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Chen K, Lu Z, Xin YC, Cai Y, Chen Y, Pan SM

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Alpha-2 agonists for long-term sedation during mechanical ventilation in critically ill patients (Review)

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[Intervention Review]

Alpha-2 agonists for long-term sedation during mechanical ventilation in critically ill patients

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ABSTRACT

Background

Sedation reduces patient levels of anxiety and stress, facilitates the delivery of care and ensures safety. Alpha-2 agonists have a range of effects including sedation, analgesia and antianxiety. They sedate, but allow staff to interact with patients and do not suppress respiration. They are attractive alternatives for long-term sedation during mechanical ventilation in critically ill patients.

Objectives

To assess the safety and efficacy of alpha-2 agonists for sedation of more than 24 hours, compared with traditional sedatives, in mechanically-ventilated critically ill patients.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL, Issue 10, 2014), MEDLINE (1946 to 9 October 2014), EMBASE (1980 to 9 October 2014), CINAHL (1982 to 9 October 2014), Latin American and Caribbean Health Sciences Literature (1982 to 9 October 2014), ISI Web of Science (1987 to 9 October 2014), Chinese Biological Medical Database (1978 to 9 October 2014) and China National Knowledge Infrastructure (1979 to 9 October 2014), the World Health Organization international clinical trials registry platform (to 9 October 2014), Current Controlled Trials metaRegister of controlled trials active registers (to 9 October 2014), the ClinicalTrials.gov database (to 9 October 2014), the conference proceedings citation index (to 9 October 2014) and the reference lists of included studies and previously published meta-analyses and systematic reviews for relevant studies. We imposed no language restriction.

Selection criteria

We included all randomized and quasi-randomized controlled trials comparing alpha-2 agonists (clonidine or dexmedetomidine) versus alternative sedatives for long-term sedation (more than 24 hours) during mechanical ventilation in critically ill patients.

Data collection and analysis

Two review authors independently assessed study quality and extracted data. We contacted study authors for additional information. We performed meta-analyses when more than three studies were included, and selected a random-effects model due to expected clinical heterogeneity. We calculated the geometric mean difference for continuous outcomes and the risk ratio for dichotomous outcomes. We described the effects by values and 95% confidence intervals (CIs). We considered two-sided $P < 0.05$ to be statistically significant.

Main results

Seven studies, covering 1624 participants, met the inclusion criteria. All included studies investigated adults and compared dexmedetomidine with traditional sedatives, including propofol, midazolam and lorazepam. Compared with traditional sedatives, dexmedetomidine reduced the geometric mean duration of mechanical ventilation by 22% (95% CI 10% to 33%; four studies, 1120 participants, low quality evidence), and consequently the length of stay in the intensive care unit (ICU) by 14% (95% CI 1% to 24%; five studies, 1223 participants, very low quality evidence). There was no evidence that dexmedetomidine decreased the risk of delirium (RR 0.85; 95% CI 0.63 to 1.14; seven studies, 1624 participants, very low quality evidence) as results were consistent with both no effect and appreciable benefit. Only one study assessed the risk of coma, but lacked methodological reliability (RR 0.69; 95% CI 0.55 to 0.86, very low quality evidence). Of all the adverse events included, the most commonly reported one was bradycardia, and we observed a doubled (111%) increase in the incidence of bradycardia (RR 2.11; 95% CI 1.39 to 3.20; six studies, 1587 participants, very low quality evidence). Our meta-analysis provided no evidence that dexmedetomidine had any impact on mortality (RR 0.99; 95% CI 0.79 to 1.24; six studies, 1584 participants, very low quality evidence). We observed high levels of heterogeneity in risk of delirium ($I^2 = 70\%$), but due to the limited number of studies we were unable to determine the source of heterogeneity through subgroup analyses or meta-regression. We judged six of the seven studies to be at high risk of bias.

Authors' conclusions

In this review, we found no eligible studies for children or for clonidine. Compared with traditional sedatives, long-term sedation using dexmedetomidine in critically ill adults reduced the duration of mechanical ventilation and ICU length of stay. There was no evidence for a beneficial effect on risk of delirium and the heterogeneity was high. The evidence for risk of coma was inadequate. The most common adverse event was bradycardia. No evidence indicated that dexmedetomidine changed mortality. The general quality of evidence ranged from very low to low, due to high risks of bias, serious inconsistency and imprecision, and strongly suspected publication bias. Future studies could pay more attention to children and to using clonidine.

PLAIN LANGUAGE SUMMARY

Dexmedetomidine and clonidine for long-term sedation during mechanical ventilation in critically ill patients

Review question

We reviewed the evidence about the safety and efficacy of dexmedetomidine and clonidine (known as alpha-2 agonists) for long-term sedation during mechanical ventilation in critically ill patients in the intensive care unit (ICU).

Background

Sedation is an important treatment for critically ill patients who need a machine to support breathing, because it reduces anxiety and stress and facilitates the delivery of nursing care. However, some commonly-used sedatives, such as propofol, midazolam and lorazepam, might decrease blood pressure, depress breathing, and delay awakening after a long-term infusion. They may prolong breathing support time and length of stay in hospital. Dexmedetomidine and clonidine sedate but allow staff to interact with patients, and they ease pain but do not depress breathing. Those treated with them could be more easy to awake, and more able to communicate their discomfort and pain. These drugs are therefore attractive alternatives for long-term sedation, and we planned to assess their efficacy and safety for long-term (more than 24 hours) sedation, compared with traditional sedatives.

Study characteristics

We searched the databases until October 2014. We included seven randomized controlled trials, with a total of 1624 participants, comparing dexmedetomidine versus traditional sedatives. All the studies required participants to have an anticipated need for sedation of more than 24 hours. The alternative sedatives included propofol, midazolam and lorazepam. We found no eligible studies in children or for clonidine. Of the seven studies, six were funded by the drug manufacturer, and one did not state any conflict of interest.

Key results

Compared with traditional sedatives, dexmedetomidine reduced the breathing support time by approximately one-fifth, and the length of stay time in ICU by one-seventh. Dexmedetomidine was at least as effective as traditional sedatives for producing sedation and maintaining a light sedation level. There was no clear evidence in support of dexmedetomidine reducing the risk of delirium (a kind of acute confusion state), as results were consistent with both no effect and appreciable benefit. We had insufficient information to draw conclusions about reducing the risk of coma. Dexmedetomidine doubled the incidence of slow heartbeat, which was the most commonly reported adverse event. Our review provides no evidence that dexmedetomidine changed the overall death rate.

Quality of the evidence

The general quality of evidence ranged from very low to low, as most of the studies were at high risk of bias, serious inconsistency and imprecision, or strongly suspected publication bias.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Dexmedetomidine compared to traditional sedative agents for long-term sedation during mechanical ventilation in critically ill patients

Dexmedetomidine compared to traditional sedative agents for long-term sedation during mechanical ventilation in critically ill patients

Patient or population: Critically ill patients requiring long-term sedation during mechanical ventilation

Settings: ICUs

Intervention: Dexmedetomidine

Comparison: traditional sedative agents

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	tradition- al sedative agents	Dexmedetomidine				
Duration of mechanical ventilation	Not estimable	Not estimable	Relative decrease 22% in the geometric mean (95% CI 10% to 33%)	1120 (4 RCTs)	⊕⊕⊕⊕ LOW 1,2	Alpha-2 agonists reduced geometric mean duration of mechanical ventilation by 0.25 (95% CI 0.10 to 0.40), corresponding to a reduction of 22% in the geometric mean (95% CI 10% to 33%). The relative change in geometric means usually produces similar results to the relative change in arithmetic means.
Risk of delirium	Study population		RR 0.85 (0.63 to 1.14)	1624 (7 RCTs)	⊕⊕⊕⊕ VERY LOW 3,4,5,6	-
	266 per 1000	226 per 1000 (167 to 303)				
	Low					
	76 per 1000 ⁸	65 per 1000 (48 to 87) ⁸				
	High					
	824 per 1000 ⁸	700 per 1000 (519 to 939) ⁸				

Risk of coma	Study population		RR 0.69 (0.55 to 0.86)	103 (1 RCT)	⊕⊕⊕⊕ VERY LOW 1,2,7	-
	922 per 1000	636 per 1000 (507 to 793)				
Incidence of bradycardia	Study population		RR 2.11 (1.39 to 3.2)	1587 (6 RCTs)	⊕⊕⊕⊕ VERY LOW 10,7,9	-
	90 per 1000	189 per 1000 (124 to 287)				
	Low					
	39 per 1000 ⁸	82 per 1000 (54 to 125) ⁸				
	High					
	188 per 1000 ⁸	397 per 1000 (261 to 602) ⁸				
Duration of weaning	See comment			85 (1 RCT)	-	Only one study assessed this outcome and only reported median and range. We were not able to estimate a relative effect.
ICU length of stay	Not estimable	Not estimable	Relative decrease 14% in the geometric mean (95% CI 0.01% to 24%)	1223 (5 RCTs)	⊕⊕⊕⊕ VERY LOW 1,11,2	Sedation using alpha-2 agonists reduced geometric mean ICU LOS by 0.15 (95% CI 0.01 to 0.28), corresponding to a reduction of 14% in the geometric mean (95% CI 0.01% to 24%). Relative change in geometric means usually produces similar results to the relative change in arithmetic means.
Mortality	Study population		RR 0.99 (0.79 to 1.24)	1584 (6 RCTs)	⊕⊕⊕⊕ VERY LOW 10,5,9	-
	205 per 1000	203 per 1000 (162 to 254)				
	Moderate					
	192 per 1000 ¹²	190 per 1000 (152 to 238) ¹²				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval;

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

- ¹Downgraded by 1 point due to all the studies being at high risk of bias, which was considered very serious.
- ²Downgraded by 1 point because all the studies received funding support from pharmaceutical firms and thus publication bias was strongly suspected.
- ³Downgraded by 1 point due to 6 of the 7 studies being at high risk of bias, which was considered serious.
- ⁴Downgraded by 1 point because the heterogeneity is substantial and thus inconsistency was serious.
- ⁵Downgraded by 1 point because results were consistent with both no effect and appreciable benefit, and thus imprecision was serious.
- ⁶Downgraded by 1 point because 6 of the 7 studies received funding support from pharmaceutical firms and thus publication bias was strongly suspected.
- ⁷Downgraded by 1 point because the sample size was small (less than 2000) and thus inconsistency was serious.
- ⁸The baseline risk varies broadly among studies, and thus we chose the lowest and highest control group risk in the included studies.
- ⁹Downgraded by 1 point due to 5 of the 6 studies being at high risk of bias, which was considered serious.
- ¹⁰Downgraded by 1 point because 5 of the 6 studies received funding support from pharmaceutical firms and thus publication bias was strongly suspected.
- ¹¹Downgraded by 1 point due to wide confidence interval, although there may still be enough precision to make decisions about the utility of the intervention.
- ¹²There was little variation in the baseline risk across the studies, and thus we calculated the median control group risk.

BACKGROUND

Description of the condition

Sedation has become an important treatment in intensive care settings, especially for those undergoing mechanical ventilation. In the United States, half of patients with mechanical ventilation received intravenous sedation for more than 70% of their ventilation time (Wunsch 2009). Sedation could reduce levels of anxiety and stress, facilitate the delivery of nursing care, prevent self extubation and ensure synchrony with mechanical ventilation (Gehlbach 2002).

Most physicians choose propofol and benzodiazepines for long-term sedation (Mehta 2011). Propofol is fast onset and offset, but decreases blood pressure, and may cause lipid metabolism disorder and fatal propofol infusion syndrome after long-term use (Kam 2007; Miller 1998). Although benzodiazepines have little effect on blood pressure, they may cause apnoea and respiratory depression (Watling 1996). Benzodiazepines tend to be accumulated in body tissues and thus lead to delayed awakening (Shelly 1991). Furthermore, benzodiazepines might be associated with high risks of delirium and coma (Agarwal 2010; Pandharipande 2006; Pandharipande 2008; Watson 2008), which increase ventilation time, mortality and healthcare costs (Dubois 2001; Ely 2004).

Increasingly, many institutions use sedation strategies, such as nursing-implemented sedation protocols and daily interruption to minimize the use of sedatives and limit the adverse events. These strategies reduce the dosage of sedatives, ventilation time and intensive care unit length of stay (ICU LOS) (Aitken 2012; Brook 1999; Burry 2014; Girard 2008), but lack of physicians' specific order and nursing acceptance have prevented them from being widely adopted. A survey of members of the Society of Critical Care Medicine showed that only 64% of respondents used sedation protocols, and 40% used interruption of sedation every day (Tanios 2009). Moreover, even when physicians applied sedation strategies, the choice of sedatives - for example, using short-acting, non-benzodiazepine sedatives rather than benzodiazepines - could still affect the ventilation time and hospital stay (Carson 2006; Pandharipande 2010). This is probably because these sedatives are easy to titrate and rapid to wake from, which in turn helps to finish sedation protocols and daily interruption.

Results from recent studies suggest that a strategy of light sedation could reduce ventilation time and ICU LOS (Shehabi 2012; Treggiari 2009). In addition, many investigators also recommend that any sedation strategy should incorporate analgesia, due to the difficulty of determining pain in critically ill patients (Fraser 2007) and the favourable results in shorter ventilation time, weaning time and ICU LOS (Breen 2005). A randomized controlled trial (RCT) found that when all the participants received intravenous analgesia (morphine), those with no infusion of sedatives had shorter ventilation time and ICU LOS, although more occurrences of delirium, than those with protocolized sedation and daily interruption (Strom 2010). The 'protocol of no sedation' in Strom 2010 was not really a protocol without any sedation, since morphine has a mild sedative effect, but it explored new challenges for sedation management: whenever possible, using the minimum level of sedation, providing adequate pain control and making a careful trade-off between the level of sedation and the patient's comfort and safety. A sedative agent that provided lighter sedation,

less pain and fewer adverse events would therefore be an attractive alternative.

Description of the intervention

Alpha-2 agonists have a wide range of effects including sedation, analgesia and relief of anxiety (Mantz 2011; Pichot 2012). These effects are mainly mediated through adrenoceptors of the alpha-2a subtype, which are distributed in the locus coeruleus (Gregoretti 2009; Mantz 2011). Unlike benzodiazepines and propofol, which inhibit the neurons in the central nervous system, alpha-2 agonists reduce the activity but preserve the reactivity of neurons in the locus coeruleus. Alpha-2 agonists therefore sedate but allow staff to interact with patients and do not suppress the respiratory drive. Alpha-2 agonists might also be involved in neuroprotection and inflammatory responses, which may potentially help protect against the occurrence of delirium or coma (Mantz 2011). The adverse events of alpha-2 agonists, such as bradycardia and hypotension, are mediated via adrenoceptors of the alpha-2 in the medullary dorsal motor nucleus and motor complex, and are thus independent of sedative effect (Gregoretti 2009; Pichot 2012).

Clonidine and dexmedetomidine are two extensively-studied alpha-2 agonists, and both have similar mechanisms and adverse events. Although physicians have used clonidine to treat hypertension and acute withdrawal syndrome (Bohrer 1990; Gregoretti 2009), or have used it as an anaesthetic adjuvant (Dahmani 2010; Gregoretti 2009; Lambert 2014), its use for sedation remains 'off label' in many countries. Dexmedetomidine has a higher alpha-2/alpha-1 selectivity ratio (dexmedetomidine 1620:1, clonidine 220:1) (Virtanen 1988). The US Food and Drug Administration (FDA) authorized it for sedation during mechanical ventilation in 1999, and it can also be used as an analgesic adjuvant for acute postoperative pain control (Aho 1991; Jessen 2013). Dexmedetomidine is now available in the United States, Asia, the Middle East, Australia and Europe (Mantz 2011; Pichot 2012).

Clonidine is usually administered to adults intravenously at a dose of 2 mcg/kg per hour, or given as a bolus of 50 mcg to 150 mcg every eight hours (Ise 2002; Jamadarkhana 2010). The oral dose of clonidine is 50 mcg to 600 mcg every eight hours (Jamadarkhana 2010). The maintenance infusion rate of dexmedetomidine is 0.2 mcg/kg per hour to 0.7 mcg/kg per hour, for less than 24 hours (Precedex Prescribing Information).

How the intervention might work

Several RCTs showed alpha-2 agonists for long-term sedation reduced the duration of mechanical ventilation compared with traditional sedatives (Riker 2009; Ruokonen 2009; Spies 2003). Two aspects of alpha-2 agonists might be related to this reduction: one could be that people treated with alpha-2 agonists were more arousable, easier to communicate with and more able to express pain and needs (Martin 2003; Ruokonen 2009). The analgesia-based sedation retained spontaneous respiration, and facilitated the delivery of care and the implementation of spontaneous breathing trials (Bailey 1991; Hall 2000; Hall 2001; Hsu 2004). A second aspect could be that alpha-2 agonists were associated with fewer occurrence of delirium and coma (Pandharipande 2007; Riker 2009; Rubino 2010), probably because they work differently to propofol and benzodiazepines, and provide sleep-like sedation (Huupponen 2008; Mason 2009).

Why it is important to do this review

Although some RCTs of long-term sedation suggest that alpha-2 agonists could reduce the duration of mechanical ventilation and delirium, other RCTs disagree: they found no improvement in ventilation time (Pandharipande 2007) and even a higher incidence of delirium (Ruokonen 2009). The FDA did not approve clonidine for sedation and only authorized dexmedetomidine infusions for less than 24 hours. There was therefore no way to know whether they were safe and effective for longer sedation. A previous meta-analysis assessed the effects of dexmedetomidine in critically ill patients and found no difference in ventilation time or incidence of delirium compared with traditional sedatives or placebo (Tan 2010). But a number of RCTs have been published since its last search in 2009 (Jakob 2012 MIDE; Jakob 2012 PRODEX; Shehabi 2013), and a comment on that meta-analysis pointed out flaws in methodology (for example, unit-of-analysis error, confusion of agitation with delirium, and inadequate investigation of heterogeneity), which weaken the value of its results (Tejani 2010). They included RCTs investigating both short-term and long-term sedation, but most were short-term, and thus provided limited information on long-term safety and efficacy.

Despite the theoretical advantages of alpha-2 agonists, their safety and efficacy for long-term use remain controversial. We also consider that people undergoing long-term ventilation and sedation are substantially different from those receiving short-term treatment; they have a different disease spectrum, are more critically ill, need more dosage of sedatives, are more exposed to the adverse events of sedatives, and are more likely to wake up later. A comprehensive synthesis is therefore needed to assess whether alpha-2 agonists are safe and whether they have advantages over traditional sedatives for long-term sedation, by reducing the duration of mechanical ventilation and the risks of delirium and coma.

OBJECTIVES

To assess the safety and efficacy of alpha-2 agonists for sedation of more than 24 hours, compared with traditional sedatives, in mechanically-ventilated critically ill patients.

METHODS

Criteria for considering studies for this review

Types of studies

We include all randomized and quasi-randomized controlled trials. Quasi-randomized controlled trials include those trials that use inappropriate randomization strategies (e.g. alternation, birth date, hospital registration number, etc.) (Higgins 2011a).

We exclude cluster-randomized, cross-over and non-randomized trials.

Types of participants

We include randomized controlled trials (RCTs) of critically ill participants of any age, except neonates, who required intensive care and invasive mechanical ventilation when recruited.

We exclude RCTs in which participants only had non-invasive mechanical ventilation.

Types of interventions

We include studies comparing clonidine or dexmedetomidine versus alternative sedative agents. The alternative sedatives included benzodiazepines, such as midazolam or diazepam, propofol and other sedatives.

We include studies which explicitly report that each participant was anticipated to need sedation for more than 24 hours. There was no limitation for dose, frequency or route of administration of alpha-2 agonists.

We exclude studies in which all participants were sedated for less than 24 hours or studies without an explicit statement that they required or anticipated participants to have sedation for more than 24 hours. We exclude studies that compare one alpha-2 agonist with another.

Types of outcome measures

Primary outcomes

1. Duration of mechanical ventilation (as defined by authors of the studies).
2. Risk of delirium, measured with any diagnostic criteria, such as the confusion assessment method for the intensive care unit (CAM-ICU).
3. Risk of coma (as defined by authors of the studies).

