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Moira Cruickshank,[1] Lorna Henderson,[1] Graeme MacLennan,[1] Cynthia Fraser,[1] Marion Campbell,[1] Bronagh Blackwood,[2] Anthony Gordon[3] and Miriam Brazzelli[1]*

[1]Health Services Research Unit, University of Aberdeen, Aberdeen, UK
[2]Centre for Infection and Immunity, School of Medicine, Dentistry and Biomedical Sciences, Queen's University Belfast, Belfast, UK
[3]Faculty of Medicine, Department of Surgery and Cancer, Charing Cross Hospital, Imperial College London, London, UK

*Corresponding author

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Abstract

Alpha-2 agonists for sedation of mechanically ventilated adults in intensive care units: a systematic review

Moira Cruickshank,[1] Lorna Henderson,[1] Graeme MacLennan,[1] Cynthia Fraser,[1] Marion Campbell,[1] Bronagh Blackwood,[2] Anthony Gordon[3] and Miriam Brazzelli[1]*

[1]Health Services Research Unit, University of Aberdeen, Aberdeen, UK
[2]Centre for Infection and Immunity, School of Medicine, Dentistry and Biomedical Sciences, Queen's University Belfast, Belfast, UK
[3]Faculty of Medicine, Department of Surgery and Cancer, Charing Cross Hospital, Imperial College London, London, UK

*Corresponding author m.brazzelli@abdn.ac.uk

Background: Care of critically ill patients in intensive care units (ICUs) often requires potentially invasive or uncomfortable procedures, such as mechanical ventilation (MV). Sedation can alleviate pain and discomfort, provide protection from stressful or harmful events, prevent anxiety and promote sleep. Various sedative agents are available for use in ICUs. In the UK, the most commonly used sedatives are propofol (Diprivan®, AstraZeneca), benzodiazepines [e.g. midazolam (Hypnovel®, Roche) and lorazepam (Ativan®, Pfizer)] and alpha-2 adrenergic receptor agonists [e.g. dexmedetomidine (Dexdor®, Orion Corporation) and clonidine (Catapres®, Boehringer Ingelheim)]. Sedative agents vary in onset/duration of effects and in their side effects. The pattern of sedation of alpha-2 agonists is quite different from that of other sedatives in that patients can be aroused readily and their cognitive performance on psychometric tests is usually preserved. Moreover, respiratory depression is less frequent after alpha-2 agonists than after other sedative agents.

Objectives: To conduct a systematic review to evaluate the comparative effects of alpha-2 agonists (dexmedetomidine and clonidine) and propofol or benzodiazepines (midazolam and lorazepam) in mechanically ventilated adults admitted to ICUs.

Data sources: We searched major electronic databases (e.g. MEDLINE without revisions, MEDLINE In-Process & Other Non-Indexed Citations, EMBASE and Cochrane Central Register of Controlled Trials) from 1999 to 2014.

Methods: Evidence was considered from randomised controlled trials (RCTs) comparing dexmedetomidine with clonidine or dexmedetomidine or clonidine with propofol or benzodiazepines such as midazolam, lorazepam and diazepam (Diazemuls®, Actavis UK Limited). Primary outcomes included mortality, duration of MV, length of ICU stay and adverse events. One reviewer extracted data and assessed the risk of bias of included trials. A second reviewer cross-checked all the data extracted. Random-effects meta-analyses were used for data synthesis.

Results: Eighteen RCTs (2489 adult patients) were included. One trial at unclear risk of bias compared dexmedetomidine with clonidine and found that target sedation was achieved in a higher number of patients treated with dexmedetomidine with lesser need for additional sedation. The remaining 17 trials compared dexmedetomidine with propofol or benzodiazepines (midazolam or lorazepam). Trials varied considerably with regard to clinical population, type of comparators, dose of sedative agents, outcome

measures and length of follow-up. Overall, risk of bias was generally high or unclear. In particular, few trials blinded outcome assessors. Compared with propofol or benzodiazepines (midazolam or lorazepam), dexmedetomidine had no significant effects on mortality [risk ratio (RR) 1.03, 95% confidence interval (CI) 0.85 to 1.24, $I^2 = 0\%$; $p = 0.78$]. Length of ICU stay (mean difference –1.26 days, 95% CI –1.96 to –0.55 days, $I^2 = 31\%$; $p = 0.0004$) and time to extubation (mean difference –1.85 days, 95% CI –2.61 to –1.09 days, $I^2 = 0\%$; $p < 0.00001$) were significantly shorter among patients who received dexmedetomidine. No difference in time to target sedation range was observed between sedative interventions ($I^2 = 0\%$; $p = 0.14$). Dexmedetomidine was associated with a higher risk of bradycardia (RR 1.88, 95% CI 1.28 to 2.77, $I^2 = 46\%$; $p = 0.001$).

Limitations: Trials varied considerably with regard to participants, type of comparators, dose of sedative agents, outcome measures and length of follow-up. Overall, risk of bias was generally high or unclear. In particular, few trials blinded assessors.

Conclusions: Evidence on the use of clonidine in ICUs is very limited. Dexmedetomidine may be effective in reducing ICU length of stay and time to extubation in critically ill ICU patients. Risk of bradycardia but not of overall mortality is higher among patients treated with dexmedetomidine. Well-designed RCTs are needed to assess the use of clonidine in ICUs and identify subgroups of patients that are more likely to benefit from the use of dexmedetomidine.

Study registration: This study is registered as PROSPERO CRD42014014101.

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List of abbreviations

APACHE	Acute Physiology and Chronic Health Evaluation
CAM-ICU	Confusion Assessment Method for the Intensive Care Unit
CI	confidence interval
DSI	daily sedation interruption
GABA	gamma-aminobutyric acid
ICNARC	Intensive Care National Audit & Research Centre
ICU	intensive care unit
MIDEX	MIdazolam compared with DEXmedetomidine trial
MV	mechanical ventilation
PAD	pain, agitation and delirium
PRODEX	PROpofol compared with DEXmedetomidine trial
RASS	Richmond Agitation–Sedation Scale
RCT	randomised controlled trial
RR	risk ratio
RSS	Ramsay Sedation Scale
SAS	Sedation–Agitation Scale
SD	standard deviation
SEDCOM	Safety and Efficacy of Dexmedetomidine COmpared with Midazolam trial

Plain English summary

Sedation involves the use of drugs to produce a state of calm or sleep in patients admitted to intensive care units (ICUs).

The most common drugs used in ICUs fall into three groups: (1) propofol (Diprivan®, AstraZeneca); (2) benzodiazepines [including midazolam (Hypnovel®, Roche) and lorazepam (Ativan®, Pfizer)]; and (3) alpha-2 adrenergic receptor agonists [including clonidine (Catapres®, Boehringer Ingelheim) and dexmedetomidine (Dexdor®, Orion Corporation)]. The effects of sedation vary between drugs and none has been shown to be clearly better than the others. The drugs called alpha-2 agonists (clonidine and dexmedetomidine) appear to be different in that patients can be awakened more easily, are better able to communicate and do not suffer from breathing problems which can occur with other drugs.

We looked at all clinical studies that have been done on these drugs in people admitted to ICUs who required assistance with breathing on a ventilator. We assessed (1) the effects of dexmedetomidine compared with clonidine and (2) the effects of dexmedetomidine compared with propofol and benzodiazepines. Results from 18 clinical studies (2489 patients) showed that, compared with other drugs, dexmedetomidine reduced the length of stay in ICUs and the time until the patient was ready to have the breathing tube removed. More people treated with dexmedetomidine, however, suffered from a slow heart rate. The numbers of deaths and other bad effects were similar regardless of the drug used. Overall, the quality of the clinical studies was low and there were some uncertainties regarding the data used for the analyses. Further clinical studies are needed to evaluate the effects of clonidine and to identify which patients are more likely to benefit from dexmedetomidine.

Scientific summary

Background

Sedation is a key component of the care of critically ill patients who may need invasive or uncomfortable procedures, such as mechanical ventilation (MV). In the intensive care unit (ICU), indications for sedation include pain control, to allow use of distressing procedures and minimise patient discomfort, to provide protection from stressful and harmful stimuli, reduction and control of agitation, and to enable nocturnal sleep and induce amnesia.

Evidence from randomised controlled trials (RCTs) and current clinical guidelines support the use of minimum possible sedation levels to achieve the desired effects, while preserving patient comfort and safety. Indeed, the recent trend has been towards lighter levels of sedation, with only a minority of patients requiring continuous deep sedation. Optimal sedation level varies widely between patients, depending on their clinical condition and treatment requirements. Prevalence of anxiety and agitation in critically ill patients undergoing MV has been reported to be > 70%. Therefore, assessment and monitoring of sedation level should be routinely performed in ICUs. Usually, sedation level is measured by means of scoring sedation scales. The most commonly used scales are the Richmond Agitation–Sedation Scale and the Ramsay Sedation Scale.

Often, sedation requirements are not optimally managed, and oversedation or undersedation may occur with important deleterious effects, such as cardiorespiratory depression, prolonged MV, hypertension and tachycardia. The recent *Clinical Practice Guidelines for the Management of Pain, Agitation, and Delirium in Adult Patients in the Intensive Care Unit* [pain, agitation and delirium (PAD) guidelines] recommend routine monitoring of the depth of sedation to address suboptimal sedation levels, use of sedation protocols and light target sedation levels using either daily sedation interruptions or titration of sedatives.

These guidelines also stress the importance of routine assessment of pain with provision of adequate analgesia to all critically ill patients and routine monitoring of delirium. Pain is the main stressor reported by patients and the most common memory patients have of their ICU stay. Delirium may occur in up to 80% of mechanically ventilated ICU patients and is associated with higher mortality, longer MV and hospital stay, and increased risk of cognitive impairment.

A variety of sedative agents are available for the management of critically ill patients in ICUs. The choice of sedative or analgesic agents to achieve appropriate levels of sedation and pain relief can be quite challenging and must take account of the pharmacological properties of the different drugs as well as the individual patient's characteristics and needs. In the UK, the most commonly used drugs are propofol (Diprivan®, AstraZeneca), benzodiazepines [midazolam (Hypnovel®, Roche) and lorazepam (Ativan®, Pfizer)] and alpha-2 adrenergic receptor agonists [dexmedetomidine (Dexdor®, Orion Corporation) and clonidine (Catapres®, Boehringer Ingelheim)]. A shift from benzodiazepines to propofol has been recently observed in ICU practice. The PAD guidelines suggest that use of non-benzodiazepines (propofol or dexmedetomidine) may improve clinical outcomes over benzodiazepine-based sedation strategies (midazolam or lorazepam).

The 2014 Intensive Care National Audit and Research Centre national survey conducted among 235 adult general ICUs in the UK showed that propofol was the most widely used sedative agent, with 88% of the units reporting it as their first choice of sedative agent. Although approximately one-third of the surveyed units (32%) reported frequent use of midazolam, only a small proportion (6%) reported that midazolam was their first choice of sedative agent. Less than 1% of the units reported use of lorazepam. Around one-third of ICUs (33%) reported frequent use of clonidine and 10% reported frequent use of dexmedetomidine.

The ideal sedation strategy for critically ill patients in ICUs should address pain, sedation and anxiety; have favourable kinetics and clinical effects; be easily titrated and monitored; have a tolerable side effect profile; and be affordable. None of the commonly used sedative agents fulfils all these criteria or has been shown to be clearly superior to the others.

Objectives

The purpose of this assessment was to review the evidence from existing RCTs on the effects of alpha-2 agonists compared with each other and compared with alternative sedative agents in intensive care practice, with the purpose of informing any future RCT.

The specific objectives of this assessment were (1) to assess the effects of sedation using dexmedetomidine compared with clonidine in mechanically ventilated adults admitted to ICUs; and (2) to assess the effects of sedation using dexmedetomidine or clonidine compared with other most commonly used sedative agents (i.e. propofol and benzodiazepines) in mechanically ventilated adults admitted to ICUs.

Methods

This assessment was conducted according to current methodological standards. Comprehensive literature searches were conducted to identify reports of RCTs assessing the effects of alpha-2 agonists, propofol and benzodiazepines for sedation in ICUs. We searched major electronic databases including MEDLINE without revisions, MEDLINE In-Process & Other Non-Indexed Citations, EMBASE, Science Citation Index, Bioscience Information Service and the Cochrane Central Register of Controlled Trials, for publications from 1999 onwards. Reports of relevant evidence synthesis were sought from the Cochrane Database of Systematic Reviews and Database of Abstracts of Reviews of Effects. The World Health Organization International Clinical Trials Registry Platform, *meta*Register of Controlled Trials and ClinicalTrials.gov were searched for evidence of ongoing studies. Final searches were carried out between 12 and 15 November 2014. Evidence for clinical effectiveness was considered from fully published RCTs comparing dexmedetomidine with clonidine or dexmedetomidine or clonidine with propofol or benzodiazepines (i.e. midazolam or lorazepam).
The population considered was critically ill adults admitted to ICUs who required MV. Primary outcomes of interest were mortality, duration of MV, ventilator-free days, length of ICU stay, adverse events and unpleasant side effects. Secondary outcomes were duration of weaning, time spent in target sedation range, proportion of patients in target sedation range, extubation readiness, discharge readiness, length of hospital stay, quality of life and costs. Data were extracted by one reviewer and double-checked by a second reviewer. The Cochrane risk-of-bias tool was used to assess the risk of bias of the included RCTs. Random-effects meta-analyses were performed when suitable data were available.

