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Pharmacological and Non-pharmacological Interventions to Prevent Delirium in Critically Ill Patients: A Systematic Review and Network Meta-analysis

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Take home message: Compared to placebo and benzodiazepines, dexmedetomidine likely reduces the occurrence of delirium in a mixed critically ill adult population compared to placebo or benzodiazepines. Compared to benzodiazepines, sedation minimization strategies may also reduce delirium occurrence, but the evidence is uncertain.

ABSTRACT

Purpose: Our primary objective was to compare the effects of prevention interventions on occurrence of delirium 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 modelling, 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 quality 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: 80 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) reduced delirium occurrence (odds ratio (OR) 0.43, 95% Credible Interval (CrI) 0.21-0.85; moderate certainty). Compared to benzodiazepines, delirium occurrence was reduced by dexmedetomidine (OR 0.21, 95% CrI 0.08 to 0.51; low-certainty), sedation interruption (OR 0.21, 95% CrI 0.06 to 0.69; very low-certainty), opioid plus benzodiazepine (OR 0.27, 95% CrI 0.10 to 0.76; very low certainty), and protocolized sedation (OR 0.27, 95% CrI 0.09 to 0.80; very low certainty).

Dexmedetomidine reduced ICU length of stay compared to placebo (Ratio of Means (RoM) 0.78, CrI 0.64-0.95; moderate certainty) and compared to antipsychotics (RoM 0.76, CrI 0.61-0.98; low certainty). Hospital length of stay may be reduced by opioids, sedative interruption, protocolized sedation but with great uncertainty. 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.

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

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 in clinical practice to mitigate agitated delirium but have not yet been shown to reduce delirium severity or resolve symptoms in ICU or hospitalised 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 that may be reported at multiple different time intervals such as mortality we used the longest 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, imprecision, publication bias) with limitations in any of these domains resulting in a downgrade of the certainty. 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 Bayesian 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 (CrI). To address transitivity or the exchangeability within the network such that participants would be likely to receive either treatment in the created network, we reviewed the extracted key clinical and methodological factors (i.e., age, severity of illness, mechanical ventilation, assessment tools for delirium and sedation, control for analgesia, sedation, agitation, and non-pharmacological interventions) and determined 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% CrI). If a trial reported multiple mortality outcomes, we prioritized selection of analysed 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 (χ^2 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 (Figure 1), with a total of 17,140 participants [34-113]. Included trials 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 2,904 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 one 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 eTable 2 in detail. 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, 40% (32) trials had high risk of bias primarily due to blinding (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) that connected to the network (random effects models were superior to fixed effects). Model fit details including posterior mean deviance contribution plots, DIC, between-study SD and funnel plots are presented in eTable 4 and eFigure 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 the evidence network (Table 1, Figure 2-A); 24% (13/55) of the pairwise comparisons included direct evidence. Compared to placebo, only alpha₂ agonists (all trials but one examined dexmedetomidine) reduced delirium occurrence (OR 0.43, 95% CrI 0.21 to 0.85; moderate certainty) (Figure 3-A, Table 2). Compared to benzodiazepines, delirium occurrence was reduced by dexmedetomidine (OR 0.21, 95% CrI 0.08 to 0.51; low-certainty), sedation interruption (OR 0.21, 95% CrI 0.06 to 0.69; very low-certainty), opioid plus benzodiazepine (OR 0.27, 95% CrI 0.10 to 0.76; very low certainty), and protocolized sedation (OR 0.27, 95% CrI 0.09 to 0.80; very low certainty). The Bayesian NMA Summary of Findings with GRADE is presented in Table 3. Pairwise comparisons for environmental or multicomponent interventions found no differences compared to standard care (0.83 95% CI 0.49 to 1.41 and 0.65 95% CI 0.40 to 1.05, respectively) (eFigure 1).

Duration of mechanical ventilation

Ten interventions studied in 23 trials (N=5,203) [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, Figure 2-B); 29% (13/45) of the pairwise comparisons included direct evidence. No intervention reduced the duration of mechanical ventilation compared to placebo or each other (Figure 3-B, eTables 6, 7 & 8). Pairwise comparisons for neither environmental nor multicomponent 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 the evidence network for ICU length of stay (Table 1, Figure 2-C); 28% (10/36) of the pairwise comparisons included direct evidence. Compared to placebo, only alpha₂ agonists (all trials but one examined dexmedetomidine) reduced ICU length of stay (RoM 0.78, 95% CrI 0.64 to 0.95; moderate certainty) (Figure 3-C; eTable 9, 10, 11). Alpha₂ agonists reduced ICU length of stay compared to antipsychotics (RoM 0.76, 95% CrI 0.61 to 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 hospital length of stay nine interventions studied in 22 trials (N=9,471) [34, 35, 40, 43, 44, 51, 55, 59, 67, 69, 76, 81, 86, 89, 97-99, 102, 105-107, 113] connected the evidence network (Table 1, Figure 2-D); 28% (10/36) of the pairwise comparisons were direct evidence. Compared to placebo, opioids (non-short acting RoM 0.47, 95% CrI 0.27 to 0.80; very low-quality evidence or short-acting opioids RoM 0.52, 95% CrI 0.32 to 0.83; very low quality), sedation interruption (RoM 0.64, 95% CrI 0.41 to 0.99; very low quality), protocolized sedation (RoM 0.68, 95% CrI 0.47 to 0.97; very low quality) and alpha₂ agonists (RoM 0.65, 95% CrI 0.52 to 0.83; moderate quality) reduced hospital length of stay (Figure 3-D; eTable 12,

13, & 14). Compared with antipsychotics, opioids (non-short acting opioids RoM 0.46, 95% CrI 0.26 to 0.81; very low quality) or short acting opioids RoM 0.51, 95% CrI 0.31 to 0.84; very low quality), protocolized sedation (RoM 0.67, 95% CrI 0.45 to 0.99; very low quality) and alpha₂ agonists (RoM 0.64, 95% CrI 0.49 to 0.85; low quality) reduced hospital length of stay. 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 OT/PT 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 the evidence network for mortality (Table 1, Figure 2-E); 25% (9/36) of the pairwise comparisons were direct evidence. No intervention reduced mortality (Figure 3-E; eTable 15, 16 & 17) 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=2,752) [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 pair-wise 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.

Adverse events identified included device removal [34, 36, 44, 47, 56, 76, 81, 85, 95, 98, 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 pair-wise comparisons or form a network. For arrhythmias, four interventions reported in seven trials (N=5,761) connected 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, Figure 3-F; Supplement eTable 18, 19 & 20); 100% direct evidence. There was no difference in NMA estimates for any other intervention comparison.

DISCUSSION

Clinicians routinely need to consider multiple available therapeutic interventions at the bedside as part of routine decision-making, without necessarily having evidence from direct comparisons or head-to-head trials. This NMA by combining direct and indirect evidence for a multitude of available delirium prevention interventions that might be considered by clinicians at the bedside fills an important evidence gap, allowing for the estimation of clinically important treatment comparisons where we currently lack estimates of relative treatment effects. Using broad selection criteria for interventions of interest, this NMA included 11 pharmacological interventions from 38 trials enrolling 11,993 critically ill participants to examine delirium occurrence. Relative to placebo, we found that only dexmedetomidine (21 of the 22 of α_2 agonist trials investigated dexmedetomidine) likely reduced the occurrence of delirium in a mixed population of critically ill adults. The included trials used similar dexmedetomidine continuous infusion ranges, the majority without a loading dose which has been associated with cardiac effects.

We note our findings regarding dexmedetomidine and occurrence of delirium are echoed by other systematic review examining its use in other populations. Lewis and colleagues examining twelve RCTs

with 738 acutely ill patients requiring non-invasive mechanical ventilation found dexmedetomidine had RR delirium of 0.34 (95% CI, 0.22-0.54) compared with placebo or other sedation strategies [114]. Wang and colleagues examined specifically cardiac surgery patients (six studies, 630 participants) and found dexmedetomidine compared to control group of any treatment without dexmedetomidine had an OR of 0.32 (95% CI 0.18, 0.57) [115]. In a systematic review examining the effect of sedation with and without dexmedetomidine in critically ill patients (36 studies, 9623 participants) found dexmedetomidine was associated with a reduced risk of delirium (RR 0.62, 95% CI 0.54-0.74).

Compared to commonly used ICU sedative class benzodiazepines, dexmedetomidine is a mild sedative with analgesic properties and minimal impact on respiratory depression. Studies suggest benzodiazepines can increase delirium prevalence, worsen sleep architecture by altering stage 1 and 2 sleep and are known to suppress respiratory drive, making dexmedetomidine an attractive alternative [5, 116, 117]. We found compared to benzodiazepines, dexmedetomidine and sedation strategies that aim to reduce sedative drug exposure such as analgesia-first or no sedation, protocolization sedation and daily interruption, may also reduce delirium occurrence but the evidence is uncertain. Although a large effect was identified, caution should be applied when interpreting these results given the very low certainty of the evidence due to the risk of bias (e.g. lack of blinding) and indirectness of the evidence applied, the precision of the results, and heterogeneity.

We were unable to conduct comparisons and rankings of non-pharmacological single or multicomponent interventions with pharmacological interventions as planned due to the number of studies reporting diverse interventions that could not be pooled and no trials that permitted connection of evidence networks. Thus, we were limited to direct pairwise comparisons and found no effect. While we have added additional studies our results are similar to the 2019 systematic review by Bannon and colleagues

that examined direct comparisons of non-pharmacological interventions for prevention of ICU delirium, we believe further investigation with adequately powered studies is required given the direction of results for multi-component and environmental interventions [9].

This review found dexmedetomidine was the only intervention that likely reduced length of stay relative to placebo and may result in slight reduction relative to antipsychotics. Relative to placebo and to antipsychotics, evidence suggests uncertain reduction in hospital length of stay by opioids, protocolized sedation, and sedative interruption. Opioids, protocolized sedation, and dexmedetomidine may reduce hospital length of stay compared with antipsychotics which are commonly used in everyday ICU practice but the evidence is very uncertain. At this point there is insufficient data to suggest antipsychotics should play a role in delirium prevention.

A systematic review by Oh and colleagues examined the role of antipsychotics for delirium prevention in a mix of ICU and non-ICU hospitalized settings in nine trials with 3412 participants [118]. Likewise, this group identified lack of effect on incident delirium compared to placebo (0.94 [CI, 0.77 to 1.16]). The addition of indirect comparisons in our evidence networks further confirms the lack of effect of antipsychotics on delirium occurrence, delirium duration (pairwise comparison to placebo only), duration of ventilation, ICU stay, or mortality compared to all other interventions in our evidence network. These findings do not support the routine use of this class of drugs in the ICU. Our review also suggests antipsychotic administration may prolong hospital stay relative to other treatments but the evidence is very uncertain.

Limitations

The main strength of this review is the inclusion of any intervention clinicians might consider at the bedside to manage ICU patients whereby direct and indirect comparisons were integrated in a NMA whenever possible. 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. While we set our inclusion criteria sufficiently broad to increase generalizability for everyday application, we acknowledge this introduces additional heterogeneity and appraising the transitivity assumption becomes more complex. We note clinical heterogeneity of patient populations across trials range from those evaluating sedation-minimization strategies which enrol mechanically ventilated participants with generally high illness severity that have high risk of delirium compared to trials whose primary objective was to evaluate a single drug for delirium prevention that often had mixed ventilation status or lower acuity of illness or lower risk of delirium. 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 those given insufficient detail to maintain the network structure. Thus, the impact of adjusting for cross trial differences or effect modifiers have 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 and had broad enough inclusion/exclusion criteria. Nearly all trials identified in the review controlled only for the exposure of the intervention in the groups and rarely control for additional background interventions such as analgesics, co-sedative, agitation, or non-pharmacological treatments that may have appeared in the network. To address these, we downgraded the evidence wherever applicable.

CONCLUSIONS

Given there are no known effective interventions to treat delirium and the high prevalence of delirium experienced in the ICU, our systematic review provides clinicians with important guidance on pharmacological, sedation, and non-pharmacological strategies that a clinician might consider using to prevent ICU delirium. Important take home messages are that relative to placebo or benzodiazepines, dexmedetomidine probably prevents delirium; using a sedation-minimization strategy that targets reduced exposure to sedatives might also prevent delirium; and routine use of antipsychotics to prevent delirium in the ICU should be avoided due to lack of benefit. Use of dexmedetomidine and sedation-minimization strategies may also reduce ICU length of stay.

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Competing Interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three 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.

Contributors

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 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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Supplemental Materials yellow is for Wei

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eTable 1. PRISMA NMA Checklist of Items to Include When Reporting a Systematic Review Involving a Network Meta-analysis

Section/Topic	Item #	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review <i>incorporating a network meta-analysis (or related form of meta-analysis)</i> .	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: Background: main objectives Methods: data sources; study eligibility criteria, participants, and interventions; study appraisal; and <i>synthesis methods, such as network meta-analysis</i> . Results: number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; <i>treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity.</i> Discussion/Conclusions: limitations; conclusions and implications of findings. Other: primary source of funding; systematic review registration number with registry name.	3-4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known, <i>including mention of why a network meta-analysis has been conducted</i> .	5
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists and if and where it can be accessed (e.g., Web address); and, if available, provide registration information, including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. <i>Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification)</i> .	7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	previously published in Cochrane treatment NMA & referenced as such
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8

Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	8
Geometry of the network	S1	Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers.	8-9
Risk of bias within individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). <i>Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses.</i>	8-9
Planned methods of analysis	14	Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to: <ul style="list-style-type: none"> • <i>Handling of multi-arm trials;</i> • <i>Selection of variance structure;</i> • <i>Selection of prior distributions in Bayesian analyses; and</i> • <i>Assessment of model fit.</i> 	8-9
Assessment of Inconsistency	S2	Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found.	8-9
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8-9
Additional analyses	16	Describe methods of additional analyses if done, indicating which were pre-specified. This may include, but not be limited to, the following: <ul style="list-style-type: none"> • Sensitivity or subgroup analyses; • Meta-regression analyses; • <i>Alternative formulations of the treatment network; and</i> • <i>Use of alternative prior distributions for Bayesian analyses (if applicable).</i> 	
RESULTS†			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	10, figure
Presentation of network structure	S3	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	10, figure
Summary of network geometry	S4	Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure.	10, figure
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	10, table 1 and etable 2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	10, Table 1 and etable 3
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals. <i>Modified approaches may be needed</i>	10

to deal with information from larger networks.

Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. <i>In larger networks, authors may focus on comparisons versus a particular comparator (e.g. placebo or standard care), with full findings presented in an appendix. League tables and forest plots may be considered to summarize pairwise comparisons.</i> If additional summary measures were explored (such as treatment rankings), these should also be presented.	10-14, figures table 2 and 3 + supplement
Exploration for inconsistency	S5	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, <i>P</i> values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.	supplement
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.	Etable3
Results of additional analyses	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses, <i>alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses,</i> and so forth).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy-makers).	14-17, table 3 and etables
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). <i>Comment on the validity of the assumptions, such as transitivity and consistency. Comment on any concerns regarding network geometry (e.g., avoidance of certain comparisons).</i>	16-17
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	17
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network.	18

ABBREVIATIONS: PICOS = population, intervention, comparators, outcomes, study design.

* Text in italics indicate wording specific to reporting of network meta-analyses that has been added to guidance from the PRISMA statement.

eTable 2. Characteristics of Included Studies

Study, Year [reference] Country, No. of centres, Registration No.	Intervention Type	N	Population	Age, Years [mean ± SD or median (IQR)]	Severity of Illness Score [mean ± SD or median (IQR)]	Intervention	Control	Additional Treatments for Pain, Sedation, or Delirium	Delirium Assessment Tool Occurrence of Delirium
Abbasi 2018 [34] Iran Single centre IRCT2015022421159 N1	P	137	Mixed ICU	Intervention: 52 ± 18.4 Control: 49.9 ± 19.0	APACHE II Intervention: 8.1 ± 4.3 Control: 7.3 ± 4.6	Melatonin PO 3mg qHS x 5d	Placebo PO 3mg qHS x 5d	Haloperidol permitted (no difference between groups, total low < 5 mg)	CAM-ICU daily Intervention: 4% Control: 1%
Abdelgalel 2016 [35] Egypt Single centre No registration reported	P	90	ICU (type unspecified) 100% Non-invasive ventilation	Intervention 1: 51.1 ± 8.4 Intervention 2: 51.0 ± 8.8 Control: 49.1 ± 8.0	APACHE II Intervention 1: 17.0 ± 2.0 Intervention 2: 16.7 ± 1.9 Control: 16.8 ± 1.9	Intervention 1: dexmedetomidine IV 0.2-0.7 mcg/kg/h preceded if needed by loading dose 1.0 mcg/kg Intervention 2: haloperidol IV 0.5-2 mg/h preceded if needed by loading dose 2.5mg Titrated to clinical status	Placebo Saline IV infusion 2-8 mL/h preceded if needed by loading dose 10 mL	Fentanyl administered based on pain scores Supplementary midazolam or propofol based on agitated sedation scores	CAM-ICU q4h Intervention 1: 10% Intervention 2: 33% Control: 43%
Al-Qadheeb 2016 [36] United States Single centre NCT01174290	P	68	Mixed ICU 100% mechanical ventilation	Intervention: 61.7 ± 16.9 Control: 59.3 ± 14.9	APACHE II Intervention: 19 (17-23) Control: 20 (17-24)	Haloperidol IV 1mg IV q6h Until delirium, 10 days of treatment or ICU discharge	Placebo IV D5W q6h Until delirium, 10 days of treatment, or ICU discharge	Aim for targeted light sedation. Choice of analgesic and sedative left to treating team. Non-study antipsychotic use discouraged	ICDSC twice daily Intervention: 35% Control: 23%
Alvarez 2017 [37] Chile Single centre NCT01555996	NP	140	Mixed ICU	Intervention: 71 (63-78.5) Control: 68 (63-75.5)	APACHE II Intervention: 10 (9-12) Control: 11 (8-12)	Occupational therapy twice daily up to 5d (polysensory stimulation, positioning, cognitive stimulation, basic activities of daily living, stimulation of upper extremity motor function, and family participation) plus standard prevention strategies	Standard prevention strategies up to 5d (re-orientation, mobilization, correction of sensory deficits, management of environment, sleep protocol)	Avoidance of deliriogenic medications	CAM, DRS twice daily Intervention: 3% Control: 20%
Azeem 2018 [38]	P	60	Cardiac ICU	Intervention: 65.3 (60-68)	NR	Dexmedetomidine IV loading dose 1 mcg/kg and	Morphine IV 10-50 mcg/kg/h as an analgesic	Fentanyl and midazolam	CAM-ICU daily

Study, Year [reference] Country, No. of centres, Registration No.	Intervention Type	N	Population	Age, Years [mean ± SD or median (IQR)]	Severity of Illness Score [mean ± SD or median (IQR)]	Intervention	Control	Additional Treatments for Pain, Sedation, or Delirium	Delirium Assessment Tool Occurrence of Delirium
Egypt Single centre NCT03078946			100% mechanical ventilation	Control: 66.7 (60-71)		continuous infusion 0.2-0.7 mcg/kg/h Titration included interruption (q4h) and reduction aimed at light sedation before (RASS -2 to +1) and after extubation (RASS 0)	and midazolam 0.05 mg/kg up to 0.2 mg/kg, as needed Titration included interruption (q4h) and reduction aimed at light sedation before (RASS -2 to +1) and after extubation (RASS 0)	permitted. No differences between groups	Intervention: 3% Control: 6%
Azuma 2018 [39] Japan Single centre UMIN000016471	P	70	Mixed ICU ~50% mechanical ventilation	Intervention: 61.9 ± 19.6 Control: 61.6 ± 21.7	APACHE II Intervention: 10.6 ± 7.8 Control: 11.5 ± 7.2	Suvorexant PO 20 mg (age <65 years) or 15 mg (age ≥65 years) daily Up to 7d or until developed delirium	Trazadone PO 25 mg daily for insomnia Up to 7d or until developed delirium	All patients permitted trazodone for insomnia Benzodiazepines not permitted. Fentanyl for analgesia if intubated. All patients received ABCDE bundle	ICDSC daily Intervention: 14% Control: 33%
van den Boogaard 2018 [40] Netherlands Multi-centre NCT01785290	P	1789	Mixed ICU ~70% mechanical ventilation	Intervention 1: 66.1 ± 12.6 Intervention 2: 66.7 ± 12.7 Intervention 3: 67.0 ± 12.6	APACHE II Intervention 1: 20.1 ± 7.1 Intervention 2: 19.2 ± 6.9 Placebo 19.0 ± 6.8	Intervention 1: Haloperidol IV 1 mg q8h Intervention 2: Haloperidol IV 2 mg q8h Dose reductions for special populations	Placebo IV saline q8h Until day 28 or ICU discharge Dose reductions for special populations	>90% of all sites routinely used non-pharmacological delirium prevention strategies	CAM-ICU or ICDSC twice daily Intervention 1: 39% Intervention 2: 33% Control: 33%
Brummel 2014 [41] United States Single centre NCT01270269	NP	87	Mixed ICU ~80% mechanical ventilation	Intervention 1: 60 (51-69) Intervention 2: 62 (48-67) Control: 62 (54-69)	Intervention 1: 21.4 (20.0-28.8) Intervention 2: 25.0 (19.5-29.5) Control: 27 (17.5-31.0)	Intervention 1: Early physical therapy daily Intervention 2: Early physical (daily) + cognitive (orientation, memory, attention, problem-solving exercises, other activities) (twice daily)	Usual care (i.e., physical therapy once ordered by physician), 1-2 sessions per week	Sedation and weaning practices were standardized	CAM-ICU twice daily Not reported
Burkhardt 2014 [42] Switzerland Single centre	P	50	Mixed ICU Sepsis or shock	Intervention: 66 ± 13	APACHE II Intervention: 26 ± 9	Lipid emulsion (2 mL/kg/d) containing highly refined fish oil (equivalent to n-3	Standard sepsis treatment Administered for 7d	Not reported	ICDSC daily

