; very low certainty), opioid plus benzodiazepine (OR 0.27, 95% CrI 0.10–0.76; very low certainty), and protocolized sedation (OR 0.27, 95% CrI 0.09–0.80; very low certainty) may reduce delirium occurrence, but the evidence is uncertain. The Bayesian NMA Summary of Findings with GRADE is presented in Table 3. Pairwise comparisons for environmental or multi-component interventions found no differences compared to standard care, with wide CIs (0.83, 95% CI 0.49–1.41 and 0.65, 95% CI 0.40–1.05, respectively) (eFigure 1).

Duration of mechanical ventilation
Ten interventions studied in 23 trials (N=5203) [36, 38, 40, 44, 50, 51, 55, 60, 61, 63, 67, 69, 71, 73, 74, 76, 93, 97, 102, 103, 107, 112, 113] connected the evidence network (Table 1, Fig. 2B, eTable 5); 29% (13/45) of the pairwise comparisons included direct evidence. No intervention reduced the duration of mechanical ventilation compared to placebo or each other (Fig. 3B, eTables 7, 8 and
9). Compared to benzodiazepines, duration of mechanical ventilation may be reduced by dexmedetomidine (OR 0.66, 95% CrI 0.44–0.98; low certainty). Pairwise comparisons for neither environmental nor multi-component interventions found differences compared to standard care (eFigure 1).

**Length of stay**

Nine interventions studied in 31 trials \( (N=10,270) \) [34–36, 38, 40, 44, 50, 51, 55, 56, 59, 63, 67, 69, 71, 73, 74, 76, 79, 81, 82, 85, 89, 93, 97, 98, 102, 103, 107, 113] connected to the evidence network for ICU length of stay (Table 1, Fig. 2C, eTable 5); 28% (10/36) of the pairwise comparisons included direct evidence. Compared to placebo, only \( \alpha_2 \) agonists (all trials but one examined dexmedetomidine) probably reduce ICU length of stay (RoM 0.78, 95% CrI 0.64–0.95; moderate certainty) (Fig. 3C; eTables 10, 11 and 12). \( \alpha_2 \) agonists may reduce ICU length of stay compared to antipsychotics (RoM 0.76, 95% CrI 0.61–0.98; low certainty). Pairwise comparisons for single or multi-component non-pharmacological interventions found no differences compared to standard care (eFigure 1).