Results

Eighteen trials, with a total of 2489 patients, were included in the clinical effectiveness review. One trial (70 patients) compared dexmedetomidine with clonidine; nine trials (1134 patients) compared dexmedetomidine with propofol; four trials (939 patients) compared dexmedetomidine with midazolam; one trial (118 patients) compared dexmedetomidine with propofol and midazolam (three treatment arms); two trials (122 patients) compared dexmedetomidine with standard care (i.e. propofol and/or midazolam); and one trial (106 participants) compared dexmedetomidine with lorazepam. Overall, four trials were judged to be at low risk of bias, seven were judged to be at high risk of bias and the remaining seven trials did not provide sufficient information on which to base a judgement. Clinical heterogeneity among trials was mainly because of patient population (i.e. patients admitted to ICUs following elective surgery and general ICU patients), comparator interventions, dosage of sedative agents, outcome measures and units of measurements, and timing of follow-up assessments. Follow-up was short term (24 to 72 hours) in most trials.

Both clonidine and dexmedetomidine produced effective sedation. However, target sedation, with less need for additional sedation, was achieved in more patients who received dexmedetomidine than in those who received clonidine. Haemodynamic parameters appeared to be more stable among patients treated with dexmedetomidine.

Compared with propofol or benzodiazepines (midazolam or lorazepam), dexmedetomidine had no significant effects on mortality [risk ratio (RR) 1.03, 95% confidence interval (CI) 0.85 to 1.24, $I^2 = 0\%$; $p = 0.78$]. Length of ICU stay (mean difference –1.26 days, 95% CI –1.96 to –0.55 days, $I^2 = 31\%$; $p = 0.0004$) and time to extubation (mean difference –1.85 days, 95% CI –2.61 to –1.09 days, $I^2 = 0\%$; $p < 0.00001$) were significantly shorter among patients who received dexmedetomidine than among those who received alternative sedative agents. The proportion of time spent in adequate sedation range was not significantly different between sedative interventions (mean difference 2.53, 95% CI –0.82 to 5.87, $I^2 = 0\%$; $p = 0.14$), but dexmedetomidine was associated with a higher risk of bradycardia (RR 1.88, 95% CI 1.28 to 2.77, $I^2 = 46\%$; $p = 0.001$). We did not find any difference between dexmedetomidine and alternative sedative agents with regard to other adverse events such as hypotension, hypertension and tachycardia. There was no clear evidence that dexmedetomidine could reduce the risk of delirium (RR 0.83, 95% CI 0.65 to 1.06, $I^2 = 60\%$; $p = 0.14$), but statistical heterogeneity was observed in the analysis. In general, patients treated with dexmedetomidine were reported to be more easily arousable, more co-operative and better able to communicate than those treated with alternative sedative agents.

Subgroup analyses according to type of comparator were generally consistent with those of the overall population.

Limitations

The majority of the included trials assessed the effects of dexmedetomidine compared with propofol or midazolam. Data on the effects of dexmedetomidine compared with clonidine were limited (one trial).

There was considerable clinical heterogeneity among included trials, and most were at high or unclear risk of bias. Few trials blinded outcome assessors.

There was substantial variation in the choice, definitions and measurements of outcome measures, especially measures of ventilator dependence.

Transformation/imputation of data was required to combine results from included trials, as units of measurements and methods for analysing results varied considerably between trials.

Subgroup analyses were performed according to the type of comparators, but subgroups were usually too small to provide reliable conclusions.

Conclusions

There is an indication that dexmedetomidine may have a better cardiovascular safety profile than clonidine, but evidence is limited. Length of stay in ICUs and time to extubation were significantly shorter among patients who received dexmedetomidine than among those who received other sedative agents other than clonidine. No difference was observed in time in target sedation range between dexmedetomidine and alternative sedative interventions.

Incidence of bradycardia was significantly higher for dexmedetomidine, but did not impact on mortality. There was no clear evidence that dexmedetomidine was superior to other sedative agents in reducing the risk of delirium. Considerable clinical heterogeneity between trials was observed, and the overall risk of bias was high or unclear.

Recommendations for future research

Large, well-designed clinical trials are needed to (1) evaluate the long-term effects of clonidine for sedation in ICUs; and (2) identify subgroups of patients who are more likely to benefit from dexmedetomidine. Main subgroups of interest would be patients who require short-term sedation after elective surgery and general critically ill patients who require long-term sedation.

Ideally, such trials would include relevant clinical outcomes sets, proper outcome definitions, validated instruments to assess level of sedation and incidence of events such as delirium and coma, longer follow-ups and a full economic evaluation. Relevant clinical outcomes from an ICU perspective would comprise MV, length of ICU stay and incidence of delirium, bradycardia and hypotension. Patient-relevant outcomes such as the patients' ability to communicate with health-care personnel and the patients' perspective of quality of sedation would also require consideration in future trials.

Study registration

This study is registered as PROSPERO CRD42014014101.

Funding

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Chapter 1 Background and research question

Description of health problem

Introduction

Sedation is 'a drug-induced depression of consciousness, a continuum culminating in general anaesthesia'.[1] Sedation is a key component of care of critically ill patients, who often need to undergo potentially invasive or uncomfortable procedures such as mechanical ventilation (MV).[2–6] Indications for the use of sedation in the intensive care unit (ICU) include: to alleviate pain; to facilitate use of distressing procedures and minimise patient discomfort; to provide protection from stressful and harmful stimuli; to reduce agitation and control agitation; and to enable nocturnal sleep and, when necessary, amnesia.[6–11] Sedation requirements vary widely between patients and sedative regimens should be tailored to individual patient's needs [Sheila Harvey, Intensive Care National Audit and Research Centre (ICNARC), 2014].

Evidence from randomised controlled trials (RCTs) and current guidelines supports the use of the minimum possible level of sedation to achieve the desired effects without compromising patient comfort and safety.[12,13] A review of international surveys of critical care clinicians published between 1999 and 2009 confirmed that the trend was towards lighter levels of sedation,[4] with only a minority of patients in need of continuous deep sedation.[13–15]

The optimal level of sedation varies according to patients' clinical conditions and treatment requirements. The prevalence of anxiety and agitation in critically ill patients undergoing MV in the ICU has been reported to be > 70%. Hence, assessment of sedation level should be routinely performed in ICUs.[14,16] Sedation level is usually measured by ICU staff by means of scoring sedation scales. Several scales have been developed to monitor sedation levels in critically ill patients. The first standardised measurement for sedation was the Ramsay Sedation Scale (RSS),[17] which has been more recently superseded by the Richmond Agitation–Sedation Scale (RASS)[18,19] and the Riker Sedation–Agitation Scale (SAS).[20] Scores on the RASS range from 4 (combative) to –5 (cannot be aroused). Riker SAS scores range from 7 (dangerous agitation) to 1 (cannot be aroused). For mechanically ventilated critically ill patients, target scores of between –2 and 0 for the RASS and between 3 and 4 for the Riker SAS are considered appropriate.[13] These scales have been shown to have good reliability and validity in the ICU setting, with neither being definitively superior.[12,14,21] Physiological methods to measure the level of sedation include heart rate variability, auditory-evoked potentials and electroencephalogram.[12,22] Among these, one of the most developed is the bispectral index, which measures the level of consciousness by an algorithmic analysis of the patient's electroencephalographic and haemodynamic parameters, such as heart rate and arterial pressure.[11,23,24] Current UK and US guidelines do not recommend the use of physiological measures of brain function (e.g. bispectral index) as the primary method to monitor level of sedation in non-comatose, non-paralysed critically ill ICU patients, as these measures cannot adequately replace the existing subjective sedation scoring systems.[12,22]

Sedation requirements are often not optimally managed, and poor sedation practice, which encompasses oversedation and undersedation, may have important deleterious effects.[3,6,25] Oversedation can result in cardiorespiratory depression, decreased gastrointestinal motility, immunosuppression and prolonged MV. Undersedation can cause hypertension, tachycardia and discomfort.[6] A variety of strategies have been proposed to address suboptimal management of levels of sedation of critically ill patients in ICUs, including use of sedation guidelines, protocols and goal-directed sedation algorithms,[26–29] light target level of sedation and daily sedation interruptions (DSIs),[30–34] and regular monitoring of sedation requirements.[35–37]

The current *Clinical Practice Guidelines from the Society of Critical Care Medicine for the Management of Pain, Agitation, and Delirium in Adult Patients in the Intensive Care Unit*[12] [pain, agitation and delirium (PAD) guidelines] strongly recommend the use of management guidelines and protocols. Protocolised target-based sedation and analgesia may be regarded as the cornerstone of effective sedation practice.[38]

The PAD guidelines also recommend DSI or a light level of sedation in mechanically ventilated adults in ICUs.[12] Current evidence on the use of DSIs is far from conclusive. A RCT conducted by Girard and colleagues[39] in four tertiary care hospitals found that a strategy comprising both daily spontaneous breathing attempts and daily spontaneous awakening attempts (i.e. DSIs) resulted in better outcomes (such as days breathing without assistance and length of stay in ICUs and hospital) than standard care. A meta-analysis of five trials published in 2011[40] highlighted the need for further RCTs with long-term survival follow-up before DSI could become standard sedation practice for critically ill patients. A multicentre RCT by Mehta and colleagues[36] found that, in mechanically ventilated patients receiving continuous sedation, the combined use of protocol-guided sedation and DSI did not improve the clinical outcomes observed with the use of protocol-guided sedation alone. Similarly, a recent Cochrane systematic review[35] did not find strong evidence that DSIs influence the duration of MV, mortality, length of stay, drug consumption, quality of life or adverse events compared with sedation strategies that do not involve the use of DSIs. The authors, however, considered the results to be unstable because of the small number of identified trials, the clinical and statistical heterogeneity observed among them and the marginally significant overall estimate of effect. Moreover, a reduction in duration of MV was detected when the analyses were restricted to trials conducted in North America.[35]

Prior to initiating sedation, it is important to provide appropriate analgesia to all critically ill patients.[3,11,15] Adequate pain control can reduce the need for sedative drugs.[41] Pain can be experienced at rest by patients in the ICU[42] or because of a number of other factors, including routine care, underlying disease processes, invasive procedures and immobility.[13,43] Pain is reported as the principal stressor by patients and is the most common memory they have of their ICU stay.[13,44,45] The PAD guidelines stress the importance of routine assessment of pain and provision of pre-emptive analgesia.[12] Analgesics and sedatives work in synergy but actually have discrete targets,[6] and some analgesics also have a secondary sedative effect.[3] For example, remifentanil (Ultiva®, GlaxoSmithKline UK Ltd), an opioid, can be administered as a sole agent because of its sedative effects, although it is not commonly used in most ICUs.[13]

Clonidine (Catapres®, Boehringer Ingelheim) also has both sedative and analgesic effects.[46] Patient's requirements for analgesia and sedation should be thoughtfully balanced[11] and sedation should never be given as a substitute for analgesia (Sheila Harvey, ICNARC, 2014).