Study, Year [reference] Country, No. of centres, Registration No.	Intervention Type	N	Population	Age, Years [mean ± SD or median (IQR)]	Severity of Illness Score [mean ± SD or median (IQR)]	Intervention	Control	Additional Treatments for Pain, Sedation, or Delirium	Delirium Assessment Tool Occurrence of Delirium
NCT00772096				Control: 72 ± 9	Control: 26 ± 11	fatty acids 0.12 mg/kg/d) plus standard sepsis treatment			Intervention: 75% Control: 71%
Chang 2018 [43] Taiwan Single centre NCT02393066	P	60	Surgical ICU	Intervention: 71 ± 12 Control: 70 ± 10	APACHE II Intervention: 13 ± 4 Control: 13 ± 3	Dexmedetomidine IV 0.1-0.7 mcg/kg/h no loading dose Administered for 24h, as required, to RASS -2 to 0	Propofol IV 0.3-1.6 mg/kg/h Administered for 24h, as required, to RASS -2 to 0	All patients received post-operative pain management titrated to pain scale	CAM-ICU daily Intervention: 0% Control: 0%
Chanques 2017 [44] France Multi-centre NCT01486121	P	137	Surgical ICU 100% mechanical ventilation	Intervention: 70 (59-76) Control: 67 (57-78)	SOFA Intervention: 8 (6-9) Control: 8 (6-10)	IV sedation interruption Until successful extubation	Usual (continuous IV) sedation Until successful extubation	Multimodal analgesia and sedation were similarly assessed in both groups	CAM-ICU daily Intervention: 43% Control: 72%
Chlan 2017 [45] United States Multi-centre NCT01606852	P	37	Mixed ICU 100% mechanical ventilation	Intervention: 53.4 ± 15.3 Control: 48.3 ± 14.9	APACHE III Intervention: 65.6 3 ± 32.0 Control: 55.2 ± 33.3	Dexmedetomidine IV by patient-controlled with a loading dose 0.5 mcg/kg then 0.2 - 0.7 mcg/kg/hour	Usual care decided by clinical team	Ventilation, weaning, and sedation standard order sets used in both groups	CAM-ICU daily Intervention: 0% Control: 5%
Damshens 2018 [46] Iran Single-center No registration reported	NP	80	Trauma ICU 100% mechanical ventilation	Intervention: 34.6 ± 17.67 Control: 33.95 ± 15.06	APACHE IV Intervention: 30.1 ± 14.1 Control: 35.7 ± 16.1	Music for 45 min twice daily	Usual care without music	Not standardized; could use haloperidol, midazolam, opioids and NSAIDs No differences between groups	CAM-ICU twice daily Intervention: 37% Control: 40%
De Jong 2018 [47] Netherlands Multi-centre NCT01362959	P	47	Mixed ICU 100% mechanical ventilation	Intervention: 60.1 ± 10.55 Control: 65. 2 ± 9.13	Intervention: 19.0 ± 5.0 Control: 21.1 ± 8.6	Nicotine replacement therapy (transdermal patch) Until ICU discharge or a maximum of 30 days	Placebo (similar non-transparent plaster) Until ICU discharge or a maximum of 30 days	Not reported	CAM-ICU three times daily Not reported

Study, Year [reference] Country, No. of centres, Registration No.	Intervention Type	N	Population	Age, Years [mean ± SD or median (IQR)]	Severity of Illness Score [mean ± SD or median (IQR)]	Intervention	Control	Additional Treatments for Pain, Sedation, or Delirium	Delirium Assessment Tool Occurrence of Delirium
Demoule 2017 [48] France Single-centre NCT02292134	NP	61	Mixed ICU ~20% mechanical ventilation	Intervention: 65 (58-74) Control: 64 (54-74)	SAPS II Intervention: 42 (26-60) Control: 45 (27-65)	Eye mask + ear plugs from 22:00-08:00 + routine night care until ICU discharge	Routine night care until ICU discharge not involving eye mask or ear plugs	Analgesia permitted and used by <50%. Patients had to be off sedation 24 h to enroll	CAM-ICU daily Intervention: 7% Control: 6%
De Jonghe ST Group 2018 [49] France Multi-centre NCT01617265	P	1174	Mixed ICU 100% mechanical ventilation	Intervention: 66 ± 13 Control: 67 ± 14	SOFA Intervention: 9 (7-12) Control: 9 (7-12)	Oversedation prevention protocol, identification of agitation, ventilator asynchrony, and pain, gradual on-demand responses, frequent reassessments, and promotion of alternatives to continuous hypnotics infusion	Sedation practice as per bedside practice	Dexmedetomidine not permitted in any group	CAM-ICU daily Intervention: 39% Control: 39%
Devlin 2014 [50] United States Single-centre NCAT00871624	P	33	Mixed ICU 100% non-invasive ventilation	Intervention: 68 ± 6 Control: 62 ± 17	APACHE II Intervention: 16 (9-22) Control: 15 (12-22)	Dexmedetomidine IV 0.2 mcg/kg/h titrated every 30 min to 0.7 mcg/kg/h to SAS 3 to 4 up to 72h Until non-invasive ventilation was stopped for >2h, or until intubation	Placebo IV Until non-invasive ventilation was stopped for >2h, or until intubation	As needed IV midazolam, fentanyl, and haloperidol was similar between the two groups	ICDSC twice daily Intervention: 37% Control: 76%
Djaiani 2016 [51] Canada Single-centre NCT01378741	P	183	Cardiac ICU 100% mechanical ventilation	Intervention: 72.7 ± 6.4 Control: 72.4 ± 6.2	NR	Dexmedetomidine IV 0.4 mcg/kg bolus followed by 0.2-0.7 mcg/kg/h, maximum of 24h	Propofol IV 25-50 mcg/kg/min	Patients requiring more than 24 hr of ventilation were switched to propofol. As needed haloperidol permitted (~25% all patients, 2x higher in the propofol group)	CAM-ICU twice daily Intervention: 17% Control: 31%
Eghbali-Babadi 2017 [52]	NP	68	Cardiac ICU	Intervention: 54.12 ± 13.11	Not reported	Family intervention (family member educated on signs of, and prevention methods	Usual care (no structure for family visits) until ICU discharge	Not reported	CAM-ICU twice daily

Study, Year [reference] Country, No. of centres, Registration No.	Intervention Type	N	Population	Age, Years [mean ± SD or median (IQR)]	Severity of Illness Score [mean ± SD or median (IQR)]	Intervention	Control	Additional Treatments for Pain, Sedation, or Delirium	Delirium Assessment Tool Occurrence of Delirium
Iran Single-centre IRCT201604107391N3				Control: 55.11 ± 12.11		for delirium, 30-40 min visits with patient) Until ICU discharge			Intervention: 11% Control: 23%
Finotto 2006 [53] Italy Single-centre	NP	48	Cardiac ICU	Not reported but all patients > 65 years to enroll	Not reported	Multicomponent delirium prevention strategies (re-orientation, correction of sensory deficits, management of environment, sleep protocol)	Standard of care Limited detail of the comparator arm	Used as needed	CAM-ICU three times daily Intervention: 17% Control: 19%
Foreman 2015 [54] United States Single-centre	M	12	Neuro ICU 60% mechanical ventilation	Intervention: 59 ± 15 Control: 56 ± 18	APACHE II Intervention: 13 ± 7 Control: 10 ± 6	Multicomponent sleep promotion (eye covers, noise cancelling headphones or ear plugs 22:00 to 06:00 plus melatonin PO 3 mg	Standard of care	Not reported	Not specified Intervention: 16% Control: 16%
Gandolfi 2020 [55] Brazil Multi-centre RBR-4d9cv7	P	203	Mixed ICU	Intervention: 60 ± 15 Control: 57 ± 15	APACHE III Intervention: 43 ± 13.4 Control: 41 ± 11.7	Melatonin 10 mg PO qHS up to 7d	Placebo PO qHS up to 7d	Use at discretion of clinical team. Details not reported	ICDSC daily Intervention: 2.3% Control: 1.7%
Girard 2008 [56] United States Multi-centre NCT00097630	P	336	Mixed ICU 100% mechanical ventilation	Intervention: 60 (48-71) Control: 64 (51-75)	APACHE II Intervention: 26 (21-33) Control: 26.5 (21-31)	Paired awakening and breathing trial - spontaneous awakening trial followed by spontaneous breathing trial daily	Usual care sedation and spontaneous breathing trials lead by bedside care providers	Not standardized. Used a mix of opioids, benzodiazepines, and propofol. Other treatments not described	CAM-ICU daily Intervention: 74% Control: 71%
Giraud 2016 [57] United Kingdom Single-centre NCT01599689	NP	223	Cardiac surgery ICU	Intervention: 77.4 ± 4.8 Control: 77.0 ± 4.9	EuroSCORE Intervention: 7 (3-16) Control: 7 (3-18)	Mirrors (use of mirrors to support mental status and attention, physical mobilization, and multisensory feedback and integration)	Usual post-operative care. If a patient brought a mirror it was permitted but not in the structured manor of the intervention (traditional use)	Not reported	CAM-ICU twice daily Intervention: 17% Control: 16%
Guo 2016 [58]	NP	160	Surgical ICU	Intervention:	Not reported	Multicomponent, non-pharmacologic	Usual post-operative ICU care. Team providing care	Not reported	CAM-ICU twice daily

Study, Year [reference] Country, No. of centres, Registration No.	Intervention Type	N	Population	Age, Years [mean ± SD or median (IQR)]	Severity of Illness Score [mean ± SD or median (IQR)]	Intervention	Control	Additional Treatments for Pain, Sedation, or Delirium	Delirium Assessment Tool Occurrence of Delirium
China Single-centre				73.3 ± 6.1 Control: 73.7 ± 5.2		interventions (pre-surgical education, re-orientation, music, correction of sensory deficits, management of environment, and sleep protocol)	to intervention group did not provide care to the usual care group		Intervention: 15% Control: 31%
Hakim 2012 [59] Egypt Single-centre	P	101	Cardiac surgery ICU 100% mechanical ventilation	Not specified All patients over 65 for inclusion	Not reported	Risperidone PO 0.5 mg q12h Continued for 24 h after subsidence of the sub-syndromal delirium or development of delirium	Placebo PO q12h Continued for 24 h after subsidence of the sub-syndromal delirium or development of delirium	Initially received propofol, morphine and NSAIDs	ICDSC three times a day Intervention: 13% Control: 34%
Hu 2015 [60] China Single-centre	P	76	Mixed ICU 100% mechanical ventilation	Intervention 1: 62.9 ± 20.5 Intervention 2: 57.7 ± 18.5 Control: 63.8 ± 16.4	APACHE II Intervention 1: 23.2 ± 3.9 Intervention 2: 21.6 ± 4.5 Control: 21.4 ± 5.4	Intervention 1: Dexmedetomidine IV plus propofol IV 5 mcg/kg/min Intervention 2: Propofol IV 5.0 mcg/kg/min, titration 2.5-10.0 mcg/kg/min	Midazolam IV 0.06 mg/kg/h, titration 0.01-0.05 mg/kg/h	NR	CAM-ICU q4h Reported no difference
Huang 2014 [61] China Single-centre	P	108	Surgical ICU 100% mechanical ventilation	Intervention: 73.7 ± 3.1 Control: 74.2 ± 4.2	APACHE II Intervention: 12.5 ± 2.3 Control: 12.7 ± 2.1	Dexmedetomidine IV 0.2-0.7 mcg/kg/h	Propofol IV 0.3-4.0 mg/kg/h	NR	CAM-ICU daily Reported no difference
Hughes 2021 [62] USA Multi-centre NCT01739933	P	432	Mixed ICU 100% sepsis with mechanical ventilation	Intervention: 59 (48-68) Control: 60 (50-68)	APACHE II Intervention: 27 (21-32) Control: 27 (22-32)	Dexmedetomidine IV weight-based titration 0.15-1.5 mcg/kg/h to RASS target	Propofol 5-50 mcg/kg/min titration to RASS target	All sites enforced the ABCDEF delirium bundle	CAM-ICU twice daily

Study, Year [reference] Country, No. of centres, Registration No.	Intervention Type	N	Population	Age, Years [mean ± SD or median (IQR)]	Severity of Illness Score [mean ± SD or median (IQR)]	Intervention	Control	Additional Treatments for Pain, Sedation, or Delirium	Delirium Assessment Tool Occurrence of Delirium
Javaherforooh 2021 [63] Iran Single-centre IRCT20180909040979 N3	P	60	Cardiac ICU	Intervention: 60.2 ± 9.5 Control: 62.9 ± 8.1	EuroSCORE Intervention: 2.6 ± 2.65 Control: 2.86 ± 2.8	Melatonin PO 3mg qHS	Placebo PO qHS	Anaesthesia with midazolam, sufentanil, ketamine and cisatracurium and isoflurane Once in ICU standard protocol for sedation, analgesia and mechanical ventilation for all patients	CAM-ICU daily Intervention: 10.0% Control: 46.6%
Johansson 2017 [64] Sweden Single-centre	NP	31	Mixed ICU ~50% mechanical ventilation	Intervention: 56.8 ± NR Control: 57.9 ± NR	SAPS III Intervention: 49.8 9 ± NR Control: 54.1 ± NR	Noise reduction, refurbished rooms with suspended wall-to-wall ceiling and low frequency sound absorber	Unaltered or standard rooms	Not standardized. No differences between groups for sedatives or opioids	CAM-ICU daily Intervention: 33% Control: 20%
Johnson 2018 [65] United States Single-centre	NP	40	Trauma ICU	Intervention: 70.20 ± 8.93 Control: 73.50 ± 9.45	NR	Music 60 min twice daily x 3 days	Usual care x 3 days	NR	CAM-ICU twice daily Intervention: 0% Control: 0%
Karadas 2016 [66] Turkey Single-centre	NP	94	Medical ICU Non-invasive ventilation	Intervention: 75 ± 7.5 Control: 72.6 ± 6.8	NR	Range of motion exercises (passive, assisted active, or active) 30 min/d until ICU discharge	Usual care until ICU discharge	Not reported No difference in antipsychotic use	CAM-ICU daily Intervention: 8% Control: 21%
Kawazoe 2017 [67] Japan Multi-centre NCT01760967	P	201	Mixed ICU 100% mechanical ventilation	Intervention: 68 ± 14.9 Control: 69 ± 13.6	APACHE II Intervention: 23 (18-29) Control: 22 (16-29.5)	Sedation with dexmedetomidine IV (dexmedetomidine and analgesia continuously, and other sedatives added as needed)	Sedation without dexmedetomidine (propofol, midazolam, and analgesia)	Sedation with fentanyl, propofol and midazolam permitted in either group. Frequency and dose of propofol and midazolam lower in	CAM-ICU daily Not reported

Study, Year [reference] Country, No. of centres, Registration No.	Intervention Type	N	Population	Age, Years [mean ± SD or median (IQR)]	Severity of Illness Score [mean ± SD or median (IQR)]	Intervention	Control	Additional Treatments for Pain, Sedation, or Delirium	Delirium Assessment Tool Occurrence of Delirium
								dexmedetomidine group	
Keh 2016 [68] Germany Multi-centre NCT00670254	P	380	Mixed ICU ~60% mechanical ventilation	Intervention: 65.5 ± 14.2 Control: 64.6 ± 14.6	APACHE II Intervention: 18.5 ± 6 Control: 19.5 ± 7	Hydrocortisone IV 50 mg, followed 200 mg infusion daily over x 5d, and 24h IV infusions 100 mg x 2d, 50 mg x 2d, and 25 mg	Placebo IV on same protocol as intervention group	Not reported	CAM-ICU daily Intervention: 11% Control: 28%
Khan 2018 [69] United States Single-centre NCT02213900	P	135	Surgical ICU 100% mechanical ventilation	Intervention: 60 (51.8 - 68) Control: 62.3 (52.6 - 69.2)	APACHE II Intervention: 16 (13-24) Control: 17 (11-24)	Haloperidol IV 0.5 mg three times daily x 11 doses	Placebo IV saline x 11 doses	Permitted use of opioids and propofol in mechanically ventilated participants and dexmedetomidine for non-mechanically ventilated participants. Open label antipsychotics discouraged	CAM-ICU twice daily Intervention: 22% Control: 28%
Khan 2020 [70] United States Single-centre	NP	52	Mixed ICU 100% mechanical ventilation	Not reported	Intervention 1: 20 (17-32) Intervention 2: 19.5 (14.0-24.5) Control: 19.5 (16-28)	Intervention 1: Personalized music 1h twice daily Intervention 2: Relaxing slow-tempo music not personalized 1 h twice daily Up to 7d	Audiobook 1h twice daily Up to 7d	Drug exposures not standardized. No differences between groups	CAM-ICU twice daily Not reported
Li 2016 [71] China Single-centre ChiCTR-IPR-15006644	P	70	Mixed ICU 100% mechanical ventilation	43.25 ± 12.51 49.93 ± 13.46 39.38 ± 15.94 45.13 ± 11.36 50.00 ± 13.99 Control: 47.69 ± 10.25	Intervention 1: 12.1 ± 3.3 Intervention 2: 17.5 ± 5.6 Intervention 3: 16.0 ± 5.3	Patients in each group sub-divided into dexmedetomidine (n=8), propofol (n=14), and dexmedetomidine with propofol (n=13)	Sedation targeted to RASS -1 to -2 during both day and night	NR	CAM-ICU daily Intervention: 37% Control: 14%

Study, Year [reference] Country, No. of centres, Registration No.	Intervention Type	N	Population	Age, Years [mean ± SD or median (IQR)]	Severity of Illness Score [mean ± SD or median (IQR)]	Intervention	Control	Additional Treatments for Pain, Sedation, or Delirium	Delirium Assessment Tool Occurrence of Delirium
					Control: 14.8 ± 3.6	Simulated circadian clock with targeted to RASS 0 to 1 during the day, and -1 to -2 at night			
Litton 2017 [72] Australia Single-centre ACTRN126150011255 16	NP	40	Mixed ICU 100% mechanical ventilation	Intervention: 70 (63-74) Control: 66 (57-74)	APACHE II Intervention: 16 (12-19) Control: 14 (11-16)	Ear plugs at time of ICU admission, once extubated, ear plugs between 22:00 and 06:00	Usual care	Not standardized No differences in fentanyl or propofol use No patients received antipsychotics	Not specified Not reported
Liu 2017 [73] China Single-centre NCT02078583	P	105	Surgical ICU 100% mechanical ventilation	Intervention 1: 66.11 ± 11.94 Intervention 2: 62.00 ± 9.96 64.49 ± 10.01	NR	<u>Intervention 1:</u> Remifentanyl IV 1 mcg/kg/h and midazolam IV 0.05 mg/kg followed by 0.02 ± 0.1 mg/kg/h <u>Intervention 2:</u> Fentanyl IV 1 mcg/kg/h and midazolam IV 0.05 mg/kg followed by 0.02 ± 0.1 mg/kg/h	Placebo IV 1 mcg/kg/h and midazolam IV 0.05 mg/kg followed by 0.02 ± 0.1 mg/kg/h	Pain assessed with CPOT or BPS Once delirium detected dexmedetomidine was used	CAM-ICU daily Intervention: 35% Control: 46%
Lyu 2015 [74] China Single-centre No registration	P	140	Surgical ICU 100% mechanical ventilation	Intervention: 64.5 ± 10.9 Control: 66.1 ± 11.9	NR	Midazolam (same as above) with remifentanyl at 1 mcg/kg/min	Midazolam loading dose 0.05 mg/kg and 0.02-0.10 mg/kg/h	NR	CAM-ICU daily Intervention: 22% Control: 57%
Mahrose 2021 [75] Egypt Single-centre No registration	P	110	Cardiac ICU 100% mechanical ventilation	Intervention: 67 ± 6.7 Control: 66.1 ± 6.3	NR	Dexmedetomidine IV loading dose then 0.2-0.7 mcg/kg/h infusion + Melatonin PO 5 mg qHS	Dexmedetomidine IV loading dose then 0.2-0.7 mcg/kg/h infusion + Placebo PO qHS	NR	CAM-ICU and CAM
Mehta 2012 [76] Canada Multi-centre NCT00675363	P	423	Mixed ICU 100% Mechanical ventilation	Intervention: 57 (46-70) Control: 60 (49-70)	APACHE II Intervention: 24 (23-34) Control: 23 (19-29)	Protocolized sedation opioids and benzodiazepines plus daily interruption	Protocolized sedation with opioids and benzodiazepines	Propofol and dexmedetomidine not permitted. Antipsychotics were permitted and balanced between groups	ICDSC daily Intervention: 53% Control: 54%

Study, Year [reference] Country, No. of centres, Registration No.	Intervention Type	N	Population	Age, Years [mean ± SD or median (IQR)]	Severity of Illness Score [mean ± SD or median (IQR)]	Intervention	Control	Additional Treatments for Pain, Sedation, or Delirium	Delirium Assessment Tool Occurrence of Delirium
Mitchell 2017 [77] Australia Single-centre	NP	61	Mixed ICU	Intervention: 51.0 ± 22 Control: 54.5 ± 22	APACHE II Intervention: 21 ± 8 Control: 18 ± 13	Family intervention, training/supervision in the provision of orientation (memory clues), therapeutic engagement (cognitive stimulation) and sensory checks (i.e. glasses and hearing aids) daily	No directed family engagement	NR	CAM-ICU daily Intervention: 50% Control: 56%
Mohammadi 2016 [78] Iran Single-centre IRCT201312203449N13	P	40	Mixed ICU	Intervention: 59.5 ± 17.9 Control: 59.9 ± 12.9	APACHE II Intervention: 14 ± 6.2 Control: 16 ± 6.1	Cyproheptadine PO 4 mg three times daily Up to 7d	Placebo PO up to 7d	Sedation protocol for all as analgo-sedation. Haloperidol was considered for patients who experienced delirium	CAM-ICU daily Intervention: 15% Control: 35%
Mokhtari 2020 [79] Iran Single-centre IRCT2017011810178N12	P	40	Neurosurgical ICU	Intervention: 44.5 ± 16.5 Control: 49.3 ± 14.5	APACHE II Intervention: 8.9 ± 2.3 Control: 8.2 ± 2.7	Aripiprazole 15 mg PO daily up to 7d	Placebo daily up to 7d	NR	CAM-ICU daily Intervention: 20% Control: 55%
Moon 2015 [80] Korea Single-centre	NP	123	Mixed ICU < 20% mechanical ventilation	Intervention: 70.4 ± 13.8 Control: 69.0 ± 12.4	APACHE II Intervention: 13.0 ± 5.8 Control: 14.9 ± 6.2	Delirium prevention protocol consisting screening for delirium risk factors, subsequent cognitive assessment and orientation, management of the environment, and therapeutic intervention x 7d	Standard care	Stated control pain, carefully use sleeping pills, anticholinergic and opiates	CAM-ICU daily Intervention: 20% Control: 33%
Nassar 2014 [81] Brazil Single-centre NCT00824239	P	60	Mixed ICU mechanical ventilation	Intervention: 47 ± 33.58 Control: 51 ± 46.59	APACHE II Intervention: 22 (18,28) Control: 18 (15.5,25)	Daily sedation interruption	Intermittent sedation	Fentanyl plus midazolam or propofol at choice of bedside team. Haloperidol was permitted	CAM-ICU twice daily Intervention: 30% Control: 40%
Nishikimi 2018 [82] Japan	P	88	Mixed ICU	Intervention: 68 (57-75)	APACHE II	Ramelteon PO 8 mg daily Until ICU discharge	Placebo PO daily Until ICU discharge	NR	CAM-ICU q4h