For the outcome of hospital length of stay, 9 interventions studied in 22 trials \( (N=9471) \) [34, 35, 40, 43, 44, 51, 55, 59, 67, 69, 76, 81, 86, 89, 97–99, 102, 105–107, 113]
| Study, year [reference] | N | Intervention | Control | Delirium occurrence | Duration of mechanical ventilation | Length of stay—ICU | Length of stay—hospital | Mortality | Arrhythmia | Risk of bias* |
|-------------------------|---|--------------|---------|---------------------|-----------------------------------|---------------------|--------------------------|-----------|------------|-------------|
| Abbasi 2018 [34]        | 137 | Melatonin PO | Placebo PO | +                   | +                                 | +                   | +                       | +          | +          | Low         |
| Abdelgalel 2016 [35]    | 90  | Dexmedetomidine IV infusion with optional LD | Placebo IV intermittent | + | + | + | + | Low |
| Al-Qadheeb 2016 [36]    | 68  | Haloperidol IV intermittent | Placebo IV intermittent | + | + | + | Len |
| Azeem 2018 [38]         | 60  | Dexmedetomidine IV LD+ infusion | Morphine IV + midazolam IV | + | + | + | Low |
| vanden Boogaard 2018 [40] | 1789 | Haloperidol IV intermittent | Placebo IV intermittent | + | + | + | + | Low |
| Chang 2018 [43]         | 60  | Dexmedetomidine IV infusion | Propofol IV infusion | + | + | + | + | High |
| Chanques 2017 [44]      | 137 | IV sedation interruption | Usual sedation | + | + | + | + | High |
| Delonghe 2018 [49]      | 1174 | IV sedation protocol | Usual sedation | + | + | + | + | High |
| Devlin 2014 [50]        | 33  | Dexmedetomidine IV infusion | Placebo IV infusion | + | + | + | + | Low |
| Djafari 2016 [51]       | 183 | Dexmedetomidine IV LD+ infusion | Propofol IV infusion | + | + | + | + | Low |
| Gandolfi 2020 [55]      | 203 | Melatonin PO | Placebo PO | + | + | + | + | Low |
| Girard 2008 [56]        | 336 | IV sedation interruption | Usual sedation | + | + | + | + | High |
| Hakim 2012 [59]         | 101 | Risperidone PO | Placebo PO | + | + | + | + | Low |
| Hu 2015 [60]            | 76  | Intervention 1: dexmedetomidine IV infusion + propofol IV infusion | Sedation IV infusion without dexmedetomidine | + | + | + | + | High |
| Huang 2014 [61]         | 108 | Dexmedetomidine IV infusion | Propofol IV infusion | + | + | + | + | High |
| Hughes 2021 [62]        | 432 | Dexmedetomidine IV infusion | Propofol IV infusion | + | + | + | + | Low |
| Javaherforooh Zadeh 2021 [63] | 60 | Melatonin PO | Placebo PO | + | + | + | + | High |
| Kawazoe 2017 [67]       | 201 | Dexmedetomidine IV infusion | Sedation IV infusion without dexmedetomidine | + | + | + | + | High |
| Khan 2018 [69]          | 135 | Haloperidol IV intermittent dose | Placebo IV intermittent dose | + | + | + | + | Low |
| Li 2016 [71]            | 70  | 3 groups of dexmedetomidine, propofol or combination IV infusion to circadian clock | Sedation IV infusion without regulation to circadian clock | + | + | + | + | High |
| Study, year [reference] | N  | Intervention                                                                 | Control                                                                 | Delirium occurrence | Duration of mechanical ventilation | Length of stay—ICU | Length of stay—hospital | Mortality | Arrhythmia | Risk of bias* |
|-------------------------|----|-------------------------------------------------------------------------------|--------------------------------------------------------------------------|---------------------|-----------------------------------|-------------------|--------------------------|-----------|------------|--------------|
| Liu 2017 [73]           | 105| Intervention 1: remifentanil IV + midazolam IV infusions  
Intervention 2: fentanyl + midazolam IV infusions  
Placebo + midazolam IV infusion | +                                                                           | +                   | +                                 | +                 | +                        | Low       |            |              |
| Lyu 2015 [74]           | 140| Remifentanil + midazolam IV infusion                                          | Midazolam IV infusion                                                   | +                   | +                                 | +                 | +                        | High      |            |              |
| Mehta 2012 [76]         | 423| Protocolized sedation + daily interruption                                   | Protocolized sedation                                                   | +                   | +                                 | +                 | +                        | High      |            |              |
| Mokhtari 2020 [79]      |    | Aripiprazole PO                                                               | Placebo PO                                                              | +                   | +                                 | +                 | +                        | High      |            |              |
| Nassar 2014 [81]        |    | Daily IV sedation interruption                                                | Intermittent IV sedation                                                | +                   | +                                 | +                 | +                        | High      |            |              |
| Nishikimi 2018 [82]     | 88 | Ramelteon PO                                                                  | Placebo PO                                                              | +                   | +                                 | +                 | +                        | Low       |            |              |
| Pandharipande 2007 [85] | 103| Dexmedetomidine IV LD + infusion                                              | Lorazepam IV LD + infusion                                              | +                   | +                                 | +                 | +                        | Low       |            |              |
| Park 2014 [86]          | 142| Dexmedetomidine IV LD + infusion                                              | Remifentanil IV infusion                                                | +                   | +                                 | +                 | +                        | High      |            |              |
| Prakanrattana 2007 [89] | 126| Risperidone PO                                                                | Placebo PO                                                              | +                   | +                                 | +                 | +                        | Low       |            |              |
| Priye 2015 [90]         | 64 | Dexmedetomidine IV infusion                                                   | Placebo IV infusion                                                     | +                   | +                                 | +                 | +                        | Low       |            |              |
| Rubino 2010 [93]        | 30 | Clonidine IV LD + infusion                                                   | Placebo IV infusion                                                     | +                   | +                                 | +                 | +                        | Moderate  |            |              |
| Ruokonen 2009 [94]      | 85 | Dexmedetomidine IV infusion                                                   | Propofol or midazolam IV infusion                                       | +                   | +                                 | +                 | +                        | Low       |            |              |
| Shehabi 2009 [97]       | 299| Dexmedetomidine IV infusion                                                   | Morphine IV infusion                                                    | +                   | +                                 | +                 | +                        | +         |            | Low          |
| Shehabi 2013 [98]       | 37 | Early goal directed sedation  
Dexmedetomidine IV infusion                                                      | Propofol or midazolam IV infusion                                       | +                   | +                                 | +                 | +                        | High      |            |              |
| Shehabi 2019 [99]       | 4000| Dexmedetomidine IV infusion                                                   | Propofol or midazolam IV infusion                                       | +                   | +                                 | +                 | +                        | +         |            | High         |
| Shu 2019 [100]          | 80 | Dexmedetomidine IV LD + infusion                                              | Midazolam IV infusion                                                   | +                   | +                                 | +                 | +                        | High      |            |              |
| Skrobik 2018 [102]      | 100| Dexmedetomidine IV infusion                                                   | Placebo IV infusion                                                     | +                   | +                                 | +                 | +                        | Low       |            |              |
| Song 2015 [103]         | 90 | Dexmedetomidine IV infusion                                                   | Midazolam IV infusion                                                   | +                   | +                                 | +                 | +                        | High      |            |              |
connected the evidence network (Table 1, Fig. 2D, eTable 5); 28% (10/36) of the pairwise comparisons included direct evidence. Compared to placebo, alpha2 agonists (RoM 0.65, 95% CrI 0.52–0.83; moderate certainty) probably reduce hospital length of stay. Opioids (non-short acting RoM 0.47, 95% CrI 0.27–0.80; very low certainty, or short-acting opioids RoM 0.52, 95% CrI 0.32–0.83; very low certainty), sedation interruption (RoM 0.64, 95% CrI 0.41–0.99; very low certainty), protocolized sedation (RoM 0.68, 95% CrI 0.47–0.97; very low certainty) may do so as well (Fig. 3D; eTables 13, 14 and 15), but the evidence is very uncertain. Compared with antipsychotics, opioids (non-short acting opioids RoM 0.46, 95% CrI 0.26–0.81; very low certainty) or short-acting opioids RoM 0.51, 95% CrI 0.31–0.84; very low certainty), protocolized sedation (RoM 0.67, 95% CrI 0.45–0.99; very low certainty) and alpha2 agonists (RoM 0.64, 95% CrI 0.49–0.85; low certainty) may reduce hospital length of stay but the evidence is uncertain. Pairwise comparisons for single or multi-component non-pharmacological interventions found no differences compared to standard care for ICU or hospital length of stay, except for mobilization with occupational or physical therapists compared to standard care (eFigure 1).