Alongside assessment of pain, the PAD guidelines recommend the routine monitoring of delirium,[12] which occurs in around 60–80% of mechanically ventilated patients in ICUs.[47–50] Delirium is associated with higher mortality, prolonged duration of MV, longer hospital stay and an increased risk of cognitive impairment among adult ICU patients [47,51,52] The Confusion Assessment Method for the Intensive Care Unit (CAM-ICU)[53] and the Intensive Care Delirium Screening Checklist[54] are the two most reliable instruments to assess delirium and their use is recommended by current guidelines.[12]

Current service provision

Management of critically ill patients in intensive care units in the UK

A variety of medication is available to treat critically ill patients in ICUs. The choice of sedative or analgesic agents to achieve appropriate levels of sedation and pain relief can be quite challenging and must take account of the pharmacological properties of the different drugs as well as the individual patient's characteristics and needs.[4,11,55] Sedative agents commonly used in ICUs include propofol (Diprivan®, AstraZeneca), benzodiazepines [midazolam and lorazepam (Ativan®, Pfizer)] and alpha-2 adrenergic receptor agonists [clonidine and dexmedetomidine (Dexdor®, Orion Corporation)].[34] Commonly used analgesic agents include alfentanil, fentanyl, morphine and remifentanil.[4,15] The current general trend in the UK, and internationally, is a shift from benzodiazepines to propofol and from morphine to alfentanil and fentanyl.[4,56,57] The 2013 PAD guidelines suggest that sedation strategies using non-benzodiazepines (either propofol or dexmedetomidine) may improve clinical outcomes in mechanically ventilated ICU patients over sedation strategies based on benzodiazepines (either midazolam or lorazepam).[12]

Ideally, the optimal sedative regimen for critically ill patients in ICUs should adequately address pain, sedation and anxiety; have favourable kinetics and clinical effects; be easily titrated and monitored; have a tolerable adverse effects profile; and be affordable.[4] At present, none of the commonly used sedative agents fulfil all of these criteria and none of them has demonstrated to be clearly superior to the others.[4,13,56]

Variation in services and/or uncertainty about best practice

A recent UK national survey conducted by the ICNARC among 235 adult general critical care units together with a point-prevalence study conducted among 52 adult general critical care units (Sheila Harvey, ICNARC, 2014) showed that just over half of the surveyed units (57%) reported the use of a written sedation or sedation/analgesia protocol and, of those that did, fewer than one-quarter assessed compliance with the protocol. Level of compliance with sedation protocols varied considerably across units, ranging from 26% to 100%. There was considerable variation with regard to the elements of pain, sedation and delirium management that were included in each protocol and the level of details provided. The majority of the units (94%) used a sedation scale/score for assessing the depth of sedation in patients. The RASS was the most frequently reported scale in use (65% of units), followed by the RSS (25%). Small proportions of units reported the use of the Riker SAS (3.5%), the modified RSS (3%), the Bloomsbury Sedation Scale (1%) and other local or modified scales. Most patients (88%) in the point-prevalence study were assessed using the same sedation scale/score reported in the survey, although variations were observed across units (from 63% to 100%). Seventy per cent of units reported screening for delirium daily and, of these, most (92%) reported using the CAM-ICU tool. Most units (94%) reported that a sedation hold was considered daily for sedated patients. The findings of the point-prevalence study indicate, however, that compliance with sedation holding may be quite low. Overall, only 53% of sedated patients who had been in the unit for at least 24 hours had been considered for a sedation hold during the previous 24 hours.

Despite the existence of numerous published studies and clinical guidelines for sedation and analgesia, there is still a great variation between units in terms of actual intensive care, suggesting that there are still some barriers to the implementation of all relevant recommendations into routine clinical practice.

Relevant national guidelines

The current clinical pathway for analgosedation in the ICU was published by the UK Intensive Care Society in 2014 and recommends sequential assessment and treatment of pain, sedation and delirium, with regular monitoring built into the pathway.[22] These guidelines are in line with the current US[12] and German[58] guidelines. The UK framework is presented in *Figure 1*.

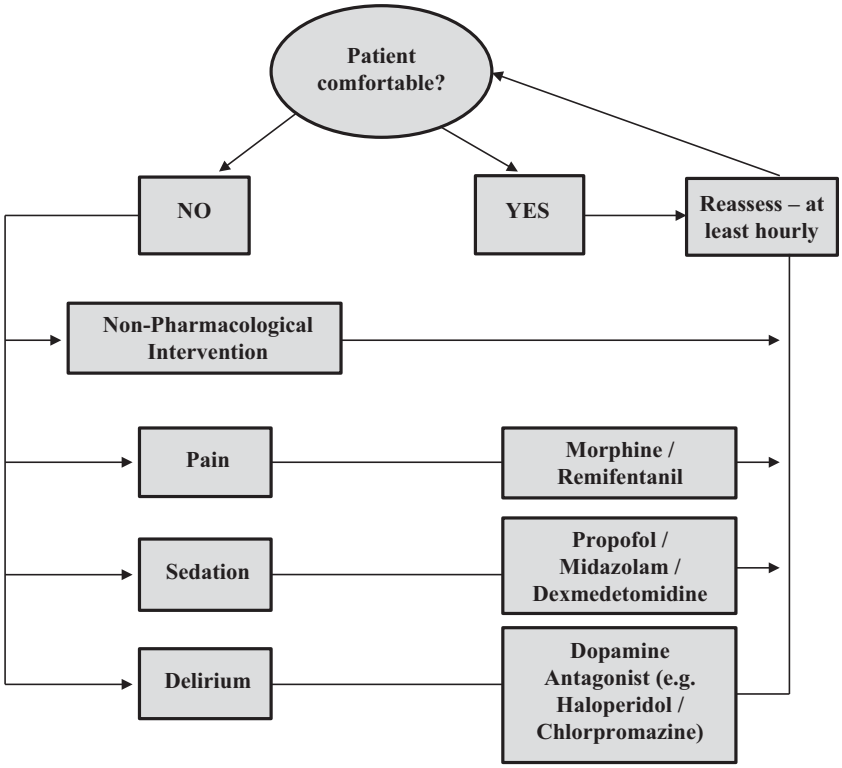

FIGURE 1 General framework for analgosedation in ICUs (the list of drugs is not exhaustive).[22] Reproduced from Grounds M, Snelson C, Whitehouse T, Wilson J, Tulloch L, Linhartova L, *et al. Intensive Care Society Review of Best Practice for Analgesia and Sedation in the Critical Care* with permission from UK Intensive Care Society (www.ics.ac.uk).

The National Institute for Health and Care Excellence Clinical Guidance Number 103,[59] published in July 2010, provides general recommendations for the diagnosis, prevention and management of delirium. The only specific recommendations for people in critical care are that the CAM-ICU should be used if indicators of delirium are identified and that consideration should be given to provision of 24-hour clocks to patients to address cognitive impairment and/or disorientation. The UK Intensive Care Society guidelines also provide recommendations for managing delirium.[22] The suggested framework consists of three stages: assess (pain, discomfort, constipation, hunger, delirium, attempts to communicate); treat (analgesia, aperients, feed, drug withdrawal, change or stop sedative regimen); and prevent (alternative analgesia, sleep, quiet and calm environment, diligent and targeted sedation, communication).

Description of technologies under assessment

Alpha-2 agonists

Dexmedetomidine is a newer, selective alpha-2 receptor agonist which has sedative, analgesic, anxiolytic and sympatholytic effects.[11,12,60] The sedative effects are mediated through decreased firing of the locus coeruleus, the predominant noradrenergic nucleus, situated in the brainstem.[61] The pattern of sedation of the alpha-2 agonists is quite different from that of other sedative agents in that patients can be aroused readily and their performance on psychometric tests is usually well preserved.[22,62,63] Moreover, dexmedetomidine does not depress the respiratory system, unlike other sedative agents.[64,65]

The dexmedetomidine terminal elimination half-life is around 2 hours.[12,13] Main adverse effects related to dexmedetomidine are hypotension and bradycardia.[11,13,66] Transient hypertension may occur during loading infusion.[13]

Dexmedetomidine was granted UK marketing authorisation in September 2011 for 'sedation of adult ICU patients requiring a sedation level not deeper than arousal in response to verbal stimulation (corresponding to RASS 0 to –3)'.[67] According to the summary of product characteristics,[61] dexmedetomidine is for hospital use only and should be administrated by a health-care professional skilled in managing patients requiring intensive care. It should be administered by intravenous infusion only, using a controlled infusion device. Doses are adjusted until the required level of sedation is attained. A loading dose is not recommended, as it is associated with increased adverse reactions. The maximum dose of dexmedetomidine is 1.4 µg/kg/hour. During infusion, all patients should undergo continuous cardiac monitoring, and respiration should be monitored in non-intubated patients. Use of dexmedetomidine for > 14 days requires monitoring and regular assessments. The combined use of dexmedetomidine with anaesthetics, other sedatives, hypnotics or opioids is likely to enhance pharmacological effects and, consequently, a reduced dosage of dexmedetomidine or the concomitant drug may be necessary.[61] In the USA, dexmedetomidine is authorised for infusion of up to 24 hours only in intubated and mechanically ventilated patients.[68]

In clinical trials, dexmedetomidine has been shown to be similar to midazolam and propofol on the time in target sedation range in a predominantly medical population requiring prolonged light to moderate sedation (RASS score of 0 to –3) in the ICU for up to 14 days.[61,69] In addition, dexmedetomidine reduced the duration of MV compared with midazolam[61,70,71] and reduced the time to extubation compared with midazolam and propofol. Compared with both propofol and midazolam, patients receiving dexmedetomidine were more easily aroused, were more co-operative and better able to communicate whether or not they had pain,[61,70] and showed a lower rate of post-operative delirium.[20,64,72] The sedative benefits of dexmedetomidine compared with midazolam are, however, not conclusive. A systematic review of six RCTs (1031 intensive care patients) published in 2013 has highlighted the need for further, more robust, research as, so far, the evidence of the advantages of dexmedetomidine compared with midazolam in the ICU setting is limited.[2] A meta-analysis of 14 trials (3029 critically ill patients) published in 2014 showed that the use of dexmedetomidine in ICUs is associated with a significant reduction in the incidence of delirium, agitation and confusion compared with other sedative agents.[73] Another meta-analysis of 27 RCTs, assessing dexmedetomidine compared with any other comparator in 3648 mechanically ventilated ICU patients, indicated that dexmedetomidine could be useful in reducing ICU stay and time to extubation, although heterogeneity was detected among included studies.[73] Similarly, a Cochrane systematic review published in January 2015 and based on seven RCTs with a total of 1624 patients, concluded that, compared with traditional sedative agents, long-term sedation with dexmedetomidine in critically ill patients may reduce the duration of MV and the length of ICU stay. However, the general methodological quality of evidence was low and there was clinical and statistical heterogeneity among studies.[74]

Clonidine is an alpha-2 agonist agent that produces a reduction in sympathetic tone and resultant fall in diastolic and systolic blood pressure and heart rate.[75] Originally marketed as an antihypertensive agent, clonidine has demonstrated sedative and analgesic-sparing properties. The current therapeutic indications include the treatment of hypertensive crises,[76] the prophylactic management of migraine or recurrent vascular headache and the management of vasomotor conditions commonly associated with the menopause and characterised by flushing.[75] There is no current marketing authorisation for clonidine as a sedative agent and no dosage recommendation for sedation in the summary of product characteristics.[76]

In the ICU setting, clonidine has been used as a treatment for delirium and as a second-line sedative agent.[77–79] The pharmacodynamics pattern of clonidine is broadly similar to that of dexmedetomidine, but clonidine is less specific for alpha-2 receptors and has a lower affinity for alpha-2 receptors than dexmedetomidine.[60,78] Clonidine has been shown to be effective in controlling delirium and withdrawal symptoms from opioids, benzodiazepines, nicotine and alcohol.[78,80–83] Clonidine is a very lipid-soluble agent. Its peak action occurs after 10 minutes and lasts for 3–7 hours after a single intravenous dose.[84] Clonidine is metabolised in the liver and is eliminated primarily through the kidney. The elimination of the half-life of clonidine is 6–23 hours (average 7.7 hours) (Sheila Harvey, ICNARC, 2014), a key difference from dexmedetomidine which has an elimination half-life of around one-quarter the length of clonidine.[85]

Sudden cessation of clonidine after prolonged use may cause a withdrawal syndrome leading to rebound hypertension and tachycardia in susceptible patients.[15,77,86] The main adverse effects of clonidine include bradycardia, hypotension and xerostomia (dry mouth).[15]

Evidence on the use of clonidine in ICU settings is limited. A recent placebo-controlled RCT found a significant reduction in the need for benzodiazepines and opioids, but not propofol, in mechanically ventilated ICU patients treated with clonidine compared with those receiving placebo. No significant differences in the incidence of adverse events were observed between the groups.[87]

A retrospective review of mechanically ventilated ICU patients' clinical records showed a significantly lower mortality index and no important adverse effects for patients receiving clonidine rather than other sedatives.[88] A prospective study assessing the effects of clonidine among mechanically ventilated ICU patients with withdrawal symptoms after sedation interruption for ventilator weaning showed that the majority responded positively to clonidine and were weaned in a median of 2 days. In addition, clonidine decreased the haemodynamic, metabolic and respiratory parameters to near those observed with sedation.[82]

The role of alpha-2 agonists (clonidine and dexmedetomidine) in the sedation of ICU patients has yet to be fully established.

Intravenous anaesthetic agents

Propofol is a short-acting intravenous general anaesthetic agent commonly used in ICUs since the 1980s. It activates gamma-aminobutyric acid (GABA) receptors and has shown a considerable array of effects including anxiolysis, anticonvulsant activity, antiemesis and the ability to reduce intracranial pressure.[13,89–93] Propofol is a lipid-soluble compound with a rapid onset of action (from seconds to minutes) and a short duration of effect following short-term administration.[12,90,94] Owing to its short duration of sedative effect, propofol may be indicated for patients who require frequent awakening and DSIs.[12,95] The half-life of propofol ranges from 30 to 60 minutes after short-term infusion, but is longer after prolonged infusion (up to 50 ± 18.6 hours).[12,13] The rapid onset and offset are specific features of propofol compared with other common sedative drugs.[96] The most significant side effects of propofol include hypotension as a result of systemic vasodilation and dose-dependent respiratory depression.