Study, Year [reference] Country, No. of centres, Registration No.	Intervention Type	N	Population	Age, Years [mean ± SD or median (IQR)]	Severity of Illness Score [mean ± SD or median (IQR)]	Intervention	Control	Additional Treatments for Pain, Sedation, or Delirium	Delirium Assessment Tool Occurrence of Delirium
Single-centre UMIN000016541				Control: 68 (52-78)	Intervention: 23.9 ± 7.3 Control: 23.9 ± 8.6				Intervention: 24% Control: 46%
Nydahl 2019 [83] Germany Multi-centre	NP	172	Mixed ICU	Intervention: 70 (58-79.7) Control: 74 (61-81)	SOFA Intervention: 7.5 (7-10) Control: 7 (8-9)	Interprofessional protocol for early mobilization	Standard care	NR	CAM-ICU or ICDS daily Intervention: 14.2% Control: 20.2%
Ono 2011 [84] Japan Single-centre	NP	22	Surgical ICU 100% mechanical ventilation	Intervention: 63.4 ± 9.7 Control: 63.8 ± 7.8	APACHE II Intervention: 7.6 ± 2.5 Control: 8.8 ± 2.2	Bright light therapy for 2 hours (07:30 to 09:30) on post-operative day 2-5	Normal lighting	NR	NEECHAM twice daily Intervention: 10% Control: 41%
Pandharipande 2007 [85] United States Multi-centre NCT00095251	P	103	Mixed ICU 100% mechanical ventilation	Intervention: 60 (49-65) Control: 59 (45-67)	APACHE II Intervention: 29 (24-32) Control: 27 (24-32)	Dexmedetomidine IV 0.15 mcg/kg/h, titrated to maximum 1.5 mcg/kg/h	Lorazepam IV 1 mg/h, titrated to maximum 10 mg/h	Antipsychotics permitted and balanced between groups. Fentanyl permitted in both groups with 3 times higher dose exposure in dexmedetomidine group	CAM-ICU twice daily Intervention: 79% Control: 82%
Park 2014 [86] Korea Single-centre	P	142	Cardiac ICU 100% mechanical ventilation	Intervention: 51.09 ± 16.10 Control: 54.35 ± 13.97	NR	Dexmedetomidine IV 0.5 mcg/kg then 0.2-0.8 mcg/kg/h	Remifentanyl IV 1,000-2,500 mcg/hr infusion rate of drugs was maintained by titration as per the specified protocol to maintain target sedation and adequate analgesia	If patient developed delirium haloperidol 5 mg q6h was used as needed.	CAM-ICU daily Intervention: 9% Control: 22%
Perbet 2018 [87] France Multi-centre NCT01560390	P	162	Mixed ICU 100% mechanical ventilation	Intervention: 63 ± 15 Control: 61 ± 14	SOFA Intervention: 9 ± 4 Control: 9 ± 4	Ketamine IV 3.3 mcg/kg/min infusion	Placebo IV 0.4 ml/kg/h NaCL infusion	Remifentanyl and midazolam or propofol titrated based on RASS needs.	CAM-ICU daily Intervention: 21% Control: 37%

Study, Year [reference] Country, No. of centres, Registration No.	Intervention Type	N	Population	Age, Years [mean ± SD or median (IQR)]	Severity of Illness Score [mean ± SD or median (IQR)]	Intervention	Control	Additional Treatments for Pain, Sedation, or Delirium	Delirium Assessment Tool Occurrence of Delirium
Potharajoen 2018 [88] Thailand Single-centre TCTR20170330001	NP	62	Surgical ICU 100% mechanical ventilation	Intervention: 68.1 ± 9.5 Control: 68.3 ± 13.1	APACHE II Intervention: 9.3 ± 3.7 Control: 11.5 ± 6.6	Bright light therapy for 2 hours (09:00 to 11:00) started within 24h of ICU admission and for 3 days	Normal lighting	Haloperidol permitted	CAM-ICU twice daily Intervention: 6% Control: 33%
Prakanattana 2007 [89] Thailand Single-centre	P	126	Cardio-surgical ICU	Intervention: 61.3 ± 9.7 Control: 60.7 ± 9.8	NR	Risperidone 1 mg SL	Listerine strip	Fentanyl and midazolam given during the surgery. Intermittent morphine in the ICU. Sedatives nor antipsychotics permitted	CAM-ICU twice daily Intervention: 11% Control: 31%
Priye 2015 [90] India Single-centre	P	64	Cardiac ICU	Intervention: 45.1 ± 14.7 Control: 41.4 ± 11.9	NR	Dexmedetomidine IV 0.4 mcg/kg/h	Placebo IV NaCl infusion	During surgery all received midazolam, fentanyl, propofol and vecuronium. Fentanyl used for pain; approximately 2x dose total exposure in the intervention group	CAM-ICU daily Intervention: 3% Control: 15%
Rice 2017 [91] United States Single-centre	NP	125	Neuro ICU	Intervention: 66.53 ± 9.41 Control: 65.59 ± 10.59	NR	Delirium care, standardized stroke care, therapeutic activities twice daily based on the Hospital Elder Life Program, and assessment of anticholinergic burden and drug risk	Standardized stroke care to optimize physiological parameters, physical function, and geriatric outcomes	Pharmacists calculated anticholinergic drug burden and guided team adjustments	CAM twice daily Intervention: 5% Control: 10%
Robinson 2014 [92] United States Single-centre NCT00865202	P	301	Surgical ICU ~10% mechanical ventilation	Intervention: 69 ± 8 Control: 69 ± 7	NR	L-tryptophan PO 1 g TID Until ICU discharge or total of 9 doses	Placebo PO Until ICU discharge or total of 9 doses	Opioids, benzodiazepines and haloperidol permitted. Balanced between groups	CAM-ICU daily Intervention: 40% Control: 37%

Study, Year [reference] Country, No. of centres, Registration No.	Intervention Type	N	Population	Age, Years [mean ± SD or median (IQR)]	Severity of Illness Score [mean ± SD or median (IQR)]	Intervention	Control	Additional Treatments for Pain, Sedation, or Delirium	Delirium Assessment Tool Occurrence of Delirium
Rubino 2010 [93] Italy Single-centre	P	30	Surgical ICU 100% mechanical ventilation for surgery	Intervention: 63.9 ± 8.9 Control: 61.3 ± 6.3	NR	Clonidine IV, bolus 0.5 mcg/kg at start of, and 1-2 mcg/kg/h throughout weaning	Placebo IV NaCl infusion	Fentanyl, propofol, cisatracurium for surgery	DSM Delirium Detection Score Intervention: 40% Control: 33%
Ruokonen 2009 [94] Finland Multi-centre NCT00226785	P	85	Mixed ICU 100% mechanical ventilation	Intervention: 64 (18-83) Control: 68 (18-83)	NR	Dexmedetomidine IV infusion without loading dose titrated to RASS	Standard IV sedation with propofol or midazolam titrated to RASS	Fentanyl boluses as needed. Rescue medication (first-line rescue propofol for patients receiving midazolam, midazolam for those receiving propofol before randomization). Antipsychotics not reported	CAM-ICU daily Intervention: 43% Control: 25%
Schaller 2016 [95] Austria, Germany, United States Multi-centre NCT01363102	NP	200	Surgical ICU 100% Mechanical ventilation	Intervention: 66 (48-73) Control: 64 (45-76)	APACHE II Intervention: 16 (12-22) Control: 17 (11-22)	Early goal-directed mobilization until ICU discharge	Standard care until ICU discharge	Sedation, analgesia, and paralysis permitted. No difference in mean opioid dose between groups	CAM-ICU twice daily Not reported
Schweikert 2009 [96] United States Multi-centre NCT00322010	NP	104	Medical ICU 100% mechanical ventilation	Intervention: 57.7 (36.3-69.1) Control: 54.4 (46.5-66.4)	APACHE II Intervention: 20.0 (15.8-32.4) Control: 19.0 (13.3-23.0)	Early exercise and mobilisation with physical and occupational therapy during daily sedation interruption	Daily interruption with mobilisation as ordered for duration of hospital stay	No difference in use of propofol, opioids, benzodiazepines, or haloperidol	CAM-ICU daily Not reported
Shehabi 2009 [97] Australia Multi-centre ACTRN12606000084583	P	299	Cardiothoracic ICU 100% mechanical ventilation	Intervention: 71.5 (66-76) Control: 71.0 (65-75)	NR	Dexmedetomidine IV 0.1-0.7 mcg/kg/h Until discharge from ICU or for up to 48h of mechanical ventilation	Morphine IV 10-70 mcg/kg/h titrate to sedation target Until discharge from ICU or for up to 48 h of mechanical ventilation	Open label morphine and propofol permitted	CAM-ICU daily Intervention: 8% Control: 15%

Study, Year [reference] Country, No. of centres, Registration No.	Intervention Type	N	Population	Age, Years [mean ± SD or median (IQR)]	Severity of Illness Score [mean ± SD or median (IQR)]	Intervention	Control	Additional Treatments for Pain, Sedation, or Delirium	Delirium Assessment Tool Occurrence of Delirium
Shehabi 2013 [98] Australia, New Zealand Multi-centre ACTRN12311000166976	P	37	Mixed ICU 100% mechanical ventilation	Intervention: 65 ± 15 Control: 61.6 ± 17	APACHE II Intervention: 18.6 ± 8.8 Control: 20.2 ± 6.2	Early goal-directed IV sedation, IV dexmedetomidine-based sedation titrated to RASS target. Until sedation no longer required or up to 28 days	Standard IV sedation with propofol and/or midazolam as clinically appropriate Until sedation no longer required or up to 28 days	Haloperidol use permitted (< 10%) and no difference between groups	CAM-ICU daily Intervention: 38% Control: 38%
Shehabi 2019 [99] Australia, Ireland, Italy, Malaysia, New Zealand, Saudi Arabia, Switzerland, United Kingdom Multi-centre NCT01728558	P	4000	Mixed ICU 100% mechanical ventilation	Intervention: 61.2 ± 15.5 Control: 61.4 ± 15.3	APAHCE II Intervention: 22.1 ± 7.7 Control: 21.9 ± 7.7	Dexmedetomidine IV as primary (or, once adequate sedation achieved, the sole) sedating agent starting at 1 mcg/kg/h (no loading dose) to maximum 1.5 mcg/kg/h until target RASS until ICU discharge or up to 28 d post randomization	Standard care with IV sedation either propofol, midazolam or other sedatives. Rescue dexmedetomidine permitted for uncontrolled agitation until ICU discharge or up to 28 d post randomization	Antipsychotics permitted (use not reported)	CAM-ICU daily Not reported
Shu 2019 [100] China Single-centre	P	80	Mixed ICU 100% Mechanical ventilation	Intervention: 73.38 ± 8.59 Control: 73.83 ± 7.96	NR	Dexmedetomidine IV 1 mcg/kg then 0.2-0.7 mcg/kg/h	Midazolam IV 0.05 mg/kg then 0.05-0.1 mg/kg/h	NR	Not reported Intervention: 0% Control: 10%
Simons 2016 [101] Netherlands Single-centre NCT01274819	NP	734	Mixed ICU 65% mechanical ventilation	Intervention: 66.3 ± 12.8 Control: 64.4 ± 13.7		Dynamic light application therapy 09:00 to 16:00 except 11:30-13:30	Normal lighting	Haloperidol permitted. Balanced between groups (~ 30%).	CAM-ICU three times daily Intervention: 38% Control: 33%
Skrobik 2018 [102] Canada, United States Multi-centre NCT01791296	P	100	Mixed ICU 90% mechanical ventilation	Intervention: 62.16 ± 13.2 Control: 62.4 ± 14.1	APAHCE II Intervention: 23.6 ± 7.8 Control: 21.9 ± 7.9	Dexmedetomidine IV 0.2 mcg/kg/h, titrated by 0.1 mcg/kg/h q15min to RASS -1 or maximum 0.7 mcg/kg/h between 21:30 to 06:15 until ICU discharge	Placebo IV NaCl infusion Until ICU discharge	Antipsychotic use was permitted but discouraged	ICDSC twice daily Intervention: 20% Control: 46%

Study, Year [reference] Country, No. of centres, Registration No.	Intervention Type	N	Population	Age, Years [mean ± SD or median (IQR)]	Severity of Illness Score [mean ± SD or median (IQR)]	Intervention	Control	Additional Treatments for Pain, Sedation, or Delirium	Delirium Assessment Tool Occurrence of Delirium
Song 2015 [103] China Single-centre	P	90	Mixed ICU 100% mechanical ventilation	Intervention: 46.33 ± 12.89 Control: 45.42 ± 10.06	NR	Dexmedetomidine IV 0.2-0.7 mcg/kg/h titrated to RASS target	Midazolam IV 2-3 mg then 0.5 mcg/kg/h titrated to RASS target	NR	CAM-ICU daily Intervention: 9% Control: 31%
Sosnowski 2018 [104] Australia Single-centre ACTRN12614000763640	NP	30	Mixed ICU 100% mechanical ventilation	Intervention: 54.9 ± 15.9 Control: 60.6 ± 11.0	APACHE II Intervention: 14.9 ± 5.9 Control: 13.7 ± 5.0	ABCDE bundle daily (awakening and breathing trials, delirium monitoring, exercise, mobility regimens)	Standard care	NR	CAM-ICU twice daily Not reported
Spies 2011 [105] Germany Multi-centre EudraCT200500190721	P	60	Mixed ICU 100% mechanical ventilation	Intervention: 64 ± 15 Control: 63 ± 12	APACHE II Intervention: 24 ± 8 Control: 26 ± 9	Remifentanyl IV 0.1-0.4 mcg/kg ideal body weight/min titrated to analgesia target up to a maximum of 30 days	Fentanyl IV 0.02-0.08 mcg/kg ideal body weight/min titrated to analgesia target up to a maximum of 30 days	Propofol, midazolam, morphine, haloperidol permitted. No difference between groups	CAM-ICU daily Intervention: 29% Control: 22%
Strom 2010 [106] Denmark Single-centre NCT00466492	P	113	Mixed ICU 100% mechanical ventilation	Intervention: 67 (54-74) Control: 65 (54-74)	APACHE II Intervention: 26 (19-30) Control: 26 (22-31)	Analgesia with opioid, no sedation	Analgesia with opioid, sedation with propofol titrated to RASS	Morphine, propofol, benzodiazepines, and haloperidol permitted. No difference in haloperidol or morphine between groups.	DSM daily Intervention: 11% Control: 7%
Su 2016 [105] China Multi-centre ChiCTR-TRC-10000802	P	700	Surgical ICU 100% mechanical ventilation	Intervention: 74.3 ± 6.7 Control: 74.4 ± 7.0	APACHE II Intervention: 10.6 ± 3.9 Control: 10.2 ± 3.3	Dexmedetomidine IV for non-intubated, 0.1 mcg/kg/h within 1 hour of ICU admission to 08:00 day after surgery; for intubated, infusion started after sedatives titrated to RASS target	Placebo IV NaCl infusion	Non-pharmacological methods for those who developed delirium. Haloperidol permitted.	CAM-ICU twice daily Intervention: 9% Control: 23%
Susheela 2017 [108] United States Single-centre NCT02546765	P	12	Cardiac ICU 100% mechanical ventilation	NR	NR	Intervention 1: Propofol IV (as above) with acetaminophen 1 g IV q6h for 48 post-operative hours	Propofol IV per doctor discretion during surgery, 25-100 mcg/kg/min post-operatively (n=3)	NR	CAM-ICU daily Intervention 1: 0%

Study, Year [reference] Country, No. of centres, Registration No.	Intervention Type	N	Population	Age, Years [mean ± SD or median (IQR)]	Severity of Illness Score [mean ± SD or median (IQR)]	Intervention	Control	Additional Treatments for Pain, Sedation, or Delirium	Delirium Assessment Tool Occurrence of Delirium
						(n=3) Intervention 2: Dexmedetomidine IV per doctor discretion during surgery, 0.1-1.0 mcg/kg/h post-operatively (n=3) Intervention 3: Dexmedetomidine IV (as above) with acetaminophen 1 g IV q6h for 48 post-operative hours (n=3)	Infusions administered until extubation or a minimum of 6 hours		Intervention 2: 67% Intervention 3: 33% Control: 67%
Taguchi 2007 [109] Japan Single-centre	NP	11	Surgical ICU	NR	NR	Bright light therapy 07:30 to 09:30 pm x 4d	Normal lighting x 4d	NR	NEECHAM twice daily Intervention: 16% Control: 40%
Takieddine 2018 [110] United States Single-centre NCT022062879	P	20	Surgical ICU 100% non-intubated	Intervention: 39 (28-47) Control: 26 (22-30)	NR	Ketamine IV 1.5-6 mg bolus (6 min lockout) until transfer out of ICU	Hydromorphone IV 0.1-0.4 mg bolus (6 min lockout) until transfer out of ICU	Lorazepam permitted	CAM-ICU Intervention: 10% Control: 0%
Van Rompaey 2012 [111] Belgium Single-centre ISRCTN36198138	NP	136	Mixed ICU	Intervention: 57 (19-81) Control: 62 (18-84)	SOFA Intervention: 7.2 (1-14) Control: 7.0 (2-15)	Ear plugs from 22:00 to 06:00 up to 5d	No intervention up to 5d	NR	NEECHAM three times daily Intervention: 19% Control: 20%
Wan 2011 [112] China Single-centre	P	200	Surgical ICU mechanical ventilation	NR	NR	Dexmedetomidine IV titration details not provided	Midazolam IV titration details not provided	NR	Not specified Intervention: 4% Control: 31%
Wang 2012 [113] China Multi-centre	P	457	Surgical ICU	Intervention: 74.0 ± 5.8 Control: 74.4 ± 7.0	NR	Haloperidol IV 0.5 mg then 0.1 mg/h	Placebo IV NaCl infusion	Post-op analgesia with morphine or fentanyl. Propofol or midazolam	CAM-ICU daily Intervention: 15%

Study, Year [reference] Country, No. of centres, Registration No.	Intervention Type	N	Population	Age, Years [mean ± SD or median (IQR)]	Severity of Illness Score [mean ± SD or median (IQR)]	Intervention	Control	Additional Treatments for Pain, Sedation, or Delirium	Delirium Assessment Tool Occurrence of Delirium
								permitted if mechanically ventilated. Open label haloperidol was permitted	Control: 23%

Abbreviations: ABCDE bundle = “A” for Assessment, Prevention, and Manage pain; “B” for Both Spontaneous Awakening Trials and Spontaneous Breathing Trials; “C” for Choice of Analgesia and Sedation; “D” for Delirium Assess, Prevent, and Manage; “E” for Early Mobility and Exercise; APACHE = Acute Physiology And Chronic Health Evaluation; BPS = Behavioral Pain Scale; CAM = Confusion Assessment Method for the ICU; CPOT = Critical Care Pain Observation Tool; d = day; D5W = 5% Dextrose in Water; DRS = Delirium Rating Scale; DSM = Diagnostic and Statistical Manual of Mental Disorders; h = hour; ICDSC = Intensive Care Delirium Screening Checklist; ICU = intensive care unit; IQR = interquartile range; IV = intravenous; kg = kilogram; M = mixed pharmacological and non-pharmacological intervention; mcg = microgram; mg = milligram; min = minute; mL = millilitre; NaCl = sodium chloride; NEECHAM = NEECHAM Confusion Scale; No. = number; NP = Non-pharmacological intervention; NR = not reported; P = Pharmacological intervention; PO = per os; q4h = every 4 hours; q6h = every 6 hours; qHS = every night; RASS = Richmond Agitation Sedation Scale; SAPS = Simplified Acute Physiology Score 3; SAS = Sedation Agitation Scale; SD = standard deviation; SOFA = Sequential Organ Failure Assessment score

eTable 3. Risk of Bias of Included Studies

Study	Selection bias Random sequence generation	Selection bias Allocation concealment	Performance Bias Blinding of participants	Detection bias Blinding of primary outcome assessors	Attrition bias Incomplete primary outcome data	Reporting bias Selective reporting	Other sources of bias Funding, baseline characteristics	Overall
Abbasi 2018	Low	Low	Low	Low	Low	Low	Low	Low
Abdelgalel 2016	Low	Low	Low	Low	Low	Low	Low	Low No trial registry but results reported match methods so likely low risk of bias.
Al-Qadheeb 2016	Low	Low	Low	Low	Low	Low	Low	Low
Alvarez 2017	Low	Low	Low	Low	Low	Low	Low	Low Difficult to blind intervention. Although participants were not blinded the lack of blinding likely low risk of influencing outcome. Blinded outcome assessment and statistical analysis.
Azeem 2018	Low	Low	Low	Low	Low	Low	Low	Low
Azuma 2018	Low	Low	Low	Low	Low	Low	Low	Low
vanden Boogaard 2018	Low	Low	Low	Low	Low	Low	Low	Low
Brummel 2014	Low	Low	Low	Low	Low	Low	Low	Low Difficult to blind intervention. Although participants were not blinded the lack of blinding likely low risk of influencing outcome. Blinded outcome assessment.
Burkhart 2014	Low	Low	Low	Low	Low	Low	Low	Low Participants were not blind but unlikely to lead to bias due to mode of administration. Blinded outcome assessment.
Chang 2018	Low	Unclear	Low	High	Low	Low	Low	High Reported computer generated randomization codes in sealed envelopes however the principal investigator or research assistant assigned the sedatives to patients. Unclear risk.
Chanques 2017	Low	Low	Low	High	Low	Low	Low	High Difficult to blind intervention. Although participants were not blinded the lack of blinding likely low risk of influencing outcome.
Chlan 2017	Low	Low	Low	High	Low	Low	Low	High Although participants were not blinded the lack of blinding likely low risk of influencing outcome.