Secondary outcomes

1. Adverse events:
 - a. incidence of bradycardia (as defined by authors of the studies);
 - b. incidence of hypotension (as defined by authors of the studies);
 - c. incidence of hypertension (as defined by authors of the studies);
 - d. any other adverse events.
2. Proportion of sedation time spent at target sedation level (as defined by authors of the studies).
3. Duration of weaning (time from weaning to extubation as defined by authors of the studies).
4. intensive care unit length of stay (ICU LOS).
5. Mortality; if mortality is assessed at various follow-up times (e.g. ICU mortality, 30-day mortality, one-year mortality), we will include only the one that most closely approximates to that used in the other included studies.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL, *The Cochrane Library*, Issue 10, 2014; see Appendix 1 for detailed search strategy), MEDLINE (Ovid SP, 1946 to 9 October 2014; see Appendix 2), EMBASE (Ovid SP, 1980 to 9 October 2014; see Appendix 3), CINAHL (EBSCO host, 1982 to 9 October 2014; see Appendix 4), Latin American and Caribbean Health Sciences Literature (LILACS, via BIREME interface, 1982 to 9 October 2014; see Appendix 5), ISI Web of Science (1987 to 9 October 2014; see Appendix 6), Chinese Biological Medical Database (CBM, 1978 to 9 October 2014; see Appendix 7) and China National Knowledge

Infrastructure (CNKI, 1979 to 9 October 2014; see [Appendix 8](#)) for relevant studies.

We imposed no language and publication status restrictions. However, we excluded studies without detailed methodological information. Detailed methodological information means that the information obtained from full copies, abstracts or study authors should be sufficient to enable us to make judgements on the overall study quality.

Searching other resources

We searched for unpublished or ongoing trials on the World Health Organization international clinical trials registry platform WHO ICTRP (www.who.int/ictip/search/en/), Current Controlled Trials metaRegister of controlled trials (www.isrctn.com/page/mrct) active registers, and the clinicaltrials.gov database.

We also searched the conference proceedings citation index.

We handsearched the reference lists of included studies and previously published meta-analyses and systematic reviews for relevant studies ([Lin 2012](#); [Tan 2010](#); [Xia 2013](#); [Zhuo 2012](#)). We contacted the first author and the corresponding author of the included studies for information on other published and unpublished studies.

Data collection and analysis

Selection of studies

Two review authors (KC and YCX) independently scanned each title and abstract retrieved by the search strategy. We excluded irrelevant studies in this step. We excluded studies in abstract only and where no detailed methodological information could be obtained from the study authors. We obtained full copies of the remaining studies for further assessment. Our methodologist (YIC) resolved any disagreements unresolved by consensus. We used Endnote X7 to manage the search results and the articles. We noted the reasons for exclusion in Endnote X7. We were not blinded to the study authors, institutions or journals.

Data extraction and management

Two review authors (KC and YCX) independently extracted data from the articles using a modified version of the Cochrane Anaesthesia Review Group's (CARG) data extraction form ([Appendix 9](#)). We selected three articles randomly to test our form before formal extraction. We exported data from these articles to doc.google.com. Our statistician (YC) resolved inconsistent data extraction between the two review authors.

Assessment of risk of bias in included studies

Two review authors (KC and YCX) independently assessed the risk of bias using the Cochrane Collaboration's tool ([Higgins 2011b](#)) in the following seven key domains:

1. Random sequence generation;
2. Allocation concealment;
3. Blinding of participants and personnel;
4. Blinding of outcome assessment;
5. Incomplete outcome data;
6. Selective reporting;

7. Other bias (whether the groups were balanced at baseline, whether the co-interventions were similar, etc.).

We assessed blinding for each outcome as recommended. We judged each domain as 'low risk', 'high risk' or 'unclear risk'. We noted the summary of known facts and the source of this information for each domain. We asked the authors of the study for clarification if any details were unclear.

We tested the 'Risk of bias' assessment tool on some similar studies. When KC and YCX disagreed, we consulted our methodologist (YIC) and content specialists (SMP and ZJL). After reaching consensus, we classified each included study into one of three categories, as follows.

1. Low risk of bias: low risk of bias for all key domains.
2. Unclear risk of bias: unclear risk of bias for one or more key domains.
3. High risk of bias: high risk of bias for one or more key domains.

We generated a 'Risk of bias' graph and a 'Risk of bias' summary. We also reported the risk of selective outcome reporting in the Results section under [Assessment of risk of bias in included studies](#).

We performed the kappa test to evaluate the interobserver reliability between two review authors (KC and YCX).

Measures of treatment effect

We calculated the geometric mean difference (GMD) for continuous outcomes and the risk ratio (RR) for dichotomous outcomes. We describe the effects by their values and 95% confidence intervals (CIs). We considered two-sided $P < 0.05$ to be statistically significant.

Unit of analysis issues

We expected all the trials to be simple parallel-group designs. The unit of analysis was a single measurement for each outcome from each participant.

Dealing with missing data

We tried to contact the study authors for missing data and further information twice by e-mail. For those missing data that could not be obtained from authors, we did the following:

1. If we judged missing data to be 'missing at random', we only analysed the available data. We categorized the data as 'missing at random' if the loss was unrelated to the actual values of the missing data ([Higgins 2011a](#)). For example, if participants died before receiving any study drugs.
2. If we judged missing data to be 'not missing at random' and meta-analysis was not feasible, we performed a qualitative synthesis.
3. If we could systematically meta-analyse missing data, we imputed average measurements for continuous outcomes and we inferred bad outcomes for categorical outcomes.

Assessment of heterogeneity

We measured heterogeneity using both the χ^2 statistic and the I^2 statistic. Values for I^2 of 25%, 50% and 75% corresponded to low, moderate and high degrees of heterogeneity, respectively ([Higgins 2003](#)). We considered there to be substantial heterogeneity when a P value of $\chi^2 < 0.10$ or $I^2 > 50\%$, or both (moderate

and high degrees of heterogeneity). If we identified substantial heterogeneity, we checked the data entered into Review Manager 5 (RevMan 5.3). If I^2 exceeded 75%, we did not perform meta-analyses.

Assessment of reporting biases

We had planned to generate funnel plots if there were more than 10 studies included in the meta-analyses of primary outcomes (Higgins 2011a). For continuous outcomes, we would have conducted the Egger test to assess funnel plot asymmetry; for dichotomous outcomes, we would have conducted the arcsine test (Sterne 2011). We would have performed all tests using STATA/SE 12.0.

Data synthesis

We performed meta-analyses only if we could include more than three studies. Otherwise, we undertook a qualitative synthesis. We selected a random-effects model due to expected clinical heterogeneity. We used the Mantel-Haenszel method to estimate dichotomous outcomes and the inverse variance method to estimate continuous outcomes. We did not perform a meta-analysis for 'Proportion of sedation time spent at target sedation level' because there was no consistent outcome measure and statistical methods for pooling such percentage rates are not well developed (Higgins 2011a). We would have synthesized the data of adult studies and paediatric studies separately if both data were available. We performed all statistical analyses using Review Manager 5 software (RevMan 5.3).

The data for the durations of mechanical ventilation, weaning and ICU LOS are always skewed. We performed meta-analyses on log-transformed data. If we could obtain means and standard deviations of raw data without log-transformation, we conducted a transformation using Method 1 mentioned in Higgins 2008. If means and standard deviations of raw data were not available, we estimated log-transformed means using log-transformed medians (Hozo 2005) and calculated approximate standard deviations by dividing the log-transformed interquartile range (log-transformed third quartile minus first quartile) by 1.35 (Higgins 2011b).

We did not make any assumptions about the distribution of censored data from time-to-event data (duration of mechanical ventilation and ICU LOS). Some of the studies analysed time-to-event data using, for instance, Cox's proportional-hazards regression model and Kaplan-Meier survival analyses. We undertook a narrative synthesis for these adjusted outcomes.

Subgroup analysis and investigation of heterogeneity

If there were adequate data we performed subgroup analyses as follows.

For duration of mechanical ventilation and duration of weaning

1. Dexmedetomidine compared with clonidine.
2. Class of alternative agents, classified according to the 'Anatomical Therapeutic Chemical' (ATC) classification system advocated by the World Health Organization's collaborating centre for drugs statistics methodology.
3. Sedation with or without analgesics/pain control.

For risk of delirium

1. Different delirium scores used.
2. Class of alternative agents.

For risk of coma and adverse events

1. Class of alternative agents.
2. Dexmedetomidine compared with clonidine.
3. Rapid-dosing regimens compared with slow-dosing regimens, where rapid-dosing regimens include intravenous bolus and continuous intravenous infusion with initial loading infusion, and where slow-dosing regimens include continuous intravenous infusion without initial loading infusion and oral or nasogastric administration.

For ICU LOS and mortality

1. Class of alternative agents.
2. Dexmedetomidine compared with clonidine.
3. Type of ICU (e.g. mixed ICU, medical ICU, surgical ICU, coronary care unit (CCU), respiratory care unit, burn unit).

We determined whether there were differences of effect size among subgroups based on the P values from tests for subgroup differences (Higgins 2011a). If differences existed, we compared the direction and magnitude of effect size in these subgroups with each other.

If there were adequate data, we performed random-effects meta-regression to investigate how mean ventilation time (log-transformed) of the included studies was associated with the risk of delirium (Thompson 2002). We performed meta-regression using R 3.0.2 with 'Metafor' package (version 1.9-2). We used a restricted maximum-likelihood estimator method to calculate the amount of heterogeneity (Viechtbauer 2010). We determined whether this difference was statistically significant based on the P value of the coefficients.

Sensitivity analysis

If there were sufficient studies, we undertook sensitivity analyses by excluding studies as follows:

1. Studies at high or unclear risk of bias;
2. Studies of a non-standardized design: RCTs without a target sedation level or using non-intravenous administration.

We also undertook sensitivity analyses by pooling observed data only, without any imputation.

Summary of findings

We used the principles of the GRADE system (Guyatt 2008) to assess the quality of the body of evidence associated with specific outcomes: duration of mechanical ventilation, rate of delirium, rate of coma, rate of bradycardia, duration of weaning, ICU length of stay and mortality. We constructed a 'Summary of findings' table using GRADE software. The GRADE approach appraised the quality of a body of evidence based on the extent to which one can be confident that an estimate of effect or association reflects the item being assessed. The quality of a body of evidence is derived from within-study risk of bias (methodological quality), the directness of the evidence, heterogeneity of the data, precision of effect estimates, and risk of publication bias.

RESULTS

Description of studies

Results of the search

Running the search strategy of electronic databases yielded 3009 citations: 1348 citations from western databases and 1661 citations from Chinese databases. We excluded 2956 citations based on abstract content alone. Three citations were in abstract only, and we failed to retrieve further information or to trace the original investigators. We performed full-text review of 53 citations, and finally included six citations in our data synthesis (and one citation in [Studies awaiting classification](#)).

One included citation reported on two independently-conducted multi-centre, randomized, double-blind studies, the MIDEK trial (clinicaltrials.gov Identifier: NCT00481312) and the PRODEX trial (clinicaltrials.gov Identifier: NCT00479661). We considered them as two discrete studies during data synthesis ([Jakob 2012 MIDEK](#): MIDEK trial; [Jakob 2012 PRODEX](#): PRODEX trial). We found two potentially relevant unpublished/ongoing studies from clinical trial registries and emailed the contact investigators ([NCT01059929](#); [NCT01760967](#)). One replied ([NCT01760967](#)), but provided no useful information ([Characteristics of ongoing studies](#) table shows detailed information about the ongoing studies). We did not obtain any information about unpublished or ongoing randomized controlled trials (RCTs) from authors of the included studies. [Figure 1](#) presents the entire study selection process.

Figure 1. Selection process for studies included in data synthesis.

Included studies

See [Characteristics of included studies](#).

We include seven studies in our review. Six studies were of a two-arm design. One used a four-arm design that compared dexmedetomidine infusion alone, midazolam infusion alone, dexmedetomidine infusion combined with midazolam infusion and dexmedetomidine infusion combined with midazolam bolus (Xu 2012). We extracted the data only from the dexmedetomidine-infusion-alone group and the midazolam-infusion-alone group. Five of the included studies were international multi-centre (Jakob 2012 MIDE; Jakob 2012 PRODE; Riker 2009; Ruokonen 2009; Shehabi 2013); one was multi-centre, conducted in the United States (Pandharipande 2007); and one was single-centre, conducted in China (Xu 2012). Six studies received funding support from pharmaceutical firms which manufacture dexmedetomidine (Jakob 2012 MIDE; Jakob 2012 PRODE; Pandharipande 2007; Riker 2009; Ruokonen 2009; Shehabi 2013), and one did not state any potential conflict of interest (Xu 2012).

Types of participants

There were 1624 participants meeting the inclusion criteria. The sample sizes of studies ranged from 37 to 501. All the studies recruited adults from mixed intensive care units (ICUs) which may include medical, surgical and trauma patients. All the studies required participants to have an anticipated need for sedation of at least 24 to 36 hours. The main exclusion criteria of the studies include conditions as follows: neurological disease, severe bradycardia, second or third degree atrioventricular conduction block, hepatic impairment and pregnancy.

Types of interventions

We found no eligible studies for clonidine. All the included studies compared dexmedetomidine with traditional sedatives. The traditional sedatives could be midazolam (Jakob 2012 MIDE; Riker 2009; Xu 2012), lorazepam (Pandharipande 2007), propofol (Jakob 2012 PRODE), or standard care (either propofol or midazolam) (Ruokonen 2009; Shehabi 2013). A total of 871 participants (53.6%) received dexmedetomidine, 393 (24.2%) midazolam, 51 (3.1%) lorazepam, 249 (15.3%) propofol or 60 (3.7%) standard care. All studies administered sedative agents intravenously. The infusion rate of dexmedetomidine varied among trials, ranging from 0.15 to 1.5 mcg/kg per hour. Only one study routinely administered loading doses of dexmedetomidine (Xu 2012).

Only four studies explicitly stated that participants might receive sedation prior to the study treatment (Jakob 2012 MIDE; Jakob 2012 PRODE; Pandharipande 2007; Riker 2009): three reported that the sedation scores at the time of study treatment initiation were similar between groups (Jakob 2012 MIDE; Jakob 2012 PRODE; Pandharipande 2007), and one started treatment only when the participants were within a prespecified range of sedation score (Riker 2009). Other studies reported no detailed information about sedation prior to the study treatment (Ruokonen 2009; Shehabi 2013; Xu 2012). All the studies stated that they titrated sedatives to a target sedation level: Jakob 2012 MIDE and Jakob 2012 PRODE set the target as a Richmond Agitation-Sedation Scale (RASS) score of 0 to -3 and assessed it every two hours; Pandharipande 2007 set it as a "clinically individualized target"

based on RASS and assessed it twice daily; Riker 2009 set it as a RASS score of -2 to 1 and assessed it every four hours; Ruokonen 2009 set it as a RASS score of -4 to 0 and assessed it every four hours; Shehabi 2013 set it as a RASS score of -2 to 1 and assessed it every four hours; Xu 2012 set it as a Motor Activity Assessment Scale (MAAS) score of 3 and assessed it every two hours. Three studies performed daily interruption as part of the study protocol (Jakob 2012 MIDE; Jakob 2012 PRODE; Ruokonen 2009). Six studies routinely gave opioids to treat pain during sedation (Jakob 2012 MIDE; Jakob 2012 PRODE; Pandharipande 2007; Riker 2009; Ruokonen 2009; Shehabi 2013) and one study did not report that they used analgesics (Xu 2012). Two studies used intravenous haloperidol to control delirium (Riker 2009; Shehabi 2013), and the others did not report any information about delirium treatment. Four studies stopped sedation after extubation (Jakob 2012 MIDE; Jakob 2012 PRODE; Pandharipande 2007; Riker 2009); two studies stopped it when the investigators thought it was no longer required (Riker 2009; Shehabi 2013); one study did not explicitly state the indication for sedation discontinuation (Xu 2012).

Types of outcome measures

Five studies reported on duration of mechanical ventilation (Jakob 2012 MIDE; Jakob 2012 PRODE; Riker 2009; Ruokonen 2009; Shehabi 2013). All the studies reported on the risk of delirium, based on the confusion assessment method for the intensive care unit (CAM-ICU). Three studies explicitly described the frequency of delirium assessment: Riker 2009 assessed it daily during sedation interruption; Ruokonen 2009 assessed it daily; Shehabi 2013 assessed it when the RASS score was more than -3. Only two studies explicitly described the follow-up period of delirium assessment: Pandharipande 2007 assessed it until hospital discharge or for 12 days; Riker 2009 assessed it during study treatment. One study reported on the risk of coma (Pandharipande 2007). The investigators defined coma as a RASS score of -4 or -5 and assessed it until hospital discharge or for 12 days.

Excluded studies

Of the 46 studies excluded during full-text review, 44 were because they did not explicitly report the required or anticipated duration of sedation or did not meet the criteria, one because it was not an RCT and one because not all the participants were mechanically ventilated. The [Characteristics of excluded studies](#) table provides detailed reasons for the exclusions.

Risk of bias in included studies

Allocation

Five studies had adequate sequence generation (Jakob 2012 MIDE; Jakob 2012 PRODE; Pandharipande 2007; Riker 2009; Shehabi 2013). Two studies reported they used stratified randomization, but did not state in detail how they randomized the participants (Ruokonen 2009; Xu 2012). We contacted the authors of Ruokonen 2009 and Xu 2012 for additional methodological information, but no-one replied. We therefore judged them to be at 'unclear risk of bias for random sequence generation. Five studies had adequate allocation concealment (Jakob 2012 MIDE; Jakob 2012 PRODE; Pandharipande 2007; Riker 2009; Shehabi 2013). Two studies did not state that they concealed the randomization sequence (Ruokonen 2009; Xu 2012), and we therefore judged them to be at 'high' risk of bias for allocation concealment. The two review authors were in complete agreement for this domain.

Figure 2 and Figure 3 illustrate the proportion of studies with those judgements and the judgement made for each study. See the [Characteristics of included studies](#) for details of those judgements. .

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias): Subjective outcomes	Blinding of outcome assessment (detection bias): Objective outcomes	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Jakob 2012 MIDEX	+	+	+	+	+	-	+	+
Jakob 2012 PRODEX	+	+	+	+	+	-	+	+
Pandharipande 2007	+	+	+	+	+	+	+	-
Riker 2009	+	+	+	+	+	+	+	+
Ruokonen 2009	?	-	-	-	+	+	+	+
Shehabi 2013	+	+	-	-	+	+	+	+
Xu 2012	?	-	-	-	+	+	+	+

Blinding

Four studies used an adequate double-blinded design and described the details of the blinding method (Jakob 2012 MIDE^X; Jakob 2012 PRODE^X; Pandharipande 2007; Riker 2009). One study used a double-dummy design, but the blinding method was brittle and we believe that the study investigators could easily have broken the blinding (Ruokonen 2009). One study did not mention that the participants or the investigators were blinded, and therefore probably did not perform blinding (Xu 2012). One study stated that they were "unblinded" (Shehabi 2013). We believed blinding had little impact on these objective outcomes, and we therefore judged Ruokonen 2009, Xu 2012 and Shehabi 2013 to be at 'low' risk for blinding of outcome assessment in objective outcomes, but at 'high' risk for blinding of participants and personnel and blinding of outcome assessment in subjective outcomes. Agreement between the two review authors for blinding of participants and personnel was at 86% (kappa = 0.70). The two review authors were in complete agreement for blinding of outcome assessment, both subjective and objective outcomes.

Figure 2 and Figure 3 illustrate the proportion of studies with those judgements and the judgement made for each study. [Characteristics of included studies](#) showed the details for the judgements.

Incomplete outcome data

Five studies had low withdrawal rates, and reasons for withdrawal were explicitly reported and balanced across groups (Pandharipande 2007; Riker 2009; Ruokonen 2009; Shehabi 2013; Xu 2012). However, in Jakob 2012 MIDE^X and Jakob 2012 PRODE^X, withdrawal due to lack of efficacy was significantly more frequent in dexmedetomidine participants and would therefore inevitably bias the results. We judged them to be at 'high' risk of bias. The two review authors were in complete agreement on this domain.

Figure 2 and Figure 3 illustrate the proportion of studies with those judgements and the judgement made for each study. [Characteristics of included studies](#) showed the details for the judgements.

Selective reporting

There was no indications of selective reporting in any of the included studies. The two review authors were in complete agreement for this domain.

