REVIEW ARTICLE

# Dexmedetomidine for the treatment of established delirium in critically ill adults: a comparator-stratified systematic review and meta-analysis

Raed Abdulkhaliq Alzahrani[1], Reman Mohammed Alghamdi[1], Mohammed Hassan Alzahrani[1*], Abdulhakeem Ali Alghamdi[1], Meshref Sultan Alghamdi[2], Rawan Mohammed Alzahrani[1], Lama Mohammed Alzahrani[2], Shahad Abdulrahman Alzahrani[2], Sultan Meshref Alghamdi[3]

## ABSTRACT

Dexmedetomidine is widely used to treat established delirium in critically ill adults, but the evidence for that use has not been synthesized since 2020 and has never been separated by comparator drug. We searched four databases from inception to March 2026, with trial registers and reference mining, for randomized and non-randomized studies of adults with instrument-confirmed delirium comparing dexmedetomidine with placebo, an antipsychotic or propofol. Two reviewers independently screened, extracted, and rated risk of bias by outcome (RoB 2, ROBINS-I) and certainty (GRADE). Comparator strata were never pooled together. Eight studies were included: six randomized trials with 532 participants and two non-randomized studies with 395. Neither co-primary outcome could be pooled, because six trials measured delirium duration as four different quantities in two units and agitation duration was quantified in one trial only. Three pooled estimates were possible, each from two trials. Rescue medication use against placebo gave a risk ratio of 0.69 (Hartung-Knapp 95% CI 0.21 to 2.26) and intensive care length of stay a mean difference of −0.56 days (−12.99 to 11.88); at two trials, the Hartung-Knapp critical value is 12.7, so no pooled estimate excluded the null. In the single trial against olanzapine, mortality at 90 days was higher with dexmedetomidine (33 of 94 *vs.* 19 of 94; risk ratio 1.74, 95% CI 1.07 to 2.83). Certainty was low or very low throughout. The randomized evidence is too sparse and too fragmented by outcome definition to support a pooled estimate for either co-primary outcome.

**Keywords**: Delirium, dexmedetomidine, critical illness, intensive care units, systematic review, meta-analysis.

## Introduction

Delirium affects about a third of patients admitted to intensive care and is associated with longer mechanical ventilation, longer stay, and cognitive decline that persists after discharge [1-3]. Once established, it has few treatments with a good evidence base: antipsychotics have repeatedly failed to shorten it [4,5], and the 2018 Society of Critical Care Medicine guidelines recommend against their routine use for treatment [6]. Dexmedetomidine, an alpha-2 agonist that produces arousable sedation without the anticholinergic burden of antipsychotics, is used instead in many units, often as de facto standard practice [7,8].

The evidence for that practice is thinner than its adoption suggests, and two questions need separating. Whether dexmedetomidine prevents delirium has been studied extensively; several dozen randomized trials and a network meta-analysis address it [9,10]. Whether it treats delirium that is already present is a different question with a much smaller literature because a prevention trial enrols patients without delirium and cannot answer it. The only dedicated synthesis of the treatment question searched to May 2020 [11].

**Correspondence to:** Mohammed Hassan Alzahrani
*Faculty of Medicine, Al-Baha University, Al-Baha, Saudi Arabia
**Email:** vMzx07@gmail.com
*Full list of author information is available at the end of the article.*
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Three randomized trials relevant to treatment have been published since that cutoff. One was the first placebo-controlled trial in non-intubated patients, one compared dexmedetomidine with propofol, and one compared it with oral olanzapine and reported a mortality signal [12-14]. None has been incorporated into a synthesis.

The existing synthesis also pooled across comparator drugs. Placebo, haloperidol, olanzapine, and propofol are not interchangeable controls: an estimate against placebo measures whether the drug works, and an estimate against propofol measures which of two sedatives works better in a population that would have received one of them anyway. Pooling them produces a number that answers no clinical question. We therefore undertook a review in which comparator strata are analyzed separately and never combined, incorporating the trials published since 2020, to determine what the randomized evidence supports for the treatment of established delirium.

## Methods

### *Protocol and registration*

We reported this review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement [15] and the narrative component according to the Synthesis Without Meta-analysis (SWiM) reporting guideline [16]. Charting of long-term neuropsychiatric outcomes follows the PRISMA extension for scoping reviews [17].

### *Eligibility criteria*

We included studies of critically ill adults aged 18 years or older in whom delirium was present and instrument-confirmed at enrolment, using the Confusion Assessment Method for the ICU (CAM-ICU), the Intensive Care Delirium Screening Checklist (ICDSC), or an equivalent [18,19] validated instrument. Trials of delirium prevention, in which delirium was not required at entry, were not eligible, nor were studies confined to palliative care, to sedation rather than delirium treatment, or to alcohol-withdrawal delirium. The intervention was dexmedetomidine at any dose, route, or duration, given to treat delirium. Comparators were placebo or standard care alone, antipsychotics, and propofol or another sedative. Randomized trials were eligible for pooling; non-randomized studies were eligible for narrative description only.

Co-primary outcomes were delirium resolution or duration and agitation control. Secondary outcomes were all-cause mortality, ICU and hospital length of stay, intubation or mechanical ventilation, rescue-medication use, bradycardia, and hypotension. Long-term neuropsychiatric outcomes were charted for presence and instrument rather than extracted as effect estimates because the sparsity of their reporting was itself a question the review set out to answer.

### *Information sources and search*

We searched PubMed, MEDLINE (via ProQuest), Web of Science Core Collection, and CINAHL (via EBSCOhost) from inception to March 2026 and ClinicalTrials.gov during April 2026 for unpublished completed studies. In PubMed, the Medical Subject Headings "Dexmedetomidine," "Delirium," and "Critical Care" were combined with AND; the other three databases used equivalent free-text terms in the title and abstract fields. No date or language limit was applied. The full strategy for each database is given in Supplementary File 1. We also mined the reference lists of two earlier syntheses, searched to May 2020 and August 2018 [20], which is how the eligible non-randomized studies were identified. Records were deduplicated in Zotero and screened in Rayyan by two blinded reviewers.

### *Study selection and data extraction*

Two reviewers screened records independently against the eligibility criteria and resolved disagreements by discussion, recording a reason for exclusion for every report assessed. The same two reviewers extracted data independently into a structured workbook covering study characteristics, population, intervention and comparator, continuous and dichotomous outcomes, risk of bias, and the neuropsychiatric charting, and reconciled their extractions into a master record.

### *Risk of bias*

Randomized trials were assessed with the Cochrane risk-of-bias tool for randomized trials (RoB 2) [21], rated separately for three outcome domains: delirium duration or resolution, safety, and mortality. Rating by outcome rather than by study was chosen because bias operates differently on a trial's pre-specified primary endpoint than on its secondary and safety endpoints. Non-randomized studies were assessed with ROBINS-I [22]. Studies rated at critical risk of bias were described in text and excluded from every pooled estimate and from the certainty ratings.

### *Effect measures and synthesis*

Dichotomous outcomes were expressed as risk ratios with dexmedetomidine as the index arm, so an estimate below 1.0 favors dexmedetomidine throughout; estimates reported the other way round were re-oriented, as was necessary for every estimate in one trial. Where an arm had no events the risk ratio is not estimable, so counts are reported, with a Peto odds ratio where a quantitative summary was needed [23]. Continuous outcomes were expressed as mean differences.

Every continuous outcome was reported as a median with an interquartile range, so conversion was unavoidable for any continuous pooling. Means and SD were estimated with the Luo and Wan estimators for a known median, both quartiles and sample size [24,25]. Because these assume approximate normality, a skewness gate was applied first: the ratio of the upper to the lower half of the interquartile range had to fall between 0.4 and 2.5 in both arms, and no conversion was attempted where the median equaled a quartile. Published medians and quartiles were not overwritten.

Comparator strata were never pooled together, and pooling within a stratum required two trials measuring the same construct in the same unit. Pooled estimates used random-effects inverse-variance weighting with restricted maximum likelihood [26] and Hartung-Knapp adjusted intervals [27], which are required at two trials and are reported beside the conventional intervals to show the size of the adjustment. Zero cells received no continuity correction, and $I^2$ is reported but was not used as a decision rule [28]. Intention-to-treat analysis was primary, and per-protocol results are labeled sensitivity analyses. No subgroup interaction test was performed across airway status, which is fully confounded with comparator, country, era, and instrument, and no funnel plots were produced, since no stratum approached the ten studies they require [29].