Study	Selection bias Random sequence generation	Selection bias Allocation concealment	Performance Bias Blinding of participants	Detection bias Blinding of primary outcome assessors	Attrition bias Incomplete primary outcome data	Reporting bias Selective reporting	Other sources of bias Funding, baseline characteristics	Overall
Damshens 2018	Unclear	High	Low	High	Low	Unclear	Low	High Stated patients were randomly assigned to two groups. No information on randomization, allocation, no blinding or participants or assessors, no trial registry. Although participants were not blinded the lack of blinding likely low risk of influencing outcome. Outcomes reported in methods also reported in results.
De Jong 2018	Low	Low	Low	Low	Low	Low	Low	Low
De Jonghe 2018	Low	Low	Low	High	Low	Low	Low	High Although participants were not blinded the lack of blinding likely low risk of influencing outcome.
Demoule 2017	Low	Low	Low	High	Low	Low	Low	High Although participants were not blinded the lack of blinding likely low risk of influencing outcome.
Devlin 2014	Low	Low	Low	Low	Low	Low	Low	Low
Djaiani 2016	Low	Low	Low	Low	Low	Low	Low	Low Stated as single blind but assessors not aware of assignment.
Eghbali-Babadi 2017	Unclear	High	Low	Low	Low	Low	Low	High Stated as randomized trial. However, also stated those who met criteria were selected through convenient sampling and assigned to groups.
Finotto 2006	Low	High	Low	High	High	Low	Unclear	High No trial registry but results reported match methods. Likely low risk. Process of allocation concealment not reported. Stated prepared 100 randomization envelopes but stopped at 48. No demographic data reported. Only outcome mentioned and reported is delirium.
Foreman 2015	Low	High	Low	High	Low	Low	Low	High Process of allocation concealment not reported. No trial registry but results reported match methods. Likely low risk. Although participants not blinded the lack of blinding likely low risk of influencing outcome.
Gandolfi 2020	Low	Low	Low	Low	Low	Low	Low	Low

Study	Selection bias Random sequence generation	Selection bias Allocation concealment	Performance Bias Blinding of participants	Detection bias Blinding of primary outcome assessors	Attrition bias Incomplete primary outcome data	Reporting bias Selective reporting	Other sources of bias Funding, baseline characteristics	Overall
								Patients were randomly assigned by pharmacy, using random assignment as only detail provided. Described as double-blind but no further details but study drug appear to be matched.
Girard 2008	Low	Low	Low	High	Low	Low	Low	High Difficult to blind intervention. Although participants were not blinded the lack of blinding likely low risk of influencing outcome.
Giraud 2016	Low	Low	Low	High	Low	Low	Low	High Difficult to blind intervention. Although participants not blinded the lack of blinding for participants likely low risk of influencing outcome.
Guo 2016	Low	Low	Low	Low	Low	Unclear	Low	Low No trial registry but results reported match methods. Likely low risk.
Hakim 2012	Low	Low	Low	Low	Low	Low	Low	Low
Hu 2015	Unclear	High	Low	High	High	Unclear	Low	High Stated as randomized without further detail. Not blinded. No trial registry. Insufficient details to determine bias risk.
Huang 2014	Low	High	Low	High	High	Unclear	Low	High No details regarding allocation concealment. No blinded assessment of outcome. No trial registry to confirm.
Hughes 2021	Low	Low	Low	Low	Low	Low	Low	Low Drug company supplied drug but no role in the design, conduct, analysis, or writing of the manuscript.
Javaherforoosh Zadeh 2021	Low	High	Low	Low	Low	Low	Low	high No details on allocation concealment. Described as double-blinded but no details provided. Study drug appears similar.
Johansson 2017	High	High	Low	High	Low	Unclear	Low	High Quasi-randomization based on room availability and charge nurse. Although participants not blinded the lack of blinding for participants likely low risk of influencing outcome. Outcome assessment not blinded. No trial registry to confirm.
Johnson 2018	Unclear	Unclear	Low	High	Low	Unclear	Low	High

Study	Selection bias Random sequence generation	Selection bias Allocation concealment	Performance Bias Blinding of participants	Detection bias Blinding of primary outcome assessors	Attrition bias Incomplete primary outcome data	Reporting bias Selective reporting	Other sources of bias Funding, baseline characteristics	Overall
								Stated as randomized without further detail. Although participants not blinded the lack of blinding for participants likely low risk of influencing outcome. Outcome assessment not blinded. No trial registry.
Karadas 2016	Unclear	High	Low	High	Unclear	Low	Low	High Stated as randomized without further detail. No information on blinding of outcome assessment or clinical team. Small attrition.
Kawazoe 2017	Low	Low	Low	High	Low	Low	Low	High Open label design. Although participants were not blinded the lack of blinding for participants likely low risk of influencing outcome. Not blinded assessment.
Keh 2016	Low	Low	Low	Low	Low	Low	Low	Low
Khan 2018	Low	Low	Low	Low	Low	Low	Low	Low
Khan 2020	Low	Low	Low	Low	Low	Low	Low	Low Stated as single blind. Lack of blinding for participants likely low risk of influencing outcome.
Li 2016	Low	Low	Low	Low	High	Low	Low	High Blinded outcome assessment. Attrition of patients based on inadequate target score or serious adverse events.
Litton 2017	Low	Low	Low	High	Low	Low	Low	High Difficult to blind the intervention. Lack of blinding for participants likely low risk of influencing outcome.
Liu 2017	Low	Low	Low	Low	Low	Low	Low	Low
Lyu 2015	Low	High	Low	High	High	Low	Low	High Method of allocation not reported. Stated single blind. Lack of blinding for participants likely low risk. Approximately 10% attrition.
Mahrose 2021	Unclear	High	Low	High	Low	Low	Low	High Stated as randomized but no details provided. No mention of allocation or blinding. Lack of blinding for participants likely low risk of influencing outcome.
Mehta 2012	Low	Low	Low	High	Low	Low	Low	High Intervention difficult to blind. Outcome assessment not blinded.

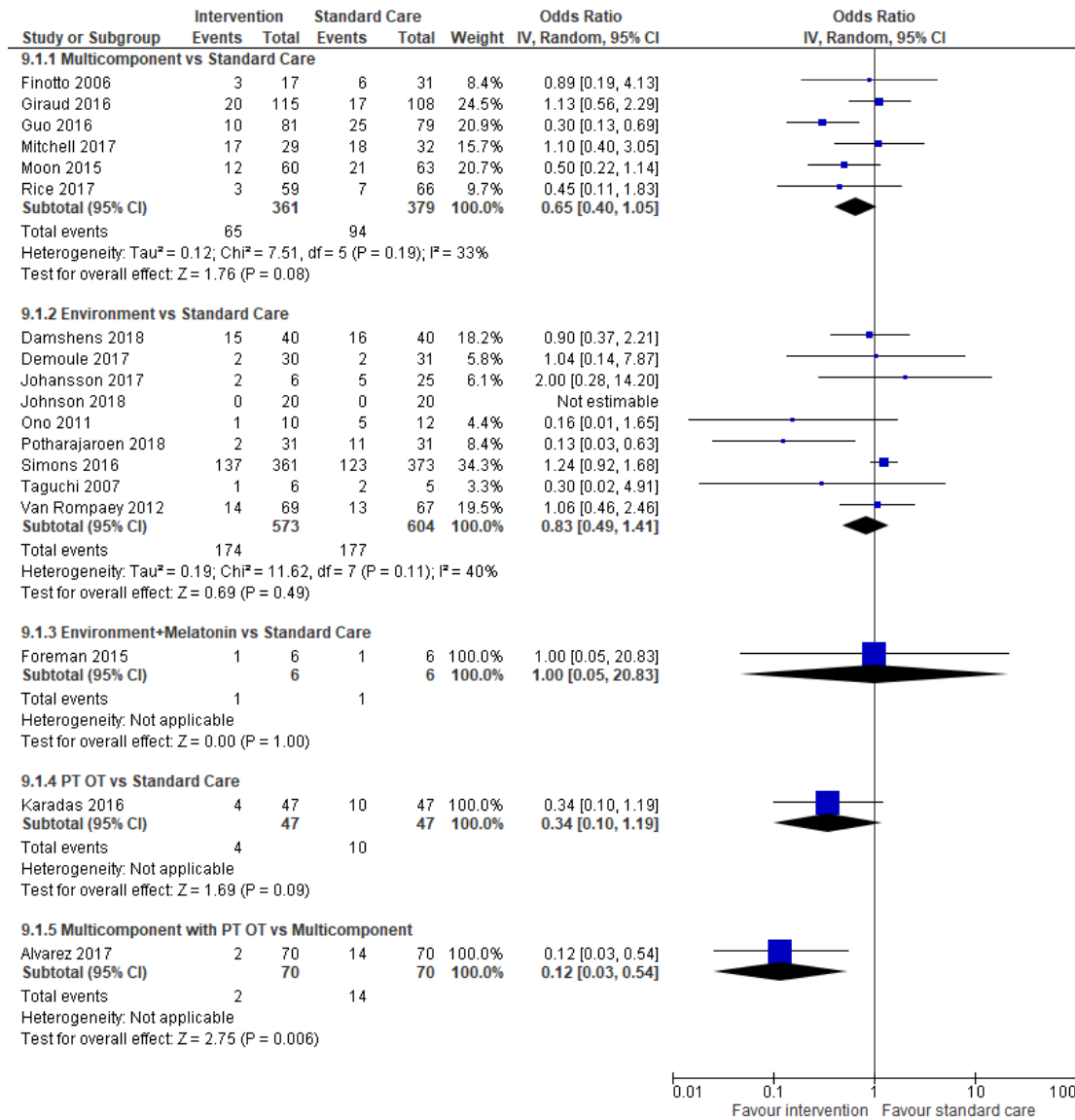
Study	Selection bias Random sequence generation	Selection bias Allocation concealment	Performance Bias Blinding of participants	Detection bias Blinding of primary outcome assessors	Attrition bias Incomplete primary outcome data	Reporting bias Selective reporting	Other sources of bias Funding, baseline characteristics	Overall
Mitchell 2017	Low	Low	Low	High	Low	Low	Low	High No information on blinding. Likely difficult to blind. Lack of blinding for participants likely low risk of influencing outcome.
Mohammadi 2016	Unclear	High	Low	Low	Unclear	Low	Low	High States simple randomization but no details provided. Attrition <5% per group and equal.
Mokhtari 2020	Low	High	Low	Low	High	Low	Low	High No description of the allocation concealment process. ~20% attrition.
Moon 2015	Low	Low	Low	High	Unclear	Low	Low	High Not blinded outcome assessment. Attrition of 5% equal between groups.
Nassar 2014	Low	Low	Low	High	Low	Low	Low	High Intervention difficult to blind. Outcome assessment not blinded.
Nishikimi 2018	Low	Low	Low	Low	Low	Low	Low	Low
Nydhal 2019	Low	Low	Low	High	Low	Low	Low	High Difficult to blind the intervention. Lack of blinding for participants likely low risk of influencing outcome. Not blinded outcome assessment.
Ono 2011	Low	Low	Low	High	Unclear	Unclear	Low	High Not blinded outcome assessment. No trial registry to check. No information to confirm attrition.
Pandharipande 2007	Low	Low	Low	Low	Low	Low	Low	Low
Park 2014	Unclear	High	Low	High	Low	Low	Low	High Stated as randomized but no details provided. No mention of allocation or blinding. Lack of blinding for participants likely low risk of influencing outcome.
Perbet 2018	Low	Low	Low	Low	Low	Low	Low	Low
Potharajoen 2018	High	High	Low	Low	Low	Low	Low	High Stated as systematically allocated to groups but not details. Difficult to blind the intervention. Lack of blinding for participants likely low risk of influencing outcome. Outcome assessor blinding.
Prakanrattana 2007	Low	Low	Low	Low	Low	Low	Low	Low

Study	Selection bias Random sequence generation	Selection bias Allocation concealment	Performance Bias Blinding of participants	Detection bias Blinding of primary outcome assessors	Attrition bias Incomplete primary outcome data	Reporting bias Selective reporting	Other sources of bias Funding, baseline characteristics	Overall
Priye 2015	Low	Low	Low	Low	Low	Low	Low	Low
Rice 2017	Low	Low	Low	High	Low	Low	Low	High Blinding of intervention difficult. Blinding not reported. However, lack of blinding for participants likely low risk of influencing outcome.
Robinson 2014	Low	Low	Low	Low	Low	Low	Low	Low
Rubino 2010	Unclear	Unclear	Low	Low	Low	Unclear	Low	Moderate Stated as randomized but method of randomization and allocation not reported. States envelop opened on admission to ICU. No trial registry to confirm.
Ruokonen 2009	Low	Low	Low	Low	Low	Low	Low	Low
Schaller 2016	Low	Low	Low	Low	Low	Low	Low	Low lack of blinding for participants likely low risk of influencing outcome. Therapists who did outcome assessment were blinded.
Schweikert 2009	Low	Low	Low	Low	Low	Low	Low	Low Therapists who did outcome assessment were blinded.
Shehabi 2009	Low	Low	Low	Low	Low	Low	Low	Low
Shehabi 2013	Low	Low	Low	High	Low	Low	Low	High Lack of blinding for participants likely low risk. Outcome assessment not blinded.
Shehabi 2019	Low	Low	Low	High	Low	Low	Low	High Lack of blinding for participants likely low risk. Outcome assessment not blinded.
Shu 2019	Unclear	High	Low	High	High	Unclear	Unclear	High Stated randomized trial but no information on randomization, allocation concealment, blinding, attrition. Lack of blinding for participants likely low risk. Outcome assessment not blinded. No trial registry to check.
Simons 2016	Low	Low	Low	High	Low	Low	Low	High Lack of blinding for participants likely low risk. Outcome assessment not blinded.
Skrobik 2018	Low	Low	Low	Low	Low	Low	Low	Low
Song 2015	Low	High	Low	High	Low	Unclear	Low	High No information on allocation concealment or blinding of

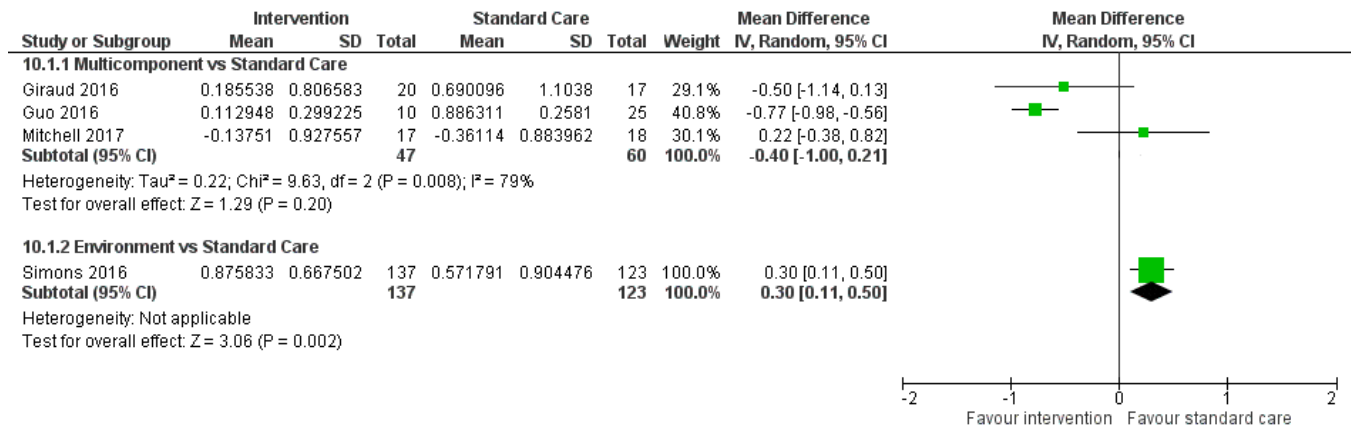
Study	Selection bias Random sequence generation	Selection bias Allocation concealment	Performance Bias Blinding of participants	Detection bias Blinding of primary outcome assessors	Attrition bias Incomplete primary outcome data	Reporting bias Selective reporting	Other sources of bias Funding, baseline characteristics	Overall
								assessment. No trial registry to confirm.
Sosnowski 2018	Low	Low	Low	Low	Low	Low	Low	Low Lack of blinding for participants likely low risk. Blinded assessment.
Spies 2011	Low	Low	Low	Low	Low	Low	Low	Low
Strom 2010	Low	Low	Low	High	Low	Low	Low	High Blinding was not possible for research staff or clinical staff. Lack of blinding for participants likely low risk.
Su 2016	Low	Low	Low	Low	Low	Low	Low	Low
Susheela 2017	Low	Low	Low	Low	Unclear	Low	Low	Moderate Attrition ~15% enrolled but not randomized in a small sample size.
Taguchi 2007	Unclear	High	Low	High	High	Unclear	Low	High Stated as randomized but no details provided. ~30% attrition. No mention of outcome assessment. No trial registry to confirm.
Takieddine 2018	Low	Low	Low	Low	Low	Low	Low	Low
Van Rompaey 2012	Low	Low	Low	Low	Low	Low	Low	Low Lack of blinding for participants likely low risk of influencing outcome. Researchers and assessors blinded.
Wan 2011	Low	High	Low	High	High	Unclear	Low	High Lack of blinding for participants likely low risk of influencing outcome. No information on assessment and attrition.
Wang 2012	Low	Low	Low	Low	Low	Low	Low	Low