Other potential sources of bias

Six studies appeared to be free of other sources of bias (Jakob 2012 MIDE^X; Jakob 2012 PRODE^X; Riker 2009; Ruokonen 2009; Shehabi 2013; Xu 2012). One study used continuous infusion of lorazepam as a comparison intervention (Pandharipande 2007). Because of the long half-life of lorazepam, such a study design might increase the risk of coma in the control group, and we suspected it to be a potential source of bias. Agreement between the two review authors for other potential sources of bias was at 86% (kappa = 0.70).

Figure 2 and Figure 3 illustrate the proportion of studies with those judgements and the judgement made for each study. [Characteristics of included studies](#) showed the details for the judgements.

Effects of interventions

See: [Summary of findings for the main comparison Dexmedetomidine compared to traditional sedative agents for long-term sedation during mechanical ventilation in critically ill patients](#)

Duration of mechanical ventilation (Analysis 1.1; Analysis 1.2)

Four studies (1448 participants) compared the duration of mechanical ventilation (Jakob 2012 MIDE^X; Jakob 2012 PRODE^X; Riker 2009; Ruokonen 2009), and showed the median time of ventilation in the dexmedetomidine group was less than control. Jakob 2012 MIDE^X, Jakob 2012 PRODE^X and Ruokonen 2009 analysed the data using Cox's proportional-hazards regression and Riker 2009 analysed it using Kaplan-Meier survival analysis. Three of them were statistically significant (Jakob 2012 MIDE^X; Jakob 2012 PRODE^X; Riker 2009), but one was not (Ruokonen 2009) (calculations from median/interquartile range to geometric mean/standard deviation (SD) are shown in Table 1). Riker 2009 reported the median but no interquartile range. We were unable to obtain the raw data, and thus could not estimate the standard deviation and add the data into our meta-analysis. We obtained data for Shehabi 2013 from the authors and pooled it with the other three studies (Jakob 2012 MIDE^X; Jakob 2012 PRODE^X; Ruokonen 2009). Meta-analysis of 1119 participants yielded a random-effects estimate of the geometric mean difference (MD) of -0.25 log hours (95% confidence interval (CI) -0.40 to -0.10, $P = 0.001$), corresponding to a reduction of 22% in the geometric mean (95% CI 10% to 33%). Neither the I^2 nor the χ^2 statistics indicated evidence of statistical heterogeneity across the trials, ($I^2 = 0\%$; $\chi^2 = 0.42$, $P = 0.94$).

We performed subgroup analysis for different classes of alternatives. The subgroups were small, with one or two studies in each. The results from all subgroups favoured dexmedetomidine, and we detected no significant difference between them ($P = 0.84$). We did not perform subgroup analyses for dexmedetomidine compared with clonidine or sedation with or without pain control, because of inadequate data.

Jakob 2012 MIDE^X and Jakob 2012 PRODE^X reported not only 'duration of mechanical ventilation', which included non-invasive ventilation time, but also 'time to extubation' which also matched our definition. We performed a post hoc sensitivity analysis to assess how the result would be changed if we extracted the data from 'time to extubation' instead of 'duration of mechanical ventilation'. The sensitivity analysis yielded a geometric mean difference of -0.34 log hours (95% CI -0.49 to -0.20, $P < 0.00001$), corresponding to a reduction of 29% in the geometric mean (95% CI 18% to 39%). We did not undertake sensitivity analyses by excluding studies at high risk of bias or studies with non-standardized design because of the small number of studies.

We were not able to conduct the Egger test because of the small number of studies, but we suspected reporting bias for this outcome, because these four studies received funding support from pharmaceutical firms which manufacture dexmedetomidine.

Risk of delirium (Analysis 1.3; Analysis 1.4)

The data for meta-analysis were available from all the studies, with 1624 participants (Jakob 2012 MIDE^X; Jakob 2012 PRODE^X; Pandharipande 2007; Riker 2009; Ruokonen 2009; Shehabi 2013; Xu 2012). The risk of delirium was numerically lower in the

dexmedetomidine group than in the control group (risk ratio (RR) 0.85; 95% CI 0.63 to 1.14), but was not statistically significant ($P = 0.27$). The heterogeneity was high across the trials ($I^2 = 70\%$).

We performed subgroup analyses for different classes of alternative agents. The number of studies within subgroups ranged from one to four, and the difference in effect size was significant among subgroups ($P = 0.02$). Pooled results from subgroups showed the risk of delirium was lower in participants with dexmedetomidine than in those with benzodiazepine derivatives (RR 0.81; 95% CI 0.59 to 1.09; 1007 participants) or propofol (RR 0.37; 95% CI 0.16 to 0.87; 495 participants), but higher than in participants with standard care (RR 1.44; 95% CI 0.86 to 2.41; 122 participants). There was a high level of heterogeneity in the subgroup of benzodiazepine derivatives ($I^2 = 72\%$), but a low level in the subgroup of standard care ($I^2 = 6\%$). Because all the studies assessed delirium based on the confusion assessment method for the intensive care unit (CAM-ICU), subgroup analyses for different delirium scores were not possible.

We performed meta-regression on log-transformed mean ventilation time using data from six studies (Jakob 2012 MIDE; Jakob 2012 PRODEX; Pandharipande 2007; Riker 2009; Ruokonen 2009; Shehabi 2013) (Table 2). The meta-regression did not show that the log-transformed mean ventilation time was associated with the risk of delirium ($P = 0.94$) and was unable to explain the heterogeneity ($R^2 = 0.00\%$).

We undertook a sensitivity analysis by pooling observed data without any imputation, and confirmed a nearly identical result (RR 0.84; 95% CI 0.63 to 1.14, $P = 0.27$). We did not undertake sensitivity analyses by excluding studies at high risk of bias or studies with non-standardized design, due to the small number of studies.

Two studies also reported on the number of delirium-free days during study treatment (Riker 2009) or a 12-day period (Pandharipande 2007). Riker 2009 showed participants treated with dexmedetomidine had more delirium-free days than those treated with midazolam (2.5 days vs 1.7 days, $P = 0.02$), but Pandharipande 2007 did not (dexmedetomidine: 9 days, lorazepam: 7 days, $P = 0.09$).

We were not able to conduct the arcsine test because of the small number of studies, but we suspected reporting bias for this outcome because six studies received funding support from pharmaceutical firms which manufacture dexmedetomidine (Jakob 2012 MIDE; Jakob 2012 PRODEX; Pandharipande 2007; Riker 2009; Ruokonen 2009; Shehabi 2013).

Risk of coma

Because only one study investigated the risk of coma (Pandharipande 2007; 103 participants), meta-analysis was impossible. In Pandharipande 2007, the risk of coma was 63% in the dexmedetomidine group and 92% in the lorazepam group ($P < 0.001$). Participants with dexmedetomidine also had more coma-free days than those in the lorazepam group (10 days vs 8 days, $P < 0.001$).

We were not able to conduct the arcsine test, but we suspected reporting bias for this outcome because Pandharipande 2007 received funding support from pharmaceutical firms which manufacture dexmedetomidine.

Adverse events

Incidence of bradycardia (Analysis 1.5; Analysis 1.6; Analysis 1.7)

Six studies, covering 1587 participants, reported on the incidence of bradycardia (Jakob 2012 MIDE; Jakob 2012 PRODEX; Pandharipande 2007; Riker 2009; Ruokonen 2009; Xu 2012). Compared with traditional sedatives, those participants allocated to dexmedetomidine had a 111% significantly higher incidence of bradycardia (RR 2.11; 95% CI 1.39 to 3.20, $P = 0.0004$). The statistical heterogeneity was moderate across the trials ($\text{Chi}^2 = 8.28$, $P = 0.14$; $I^2 = 40\%$).

We conducted two subgroup analyses, one for the class of alternative agents and one for the dosing regimens:

For subgroup analyses of different classes of alternative agents, the difference in effect size was significant ($P = 0.04$). Although all the pooled results from subgroups showed a higher incidence associated with dexmedetomidine, the standard care group had the highest risk ratio (RR 7.50; 95% CI 0.40 to 140.91; 85 participants) and the propofol group had the lowest (RR 1.20; 95% CI 0.74 to 1.94; 495 participants).

For subgroup analyses of different dosing regimens (rapid or slow), no between-groups difference was detected ($P = 0.32$).

We undertook a sensitivity analysis by pooling the observed data without any imputation, and confirmed almost the same result (RR 2.11; 95% CI 1.39 to 3.21). We did not undertake sensitivity analyses by excluding studies at high risk of bias or studies with non-standardized designs, due to the small number of studies.

Incidence of hypotension (Analysis 1.8; Analysis 1.9)

Six studies, covering 1587 participants, reported on the incidence of hypotension (Jakob 2012 MIDE; Jakob 2012 PRODEX; Pandharipande 2007; Riker 2009; Ruokonen 2009; Xu 2012). The risk of hypotension was higher with dexmedetomidine, but this difference was not statistically significant (RR 1.22; 95% CI 0.86 to 1.74, $P = 0.26$). The level of heterogeneity was high ($I^2 = 53\%$, $P = 0.07$).

We conducted two subgroup analyses, one for the class of alternative agents and one for the dosing regimens, but none of them indicated differences in effect size between subgroups (class of alternative agents, $P = 0.57$; dosing regimens, $P = 0.17$).

We undertook a sensitivity analysis by pooling the observed data without any imputation, and confirmed almost the same result (RR 1.22; 95% CI 0.86 to 1.73, $P = 0.27$). We did not undertake sensitivity analyses by excluding trials at high risk of bias or trials with non-standardized designs, due to the small number of trials.

Incidence of hypertension

Three trials, covering 1356 participants, reported on the incidence of hypertension (Jakob 2012 MIDE; Jakob 2012 PRODEX; Riker 2009). None of the trials reported a difference between dexmedetomidine and alternatives: in Jakob 2012 MIDE, the incidence of hypertension was 21.5% in the dexmedetomidine group and 20.8% in the midazolam group ($P = 0.913$). In Jakob 2012 PRODEX, the incidence of hypertension was 21.1% in the dexmedetomidine group and 15.0% in the propofol group ($P =$

0.08). In [Riker 2009](#), the incidence of hypertension was 18.9% in the dexmedetomidine group and 29.5% in the midazolam group ($P = 0.91$).

Other adverse events possibly caused by alpha-2 agonist

We added other alpha-2-associated adverse events that were reported to be significant in at least one study. Other adverse events included tachycardia, first-degree atrioventricular block, hyperglycaemia and hypoglycaemia.

1. Tachycardia

[Jakob 2012 PRODEX](#) reported tachycardia as a significant adverse event, and we therefore include it in our assessment. Four studies, covering 1462 participants, reported on the incidence of tachycardia ([Jakob 2012 MIDEX](#); [Jakob 2012 PRODEX](#); [Pandharipande 2007](#); [Riker 2009](#)). One of them indicated that dexmedetomidine was more likely to induce tachycardia than propofol (19.5% vs 11.3%, respectively; $P = 0.02$) ([Jakob 2012 PRODEX](#)). Two studies showed that participants allocated to dexmedetomidine compared with midazolam had a statistically significantly lower risk of tachycardia ([Jakob 2012 MIDEX](#): dexmedetomidine 13.8%, midazolam 21.6%, $P = 0.025$; [Riker 2009](#): dexmedetomidine 25.4%, midazolam 44.3%, $P < 0.001$), but one study comparing dexmedetomidine with lorazepam did not find a significant difference (dexmedetomidine 69%, lorazepam 73%, $P = 0.71$) ([Pandharipande 2007](#)). When we tried to pool these data, we detected an extremely high level of statistical heterogeneity ($I^2 = 84\%$), and therefore abandoned the analysis.

2. First-degree atrioventricular block

[Jakob 2012 PRODEX](#) reported first-degree atrioventricular block as a significant adverse event. Two studies, covering 993 participants, reported on the incidence of first-degree atrioventricular block ([Jakob 2012 MIDEX](#); [Jakob 2012 PRODEX](#)). In [Jakob 2012 PRODEX](#), the incidence was significantly higher in the dexmedetomidine group than in the propofol group (0.8% vs 3.7%, respectively; $P = 0.04$), but in [Jakob 2012 MIDEX](#), comparing dexmedetomidine with midazolam (1.2% in each group; $P = 0.99$), we did not find any difference.

3. Hyperglycaemia

[Riker 2009](#) reported hyperglycaemia as a significant adverse event. Three studies, totaling 1359 participants, reported on the incidence of hyperglycaemia ([Jakob 2012 MIDEX](#); [Jakob 2012 PRODEX](#); [Riker 2009](#)). Only in [Riker 2009](#) was the incidence higher in the dexmedetomidine group than in the midazolam group (56.6% vs 42.6%, respectively; $P = 0.02$). In the other studies, the incidence was low or absent, and did not reach statistical significance ([Jakob 2012 MIDEX](#): 2% in dexmedetomidine group and 2% in midazolam group; [Jakob 2012 PRODEX](#): 0.8% in dexmedetomidine group and 0% in propofol group).

4. Hypoglycaemia

[Jakob 2012 MIDEX](#) reported hypoglycaemia as a significant adverse event. Two studies, covering 993 participants, reported on the incidence of hypoglycaemia ([Jakob 2012 MIDEX](#); [Jakob 2012 PRODEX](#)). [Jakob 2012 MIDEX](#), comparing dexmedetomidine with midazolam, showed that the incidence in the dexmedetomidine group was higher (4% vs 0.8%, respectively; $P = 0.02$), while [Jakob](#)

[2012 PRODEX](#) compared dexmedetomidine with propofol, and showed the same incidence in both groups (1.2%; $P = 0.99$).

Proportion of sedation time spent at target sedation level (Analysis 1.11)

All the studies evaluated the proportion of sedation time spent at target sedation level. [Pandharipande 2007](#) reported that participants treated with dexmedetomidine spent a higher proportion of time at the target sedation level than did those treated with lorazepam. Both physicians and nurses assessed the sedation level in this study: the proportion assessed by nurses was 80% for the dexmedetomidine group and 67% for the lorazepam group ($P = 0.04$); the proportion assessed by physicians was 67% for the dexmedetomidine group and 55% for the lorazepam group ($P = 0.008$). Similarly, in [Shehabi 2013](#), there were more Richmond Agitation-Sedation Scale (RASS) assessment scores in the target range in the dexmedetomidine group (66%) than in the standard sedation group (38%) during the first 48 hours of the trial ($P = 0.01$). The other five trials showed similar proportions of time between study groups: in [Jakob 2012 MIDEX](#), 60.7% for the dexmedetomidine group and 56.6% for the midazolam group ($P = 0.15$); in [Jakob 2012 PRODEX](#), 64.6% for the dexmedetomidine group and 64.7% for the propofol group ($P = 0.97$); in [Riker 2009](#), 77.3% for the dexmedetomidine group and 75.1% for the midazolam group ($P = 0.18$); in [Ruokonen 2009](#), 64% for the dexmedetomidine group and 63% for the standard care group; in [Xu 2012](#), 52.8% for the dexmedetomidine group and 48.6% for the midazolam group. [Ruokonen 2009](#) also separately calculated the proportion of participants with a different sedation target: RASS -4 and RASS -3 to 0. Of those with RASS -4, participants on dexmedetomidine spent 42% of the time at the target level, compared with 62% for participants on standard care; of those with RASS -3 to 0, participants on dexmedetomidine spent 74% of the time at the target level, compared with 64% for participants on standard care.

Duration of weaning

One study reported on the duration of weaning ([Ruokonen 2009](#); 85 participants). The data for [Ruokonen 2009](#), sourced from the electronic supplementary material which was available online, show that the median weaning times were 59.4 hours for the dexmedetomidine group (range 0 - 259 hours) and 78.0 hours for the standard care group (either propofol or midazolam) (range 0 - 565 hours), but the difference was not statistically significant ($P = 0.270$).

Intensive care unit length of stay (ICU LOS) (Analysis 1.12)

Six trials, covering 1589 participants, compared intensive care unit (ICU) lengths of stay ([Jakob 2012 MIDEX](#); [Jakob 2012 PRODEX](#); [Pandharipande 2007](#); [Riker 2009](#); [Ruokonen 2009](#); [Shehabi 2013](#)). [Jakob 2012 MIDEX](#), [Jakob 2012 PRODEX](#) and [Ruokonen 2009](#) analysed the data using Cox's proportional-hazards regression, [Riker 2009](#) and [Pandharipande 2007](#) analysed it using Kaplan-Meier survival analysis and [Shehabi 2013](#) analysed it using Wilcoxon rank-sum tests. All the studies showed that the median ICU length of stay was shorter in the dexmedetomidine groups than in the control groups, but none of the studies showed statistically significant results. Since [Riker 2009](#) reported only the median without the interquartile range, we carried out meta-analysis only on the other five trials (calculations from median/interquartile range to

geometric mean/SD are shown in Table 1). Meta-analysis yielded a random-effects estimate of the geometric mean difference of -0.15 log days (95% CI -0.28 to -0.01, $P = 0.04$), a statistically significant finding corresponding to a reduction of 14% in the geometric mean (95% CI 1% to 24%). Neither the I^2 test (0%) nor the χ^2 test (0.28, $P = 0.99$) indicate the presence of statistical heterogeneity. Subgroup analyses for different classes of alternative agents did not find any significant difference in effect size between subgroups ($P = 0.93$). We did not undertake sensitivity analyses by excluding studies at high risk of bias or studies with non-standardized designs, due to the small number of studies.

Mortality (Analysis 1.13; Analysis 1.14)

Six studies, covering 1584 participants, assessed mortality (Jakob 2012 MIDE; Jakob 2012 PRODEX; Pandharipande 2007; Riker 2009; Ruokonen 2009; Shehabi 2013). We did not observe a significant difference between the dexmedetomidine and traditional sedative agents (RR 0.99; 95% CI 0.79 to 1.24, $P = 0.92$). The level of heterogeneity was low ($\chi^2 = 6.05$, $P = 0.30$; $I^2 = 17\%$). We undertook subgroup analyses of different classes of alternative agents and found no significant differences in effect size among subgroups ($P = 0.42$). A sensitivity analysis pooling observed data only, without any imputation, did not change the result (RR 0.99; 95% CI 0.78 to 1.24, $P = 0.90$) (Analysis 1.14). We did not undertake sensitivity analyses by excluding studies at high risk of bias or studies with non-standardized designs, due to the small number of studies.

DISCUSSION

Summary of main results

In this systematic review, we assessed evidence from seven studies, involving 1624 critically ill participants, to investigate the effectiveness and safety of alpha-2 agonists for long-term sedation during mechanical ventilation. All the included studies investigated adults, and compared dexmedetomidine with traditional sedatives. Our meta-analyses show that the use of dexmedetomidine in people who need more than 24 hours sedation was associated with a reduction of 22% in the geometric mean for ventilation time (95% confidence interval (CI) 10% to 33%). Because the relative change in geometric means usually produces results similar to the relative change in arithmetic means (Friedrich 2012), dexmedetomidine could cut approximately one-fifth of the ventilation time. Our meta-analysis provides no clear evidence that dexmedetomidine could reduce the risk of delirium. We found only one study reporting the risk of coma, but some methodological flaws prevented us from drawing a robust conclusion (Pandharipande 2007).

The results of our meta-analyses, along with subgroup analyses for different classes of alternatives, showed a consistent trend across all the studies indicating a reduction in ventilation time. Two studies, Jakob 2012 MIDE and Jakob 2012 PRODEX, which contributed most weight to the meta-analysis, assessed both invasive and noninvasive ventilation time, and thus offer a wider application for this outcome. As a likely consequence of less ventilation time, we also observed a 14% reduction in intensive care unit (ICU) length of stay. However, the reason for this effect was unclear. One potential explanation might be that dexmedetomidine could provide adequate pain control. Early studies in rats and healthy volunteers suggested that dexmedetomidine offered additive or synergist analgesic effects

(Hall 2000; Jaakola 1991; Meert 1994; Tham 2005). Results from previous meta-analyses on perioperative use of dexmedetomidine for postoperative pain also found that dexmedetomidine decreased pain intensity and opioid consumption (Blaudszun 2012; Schnabel 2013). The importance of analgesia in reducing ventilation time and hospital stay has been confirmed by other randomized controlled trials (RCTs) (Breen 2005; Strom 2010). In our review, Ruokonen 2009 compared the visual analogue scale (VAS) scores of nurses' assessments in those patients who were able to communicate, and found that the mean VAS scores in the dexmedetomidine group were lower than in the standard care group (30.6 vs 47.5; $P < 0.001$). Both Jakob 2012 MIDE and Jakob 2012 PRODEX confirmed better pain scores in the dexmedetomidine group, although Ruokonen 2009 showed no difference in the cumulative dose of fentanyl for pain control between both groups, probably because the dexmedetomidine participants might request more additional analgesics. In Jakob 2012 MIDE and Jakob 2012 PRODEX, participants on dexmedetomidine were more able to communicate pain, more arousable and more co-operative. This characteristic of dexmedetomidine might promote the rational use of opioids and facilitate the delivery of patient care and medical examination. Another candidate explanation was suggested by a subgroup analysis of Pandharipande 2007. This post hoc analysis revealed that dexmedetomidine provided greater improvement in ventilation time among septic participants than among non-septic participants, with the investigators attributing this effect to the anti-inflammatory, organ-protective and anti-sympathetic properties of dexmedetomidine.