Outcomes that could not be pooled were synthesized narratively following SWiM, grouped by comparator stratum and then by outcome construct, with only constructs measuring the same quantity described together. The standardized metric was the direction of effect after re-orientation, reported with each trial's own estimate in its original units; vote counting used direction alone, never statistical significance, and the number of trials in each direction is stated. Heterogeneity was examined by tabulating clinical modifiers beside each estimate.

### *Certainty of evidence and software*

Certainty was rated with GRADE for each outcome within each stratum [30], applied to narrative and pooled outcomes alike. Where one trial contributed, imprecision was downgraded by at least one level, and inconsistency was recorded as not assessable rather than as not serious. Analyses were scripted end to end from the extraction workbook in Python 3 (numpy 2.4, scipy 1.17) with no manual re-entry of any value. The Luo, Wan, Hartung-Knapp, and Peto estimators were implemented directly and checked against published worked examples.

## Results

### *Study selection*

Eight studies met the eligibility criteria: six randomized trials and two non-randomized studies (Figure 1). The

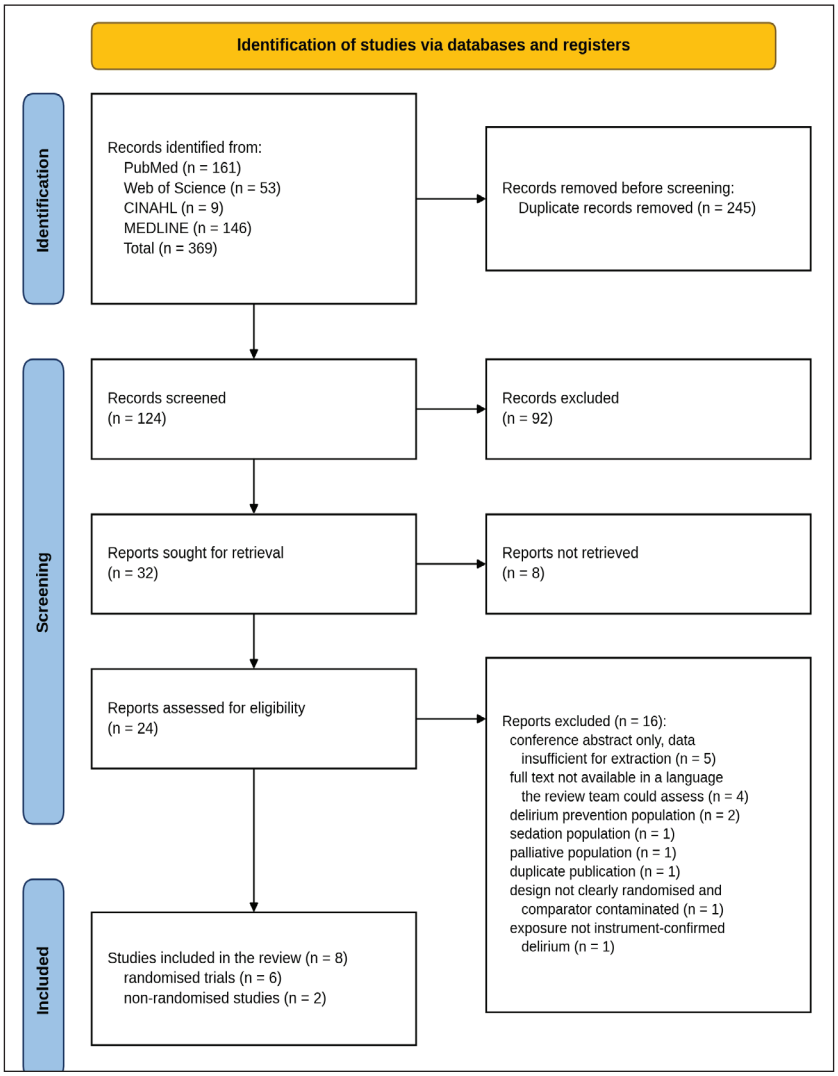



***Figure 1.*** *PRISMA 2020 flow diagram of study selection. Adapted from the PRISMA 2020 flow diagram template [15].*

searches returned 369 records; after removal of 245 duplicates, 124 records were screened and 92 were excluded at title and abstract. Of the 32 reports sought, eight could not be retrieved because the full text required a paid subscription. Twenty-four reports were assessed for eligibility and 16 were excluded, most often because the report was a conference abstract with data insufficient for extraction, or because the full text was not available in a language the review team could assess. Figure 1 gives the reason for every exclusion. A further five registered trials were identified and tracked but unpublished.

## *Characteristics of included studies*

The six randomized trials contributed 532 participants and were conducted in Australia and New Zealand, France, Switzerland, China, and Saudi Arabia, with enrolment spanning 2006 to 2022 and publication 2009 to 2026. Two compared dexmedetomidine with placebo, two with haloperidol, one with olanzapine, and one with propofol. One trial had three arms and only its dexmedetomidine and haloperidol arms were used because merging the third arm into a combined control reverses the direction of the point estimate. The two non-randomized studies contributed a further 395 participants. Table 1 gives the characteristics of each study [12-14,31-35].

The set is small and clinically heterogeneous. Populations range from a fully intubated cohort to one in which intubation was an exclusion criterion, two instruments were used to ascertain delirium, and the largest trial stopped early for efficacy while another stopped for slow recruitment after 38 of a planned 316 patients.

## *Risk of bias*

Rating by outcome changed the picture in both directions. For delirium duration or resolution, four of the six randomized trials were rated at high risk of bias and two at some concerns, and the outcome-specific rating was worse than the study-level rating for both placebo trials, where the endpoint was never a stated outcome in one and one of many secondary outcomes in the other. For mortality, which is objectively ascertained and insensitive to unblinding, three trials were rated at some concerns, better than their study-level ratings, and one did not measure mortality at all. Only one rating was low: safety outcomes in the largest placebo trial, which pre-specified bradycardia and hypotension both as any episode and as episodes requiring treatment.

## *Delirium duration and resolution*

No two trials within a stratum measured delirium duration in the same way, so this co-primary outcome was not pooled. Seven rows across the dataset carry the label delirium duration while measuring four distinct quantities in two units: time spent CAM-ICU positive, time to a negative CAM-ICU, time to a satisfactory ICDSC score, and cause-specific time to resolution with death treated as a competing risk. Table 2 maps each construct against the others. Not one pair is an exact match within a stratum.

***Table 1.*** *Characteristics of the included studies.*

| Study | Design | Country | Comparator | Airway status | *n* (dex/comp) | Synthesis |
|---|---|---|---|---|---|---|
| *Reade [31]* | *RCT, open label* | *Australia* | *Haloperidol* | *Intubated* | *10/10* | *Quantitative* |
| *Bakri [32]* | *RCT, three arm* | *Saudi Arabia* | *Haloperidol* | *Mixed, mostly not ventilated* | *32/32* | *Quantitative* |
| *DahLIA [33]* | *RCT, double blind, 15 centres* | *Australia, New Zealand* | *Placebo* | *Intubated* | *39/32* | *Quantitative* |
| *Carrasco [34]* | *Non-randomized, refractory design* | *Spain* | *Haloperidol* | *Not intubated* | *46/86* | *Narrative only* |
| *Liu SB [11]* | *Retrospective cohort* | *China* | *Olanzapine* | *Not intubated* | *118/145* | *Narrative only* |
| *4D [12]* | *RCT, double blind, 9 centers* | *France* | *Placebo* | *Not intubated* | *77/74* | *Quantitative* |
| *BaProDex [13]* | *RCT, open label* | *Switzerland* | *Propofol* | *Mixed* | *19/19 ITT; 15/19 PP* | *Quantitative* |
| *Liu [14]* | *RCT, double dummy* | *China* | *Olanzapine* | *Mixed, 40% ventilated* | *94/94* | *Quantitative* |

dex, dexmedetomidine; ITT, intention to treat; PP, per protocol; RCT, randomized-controlled trial. Studies are ordered by publication year. Bakri 2015 randomized 96 patients to three arms; only the dexmedetomidine and haloperidol arms are used here.