eFigure 1 Pairwise Comparisons for Non-Pharmacological Interventions

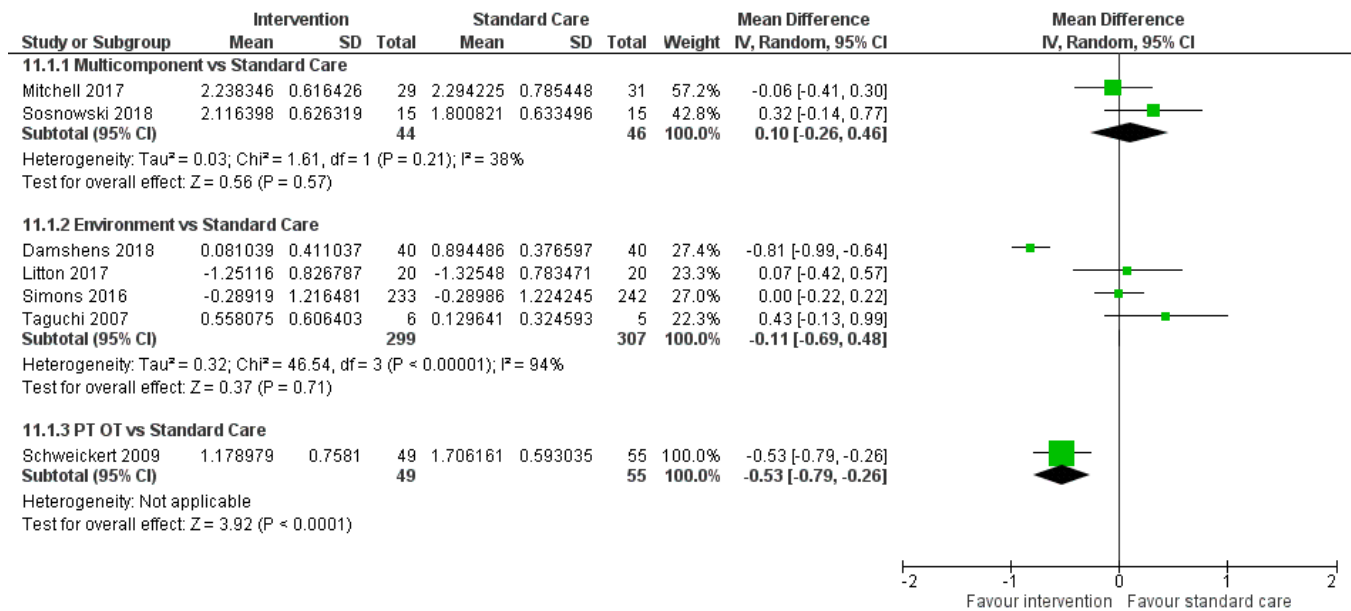
1A: Delirium Occurrence



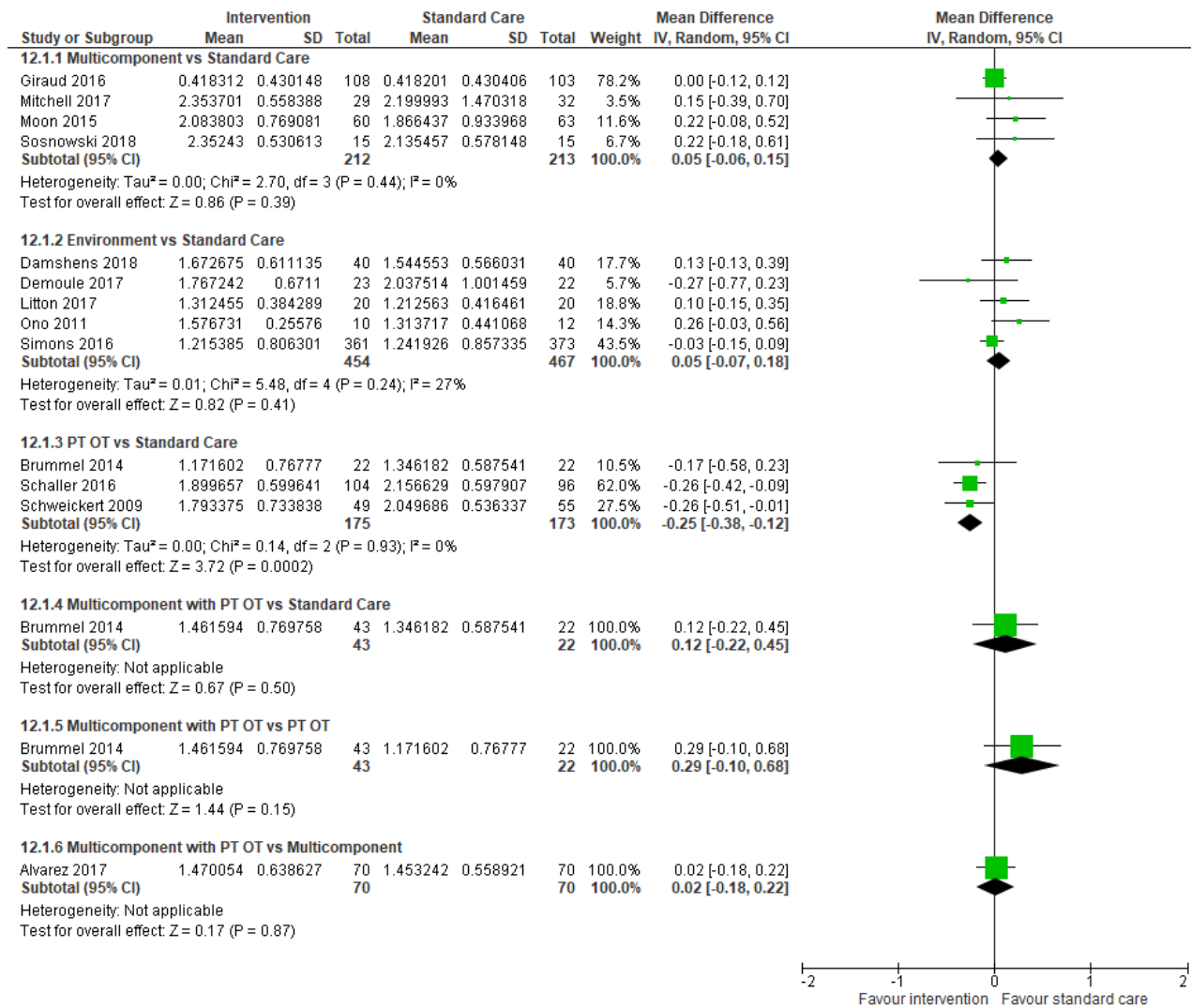
1B: Duration of Delirium



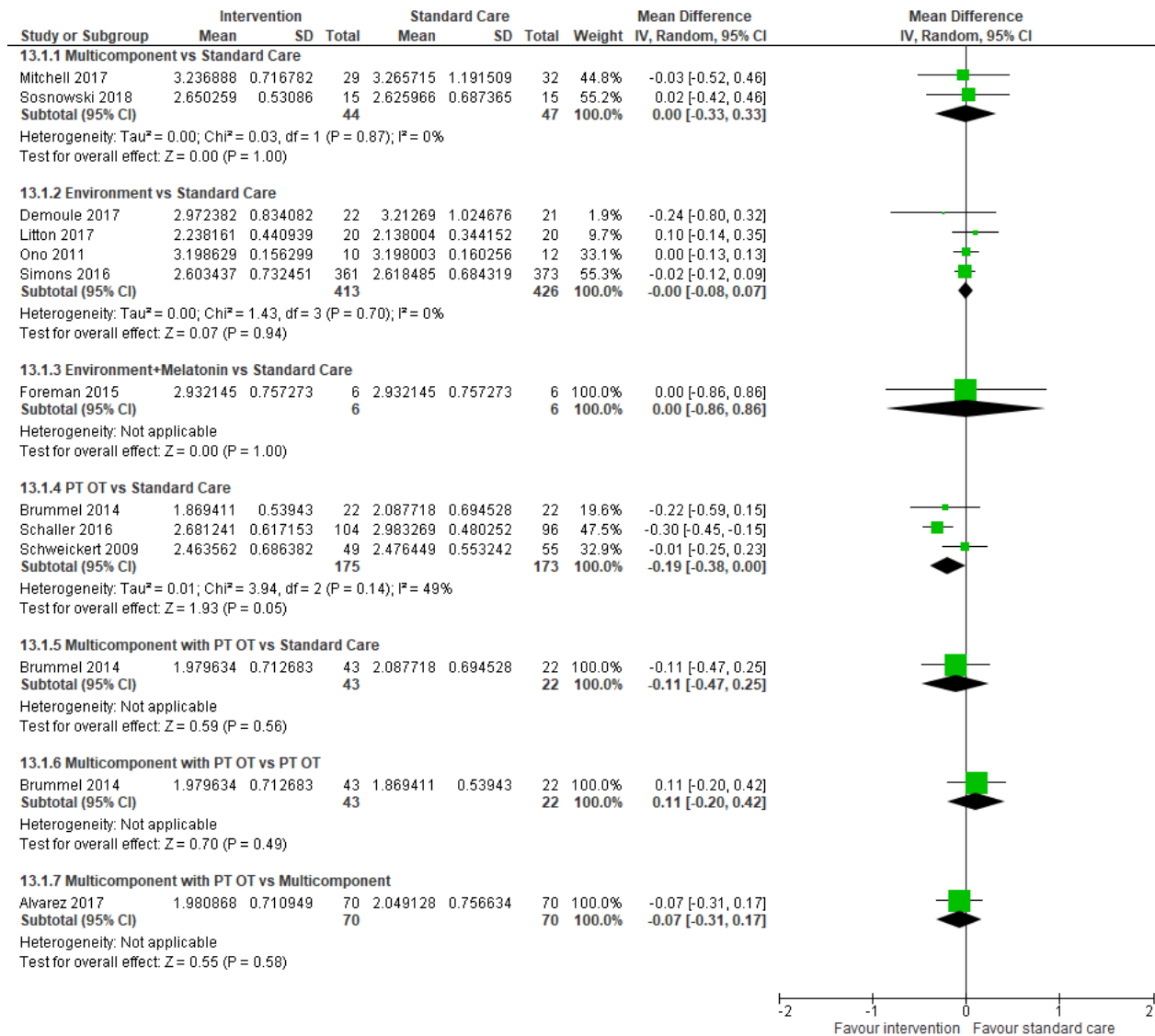
1C: Duration of Mechanical Ventilation



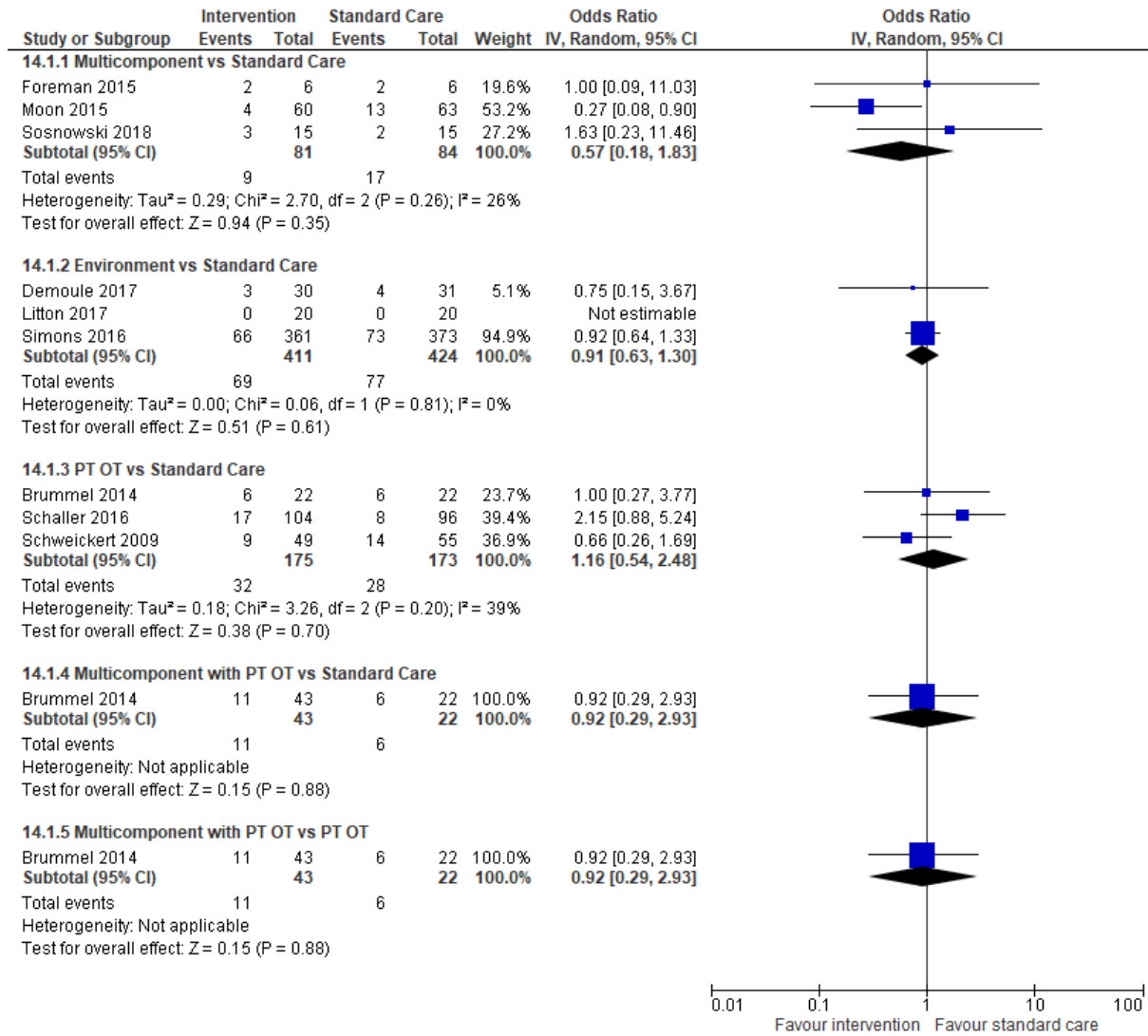
1D: Length of ICU Stay



1E: Length of Hospital Stay



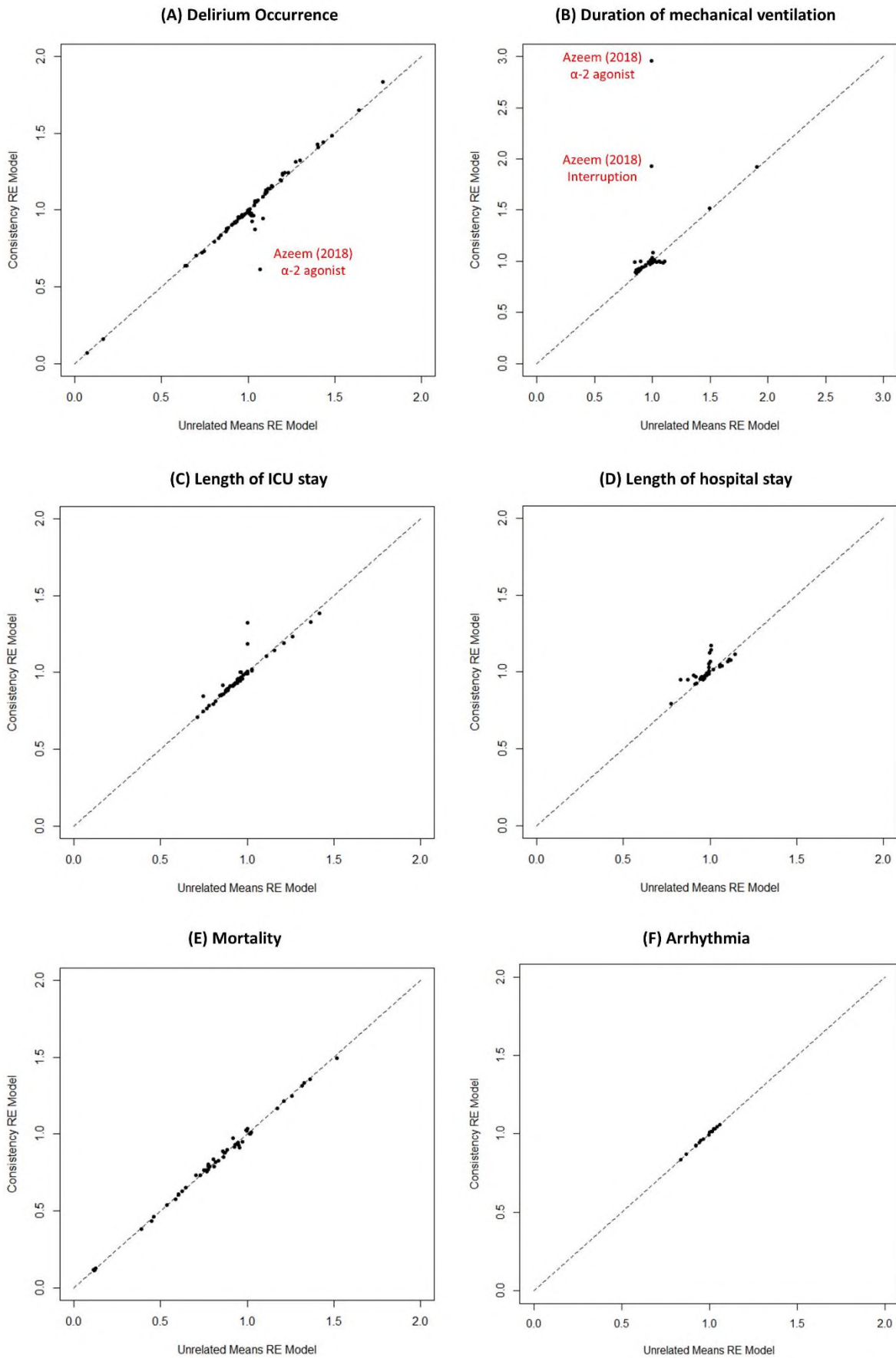
1F: Mortality



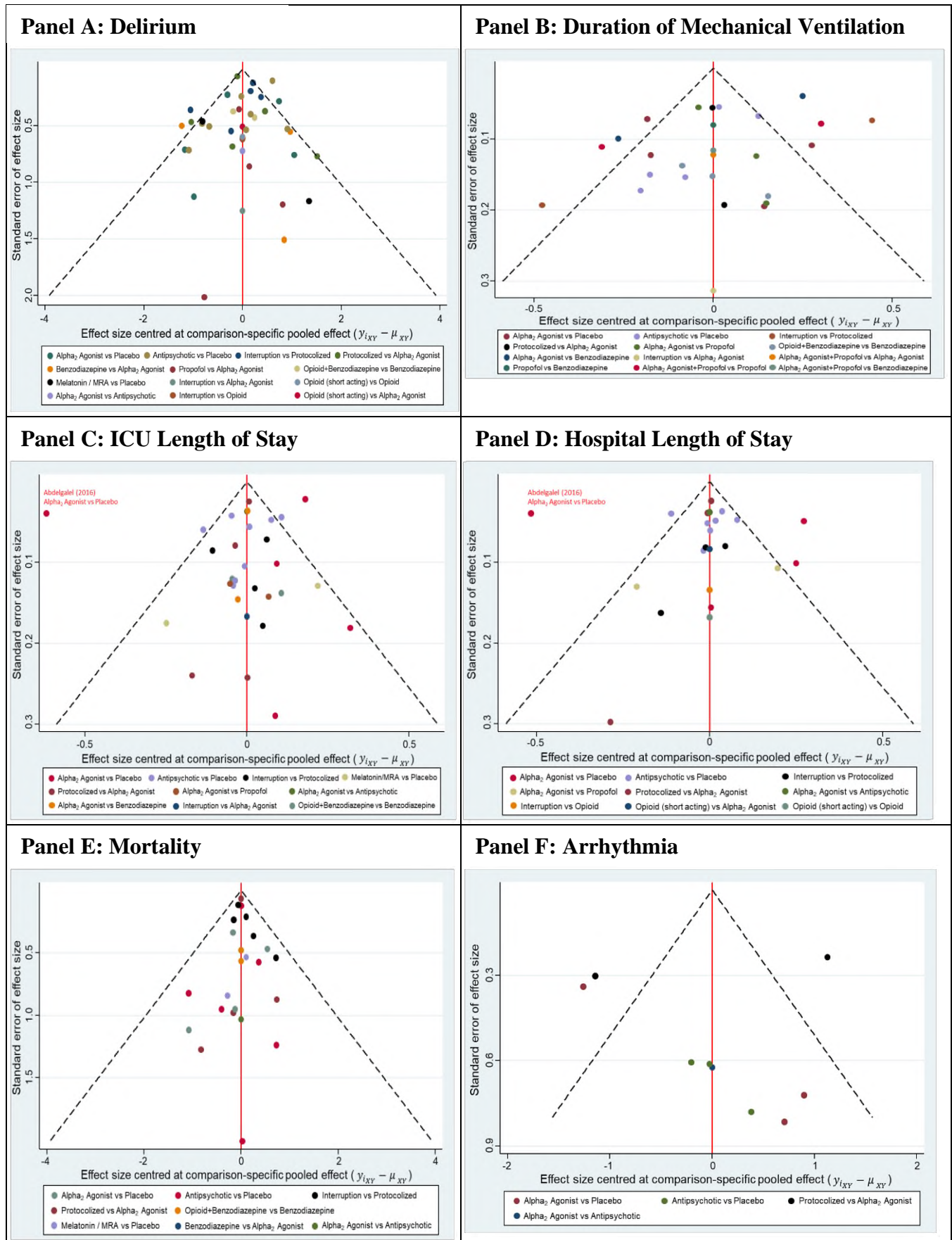
eTable 4: Model fit statistics and assessment of heterogeneity

Delirium occurrence	<p>The random-effects consistency model for delirium occurrence was an adequate fit, with a posterior total residual deviance of 77.61 (compared to 77 unconstrained data points). The between-study SD, as a measure of heterogeneity, was estimated as 0.60 (95% CrI 0.34 to 0.95).</p> <p>Comparison of Deviance Information Criterion (DIC) values between the random-effects consistency model (451.8) and the corresponding random-effects unrelated means model (454.0) as well as inspection of a scatterplot of posterior mean deviance contributions from both models (eFigure 2, Panel A) suggested a slight violation to the consistency assumption, possibly attributed to a cardiac surgery study that had very short duration of mechanical ventilation. The comparison-adjusted funnel plot to assess for small-study effects provided evidence of minimal asymmetry (eFigure 3, Panel A).</p>
Duration of mechanical ventilation	<p>The random-effects consistency model for duration of mechanical ventilation was an adequate fit, with posterior total residual deviance of 53.03 (compared to 50 unconstrained data points). The between-study SD, as a measure of heterogeneity, was estimated as 0.33 (95% CrI 0.20 to 0.51).</p> <p>Comparison of DIC values between the random-effects consistency model (-61.91) and the corresponding random-effects unrelated means model (-66.03, but the DIC difference was < 5) as well as inspection of a scatterplot of posterior mean deviance contributions from both models (eFigure 2, Panel B) suggested a slight violation to the consistency assumption, possibly attributed to a cardiac surgery study that had very short duration of mechanical ventilation. The comparison-adjusted funnel plot to assess for small-study effects provided minimal evidence of asymmetry (eFigure 3, Panel B).</p>
Length of ICU stay	<p>The random-effects consistency model for length of ICU stay was an adequate fit, with a posterior total residual deviance of 62.40 (compared to 65 unconstrained data points). The between-study SD, as a measure of heterogeneity, was estimated as 0.20 (95% CrI 0.14 to 0.28).</p> <p>Comparison of DIC values between the random-effects consistency model (-104.90) and the corresponding random-effects unrelated means model (-105.30) as well as inspection of a scatterplot of posterior mean deviance contributions from both models (eFigure 2, Panel C) suggested no evidence of violation to the consistency assumption. The comparison-adjusted funnel plot to assess for small-study effects provided minimal evidence of asymmetry (eFigure 3, Panel C).</p>
Length of hospital stay	<p>The random-effects consistency model for length of hospital stay was an adequate fit, with posterior total residual deviance of 46.03 (compared to 46 unconstrained data points). The between-study SD, as a measure of heterogeneity, was estimated as 0.22 (95% CrI 0.14 to 0.34).</p> <p>Comparison of DIC values between the random-effects consistency model (-90.11) and the corresponding random-effects unrelated means model (-90.99) as well as inspection of a scatterplot of posterior mean deviance contributions from both models (eFigure 2, Panel D) suggested no evidence of violation to the consistency assumption. The comparison-adjusted funnel plot to assess for small-study effects provided minimal evidence of asymmetry (eFigure 3, Panel D).</p>
Mortality	<p>The random-effects consistency model for mortality had a posterior total residual deviance of 43.65 (smaller than 53 unconstrained data points, due to 0 mortality in both study arms in two studies). The between-study SD, as a measure of heterogeneity, was estimated as 0.13 (95% CrI 0.01 to 0.42).</p> <p>Comparison of DIC values between the random-effects consistency model (280.40) and the corresponding random-effects unrelated means model (280.10) as well as inspection of a scatterplot of posterior mean deviance contributions from both models (eFigure 2, Panel E) suggested no evidence of violation to the consistency assumption. The comparison-adjusted funnel plot to assess for small-study effects provided minimal evidence of asymmetry (eFigure 3, Panel E).</p>
Adverse events - Arrhythmias	<p>The random-effects consistency model was an adequate fit, with posterior total residual deviance of 14.63 (compared to 15 unconstrained data points). The between-study SD, as a measure of heterogeneity, was estimated as 1.39 (95% CrI 0.64 to 2.67), suggests high heterogeneity.</p> <p>Comparison of DIC values between the random-effects consistency model (90.51) and the corresponding random-effects unrelated means model (DIC 90.44) as well as inspection of a scatterplot of posterior mean deviance contributions from both models (eFigure 2, Panel F) suggested no evidence of violation to the consistency assumption. The comparison-adjusted funnel plot to assess for small-study effects provided minimal evidence of asymmetry (eFigure 3, Panel F).</p>

eFigure 2 Checking for the consistency assumption (posterior mean deviance contribution plots)



eFigure 3 Comparison-adjusted funnel plots (TO BE UPDATED)