We found no evidence for the risk of delirium, with a high level of statistical heterogeneity. Two studies compared the number of ICU days without delirium but demonstrated inconsistent results (Pandharipande 2007; Riker 2009). Subgroup analysis of different classes of alternative agents found that both the benzodiazepine derivatives subgroup and the propofol subgroup favoured dexmedetomidine, while the standard care subgroup favoured the control condition. Because standard care participants used midazolam or propofol (both drugs were analysed alone in other subgroups), we were unable to attribute this difference to the characteristics of the control drugs. One possible explanation could be that in standard care both studies were at high risk for blinding of personnel and outcome assessment, which may have biased the results. Meta-regression on geometric mean ventilation time found little statistical evidence to explain the heterogeneity, probably due to the small number of studies. We noted considerable variation among the studies for risk of delirium, which might be another important source of heterogeneity. There were several reasons for this: firstly, the time in ICU prior to study treatment ranged from 12 hours to 96 hours between the studies, which therefore altered the baseline risk of delirium; secondly, although all the studies used the confusion assessment method for the intensive care unit (CAM-ICU), the frequency of assessments and the follow-up periods were different; thirdly, even within same study the frequency might vary between groups, because a successful CAM-ICU assessment was highly dependent on the participant's sedation level (within a RASS score of -3 or eightermrhigher), which may explain in Ruokonen 2009 why more CAM-ICU assessments were performed in the dexmedetomidine group than in the standard care group. Furthermore, because the sensitivity of the CAM-ICU is poor (Van Eijk 2011), interpreting a positive CAM-ICU assessment as

an occurrence of delirium might overestimate the incidence and increase the uncertainty of the intervention effects.

[Pandharipande 2007](#) showed that dexmedetomidine reduced the risk of coma and increased the number of ICU days without coma. However, because of its long half-life, continuous infusion of lorazepam, which was used in the control group, could result in higher concentrations and could induce deeper sedation ([De Wit 2006](#)). On the one hand, such methodological limitation might increase the risk of iatrogenic coma (oversedation) in the control group, especially where the investigators assessed the sedation level infrequently (twice daily), but on the other hand dexmedetomidine caused less oversedation, even without frequent adjustment.

Bradycardia was the most commonly-reported adverse event. Our meta-analysis found that dexmedetomidine doubled the incidence of bradycardia. Subgroup analysis indicated that the risk ratio might differ depending on which alternatives were used as the comparator. For example, the risk ratio in the propofol subgroup was lower than in the benzodiazepine derivatives subgroup, probably because propofol itself could also induce bradycardia ([Hashiba 2003](#)). [Riker 2009](#) showed the risk of bradycardia requiring an intervention (including readjusting or interruption of study drugs and use of atropine) in the dexmedetomidine group was low (4.9%) and not significantly increased. The bradycardiac effect of dexmedetomidine might therefore be mild. We did not find an increase in the risk of hypotension or hypertension. We included tachycardia, first-degree atrioventricular block, hyperglycaemia and hypoglycaemia, which were reported to be significant in at least one study, as outcomes of adverse events post hoc. The results of the post hoc adverse events were inconsistent among studies, probably due to the different comparators. Because of the small number of studies, there was insufficient power to investigate any impact of these rare adverse events.

With respect to other secondary outcomes, we found dexmedetomidine was at least as effective as traditional sedatives on maintaining the target sedation level. In [Ruokonen 2009](#), among participants with a target RASS score of -4 compared with -3 to 0, those on dexmedetomidine spent less time at target level than did those on standard care, which implies that dexmedetomidine may be a poor sedative choice when deep sedation is needed. Additionally, in both [Jakob 2012 MIDEX](#) and [Jakob 2012 PRODEX](#), approximately one in every eight to ten participants ceased participation due to lack of efficacy, even on the maximum dose, and hence these two studies may overestimate the effectiveness of dexmedetomidine. Lack of blinding in some studies ([Ruokonen 2009](#); [Shehabi 2013](#); [Xu 2012](#)) would also have an unpredictable impact on this subjective outcome. We failed to identify any evidence for reducing duration of weaning.

Our meta-analysis provides no evidence that dexmedetomidine had any impact on overall mortality. On the one hand the adverse events which might potentially influence haemodynamic stability, such as bradycardia and hypotension, did not contribute to an increase in mortality, while on the other it would seem that choosing sedatives still occurs 'downstream' in a framework of intensive care, and has limited effect on the prognosis for survival.

When we compared dexmedetomidine sedation in our review to 'no sedation protocol' in [Strom 2010](#), we found some common patterns which might result in reduced ventilation time: using analgesia-

based sedation, retaining some degree of participant's cognitive function, and providing on-demand pain control. It is also clear that dexmedetomidine was a more 'professional' sedative than the morphine used in the 'no sedation protocol'. A cost-minimization analysis of [Riker 2009](#) showed that dexmedetomidine could reduce total intensive care unit costs by about USD 10,000, because of decreased mechanical ventilation costs and ICU stay costs ([Dasta 2010](#)). All these properties of dexmedetomidine seemed to make it a cost-effective choice for ICU sedation. But we must also consider any negative aspects to offset the beneficial effects. Firstly, patients might request additional sedatives or analgesics because they could express discomfort ([Corbett 2005](#); [Jakob 2012 MIDEX](#); [Jakob 2012 PRODEX](#); [Maclaren 2013](#)). Secondly, despite a theoretical advantage of dexmedetomidine in providing nature-like sleep, patients on dexmedetomidine were more likely to have sleeping difficulties ([Corbett 2005](#); [Oto 2012](#)). Thirdly, a recent study focusing on psychological outcomes showed that dexmedetomidine was associated with greater recall of ICU experiences and higher risk of acute stress disorder ([Maclaren 2013](#)). As more frequent assessment of discomfort or pain and appropriate supplemental sedatives or analgesic would be needed, dexmedetomidine for sedation might potentially increase the workload for medical staff.

Overall completeness and applicability of evidence

Although the results of our meta-analyses seem to support beneficial outcomes for the use of alpha-2 agonists for long-term sedation, there were several limitations. Firstly, the included studies investigated only adults treated with dexmedetomidine. Our findings therefore should not be extrapolated to children or to patients treated with clonidine. Secondly, none of the studies described in sufficient detail how they predicted that a patient would require long-term ventilation and sedation. We believe that clinicians in different healthcare system may have different opinions on this point, so that the participants in our review might be substantially different from those in other healthcare systems. Thirdly, most studies excluded people with severe bradycardia, second- or third-degree atrioventricular conduction block or hepatic impairment, and used a dose of dexmedetomidine of no more than 1.5 mcg/kg per hour. Thus, it was not clear whether dexmedetomidine could be used safely in these excluded patients, or whether it could safely be used in higher doses. Fourthly, most studies incorporated new ICU sedation strategies which were recommended by recent guideline ([Barr 2013](#)): light level of sedation protocols, daily interruptions, analgesia-based sedation and monitoring of delirium. It is unclear whether our findings can be generalized to other healthcare systems where these revised sedation strategies do not apply.

Quality of the evidence

In our systematic review, six of the seven studies were at high risk of bias across the six domains (Figure 3). As a consequence, the general quality of evidence ranged from very low to low, based on the GRADE system ([Summary of findings for the main comparison](#)). We noted several methodological limitations in the included studies. Firstly, the risk of breaking blinding might be high, even when double-blinding and a double-dummy design were used. [Wunsch 2012](#) has pointed out that when the comparator was propofol, even a single drop visible at the end of an infusion would break the blinding. We also suspect that a sophisticated clinician could easily guess the identity of the study drugs from the bradycardiac effect of dexmedetomidine. Secondly, high

withdrawal rates in some studies might bias the overall results, especially in [Jakob 2012 MIDEX](#) and [Jakob 2012 PRODEX](#), where more than 20% of participants withdrew from each study group. Most reasons for withdrawal were unbalanced between the groups and were related to outcomes, such as lack of efficacy and adverse events, which might lead to an underestimate of the adverse consequences and might have unpredictable impacts on the other outcomes. Thirdly, some participants from [Jakob 2012 MIDEX](#), [Jakob 2012 PRODEX](#) and [Ruokonen 2009](#) received continuous sedation prior to the study treatment. The carry-over effect of preceding sedation might reduce the required dosages of dexmedetomidine and have unpredictable impacts on the intervention effect.

Potential biases in the review process

There were several potential biases in the review process which should be reiterated. Firstly, our systematic review includes only seven studies, and thus we were not able to generate funnel plots or to assess publication bias by using the Egger test and the arcsine test. Secondly, we emailed the first and corresponding authors of all seven included studies twice, but received only two responses ([Pandharipande 2007](#); [Shehabi 2013](#)), with one providing study data ([Shehabi 2013](#)). In the absence of individual patient data or log-transformed data, we estimated means using medians. We do not consider that this estimation would excessively influence the results of the meta-analyses, since log-transformed means will be approximately equal to log-transformed median under the assumption that the log-transformation of the raw data may substantially reduce skew. Thirdly, due to small numbers of included studies, our predefined subgroup analyses might be underpowered to explore and eliminate heterogeneity.

Agreements and disagreements with other studies or reviews

Previous meta-analyses have investigated the effect of dexmedetomidine in an ICU setting. [Tan 2010](#) reached similar conclusions to our findings for the ICU length of stay, risk of delirium and adverse events, but not for duration of mechanical ventilation. Two meta-analyses comparing propofol head-to-head with dexmedetomidine both suggested that dexmedetomidine did not reduce ventilation time ([Xia 2013](#); [Zhuo 2012](#)). One reported that dexmedetomidine reduced the risk of delirium ([Zhuo 2012](#)), which was confirmed in our subgroup analysis. Another meta-analysis ([Lin 2012](#)) compared dexmedetomidine with placebo or traditional sedatives in the setting of a post-cardiac surgery unit and found that dexmedetomidine reduced ventilation time and risk of delirium. However, this review included both randomized controlled trials and cohort studies, which may have increased heterogeneity and the risk of publication bias.

AUTHORS' CONCLUSIONS

Implications for practice

In this review, we found the use of dexmedetomidine for long-term sedation in critically ill, mechanically-ventilated adults could help to reduce ventilation time and intensive care unit (ICU) length of stay. The premise behind this beneficial effect might be that medical staff carefully administered dexmedetomidine based on sedation level assessment, used a light level of sedation protocols, treated pain during sedation, and routinely monitored delirium.

There was no evidence to support the use of dexmedetomidine in reducing risk of delirium, and inadequate evidence for it reducing the risk of coma. The most common adverse event of dexmedetomidine was bradycardia, but in most cases the bradycardiac effect was harmless and did not need to be treated. Dexmedetomidine was as effective as traditional sedatives for producing sedation and maintaining a light sedation level (a RASS score greater than or equal to -3). However, it might be a poor choice for a deeper sedation; even for light sedation, dexmedetomidine might still result in insufficient sedation in approximately one in every eight to 10 patients. We failed to identify any evidence concerning reducing duration of weaning or overall mortality.

Implications for research

In this review, we found no eligible studies investigating clonidine, although a pilot randomized controlled trial (RCT) has shown clonidine to be as safe and effective as dexmedetomidine in critically ill patients ([Machado 2011](#)). There is therefore a need for a larger prospective study which could evaluate the efficacy, safety and cost effectiveness of clonidine for long-term sedation. We found no studies in children, although many retrospective studies have shown the efficacy and safety of alpha-2 agonists in children ([Arenas 2004](#); [Carney 2013](#); [Czaja 2009](#); [Gupta 2012](#)). Future RCTs of alpha-2 agonists could be conducted in children. Although our systematic review includes a broad range of populations, some confounding factors, such as participants' physical characteristics, medical conditions and reasons for ventilation, might affect the magnitude of the intervention effects. For example, participants with sepsis might benefit more from dexmedetomidine than those without sepsis ([Pandharipande 2010](#)). Future studies could focus more directly on specific populations, such as people with chronic obstructive pulmonary disease (COPD), people with adult respiratory distress syndrome (ARDS) or brain-injured people. We observed a high level of heterogeneity for the risk of delirium, which may be associated with the imprecision of the screening tool. Future studies evaluating the efficacy of alpha-2 agonists for ICU delirium could stratify randomized participants by similar risks, could use more validated diagnostic tools, and could focus on long-term cognitive outcomes.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Jakob 2012 MIDEX

Methods	Parallel group randomized controlled trial
Participants	<p>Inclusion criteria:</p> <ul style="list-style-type: none"> • Age > 18 years • Clinical need for sedation of an initially intubated (or tracheostomized) and ventilated (with inspiratory assistance) patient • Prescribed light to moderate sedation (target RASS = 0 to -3) using midazolam or propofol • Participants should be randomized within 72 hours from ICU admission and within 48 hours of commencing continuous sedation in the ICU • Participants should have an expected requirement for sedation > 24 hours from time of randomization • Written informed consent must be obtained according to local regulations before starting any study procedures other than pre-screening <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • Acute severe intracranial or spinal neurological disorder due to vascular causes, infection, intracranial expansion or injury • Uncompensated acute circulatory failure at time of randomization (severe hypotension with mean arterial pressure < 55 mmHg despite volume and pressors) • Severe bradycardia (heart rate < 50 beats/min) • Atrioventricular-conduction block II - III (unless pacemaker installed) • Severe hepatic impairment (bilirubin > 101 µmol/L) • Need for muscle relaxation at the time of randomization (may only be used for intubation and initial stabilization) • Loss of hearing or vision, or any other condition which would significantly interfere with the collection of study data • Burn injuries requiring regular anaesthesia or surgery • Use of centrally-acting α-2 agonists or antagonists at the time of randomization, notably clonidine • Patients who have or are expected to have treatment withdrawn or withheld due to poor prognosis • Patients receiving sedation for therapeutic indications rather than to tolerate the ventilator (e.g. epilepsy) • Patients unlikely to require continuous sedation during mechanical ventilation (e.g. Guillain-Barré syndrome) • Patients who are unlikely to be weaned from mechanical ventilation; e.g. diseases/injuries primarily affecting the neuromuscular function of the respiratory apparatus such as clearly irreversible disease requiring prolonged ventilatory support (e.g. high spinal cord injury or advanced amyotrophic lateral sclerosis)

Jakob 2012 MIDEX (Continued)

- Distal paraplegia
- Positive pregnancy test or currently lactating
- Received any investigational drug within the preceding 30 days
- Concurrent participation in any other interventional study (any study in which participants are allocated to different treatment groups and/or non-routine diagnostic or monitoring procedures are performed)
- Previous participation in this study
- Any other condition which, in the investigator's opinion, would make it detrimental for the person to participate in the study

249 randomized to receive dexmedetomidine; 252 randomized to receive midazolam, 2 in the dexmedetomidine group and 1 in the midazolam group were withdrawn but did not receive any study drugs. We excluded them from our analyses of dichotomous outcomes but not for continuous outcomes. This is because in the absence of raw data, we were unable to distinguish the continuous data from them. The analyses of continuous outcomes, duration of mechanical ventilation and ICU LOS, were based on intention-to-treat analysis (249 in the dexmedetomidine group included and 251 in midazolam group included, 1 in midazolam group excluded due to 'withdrew consent').

The median age of the dexmedetomidine group was 65 years. The median age of the midazolam group was 65 years.

Interventions	<ul style="list-style-type: none"> • Intervention group: Dexmedetomidine, 0.2 - 1.4 mcg/kg per hour • Control group: Midazolam, 0.03 - 0.2 mg/kg per hour • Target sedation level and sedation level measurement: Target RASS score: -3 to 0; measurement was performed every 2 hours • Rescue medication to reach target sedation level: Propofol; further rescue medication decided by treating clinician • Daily interruption: Yes • Description of pain control: Pain was treated with fentanyl boluses • Endpoint: Up to a maximum of 14 days from randomization and stopped at the time of extubation
Outcomes	<ul style="list-style-type: none"> • Duration of mechanical ventilation: From transmigration until participants were free of mechanical ventilation (including noninvasive) without reinstitution for the following 48 hours. • Risk of delirium: Delirium was assessed based on the clinician's judgement, supplemented by the CAM-ICU procedure during the study treatment. • Adverse events: An adverse event was any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product and which did not necessarily have a causal relationship with this treatment. Adverse events could therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product, whether or not related to the investigational medicinal product. Adverse events with incidence > 2% in any treatment group, 45-day follow-up including bradycardia, hypotension, hypertension, sinus tachycardia, atrial fibrillation, agitation, respiratory failure, pleural effusion, pneumonia, anxiety, diarrhoea, pyrexia, multi-organ failure, gamma-glutamyl transpeptidase increased, sepsis, septic shock, nausea, anaemia, supraventricular tachycardia, withdrawal syndrome, hypokalaemia, vomiting, acute respiratory distress syndrome, renal failure, confusional state, decubitus ulcer, pneumothorax, endotracheal intubation complication, cardiac arrest, constipation, hypoxia, ventricular tachycardia, oxygen saturation decreased, urinary tract infection, haemoglobin decreased, acute renal failure, pulmonary oedema, cardiac failure, acute respiratory failure, hepatic enzyme increased, insomnia, impaired gastric emptying, restlessness, hypoglycaemia, atelectasis, atrioventricular block 1st degree, bronchitis, hypernatraemia, gastrointestinal haemorrhage, peritonitis, depression, sedation, thrombocytopenia, critical illness polyneuropathy, myocardial ischaemia, blood potassium decreased, hyperkalaemia, headache, wound infection, hyperthermia, hyperglycaemia, acute pulmonary oedema, alanine aminotransferase increased, circulatory collapse, tachyarrhythmia, drug ineffective, abdominal pain upper, bronchopneumonia, ventricular extrasystoles, C-reactive protein increased, abdominal abscess, subcutaneous emphysema, blood triglycerides increased, shock, extubation, palpitations, hypercapnia and haemorrhagic shock. • Proportion of sedation time spent at target sedation level: The proportion of time in target sedation range (RASS score, 0 to -3) without use of rescue therapy of the total duration of study drug infusion.

Jakob 2012 MIDEX (Continued)

- ICU LOS: From randomization to being medically fit for discharge or transfer from the study ICU. If participants were re-admitted to study ICU within 48 hours of initial discharge then the time to subsequent successful discharge was used instead.
- Mortality: Rate of death during 45-day follow-up

Dates	June 2007 to August 2009
Setting and Country	Setting: intensive care units Country: Belgium, Estonia, Finland, France, Germany, Netherlands, Norway, Switzerland, United Kingdom
Funding source and Declarations of interest	Sources of funding: Orion Corporation, Orion Pharma Declaration of investigators' conflicts of interest: On behalf of Drs Jakob and Takala, a grant and consulting fees were paid to the Bern University Hospital Department of Intensive Care Medicine to cover the costs of performing the study. The department was reimbursed for the authors' travel costs to publication committee meetings. Dr Jakob served as an expert for preparing the regulatory filing of the drug; the money was also paid into a departmental fund. Dr Grounds received a consulting fee from Orion Pharma during planning and execution of the study. He and members of his clinical staff at St George's Hospital received monetary support from Orion for travel to study-related meetings to ensure compliance with the study protocol. His department received payment of a fee per patient recruited to the study, as well as drugs used in the study and support personnel to assist with data input. Dr Ruokonen's institution, Kuopio University, received a grant from Orion to carry out the study, as well as consulting fees and reimbursement of travel funds. Messrs Sarapohja, Garratt, and Bratty were full-time employees of Orion Pharma through-out the period of the project. Their routine travel expenses were reimbursed as part of their employment. Dr Pocock of the London School of Hygiene and Tropical Medicine received a consulting fee from Orion in connection with the study, and his institution received a grant. London School of Hygiene and Tropical Medicine also received a grant for independent statistical review performed by Dr Duolao Wang.