***Table 2.*** *Construct mapping for delirium duration and resolution.*

| Study | Stratum | Construct as reported | Unit | Match |
|---|---|---|---|---|
| *DahLIA [33]* | *Placebo* | *Time spent with a positive CAM-ICU* | *hours* | *reference* |
| *4D [12]* | *Placebo* | *Time to a negative CAM-ICU* | *days* | *approximate* |
| *Reade [31]* | *Haloperidol* | *Time to a satisfactory ICDSC score below 4* | *hours* | *proxy* |
| *Bakri [32]* | *Haloperidol* | *Patients still delirious after the sixth dose (day 3)* | *proportion* | *proxy* |
| *Liu [14]* | *Olanzapine* | *Duration of delirium, adjusted beta* | *days* | *approximate* |
| *BaProDex [13]* | *Propofol* | *Time to resolution, death as a competing risk* | *hours* | *approximate* |

CAM-ICU, Confusion Assessment Method for the ICU; ICDSC, Intensive Care Delirium Screening Checklist. Match is judged against the construct in the first row. No pair within a stratum is an exact match, which is why this outcome was not pooled.

Direction of effect across the six trials was mixed and did not track sample size. The strongest signal came from the intubated placebo trial, where time spent delirious was 24 hours shorter (median difference −24 hours, 95% CI −41 to −6). The larger non-intubated placebo trial found no difference in time to a negative CAM-ICU (median 0.8 *vs.* 1.0 days; effect size −0.09, 95% CI −0.41 to 0.23). In the propofol trial, the intention-to-treat result was null (hazard ratio 1.92, 95% CI 0.89 to 4.15) while the per-protocol result reached significance; the intention-to-treat result is reported here. Figure 2 plots these results on the only axis they share [36].

### *Agitation control*

Agitation control was quantified in one randomized trial. In the non-intubated placebo trial, the median time to a Richmond Agitation-Sedation Scale score below +1 was 1.0 hour [37] with dexmedetomidine and 2.0 hours with placebo (effect size −0.60, 95% CI −0.92 to −0.27, = 0.001), and the trial investigators described a difference of roughly one hour as of debatable clinical meaning. No other randomized trial measured agitation duration. The second co-primary outcome therefore rests on a single trial rated at low certainty *p*.

### *Rescue-medication use*

Rescue-medication use was the only outcome for which two trials in one stratum measured a commensurate construct with both arms well populated. In the placebo stratum, receipt of any rescue antipsychotic was less frequent with dexmedetomidine in both trials (14 of 38 *vs.* 21 of 32, risk ratio 0.56, 95% CI 0.35 to 0.91; and 45 of 77 *vs.* 60 of 74, risk ratio 0.72, 95% CI 0.58 to 0.90). The pooled risk ratio was 0.69 (inverse variance 0.57 to 0.84; Hartung-Knapp 0.21 to 2.26; $k = 2$; $\tau^2 = 0.000$; $I^2 = 0.0\%$; Figure 3a). At two trials, the Hartung-Knapp interval rests on one degree of freedom and the critical value is 12.7, so the adjusted interval runs from a 79% relative reduction to a 126% relative increase, consistent with the benefit both trials detected individually but not establishing one.

In the haloperidol stratum, the two trials ran in opposite directions, so the pooled estimate is a sensitivity analysis only and the trials are shown separately. Supplemental propofol was used less often with dexmedetomidine in one trial (6 of 10 *vs.* 8 of 10, risk ratio 0.75, 95% CI 0.41 to 1.36) and rescue haloperidol more often in the other (5 of 32 *vs.* 3 of 32, risk ratio 1.67, 95% CI 0.43 to 6.40); the rescue drug differed and the combined sample was 84 patients. The pooled risk ratio was 0.88 (Hartung-Knapp 0.01 to 52.08; Figure 3c), an interval too wide to carry information.

### *Length of stay*

ICU length of stay was the only continuous outcome for which two trials in one stratum shared a construct and a unit and both passed the skewness gate. After conversion, the mean difference was −1.35 days in the intubated trial and +0.65 days in the non-intubated trial, so the point estimates run in opposite directions. The pooled mean difference was −0.56 days (inverse variance −2.47 to

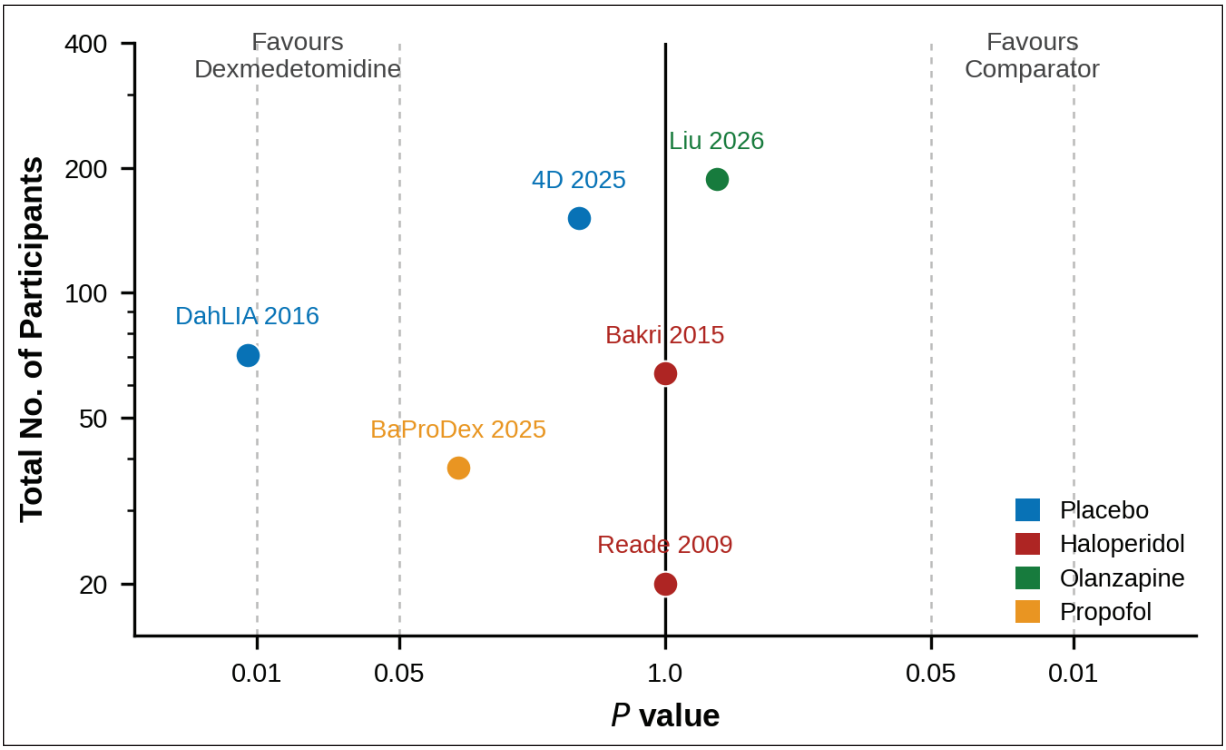



***Figure 2.*** *Albatross plot of the delirium duration and resolution results, plotting total sample size against p value, with the side of the vertical line showing the direction of effect. Colour indicates the comparator stratum. Effect contours are omitted because the six trials share no common effect metric, which is the reason this outcome was not pooled. p values for three trials were derived from the reported confidence interval or from the two-by-two table.*