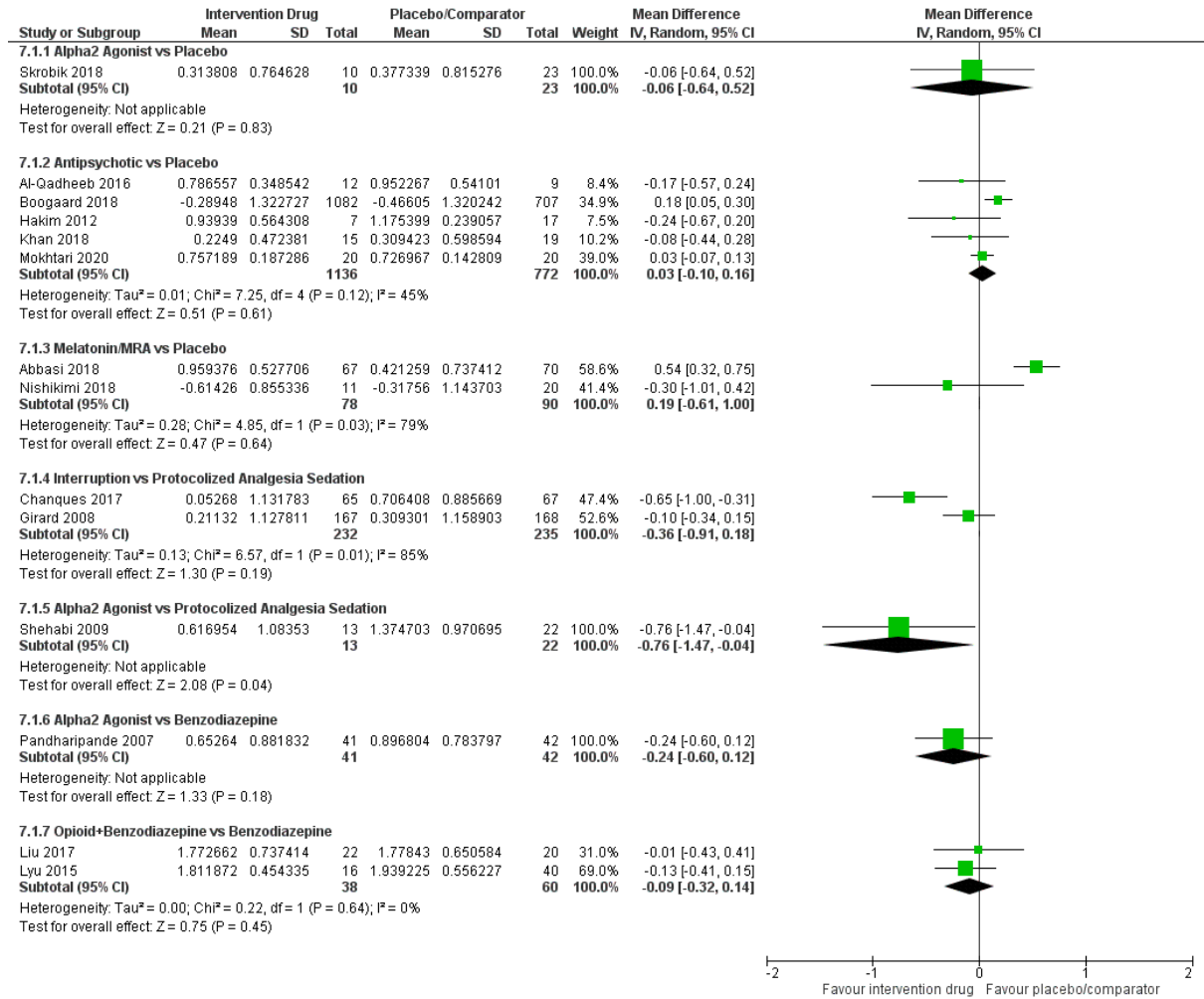
eTable 5: Mean SUCRA value and mean rank for each treatment based on delirium occurrence

Interventions	Mean SUCRA	Mean Rank (95% CrI*)
Alpha ₂ Agonist	0.827	2.73 (1 to 5)
Sedation interruption	0.819	2.81 (1 to 7)
Protocolized sedation	0.673	4.27 (1 to 8)
Opioid + Benzodiazepine	0.664	4.36 (1 to 10)
Antipsychotic	0.620	4.80 (1 to 9)
Melatonin/MRA	0.578	5.22 (1 to 11)
Placebo	0.347	7.53 (4 to 10)
Propofol	0.323	7.77 (2 to 11)
Opioid	0.309	7.91 (2 to 11)
Opioid (short acting)	0.227	8.73 (3 to 11)
Benzodiazepine	0.113	9.87 (6 to 11)

Abbreviations: CrI = 95% credible interval; MRA = melatonin receptor agonist

* Mean rank with 2.5% and 97.5% quantiles in the parentheses.

eFigure 4: Pairwise comparison pharmacological interventions for delirium duration



eTable 6 Duration of mechanical ventilation - league table of pairwise ORs with 95% CrI (lower triangle) and pairwise probabilities of superiority (upper triangle)

Alpha₂ Agonist + Propofol	0.668	0.632	0.922	0.887	0.913	0.931	0.931	0.974	0.892
0.90 (0.55-1.48)	Alpha₂ Agonist	0.533	0.890	0.898	0.890	0.958	0.944	0.978	0.933
0.88 (0.40-1.95)	0.98 (0.53-1.81)	Melatonin / MRA	0.720	0.839	0.800	0.836	0.849	0.870	0.847
0.72 (0.45-1.15)	0.80 (0.55-1.16)	0.82 (0.40-1.67)	Propofol	0.620	0.687	0.712	0.743	0.816	0.573
0.66 (0.33-1.34)	0.73 (0.44-1.21)	0.75 (0.41-1.37)	0.91 (0.49-1.71)	Antipsychotic	0.568	0.583	0.632	0.640	0.391
0.62 (0.30-1.26)	0.69 (0.36-1.28)	0.70 (0.29-1.68)	0.86 (0.44-1.67)	0.94 (0.41-2.09)	Opioid + Benzodiazepine	0.504	0.556	0.576	0.374
0.62 (0.30-1.18)	0.68 (0.42-1.06)	0.70 (0.32-1.47)	0.85 (0.46-1.51)	0.93 (0.46-1.79)	1.00 (0.44-2.14)	Protocolized	0.596	0.556	0.342
0.59 (0.26-1.21)	0.65 (0.35-1.11)	0.66 (0.28-1.47)	0.81 (0.40-1.55)	0.89 (0.40-1.82)	0.94 (0.39-2.15)	0.95 (0.59-1.49)	Interruption	0.485	0.301
0.59 (0.35-1.00)	0.66 (0.44-0.98)	0.67 (0.32-1.40)	0.82 (0.51-1.30)	0.90 (0.47-1.70)	0.96 (0.59-1.55)	0.96 (0.53-1.82)	1.01 (0.52-2.11)	Benzodiazepine	0.273
0.69 (0.37-1.28)	0.77 (0.53-1.10)	0.78 (0.48-1.29)	0.96 (0.57-1.60)	1.05 (0.74-1.48)	1.12 (0.54-2.31)	1.12 (0.64-2.07)	1.18 (0.62-2.40)	1.17 (0.68-2.02)	Placebo

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

NOTE: For pairwise probabilities of each comparison (i.e., a treatment is better than another), the lower/right-most treatment is the reference treatment, and 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.

eTable 7: Mean SUCRA value and mean rank for each treatment based on duration of mechanical ventilation

Interventions	Mean SUCRA	Mean Rank (95% CrI*)
Alpha ₂ Agonist + Propofol	0.861	2.25 (1 to 7)
Alpha ₂ Agonist	0.818	2.64 (1 to 5)
Melatonin / MRA	0.733	3.40 (1 to 9)
Propofol	0.513	5.38 (2 to 10)
Placebo	0.453	5.93 (2 to 9)
Antipsychotic	0.397	6.43 (2 to 10)
Opioid + Benzodiazepine	0.350	6.85 (1 to 10)
Protocolized sedation	0.330	7.03 (2 to 10)
Sedation interruption	0.282	7.46 (2 to 10)
Benzodiazepine	0.264	7.62 (3 to 10)

Abbreviations: CrI = 95% credible intervals; MRA = melatonin receptor agonist

* Mean rank with 2.5% and 97.5% quantiles in the parentheses

eTable 8 Bayesian NMA-Summary of Findings – Duration of Mechanical Ventilation

Patient or population: critically ill adults Interventions: any interventions and strategies for sedation titration (e.g., protocolized, interruption) Comparator (reference): placebo Outcome: duration of mechanical ventilation (MV) Setting(s): mixed intensive care unit setting						
Total studies: 23 Total Participants: 5203	Relative effect * (95% CrI)	Assumed risk (duration of mechanical ventilation) for placebo	Corresponding risk (duration of MV) for intervention based on ratio of means (RoM) estimates	Number of participants (trials)	Ranking ** (95% CrI)	Certainty of the evidence
Alpha ₂ Agonist vs Placebo	RoM 0.77 (0.53 to 1.10) NMA estimate	Mean duration of MV ranged 0.29 to 6.67 days (based on 4 trials)	2.30 days of mechanical ventilation (95% CrI 1.60 to 3.30) corresponding to 3 days in the placebo group	Direct evidence: 702 (4 trials)	2.64 (1 to 5)	⊕⊕○○ Low Due to Inconsistency ² and Imprecision ³
Antipsychotic vs Placebo	RoM 1.05 (0.74 to 1.48) NMA estimate	Mean duration of MV ranged 0.31 to 5.33 days (based on 4 trials)	3.14 days of mechanical ventilation (95% CrI 2.22 to 4.43) corresponding to 3 days in the placebo group	Direct evidence: 2349 (4 trials)	6.43 (2 to 10)	⊕⊕⊕○ Moderate Due to Imprecision ³
Melatonin / MRA vs Placebo	RoM 0.78 (0.48 to 1.29) NMA estimate	Mean duration of MV ranged 0.27 to 4.17 days (based on 2 trials)	2.35 days of mechanical ventilation (95% CrI 1.43 to 3.86) corresponding to 3 days in the placebo group	Direct evidence: 263 (2 trials)	3.40 (1 to 9)	⊕⊕○○ Low Due to Inconsistency ² and Imprecision ³
Alpha ₂ Agonist + Propofol vs Placebo	RoM 0.69 (0.37 to 1.28) NMA estimate	Mean duration of MV ranged 0.27 to 6.67 days ¹	2.08 days of mechanical ventilation (95% CrI 1.12 to 3.83) corresponding to 3 days in the placebo group	No direct evidence. Indirect evidence only.	2.25 (1 to 7)	⊕○○○ Very Low Due to Imprecision ³ , Indirectness ⁴ , and Inconsistency ⁵
Sedation interruption vs Placebo	RoM 1.18 (0.62 to 2.40) NMA estimate	Mean duration of MV ranged 0.27 to 6.67 days ¹	3.55 days of mechanical ventilation (95% CrI 1.87 to 7.21) corresponding to 3 days in the placebo group	No direct evidence. Indirect evidence only.	7.46 (2 to 10)	⊕○○○ Very Low Due to Imprecision ³ , Indirectness ⁴ , and Inconsistency ⁵
Protocolized sedation vs Placebo	RoM 1.12 (0.64 to 2.07) NMA estimate	Mean duration of MV ranged 0.27 to 6.67 days ¹	3.36 days of mechanical ventilation (95% CrI 1.92 to 6.22) corresponding to 3 days in the placebo group	No direct evidence. Indirect evidence only.	7.03 (2 to 10)	⊕○○○ Very Low Due to Imprecision ³ , Indirectness ⁴ , and Inconsistency ⁶

Opioid+Benzodiazepine vs Placebo	RoM 1.12 (0.54 to 2.31) NMA estimate	Mean duration of MV ranged 0.27 to 6.67 days ¹	3.35 days of mechanical ventilation (95% CrI 1.63 to 6.94) corresponding to 3 days in the placebo group	No direct evidence. Indirect evidence only.	6.85 (1 to 10)	⊕○○○ Very Low Due to Imprecision ³ , Serious Indirectness ⁷ , and Inconsistency ⁸
Propofol vs Placebo	RoM 0.96 (0.57 to 1.60) NMA estimate	Mean duration of MV ranged 0.27 to 6.67 days ¹	2.87 days of mechanical ventilation (95% CrI 1.71 to 4.82) corresponding to 3 days in the placebo group	No direct evidence. Indirect evidence only.	5.38 (2 to 10)	⊕○○○ Very Low Due to Imprecision ³ , Indirectness ⁴ , and Inconsistency ⁵
Benzodiazepine vs Placebo	RoM 1.17 (0.68 to 2.02) NMA estimate	Mean duration of MV ranged 0.27 to 6.67 days ¹	3.50 days of mechanical ventilation (95% CrI 2.04 to 6.05) corresponding to 3 days in the placebo group	No direct evidence. Indirect evidence only.	7.62 (3 to 10)	⊕○○○ Very Low Due to Imprecision ³ , Indirectness ⁴ , and Inconsistency ⁵
Placebo	Reference Comparator	-	-	-	5.93 (2 to 9)	

NMA-SoF table definitions

* Network meta-analysis estimates are reported as ratio of means (RoM). CrI: credible interval (rather than confidence interval), since a Bayesian network meta-analysis has been conducted.

** Median and credible intervals are presented. Rank statistics is defined as the probabilities that a treatment out of *n* treatments in a network meta-analysis is the best, the second, the third and so on until the least effective treatment.

GRADE Working Group grades of evidence (or certainty in the evidence)

High quality: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanatory Footnotes

¹ Given that there were no head-to-head trials for these comparisons, we took the range for mean duration of mechanical ventilation in the placebo group among 10 randomized control trials. For example, Skrobik (2018) reported the median of 4 days (IQR 2 to 10) in the placebo group and the approximated mean was 5.33. The median of the reported or calculated mean length of ICU stay in the placebo group was 3.183 (rounded to 3).

² Inconsistency: due to heterogeneity in the direct comparison.

³ Imprecision: due to wide credible intervals in the OR estimate.

⁴ Indirectness: only indirect evidence available (through one degree of intermediary, alpha₂ agonist).

⁵ Inconsistency: due to heterogeneity in the direct comparison of alpha₂ agonist vs. placebo.

⁶ Inconsistency: due to heterogeneity in the direct comparison of alpha₂ agonist vs. placebo and the direct comparison of protocolized vs. alpha₂ agonist.

⁷ Serious indirectness: only indirect evidence available (through two degrees of intermediaries, alpha₂ agonist and benzodiazepine).

⁸ Inconsistency: due to heterogeneity in the direct comparison of alpha₂ agonist vs. placebo and the direct comparison of benzodiazepine vs. alpha₂ agonist.

eTable 9: Length of ICU stay - league table of pairwise OR with 95% CrI (lower triangle) and pairwise probabilities of superiority (upper triangle)

Opioid + Benzodiazepine	0.586	0.559	0.626	0.709	0.826	0.830	0.898	0.895
0.95 (0.62-1.47)	Alpha₂ Agonist	0.474	0.596	0.782	0.735	0.907	0.983	0.991
0.96 (0.58-1.61)	1.01 (0.76-1.33)	Sedation interruption	0.591	0.814	0.695	0.850	0.932	0.934
0.92 (0.53-1.58)	0.96 (0.69-1.34)	0.95 (0.62-1.47)	Propofol	0.589	0.596	0.770	0.866	0.863
0.88 (0.54-1.42)	0.92 (0.74-1.15)	0.91 (0.74-1.12)	0.96 (0.64-1.43)	Protocolized sedation	0.521	0.742	0.871	0.872
0.87 (0.64-1.18)	0.91 (0.67-1.24)	0.90 (0.60-1.36)	0.95 (0.60-1.49)	0.99 (0.68-1.45)	Benzodiazepine	0.698	0.817	0.810
0.78 (0.46-1.33)	0.81 (0.60-1.11)	0.81 (0.54-1.23)	0.85 (0.54-1.34)	0.89 (0.61-1.30)	0.89 (0.58-1.39)	Melatonin / MRA	0.673	0.660
0.73 (0.45-1.20)	0.76 (0.61-0.98)	0.76 (0.53-1.10)	0.80 (0.53-1.21)	0.83 (0.61-1.16)	0.84 (0.58-1.25)	0.94 (0.71-1.24)	Antipsychotic	0.426
0.74 (0.46-1.19)	0.78 (0.64-0.95)	0.77 (0.55-1.09)	0.81 (0.55-1.20)	0.84 (0.63-1.14)	0.85 (0.59-1.24)	0.95 (0.75-1.20)	1.01 (0.87-1.18)	Placebo

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

NOTE: A complete summary of estimates for efficacy from the random effects consistency model assuming vague priors is displayed. Treatments other than placebo are in the order of decreasing SUCRA value from upper left to lower right. 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, and 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.

eTable 10: Mean SUCRA value and mean rank for each treatment based on length of ICU stay

Interventions	Mean SUCRA	Mean Rank (95% CrI*)
Opioid + Benzodiazepine	0.741	3.07 (1 to 9)
Alpha ₂ Agonist	0.735	3.12 (1 to 6)
Sedation interruption	0.723	3.22 (1 to 8)
Propofol	0.609	4.13 (1 to 9)
Protocolized sedation	0.514	4.89 (2 to 9)
Benzodiazepine	0.494	5.05 (2 to 9)
Melatonin / MRA	0.317	6.46 (1 to 9)
Placebo	0.194	7.45 (4 to 9)
Antipsychotic	0.173	7.61 (4 to 9)

Abbreviations: CrI = 95% credible intervals; MRA = melatonin receptor agonist

* Mean rank with 2.5% and 97.5% quantiles in the parentheses

eTable 11 Bayesian NMA-Summary of Findings – Length of ICU Stay

Patient or population: critically ill adults Interventions: any interventions and strategies for sedation titration (e.g., protocolized, interruption) Comparator (reference): placebo Outcome: length of ICU stay Setting(s): mixed intensive care unit setting						
Total studies: 31 Total Participants: 10270	Relative effect * (95% CrI)	Assumed risk (length of ICU stay) for placebo	Corresponding risk (length of ICU stay) for intervention based on ratio of means (RoM) estimates	Number of participants (trials)	Ranking ** (95% CrI)	Certainty of the evidence
Alpha ₂ Agonist vs Placebo	RoM 0.78 (0.64 to 0.95) NMA estimate	Mean length of ICU stay ranged 0.90 to 10.33 days (based on 5 trials)	3.88 days of ICU stay (95% CrI 3.20 to 4.76) corresponding to 5 days in the placebo group	Direct evidence: 1091 (5 trials)	3.12 (1 to 6)	⊕⊕⊕○ Moderate Due to inconsistency ²
Antipsychotic vs Placebo	RoM 1.01 (0.87 to 1.18) NMA estimate	Mean length of ICU stay ranged 0.96 to 11.55 days (based on 8 trials)	5.07 days of ICU stay (95% CrI 4.36 to 5.88) corresponding to 5 days in the placebo group	Direct evidence: 2776 (8 trials)	7.61 (4 to 9)	⊕⊕○○ Low Due to Imprecision ³ and Inconsistency ²
Melatonin / MRA vs Placebo	RoM 0.95 (0.75 to 1.20) NMA estimate	Mean length of ICU stay ranged 3.83 to 9.80 days (based on 4 trials)	4.77 days of ICU stay (95% CrI 3.77 to 6.00) corresponding to 5 days in the placebo group	Direct evidence: 488 (4 trials)	6.46 (1 to 9)	⊕⊕○○ Low Due to Imprecision ³ and Inconsistency ²
Sedation interruption vs Placebo	RoM 0.77 (0.55 to 1.09) NMA estimate	Mean length of ICU stay ranged 0.90 to 10.33 days ¹	3.84 days of ICU stay (95% CrI 2.75 to 5.44) corresponding to 5 days in the placebo group	No direct evidence. Indirect evidence only.	3.22 (1 to 8)	⊕○○○ Very Low Due to Imprecision ³ , Indirectness ⁴ , and Inconsistency ⁵
Protocolized sedation vs Placebo	RoM 0.84 (0.63 to 1.14) NMA estimate	Mean length of ICU stay ranged 0.90 to 10.33 days ¹	4.22 days of ICU stay (95% CrI 3.15 to 5.72) corresponding to 5 days in the placebo group	No direct evidence. Indirect evidence only.	4.89 (2 to 9)	⊕○○○ Very Low Due to Imprecision ³ , Indirectness ⁴ , and Inconsistency ⁶
Opioid+Benzodiazepine vs Placebo	RoM 0.74 (0.46 to 1.19) NMA estimate	Mean length of ICU stay ranged 0.90 to 10.33 days ¹	3.70 days of ICU stay (95% CrI 2.32 to 5.97) corresponding to 5 days in the placebo group	No direct evidence. Indirect evidence only.	3.07 (1 to 9)	⊕○○○ Very Low Due to Imprecision ³ , Serious Indirectness ⁷ , and Inconsistency ⁸

Propofol vs Placebo	RoM 0.81 (0.55 to 1.20) NMA estimate	Mean length of ICU stay ranged 0.90 to 10.33 days ¹	4.04 days of ICU stay (95% CrI 2.76 to 5.98) corresponding to 5 days in the placebo group	No direct evidence. Indirect evidence only.	4.13 (1 to 9)	⊕○○○ Very Low Due to Imprecision ³ , Indirectness ⁴ , and Inconsistency ⁵
Benzodiazepine vs Placebo	RoM 0.85 (0.59 to 1.24) NMA estimate	Mean length of ICU stay ranged 0.90 to 10.33 days ¹	4.26 days of ICU stay (95% CrI 2.97 to 6.18) corresponding to 5 days in the placebo group	No direct evidence. Indirect evidence only.	5.05 (2 to 9)	⊕○○○ Very Low Due to Imprecision ³ , Indirectness ⁴ , and Inconsistency ⁵
Placebo	Reference Comparator	-	-	-	7.45 (4 to 9)	-

NMA-SoF table definitions

* Network meta-analysis estimates are reported as ratio of means (RoM). CrI: credible interval (rather than confidence interval), since a Bayesian network meta-analysis has been conducted.

** Median and credible intervals are presented. Rank statistics is defined as the probabilities that a treatment out of n treatments in a network meta-analysis is the best, the second, the third and so on until the least effective treatment.