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was stratified for study centre in blocks of 4."
Allocation concealment (selection bias)	Low risk	Quote: "Eligible study participants were randomized 1:1 by a central interactive voice-response system funded by the sponsor to either continue their current standard care (midazolam [MIDEX trial] or propofol [PRODEX trial]) or switch to dexmedetomidine."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Treatments were administered in a double-dummy design, with 0.9% sodium chloride as dummy for all treatments."
Blinding of outcome assessment (detection bias) Subjective outcomes	Low risk	Subjective outcome: risk of delirium, proportion of sedation time spent at target sedation level Quote: "Treatments were administered in a double-dummy design, with 0.9% sodium chloride as dummy for all treatments."
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	Objective outcome: duration of mechanical ventilation, adverse events, ICU length of stay (LOS), mortality

Jakob 2012 MIDEX (Continued)

<p>Quote: "Treatments were administered in a double-dummy design, with 0.9% sodium chloride as dummy for all treatments."</p>		
<p>Incomplete outcome data (attrition bias) All outcomes</p>	<p>High risk</p>	<p>Dexmedetomidine group: 249 included in intention-to-treat analyses; 60/249 withdrawals (23 due to 'lack of efficacy'; 23 due to 'adverse or serious adverse event'; 2 due to 'protocol violation'; 16 due to 'other reasons'); 227 included in per-protocol analyses, 22 excluded (8 due to 'missing inclusion criteria'; 8 due to 'incorrect dosing'; 1 due to 'received excluded medication'; 5 due to 'missing assessments');</p> <p>Midazolam group: 251 included in intention-to-treat analyses, 1 excluded due to 'withdrew consent'; 51/252 withdrawals (10 due to 'lack of efficacy'; 19 due to 'adverse or serious adverse event'; 2 due to 'protocol violation'; 21 due to 'other reasons'); 233 included in per-protocol analyses, 18 excluded (7 due to 'missing inclusion criteria'; 1 due to 'met exclusion criteria'; 6 due to 'incorrect dosing'; 2 due to 'received excluded medication'; 2 due to 'missing assessments')</p> <p>Comment: > 20% participants in each group withdrew. Reasons for withdrawal and exclusion were not balanced between study groups. These missing data would inevitably bias the results.</p>
<p>Selective reporting (reporting bias)</p>	<p>Low risk</p>	<p>Comment: All the outcomes listed in Methods section are reported.</p>
<p>Other bias</p>	<p>Low risk</p>	<p>Comment: The study appears to be free of other sources of bias.</p>

Jakob 2012 PRODEX

<p>Methods</p>	<p>Parallel group randomized controlled trial</p>
<p>Participants</p>	<p>Inclusion criteria:</p> <p>Age > 18 years</p> <ul style="list-style-type: none"> • Clinical need for sedation of an initially intubated (or tracheostomized) and ventilated (with inspiratory assistance) patient • Prescribed light to moderate sedation (target RASS = 0 to -3) using propofol • Participants should be randomized within 72 hours from ICU admission and within 48 hours of commencing continuous sedation in the ICU • Participants should have an expected requirement for sedation > 24 hours from time of randomization • Written informed consent must be obtained according to local regulations before starting any study procedures other than pre-screening <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • Acute severe intracranial or spinal neurological disorder due to vascular causes, infection, intracranial expansion or injury • Uncompensated acute circulatory failure at time of randomization (severe hypotension with mean arterial pressure < 55 mmHg despite volume and pressors) • Severe bradycardia (heart rate < 50 beats/min) • Atrioventricular-conduction block II - III (unless pacemaker installed) • Severe hepatic impairment (bilirubin > 101 µmol/L) • Need for muscle relaxation at the time of randomization (may only be used for intubation and initial stabilization) • Loss of hearing or vision, or any other condition which would significantly interfere with the collection of study data

Jakob 2012 PRODEX (Continued)

- Burn injuries requiring regular anaesthesia or surgery
- Use of centrally-acting α_2 agonists or antagonists at the time of randomization, notably clonidine
- Patients who have or are expected to have treatment withdrawn or withheld due to poor prognosis
- Patients receiving sedation for therapeutic indications rather than to tolerate the ventilator (e.g. epilepsy)
- Patients unlikely to require continuous sedation during mechanical ventilation (e.g. Guillain-Barré syndrome)
- Patients who are unlikely to be weaned from mechanical ventilation; e.g. diseases/injuries primarily affecting the neuromuscular function of the respiratory apparatus such as clearly irreversible disease requiring prolonged ventilatory support (e.g. high spinal cord injury or advanced amyotrophic lateral sclerosis)
- Distal paraplegia
- Positive pregnancy test or currently lactating
- Received any investigational drug within the preceding 30 days
- Concurrent participation in any other interventional study (any study in which participants are allocated to different treatment groups and/or non-routine diagnostic or monitoring procedures are performed)
- Previous participation in this study
- Any other condition which, in the investigator's opinion, would make it detrimental for the person to participate in the study

251 randomized to receive dexmedetomidine; 249 randomized to receive propofol, 5 in dexmedetomidine group were withdrawn but did not receive any study drugs. We excluded them in our analyses of dichotomous outcomes but not for continuous outcomes. This is because in the absence of raw data, we were unable to distinguish the continuous data from them. The analyses of continuous outcomes, duration of mechanical ventilation and ICU LOS, were based on intention-to-treat analysis (251 in dexmedetomidine group included and 247 in propofol group included, 2 in propofol group excluded due to 'withdrew consent').

The median age of the dexmedetomidine group was 65 years; the median age of the propofol group was 65 years.

Interventions	<ul style="list-style-type: none"> • Intervention group: Dexmedetomidine, 0.2 - 1.4 mcg/kg per hour • Control group: propofol, 0.3 - 4.0 mg/kg per hour • Target sedation level and sedation level measurement: Target RASS score: -3 to 0; measurement was performed every 2 hours • Rescue medication to reach target sedation level: Propofol; further rescue medication decided by treating clinician • Daily interruption: Yes • Description of pain control: Pain was treated with fentanyl boluses • Endpoint: Up to a maximum of 14 days from randomization and stopped at the time of extubation
Outcomes	<ul style="list-style-type: none"> • Duration of mechanical ventilation: From randomization until participants were free of mechanical ventilation (including noninvasive) without reinstitution for the following 48 hours. • Risk of delirium: Delirium was assessed based on the clinician's judgement, supplemented by the CAM-ICU procedure during the study treatment. • Adverse events: An adverse event was any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product and which did not necessarily have a causal relationship with this treatment. Adverse events could therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product, whether or not related to the investigational medicinal product. Adverse events with incidence > 2% in any treatment group, 45-day follow-up including bradycardia, hypotension, hypertension, sinus tachycardia, atrial fibrillation, agitation, respiratory failure, pleural effusion, pneumonia, anxiety, diarrhoea, pyrexia, multi-organ failure, gamma-glutamyl transpeptidase increased, sepsis, septic shock, nausea, anaemia, supraventricular tachycardia, withdrawal syndrome, hypokalaemia, vomiting, acute respiratory distress syndrome, renal failure, confusional state, decubitus ulcer, pneumothorax, endotracheal intubation complication,

Jakob 2012 PRODEX (Continued)

cardiac arrest, constipation, hypoxia, ventricular tachycardia, oxygen saturation decreased, urinary tract infection, haemoglobin decreased, acute renal failure, pulmonary oedema, cardiac failure, acute respiratory failure, hepatic enzyme increased, insomnia, impaired gastric emptying, restlessness, hypoglycaemia, atelectasis, atrioventricular block 1st degree, bronchitis, hypernatraemia, gastrointestinal haemorrhage, peritonitis, depression, sedation, thrombocytopenia, critical illness polyneuropathy, myocardial ischaemia, blood potassium decreased, hyperkalaemia, headache, wound infection, hyperthermia, hyperglycaemia, acute pulmonary oedema, alanine aminotransferase increased, circulatory collapse, tachyarrhythmia, drug ineffective, abdominal pain upper, bronchopneumonia, ventricular extrasystoles, C-reactive protein increased, abdominal abscess, subcutaneous emphysema, blood triglycerides increased, shock, extubation, palpitations, hypercapnia and haemorrhagic shock.

- Proportion of sedation time spent at target sedation level: The proportion of time in target sedation range (RASS score, 0 to -3) without use of rescue therapy of the total duration of study drug infusion.
- ICU LOS: From randomization to being medically fit for discharge or transfer from the study ICU. If participants were re-admitted to study ICU within 48 hours of initial discharge then the time to subsequent successful discharge was used instead.
- Mortality: Rate of death during 45-day follow-up

Dates	May 2007 to March 2010
Setting and Country	Setting: intensive care units Country: Belgium, Finland, Germany, Netherlands, Russian Federation, Switzerland, United Kingdom
Funding source and Declarations of interest	Sources of funding: Orion Corporation, Orion Pharma Declaration of investigators' conflicts of interest: On behalf of Drs Jakob and Takala, a grant and consulting fees were paid to the Bern University Hospital Department of Intensive Care Medicine to cover the costs of performing the study. The department was reimbursed for the authors' travel costs to publication committee meetings. Dr Jakob served as an expert for preparing the regulatory filing of the drug; the money was also paid into a departmental fund. Dr Grounds received a consulting fee from Orion Pharma during planning and execution of the study. He and members of his clinical staff at St George's Hospital received monetary support from Orion for travel to study-related meetings to ensure compliance with the study protocol. His department received payment of a fee per patient recruited to the study, as well as drugs used in the study and support personnel to assist with data input. Dr Ruokonen's institution, Kuopio University, received a grant from Orion to carry out the study, as well as consulting fees and reimbursement of travel funds. Messrs Sarapohja, Garratt, and Bratty were full-time employees of Orion Pharma through-out the period of the project. Their routine travel expenses were reimbursed as part of their employment. Dr Pocock of the London School of Hygiene and Tropical Medicine received a consulting fee from Orion in connection with the study, and his institution received a grant. London School of Hygiene and Tropical Medicine also received a grant for independent statistical review performed by Dr Duolao Wang.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was stratified for study centre in blocks of 4."
Allocation concealment (selection bias)	Low risk	Quote: "Eligible study participants were randomized 1:1 by a central interactive voice-response system funded by the sponsor to either continue their current standard care (midazolam [MIDEX trial] or propofol [PRODEX trial]) or switch to dexmedetomidine."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Propofol and propofol dummy were prepared, connected, and removed by independent personnel and infused with nontransparent black syringes, infusion tubings, and connectors."

Jakob 2012 PRODEX (Continued)

Blinding of outcome assessment (detection bias) Subjective outcomes	Low risk	Subjective outcome: risk of delirium, proportion of sedation time spent at target sedation level Quote: "Propofol and propofol dummy were prepared, connected, and removed by independent personnel and infused with nontransparent black syringes, infusion tubings, and connectors."
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	Objective outcome: duration of mechanical ventilation, adverse events, ICU length of stay (LOS), mortality Quote: "Propofol and propofol dummy were prepared, connected, and removed by independent personnel and infused with nontransparent black syringes, infusion tubings, and connectors."
Incomplete outcome data (attrition bias) All outcomes	High risk	Dexmedetomidine group: 251 included in intention-to-treat analyses; 71/251 withdrawals (36 due to 'lack of efficacy'; 29 due to 'adverse or serious adverse event'; 1 due to 'Nonpharmacological intervention'; 1 due to 'protocol violation'; 7 due to 'other reasons'); 223 included in per-protocol analyses, 28 excluded (3 due to 'missing inclusion criteria'; 1 due to 'met exclusion criteria'; 7 due to 'incorrect dosing'; 1 due to 'received excluded medication'; 16 due to 'missing assessments') Propofol group: 247 included in intention-to-treat analyses, 2 excluded due to 'withdrew consent'; 60/249 withdraws from propofol group (13 due to 'lack of efficacy'; 28 due to 'adverse or serious adverse event'; 4 due to 'nonpharmacological intervention'; 3 due to 'protocol violation'; 16 due to 'other reasons'); 214 included in per-protocol analyses, 33 excluded (7 due to 'missing inclusion criteria'; 2 due to 'met exclusion criteria'; 10 due to 'incorrect dosing'; 6 due to 'received excluded medication'; 8 due to 'missing assessments') Comment: > 20% participants in each group withdrew. Reasons for withdrawal and exclusions were not balanced between study groups. These missing data would inevitably bias the results.
Selective reporting (reporting bias)	Low risk	All the outcomes listed in Methods section are reported.
Other bias	Low risk	The study appears to be free of other sources of bias.

Pandharipande 2007

Methods	Parallel group randomized controlled trial
Participants	<p>Inclusion criteria:</p> <ul style="list-style-type: none"> Men or women admitted to the medical and surgical ICU for critical illnesses requiring mechanical ventilation with expectation of being mechanically ventilated for > 24 hours <p>Exclusion criteria:</p> <ul style="list-style-type: none"> < 18 years of age Pregnant (a pregnancy test to be performed on all women of child-bearing age) Inability to obtain informed consent from the patient or his/her surrogate In the ICU due to a lack of beds elsewhere in the hospital, triage issues, or withdrawal of care decisions rather than severity of illness Admitted with alcohol or drug overdoses, suicide attempts, or alcohol/delirium tremens Physiologically benzodiazepine-dependent, and at risk for withdrawal syndromes

Pandharipande 2007 (Continued)

- Chronic pain syndromes on maintenance narcotics
- Treated within the last 30 days with a drug or device that has not received regulatory approval as of study entry
- Psychiatric history for which they are on neuroleptic treatment
- Documented moderate to severe dementia
- Anoxic brain injuries, strokes, neurotrauma, or neuromuscular disorders such as myasthenia gravis or Guillain-Barré syndrome
- Medical team following patient unwilling to use the sedation regimens
- Family and/or physician have not committed to aggressive support for 72 hours or who are likely to withdraw within 72 hours
- Moribund and not expected to survive 24 hours
- Not expected to survive hospital discharge due to pre-existing uncorrectable medical condition
- Documented allergy to study medications
- Either Child-Pugh Class B or C cirrhosis
- Active coronary artery disease at time of screening as defined by any recent evidence of ischaemia, documented myocardial infarction, or coronary intervention within the past 6 months.
- Advanced heart block at time of screening

54 randomized to receive dexmedetomidine; 52 randomized to receive lorazepam, 2 in the dexmedetomidine group and 1 in the lorazepam group were withdrawn but did not receive any study drugs and therefore were excluded in our review. These participants were not included in intention-to-treat analysis.

The median age of the dexmedetomidine group was 60 years. The median age of the lorazepam group was 59 years.

Interventions	<ul style="list-style-type: none"> • Intervention group: Dexmedetomidine, 0.15 - 1.5 mcg/kg per hour • Control group: Lorazepam, 1 - 10 mg/hour • Target sedation level and sedation level measurement: Sedation target was set by the participant's medical team using the RASS; measurement was performed every 2 hours • Rescue medication to reach target sedation level: If the maximum infusion rate of the study drug did not result in adequate sedation or if participants required frequent intermittent doses of fentanyl for pain, a continuous infusion of fentanyl was permitted. If a participant experienced sudden and urgent levels of agitation that had the potential to cause harm to the participant or to staff, a propofol bolus of 25 to 50 mg was allowed, while the study drug or fentanyl infusions were titrated upwards • Daily interruption: part of the managing team's protocol, but not part of the study protocol • Description of pain control: Pain was treated with fentanyl boluses or infusion • Endpoint: Until extubation or for the maximum time allowed by the FDA (120 hours)
Outcomes	<ul style="list-style-type: none"> • Ventilator-free days: The number of days alive and not using mechanical ventilation over a 28-day period • Risk of delirium: Delirium was measured until hospital discharge or for 12 days using the CAM-ICU • Risk of coma: Coma was defined as a RASS score of -4 (responsive only to physical stimulus) or -5 (unresponsive to physical stimulus) • Adverse events: Bradycardia, hypotension, sinus tachycardia, atrial fibrillation, seizures, self extubations • Proportion of sedation time spent at target sedation level: The percentage of days while on study drug when participants were either at target RASS or within 1 RASS point of the target • ICU LOS: From randomization to being medically fit for discharge or transfer from the study ICU. If participants were re-admitted to study ICU within 48 hours of initial discharge then the time to subsequent successful discharge was used instead • Mortality
Dates	August 2004 to August 2007
Setting and Country	Setting: intensive care units

Pandharipande 2007 (Continued)

Country: United States

Funding source and Declarations of interest

Sources of funding: Hospira Inc, Lake Forest, Illinois

Declaration of investigators' conflicts of interest: This investigator-initiated study was aided by the receipt of the study drug and an unrestricted research grant for laboratory and investigational studies from Hospira Inc. Dr Pandharipande is the recipient of the ASCCA-FAER-Abbott Physician Scientist Award and the Vanderbilt Physician Scientist Development Award. Dr Girard is supported by the Hartford Geriatrics Health Outcomes Research Scholars Award Program and the Vanderbilt Physician Scientist Development Program. Dr Ely is supported by the VA Clinical Science Research and Development Service (VA Merit Review Award) and a grant from the National Institutes of Health (AG0727201).

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomized using computer-generated, permuted block randomization (known only to the investigational pharmacists) and stratified by site to receive sedation with either dexmedetomidine or lorazepam."
Allocation concealment (selection bias)	Low risk	Quote: "Patients were randomized using computer-generated, permuted block randomization (known only to the investigational pharmacists) and stratified by site to receive sedation with either dexmedetomidine or lorazepam."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "We used infusion instead of bolus dosing to preserve the blinding and to minimize potential adverse events. The study drug was prepared in clear bags containing either dexmedetomidine (prepared for a final concentration of 0.15 µg/kg per mL) or lorazepam (1 mg/mL). The study drug infusion was started at 1 mL/h (0.15 µg/kg per hour dexmedetomidine or 1 mg/h lorazepam) and titrated by the bedside nurse to a maximum of 10 mL/h (1.5 µg/kg per hour dexmedetomidine or 10 mg/h lorazepam) to achieve the sedation goal set by the patient's medical team using the Richmond Agitation-Sedation Scale (RASS)."
Blinding of outcome assessment (detection bias) Subjective outcomes	Low risk	Subjective outcome: risk of delirium, risk of coma, proportion of sedation time spent at target sedation level Quote: "We used infusion instead of bolus dosing to preserve the blinding and to minimize potential adverse events. The study drug was prepared in clear bags containing either dexmedetomidine (prepared for a final concentration of 0.15 µg/kg per mL) or lorazepam (1 mg/mL). The study drug infusion was started at 1 mL/h (0.15 µg/kg per hour dexmedetomidine or 1 mg/h lorazepam) and titrated by the bedside nurse to a maximum of 10 mL/h (1.5 µg/kg per hour dexmedetomidine or 10 mg/h lorazepam) to achieve the sedation goal set by the patient's medical team using the Richmond Agitation-Sedation Scale (RASS)."
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	Objective outcome: ventilator-free days, adverse effects, ICU LOS, mortality Quote: "We used infusion instead of bolus dosing to preserve the blinding and to minimize potential adverse events. The study drug was prepared in clear bags containing either dexmedetomidine (prepared for a final concentration of 0.15 µg/kg per mL) or lorazepam (1 mg/mL). The study drug infusion was started at 1 mL/h (0.15 µg/kg per hour dexmedetomidine or 1 mg/h lorazepam) and titrated by the bedside nurse to a maximum of 10 mL/h (1.5 µg/kg per hour dexmedetomidine or 10 mg/h lorazepam) to achieve the sedation goal set by the patient's medical team using the Richmond Agitation-Sedation Scale (RASS)."

Pandharipande 2007 (Continued)

		goal set by the patient's medical team using the Richmond Agitation-Sedation Scale (RASS)."
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 withdrawals from dexmedetomidine group (due to 'withdrawn by family'), 52 completed study protocol; 1 withdrawal from lorazepam group (due to 'withdrawn by family'), 51 completed study protocol. Comment: Reasons for withdrawal were explicitly reported and balanced across study groups.
Selective reporting (reporting bias)	Low risk	All the outcomes listed in Methods section are reported.
Other bias	High risk	Comment: This study used continuous infusion of lorazepam as a comparator, did not mandate daily interruption, and assessed sedation level infrequently. Such a study design might potentially increase the risk of coma in the control group and was considered to be a source of bias.