Other side effects include hypertriglyceridaemia, acute pancreatitis, arrhythmia, bradycardia and cardiac arrest.[11–13] Propofol administration may rarely cause propofol infusion syndrome, an adverse reaction characterised by lactic acidosis, hypertriglyceridaemia, hypotension and arrhythmia.[12]

A systematic review of 16 RCTs with a total of 1386 critically ill adult patients, which compared propofol with alternative sedative agents for medium- or long-term sedation, concluded that propofol is safe and can reduce the duration of MV. In addition, propofol also reduced the length of ICU stay when compared with long-acting benzodiazepines but not when compared with midazolam.[97]

Benzodiazepines

Benzodiazepines bind to the GABA receptor complex modulating GABA release in the central nervous system, causing downregulation of neuronal excitation (neurons become less excitable).[11] Depending on the dose used, they can cause sedation, anxiolysis or hypnosis (Sheila Harvey, ICNARC, 2014). Benzodiazepines vary in their potency, onset and duration of effect, uptake, distribution, metabolism and presence or absence of active metabolites.[15,94] Lorazepam is more potent than midazolam, which, in turn, is more potent than diazepam (Diazemuls®, Actavis UK Ltd). As midazolam and diazepam are more lipid soluble than lorazepam, they cross the blood–brain barrier quicker and result in a more rapid onset of action (from 2 to 10 minutes) than lorazepam (from 5 to 20 minutes).[11,13,98–100] The half-life of midazolam is 3–11 hours, compared with 8–15 hours for lorazepam and 20–120 hours for diazepam.[12,13] Midazolam and diazepam metabolites are active and tend to accumulate with prolonged administration, especially in patients with renal dysfunction.[11,101] Lorazepam metabolites are not active and, for this reason, it is the preferred benzodiazepine in patients with renal failure.[11] As all benzodiazepines are metabolised

predominantly in the liver, clearance is reduced in patients with hepatic dysfunction.[12] Adverse effects of benzodiazepines include hypotension, respiratory depression, paradoxical agitation, tolerance with acute discontinuation and delirium.[13,15,102]

A recent systematic review of six trials (1235 patients) concluded that the use of a dexmedetomidine- or propofol-based sedation regimen rather than a benzodiazepine-based regimen in critically ill patients may reduce ICU length of stay and duration of MV.[103] Indeed, current PAD guidelines suggest that sedation strategies using non-benzodiazepines (either propofol or dexmedetomidine) may be preferred over sedation with benzodiazepines (either midazolam or lorazepam) to improve outcomes in mechanically ventilated adult ICU patients.[12]

Identification of important subgroups

Specific subgroups of interests are usually based on severity of disease, primary reasons for admission to the ICU (e.g. admission after elective surgery) and duration of MV. Severity of disease is usually assessed by means of severity scores and risk prediction models. One of the most commonly used methods is the Acute Physiology and Chronic Health Evaluation (APACHE) II severity score system, which uses a point score based on initial values of 12 routine physiological measurements, age and previous health status to provide a general measure of severity of disease. Scores can range from 0 to 71, with higher scores indicating more severe disease and a higher risk of mortality. This severity index has been used to evaluate the use of hospital resources and compare the efficacy of intensive care over time and across different hospitals. The APACHE II scores combined with an accurate description of disease can also be used to stratify, prognostically, acutely ill patients and compare the success of new or differing forms of therapy.[104]

Current usage in the NHS

The 2014 ICNARC national survey, conducted among 235 adult general ICUs, together with a point prevalence study conducted among 52 ICUs in the UK, showed that propofol was the most widely used sedative agent, with 88% of the units reporting it as their first choice of agent. Although approximately one-third of the surveyed units (32%) reported frequent use of midazolam, only a small proportion (6%) reported that midazolam was their first choice of sedative agent. Less than 1% of the units reported use of lorazepam. Approximately one-third of the ICUs reported frequent use of clonidine and 10% reported frequent use of dexmedetomidine. The most frequently used agents for analgesia were alfentanil (51% of the units), morphine (42%) and fentanyl (36%). The largest proportion of units (40%) reported that alfentanil was their first choice of analgesic agent. In general, the trend was away from morphine, the first choice of analgesic agent in 20% of the ICUs, towards alfentanil and fentanyl (Sheila Harvey, ICNARC, 2014).

With regard to the strategies on how sedatives and analgesics were used, 66% of surveyed units reported that they occasionally or rarely opted for a single sedative agent and 76% of units for multiple sedative agents together. Most units (82.7%) reported that their first and preferred approach was to use one or more sedatives in combination with one or more analgesics. The expected duration for sedation and/or analgesia was reported to be an important determinant in the choice of sedative and/or analgesic agent. In the point prevalence study, 69% of sedated patients had received both a sedative agent and an analgesic agent in the previous 24 hours and the most frequent choice was propofol combined with either alfentanil or fentanyl (Sheila Harvey, ICNARC, 2014).

Chapter 2 Definition of the decision problem

This chapter defines the main components of this assessment. The current clinical pathway for analgosedation in the ICU is that of the UK Intensive Care Society, shown in *Figure 1*.[22] The clinical characteristics of the interventions under investigation were reported in *Chapter 1*. Detailed information on the population, interventions, comparators and relevant outcomes considered for this assessment will be presented in *Chapter 3*.

Population

The population considered for this assessment was critically ill adults admitted to ICUs who require MV. People with primary brain injuries such as trauma or intracerebral bleed/infarct are not deemed suitable for inclusion, as their clinical conditions require very specific ICU management and, often, a deeper level of sedation.

Interventions assessed

Dexmedetomidine and clonidine for sedation in ICUs.

Relevant comparators

Propofol and benzodiazepines (e.g. midazolam and lorazepam) for sedation in ICUs.

In this assessment, the term 'standard care' refers to the use of propofol and/or midazolam, at the discretion of the treating clinician, for sedation of critically ill patients admitted to ICUs, who require MV. The specific use of sedation interruptions and sedation protocols is not included in this definition.

Relevant outcomes

The main outcomes of interest were mortality, duration of MV, ventilator-free days, length of ICU stay, adverse events and unpleasant side effects. Secondary outcomes of interest include duration of weaning, time spent in target sedation range, proportion of patients in target sedation range, discharge readiness, extubation readiness, length of hospital stay, quality of life and cost.

Overall aims and objectives of the assessment

The purpose of this assessment was to systematically review the evidence of the clinical effectiveness of the alpha-2 agonists, propofol and benzodiazepines in ICUs, with the purpose of informing future RCTs.

The specific objectives of this assessment were to (1) compare the effects of dexmedetomidine with those of clonidine in mechanically ventilated adults admitted to ICUs and (2) compare the sedative effects of dexmedetomidine or clonidine with those of other most commonly used sedatives (i.e. propofol and benzodiazepines) in mechanically ventilated adults admitted to ICUs. The structure of this assessment will be that of a Health Technology Assessment short report.

Chapter 3 Assessment of clinical effectiveness

This chapter reports the evidence of the clinical effectiveness of dexmedetomidine compared with clonidine and of dexmedetomidine or clonidine compared with propofol or benzodiazepines (midazolam or lorazepam) in mechanically ventilated adults admitted to ICUs.

Methods for assessing the outcomes arising from the use of the intervention

The methods for this assessment were prespecified in a research protocol (www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42014014101).[105]

Identification of studies (search strategy and information sources/dates)

Highly sensitive literature searches, using an appropriate combination of controlled vocabulary and text word terms, were developed to identify reports of published, ongoing and unpublished studies reporting the clinical effectiveness of dexmedetomidine or clonidine in comparison with propofol and benzodiazepines (e.g. midazolam, lorazepam and diazepam) in mechanically ventilated adults admitted to ICUs. Literature searches were carried out from 12 to 15 November 2014 for publications from 1999 onwards. Details of the search strategies are reported in *Appendix 1*. Major electronic databases were searched including MEDLINE without revisions, MEDLINE In-Process & Other Non-Indexed Citations, EMBASE, Science Citation Index, Bioscience Information Service and the Cochrane Central Register of Controlled Trials. Reports of relevant evidence synthesis were sought from the Cochrane Database of Systematic Reviews and Database of Abstracts of Reviews of Effects. The World Health Organization International Clinical Trials Registry Platform, *meta*Register of Controlled Trials and ClinicalTrials.gov were searched for evidence of ongoing studies.

Websites of regulatory bodies and Health Technology Assessment agencies were checked for relevant unpublished reports, while websites of relevant pharmaceutical companies and professional organisations were searched for further pertinent information and reports.

In addition, reference lists of all included studies were perused for further citations.

Inclusion and exclusion criteria

Types of studies

Evidence was considered from RCTs comparing dexmedetomidine with clonidine or dexmedetomidine or clonidine with propofol or benzodiazepines such as midazolam, lorazepam and diazepam.

The following types of reports were excluded:

- narrative reviews, editorials and opinions
- case reports
- conference abstracts for which a full publication or further methodological information could not be found
- non-English-language reports for which a translation could not be organised
- studies that focused predominantly on people with primary brain injuries.

Types of participants

The types of participants considered were critically ill adults in ICUs who required MV. We did not prespecify definitions for ‘critically ill’ or ‘adults’, so any study population described as such was deemed suitable for inclusion.

Interventions
The sedative interventions considered were dexmedetomidine and clonidine.

Comparator interventions
The comparator interventions assessed were propofol and benzodiazepines such as midazolam, lorazepam and diazepam.

Outcomes
The following primary outcomes were considered:

- mortality
- duration of MV
- ventilator-free days
- length of ICU stay
- adverse events as reported by trial investigators and including the rate of:
    - hypotension
    - hypertension
    - bradycardia
    - respiratory depression
    - delirium
    - coma
    - non-planned or accidental removal of lines (e.g. extubation) or catheters
- unpleasant side effects as reported by trial investigators (e.g. unpleasant memories, constipation or diarrhoea).

Secondary outcomes considered were:

- duration of weaning
- time spent in target sedation range
- proportion of patients in target sedation range
- discharge readiness
- extubation readiness
- length of hospital stay
- quality of life
- cost.

Data extraction strategy (study selection and data collection)
One reviewer (MC) screened all titles and abstracts identified by the search strategies. A second reviewer (MB) independently double-screened the first 100 abstracts and titles of the 2011–14 list. Agreement between the two reviewers was 100%.

All potentially relevant reports were retrieved in full and assessed independently by one reviewer (MC). A total of 40 reports were double-assessed by a second reviewer (Pawana Sharma or MB). Any disagreements were resolved by consensus. The full-text screening form is presented in *Appendix 2*. A data extraction spreadsheet (Microsoft Excel®, 2013; Microsoft Corporation, Redmond, WA, USA) was developed specifically for the purpose of this assessment, piloted and amended as necessary. From each study, one reviewer (MC) extracted information on geographical location, sponsor, study design, participants' characteristics, setting and characteristics of ICU practice, characteristics of sedative intervention and outcome measures. Data extraction was double-checked by a second reviewer (MB). Any disagreements were resolved by discussion.

Critical appraisal strategy

The risk of bias of included RCTs was initially assessed by one reviewer (MC) using Cochrane's risk-of-bias tool[106] and, subsequently, cross-checked by a second reviewer (MB). The following domains were assessed: sequence generation, allocation concealment, blinding of participants and medical personnel, blinding of outcome assessors, incomplete outcome data and selective outcome reporting. Assessment of 'other bias' was based on the funding source, and a study was judged to be at high risk of bias if it was funded by the manufacturer(s) of the sedative agent(s) under investigation. Individual outcomes were judged as being at 'high', 'low' or 'unclear' risk of bias. Overall, risk of bias for each study was based on the findings of three key domains: sequence generation, allocation concealment and blinding of outcome assessor.

Studies were classified as follows: (1) high risk of bias if one or more key domains were at high risk; (2) unclear risk of bias if one or more key domains were judged to be at unclear risk; and (3) low risk of bias if all key domains were judged to be at low risk. Any disagreements between reviewers were resolved by discussion.

Method of analysis/synthesis

The general approach recommended by Cochrane was used for data analysis and synthesis.[106] For binary outcomes, the Mantel–Haenszel approach was used to pool risk ratios (RRs) derived from each study. A random-effects model was used to calculate the pooled estimates of effect. For continuous outcomes (duration of MV, ICU length of stay, hospital length of stay, time to extubation, time in target sedation range and ventilator-free days), mean differences between groups were pooled when possible using the inverse variance weighted mean difference method and a random-effects model. Random-effects methods, rather than fixed-effects methods, as outlined in the original protocol, were chosen because of the clinical and statistical heterogeneity observed among included studies.