GRADE Working Group grades of evidence (or certainty in the evidence)

High quality: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanatory Footnotes

¹ Given that there were no head-to-head trials for these comparisons, we took the range for mean length of ICU stay in the placebo group among 16 randomized control trials. For example, Skrobik (2018) reported the median of 9 days (IQR 3 to 19) in the placebo group and the approximated mean was 10.33. The median of the reported or calculated mean length of ICU stay in the placebo group was 5.167 (rounded to 5).

² Inconsistency: due to heterogeneity in the direct comparison.

³ Imprecision: due to wide credible intervals in the RoM estimate.

⁴ Indirectness: only indirect evidence available (through one degree of intermediary, alpha₂ agonist).

⁵ Inconsistency: due to heterogeneity in the direct comparison of alpha₂ agonist vs. placebo.

⁶ Inconsistency: due to heterogeneity in the direct comparison of alpha₂ agonist vs. placebo and the direct comparison of protocolized vs. alpha₂ agonist.

⁷ Serious indirectness: only indirect evidence available (through two degrees of intermediaries, alpha₂ agonist and benzodiazepine).

⁸ Inconsistency: due to heterogeneity in the direct comparison of alpha₂ agonist vs. placebo and the direct comparison of benzodiazepine vs. alpha₂ agonist.

eTable 12: Length of hospital stay - league table of pairwise OR with 95% CrI (lower triangle) and pairwise probabilities of superiority (upper triangle)

Opioid	0.689	0.922	0.916	0.893	0.941	0.979	0.995	0.995
0.89 (0.57-1.43)	Opioid (short acting)	0.803	0.866	0.836	0.877	0.971	0.994	0.995
0.73 (0.47-1.14)	0.82 (0.50-1.32)	Sedation interruption	0.553	0.596	0.674	0.907	0.975	0.978
0.71 (0.44-1.17)	0.80 (0.52-1.20)	0.98 (0.67-1.41)	Alpha₂ Agonist	0.586	0.607	0.946	0.998	0.999
0.69 (0.37-1.26)	0.77 (0.44-1.32)	0.94 (0.56-1.57)	0.96 (0.67-1.37)	Propofol	0.498	0.869	0.961	0.963
0.69 (0.43-1.11)	0.77 (0.48-1.22)	0.94 (0.72-1.24)	0.96 (0.73-1.28)	1.00 (0.64-1.59)	Protocolized sedation	0.893	0.978	0.982
0.50 (0.26-0.97)	0.56 (0.31-1.02)	0.69 (0.39-1.22)	0.71 (0.46-1.09)	0.73 (0.42-1.29)	0.73 (0.44-1.22)	Melatonin / MRA	0.688	0.680
0.46 (0.26-0.81)	0.51 (0.31-0.84)	0.63 (0.39-1.00)	0.64 (0.49-0.85)	0.67 (0.43-1.05)	0.67 (0.45-0.99)	0.91 (0.61-1.36)	Antipsychotic	0.437
0.47 (0.27-0.80)	0.52 (0.32-0.83)	0.64 (0.41-0.99)	0.65 (0.52-0.83)	0.68 (0.44-1.04)	0.68 (0.47-0.97)	0.92 (0.64-1.32)	1.01 (0.85-1.21)	Placebo

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

NOTE: A complete summary of estimates for efficacy from the random effects consistency model assuming vague priors is displayed. Treatments other than placebo are in the order of decreasing SUCRA value from upper left to lower right. For pairwise probabilities of each comparison (i.e., a treatment is better than another), the lower/right-most treatment is the reference treatment, and thus values <1 favor the upper/left-most intervention. Statistically significant differences based on pairwise RoM estimates are shown in bold font.

eTable 13: Mean SUCRA value and mean rank for each treatment based on length of hospital stay

Interventions	Mean SUCRA	Mean Rank (95% CrI*)
Opioid	0.916	1.67 (1 to 5)
Opioid (short acting)	0.832	2.35 (1 to 6)
Sedation interruption	0.620	4.04 (1 to 7)
Alpha ₂ Agonist	0.600	4.20 (2 to 6)
Propofol	0.547	4.62 (1 to 8)
Protocolized sedation	0.532	4.74 (2 to 7)
Melatonin / MRA	0.225	7.20 (3 to 9)
Placebo	0.121	8.03 (7 to 9)
Antipsychotic	0.106	8.15 (6 to 9)

Abbreviations: CrI = 95% credible intervals; MRA = melatonin receptor agonists

* Mean rank with 2.5% and 97.5% quantiles in the parentheses

eTable 14 Bayesian NMA-Summary of Findings – Length of Hospital Stay

Patient or population: critically ill adults Interventions: any interventions and strategies for sedation titration (e.g., protocolized, interruption) Comparator (reference): placebo Outcome: length of hospital stay Setting(s): mixed intensive care unit setting						
Total studies: 22 Total Participants: 9471	Relative effect * (95% CrI)	Assumed risk (length of hospital stay) for placebo	Corresponding risk (length of hospital stay) for intervention based on ratio of means (RoM) estimates	Number of participants (trials)	Ranking ** (95% CrI)	Certainty of the evidence
Alpha ₂ Agonist vs Placebo	RoM 0.65 (0.52 to 0.83) NMA estimate	Mean length of hospital stay ranged 11 to 35.33 days (based on 4 trials)	7.81 days of hospital stay (95% CrI 6.21 to 9.91) corresponding to 12 days in the placebo group	Direct evidence: 1061 (4 trials)	4.20 (2 to 6)	⊕⊕⊕○ Moderate Due to nconsistency ²
Antipsychotic vs Placebo	RoM 1.01 (0.85 to 1.21) NMA estimate	Mean length of hospital stay ranged 6.33 to 16.67 days (based on 6 trials)	12.17 days of hospital stay (95% CrI 10.15 to 14.57) corresponding to 12 days in the placebo group	Direct evidence: 1961 (6 trials)	8.15 (6 to 9)	⊕⊕○○ Low Due to Imprecision ³ and Inconsistency ²
Melatonin / MRA vs Placebo	RoM 0.92 (0.64 to 1.32) NMA estimate	Mean length of hospital stay ranged 12.33 to 18.6 days (based on 2 trials)	11.06 days of hospital stay (95% CrI 7.73 to 15.82) corresponding to 12 days in the placebo group	Direct evidence: 340 (2 trials)	7.20 (3 to 9)	⊕⊕⊕○ Moderate Due to Imprecision ³
Sedation interruption vs Placebo	RoM 0.64 (0.41 to 0.99) NMA estimate	Mean length of hospital stay ranged 6.33 to 35.33 days ¹	7.63 days of hospital stay (95% CrI 4.91 to 11.85) corresponding to 12 days in the placebo group	No direct evidence. Indirect evidence only.	4.04 (1 to 7)	⊕○○○ Very Low Due to Serious Indirectness ⁴ , and Inconsistency ⁵
Protocolized sedation vs Placebo	RoM 0.68 (0.47 to 0.97) NMA estimate	Mean length of hospital stay ranged 6.33 to 35.33 days ¹	8.10 days of hospital stay (95% CrI 5.63 to 11.67) corresponding to 12 days in the placebo group	No direct evidence. Indirect evidence only.	4.74 (2 to 7)	⊕⊕○○ Low Due to Indirectness ⁶ , and Inconsistency ⁵
Propofol vs Placebo	RoM 0.68 (0.44 to 1.04) NMA estimate	Mean length of hospital stay ranged 6.33 to 35.33 days ¹	8.11 days of hospital stay (95% CrI 5.32 to 12.52) corresponding to 12 days in the placebo group	No direct evidence. Indirect evidence only.	4.62 (1 to 8)	⊕○○○ Very Low Due to Imprecision ³ , Indirectness ⁶ , and Inconsistency ⁵

Opioid vs Placebo	RoM 0.47 (0.27 to 0.80) NMA estimate	Mean length of hospital stay ranged 6.33 to 35.33 days ¹	5.59 days of hospital stay (95% CrI 3.24 to 9.63) corresponding to 12 days in the placebo group	No direct evidence. Indirect evidence only.	1.67 (1 to 5)	⊕○○○ Very Low Due to Serious Indirectness ⁴ and Inconsistency ⁵
Opioid (short acting) vs Placebo	RoM 0.52 (0.32 to 0.83) NMA estimate	Mean length of hospital stay ranged 6.33 to 35.33 days ¹	6.25 days of hospital stay (95% CrI 3.84 to 10.02) corresponding to 12 days in the placebo group	No direct evidence. Indirect evidence only.	2.35 (1 to 6)	⊕⊕○○ Low Due to Indirectness ⁶ , and Inconsistency ⁵
Placebo	Reference Comparator	-	-	-	8.03 (7 to 9)	-

NMA-SoF table definitions

* Network meta-analysis estimates are reported as ratio of means (RoM). CrI: credible interval (rather than confidence interval), since a Bayesian network meta-analysis has been conducted.

** Median and credible intervals are presented. Rank statistics is defined as the probabilities that a treatment out of *n* treatments in a network meta-analysis is the best, the second, the third and so on until the least effective treatment.

GRADE Working Group grades of evidence (or certainty in the evidence)

High quality: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanatory Footnotes

¹ Given that there were no head-to-head trials for these comparisons, we took the range for mean length of hospital stay in the placebo group among 12 randomized control trials. For example, Skrobik (2018) reported the median of 29 days (IQR 17 to 41) in the placebo group and the approximated mean was 29. The median of the reported or calculated mean length of hospital stay in the placebo group was 12.333 (rounded to 12).

² Inconsistency: due to heterogeneity in the direct comparison.

³ Imprecision: due to wide credible intervals in the RoM estimate.

⁴ Serious indirectness: only indirect evidence available (through two degrees of intermediary nodes).

⁵ Inconsistency: due to heterogeneity in the direct comparison of alpha₂ agonist vs. placebo.

⁶ indirectness: only indirect evidence available (through one degree of intermediary, alpha₂ agonist).

eTable 15: Mortality - league table of pairwise OR with 95% CrI (lower triangle) and pairwise probabilities of superiority (upper triangle)

Sedation interruption	0.734	0.542	0.832	0.685	0.848	0.827	0.901	0.899
0.89 (0.60-1.45)	Alpha₂ Agonist	0.489	0.534	0.592	0.810	0.792	0.891	0.887
0.92 (0.24-3.73)	1.02 (0.30-3.80)	Opioid + Benzodiazepine	0.517	0.537	0.654	0.677	0.946	0.683
0.88 (0.70-1.19)	0.99 (0.69-1.40)	0.97 (0.25-3.54)	Protocolized sedation	0.553	0.776	0.764	0.867	0.836
0.85 (0.44-1.74)	0.95 (0.56-1.60)	0.93 (0.22-3.44)	0.96 (0.51-1.80)	Propofol	0.726	0.731	0.839	0.780
0.68 (0.34-1.53)	0.77 (0.41-1.45)	0.75 (0.19-3.06)	0.78 (0.39-1.61)	0.80 (0.37-1.83)	Antipsychotic	0.595	0.719	0.639
0.63 (0.24-1.64)	0.70 (0.28-1.67)	0.69 (0.15-3.00)	0.71 (0.28-1.77)	0.73 (0.27-1.97)	0.92 (0.41-1.94)	Melatonin / MRA	0.667	0.466
0.49 (0.16-1.40)	0.55 (0.19-1.41)	0.52 (0.23-1.19)	0.56 (0.19-1.52)	0.56 (0.18-1.73)	0.71 (0.20-2.20)	0.78 (0.20-2.66)	Benzodiazepine	0.305
0.65 (0.34-1.30)	0.72 (0.42-1.24)	0.70 (0.18-2.68)	0.73 (0.39-1.38)	0.76 (0.37-1.61)	0.95 (0.65-1.32)	1.03 (0.52-2.11)	1.33 (0.44-4.47)	Placebo

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

NOTE: Treatments other than placebo are in order (upper left to lower right) of decreasing SUCRA value. For pairwise probabilities of 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. We prioritized selection of mortality data as follows: 90-day, hospital, 28/30-day, and ICU mortality, if a trial reported multiple mortality outcomes. In this NMA, 95% CrI are wide and no significant differences between regimens are identified.

eTable 16: Mean SUCRA value and mean rank for each treatment based on mortality

Interventions	Mean SUCRA	Mean Rank (95% CrI*)
Sedation interruption	0.783	2.73 (1 to 7)
Alpha ₂ Agonist	0.658	3.74 (1 to 7)
Opioid + Benzodiazepine	0.623	4.02 (1 to 9)
Protocolized sedation	0.614	4.09 (2 to 8)
Propofol	0.589	4.29 (1 to 9)
Antipsychotic	0.392	5.86 (1 to 9)
Melatonin / MRA	0.343	6.25 (1 to 9)
Placebo	0.313	6.49 (2 to 9)
Benzodiazepine	0.184	7.52 (2 to 9)

NOTE: Order of mortality outcomes to use in priority: 90-day, hospital, 28/30-day, and ICU mortality, if multiple were reported.

Abbreviations: CrI = credible interval; MRA = melatonin receptor agonist

* Mean rank with 2.5% and 97.5% quantiles in the parentheses

eTable 17 Bayesian NMA-Summary of Findings – Mortality

Patient or population: critically ill adults Interventions: any interventions and strategies for sedation titration (e.g., protocolized, interruption) Comparator (reference): placebo Outcome: Mortality; we prioritized selection of mortality data as follows: 90-day, hospital, 28/30-day, and ICU mortality, if a trial reported multiple mortality outcomes. Setting(s): mixed intensive care unit setting							
Total studies: 26 Total Participants: 11385	Relative effect * (95% CrI)	Anticipated absolute effect (95% CrI)			Number of participants (trials)	Ranking *** (95% CrI)	Certainty of the evidence
		Placebo	Intervention	Risk Difference **			
Alpha ₂ Agonist vs Placebo	OR 0.72 (0.42 to 1.24) NMA estimate	87 per 1000 (46 / 531 based on 4 trials)	66 per 1000 (35 / 530 based on 4 trials)	22 fewer per 1000 (from 48 fewer to 19 more)	Direct evidence: 1061 (4 trials)	3.74 (1 to 7)	⊕⊕⊕○ Moderate Due to Imprecision ²
Antipsychotics vs Placebo	OR 0.95 (0.65 to 1.32) NMA estimate	133 per 1000 (147 / 1103 based on 6 trials)	142 per 1000 (208 / 1469 based on 6 trials)	6 fewer per 1000 (from 42 fewer to 36 more)	Direct evidence: 2572 (6 trials)	5.86 (1 to 9)	⊕⊕⊕○ Moderate Due to Imprecision ²
Melatonin / MRA vs Placebo	OR 1.03 (0.52 to 2.11) NMA estimate	98 per 1000 (21 / 214 based on 3 trials)	98 per 1000 (21 / 214 based on 3 trials)	2 more per 1000 (from 44 fewer to 89 more)	Direct evidence: 428 (3 trials)	6.25 (1 to 9)	⊕⊕⊕○ Moderate Due to Imprecision ²
Sedation interruption vs Placebo	OR 0.65 (0.34 to 1.30) NMA estimate	187 per 1000 ¹	No head-to-head comparison with placebo	58 fewer per 1000 (from 115 fewer to 44 more)	No direct evidence. Indirect evidence only.	2.73 (1 to 7)	⊕○○○ Very Low Due to Imprecision ² , and Serious Indirectness ³
Protocolized sedation vs Placebo	OR 0.73 (0.39 to 1.38) NMA estimate	187 per 1000 ¹	No head-to-head comparison with placebo	43 fewer per 1000 (from 105 fewer to 54 more)	No direct evidence. Indirect evidence only.	4.09 (2 to 8)	⊕⊕○○ Low Due to Imprecision ² , and Indirectness ⁴
Opioid+Benzodiazepine vs Placebo	OR 0.70 (0.18 to 2.68) NMA estimate	187 per 1000 ¹	No head-to-head comparison with placebo	49 fewer per 1000 (from 147 fewer to 195 more)	No direct evidence. Indirect evidence only.	4.02 (1 to 9)	⊕○○○ Very Low Due to Imprecision ² , Serious Indirectness ⁵

Propofol vs Placebo	OR 0.76 (0.37 to 1.61) NMA estimate	187 per 1000 ¹	No head-to-head comparison with placebo	39 fewer per 1000 (from 109 fewer to 83 more)	No direct evidence. Indirect evidence only.	4.29 (1 to 9)	⊕⊕○○ Low Due to Imprecision ² , and Indirectness ⁴
Benzodiazepine vs Placebo	OR 1.33 (0.44 to 4.47) NMA estimate	187 per 1000 ¹	No head-to-head comparison with placebo	48 more per 1000 (from 95 fewer to 320 more)	No direct evidence. Indirect evidence only.	7.52 (2 to 9)	⊕⊕○○ Low Due to Imprecision ² , and Indirectness ⁴
Placebo	Reference Comparator	-	-	-	-	6.49 (2 to 9)	-

Abbreviations: CrI = credible interval; OR = odds ratio

NMA-SoF table definitions

* Network meta-analysis estimates are reported as odds ratio. CrI: credible interval (rather than confidence interval), since a Bayesian network meta-analysis has been conducted.

** Anticipated absolute effect: risk difference is calculated based on the control group risk and the estimated odds ratio.

*** Median and credible intervals are presented. Rank statistics is defined as the probabilities that a treatment out of n treatments in a network meta-analysis is the best, the second, the third and so on until the least effective treatment.

GRADE Working Group grades of evidence (or certainty in the evidence)

High quality: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanatory Footnotes

¹ Given that there were no head-to-head trials for these comparisons, the control group rate is based on the placebo arm of a large, randomized control trial (Boogaard et al 2018, antipsychotic vs placebo).

² Imprecision: due to wide credible intervals in the OR estimate.

³ Serious indirectness: only indirect evidence available (through two degrees of intermediaries, alpha₂ agonist and protocolized).

⁴ Indirectness: only indirect evidence available (through one degree of intermediary, alpha₂ agonist).

⁵ Serious indirectness: only indirect evidence available (through two degrees of intermediaries, alpha₂ agonist and benzodiazepine).

eTable 18 Side Effect-Arrhythmia - league table of pairwise OR with 95% CrI (lower triangle) and pairwise probabilities of superiority (upper triangle)

Protocolized	0.709	0.903	0.707
0.48 (0.02-11.59)	Antipsychotic	0.705	0.456
0.28 (0.03-2.41)	0.59 (0.06-5.45)	Alpha₂ Agonist	0.213
0.52 (0.03-9.35)	1.09 (0.18-6.93)	1.86 (0.33-12.29)	Placebo

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

NOTE: Treatments other than placebo are in order (upper left to lower right) of decreasing SUCRA value. For pairwise probabilities of 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. In this NMA, 95% CrI are wide and no significant differences between regimens are identified.

Table 19: Mean SUCRA value and mean rank for each treatment based on arrhythmia

Interventions	Mean SUCRA	Mean Rank (95% CrI*)
Protocolized sedation	0.773	1.68 (1 to 4)
Placebo	0.541	2.38 (1 to 4)
Antipsychotic	0.484	2.55 (1 to 4)
Alpha ₂ Agonist	0.202	3.39 (2 to 4)

Abbreviations: CrI = credible intervals

* Mean rank with 2.5% and 97.5% quantiles in the parentheses

eTable 20 Bayesian NMA-Summary of Findings – Arrhythmia

Patient or population: critically ill adults
Interventions: any interventions and strategies for sedation titration (e.g., protocolized, interruption)
Comparator (reference): placebo
Outcome: Arrhythmia
Setting(s): mixed intensive care unit setting

Total studies: 7 Total Participants: 5791	Relative effect * (95% CrI)	Anticipated absolute effect (95% CrI)			Number of participants (trials)	Ranking *** (95% CrI)	Certainty of the evidence
		Placebo	Intervention	Risk Difference **			
Alpha ₂ Agonist vs Placebo	OR 1.86 (0.33 to 12.29) NMA estimate	64 per 1000 (31 / 481 based on 3 trials)	65 per 1000 (31 / 480 based on 4 trials)	49 more per 1000 (from 42 fewer to 394 more)	Direct evidence: 961 (3 trials)	3.39 (2 to 4)	⊕⊕⊕○ Moderate Due to Imprecision ²
Antipsychotics vs Placebo	OR 1.09 (0.18 to 6.93) NMA estimate	44 per 1000 (14 / 321 based on 3 trials)	53 per 1000 (17 / 322 based on 3 trials)	4 more per 1000 (from 35 fewer to 197 more)	Direct evidence: 643 (3 trials)	2.55 (1 to 4)	⊕⊕⊕○ Moderate Due to Imprecision ²
Protocolized sedation vs Placebo	OR 0.52 (0.03 to 9.35) NMA estimate	74 per 1000 ¹	No head-to-head comparison with placebo	34 fewer per 1000 (from 72 fewer to 354 more)	No direct evidence. Indirect evidence only.	1.68 (1 to 4)	⊕⊕○○ Low Due to Imprecision ² , and Indirectness ³
Placebo	Reference Comparator	-	-	-	-	2.38 (1 to 4)	-

Abbreviations: CrI = credible interval; OR = odds ratio

NMA-SoF table definitions

* Network meta-analysis estimates are reported as odds ratio. CrI: credible interval (rather than confidence interval), since a Bayesian network meta-analysis has been conducted.

** Anticipated absolute effect: risk difference is calculated based on the control group risk and the estimated odds ratio.

*** Median and credible intervals are presented. Rank statistics is defined as the probabilities that a treatment out of *n* treatments in a network meta-analysis is the best, the second, the third and so on until the least effective treatment.

GRADE Working Group grades of evidence (or certainty in the evidence)

High quality: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanatory Footnotes

¹ Given that there were no head-to-head trials for this comparison, the control group rate is based on the placebo arm of a large, randomized control trial (Su et al 2016, alpha2 agonist vs placebo).

² Imprecision: due to wide credible intervals in the OR estimate.

³ Indirectness: only indirect evidence available (through one degree of intermediary, alpha₂ agonist).