Riker 2009

Methods	Parallel group randomized controlled trial
Participants	<p>Inclusion criteria:</p> <ul style="list-style-type: none"> Participant is initially intubated, mechanically ventilated, and is anticipated to require continuous sedation for at least 72 hours Participant is sedated within a protocol-specified range at the time of study drug administration <p>Exclusion criteria:</p> <ul style="list-style-type: none"> Intubated for > 96 hours prior to the initiation of study drug Serious central nervous system pathology/trauma Opiates, benzodiazepines, or dexmedetomidine are contraindicated or who has known or suspected serious allergy to any drug that might be administered during the course of the study History or current evidence of cardiovascular disease Participated in a trial with any experimental drug within 30 days prior to enrolment in the study or has ever been enrolled in this study Laboratory results indicating the presence of liver disease consistent with a Child Pugh Score > 9 (Grade C) Acute hepatitis, history or presence of chronic hepatitis, and/or has had a positive result for Hepatitis B Surface Antigen Test. Requires dialysis Terminally ill with a life duration expectancy of < 60 days <p>250 randomized to receive dexmedetomidine; 125 randomized to receive midazolam, 6 in dexmedetomidine group and 3 in midazolam group were withdrawn but did not receive any study drugs and therefore excluded in our review. These participants were not included in intention-to-treat analysis.</p> <p>The mean age of the dexmedetomidine group was 61.5 years; the mean age of the midazolam group was 62.9 years</p>
Interventions	<ul style="list-style-type: none"> Intervention group: Dexmedetomidine. Optional loading doses: up to 1 mcg/kg. The starting maintenance infusion dose: 0.8 mcg/kg per hour Control group: Midazolam. Optional loading doses: up to 0.05 mg/kg. The starting maintenance infusion dose: 0.06 mg/kg per hour Target sedation level and sedation level measurement: Target RASS score: -2 to 1; measurement was performed every 4 hours

Riker 2009 (Continued)

- Rescue medication to reach target sedation level: Open-label midazolam bolus doses of 0.01 to 0.05 mg/kg at 10- to 15-minute intervals until adequate sedation was achieved with a maximum dose of 4 mg in 8 hours
- Daily interruption: No
- Description of pain control: Pain was treated with fentanyl bolus doses (0.5 - 1.0 mcg/kg)
- Endpoint: Study drug infusion was stopped at the time of extubation, after a maximum of 30 days, or if the investigator felt it was in the best interest of the participant

Outcomes	<ul style="list-style-type: none"> • Duration of mechanical ventilation: From the start of study drug to the time of extubation without reintubation • Risk of delirium: Delirium was assessed daily during the arousal assessment with participants in the RASS range of -2 to +1 using the CAM-ICU • Adverse events: Bradycardia, hypotension, hypertension, sinus tachycardia, hyperglycaemia, infections, urinary tract infections, hospital-acquired pneumonia, investigator-reported adrenal insufficiency • Proportion of sedation time spent at target sedation level: Calculated by dividing the total time that the participant remained within the target RASS range by the amount of time the participant remained in the treatment period, multiplied by 100% • ICU LOS: From start of study drug to time of order for ICU transfer • Mortality: Mortality rate for 30 days after ICU admission
Dates	March 2005 to August 2007
Setting and Country	Setting: intensive care units Country: United States
Funding source and Declarations of interest	<p>Sources of funding: Hospira Inc, Lake Forest, Illinois</p> <p>Declaration of investigators' conflicts of interest: Dr Riker reports that he has received honoraria and/or grant support from Aspect Medical Systems Inc, AstraZeneca, Eli Lilly, Hospira, Takeda, and the Academy for Continued Healthcare Learning. Dr Shehabi reports that he has received honoraria and/or grant support from Hospira, Edward Life- sciences, Theravance, and the Intensive Care Foundation. Dr Ceraso reports that he has received honoraria and/or grant support from Hospira. Dr Koura reports that he has received honoraria and/or grant support from Altana, Artisan Pharma, Boehringer-Ingelheim, CSL, Hospira, Ortho-McNeil, Sepracor, Schering-Plough, and United BioScience Corp. Dr Whitten reports that he has received honoraria and/or grant support from Hospira. Dr Margolis reports that he has received honoraria and/or grant support from Hospira. Mr Byrne reports that he was paid a consulting fee for serving as the independent statistical reviewer by the sponsor. Dr Ely reports that he has received honoraria and/or grant support from Hospira, Pfizer, Eli Lilly, GlaxoSmithKline, and Aspect Medical, and is an advisor to Healthways. Dr Rocha reports that he has received honoraria and/or grant support from Hospira, Theravance, Altana, Novartis and the Canadian Institute of Health Research. Dr Bokesch and Mr Wisemandle reported no disclosures.</p>

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Eligible patients were randomized 2:1 to receive dexmedetomidine to obtain more comprehensive safety data during prolonged dexmedetomidine use."; "All patients were centrally randomized using an interactive voice-response system and a computer-generated schedule."
Allocation concealment (selection bias)	Low risk	Quote: "All patients were centrally randomized using an interactive voice-response system and a computer-generated schedule."

Riker 2009 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blind"; "Optional blinded loading doses (up to 1 µg/kg dexmedetomidine or 0.05 mg/kg midazolam) could be administered at the investigator's discretion. The starting maintenance infusion dose of blinded study drug was 0.8 µg/kg per hour for dexmedetomidine and 0.06 mg/kg per hour for midazolam, corresponding to the mid-point of the allowable infusion dose range."
Blinding of outcome assessment (detection bias) Subjective outcomes	Low risk	Subjective outcome: risk of delirium, proportion of sedation time spent at target sedation level Quote: "Optional blinded loading doses (up to 1 µg/kg dexmedetomidine or 0.05 mg/kg midazolam) could be administered at the investigator's discretion. The starting maintenance infusion dose of blinded study drug was 0.8 µg/kg per hour for dexmedetomidine and 0.06 mg/kg per hour for midazolam, corresponding to the mid-point of the allowable infusion dose range."
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	Objective outcome: duration of mechanical ventilation, adverse events, ICU LOS, mortality Quote: "Optional blinded loading doses (up to 1 µg/kg dexmedetomidine or 0.05 mg/kg midazolam) could be administered at the investigator's discretion. The starting maintenance infusion dose of blinded study drug was 0.8 µg/kg per hour for dexmedetomidine and 0.06 mg/kg per hour for midazolam, corresponding to the mid-point of the allowable infusion dose range."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "A total of 375 eligible patients were randomized and 366 patients received study drug, comprising the primary analyses study population (244 patients received dexmedetomidine, 122 received midazolam). Nine patients randomized (6 in the dexmedetomidine group, 3 in the midazolam group) never received study drug" 194 included in long-term use analyses in dexmedetomidine group, 50 excluded (received study drug ≤ 24 hours) (21 due to "extubated"; 17 due to "adverse event"; 7 due to "lack of efficacy"; 3 due to "withdrew consent"; 1 due to "entry criteria" (patient had new information after consent that identified an exclusion criterion (e.g., need for general anaesthesia, unexpected liver or cardiac disease)); 1 due to "investigator opinion" (investigator felt that patient no longer met entry criteria (e.g., extubated, no longer required sedation, required deeper sedation)); 103 included in long-term use analyses in midazolam group, 19 excluded (5 due to "adverse event"; 5 due to "lack of efficacy"; 4 due to "withdrew consent"; 4 due to "entry criteria"; 1 due to "investigator opinion") Comment: Reasons for withdrawal and exclusion were explicitly reported and balanced across study groups
Selective reporting (reporting bias)	Low risk	All the outcomes listed in Methods section are reported.
Other bias	Low risk	The study appears to be free of other sources of bias.

Ruokonen 2009

Methods	Parallel group randomized controlled trial
Participants	Inclusion criteria: <ul style="list-style-type: none"> Clinical need for sedation and mechanical ventilation

Ruokonen 2009 (Continued)

- Receiving full intensive care life support
- Expected stay in ICU of at least 48 hours from time of admission
- Expected requirement for sedation of at least 24 hours from time of randomization
- Written informed consent within 36 hours of ICU admission

Exclusion criteria:

- Acute severe neurological disorder
- Acute uncompensated circulatory failure at time of randomization
- Severe bradycardia
- Atrioventricular conduction block II - III unless pacemaker fitted
- Severe hepatic impairment
- Need for muscle relaxation at time of randomization
- Loss of hearing or vision or any condition interfering significantly with RASS assessment
- Positive pregnancy test or currently lactating

41 randomized to receive dexmedetomidine; 44 randomized to receive midazolam/propofol (previous standard care).

The median age of the dexmedetomidine was 64 years; the median age of the standard care group was 68 years

Interventions	<ul style="list-style-type: none"> • Intervention group: Dexmedetomidine was infused without a loading dose at 0.8 mcg/kg for an hour and then adjusted stepwise at 0.25, 0.5, 0.8, 1.1, and 1.4 mcg/kg per hour • Control group: Propofol or midazolam. Propofol was infused at 2.4 mg/kg for an hour and then adjusted stepwise at 0.8, 1.6, 2.4, 3.2, and 4.0 mg/kg per hour. Depending on standard care at time of randomization, midazolam was given either as intravenous boluses (1 – 2 mg), starting at 3 boluses for an hour, and thereafter 1 - 4 boluses per hour, or as a continuous infusion at 0.12 mg/kg for an hour, followed by adjustments at 0.04, 0.08, 0.12, 0.16, and 0.20 mg/kg per hour. The initial dose could be reduced, if considered necessary by the treating clinician • Target sedation level and sedation level measurement: Target RASS score: -4 to 0; measurement was performed every 2 hours • Rescue medication to reach target sedation level: 1st-line rescue medication was propofol for participants receiving midazolam, and midazolam for those receiving propofol before randomization. • Daily interruption: Yes • Description of pain control: Pain was treated with fentanyl boluses • Endpoint: The study treatment lasted a maximum of 14 days from randomization and the follow-up for 45 days
Outcomes	<ul style="list-style-type: none"> • Duration of mechanical ventilation • Risk of delirium: Delirium was assessed by trained study personnel with the CAM-ICU • Adverse events: Bradycardia, hypotension, cardiac failure, pneumonia, pyothorax, sepsis, septic shock, epilepsy, pulmonary oedema, respiratory failure, shock • Proportion of sedation time spent in target sedation level: Proportion of sedation time within RASS target, without rescue medication • Duration of weaning • ICU LOS: From admission and randomization to medically fit for discharge from the ICU • Mortality: mortality for 45 days
Dates	October 2005 to July 2006
Setting and Country	Setting: intensive care units Country: Finland, Switzerland
Funding source and Declarations of interest	Sources of funding: Orion Pharma, Helsinki, Finland

Ruokonen 2009 (Continued)

Declaration of investigators' conflicts of interest: Not reported

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Randomization was stratified for study centre, current sedative, sedation target (Richmond Agitation-Sedation Scale; RASS) 0 to -3 vs. RASS -4, and admission type (medical vs. postoperative/trauma)." Comment: The authors reported they used stratified randomization, but did not state how they randomly divide participants in detail.
Allocation concealment (selection bias)	High risk	Comment: The authors did not explicitly state how they concealed randomization sequence
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "double-blind"; "Dexmedetomidine and dexmedetomidine dummy (0.9% NaCl), propofol 2% and propofol dummy (0.9% NaCl) and midazolam (0.1%) and midazolam dummy (0.9% NaCl) were prepared by personnel not involved in the study or the patient's care; infusion systems for propofol and its dummy were nontransparent."; "Depending on standard care at time of randomization, midazolam was given either as intravenous boluses (1-2 mg), starting at 3 boluses per hour for 1 h, and thereafter 1-4 boluses per hour, and if not sufficient as continuous infusion of 0.2 mg/kg/h, or as a continuous infusion at 0.12 mg/kg/h for 1 h, followed by adjustments at 0.04, 0.08, 0.12, 0.16, and 0.20 mg/kg/h." Comment: Bolus injection of midazolam usually acts much faster than continuous infusion of dexmedetomidine and therefore blinding could be easily broken. It is therefore possible that the investigators' decisions and actions could have been influenced.
Blinding of outcome assessment (detection bias) Subjective outcomes	High risk	Subjective outcome: risk of delirium, proportion of sedation time spent at target sedation level Quote: "Dexmedetomidine and dexmedetomidine dummy (0.9% NaCl), propofol 2% and propofol dummy (0.9% NaCl) and midazolam (0.1%) and midazolam dummy (0.9% NaCl) were prepared by personnel not involved in the study or the patient's care; infusion systems for propofol and its dummy were nontransparent."; "Depending on standard care at time of randomization, midazolam was given either as intravenous boluses (1-2 mg), starting at 3 boluses per hour for 1 h, and thereafter 1-4 boluses per hour, and if not sufficient as continuous infusion of 0.2 mg/kg/h, or as a continuous infusion at 0.12 mg/kg/h for 1 h, followed by adjustments at 0.04, 0.08, 0.12, 0.16, and 0.20 mg/kg/h." Comment: Blinding could be easily broken. Lack of blinding might bias the assessment of subjective outcomes.
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	Objective outcome: duration of mechanical ventilation, adverse events, duration of weaning, ICU LOS, mortality Comment: Objective outcomes were not likely to be biased by lack of blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "85 were randomized (intention-to-treat patients) to receive dexmedetomidine (DEX; n = 41) or to continue their previous standard care (SC; n = 44)" 31 completed study treatment in dexmedetomidine group, 10 withdraws (6 due to "lack of efficacy"; 3 due to "adverse event"; 1 due to "discharge to an-

Ruokonen 2009 (Continued)

other hospital"); 37 completed study treatment in standard group, 7 with-draws (1 due to "lack of efficacy"; 5 due to "adverse event"; 1 due to "protocol violation")

Imputation roles:

- If ICU discharge date exists but end of mechanical ventilation (MV) is missing → MV end date is set equal to ICU discharge and participant is assumed to have been weaned from any mechanical ventilation.
- If ICU discharge date and end of MV are missing → length of ICU stay and duration of MV are set to 45 days.
- If ICU discharge date is missing but end of MV exists → length of ICU stay is set to 45 days and duration of MV is as observed.

Comment: Reasons for withdrawal were explicitly reported and generally balanced across study groups. Conservative imputation rules were applied.

Selective reporting (reporting bias)	Low risk	All the outcomes listed in Methods section are reported.
Other bias	Low risk	The study appears to be free of other sources of bias.

Shehabi 2013

Methods	Parallel group randomized controlled trial
Participants	<p>Inclusion criteria:</p> <ul style="list-style-type: none"> • Patients were included if they had been intubated within the previous 12 hours, were expected to need mechanical ventilation for longer than 24 hours, and required immediate and ongoing sedation <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • Age less than 18 years • Pregnancy • Proven or suspected primary neurological injury • Diagnosis likely to result in prolonged weakness • Drug overdose • Burn injury • Acute liver failure • Dementia, or psychiatric illness • Need for ongoing neuromuscular blockade • Palliative care, or treatment limitations • Inability to communicate in English • Mean blood pressure less than 55 mm Hg • Heart rate less than 55/min • High-grade atrioventricular block in the absence of a functioning pacemaker <p>21 randomized to receive dexmedetomidine; 16 randomized to receive midazolam/propofol</p> <p>The mean age of the dexmedetomidine group was 61.6 years; the mean age of the standard care group was 65 years.</p>
Interventions	<ul style="list-style-type: none"> • Intervention group: Dexmedetomidine, 0 - 1.5 mcg/kg per hour • Control group: Midazolam and/or propofol

Shehabi 2013 (Continued)

- Target sedation level and sedation level measurement: Target RASS score: -2 to 1; measurement was performed every 4 hours.
- Rescue medication to reach target sedation level: Propofol
- Daily interruption: No
- Description of pain control: Pain was treated with infusion or boluses of an opioid (fentanyl or morphine) or other agents such as ketamine, as determined by the treating clinician
- Endpoint: Until sedation was no longer required or up to 28 days of therapy

Outcomes	<ul style="list-style-type: none"> • Risk of delirium: Identified by the positive CAM-ICU • Proportion of sedation time spent at target sedation level: Time spent in the light sedation range in the 48 hours after randomization • ICU LOS • Mortality: Hospital mortality, 90-day mortality
Dates	July 2011 to December 2011
Setting and Country	Setting: Intensive care units Country: Australia, New Zealand

Funding source and Declarations of interest	<p>Sources of funding: Hospira, Lake Forest, IL</p> <p>Declaration of investigators' conflicts of interest: Dr Shehabi has received unrestricted Grant-In-Aid research grants from Hospira Inc. (Lake Forest, IL); research grants from Roche Diagnostics and Ther-mofisher Scientific; competitive research funding grants from the National Health and Medical Research Council, Australia. Dr Shehabi's research department has received payment for article preparation for being part of SEDCOM delirium manuscript review 2009; and speakers' honoraria and consulting fee from Hospira and Roche Diagnostics. He was on an advisory board for Hospira and GSK and has received payment from GSK for the development of educational material approved by College of Intensive Care Medicine of ANZ. Dr Reade has received a consulting fee and research grants from Hospira. Dr McArthur has received grant support, travel reimbursements, and provisions for writing assistance from Hospira Australia. Dr Seppelt was on an advisory board in Intensive Care supported by Hospira; has received competitive research funding grants from National Health and Medical Research Council, Australia; and has received payment for the development of educational presentations from Asklepios Medical Education. Dr Webb has consulted for Aalix Healthcare Services Consulting, Ibis Biosciences, Astra Zeneca, Jansen Cilag, and has received grant support from Fresenius Kabi. The remaining authors have not disclosed any potential conflicts of interest.</p>
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Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Block randomization was undertaken with concealed envelopes."
Allocation concealment (selection bias)	Low risk	Quote: "Block randomization was undertaken with concealed envelopes."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "unblinded" Comment: It was possible that the investigators' decisions and actions could have been influenced.
Blinding of outcome assessment (detection bias) Subjective outcomes	High risk	Subjective outcome: rate of delirium, proportion of sedation time spent at target sedation level Quote: "unblinded"

Shehabi 2013 (Continued)

		Comment: Lack of blinding might influence the subjective outcomes.
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	Objective outcome: ICU LOS, mortality Comment: Objective outcomes were not likely to be biased by lack of blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed the study and there were no losses to follow-up, no treatment withdrawals, no trial group changes and no major adverse events.
Selective reporting (reporting bias)	Low risk	All the outcomes listed in Methods are reported.
Other bias	Low risk	The study appears to be free of other sources of bias.

Xu 2012

Methods	Randomized controlled trial
Participants	<p>Inclusion criteria:</p> <ul style="list-style-type: none"> • Patient is conscious, intubated, mechanically ventilated and expected to require sedation for more than 72 hours <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • Disorders of consciousness • Bradycardia • Unstable haemodynamics • Expected requirement for sedation less than 72 hours • Children and pregnant women • Severe hepatic and renal dysfunction <p>20 randomized to dexmedetomidine infusion alone, 20 randomized to midazolam infusion alone, 20 randomized to dexmedetomidine infusion combined with midazolam infusion and 20 randomized to dexmedetomidine infusion combined with midazolam bolus. We only included dexmedetomidine-infusion-alone group and midazolam-infusion-alone group in our review.</p> <p>The mean age of the dexmedetomidine was 59.52 years; the mean age of the midazolam group was 58.77 years.</p>
Interventions	<ul style="list-style-type: none"> • Intervention group: Dexmedetomidine. Loading does was 1 mcg/kg for 10 minutes; maintenance dose was 0.2 - 0.7 mcg/kg per hour • Control group: Midazolam. Loading does was 0.05 mg/kg; maintenance dose was 0.02 - 0.1 mg/kg per hour • Target sedation level and sedation level measurement: The sedation level was required to be at MAAS target of 3. MAAS was assessed every 2 hours • Rescue medication to reach target sedation level: Unreported • Daily interruption: No • Description of pain control: Unreported • Endpoint: Unreported
Outcomes	<p>Risk of delirium: Delirium was assessed using the CAM-ICU</p> <p>Adverse events: Hypotension, bradycardia, nausea</p>

Xu 2012 (Continued)

Proportion of sedation time spent at target sedation level: Proportion of sedation time within MAAS target

Dates	February 2010 to September 2012
Setting and Country	Setting: intensive care units Country: China
Funding source and Declarations of interest	Sources of funding: Not reported Declaration of investigators' conflicts of interest: Not reported
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: The authors stated that they used stratified randomization, but they did not state how they did this.
Allocation concealment (selection bias)	High risk	Comment: The authors did not state how they concealed their randomization sequence. Allocation concealment was probably not done.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Subjective outcome: risk of delirium, proportion of sedation time spent at target sedation level. Comment: The authors did not state they used blinded methods. It was possible that the investigators' decisions and actions could have been influenced.
Blinding of outcome assessment (detection bias) Subjective outcomes	High risk	Comment: The authors did not state they used blinded methods. Lack of blinding might bias the assessment of subjective outcomes, but not objective outcomes.
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	Objective outcome: adverse events. Comment: Objective outcomes were not likely to be biased by lack of blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All the participants completed the study protocol.
Selective reporting (reporting bias)	Low risk	All the outcomes listed in the Methods section are reported.
Other bias	Low risk	The study appears to be free of other sources of bias.