Mortality
Nine interventions studied in 26 trials (N=11,385) [34–36, 40, 44, 49–51, 55, 56, 59, 62, 67, 69, 73, 74, 76, 81, 82, 85, 97–99, 102, 107, 113] connected to the evidence network for mortality (Table 1, Fig. 2E, eTable 5); 25% (9/36) of the pairwise comparisons were direct evidence. No intervention reduced mortality (Fig. 3E; eTables 16, 17 and 18) compared to placebo or compared to each other. There were no differences detected for single or multi-component non-pharmacological interventions compared to standard care (eFigure 1).

Other outcomes
For delirium duration, eight interventions were reported in 13 trials (N=2752) [34, 36, 40, 44, 56, 59, 69, 73, 74, 82, 85, 97, 102]. However, there were insufficient trials of comparable interventions to connect to an evidence network. Treatment effect estimates from pairwise meta-analyses indicated no intervention was effective for reducing delirium duration compared to placebo (eFigure 4); nor for non-pharmacological interventions compared to standard care (eFigure 1). There were insufficient trials of comparable interventions to conduct pairwise comparisons for delirium-free and coma-free days, delirium severity, incidence of sub-syndromal delirium, long-term outcomes of cognition, discharge disposition, and health-related quality of life.
Fig. 2  Network plots for delirium prevention strategies for outcomes. Network geometry displays nodes as interventions and head-to-head direct comparisons as lines connecting these nodes. The width of the edges each representing a pairwise comparison was weighted by the corresponding number of studies, while the size of treatment nodes was weighted by the number of patients.
Fig. 3 Forest plots with interventions ordered in descending order of SUCRA values for each network. All outcomes are reported as network odds or ratio of means with 95% credible intervals (Crl).
Table 2  Delirium occurrence league table of pairwise ORs with 95% CrI (lower triangle) and pairwise probabilities of superiority (upper triangle)