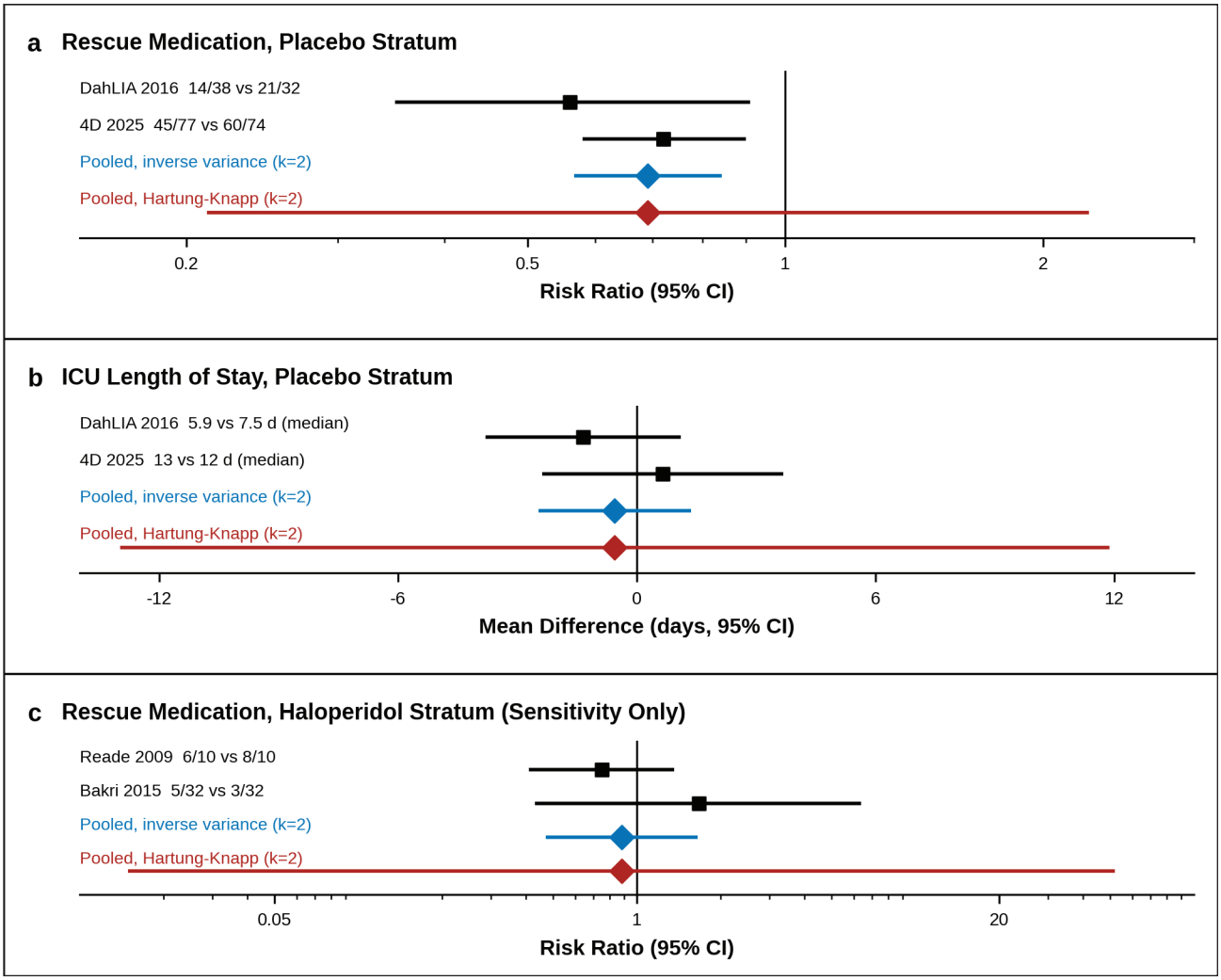



***Figure 3.*** *The three pooled estimates the data support, each based on two trials. Black squares are individual trials, blue diamonds are pooled estimates with conventional inverse-variance confidence intervals, and red diamonds are the same pooled estimates with Hartung-Knapp adjusted intervals. Panel a shows rescue-medication use in the placebo stratum, panel b ICU length of stay in the placebo stratum after median-to-mean conversion, and panel c rescue-medication use in the haloperidol stratum, a sensitivity analysis only because the rescue drug differs between the two trials. The inverse-variance intervals are shown to make the size of the Hartung-Knapp adjustment visible and should not be interpreted on their own at two studies.*

1.36; Hartung-Knapp −12.99 to 11.88; $k = 2$; $\tau^2 = 0.024$; $I^2 = 1.2\%$; Figure 3b). The adjusted interval spans nearly 25 days, longer than either trial's median stay, and supports no clinically useful statement.

Two sensitivity analyses were run. Analyzing the same data as a ratio of means gave 0.97 [38] (inverse variance 0.78 to 1.20), and repeating the conversion with the interquartile range divided by 1.35 in place of the Wan estimator gave a mean difference of −0.47 days (inverse variance −2.99 to 2.06). Neither changed the conclusion. The derived mean differences also agree with the median differences the trials themselves reported, −1 day and +1 day, which supports the conversion. A prediction interval could not be computed at two studies.

### *Mortality*

Per-trial risk ratios for every dichotomous outcome are shown in Figure 4, and their direction of effect in Table 3. Mortality at 28 to 30 days was reported by one trial in each of three strata and by none in the fourth. Against placebo, 10 of 74 patients died by day 30 versus 13 of 72 (risk ratio 0.75, 95% CI 0.35 to 1.60); against propofol, 1 of 19 versus 5 of 19 by day 28 (risk ratio 0.20, 95% CI 0.03 to 1.55); and against olanzapine, 23 of 94 versus 13 of 94 by day 30 (risk ratio 1.77, 95% CI 0.95 to 3.28), rising to 33 of 94 versus 19 of 94 by day 90 (risk ratio 1.74, 95% CI 1.07 to 2.83). This is the only mortality interval in the review that excludes the null, and it runs against dexmedetomidine. Mortality at a fixed timepoint is available in three of six trials; hospital mortality is reported separately and was not treated as a proxy.

Two estimates exist in the source for the 90-day contrast in the olanzapine trial. The adjusted hazard ratio from the survival figure was used, and the value quoted in the running text as a hazard ratio was not because it is numerically identical to the odds ratio in the accompanying forest figure. The discrepancy is noted in the Limitations.