CAM-ICU: confusion assessment method for the intensive care unit

FDA: Food and Drug Administration

ICU: intensive care unit

LOS: length of stay

MAAS: Motor Activity Assessment Scale

RASS: Richmond Agitation-Sedation Scale

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Arenas 2004	Non-RCT
Corbett 2005	Study did not require or anticipate participants to have more than 24 hours sedation
Fang 2012	Study did not require or anticipate participants to have more than 24 hours sedation
Feng 2012	Study did not require or anticipate participants to have more than 24 hours sedation
Guo 2012	Duration of sedation was < 6 hours
Herr 2003	Duration of sedation was limited to 6 - 24 hours
Hu 2013	Study did not require or anticipate participants to have more than 24 hours sedation
Jiang 2012	Study did not require or anticipate participants to have more than 24 hours sedation
Kadoi 2008	Study did not require or anticipate participants to have more than 24 hours sedation
Kaneko 2008	Duration of sedation was < 24 hours
Li 2011	Duration of sedation was < 24 hours
Li 2012	Duration of sedation was < 24 hours
Li 2013	Not all the participants were mechanically ventilated
Linj 2012	Study did not require or anticipate participants to have more than 24 hours sedation
Liu 2013a	Study did not require or anticipate participants to have more than 24 hours sedation
Liu 2013b	Study did not require or anticipate participants to have more than 24 hours sedation
Luo 2012a	Study did not require or anticipate participants to have more than 24 hours sedation
Luo 2012b	Study did not require or anticipate participants to have more than 24 hours sedation
Luo 2012c	Duration of sedation was limited to 12 hours
Peng 2011	Study did not require or anticipate participants to have more than 24 hours sedation
Pu 2012	Duration of sedation was limited to 24 hours
Qu 2011	Study did not require or anticipate participants to have more than 24 hours sedation
Su 2014	Study did not require or anticipate participants to have more than 24 hours sedation
Tasdogan 2009	Duration of sedation was < 24 hours
Tian 2010	Duration of sedation was limited to 12 hours
Tobias 2004	The use of dexmedetomidine was limited to up to 24 hours
Venn 2001	Study did not require or anticipate participants to have more than 24 hours sedation
Wan 2011	Study did not require or anticipate participants to have more than 24 hours sedation

Study	Reason for exclusion
Wang 2011a	Duration of sedation was limited to 24 hours
Wang 2011b	Study did not require or anticipate participants to have more than 24 hours sedation
Wang 2011c	Study did not require or anticipate participants to have more than 24 hours sedation
Wang 2012a	Study did not require or anticipate participants to have more than 24 hours sedation
Wang 2012b	Duration of sedation was limited to 24 hours
Wang 2014	Study did not require or anticipate participants to have more than 24 hours sedation
Xiao 2013	Study did not require or anticipate participants to have more than 24 hours sedation
Yang 2013	Study did not require or anticipate participants to have more than 24 hours sedation
Yao 2010	Study did not require or anticipate participants to have more than 24 hours sedation
Yuan 2014	Study did not require or anticipate participants to have more than 24 hours sedation
Zhang 2012a	Study did not require or anticipate participants to have more than 24 hours sedation
Zhang 2012b	Duration of sedation was limited to 12 - 72 hours
Zhang 2013	Study did not require or anticipate participants to have more than 24 hours sedation
Zhang 2014a	Study did not require or anticipate participants to have more than 24 hours sedation
Zhang 2014b	Study did not require or anticipate participants to have more than 24 hours sedation
Zheng 2012	Study did not require or anticipate participants to have more than 24 hours sedation
Zhou 2012a	Study did not require or anticipate participants to have more than 24 hours sedation
Zhou 2012b	Study did not require or anticipate participants to have more than 24 hours sedation

Characteristics of studies awaiting assessment *[ordered by study ID]*

Tao 2011

Methods	Randomized controlled trial
Participants	<p>Inclusion criteria:</p> <ul style="list-style-type: none"> • Patient aged > 18 years, admitted to the ICU, expected to be mechanically ventilated for more than 24 hours <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • Pregnancy • Receiving epidural or spinal anaesthesia or muscle relaxants within 24 hour before enrolment • Planned to receive general anaesthesia within 24 hour before enrolment or after enrolment • Severe neurological disorder (acute stroke, uncontrolled epilepsy, severe dementia) • Unstable angina pectoris and/or acute myocardial infarction

Tao 2011 (Continued)

- Heart rate < 50 beats/min
- Atrioventricular-conduction block II - III
- Diastolic blood pressure < 90 mmHg, even if vasopressor is administered

30 randomized to receive dexmedetomidine; 30 randomized to receive midazolam.

Interventions	<ul style="list-style-type: none"> • Intervention group: Dexmedetomidine. Loading does was 1 mc/kg; maintenance dose was 0.2 - 0.7 mcg/kg per hour • Control group: Midazolam. Loading does was 0.05 mg/kg; maintenance dose was 0.03 - 0.2 mg/kg per hour • Target sedation level and sedation level measurement: The sedation level was required to be at the Riker scale target range of 3 to 4 and assessed every 4 hours • Rescue medication to reach target sedation level: Unreported • Daily interruption: Yes • Description of pain control: Unreported • Endpoint: Unreported
Outcomes	<ul style="list-style-type: none"> • Duration of mechanical ventilation • Rate of delirium: Delirium was assessed daily during the arousal assessment using the CAM-ICU • Proportion of sedation time spent in target sedation level: Proportion of sedation time within the Riker scale target • Adverse events: Bradycardia, tachycardia, hypotension, hypertension • ICU LOS
Notes	This study appears to duplicate Riker 2009

CAM-ICU: confusion assessment method for the intensive care unit

ICU: intensive care unit

LOS: length of stay

Characteristics of ongoing studies [ordered by study ID]

NCT01059929

Trial name or title	A double-blinded randomized controlled trial of dexmedetomidine versus propofol for sedation in mechanically ventilated medical intensive care unit patients
Methods	Randomized control trial
Participants	<p>Inclusion criteria:</p> <ul style="list-style-type: none"> • >18 years old • mechanically ventilated through endotracheal tube • anticipated need for ventilation > 48 hours • requiring sedative/analgesic medication <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • On mechanical ventilator > 96 hours • Primary neurologic disease • Post-cardiac arrest • Does not speak English (assessment only English-language-validated) • Pregnancy or lactation • Active myocardial ischaemia • Second or third degree heart block • Pancreatitis

Alpha-2 agonists for long-term sedation during mechanical ventilation in critically ill patients (Review)

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NCT01059929 (Continued)

	<ul style="list-style-type: none"> Elevated serum triglycerides (> 400 mg/dL)
Interventions	<ul style="list-style-type: none"> Intervention group: Dexmedetomidine, 0.2 - 1.5 mcg/kg per hour Control group: Propofol, 5 - 50 mcg/kg per minute
Outcomes	<p>Primary outcome measures:</p> <ul style="list-style-type: none"> Delirium: CAM-ICU assessment <p>Secondary outcome measures</p> <ul style="list-style-type: none"> Drug efficacy: Richmond Agitation Sedation Scale (RASS) Mobility milestones Days on ventilator Days in ICU Mortality ICU complications Fentanyl requirement Midazolam requirement Days in hospital Activities of daily living Adverse medication events
Starting date	September 2009
Contact information	Contact: Anne S Pohlman 773-702-3804 apohlman@medicine.bsd.uchicago.edu
Notes	

NCT01760967

Trial name or title	Effect of dexmedetomidine on mortality, duration of mechanical ventilation and multi-organ function in sepsis patients under lighter sedation by randomized control trial
Methods	Randomized control trial
Participants	<p>Inclusion criteria:</p> <ul style="list-style-type: none"> Adult Transferred to ICU Anticipation of a need for mechanical ventilation at least 24 hours <p>Exclusion criteria:</p> <ul style="list-style-type: none"> Sever chronic liver disease Acute myocardial infarction, heart disease Drug dependence, alcoholism Psychological illness, severe cognitive dysfunction Patients who have allergy for dexmedetomidine Attending physician's decision
Interventions	<ul style="list-style-type: none"> Intervention group: Dexmedetomidine, 0.1 - 0.7 mcg/kg per hour Control group: non-Dexmedetomidine. Administer sedatives except Dexmedetomidine.
Outcomes	Primary outcome measures:

NCT01760967 (Continued)

- Mortality: mortality of participants for 28 days or on day of discharge if participant is discharged earlier than 28 days
- Duration of mechanical ventilation: duration of mechanical ventilation in the ICU involving non-invasive ventilation

Secondary Outcome Measures:

- Length of stay in the ICU
- Length of stay in the hospital
- Evaluation of restlessness and delirium: evaluation of RASS and CAM-ICU
- Evaluation of cognitive function: evaluation of Mini mental state examination for 28 days or on day of discharge if participant is discharged earlier than 28 days
- Occurrence of arrhythmia or myocardial ischaemia
- Renal function: blood urea nitrogen, creatinine, estimated glomerular filtration rate, daily urinary output, need for renal replacement therapy
- Infection control: Duration of antimicrobial agents use within 28 days or up to day of discharge if participant is discharged earlier than 28 days
- Inflammation marker: Laboratory marker of inflammation on 1,3,7,14 days
- Organ failure control: Sequential Organ Failure Assessment score during stay in the ICU
- Coagulopathy control: Disseminated Intravascular Coagulation score by the Japanese Association for Acute Medicine during stay in the ICU
- Nutrition control: daily energy intake by enteral nutrition
- Sedation control: dose of sedative drugs and analgesic drugs during stay in the ICU

Starting date	January 2013
Contact information	Contact: Yu Kawazoe +81-73-441-0603 ukz411@gmail.com Contact: Kyohei Miyamoto +81-73-441-0603 go.go.kyohei.miyamoto@gmail.com
Notes	

ICU: intensive care unit

LOS: length of stay

RASS: Richmond Agitation-Sedation Scale

DATA AND ANALYSES

Comparison 1. Dexmedetomidine versus traditional sedative agents

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duration of mechanical ventilation (subgroup: class of alternative agents)	4	1120	Mean Difference (IV, Random, 95% CI)	-0.25 [-0.40, -0.10]
1.1 Benzodiazepine derivatives	1	500	Mean Difference (IV, Random, 95% CI)	-0.29 [-0.49, -0.09]
1.2 Propofol	1	498	Mean Difference (IV, Random, 95% CI)	-0.20 [-0.43, 0.04]
1.3 Standard care (propofol and midazolam)	2	122	Mean Difference (IV, Random, 95% CI)	-0.31 [-1.26, 0.64]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Duration of mechanical ventilation (sensitivity analysis using data from 'time to extubation')	4	1120	Mean Difference (IV, Random, 95% CI)	-0.34 [-0.49, -0.20]
3 Risk of delirium (subgroup: class of alternative agents)	7	1624	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.63, 1.14]
3.1 Benzodiazepine derivatives	4	1007	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.59, 1.09]
3.2 Propofol	1	495	Risk Ratio (M-H, Random, 95% CI)	0.37 [0.16, 0.87]
3.3 Standard care (propofol and midazolam)	2	122	Risk Ratio (M-H, Random, 95% CI)	1.44 [0.86, 2.41]
4 Risk of delirium (sensitivity analysis for observed data only)	7	1621	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.63, 1.14]
5 Incidence of bradycardia (subgroup: class of alternative agents)	6	1587	Risk Ratio (M-H, Random, 95% CI)	2.11 [1.39, 3.20]
5.1 Benzodiazepine derivatives	4	1007	Risk Ratio (M-H, Random, 95% CI)	2.44 [1.77, 3.36]
5.2 Propofol	1	495	Risk Ratio (M-H, Random, 95% CI)	1.20 [0.74, 1.94]
5.3 Standard care (propofol and midazolam)	1	85	Risk Ratio (M-H, Random, 95% CI)	7.50 [0.40, 140.91]
6 Incidence of bradycardia (subgroup: dosing regimens)	6	1587	Risk Ratio (M-H, Random, 95% CI)	2.11 [1.39, 3.20]
6.1 Rapid dosing regimens	1	40	Risk Ratio (M-H, Random, 95% CI)	9.00 [0.52, 156.91]
6.2 Slow dosing regimens	5	1547	Risk Ratio (M-H, Random, 95% CI)	2.05 [1.35, 3.11]
7 Incidence of bradycardia (sensitivity analysis for observed data only)	6	1584	Risk Ratio (M-H, Random, 95% CI)	2.11 [1.39, 3.21]
8 Incidence of hypotension (subgroup: class of alternative agents)	6	1587	Risk Ratio (M-H, Random, 95% CI)	1.22 [0.86, 1.74]
8.1 Benzodiazepine derivatives	4	1007	Risk Ratio (M-H, Random, 95% CI)	1.39 [0.77, 2.53]
8.2 Propofol	1	495	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.62, 1.54]
8.3 Standard care (propofol and midazolam)	1	85	Risk Ratio (M-H, Random, 95% CI)	2.15 [0.20, 22.79]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9 Incidence of hypotension (subgroup: dosing regimens)	6	1587	Risk Ratio (M-H, Random, 95% CI)	1.22 [0.86, 1.74]
9.1 Rapid dosing regimens	1	40	Risk Ratio (M-H, Random, 95% CI)	9.00 [0.52, 156.91]
9.2 Slow dosing regimens	5	1547	Risk Ratio (M-H, Random, 95% CI)	1.18 [0.86, 1.62]
10 Incidence of hypotension (sensitivity analysis for observed data only)	6	1584	Risk Ratio (M-H, Random, 95% CI)	1.22 [0.86, 1.73]
11 Proportion of sedation time spent at target sedation level			Other data	No numeric data
12 ICU length of stay (LOS) (subgroup: class of alternative agents)	5	1223	Mean Difference (IV, Random, 95% CI)	-0.15 [-0.28, -0.01]
12.1 Benzodiazepine derivatives	2	603	Mean Difference (IV, Random, 95% CI)	-0.15 [-0.34, 0.03]
12.2 Propofol	1	498	Mean Difference (IV, Random, 95% CI)	-0.12 [-0.34, 0.10]
12.3 Standard care (propofol and midazolam)	2	122	Mean Difference (IV, Random, 95% CI)	-0.21 [-0.69, 0.26]
13 Mortality (subgroup: class of alternative agents)	6	1584	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.79, 1.24]
13.1 Benzodiazepine derivatives	3	967	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.68, 1.41]
13.2 Propofol	1	495	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.55, 1.21]
13.3 Standard care (propofol and midazolam)	2	122	Risk Ratio (M-H, Random, 95% CI)	1.44 [0.67, 3.11]
14 Mortality (sensitivity analysis for observed data only)	6	1581	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.78, 1.24]

Analysis 1.1. Comparison 1 Dexmedetomidine versus traditional sedative agents, Outcome 1 Duration of mechanical ventilation (subgroup: class of alternative agents).

Study or subgroup	Dexmedetomidine		Traditional sedatives		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI		Random, 95% CI
1.1.1 Benzodiazepine derivatives							
Jakob 2012 MIDEK	249	4.8 (1.2)	251	5.1 (1.1)		57.84%	-0.29[-0.49,-0.09]
Subtotal ***	249		251			57.84%	-0.29[-0.49,-0.09]

Favours dexmedetomidine

-2 -1 0 1 2

Favours traditional

Analysis 1.2. Comparison 1 Dexmedetomidine versus traditional sedative agents, Outcome 2 Duration of mechanical ventilation (sensitivity analysis using data from 'time to extubation''').

Analysis 1.3. Comparison 1 Dexmedetomidine versus traditional sedative agents, Outcome 3 Risk of delirium (subgroup: class of alternative agents).

Analysis 1.4. Comparison 1 Dexmedetomidine versus traditional sedative agents, Outcome 4 Risk of delirium (sensitivity analysis for observed data only).

Analysis 1.5. Comparison 1 Dexmedetomidine versus traditional sedative agents, Outcome 5 Incidence of bradycardia (subgroup: class of alternative agents).

Analysis 1.6. Comparison 1 Dexmedetomidine versus traditional sedative agents, Outcome 6 Incidence of bradycardia (subgroup: dosing regimens).

Analysis 1.7. Comparison 1 Dexmedetomidine versus traditional sedative agents, Outcome 7 Incidence of bradycardia (sensitivity analysis for observed data only).

Analysis 1.8. Comparison 1 Dexmedetomidine versus traditional sedative agents, Outcome 8 Incidence of hypotension (subgroup: class of alternative agents).

Analysis 1.9. Comparison 1 Dexmedetomidine versus traditional sedative agents, Outcome 9 Incidence of hypotension (subgroup: dosing regimens).

Analysis 1.10. Comparison 1 Dexmedetomidine versus traditional sedative agents, Outcome 10 Incidence of hypotension (sensitivity analysis for observed data only).

Analysis 1.11. Comparison 1 Dexmedetomidine versus traditional sedative agents, Outcome 11 Proportion of sedation time spent at target sedation level.

Study	Proportion of sedation time spent at target sedation level	
	Dexmedetomidine	Traditional sedatives
Jakob 2012 MIDEX	60.7%	56.6%
Jakob 2012 PRODEX	64.6%	64.7%
Pandharipande 2007	80% (nurse); 67% (physician)	67% (nurse); 55% (physician)
Riker 2009	77.3%	75.1%
Ruokonen 2009	64%	63%
Shehabi 2013	66%	38%
Xu 2012	52.8%	48.6%

Analysis 1.12. Comparison 1 Dexmedetomidine versus traditional sedative agents, Outcome 12 ICU length of stay (LOS) (subgroup: class of alternative agents).

Analysis 1.13. Comparison 1 Dexmedetomidine versus traditional sedative agents, Outcome 13 Mortality (subgroup: class of alternative agents).

Analysis 1.14. Comparison 1 Dexmedetomidine versus traditional sedative agents, Outcome 14 Mortality (sensitivity analysis for observed data only).