For each continuous outcome, an initial analysis was conducted using only studies where the mean and standard deviation (SD) were provided. In studies that did not report a mean and SD [and we could not derive these summary measures from reported *p*-values, standard errors or confidence intervals (CIs)], we tried to impute these from the data reported. The imputation strategy was as follows:

i. Where the median, range and *n* for each group were available, we used the formulae reported by Hozo and colleagues[107] to estimate the mean and SD.
ii. Where this method proved unfeasible, we imputed a SD from the available data using the methods outlined by Furukawa and colleagues.[108]
iii. In studies where a median and interquartile range were reported, we used two methods to calculate the mean. If the sample size was < 25, then first the median was used and second the value midway between the lower quartile and upper quartile was used. If the two methods yielded results that reversed the direction of treatment effect for a certain outcome within a study, then the study was excluded from the pooled analysis of that outcome.

For each outcome where the above provided extra data, a second analysis was done using the imputed data.

Heterogeneity across studies was explored by visual inspection of forest plots and using the chi-squared test and I^2-statistics.

When data were available, subgroup analyses were performed according to type of comparator intervention.

Results of the evidence synthesis

Quantity of the evidence (studies included and excluded)

The literature searches identified 1182 potentially relevant citations, of which 83 were selected for full-text assessment and 107 for background information. Of these, 59 were subsequently excluded because the patient population, study design, outcomes reported or publication type were not eligible. A total of 18 RCTs published in 24 papers with a total of 2489 people were included in this assessment.[5,52,69–72,102,109–125] It is worth noting that the results of the two large multicentre trials of PROpofol compared with DEXmedetomidine (the PRODEX trial) and of MIdazolam compared with DEXmedetomidine (the MIDEX trial) were published in a single report by Jakob and colleagues[70] for the Dexmedetomidine for Long-Term Sedation investigators. *Figure 2* presents the flow chart of the selection process. *Appendix 3* provides the details of the 18 included trials and related secondary publications. *Appendix 4* categorises the excluded studies according to the main reasons for their exclusion.

Study characteristics

Appendix 5 details the study characteristics of the 18 included trials. All 18 trials were published in full. Four different comparators were assessed. One trial, with a total of 70 randomised patients, compared the effects and safety of dexmedetomidine with clonidine;[55] nine trials, with a total of 1134 randomised patients, compared dexmedetomidine with propofol;[70,109–111,114,117,120,122,123] four trials, with a total of 939 randomised patients, compared dexmedetomidine with midazolam;[70,71,112,116] one trial, with a total of 118 randomised patients, compared dexmedetomidine with propofol or midazolam (three arms);[72] two trials, with a total of 122 randomised patients, compared dexmedetomidine with 'standard care' (i.e. propofol and/or midazolam);[69,121] and one trial with a total of 106 randomised patients, compared dexmedetomidine with lorazepam.[102] A total of 2446 patients were analysed in the 18 included trials.

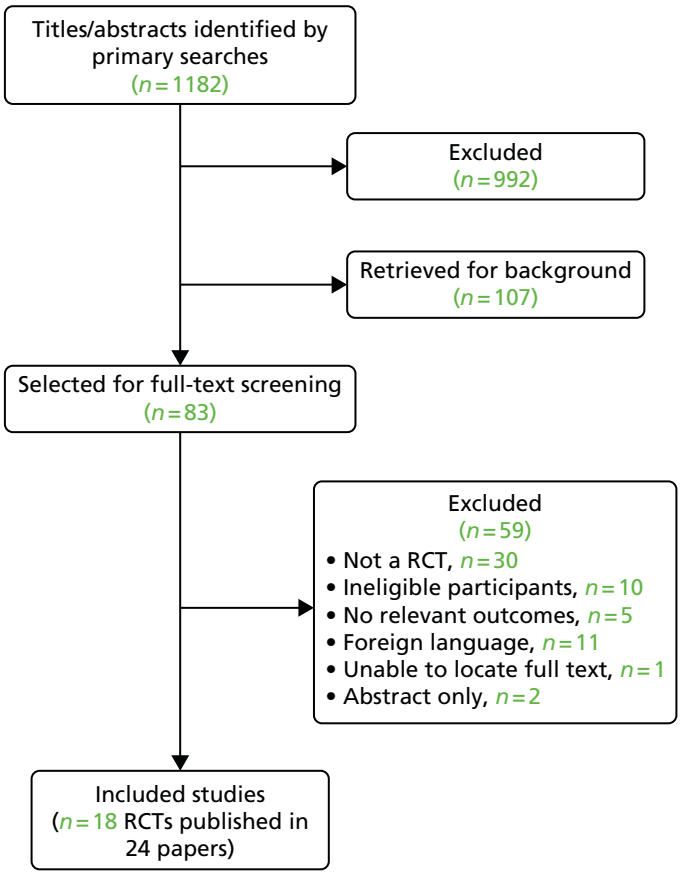

FIGURE 2 Flow chart of the study selection process.

Six trials assessed dexmedetomidine in patients admitted to ICUs following elective surgery,[72,110,111,114,120,123] whereas the remaining trials included general ICU patients.

Four trials were conducted in the USA,[72,102,110,116] two in India,[55,120] three in Turkey,[112,117,122] two in Egypt,[109,111] one in the UK,[123] one in North America (USA and Canada),[114] one in Finland and Switzerland,[69] and one in Australia and New Zealand.[121] The MIDEX multicentre trial[70] was conducted in nine European countries; the PRODEX multicentre trial[70] was conducted in six European countries and in Russia; and the SEDCOM[71] (Safety and Efficacy of Dexmedetomidine COmpared with Midazolam) multicentre trial was conducted in the USA, Argentina, Brazil, Australia and New Zealand. All included trials involved prospective collection of data.

Three trials assessed patients up to 45 days[69,70] and one up to 90 days.[121] In one trial,[102] participants were observed in the hospital from enrolment until discharge from hospital or death, and survivors were observed for vital status until 1 year after enrolment using hospitals' electronic record systems and a commercial version of the Social Security Death Master File (http://ssdi.rootsweb.com). One trial[114] followed up patients for 24 hours after discharge from ICUs and another trial[71] for 48 hours after study drug cessation. One trial[72] reported that patients were followed up for 3 days post operatively. In one trial,[109] length of follow-up was reported to be 6 hours, in two trials[55,120] it was 24 hours and in another trial[123] it was 48–72 hours. Two trials reported follow-up in terms of time post extubation: one trial[110] assessed patients at least 24 hours post extubation and another trial[116] at least 72 hours post extubation. Length of follow-up was not reported in four trials.[111,112,117,122]

Appendix 6 presents details of dosage and route of administration of the respective sedative agents.

In general, dexmedetomidine was initiated with a loading dose of 1 µg/kg, administered intravenously over a period of 10–20 minutes.[109,110,112,114,117,120,122] Some trials involved lower[55,72,102,116] or higher[111,123] loading doses, four trials did not use a loading dose[69,70,121] and, in one trial, the loading dose was optional.[71] Dexmedetomidine maintenance doses were fixed in two trials: 0.4 µg/kg/hour[110] or 0.7 µg/kg/hour.[112] The remaining trials specified lower and upper limits for maintenance doses, with lower limits ranging from 0 µg/kg/hour[121] to 0.015 µg/kg/hour,[102,116] 0.2 µg/kg/hour,[55,70,72,111,114,117,120,122,123] 0.4 µg/kg/hour,[110] 0.5 µg/kg/hour[109] and 0.7 µg/kg/hour.[112] The maximum allowable dose was 2.5 µg/kg/hour.[117,122,123]

Clonidine was used in one trial. Patients received an infusion of clonidine at 1 µg/kg/hour. Titration was achieved with dosage increments up to 2 µg/kg/hour.[55]

Of the 12 trials that included a propofol arm, four trials reported a loading dose: an initial bolus dose of 1 mg/kg in one trial[111] and 1 mg/kg over 10–15 minutes in three trials.[117,122,123] Six trials did not use a loading dose[69,70,72,109,110,120] and two trials did not provide information on dosage.[114,121] Maintenance infusions of propofol ranged from 0.5–1 mg/kg/hour[111] to 4 mg/kg/hour across trials.[69,70]

Out of the seven trials that included a midazolam arm, one trial reported a loading dose of 0.05 mg/kg[112] and another trial reported an optional loading dose of the same level.[71] The remaining trials did not use a loading dose. One trial did not specify dosage of midazolam.[121] Maintenance doses of midazolam were between 0.03 mg/kg/hour[70] and 10 mg/hour across trials.[116]

In one trial, lorazepam infusion started at 1 mg/hour and was titrated to a maximum of 10 mg/hour.[102]

All trials titrated sedatives to a target sedation level.[55,69–72,102,109–112,114,116,117,120–123] Target sedation level was measured by means of the RSS score in 11 trials,[55,72,109–112,114,117,120,122,123] the RASS in six trials[69–71,102,121] and the Riker SAS score in one trial.[116]

The main characteristics of the 18 included studies are shown in *Table 1*.

TABLE 1 Summary of the main features of the included studies

Study	Double blind	Population	Number of patients randomised		Comparator	Sponsored by industry	Overall risk-of-bias assessment
			Dexmedetomidine	Comparator			
Abdulatif *et al.*, 2004[109]	No	Patients with established respiratory failure requiring MV using pressure support ventilation with or without continuous positive airway pressure	20	20	Propofol	Unclear	Unclear
Corbett *et al.*, 2005[110]	Unclear	After non-emergent CABG surgery (elective surgery)	43	46	Propofol	Unclear	Unclear
Elbaradie *et al.*, 2004[111]	No	After major thoracic, abdominal or pelvic cancer surgeries (elective surgery)	30	30	Propofol	Unclear	High
Esmaoglu *et al.*, 2009[112]	Unclear	Patients whose pregnancies were terminated via caesarean delivery because of eclampsia	20	20	Midazolam	Unclear	Unclear
Herr *et al.*, 2003[114]	No	After CABG surgery (elective surgery)	148	147	Propofol	Yes	High
Jakob *et al.*, 2012[70] (MIDEX trial)	Yes	ICU patients requiring MV and light to moderate sedation	249	252	Midazolam	Yes	Low
Jakob *et al.*, 2012[70] (PRODEX trial)	Yes	ICU patients requiring MV and light to moderate sedation	251	249	Propofol	Yes	Low
MacLaren *et al.*, 2013[116]	Yes	Medical or surgical ICU patients requiring MV and receiving benzodiazepines	11	12	Midazolam	Yes	Unclear
Maldonado *et al.*, 2009[72]	No	After cardiac valve surgery (elective surgery)	40	78 (38 propofol, 40 midazolam)	Midazolam, propofol	Unclear	High
Memis *et al.*, 2009[117]	No	Patients fulfilling laboratory criteria of septic shock	20	20	Propofol	Unclear	High
Pandharipande *et al.*, 2007[102]	Yes	Medical and surgical ICU patients	54	52	Lorazepam	Yes	Low
Riker *et al.*, 2009[71]	Yes	General ICU patients on MV	250	125	Midazolam	Yes	Low
Ruokonen *et al.*, 2009[69]	Yes	General ICU patients on MV	41	44 (28 propofol, 16 midazolam)	Midazolam, propofol	Yes	Unclear

Study	Double blind	Population	Number of patients randomised		Comparator	Sponsored by industry	Overall risk-of-bias assessment
			Dexmedetomidine	Comparator			
Shah *et al.*, 2014[120]	No	Surgical patients requiring post-operative MV and sedation (elective surgery)	15	15	Propofol	Yes	High
Shehabi *et al.*, 2013[121]	No	Medical, operative elective and operative emergency patients	16	21	Standard care (propofol and/or midazolam)	Yes	High
Srivastava *et al.*, 2014[55]	Unclear	General ICU patients on MV	35	35	Clonidine	No	Unclear
Tasdogan *et al.*, 2009[122]	No	Patients with sepsis after ileus surgery	20	20	Propofol	Unclear	High
Venn and Grounds, 2001[123]	Unclear	After complex major abdominal or pelvic surgery (elective surgery)	20	20	Propofol	Yes	Unclear

CABG, coronary artery bypass graft.

Participant characteristics

The 18 included trials randomised a total of 1283 participants to dexmedetomidine and 1206 participants to a control intervention. The sample sizes of included studies ranged from 23 to 501 participants.

There was some doubt whether or not the trial by Memis and colleagues (40 patients in total)[117] and that by Tasdogan and colleagues (40 patients in total)[122] were mutually exclusive with regard to participants. Even though a number of similarities between the two trials were observed, the characteristics of the two patient populations were clearly not identical and, therefore, we treated them as two separate trials. Correspondence with the trials investigators (Dr Dilek Memis named as corresponding author for both trials) proved unsuccessful and did not elicit any response.