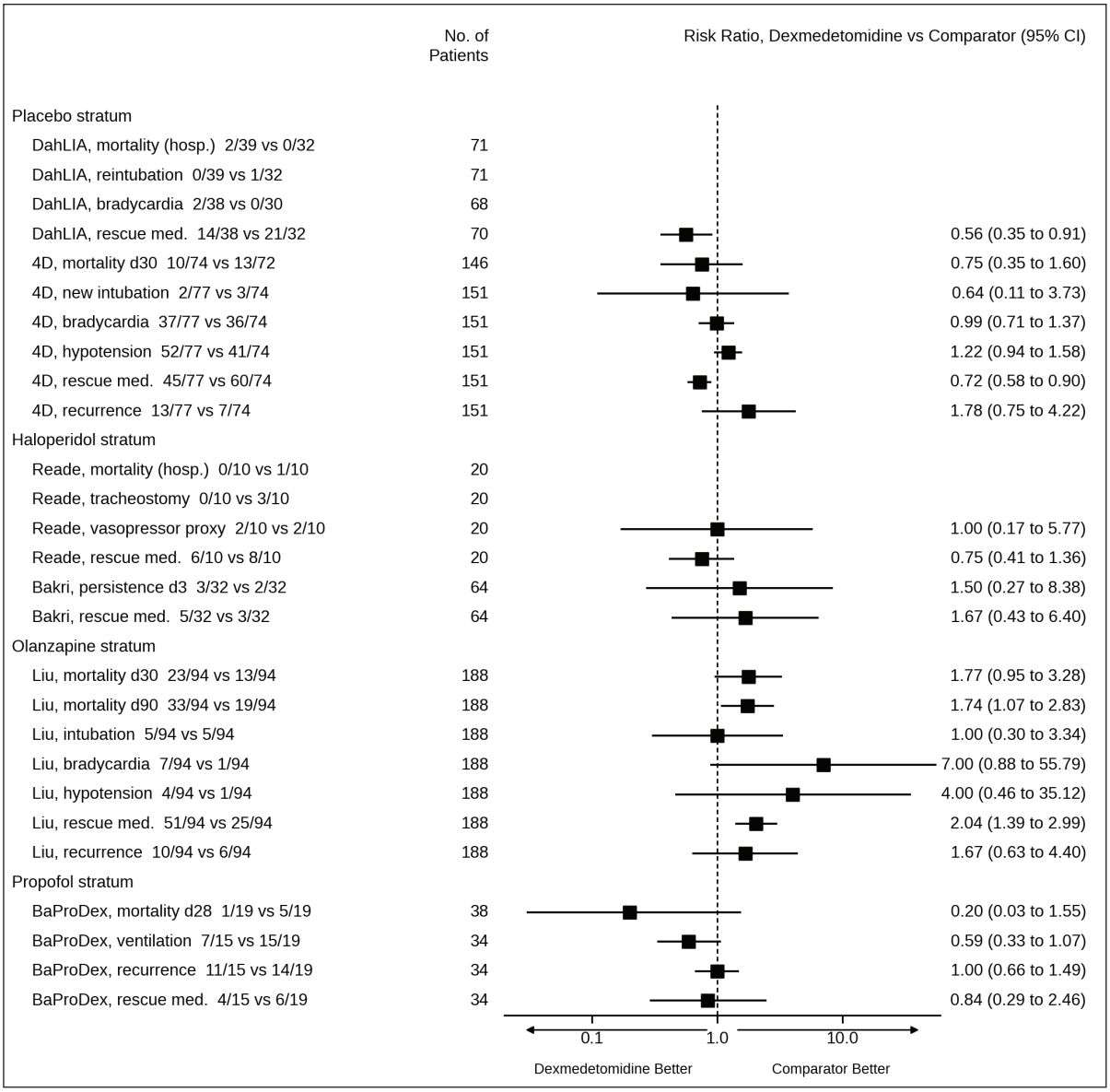



***Figure 4.*** *Risk ratios for every dichotomous outcome, by comparator stratum, with dexmedetomidine as the index arm. Squares are point estimates, and horizontal lines are 95% confidence intervals. There is no summary diamond and no weighting: this figure displays the individual results and is not a meta-analysis. Rows without a marker had no events in one arm, so the risk ratio is not estimable; the counts appear in the row label. The number of patients is the total contributing to that outcome row, which differs from the trial size where adverse-event data were incomplete.*

***Table 3.*** *Effect direction for every dichotomous outcome, by comparator stratum, with dexmedetomidine as the index arm.*

| Stratum | Study | Outcome | Set | Events | RR (95% CI) | Favors |
|---|---|---|---|---|---|---|
| *Placebo* | *DahLIA [33]* | *Hospital mortality* | *mITT* | *2/39 vs 0/32* | *Not estimable* | *Comparator* |
| *Placebo* | *DahLIA [33]* | *Reintubation* | *mITT* | *0/39 vs 1/32* | *Not estimable* | *Dexmedetomidine* |
| *Placebo* | *DahLIA [33]* | *Bradycardia (drug modification)* | *mITT (AE set)* | *2/38 vs 0/30* | *Not estimable* | *Comparator* |
| *Placebo* | *DahLIA [33]* | *Rescue medication* | *mITT* | *14/38 vs 21/32* | *0.56 (0.35 to 0.91)* | *Dexmedetomidine* |
| *Placebo* | *4D [12]* | *Mortality at day 30* | *ITT* | *10/74 vs 13/72* | *0.75 (0.35 to 1.60)* | *Dexmedetomidine* |
| *Placebo* | *4D [12]* | *New intubation* | *ITT* | *2/77 vs 3/74* | *0.64 (0.11 to 3.73)* | *Dexmedetomidine* |
| *Placebo* | *4D [12]* | *Bradycardia (>=1 episode)* | *ITT* | *37/77 vs 36/74* | *0.99 (0.71 to 1.37)* | *Dexmedetomidine* |
| *Placebo* | *4D [12]* | *Hypotension (>=1 episode)* | *ITT* | *52/77 vs 41/74* | *1.22 (0.94 to 1.58)* | *Comparator* |
| *Placebo* | *4D [12]* | *Rescue medication* | *ITT* | *45/77 vs 60/74* | *0.72 (0.58 to 0.90)* | *Dexmedetomidine* |
| *Placebo* | *4D [12]* | *Delirium recurrence* | *ITT* | *13/77 vs 7/74* | *1.78 (0.75 to 4.22)* | *Comparator* |
| *Haloperidol* | *Reade [31]* | *Hospital mortality* | *All randomized* | *0/10 vs 1/10* | *Not estimable* | *Dexmedetomidine* |
| *Haloperidol* | *Reade [31]* | *Tracheostomy (failure to wean)* | *All randomized* | *0/10 vs 3/10* | *Not estimable* | *Cexmedetomidine* |

***Continued***

| Stratum | Study | Outcome | Set | Events | RR (95% CI) | Favors |
|---|---|---|---|---|---|---|
| Haloperidol | Reade [31] | Vasopressor proxy (hypotension) | All randomized | 2/10 vs 2/10 | 1.00 (0.17 to 5.77) | No difference |
| Haloperidol | Reade [31] | Rescue medication | All randomized | 6/10 vs 8/10 | 0.75 (0.41 to 1.36) | Dexmedetomidine |
| Haloperidol | Bakri [32] | Delirium persistence at day 3 | All randomized | 3/32 vs 2/32 | 1.50 (0.27 to 8.38) | Comparator |
| Haloperidol | Bakri [32] | Rescue medication | All randomized | 5/32 vs 3/32 | 1.67 (0.43 to 6.40) | Comparator |
| Olanzapine | Liu [14] | Mortality at day 30 | ITT | 23/94 vs 13/94 | 1.77 (0.95 to 3.28) | Comparator |
| Olanzapine | Liu [14] | Mortality at day 90 | ITT | 33/94 vs 19/94 | 1.74 (1.07 to 2.83) | Comparator |
| Olanzapine | Liu [14] | Intubation after randomization | ITT | 5/94 vs 5/94 | 1.00 (0.30 to 3.34) | No difference |
| Olanzapine | Liu [14] | Bradycardia (<40/minutes) | ITT | 7/94 vs 1/94 | 7.00 (0.88 to 55.79) | Comparator |
| Olanzapine | Liu [14] | Hypotension (<80/50) | ITT | 4/94 vs 1/94 | 4.00 (0.46 to 35.12) | Comparator |
| Olanzapine | Liu [14] | Rescue medication | ITT | 51/94 vs 25/94 | 2.04 (1.39 to 2.99) | Comparator |
| Olanzapine | Liu [14] | Delirium recurrence | ITT | 10/94 vs 6/94 | 1.67 (0.63 to 4.40) | Comparator |
| Propofol | BaProDex [13] | Mortality at day 28 | ITT | 1/19 vs 5/19 | 0.20 (0.03 to 1.55) | Dexmedetomidine |
| Propofol | BaProDex [13] | Mechanical ventilation | PP | 7/15 vs 15/19 | 0.59 (0.33 to 1.07) | Dexmedetomidine |
| Propofol | BaProDex [13] | Delirium recurrence | PP | 11/15 vs 14/19 | 1.00 (0.66 to 1.49) | No difference |
| Propofol | BaProDex [13] | Rescue medication | PP | 4/15 vs 6/19 | 0.84 (0.29 to 2.46) | Dexmedetomidine |

CI, confidence interval; ITT, intention to treat; PP, per protocol; RR, risk ratio. A risk ratio below 1.0 favors dexmedetomidine. Where one arm had no events the risk ratio is not estimable and the direction is read from the counts. Estimates are crude and computed from the counts shown; adjusted estimates reported by one trial are described in the text.

### *Bradycardia and hypotension*

Bradycardia was reported as an event count in three randomized trials using three incompatible definitions: an adverse event forcing modification of the study drug (2 of 38, 5%), any recorded episode (37 of 77, 48%), and a heart rate below 40 per minute judged related to the intervention (7 of 94, 7%). The gap between 5% and 48% within one stratum is definitional rather than statistical, so no pooled figure is given. Table 4 sets out the verbatim definition and denominator beside each estimate. Hypotension counts exist in two trials in different strata; one recorded a vasopressor proxy rather than a blood-pressure threshold, and one states that hypotension was recorded and was rare but carries no table row.