| Alpha2 Agonist | Sedation interruption | 0.478 | 0.765 | 0.635 | 0.818 | 0.721 | 0.970 | 0.926 | 0.970 | 0.999 | 0.991 |
|----------------|-----------------------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
| 1.02 (0.44 - 2.33) | Protocolized sedation | 0.810 | 0.627 | 0.755 | 0.706 | 0.934 | 0.938 | 0.962 | 0.994 | 0.947 |
| 0.80 (0.41 - 1.50) | Opioid + Antipsychotic | 0.502 | 0.612 | 0.599 | 0.891 | 0.876 | 0.929 | 0.990 | 0.906 |
| 0.80 (0.20 - 3.04) | Antipsychotic | 0.86 | 0.86 (0.18 - 4.42) | 0.95 (0.22 - 3.64) | 0.573 | 0.578 | 0.809 | 0.799 | 0.861 | 0.992 | 0.791 |
| 0.69 (0.29 - 1.59) | Melatonin / MRA | 1.00 | 0.69 | 0.60 | 0.58 (0.07 - 1.49) | 0.820 | 0.798 | 0.874 | 0.972 | 0.965 |
| 0.66 (0.14 - 2.68) | Opioid (short acting) | 0.86 | 0.86 | 0.86 | 0.86 (0.18 - 4.42) | 0.573 | 0.733 | 0.734 | 0.802 | 0.901 | 0.741 |
| 0.38 (0.13 - 1.05) | Opioid | 0.54 | 0.54 | 0.54 | 0.54 (0.10 - 3.62) | 0.542 | 0.636 | 0.794 | 0.411 |
| 0.34 (0.07 - 1.49) | Propofol | 0.47 | 0.47 | 0.47 | 0.47 (0.08 - 2.68) | 0.510 | 0.706 | 0.387 |
| 0.28 (0.07 - 1.06) | Benzodiazepine | 0.43 | 0.43 | 0.43 | 0.43 (0.06 - 3.25) | 0.52 | 0.91 | 0.52 | 0.283 |
| 0.21 (0.08 - 0.51) | Placebo | 0.35 | 0.35 | 0.35 | 0.35 (0.05 - 2.42) | 0.41 | 0.74 | 0.82 | 0.30 |
| 0.43 (0.21 - 0.85) | | 0.27 | 0.27 | 0.27 | 0.27 (0.10 - 0.76) | 0.31 | 0.57 | 0.62 | 0.105 |

**Abbreviations:** CrI = credible intervals; OR = odds ratio; RoM = ratio of means; SUCRA = Surface Under the Cumulative Ranking

A complete summary of estimates for efficacy from the random-effects consistency model assuming vague priors.

Treatments other than placebo are ranked in order (upper left–lower right) of decreasing SUCRA value. For pairwise probabilities of superiority for each comparison (i.e., a treatment is better than another), the lower/right-most treatment is the reference treatment. Thus, values < 1 favor the upper/left-most intervention. Differences where the 95% CrI excludes the null value of 1 are shown in bold font.

Adverse events identified included device removal [34, 36, 44, 47, 56, 76, 81, 86, 97, 106], reintubation [44, 56, 76, 81, 86, 97, 106], arrhythmias [35, 67, 89, 97, 99, 107, 113], tracheostomy [44, 56, 76, 81, 106], and extrapyramidal side effects [36, 40, 59, 113]. Except for arrhythmias, we identified insufficient data to conduct pairwise comparisons or form a network. For arrhythmias, four interventions reported in seven trials (N=5761) connected to the evidence network [35, 67, 89, 97, 99, 107, 113]. Compared to placebo, there was no difference in occurrence of arrhythmia with any intervention in trials reporting this outcome (Table 1, Fig. 3F; eTables 5, 19, 20 and 21); 100% direct evidence. There was no difference in NMA estimates for any other intervention comparison.

**Discussion**

In this systematic review and network meta-analysis of 11 pharmacological interventions from 38 trials enrolling 11,993 critically ill participants, we found that dexmedetomidine (studied in 21/22 alpha2 agonist trials) probably reduces the odds of delirium occurrence relative to placebo. The included trials used similar dexmedetomidine dose ranges, mostly without a loading dose that has been associated with bradycardia. Relative to benzodiazepine sedation, we found dexmedetomidine and strategies to reduce sedative exposure such as analgesia-first, protocolization and daily interruption, also may reduce delirium occurrence, but the evidence is uncertain. Dexmedetomidine was the only intervention identified that probably reduces length of ICU or hospital stay relative to placebo and may also do so relative to antipsychotics, but with less certainty. Opioids, sedation strategies, and dexmedetomidine may reduce hospital length of stay compared with antipsychotics commonly used in everyday ICU practice, but the evidence is very certain. No pharmacological intervention evaluated influenced mortality or arrhythmias. Non-pharmacological interventions did not connect to the evidence network; however, pairwise comparisons did not detect differences compared to standard care.