The mean age was reported in 12 trials.[71,72,109–112,114,116,117,120–122] With the exception of one trial[112] that focused exclusively on young pregnant women (mean age 25.1 years in the dexmedetomidine group and 26.8 years in the control intervention group), the 11 remaining trials mean age ranged from 43 to 65 years for dexmedetomidine and from 40 to 67 years for the comparator interventions. The median age was reported in six trials[55,69,70,102,123] and ranged from 49 to 65 years for dexmedetomidine and from 46 to 67 years for the comparator interventions.

Sixteen studies reported information regarding the sex of participants.[55,69–72,102,109,110,112,114,116,117,120–122] Study populations tended to involve more men than women, with the exception of one trial that involved only pregnant women[112] (see *Appendix 5* for further details).

The severity of illness at baseline was reported in eight trials[55,71,102,112,117,121–123] by means of the APACHE II scores or APACHE III scores (one trial).[116] The APACHE II scores have a possible range of 0–71, whereas the APACHE III scores can range from 0 to 299. In both cases, higher scores indicate more severe disease and a higher risk of death.[104] Across the eight trials that used APACHE II, scores ranged from a mean of 5.1[112] to a mean of 22 for dexmedetomidine[117] and a mean of 6[112] to a mean of 20[117] for the control sedative intervention. One trial[102] reported a median APACHE II score of 29 for dexmedetomidine and of 27 for the control sedative intervention. The trial[116] that assessed severity of disease using the APACHE III scores reported mean scores of 74.1 for dexmedetomidine and of 70.4 for midazolam.

Table 2 presents an overview of the participants' characteristics of the 18 included trials. It is worth noting that not all trials provided the same participant details or used the same measures to assess them.

Risk-of-bias assessment of included studies

Figure 3 presents the summary of the risk-of-bias assessments for all included trials. The risk of bias of individual studies is presented in *Figure 4*.

Overall, out of the 18 included trials, four were judged to be at low risk of bias[70,71,102] and seven at high risk of bias.[72,111,114,117,120–122] For the remaining seven trials, there was not sufficient information to make an overall judgement.[55,69,109,110,112,116,123]

With regard to the assessment of selection bias, around half of the trials were judged to be at low risk (i.e. adequate sequence generation and allocation concealment),[55,70,71,102,110,112,116,117,122] whereas the remaining eight trials did not provide sufficient information to formulate a proper judgement.[69,72,109,111,114,120,121,123]

TABLE 2 Summary of main participants' characteristics (for trials that reported this information)

Characteristic	Dexmedetomidine compared with propofol RCTs	Dexmedetomidine compared with midazolam RCTs	Dexmedetomidine compared with other comparators
Total number of participants randomised	1134 ($n = 9$ trials)	939 ($n = 4$ trials)	Dexmedetomidine compared with clonidine: 70 ($n = 1$ trial) Dexmedetomidine compared with propofol and midazolam: 118 ($n = 1$ trial) Dexmedetomidine compared with standard care: 122 ($n = 2$ trials) Dexmedetomidine compared with lorazepam: 106 ($n = 1$ trial)
Age (years), median of means (range)	Dexmedetomidine: 60 (43–65); propofol: 58 (40–67) ($n = 9$ trials)	Dexmedetomidine: 41.7 (25.1–58.3); midazolam: 42.3 (26.8–57.8) ($n = 2$ trials)	Dexmedetomidine: 65; standard care: 61.6 ($n = 1$ trial)
Sex (% men), median of means (range)	65.5 (51.5–89.9) ($n = 7$ trials)	52.7 (0–65.6) ($n = 4$ trials)	Dexmedetomidine compared with clonidine: 54.3 ($n = 1$ trial) Dexmedetomidine compared with lorazepam: 51.4 ($n = 1$ trial) Dexmedetomidine compared with propofol and midazolam: 61.5 ($n = 1$ trial) Dexmedetomidine compared with standard care: 68.3 (54.4–82.2) ($n = 2$ trials)
APACHE II scores, median of means (range)	Dexmedetomidine: 19 (18–22); propofol: 18 (16.5–20) ($n = 3$ trials)	Dexmedetomidine: 12.1 (5.1–19.1); midazolam: 12.2 (6–18.3) ($n = 2$ trials)	Dexmedetomidine (median 15) compared with clonidine (median 16.5) ($n = 1$ trial) Dexmedetomidine (median 29) compared with lorazepam (median 27) ($n = 1$ trial) Dexmedetomidine (median 20.2) compared with standard care (median 18.6) ($n = 1$ trial)

Note
Owing to incomplete reporting or differences in the way this information was summarised in some included trials, the number of trials varies between rows.

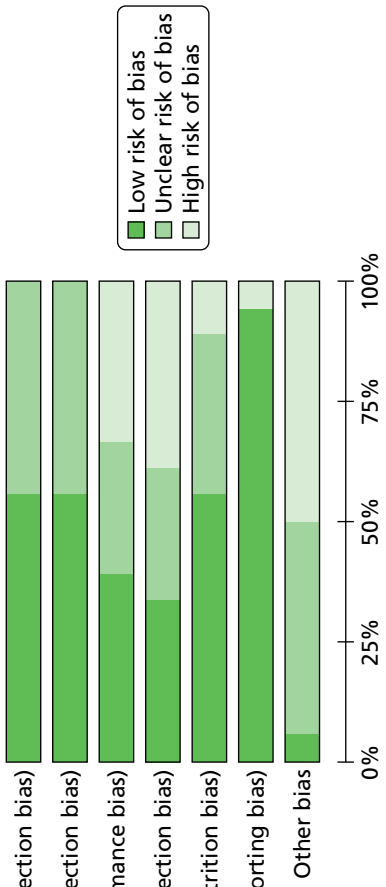

FIGURE 3 Summary of risk-of-bias assessments of all included trials.

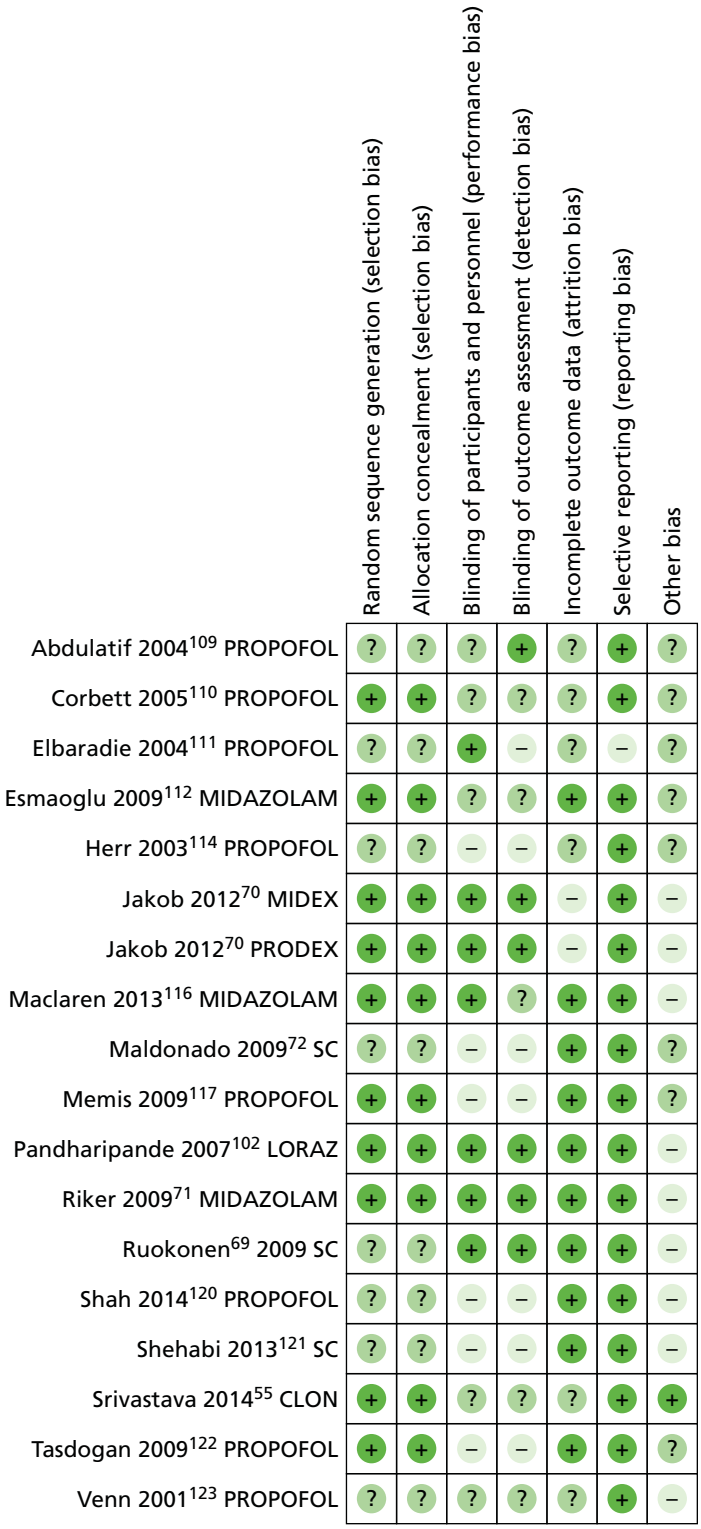

FIGURE 4 Risk-of-bias assessments of individual studies. CLON, clonidine compared with dexmedetomidine, LORAZ, lorazepam compared with dexmedetomidine; MIDAZOLAM, midazolam compared with dexmedetomidine; PROPOFOL, propofol compared with dexmedetomidine; SC, standard care compared with dexmedetomidine.

In eight of the included trials, participants were reported to be blinded to the intervention received,[69–71,102,109,111,116] whereas in six trials they were not.[72,114,117,120–122] The remaining four trials did not report information on blinding of participants.[55,110,112,123] Blinding of outcome assessor was addressed adequately in five trials,[69–71,102] not adequately in seven trials[72,111,114,117,120–122] and not reported in six trials.[55,109,110,112,116,123]

With regard to 'incomplete outcome data',10 trials had low withdrawal/discontinuation rates, which were balanced between intervention groups and, therefore, judged to be at low risk of bias.[69,71,72,102,112,116,117,120–122] Two trials reported significantly higher discontinuation rates, owing to lack of efficacy, among people treated with dexmedetomidine, and were judged to be at high risk of bias.[70] The remaining six trials did not provide sufficient information on which to make a definitive judgement.[55,109–111,114,123]

There was no evidence of selective reporting in any of the included trials, with the exception of one trial[111] in which data on hypotension and bradycardia were mentioned only in the discussion section of the published paper and not properly reported in the results section. For this reason, the study was judged to be at high risk of selective reporting.

With regard to 'other sources of bias', nine trials declared financial support by manufacturers of sedative agents and were, therefore, judged to be at high risk of bias.[69–71,102,116,120,121,123] One trial was judged at low risk of bias, as the authors clearly stated that no funding was received from manufacturers.[55] The remaining eight studies were judged to be at unclear risk of bias, as the authors did not explicitly report their source of funding.[72,109–112,114,117,122]

Summary of clinical effectiveness

Random-effects meta-analyses of relevant clinical outcomes were performed when appropriate.

We had initially planned to perform subgroup analyses according to the type of clinical setting (patients admitted to ICUs following elective surgery compared with general ICU patients) if enough data had been available. However, only 6 of the 18 studies included patients who were admitted to the ICU after elective surgery, and not all of them provided data for all efficacy outcomes. Therefore, because of the dearth of suitable data, subgroup analyses according to the type of clinical setting were deemed unfeasible. As patients admitted to the ICU after elective surgery represent a distinct type of patient population (short duration of sedation and MV, and lower mortality rate), we deemed it inappropriate to combine trials that included patients after elective surgery with those that enrolled more general, critically ill ICU patients. The results of trials that enrolled patients after elective surgery were instead summarised narratively.