Counting by direction alone, the safety signal is consistent within the olanzapine stratum, where bradycardia, hypotension, and both mortality timepoints favor the comparator, and inconsistent elsewhere. Across all 27 dichotomous results, 12 favored dexmedetomidine, 12 favored the comparator, and 3 gave a risk ratio of 1.00; five were not estimable for want of events in one arm, and in four more the absolute difference was under one percentage point.

### *Intubation, ventilation and recurrence*

Constructs differ within the placebo stratum, where one trial recorded reintubation in an already intubated cohort (0 of 39 *vs.* 1 of 32) and the other new intubation with deep sedation in a non-intubated cohort (2 of 77 *vs.* 3 of 74). Events are sparse. A Peto odds ratio combining them, presented as a sensitivity analysis and not as a synthesis of a common outcome, was 0.47 (inverse variance 0.09 to 2.39). Delirium recurrence was reported by one trial in each of three strata and was numerically more frequent with dexmedetomidine in two of them.

### *Non-randomized evidence*

Both non-randomized studies were rated at critical risk of bias on ROBINS-I, so neither contributes an effect estimate nor a certainty rating. In the first, the 46 patients who did not respond to haloperidol titration were then given dexmedetomidine, so allocation followed treatment response and confounding by indication cannot be removed analytically; treatment failure forcing withdrawal occurred in none of the dexmedetomidine group and 12 of 86 haloperidol patients. In the second, a retrospective cohort aged 75 years and over, intubation during drug use was about twice as frequent with dexmedetomidine (27 of 118 *vs*. 18 of 145). These are reported as observations only.

### *Long-term neuropsychiatric outcomes*

Of the nine records with a retrieved full text, none reported post-traumatic stress, depression, or anxiety at any timepoint. One reported a cognitive outcome at three months without naming the instrument and with much of each arm unevaluable; one measured cognition at baseline only; and one followed patients to twelve months with a measure of daily function rather than cognition. Follow-up elsewhere ended at hospital discharge or, in one trial, at day 3.

### *Certainty of evidence*

Certainty was very low for 16 of the 19 rated outcome and stratum combinations and low for the remaining three (Table 5). Every rating was downgraded for imprecision and all but one for risk of bias; none reached moderate. Bradycardia and hypotension in the haloperidol stratum were not rated because neither trial reported them as event counts.

## Discussion

This comparator-stratified systematic review covered eight studies in 927 critically ill adults across five

***Table 4.*** *Bradycardia and hypotension: verbatim outcome definitions and denominators.*

| Outcome | Study | Stratum | Definition as reported | Events | Percent |
|---|---|---|---|---|---|
| Bradycardia | DahLIA [33] | Placebo | Adverse event related to bradycardia requiring study-drug interruption | 2/38 vs 0/30 | 5.3% vs 0% |
| Bradycardia | 4D [12] | Placebo | Patients with at least 1 episode of bradycardia | 37/77 vs 36/74 | 48.1% vs 48.6% |
| Bradycardia | Liu [14] | Olanzapine | Heart rate <40/minute judged related to the intervention | 7/94 vs 1/94 | 7.4% vs 1.1% |
| Bradycardia | Reade [31] | Haloperidol | Not reported as an event category (arrhythmia of any type, 20% vs 20%) | not reported | – |
| Bradycardia | Bakri [32] | Haloperidol | Not reported as event counts | not reported | – |
| Bradycardia | BaProDex [13] | Propofol | Not reported; bradycardia of any origin was an exclusion criterion | not reported | – |
| Hypotension | 4D [12] | Placebo | Patients with at least 1 episode of hypotension | 52/77 vs 41/74 | 67.5% vs 55.4% |
| Hypotension | Liu [14] | Olanzapine | Blood pressure <80/50 mmHg judged related to the intervention | 4/94 vs 1/94 | 4.3% vs 1.1% |
| Hypotension | Reade [31] | Haloperidol | Proxy: new or substantially increased norepinephrine within 8 hours | 2/10 vs 2/10 | 20% vs 20% |
| Hypotension | DahLIA [33] | Placebo | Stated in text as recorded and rare; no table row exists | not reported | – |
| Hypotension | Bakri [32] | Haloperidol | Not reported as event counts; group mean arterial pressures only | not reported | – |
| Hypotension | BaProDex [13] | Propofol | Not reported; uncontrolled hypotension was an exclusion criterion | not reported | – |

Definitions are not interchangeable and no pooled estimate is given. Percentages use the denominator recorded for that outcome row, which differs from the trial size where adverse-event data were incomplete.

**Table 5.** *GRADE certainty of evidence, by outcome and comparator stratum.*

| Stratum | Outcome | *k* | *n* | Effect (95% CI) | Certainty | Downgraded for |
|---|---|---|---|---|---|---|
| Placebo | Delirium duration | 2 | 222 | Not pooled, constructs differ | Very low | RoB; indirectness; imprecision |
| Placebo | Agitation control | 1 | 151 | ES −0.60 (−0.92 to −0.27) | Low | RoB (stopped early); imprecision |
| Placebo | Rescue medication | 2 | 222 | RR 0.69 (0.21 to 2.26) | Very low | RoB; imprecision (2 levels) |
| Placebo | ICU length of stay | 2 | 222 | MD −0.56 d (−12.99 to 11.88) | Very low | RoB; indirectness; imprecision |
| Placebo | Mortality, day 30 | 2 | 222 | RR 0.75 (0.35 to 1.60) | Very low | RoB; imprecision (23 events) |
| Placebo | Bradycardia | 2 | 219 | Not pooled, definitions differ | Very low | RoB; inconsistency; imprecision |
| Placebo | Hypotension | 1 | 151 | RR 1.22 (0.94 to 1.58) | Low | Indirectness; imprecision |
| Placebo | Intubation | 2 | 222 | Peto OR 0.47 (0.09 to 2.39) | Very low | RoB; indirectness; imprecision |
| Placebo | Delirium recurrence | 1 | 151 | RR 1.78 (0.75 to 4.22) | Very low | RoB; imprecision (2 levels) |
| Haloperidol | Delirium duration | 2 | 84 | Not pooled, constructs differ | Very low | RoB (2 levels); indirectness; imprecision |
| Haloperidol | Rescue medication | 2 | 84 | RR 0.88 (0.01 to 52.08) | Very low | RoB; inconsistency; imprecision |
| Haloperidol | Mortality | 1 | 20 | Hospital only, 0/10 vs 1/10 | Very low | RoB; indirectness; imprecision |
| Olanzapine | Delirium resolution | 1 | 188 | Adjusted beta 0.19 (−0.45 to 0.83) | Low | RoB; imprecision |
| Olanzapine | Mortality, day 30 | 1 | 188 | RR 1.77 (0.95 to 3.28) | Very low | RoB (2 levels); imprecision |
| Olanzapine | Mortality, day 90 | 1 | 188 | RR 1.74 (1.07 to 2.83) | Very low | RoB (2 levels); imprecision |
| Olanzapine | Bradycardia | 1 | 188 | RR 7.00 (0.88 to 55.79) | Very low | RoB (2 levels); imprecision |
| Olanzapine | Rescue medication | 1 | 188 | RR 2.04 (1.39 to 2.99) | Very low | RoB (2 levels); indirectness |
| Propofol | Delirium duration | 1 | 38 | HR 1.92 (0.89 to 4.15), ITT | Very low | RoB (2 levels); imprecision |
| Propofol | Mortality, day 28 | 1 | 38 | RR 0.20 (0.03 to 1.55) | Very low | RoB; imprecision (2 levels) |

CI, confidence interval; ES, effect size; HR, hazard ratio; ITT, intention to treat; *k*, number of studies; MD, mean difference; OR, odds ratio; RoB, risk of bias; RR, risk ratio. Every body of evidence starts at high certainty because all contributing studies are randomized. Pooled intervals are Hartung-Knapp adjusted. Bradycardia and hypotension against haloperidol are unrated: neither trial reported event counts.

countries. Neither co-primary outcome could be pooled in any stratum. The data supported only three pooled estimates, each resting on two trials, and none excluded the null once the small-sample adjustment was applied. Certainty was low or very low throughout.