Clinicians need to consider multiple available therapeutic interventions as part of routine decision-making, without necessarily having evidence from direct comparisons or head-to-head trials. This NMA combines direct and indirect evidence for a multitude of available delirium prevention interventions and thus fills an important evidence gap, allowing for the assessment of clinically important treatment comparisons where direct
**Table 3 Bayesian NMA Summary of Findings—delirium occurrence.**

Patient or population: critically ill adults, includes both non-ventilated and mechanically ventilated patients.

Interventions: any interventions and strategies for sedation titration (e.g., protocolized and interruption).

Comparator (reference): placebo.

Outcome: delirium occurrence.

Setting(s): mixed intensive care unit settings.

| Total studies: 38 | Relative effect * (95% CrI) | Anticipated absolute effect (95% CrI) | Certainty of the evidence | Number of participants (trials) | Ranking*** (95% CrI) |
|-------------------|-----------------------------|--------------------------------------|---------------------------|-------------------------------|---------------------|
| Total partici-pants: 11,993 | Placebo Intervention Risk difference** | | | | |
| Alpha2 agonist vs placebo | NMA estimate | OR 0.43 (0.21–0.85) | 278 per 1000 (147/528 based on 5 trials) | 163 per 1000 (86/527 based on 5 trials) | 136 fewer per 1000 (from 204 to 30 fewer) | Moderate Due to inconsistency^2 | Direct evidence: 1055 (5 trials) | 2.73 (1–5) |
| Antipsychotics vs placebo | NMA estimate | OR 0.63 (0.36–1.04) | 309 per 1000 (375/1199 based on 8 trials) | 301 per 1000 (473/1577 based on 8 trials) | 91 fewer per 1000 (from 170 fewer to 9 more) | Low Due to imprecision^1, and inconsistency^2 | Direct evidence: 2776 (8 trials) | 4.80 (1–9) |
| Melatonin/MRA vs placebo | NMA estimate | OR 0.66 (0.19–2.50) | 186 per 1000 (21/113 based on 2 trials) | 125 per 1000 (14/112 based on 2 trials) | 55 fewer per 1000 (from 144 fewer to 178 more) | Low Due to imprecision^1 and inconsistency^2 | Direct evidence: 225 (2 trials) | 5.22 (1–11) |
| Sedation interruption vs placebo | NMA estimate | OR 0.42 (0.14–1.22) | 330 per 1000 | No head-to-head comparison with placebo | 157 fewer per 1000 (from 265 fewer to 46 more) | Very low Due to imprecision^1, indirectness^2, inconsistency^2 and risk of bias | No direct evidence. Indirect evidence only | 2.81 (1–7) |
| Protocolized sedation vs placebo | NMA estimate | OR 0.54 (0.21–1.40) | 330 per 1000 | No head-to-head comparison with placebo | 119 fewer per 1000 (from 238 fewer to 77 more) | Very low Due to imprecision^1, indirectness^2, inconsistency^2 and risk of bias | No direct evidence. Indirect evidence only | 4.27 (1–8) |
| Opioid + benzodiazepine vs placebo | NMA estimate | OR 0.54 (0.12–2.54) | 330 per 1000 | No head-to-head comparison with placebo | 119 fewer per 1000 (from 275 fewer to 225 more) | Very low Due to imprecision^1, Serious indirectness^2, inconsistency^2 and risk of bias | No direct evidence. Indirect evidence only | 4.36 (1–10) |
| Propofol vs placebo | NMA estimate | OR 1.15 (0.32–4.13) | 330 per 1000 | No head-to-head comparison with placebo | 31 more per 1000 (from 192 fewer to 341 more) | Very low Due to imprecision^1, and inconsistency^2 | No direct evidence. Indirect evidence only | 7.77 (2–11) |
| Opioid vs placebo | NMA estimate | OR 1.26 (0.24–6.56) | 330 per 1000 | No head-to-head comparison with placebo | 53 more per 1000 (from 222 fewer to 434 more) | Very low Due to imprecision^1, Serious indirectness^2, and inconsistency^2 | No direct evidence. Indirect evidence only | 7.91 (2–11) |
comparisons are lacking. Through the use of NMA and inclusive selection criteria for interventions of interest, this review determined that dexmedetomidine reduces delirium occurrence compared to placebo and probably compared to benzodiazepines. We note our findings regarding dexmedetomidine and the occurrence of delirium are echoed by other systematic reviews including acutely ill patients requiring non-invasive mechanical ventilation [114] and cardiac surgery patients [115]. Dexmedetomidine’s pharmacological properties of minimal impact on respiratory effort, modest sedative effects with some analgesic properties make it an attractive alternative to benzodiazepines. Since benzodiazepines can increase delirium prevalence, worsen sleep architecture by altering stage 1 and 2 sleep, and suppress respiratory drive, dexmedetomidine is an attractive alternative [5, 116, 117]. Based on these properties and evidence from this review, clinicians may wish to consider dexmedetomidine for delirium prophylaxis. Other sedation strategies that reduce sedative drug exposure, such as analgesia-first or no sedation, protocolized sedation,
and daily interruption, may also be considered to reduce delirium occurrence but the evidence remains uncertain.