Table 1. Summary of randomized trials and interventions included in the network meta-analysis

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	+		+		+		Low
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
DeJonghe 2018 [49]	1174	IV sedation protocol	Usual sedation	+				+		High
Devlin 2014 [50]	33	Dexmedetomidine IV infusion	Placebo IV infusion	+	+	+		+		Low
Djaiani 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 Intervention 2: propofol IV infusion	Midazolam IV infusion		+					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
Liu 2017 [73]	105	Intervention 1: Remifentanyl 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]		Apipiprazole 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	+	+	+				Mode rate
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
Spies 2011 [105]	60	Remifentanyl IV infusion	Fentanyl IV infusion	+			+			Low
Strom 2010 [106]	113	No sedation; analgesia with opioid	Analgesia with opioid + propofol IV infusion	+			+			High
Su 2016 [107]	700	Dexmedetomidine IV infusion	Placebo IV infusion	+	+	+	+	+	+	Low
Wan 2011 [112]	200	Dexmedetomidine IV infusion	Midazolam IV infusion	+	+					High
Wang 2012 [113]	457	Haloperidol IV infusion	Placebo IV infusion	+	+	+	+	+	+	Low

Legend for Table 1. See supplementary eTable 2 and 3 for detailed description of included studies and risk of bias assessment

* The overall risk of bias was the lowest for any domain in the risk of bias tool (i.e., sequence generation, allocation concealment, incomplete outcome data, selective reporting, or other bias).

Abbreviations: IV = intravenous; LD = loading dose; PO = per os

Table 2. Delirium Occurrence League table of pairwise ORs with 95% CrI (lower triangle) and pairwise probabilities of superiority (upper triangle)

Alpha₂ Agonist	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)	Sedation interruption	0.810	0.627	0.755	0.706	0.934	0.938	0.962	0.994	0.947
0.80 (0.41 - 1.50)	0.78 (0.43 - 1.39)	Protocolized sedation	0.502	0.612	0.599	0.891	0.876	0.929	0.990	0.906
0.80 (0.20 - 3.04)	0.78 (0.15 - 3.79)	1.00 (0.22 - 4.46)	Opioid + Benzodiazepine	0.573	0.578	0.809	0.799	0.861	0.992	0.791
0.69 (0.29 - 1.59)	0.67 (0.21 - 3.27)	0.86 (0.30 - 2.51)	0.86 (0.18 - 4.42)	Antipsychotic	0.528	0.820	0.798	0.874	0.972	0.965
0.66 (0.14 - 2.68)	0.64 (0.11 - 3.27)	0.82 (0.16 - 3.85)	0.83 (0.11 - 5.92)	0.95 (0.22 - 3.64)	Melatonin / MRA	0.733	0.734	0.802	0.901	0.741
0.38 (0.13 - 1.05)	0.37 (0.09 - 1.38)	0.47 (0.13 - 1.61)	0.47 (0.08 - 2.68)	0.54 (0.14 - 2.08)	0.57 (0.10 - 3.62)	Propofol	0.542	0.636	0.794	0.411
0.34 (0.07 - 1.49)	0.33 (0.08 - 1.37)	0.43 (0.10 - 1.86)	0.43 (0.06 - 3.25)	0.50 (0.09 - 2.72)	0.52 (0.07 - 4.38)	0.91 (0.15 - 5.67)	Opioid	0.613	0.706	0.387
0.28 (0.07 - 1.06)	0.27 (0.06 - 1.16)	0.35 (0.08 - 1.45)	0.35 (0.05 - 2.42)	0.41 (0.08 - 1.99)	0.43 (0.06 - 3.33)	0.74 (0.13 - 4.20)	0.82 (0.20 - 3.41)	Opioid (short acting)	0.630	0.283
0.21 (0.08 - 0.51)	0.21 (0.06 - 0.69)	0.27 (0.09 - 0.80)	0.27 (0.10 - 0.76)	0.31 (0.09 - 1.04)	0.32 (0.06 - 1.89)	0.57 (0.14 - 2.29)	0.62 (0.11 - 3.55)	0.76 (0.15 - 3.85)	Benzodia zepine	0.105
0.43 (0.21 - 0.85)	0.42 (0.14 - 1.22)	0.54 (0.22 - 1.40)	0.54 (0.12 - 2.54)	0.63 (0.36 - 1.04)	0.66 (0.19 - 2.50)	1.15 (0.32 - 4.13)	1.26 (0.24 - 6.56)	1.54 (0.34 - 7.07)	2.02 (0.65 - 6.40)	Placebo

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.

NOTE: Treatments other than placebo are ranked in order (upper left to 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.

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, interruption)
Comparator (reference): placebo
Outcome: delirium occurrence
Setting(s): mixed intensive care unit settings

Total studies: 38 Total Participants: 11993	Relative effect * (95% CrI)	Anticipated absolute effect (95% CrI)			Certainty of the evidence	Number of participants (trials)	Ranking *** (95% CrI)
		Placebo	Intervention	Risk Difference **			
Alpha ₂ Agonist vs Placebo	OR 0.43 (0.21 to 0.85) NMA estimate	278 per 1000 (147 / 528 based on 5 trials)	163 per 1000 (86 / 527 based on 5 trials)	136 fewer per 1000 (from 204 fewer to 30 fewer)	⊕⊕⊕○ Moderate Due to Inconsistency ²	Direct evidence: 1065 (5 trials)	2.73 (1 to 5)
Antipsychotics vs Placebo	OR 0.63 (0.36 to 1.04) NMA estimate	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 ³ , and Inconsistency ²	Direct evidence: 2776 (8 trials)	4.80 (1 to 9)
Melatonin / MRA vs Placebo	OR 0.66 (0.19 to 2.50) NMA estimate	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 ³ and Inconsistency ²	Direct evidence: 225 (2 trials)	5.22 (1 to 11)
Sedation interruption vs Placebo	OR 0.42 (0.14 to 1.22) NMA estimate	330 per 1000 ¹	No head-to-head comparison with placebo	157 fewer per 1000 (from 265 fewer to 46 more)	⊕○○○ Very Low Due to Imprecision ³ , Indirectness ⁴ , and Inconsistency ⁵	No direct evidence. Indirect evidence only.	2.81 (1 to 7)
Protocolized sedation vs Placebo	OR 0.54 (0.21 to 1.40) NMA estimate	330 per 1000 ¹	No head-to-head comparison with placebo	119 fewer per 1000 (from 238 fewer to 77 more)	⊕○○○ Very Low Due to Imprecision ³ , Indirectness ⁴ , and Inconsistency ⁶	No direct evidence. Indirect evidence only.	4.27 (1 to 8)
Opioid+Benzodiazepine vs Placebo	OR 0.54 (0.12 to 2.54) NMA estimate	330 per 1000 ¹	No head-to-head comparison with placebo	119 fewer per 1000 (from 275 fewer to 225 more)	⊕○○○ Very Low Due to Imprecision ³ , Serious Indirectness ⁷ , and Inconsistency ⁸	No direct evidence. Indirect evidence only.	4.36 (1 to 10)

Propofol vs Placebo	OR 1.15 (0.32 to 4.13) NMA estimate	330 per 1000 ¹	No head-to-head comparison with placebo	31 more per 1000 (from 192 fewer to 341 more)	⊕○○○ Very Low Due to Imprecision ³ , Indirectness ⁴ , and Inconsistency ⁵	No direct evidence. Indirect evidence only.	7.77 (2 to 11)
Opioid vs Placebo	OR 1.26 (0.24 to 6.56) NMA estimate	330 per 1000 ¹	No head-to-head comparison with placebo	53 more per 1000 (from 222 fewer to 434 more)	⊕○○○ Very Low Due to Imprecision ³ , Serious Indirectness ⁹ , and Inconsistency ⁶	No direct evidence. Indirect evidence only.	7.91 (2 to 11)
Opioid (short acting) vs Placebo	OR 1.54 (0.34 to 7.07) NMA estimate	330 per 1000 ¹	No head-to-head comparison with placebo	102 more per 1000 (from 188 fewer to 447 more)	⊕○○○ Very Low Due to Imprecision ³ , Indirectness ⁴ , and Inconsistency ⁵	No direct evidence. Indirect evidence only.	8.73 (3 to 11)
Benzodiazepine vs Placebo	OR 2.02 (0.65 to 6.40) NMA estimate	330 per 1000 ¹	No head-to-head comparison with placebo	169 more per 1000 (from 86 fewer to 429 more)	⊕○○○ Very Low Due to Imprecision ³ , Indirectness ⁴ , and Inconsistency ⁵	No direct evidence. Indirect evidence only.	9.87 (6 to 11)
Placebo	Reference Comparator	-	-	-		-	7.53 (4 to 10)
<p>Abbreviations: CrI = credible interval; OR = odds ratio</p> <p>NMA-SoF table definitions</p> <p>* Network meta-analysis estimates are reported as odds ratio. CrI: credible interval (rather than confidence interval), since a Bayesian network meta-analysis has been conducted.</p> <p>** Anticipated absolute effect: risk difference is calculated based on the control group risk and the estimated odds ratio.</p> <p>*** Median and credible intervals are presented. Rank statistics is defined as the probabilities that a treatment out of <i>n</i> treatments in a network meta-analysis is the best, the second, the third and so on until the least effective treatment.</p>							
<p>GRADE Working Group grades of evidence (or certainty in the evidence)</p> <p>High quality: We are very confident that the true effect lies close to that of the estimate of the effect</p> <p>Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different</p> <p>Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect</p> <p>Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect</p>							

Explanatory Footnotes

¹ Given that there were no head-to-head trials for these comparisons, the control group rate is based on the placebo arm of a large, randomized control trial (Boogaard et al 2018, antipsychotic vs placebo).

² Inconsistency: due to heterogeneity in the direct comparison.

³ Imprecision: due to wide credible intervals in the OR estimate.

⁴ Indirectness: only indirect evidence available (through one degree of intermediary, alpha₂ agonist).

⁵ Inconsistency: due to heterogeneity in the direct comparison of alpha₂ agonist vs. placebo.

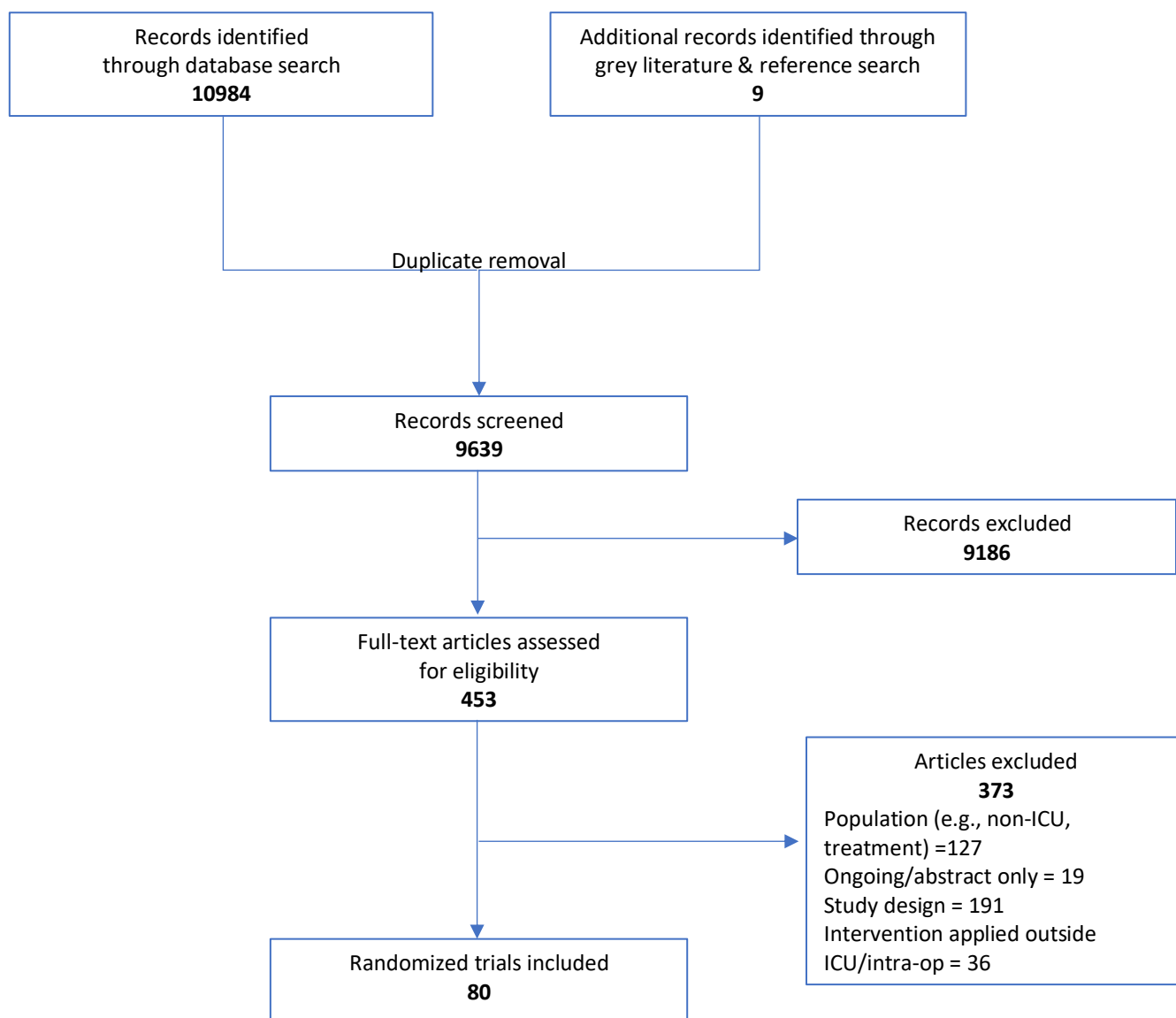
⁶ Inconsistency: due to heterogeneity in the direct comparison of alpha₂ agonist vs. placebo and the direct comparison of protocolized vs. alpha₂ agonist.

⁷ Serious indirectness: only indirect evidence available (through two degrees of intermediaries, alpha₂ agonist and benzodiazepine).

⁸ Inconsistency: due to heterogeneity in the direct comparison of alpha₂ agonist vs. placebo and the direct comparison of benzodiazepine vs. alpha₂ agonist.

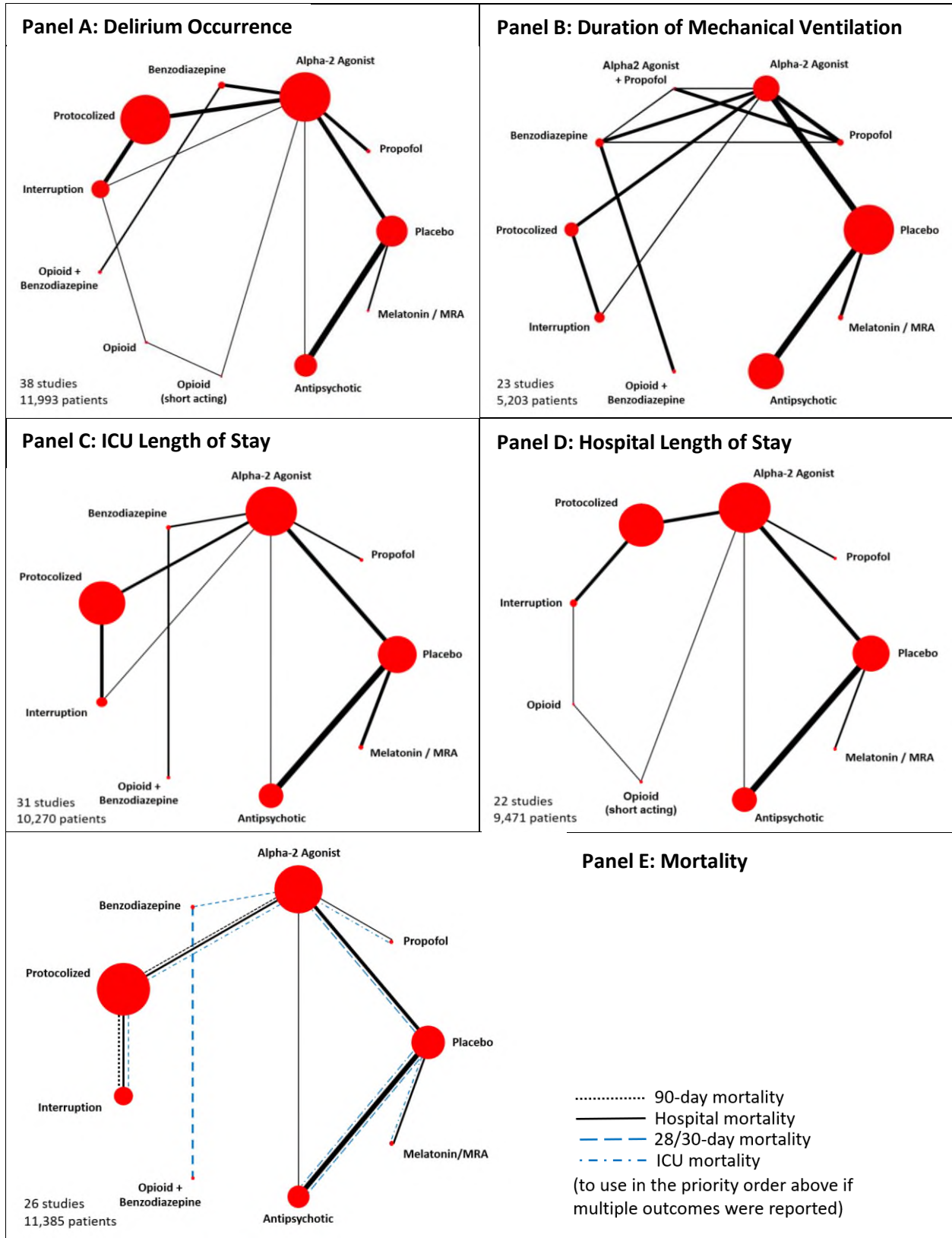
⁹ Serious indirectness: only indirect evidence available (through three degrees of intermediaries, interruption / opioid (short acting), alpha₂ agonist and benzodiazepine).

Figure 1. Summary of Study Retrieval and Identification



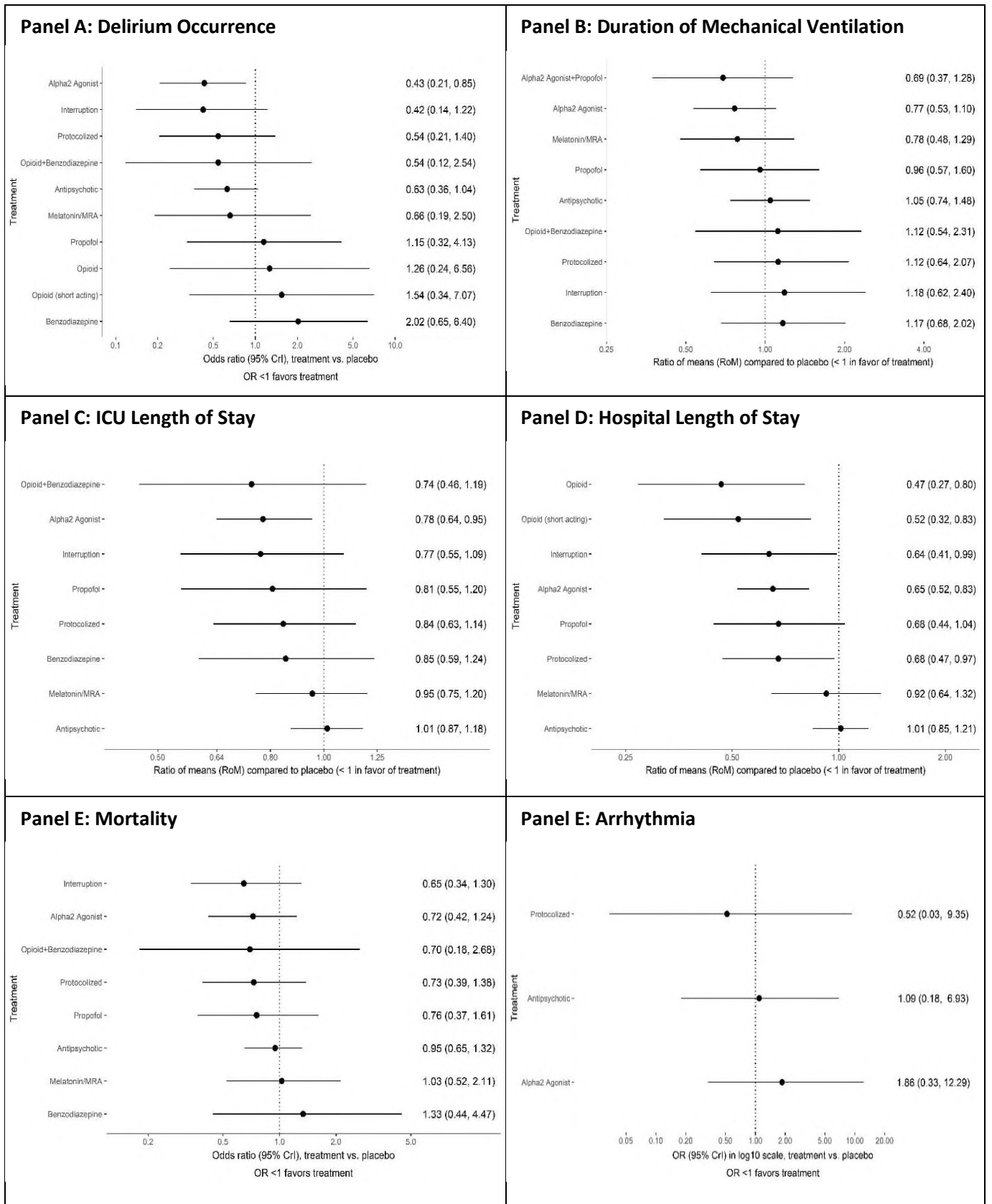
Legend: Figure 1 describes the flow of selection of included trials. Inclusion criteria applied included: randomized controlled trials, examined any pharmacological, sedation, non-pharmacological or multi-component intervention for prevention of delirium in critically ill adults.

Figure 2: Network Plots for Delirium Prevention Strategies for Outcomes



Legend: 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.

Figure 3: Forest plots with interventions ordered in descending order of SUCRA Values for each Network



Legend: All outcomes are reported as network odds ratios or ratio of means with 95% credible intervals (CrI).