The earlier treatment-focused synthesis reported a pooled reduction in delirium duration favoring dexmedetomidine. Our review reaches a more cautious conclusion from a larger evidence base, for three reasons. The first is stratification: pooling placebo-controlled and antipsychotic-controlled trials together produces a summary no clinician can act on. The second is the handling of the three-arm trial, where merging the two control arms reverses the direction of the point estimate. The third is the small-sample adjustment: a conventional random-effects interval at two studies

is anticonservative, and the Hartung-Knapp correction moved every pooled estimate here from apparently precise to uninformative. The 2019 Cochrane review of pharmacological treatments reached a similar position, finding only three alpha-2 agonist trials among 14 studies [39].

What the instruments allow deserves attention before any of these numbers are interpreted. Delirium duration is not one quantity. Time spent CAM-ICU positive, time to first negative CAM-ICU, and cause-specific time to resolution with death as a competing risk answer different clinical questions and respond differently to a sedating drug. A drug that makes a patient calmer will shorten time to a negative CAM-ICU whether or not it shortens the underlying encephalopathy, and no instrument used here distinguishes them. The same problem appears in the safety data: reviewers who pool bradycardia counts across these trials are pooling definitions, not events.

Set against the prevention literature the imbalance is stark. Network meta-analyses of prevention have assembled eighty trials in critical care alone [9,40], an order of magnitude more than exists for treatment, which is the decision clinicians actually face once delirium has developed. The most useful finding in this review may be the one that requires no pooling at all: across nine retrieved reports, not one measured post-traumatic stress, depression or anxiety, and only one measured cognition after discharge, with an instrument it never named. A drug given to protect the brain has not been evaluated against any long-term measure of brain function.

Two findings deserve to be carried forward, with caution. Reduced use of rescue antipsychotics against placebo was consistent in both trials and, if confirmed, would mean fewer patients exposed to a second psychoactive drug. Against that, mortality at 90 days was higher with dexmedetomidine than olanzapine in the single trial reporting it, which also showed more bradycardia, more hypotension and more concomitant sedative use in the dexmedetomidine arm. One trial at high risk of bias cannot establish harm, but a consistent pattern across four outcomes should not be set aside either, and it is the finding most in need of replication.

### *Limitations*

All continuous pooling required conversion from medians to means, and although two sensitivity analyses left the conclusions unchanged, no conversion recovers information the original data did not contain. No prediction interval could be computed at two studies. Publication bias could not be assessed statistically, and one instance of selective reporting was documented directly, where a trial states that hypotension was recorded but gives no corresponding table row. The olanzapine trial also quotes two different estimates for the 90-day mortality contrast; the adjusted hazard ratio was used here and the discrepancy remains unresolved.

### *Future directions*

A randomized trial comparing dexmedetomidine with haloperidol in non-intubated patients with hyperactive delirium, powered for a single pre-specified delirium-duration metric and followed to at least 90 days for mortality and cognition, would resolve most of what this review could not. Two such trials are registered and unpublished [41]. Short of a new trial, agreement on a single reported delirium-duration construct would allow the existing evidence to be pooled, since the barrier here is definitional rather than statistical.

## Conclusions

The randomized evidence for treating established delirium with dexmedetomidine is too sparse and too fragmented by outcome definition to support a pooled estimate for either delirium duration or agitation control in any comparator stratum. Where pooling was possible, it produced intervals too wide to guide practice. Less frequent use of rescue antipsychotics compared with placebo is the most consistent finding, and an excess of deaths at 90 days compared with olanzapine is the most concerning; both rest on evidence of low or very low certainty and neither should change practice on its own.

**List of Abbreviations**

| | |
|---|---|
| **CAM-ICU** | Confusion Assessment Method for the Intensive Care Unit |
| **CI** | Confidence interval |
| **GRADE** | Grading of Recommendations, Assessment, Development and Evaluation |
| **ICDSC** | Intensive Care Delirium Screening Checklist |
| **ICTRP** | International Clinical Trials Registry Platform |
| **ICU** | Intensive care unit |
| **ITT** | Intention to treat |
| **MeSH** | Medical Subject Headings |
| **PP** | Per protocol |
| **PRISMA** | Preferred Reporting Items for Systematic Reviews and Meta-Analyses |
| **RASS** | Richmond Agitation-Sedation Scale |
| **RoB 2** | Cochrane risk-of-bias tool for randomized trials, version 2 |
| **ROBINS-I** | Risk of bias in non-randomized studies of interventions |
| **RR** | Risk ratio |
| **SWiM** | Synthesis without meta-analysis |

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**Ethics approval**
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**Data availability**
All data analyzed in this review were extracted from the published reports of the included studies, which are cited in the reference list. The data-extraction workbook, the

derived datasets underlying every table and figure, and the analysis scripts used to produce the pooled estimates and the median-to-mean conversions are available from the corresponding author on reasonable request.

## Author details

Raed Abdulkhaliq Alzahrani[1], Reman Mohammed Alghamdi[1], Mohammed Hassan Alzahrani[1], Abdulhakeem Ali Alghamdi[1], Meshref Sultan Alghamdi[2], Rawan Mohammed Alzahrani[1], Lama Mohammed Alzahrani[2], Shahad Abdulrahman Alzahrani[2], Sultan Meshref Alghamdi[3]

1. Medical Intern, Faculty of Medicine, Al-Baha University, Al-Baha, Saudi Arabia
2. Medical Student, Faculty of Medicine, Al-Baha University, Al-Baha, Saudi Arabia
3. King Fahad Hospital, Al-Baha Health Cluster, Al-Baha, Saudi Arabia