It is worth pointing out that there was considerable variation among included trials in the choice, definitions and measurements of outcomes, especially with regard to measures of ventilator dependence such as duration of MV, ventilator-free days, time to extubation or duration of weaning. Often, trials that assessed duration of MV did not report ventilator-free days as an outcome. The number of ventilator-free days was available from three trials, but details on measurement were lacking.[69,118,121] Information on time to extubation was reported in six trials,[70,71,111,114,123] but definition and criteria for extubation were not consistent across trials. Two large trials (MIDEX and PRODEX)[70] reported both duration of MV and time to extubation, but did not provide a clear definition or measurement criteria for time to extubation and failed to discuss the clinical difference between the two measures. Similarly, duration of weaning was reported by two trials,[69,114] but only one provided a proper outcome definition and a description of the measurement criteria.[114]

Clonidine compared with dexmedetomidine

One trial, at unclear risk of bias, randomised a total of 70 general ICU patients requiring MV to dexmedetomidine (35 patients) or to clonidine (35 patients).[55] Both clonidine and dexmedetomidine produced effective sedation. Target sedation was achieved in 86% of observations among patients who received dexmedetomidine and in 62% of observations among patients who received clonidine ($p = 0.04$). Additional sedation was needed by more patients treated with clonidine than those treated with dexmedetomidine (14 patients and 8 patients, respectively; $p = 0.034$). Hypotension was observed significantly more frequently among patients who received clonidine (11 out of 35 patients) than among patients who received dexmedetomidine (3 out of 35) ($p = 0.02$). Rebound hypertension was seen only in four patients receiving clonidine. The authors concluded that both clonidine and dexmedetomidine produced effective sedation. However, the haemodynamic stability provided by dexmedetomidine makes it a preferable option over clonidine for short-term sedation of ICU patients.

Propofol and benzodiazepines (i.e. midazolam and lorazepam) compared with dexmedetomidine

Primary outcomes

Mortality

Nine trials reported mortality data (*Figure 5*).[69–71,102,116,117,120,121] A total of 196 out of 909 (22%) patients who received dexmedetomidine and 162 out of 783 (21%) of patients who received a control intervention died. Compared with alternative sedative agents, dexmedetomidine had no significant effects on mortality (RR 1.03, 95% CI 0.85 to 1.24, $I^2 = 0\%$; $p = 0.78$).

Two trials assessing patients after elective surgery reported mortality data.[72,123] In one trial,[72] two deaths not attributable to sedation occurred among patients who received the control intervention (propofol), whereas in the other trial[123] two patients receiving dexmedetomidine died, compared with one patient receiving the control intervention (propofol).

Duration of mechanical ventilation

Two trials reported mean duration of MV (*Figure 6*).[70] There were no significant differences in the duration of MV between dexmedetomidine and control interventions (mean difference –0.36, 95% CI –1.59 to 0.86, $I^2 = 0\%$; $p = 0.56$).

Similarly, there was no difference (mean difference –0.30, 95% CI –1.70 to 1.11; $p = 0.68$) in the duration of MV between dexmedetomidine and control interventions (*Figure 7*) when all available data suitable for the analysis were considered (including transformed and imputed data). Statistical heterogeneity was observed among trials ($I^2 = 70\%$).

One trial that assessed patients after elective surgery[110] reported no difference between dexmedetomidine and propofol ($p > 0.05$) with regard to length of intubation.

Ventilator-free days

One trial provided suitable data for ventilator-free days (*Figure 8*).[121] There was no evidence of a statistically significant difference (mean difference 1.20, 95% CI –5.12 to 7.52; $p = 0.71$) between patients who received dexmedetomidine and those who received standard care (propofol or midazolam).

When all available data suitable for the analysis were considered (including transformed and imputed data) (*Figure 9*), the mean difference was 3.28 ventilator-free days (95% CI 0.06 to 6.49 ventilator-free days, $I^2 = 0\%$; $p = 0.046$) favouring dexmedetomidine.

Study or subgroup	Dexmedetomidine Events	Total	Control Events	Total	Weight	RR IV, random, 95% CI
Jakob 2012 PRODEX[70]	43	251	48	247	25.1%	0.88 (0.61 to 1.28)
Memis 2009 PROPOFOL[117]	3	20	4	20	1.9%	0.75 (0.19 to 2.93)
Tasdogan 2009 PROPOFOL[120]	1	20	2	20	0.6%	0.50 (0.05 to 5.08)
Jakob 2012 MIDEX[70]	68	249	53	251	35.4%	1.29 (0.95 to 1.77)
Maclaren 2013 MIDAZOLAM[116]	2	11	1	12	0.7%	2.18 (0.23 to 20.84)
Riker 2009 MIDAZOLAM[71]	55	244	31	122	23.8%	0.89 (0.60 to 1.30)
Ruokonen 2009 SC[69]	10	41	7	44	4.6%	1.53 (0.64 to 3.65)
Shehabi 2013 SC[121]	5	21	2	16	1.5%	1.90 (0.42 to 8.58)
Pandharipande 2007 LORAZ[102]	9	52	14	51	6.3%	0.63 (0.30 to 1.33)
Total (95% CI)		**909**		**783**	**100.0%**	**1.03 (0.85 to 1.24)**
Total events	196		162			

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 7.41$, df = 8 ($p = 0.49$); $I^2 = 0\%$
Test for overall effect: $z = 0.28$ ($p = 0.78$)

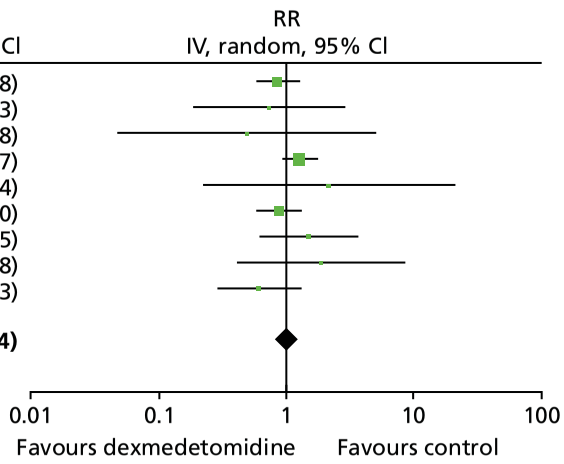

FIGURE 5 Meta-analysis for mortality. df, degrees of freedom; IV, inverse variance; LORAZ, lorazepam compared with dexmedetomidine; MIDAZOLAM, midazolam compared with dexmedetomidine; PROPOFOL, propofol compared with dexmedetomidine; SC, standard care compared with dexmedetomidine.

Study or subgroup	Dexmedetomidine Mean	SD	Total	Control Mean	SD	Total	Weight	Mean difference IV, random, 95% CI
Jakob 2012 PRODEX[70]	7.533	10.575	251	7.413	8.688	247	51.9%	0.12 (–1.58 to 1.82)
Jakob 2012 MIDEX[70]	8.067	10.617	249	8.95	9.463	251	48.1%	–0.88 (–2.65 to 0.88)
Total (95% CI)			**500**			**498**	**100.0%**	**–0.36 (–1.59 to 0.86)**

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.64$, df = 1 ($p = 0.42$); $I^2 = 0\%$
Test for overall effect: $z = 0.58$ ($p = 0.56$)

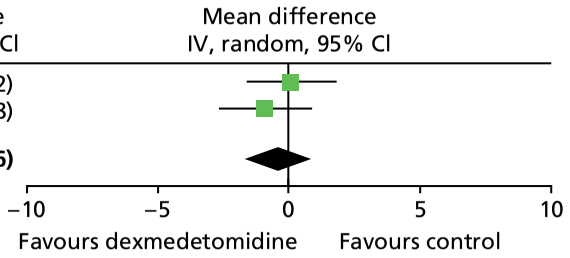

FIGURE 6 Meta-analysis for duration of MV. df, degrees of freedom; IV, inverse variance.

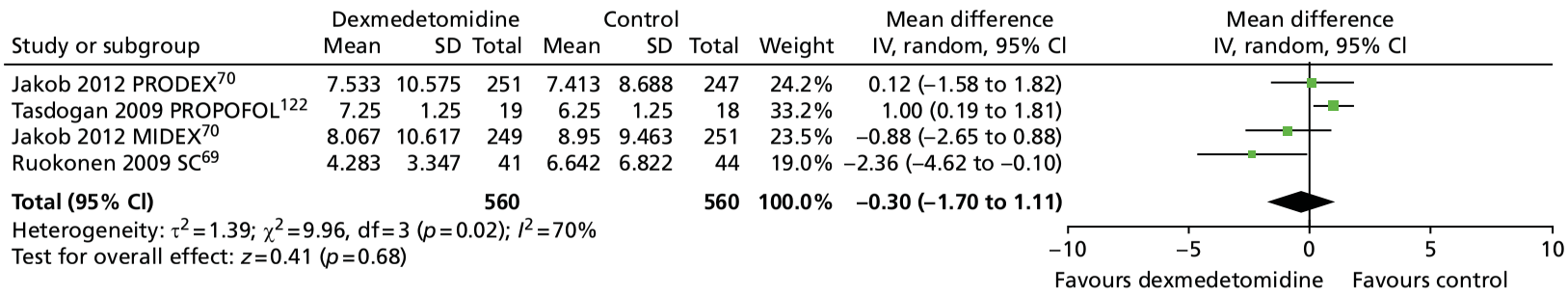

FIGURE 7 Meta-analysis for duration of MV: all available data (including transformed and imputed data). df, degrees of freedom; IV, inverse variance; PROPOFOL, propofol compared with dexmedetomidine; SC, standard care compared with dexmedetomidine.

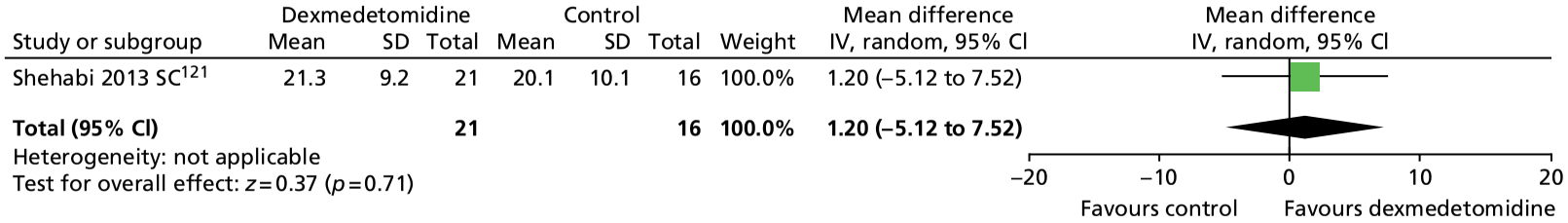

FIGURE 8 Meta-analysis for ventilator-free days. IV, inverse variance; SC, standard care compared with dexmedetomidine.

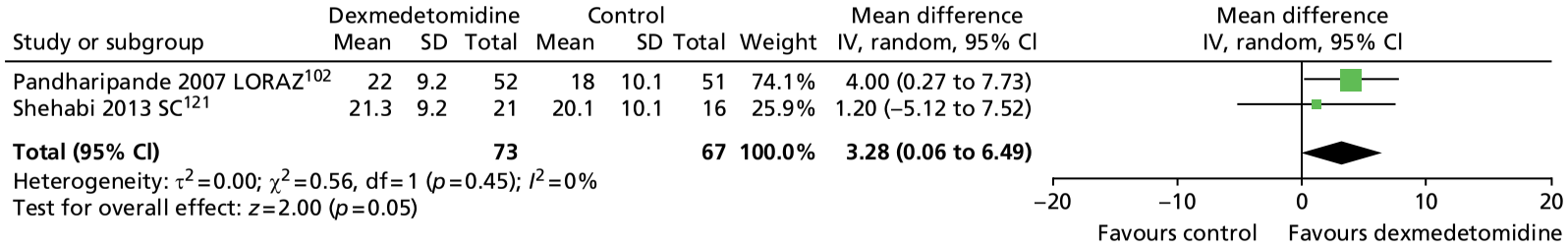

FIGURE 9 Meta-analysis for ventilator-free days: all available data (including transformed and imputed data). df, degrees of freedom; IV, inverse variance; LORAZ, lorazepam compared with dexmedetomidine; SC, standard care compared with dexmedetomidine.

Intensive care unit length of stay

One trial provided mean length of ICU stay data (*Figure 10*).[117] There was no evidence of a significant difference between sedative agents (mean difference 2.00 days, 95% CI –3.12 to 7.12 days; $p = 0.44$).

However, *Figure 11* shows that when all available data suitable for the analysis were considered (including transformed and imputed data), ICU length of stay was significantly shorter among patients who received dexmedetomidine than among those who received an alternative sedative agent (mean difference –1.26 days, 95% CI –1.96 to –0.55 days, $I^2 = 31\%$; $p = 0.0004$).

Hypotension

Five trials provided suitable data to assess the incidence of hypotension (*Figure 12*).[69–71,116] There were no statistically significant differences between participants who received dexmedetomidine (232 out of 789, 29%) and those who received an alternative sedative agent (137 out of 675, 20%) (RR 1.28, 95% CI 0.93 to 1.75, $I^2 = 55\%$; $p = 0.12$).

The proportion of patients who developed hypotension was reported in two trials that assessed patients after elective surgery.[110,114] No statistically significant differences were found. In one trial,[110] 35 out of 43 patients who received dexmedetomidine experienced severe hypotension, compared with 31 out of 46 of those who received propofol ($p = 0.132$). In the other trial,[114] hypotension occurred in 36 out of 148 (24%) participants who received dexmedetomidine and in 24 out of 147 (16%) participants who received propofol ($p = 0.111$).