ADDITIONAL TABLES

Table 1. Calculation from median/interquartile range to geometric mean/standard deviation (SD)

Study ID	Outcome	Study group	Median	Interquartile range	Geometric mean	Geometric SD
Jakob 2012 MIDEX	Duration of mechanical ventilation	Intervention	123 hours	67 - 337 hours	4.812	1.197
		Control	164 hours	92 - 380 hours	5.1	1.051

Table 1. Calculation from median/interquartile range to geometric mean/standard deviation (SD) (Continued)

Jakob 2012 PRODEX	Duration of mechanical ventilation	Intervention	97 hours	45 - 257 hours	4.575	1.291
		Control	118 hours	48 - 327 hours	4.771	1.421
Ruokonen 2009	Duration of mechanical ventilation	Intervention	77.2 hours	17.5 – 338.8 hours	4.346	2.195
		Control	110.6 hours	20.1 – 675.0 hours	4.706	2.603
Jakob 2012 MIDEX	ICU LOS	Intervention	8.8 days (211 hours)	4.8 - 34.6 days (115 - 831 hours)	2.174	1.465
		Control	10.1 days (243 hours)	5.8 - 26.2 days (140 - 630 hours)	2.315	1.114
Jakob 2012 PRODEX	ICU LOS	Intervention	6.8 days (164 hours)	3.8 - 20.0 days (90 - 480 hours)	1.922	1.24
		Control	7.7 days (185 hours)	3.9 - 21.7 days (93 - 520 hours)	2.042	1.275
Pandhari-pande 2007	ICU LOS	Intervention	7.5 days	5 - 19 days	2.015	0.989
		Control	9 days	6 - 15 days	2.197	0.679
Ruokonen 2009	ICU LOS	Intervention	5.5 days	1.7 – 19.5 days	1.705	1.807
		Control	5.7 days	1.7 – 29.0 days	1.74	2.101

ICU: intensive care unit

LOS: length of stay

Table 2. Meta-regression for incidence of delirium on geometric mean ventilation time

tau² (estimated amount of residual heterogeneity)	0.1460 (SE = 0.1596)
tau (square root of estimated tau ² value)	0.3820
I² (residual heterogeneity / unaccounted variability)	70.09%
H² (unaccounted variability / sampling variability)	3.34
R² (amount of heterogeneity accounted for)	0.00%
Intercept	0.0895 (95% CI -5.4218 to 5.6007, P = 0.9746)
Coefficient for log-transformed mean ventilation time	-0.0442 (95% CI -1.1989 to 1.1105, P = 0.9403)

APPENDICES

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor: [Adrenergic alpha-Agonists] explode all trees
 #2 MeSH descriptor: [Dexmedetomidine] explode all trees
 #3 MeSH descriptor: [Clonidine] explode all trees
 #4 alpha?2 adrenergic agonist* or dexmed* or precede or clonidin* or catapresan* or isoglancon or ST-155
 #5 #1 or #2 or #3 or #4
 #6 MeSH descriptor: [Respiration, Artificial] explode all trees
 #7 MeSH descriptor: [Ventilation] this term only
 #8 ((invasive or intubat* or mechanical or artificial) near (ventilat* or respire*)) or ventilat*:ti,ab
 #9 #6 or #7 or #8
 #10 #5 and #9

Appendix 2. OVID MEDLINE search strategy

1. exp Adrenergic alpha-Agonists/ or exp Dexmedetomidine/ or exp Clonidine/ or alpha?2 adrenergic agonist*.af. or (dexmed* or precede* or clonidin* or catapresan* or isoglancon or ST-155).mp.
 2. exp Respiration, Artificial/ or Ventilation/ or ((invasive or intubat* or mechanical or artificial) adj3 (ventilat* or respire*)).mp. or ventilat*.ti,ab.
 3. 1 and 2
 4. ((randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.) not (animals not (humans and animals)).sh.
 5. 3 and 4

Appendix 3. EMBASE (Ovid SP) search strategy

1. exp alpha adrenergic receptor stimulating agent/ or exp dexmedetomidine/ or exp clonidine/ or alpha?2 adrenergic agonist*.af. or (dexmed* or precede* or clonidin* or catapresan* or isoglancon or ST-155).mp.
 2. exp artificial ventilation/ or air conditioning/ or ((invasive or intubat* or mechanical or artificial) adj3 (ventilat* or respire*)).mp. or ventilat*.ti,ab.
 3. 1 and 2
 4. (placebo.sh. or controlled study.ab. or random*.ti,ab. or trial*.ti,ab. or ((singl* or doubl* or trebl* or tripl*) adj3 (blind* or mask*))).ti,ab.) not (animals not (humans and animals)).sh
 5. 3 and 4

Appendix 4. CINAHL (EBSCO host) search strategy

S1 (MM "Adrenergic Alpha-Agonists") OR (MM "Clonidine") OR alpha?2 adrenergic agonist* OR dexmed* or precede or clonidin* or catapresan* or isoglancon or ST-155
 S2 (MM "Respiration, Artificial") OR (MM "Ventilation") OR ((invasive or intubat* or mechanical or artificial) N3 (ventilat* or respire*)) OR AB ventilat*S3 S1 AND S2

Appendix 5. LILACS (BIREME) search strategy

alpha 2 adrenergic agonist\$ or dexmed\$ or precede\$ or clonidin\$ or catapresan\$ or isoglancon or ST-155 [Palavras] and ((invasive or intubat\$ or mechanical or artificial) and (ventilat\$ or respire\$)) or ventilat\$ [Palavras]

Appendix 6. ISI Web of Science search strategy

#1 TS=(alpha?2 adrenergic agonist* or dexmed* or precede* or clonidin* or catapresan* or isoglancon or ST-155)
 #2 TS=((invasive or intubat* or mechanical or artificial) SAME (ventilat* or respire*)) or TI=ventilat*
 #3 #2 AND #1

Appendix 7. Chinese Biological Medical Database (CBM) search strategy

("肾上腺素能α激动剂"[主题词] OR "右美托咪啉"[主题词] OR "可乐定"[主题词] OR "肾上腺素能α激动剂"[全字段] OR "dexmedetomidine"[全字段] OR "右美托咪啉"[全字段] OR "艾贝宁"[全字段] OR "clonidine"[全字段] OR "可乐定"[全字段]) AND ("通气机, 机械"[主题词] OR "Ventilators, Mechanical"[全字段] OR "机械通气"[全字段] OR "肺通气机"[全字段] OR "呼吸机"[全字段] OR "呼吸器"[全字段] OR "辅助通气"[全字段] OR "人工气道"[全字段] OR "intubation"[全字段] OR "气管插管"[全字段]) AND (治疗应用 OR 随机 OR 对照)

Appendix 8. China National Knowledge Infrastructure (CNKI) search strategy

((SU=α₂肾上腺素受体激动药 OR SU=右美托咪啶 OR SU=可乐定) OR (FT=α₂肾上腺素受体激动药 OR FT=α₂受体激动药 OR FT=右美托咪啶 OR FT=可乐定 OR FT=艾贝宁)) AND (SU=机械通气 OR (FT=机械通气 OR FT=肺通气机 OR FT=呼吸器 OR FT=呼吸机 OR FT=辅助通气 OR FT=人工气道 OR FT=气管插管)) AND (TI=多中心 OR TI=疗效 OR TI=随机 OR AB=多中心 OR AB=疗效 OR AB=随机)

Appendix 9. Data extraction form

Review title or ID

Study ID (*surname of first author and year first full report of study was published e.g. Smith 2001*)

Report IDs of other reports of this study (*e.g. duplicate publications, follow-up studies*)

Notes:

1. General Information

Date form completed (*dd/mm/yyyy*)

Name/ID of person extracting data

Report title

(*title of paper/ abstract/ report that data are extracted from*)

Report author contact details

(Continued)

Publication type

(e.g. full report, abstract, letter)

Possible conflicts of interest

(for study authors)

Notes:
2. Study Eligibility

Study Characteristics	Eligibility criteria	Yes	No	Unclear
Type of study	Randomized controlled trial or quasi-randomized controlled Trial?			
	Simple parallel group design?			
Participants	Were the participants of any age, except neonates, who required intensive care and invasive mechanical ventilation when recruited?			
Types of intervention	Did the study compare clonidine or dexmedetomidine versus alternative sedative agents?			
	Did the study explicitly report that each participant is anticipated to need long-term sedation (> 24 hours)?			
Types of outcome measures	Did the study report any one of 1. Duration of mechanical ventilation? 2. Rate of acute brain dysfunction (rate of delirium and rate of coma)? 3. Adverse effects? 4. Proportion of sedation time spent in target sedation level? 5. Duration of weaning? 6. ICU Length of Stay (LOS)? 7. Mortality?			
The study will be excluded if any of the above answers are "No".				
INCLUDE ☐		EXCLUDE ☐		
Notes:				

(Continued)

DO NOT PROCEED IF STUDY EXCLUDED FROM REVIEW

3. Setting and methods

Description	
Country/countries	
Setting	☐ Single-centre ☐ Multi-centre (centre number =)
Type of ICU	☐ Mixed intensive care unit ☐ Medical intensive care unit ☐ Surgical intensive care unit ☐ Coronary care unit ☐ Respiratory care unit ☐ Burn unit ☐ Other (specify:)
Inclusion criteria	
Exclusion criteria	
Informed consent obtained	Yes ☐ No ☐ Unclear ☐
Ethical approval needed/obtained for study	Yes ☐ No ☐ Unclear ☐
Notes:	

4. Risk of Bias assessment

See Chapter 8 of the Cochrane Handbook

Domain	Risk of bias			Support for judgement	Location in text <i>(pg & ¶/fig/table)</i>
	Low risk	High risk	Unclear		
Random sequence generation <i>(selection bias)</i>					
Allocation concealment <i>(selection bias)</i>					
Blinding of participants and personnel <i>(performance bias)</i>				Outcome group: duration of mechanical ventilation	
				Outcome group: rate of delirium	
				Outcome group: rate of coma	
				Outcome group: adverse events	
				Outcome group: proportion of sedation time spent in target sedation level	
				Outcome group: duration of weaning	
				Outcome group: ICU Length of Stay (LOS)	
Blinding of outcome assessment <i>(detection bias)</i>				Outcome group: mortality	
				Outcome group: duration of mechanical ventilation	
				Outcome group: rate of delirium	

(Continued)

	Outcome group: rate of coma
	Outcome group: adverse events
	Outcome group: duration of weaning
	Outcome group: proportion of sedation time spent in target sedation level
	Outcome group: ICU Length of Stay (LOS)
	Outcome group: mortality
Incomplete outcome data <i>(attrition bias)</i>	Outcome group: duration of mechanical ventilation
	Outcome group: rate of delirium
	Outcome group: rate of coma
	Outcome group: adverse events
	Outcome group: proportion of sedation time spent in target sedation level
	Outcome group: duration of weaning
	Outcome group: ICU Length of Stay (LOS)
	Outcome group: Mortality
Selective outcome reporting?	

(Continued)
(reporting bias)

Other bias

(whether the groups
were balanced at
baseline, whether
the co-interventions
were avoided or
similar)

Quality classification Low risk of bias ☐ Unclear risk of bias ☐ High risk of bias ☐

Notes:

5. Participants

Provide overall data and, if available, comparative data for each intervention or comparison group.

Description as stated in re-
port/paper

Total no. randomized

(or total pop. at start of study for NRCTs)

Total no. analysed

Withdrawals and exclusions

Age

(mean or median)

Co-morbidities

Notes:

6. Intervention groups

Copy and paste table if more than two groups

Description as stated in report/paper		
Anticipated duration of sedation (if no limitation of anticipated duration of sedation, please mark "no limitation")		
No. randomized to group	Intervention group:	Control group 1:
No. included in analyses	Intervention group:	Control group 1:
Sedative agent	Intervention group:	Control group 1:
Description of route, dose and frequency	Intervention group:	Control group 1:
Target sedation level and sedation level measurement (if no target sedation level, please mark "no target sedation level")		
Rescue medication to reach target sedation level (if no rescue medication, please mark "/")	Intervention group:	Control group 1:
Study design	☐ Standardized design	☐ Non-standardized design
Daily interruption	Yes ☐	No ☐
Description of pain control (if no pain control, please mark "no pain control")		
Economic variables (i.e. intervention cost, changes in other costs as result of intervention)	Intervention group:	Intervention group:
Notes:		

7. Outcomes

Outcome name	Outcome reported	Outcome definition or measurement as stated in report/paper
Duration of mechanical ventilation	Yes ☐ No ☐	
Risk of delirium	Yes ☐ No ☐	
Risk of coma	Yes ☐ No ☐	
Adverse events	Incidence of bradycardia Yes ☐ No ☐	
	Incidence of hypotension Yes ☐ No ☐	
	Incidence of hypertension Yes ☐ No ☐	
	Other (specify:)	
Proportion of sedation time spent in target sedation level	Yes ☐ No ☐	
Duration of weaning	Yes ☐ No ☐	
ICU Length of Stay (LOS)	Yes ☐ No ☐	
Mortality	Yes ☐ No ☐	
Other	(specify:)	
Notes:		

8. Results

Copy and paste table if more than two groups

Dichotomous outcome

Outcome	Intervention group				Control group 1				Follow-up time point
	No. events	No. participants	No. missing participants	Other information	No. events	No. participants	No. missing participants	Other information	
Risk of delirium									
Risk of coma									
Adverse events	Incidence of bradycardia								
	Incidence of hypotension								
	Incidence of hypertension								
	Other								
	(specify:)								
Mortality									
Notes:									

Continuous outcome

Outcome	Log scale	Intervention group				Control group 1			
		No. participants	Mean (SD)	95% CI	Other information	No. participants	Mean (SD)	95% CI	Other information
Duration of mechanical ventilation	Yes/No								
Duration of weaning	Yes/No								
ICU Length of Stay (LOS)	Yes/No								
Notes:									

Other outcome

Outcome	Result stated in report/paper
Proportion of sedation time spent in target sedation level	
Notes:	

9. Applicability

	Yes	No	Unclear
Have important populations been excluded from the study? <i>(consider disadvantaged populations, and possible differences in the intervention effect)</i>			
Is the intervention likely to be aimed at disadvantaged groups? <i>(e.g. lower socioeconomic groups)</i>			
Does the study directly address the review question? <i>(any issues of partial or indirect applicability)</i>			
Notes:			

10. Other information

	Description as stated in report/paper
Key conclusions of study authors	
References to other relevant studies	
Correspondence required for further study information <i>(from whom, what and when)</i>	
Notes:	

FEEDBACK

Suggest standardized definition for delirium and more transparency in how data is extracted

Summary

Comment one

Given the significant heterogeneity observed in the incidence of delirium data, we would suggest using a standardized definition for delirium. For example, the [Riker 2009](#) study defined delirium as the presence of a positive CAM-ICU score. However, the [Jakob 2012 PRODEX](#) and [Jakob 2012 MIDEX](#) authors reported delirium separately in two ways:

1. positive CAM-ICU score, and
2. clinician-reported delirium.

The data for these methods of reporting were not concordant. That is, many patients with positive CAM-ICU scores were not counted as having delirium by the more subjective clinician-reported method. In the meta-analysis, data for clinician-reported delirium in the PRODEX, MIDEX, and [Ruokonen 2009](#) studies was used, but the presence of a positive CAM-ICU score to determine delirium was used in the remaining studies. We feel that counting delirium in two separate ways introduces avoidable heterogeneity.

Comment two

Additionally, we suggest more transparency in how data is extracted. We noticed some inconsistencies in data obtained from the PRODEX and MIDEX trials. For example, in [Analysis 1.3](#), delirium was recorded as having occurred in 7/246 dexmedetomidine patients and 19/249 propofol patients. However, in the PRODEX dataset, 7 (2.8%) dexmedetomidine patients were reported to have developed delirium while 17 (6.9%) developed delirium in the propofol group. We were unable to identify where the numbers of patients who developed delirium were obtained in the Cochrane meta-analysis. To improve reader comprehension, we suggest that a base analysis be performed using raw extracted values from the study with a best and worst case sensitivity analysis performed to assess differences between the exposed population and all randomized patients.

Reply

Reply to comment one

We were aware that the [Jakob 2012 PRODEX](#) and [Jakob 2012 MIDEX](#) trials reported the rate of both positive CAM-ICU score and clinician-reported delirium (which was also based on the CAM-ICU score). We agree that patients with positive CAM-ICU scores might not be counted as having delirium by the clinician-reported method. However, the rate of positive CAM-ICU score was only counted at a single time point of 48 hours after stopping study sedation rather than whole study follow-up. We aimed to compare the delirium rate during ventilation time or sedation time, and thus we did not consider it as representative of the delirium rate. Although the clinician-reported delirium rate during study follow-up was more subjective, we thought it was more appropriate to be included in our analyses.

Reply to comment two

In the [Jakob 2012 PRODEX](#) trial, two patients in the propofol group were excluded because they 'withdrew consent' (this was clarified in the [Characteristics of included studies](#)). We judged the data of the two patients to be "not missing at random", and thus we inferred bad outcomes (having delirium) and performed analyses using both imputed data and raw extracted data (sensitivity analyses).

Contributors

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We certify that we have no affiliations with or involvement in any organization or entity with a financial interest in the subject matter of our feedback.

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WHAT'S NEW

Date	Event	Description
3 January 2019	Amended	Editorial team changed to Cochrane Emergency and Critical Care

HISTORY

Protocol first published: Issue 12, 2012

Review first published: Issue 1, 2015

Date	Event	Description
19 August 2015	Feedback has been incorporated	see Feedback 1

CONTRIBUTIONS OF AUTHORS

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Conceiving the review: KC

Co-ordinating the review: SMP and KC

Undertaking manual searches: KC and YCX

Screening search results: KC and YCX

Organizing retrieval of papers: KC

Screening retrieved papers against inclusion criteria: KC, YCX and YIC

Appraising quality of papers: KC, YCX, YIC, SMP and ZJL

Abstracting data from papers: KC and YCX

Writing to authors of papers for additional information: KC

Providing additional data about papers: KC, SMP and ZJL

Obtaining and screening data on unpublished studies: KC and YCX

Data management for the review: KC

Entering data into Review Manager 5 (RevMan) ([RevMan 5.3](#)): KC and YCX

RevMan statistical data: KC and YC

Other statistical analyses not using RevMan: KC and YC

Interpretation of data: KC, SMP and ZJL

Statistical inferences: KC and YC

Writing the review: KC

Securing funding for the review: SMP and ZJL

Performing previous work that was the foundation of the present study: None

Guarantor for the review (one author): KC

Person responsible for reading and checking review before submission: KC and SMP

DECLARATIONS OF INTEREST

Ken Chen: none known

Zhijun Lu: none known

Yi Chun Xin: none known

Yong Cai: none known

Yi Chen: none known

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SOURCES OF SUPPORT

Internal sources

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External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

1. We did not limit the follow-up time for mortality in the protocol ([Chen 2012](#)). However, some studies assessed mortality at various follow-up times (e.g. 30-day mortality, one-year mortality). We only included the follow-up that was most comparable to those used in other studies.
2. We had planned to generate funnel plots and conduct the Egger test or arcsine test in the protocol. However, there were fewer than 10 studies included, and thus we were not able to perform them.
3. For these continuous outcomes, we planned to estimate log-transformed means and standard deviations by using Method 1 mentioned in [Higgins 2008](#) in the protocol, if we could obtain means and standard deviations of raw data. However, we were not able to obtain these data from study authors. Consequently, we estimated means using medians ([Hozo 2005](#)), and calculated approximate standard deviations by dividing the log-transformed interquartile range by 1.35 ([Higgins 2011b](#)). We calculated the geometric mean difference rather than standardized mean difference for continuous outcomes.
4. We did not perform subgroup analyses on different follow-up time points, since the cut-off time point (72 hours) used to divide the subgroups was arbitrary, and subgroup analyses were insufficient to explore how the risk of delirium changed with follow-up time. Instead, because most studies only measure delirium during mechanical ventilation, we performed a meta-regression to investigate how log-transformed mean ventilation time was associated with risk of delirium.
5. We had planned to undertake sensitivity analyses by excluding studies with imputed data to explore the influence of our imputation rule in the protocol. However, we found that excluding a whole study with imputed data would lead to massive loss of information. Thus, we undertook sensitivity analyses by pooling observed data only, without any imputation.
6. We had planned to use the principles of the GRADE system to assess the quality of the body of evidence associated with the proportion of sedation time spent at the target sedation level in the protocol. However, we did not perform a meta-analysis for 'proportion of sedation time spent at target sedation level' and thus we were not able to calculate a relative effect. Bradycardia was the most commonly reported adverse event but we did not list it as one of the outcomes for our 'Summary of findings' in the protocol. Thus, we decided to use the GRADE system to assess the quality of evidence associated with 'incidence of bradycardia' instead of 'proportion of sedation time spent at target sedation level'.
7. [Jakob 2012 MIDEX](#) and [Jakob 2012 PRODEX](#) reported not only 'duration of mechanical ventilation', but also 'time to extubation', which matched our definition of duration of mechanical ventilation. We performed a post hoc sensitivity analysis to assess how the result would change if we extracted the data from 'time to extubation' instead of 'duration of mechanical ventilation'.

INDEX TERMS

Medical Subject Headings (MeSH)

*Critical Illness; Adrenergic alpha-2 Receptor Agonists [adverse effects] [*therapeutic use]; Bradycardia [chemically induced]; Clonidine [therapeutic use]; Conscious Sedation [*methods]; Dexmedetomidine [adverse effects] [*therapeutic use]; Lorazepam [adverse effects] [therapeutic use]; Midazolam [adverse effects] [therapeutic use]; Propofol [adverse effects] [therapeutic use]; Randomized Controlled Trials as Topic; Respiration, Artificial [*statistics & numerical data]; Selection Bias; Time Factors

MeSH check words

Adult; Humans