*Supplementary content (if any) is available online.*

## References

1. Salluh JIF, Wang H, Schneider EB, Nagaraja N, Yenokyan G, Damluji A, et al. Outcome of delirium in critically ill patients: systematic review and meta-analysis. BMJ. 2015;350(may19 3):h2538. https://doi.org/10.1136/bmj.h2538
2. Ely EW, Shintani A, Truman B, Speroff T, Gordon SM, Harrell FE, et al. Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. JAMA. 2004;291(14):1753–62. https://doi.org/10.1001/jama.291.14.1753
3. Pandharipande P, Girard T, Jackson J, Morandi A, Thompson J, Pun B, et al. Long-term cognitive impairment after critical illness. N Engl J Med. 2013;369(14):1306–16. https://doi.org/10.1056/nejmoa1301372
4. Girard TD, Exline MC, Carson SS, Hough CL, Rock P, Gong MN. Haloperidol and ziprasidone for treatment of delirium in critical illness. N Engl J Med. 2019;380(18):1778–80. https://doi.org/10.1056/nejmc1901272
5. Smit L, Slooter AJC, Devlin JW, Trogrlic Z, Hunfeld NGM, Osse RJ, et al. Efficacy of haloperidol to decrease the burden of delirium in adult critically ill patients: the EuRIDICE randomized clinical trial. Crit Care. 2023;27(1):413. https://doi.org/10.1186/s13054-023-04692-3
6. Devlin JW, Skrobik Y, Gélinas C, Needham DM, Slooter AJC, Pandharipande PP, et al. Clinical practice guidelines for the prevention and management of pain, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the ICU. Crit Care Med. 2018;46(9):e825–73. https://doi.org/10.1097/ccm.0000000000003299
7. Riker RR, Shehabi Y, Bokesch PM, Ceraso D, Wisemandle W, Koura F, et al. Dexmedetomidine vs midazolam for sedation of critically ill patients: a randomized trial. JAMA. 2009;301(5):489–99. https://doi.org/10.1001/jama.2009.56
8. Shehabi Y, Howe BD, Bellomo R, Arabi YM, Bailey M, Bass FE, et al. Early sedation with dexmedetomidine in critically ill patients. N Engl J Med. 2019;380(26):2506–17. https://doi.org/10.1056/nejmoa1904710
9. Burry LD, Cheng W, Williamson DR, Adhikari NK, Egerod I, Kanji S, et al. Pharmacological and non-pharmacological interventions to prevent delirium in critically ill patients: a systematic review and network meta-analysis. Intensive Care Med. 2021;47(9):943–60. https://doi.org/10.1007/s00134-021-06490-3
10. Skrobik Y, Duprey MS, Hill NS, Devlin JW. Low-dose nocturnal dexmedetomidine prevents ICU delirium. a randomized, placebo-controlled trial. Am J Respir Crit Care Med. 2018;197(9):1147–56. https://doi.org/10.1164/rccm.201710-1995oc
11. Liu X, Xiong J, Tang Y, Gong CC, Wang DF. Role of dexmedetomidine in the treatment of delirium in critically ill patients: a systematic review and meta-analysis. Minerva Anestesiol. 2021;87(1):65–76. https://doi.org/10.23736/s0375-9393.20.14492-4
12. Godet T, Louis C, Rieu B, Jong AD, Couhault P, Pradel G, et al. Dexmedetomidine for treatment of hyperactive delirium in non-intubated ICU patients: the 4D randomized clinical trial. Intensive Care Med. 2025;51(12):2305–17. https://doi.org/10.1007/s00134-025-08135-1
13. Zimmermann S, Hollinger A, Achermann R, von Felten S, Sutter R, Rüegg S, et al. Comparison of propofol and dexmedetomidine infused overnight to treat hyperactive and mixed ICU delirium: a prospective randomised controlled clinical trial. J Clin Med. 2025;14(12):4348. https://doi.org/10.3390/jcm14124348
14. Liu J, Wang C, Nie X, Yang R, Wang M, Ma X, et al. Olanzapine versus low-dose dexmedetomidine for delirium in patients with critical illness: a randomized clinical trial. Am J Respir Crit Care Med. 2026;212(8):1845–8. https://doi.org/10.1093/ajrccm/aamag235
15. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71. https://doi.org/10.1136/bmj.n71
16. Campbell M, McKenzie JE, Sowden A, Katikireddi SV, Brennan SE, Ellis S, et al. Synthesis without meta-analysis (SWiM) in systematic reviews: reporting guideline. BMJ. 2020;368:l6890. https://doi.org/10.1136/bmj.l6890
17. Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA extension for scoping reviews (PRISMA-ScR): checklist and explanation. Ann Intern Med. 2018;169(7):467–73. https://doi.org/10.7326/m18-0850
18. Ely EW, Inouye SK, Bernard GR, Gordon S, Francis J, May L, et al. Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). JAMA. 2001;286(21):2703–10. https://doi.org/10.1001/jama.286.21.2703
19. Bergeron N, Dubois MJ, Dumont M, Dial S, Skrobik Y. Intensive care delirium screening checklist: evaluation of a new screening tool. Intensive Care Med. 2001;27(5):859–64. https://doi.org/10.1007/s001340100909
20. Flükiger J, Hollinger A, Speich B, Meier V, Tontsch J, Zehnder T, et al. Dexmedetomidine in prevention and treatment of postoperative and intensive care unit delirium: a systematic review and meta-analysis. Ann Intensive Care. 2018;8(1):92. https://doi.org/10.1186/s13613-018-0437-z
21. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366:l4898. https://doi.org/10.1136/bmj.l4898
22. Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al. ROBINS-i: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ. 2016;355:i4919. https://doi.org/10.1136/bmj.i4919

23. Yusuf S, Peto R, Lewis J, Collins R, Sleight P. Beta blockade during and after myocardial infarction: an overview of the randomized trials. Prog Cardiovasc Dis. 1985;27(5):335–71. https://doi.org/10.1016/s0033-0620(85)80003-7

24. Luo D, Wan X, Liu J, Tong T. Optimally estimating the sample mean from the sample size, median, mid-range, and/or mid-quartile range. Stat Methods Med Res. 2018;27(6):1785–805. https://doi.org/10.1177/0962280216669183

25. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Methodol. 2014;14(1):135. https://doi.org/10.1186/1471-2288-14-135

26. Veroniki AA, Jackson D, Viechtbauer W, Bender R, Bowden J, Knapp G, et al. Methods to estimate the between-study variance and its uncertainty in meta-analysis. Res Synth Methods. 2016;7(1):55–79. https://doi.org/10.1002/jrsm.1164

27. IntHout J, Ioannidis JPA, Borm GF. The hartung-knapp-sidik-jonkman method for random effects meta-analysis is straightforward and considerably outperforms the standard DerSimonian-laird method. BMC Med Res Methodol. 2014;14(1):25. https://doi.org/10.1186/1471-2288-14-25

28. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327(7414):557–60. https://doi.org/10.1136/bmj.327.7414.557

29. Sterne JAC, Sutton AJ, Ioannidis JPA, Terrin N, Jones DR, Lau J, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. BMJ. 2011;343(jul22 1):d4002. https://doi.org/10.1136/bmj.d4002

30. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008;336(7650):924–6. https://doi.org/10.1136/bmj.39489.470347

31. Reade MC, O'Sullivan K, Bates S, Goldsmith D, Ainslie WR, Bellomo R. Dexmedetomidine vs. haloperidol in delirious, agitated, intubated patients: a randomised open-label trial. Crit Care. 2009;13(3):R75. https://doi.org/10.1186/cc7890

32. Bakri MH, Ismail EA, Ibrahim A. Comparison of dexmedetomidine or ondansetron with haloperidol for treatment of postoperative delirium in trauma patients admitted to intensive care unit: randomized controlled trial. Anaesth Pain Intensive Care. 2015;19(2):118–23.

33. Reade MC, Eastwood GM, Bellomo R, Bailey M, Bersten A, Cheung B, et al. Effect of dexmedetomidine added to standard care on ventilator-free time in patients with agitated delirium: a randomized clinical trial. JAMA. 2016;315(14):1460–8. https://doi.org/10.1001/jama.2016.2707

34. Carrasco G, Baeza N, Cabré L, Portillo E, Gimeno G, Manzanedo D, et al. Dexmedetomidine for the treatment of hyperactive delirium refractory to haloperidol in nonintubated ICU patients: a nonrandomized controlled trial. Crit Care Med. 2016;44(7):1295–306. https://doi.org/10.1097/ccm.0000000000001622

35. Liu S, Zhao R, Yang R, Zhao H, Ji C, Duan M, et al. Are dexmedetomidine and olanzapine suitable to control delirium in critically ill elderly patients? a retrospective cohort study. Biomed Pharmacother. 2021;139:111617. https://doi.org/10.1016/j.biopha.2021.111617

36. Harrison S, Jones HE, Martin RM, Lewis SJ, Higgins JPT. The albatross plot: a novel graphical tool for presenting results of diversely reported studies in a systematic review. Res Synth Methods. 2017;8(3):281–9. https://doi.org/10.1002/jrsm.1239

37. Sessler CN, Gosnell MS, Grap MJ, Brophy GM, O'Neal PV, Keane KA, et al. The richmond agitation-sedation scale: validity and reliability in adult intensive care unit patients. Am J Respir Crit Care Med. 2002;166(10):1338–44. https://doi.org/10.1164/rccm.2107138

38. Friedrich JO, Adhikari NKJ, Beyene J. The ratio of means method as an alternative to mean differences for analyzing continuous outcome variables in meta-analysis: a simulation study. BMC Med Res Methodol. 2008;8(1):32. https://doi.org/10.1186/1471-2288-8-32

39. Burry L, Hutton B, Williamson DR, Mehta S, Adhikari NK, Cheng W, et al. Pharmacological interventions for the treatment of delirium in critically ill adults. Cochrane Database Syst Rev. 2019;9(9):CD011749. https://doi.org/10.1002/14651858.cd011749.pub2

40. Lee JM, Cho YJ, Ahn EJ, Choi GJ, Kang H. Pharmacological strategies to prevent postoperative delirium: a systematic review and network meta-analysis. Anesth Pain Med (Seoul). 2021;16(1):28–48. https://doi.org/10.17085/apm.20079

41. Minami T, Watanabe H, Kato T, Ikeda K, Ueno K, Matsuyama A, et al. Dexmedetomidine versus haloperidol for sedation of non-intubated patients with hyperactive delirium during the night in a high dependency unit: study protocol for an open-label, parallel-group, randomized controlled trial (DEX-HD trial). BMC Anesthesiol. 2023;23(1):193. https://doi.org/10.1186/s12871-023-02158-1