The evidence networks in our review provide further evidence, although very uncertain, of the lack of effect of antipsychotics on important patient outcomes including delirium occurrence, delirium duration, duration of ventilation, ICU stay or mortality. Caution should be applied when interpreting and applying these results given the very low certainty of evidence due to risk of bias (e.g., lack of blinding), indirectness, imprecision, and heterogeneity. A recent review of antipsychotics for delirium prevention similarly identified lack of effect on incident delirium or hospital length of stay compared to placebo in a mix of ICU and non-ICU hospitalized settings [118].

**Strengths and limitations**

The main strength of this review is the inclusion of a broad range of interventions in a NMA. Compared to previous reviews, we did not apply any restrictions on language, sample size, types of interventions, types of delirium assessment tools, or types of ICU patient populations enrolled, with the intent of increasing the generalizability of findings. However, this decision introduces clinical heterogeneity, and appraising the transitivity assumption inherent to NMA, therefore, becomes more complex. Patient populations ranged from mechanically ventilated participants with high illness severity and high risk of delirium (for example, in trials of sedation-minimization strategies) to non-ventilated participants, with lower illness acuity and lower risk of delirium (for example, in trials of a single drug for delirium prevention). We extracted covariates that may influence delirium occurrence and response to treatment such as age, severity of illness, and exposure to treatments for pain, sedation, and agitation, but were unable to adjust for these. Thus, the lack of adjustment for effect modifiers has unknown implications on our results. Except for sedation strategies, which are studied only in mechanically ventilated patients, the other interventions could be applied to mixed ICU patients. Included trials rarely controlled for co-interventions such as analgesics, co-sedative, agitation, or non-pharmacological treatments. We used GRADE to downgrade the evidence for risk of bias related to lack of blinding and differential co-interventions wherever applicable.

We were unable to conduct comparisons and rankings of single or multi-component non-pharmacological interventions compared with pharmacological interventions due to the number of studies reporting diverse interventions and no trials that permitted connection to evidence networks. Thus, we were limited to direct pairwise comparisons only for non-pharmacological strategies. While we found no effect of these strategies, similar to another review [9], further investigation is warranted given their common use. Finally, outcomes recently recommended as part of a core set, such delirium severity, time to delirium resolution, health-related quality of life, and emotional distress were generally not reported [18].

**Conclusions**

Given no known effective interventions to treat delirium and the high incidence of delirium in the ICU, this review provides clinicians with evidence on pharmacological, sedation management, and non-pharmacological strategies to prevent ICU delirium. Important take-home messages are that compared to placebo or benzodiazepines, dexmedetomidine probably prevents delirium; a sedation-minimization strategy that targets reduced exposure to sedatives might prevent delirium; and antipsychotics may not prevent delirium.

**Supplementary Information**

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**Author contributions**

LB, BH and LR generated the research question and designed and lead the conduct of the review. WC, LB, and BH lead the statistical analysis. DW, NA, SK, IE, CM contributed to the protocol, extracted data, and interpretation of the results. All the authors approved of the final manuscript and had final responsibility for the decision to submit for publication. LB is the guarantor.

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Declarations

Conflicts of interest
All the authors declare no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work. BH has previously provided methodologic advice to Eversana Inc for the conduct of systemic reviews and meta-analysis on unrelated topics.

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