Hypertension

Three trials reported the incidence of hypertension during sedation (*Figure 13*).[70,71] There was no evidence of statistically significant differences (RR 1.09, 95% CI 0.89 to 1.33, $I^2 = 21\%$; $p = 0.43$) between dexmedetomidine (211 out of 737, 29%) and alternative sedative agents (143 out of 619, 23%).

In one trial, in which patients were sedated after elective coronary artery bypass graft (CABG) surgery,[114] hypertension occurred more frequently among patients who received dexmedetomidine than among those who received propofol ($p = 0.018$).

Bradycardia

Six trials assessed the incidence of bradycardia during sedation (*Figure 14*).[69–71,102,116] Significantly more participants who received dexmedetomidine (189 out of 841, 22%) experienced bradycardia than those who received alternative sedative agents (70 out of 726, 10%) (RR 1.88, 95% CI 1.28 to 2.77, $I^2 = 46\%$; $p = 0.001$).

In one trial, which enrolled patients after elective coronary artery bypass graft surgery,[114] the frequency of bradycardia was similar between intervention groups [5 out of 148 (3%) in the dexmedetomidine group, compared with 2 out of 147 (1%) in the propofol group; $p = 0.448$].

Delirium

Seven trials reported the proportion of patients who experienced episodes of delirium during sedation.[69–71,102,116,121] A total of 234 out of 862 (27%) participants who received dexmedetomidine and 209 out of 742 (28%) participants who received an alternative sedative agent experienced delirium (*Figure 15*). The difference between sedatives was not statistically significant (RR 0.83, 95% CI 0.65 to 1.06, $I^2 = 60\%$; $p = 0.14$). Statistical heterogeneity was observed among trials ($I^2 = 60\%$).

Two trials, which enrolled patients after elective surgery, reported the proportion of patients with episodes of delirium.[72,110] In one trial,[110] the number of patients with episodes of delirium was similar in both intervention groups (1 out of 43 in the dexmedetomidine group compared with 1 out of 46 in the propofol group). In the other trial,[72] the incidence of delirium was 10% (4 out of 40) among patients who received dexmedetomidine, 44% (16 out of 36) among those who received propofol and 44% (17 out of 40) for those who received midazolam.

Study or subgroup	Dexmedetomidine Mean	SD	Total	Control Mean	SD	Total	Weight	Mean difference IV, random, 95% CI
Memis 2009 PROPOFOL[117]	14	8	17	12	7	16	100.0%	2.00 (–3.12 to 7.12)
Total (95% CI)			**17**			**16**	**100.0%**	**2.00 (–3.12 to 7.12)**

Heterogeneity: not applicable
Test for overall effect: $z = 0.77$ ($p = 0.44$)

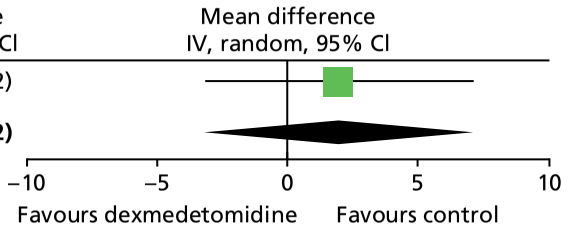

FIGURE 10 Meta-analysis for ICU length of stay. IV, inverse variance; PROPOFOL, propofol compared with dexmedetomidine.

Study or subgroup	Dexmedetomidine Mean	SD	Total	Control Mean	SD	Total	Weight	Mean difference IV, random, 95% CI
Jakob 2012 PRODEX[70]	6.833	6.394	251	7.708	6.394	247	20.5%	–0.88 (–2.00 to 0.25)
Memis 2009 PROPOFOL[117]	14	8	17	12	7	16	1.8%	2.00 (–3.12 to 7.12)
Tasdogan 2009 PROPOFOL[122]	9.8	2.25	19	9.5	3	18	12.0%	0.30 (–1.42 to 2.02)
Esmaoglu 2009 MIDAZOLAM[112]	2.334	1.073	20	5.135	3.094	20	15.4%	–2.80 (–4.24 to –1.37)
Jakob 2012 MIDEX[70]	8.792	6.394	249	10.125	6.394	251	20.5%	–1.33 (–2.45 to –0.21)
Riker 2009 MIDAZOLAM[71]	5.9	6.394	244	7.6	6.394	122	16.0%	–1.70 (–3.09 to –0.31)
Pandharipande 2007 LORAZ[102]	7.5	6.394	52	9	6.394	51	6.8%	–1.50 (–3.97 to 0.97)
Ruokonen 2009 SC[69]	6.9	4.5	41	7.9	6.8	44	7.0%	–1.00 (–3.44 to 1.44)
Total (95% CI)			**893**			**769**	**100.0%**	**–1.26 (–1.96 to –0.55)**

Heterogeneity: $\tau^2 = 0.30$; $\chi^2 = 10.09$, df = 7 ($p = 0.18$); $I^2 = 31\%$
Test for overall effect: $z = 3.51$ ($p = 0.0004$)

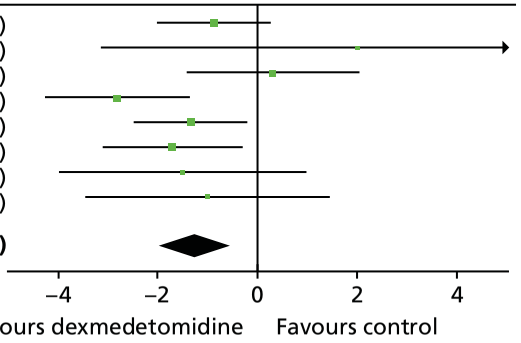

FIGURE 11 Meta-analysis for ICU length of stay: all available data (including transformed and imputed data). IV, inverse variance; LORAZ, lorazepam compared with dexmedetomidine; MIDAZOLAM, midazolam compared with dexmedetomidine; PROPOFOL, propofol compared with dexmedetomidine; SC, standard care compared with dexmedetomidine.

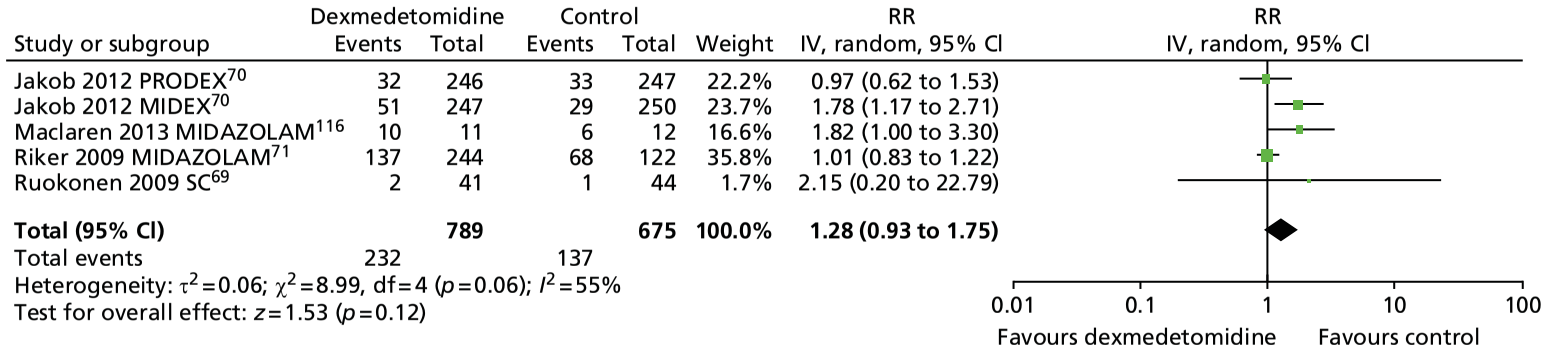

FIGURE 12 Meta-analysis for incidence of hypotension. IV, inverse variance; MIDAZOLAM, midazolam compared with dexmedetomidine; SC, standard care compared with dexmedetomidine.

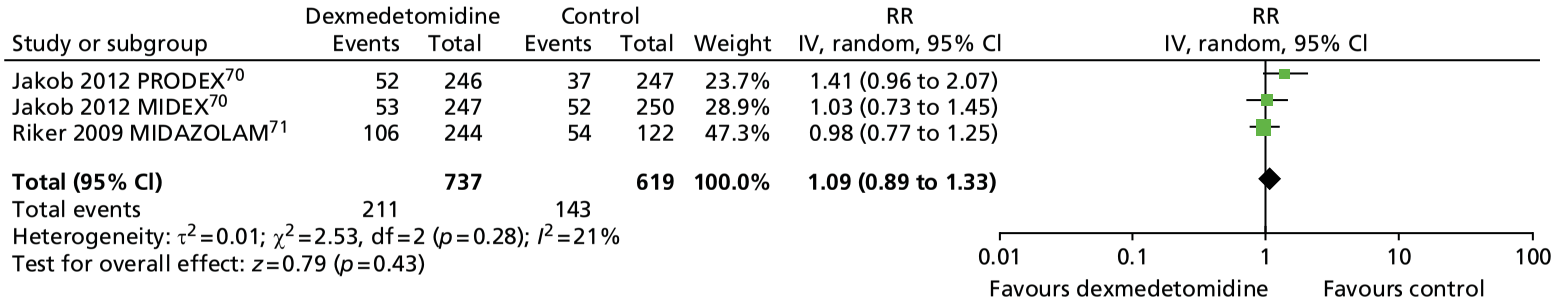

FIGURE 13 Meta-analysis for incidence of hypertension. IV, inverse variance; MIDAZOLAM, midazolam compared with dexmedetomidine.

Study or subgroup	Dexmedetomidine Events	Total	Control Events	Total	Weight	RR IV, random, 95% CI
Jakob 2012 PRODEX[70]	32	246	25	247	24.7%	1.29 (0.79 to 2.10)
Jakob 2012 MIDEX[70]	35	247	13	250	20.3%	2.73 (1.48 to 5.02)
Maclaren 2013 MIDAZOLAM[116]	7	11	7	12	18.9%	1.09 (0.57 to 2.10)
Riker 2009 MIDAZOLAM[71]	103	244	23	122	28.7%	2.24 (1.51 to 3.33)
Ruokonen 2009 SC[69]	3	41	0	44	1.7%	7.50 (0.40 to 140.91)
Pandharipande 2007 LORAZ[102]	9	52	2	51	5.8%	4.41 (1.00 to 19.44)
Total (95% CI)		**841**		**726**	**100.0%**	**1.88 (1.28 to 2.77)**
Total events	189		70			

Heterogeneity: $\tau^2 = 0.09$; $\chi^2 = 9.23$, df = 5 ($p = 0.10$); $I^2 = 46\%$
Test for overall effect: $z = 3.21$ ($p = 0.001$)

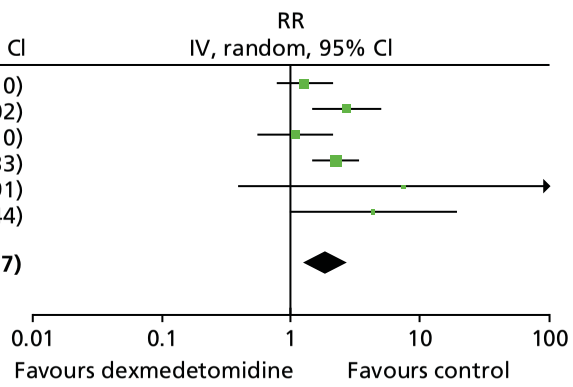

FIGURE 14 Meta-analysis for incidence of bradycardia. IV, inverse variance; LORAZ, lorazepam compared with dexmedetomidine; MIDAZOLAM, midazolam compared with dexmedetomidine; SC, standard care compared with dexmedetomidine.

Study or subgroup	Dexmedetomidine Events	Total	Control Events	Total	Weight	RR IV, random, 95% CI
Jakob 2012 PRODEX[70]	12	246	24	247	9.3%	0.50 (0.26 to 0.98)
Jakob 2012 MIDEX[70]	19	247	25	250	11.6%	0.77 (0.44 to 1.36)
Maclaren 2013 MIDAZOLAM[116]	4	11	8	12	6.2%	0.55 (0.23 to 1.31)
Riker 2009 MIDAZOLAM[71]	132	244	93	122	28.7%	0.71 (0.61 to 0.83)
Ruokonen 2009 SC[69]	18	41	11	44	10.5%	1.76 (0.95 to 3.26)
Shehabi 2013 SC[121]	8	21	6	16	6.7%	1.02 (0.44 to 2.34)
Pandharipande 2007 LORAZ[102]	41	52	42	51	27.0%	0.96 (0.79 to 1.16)
Total (95% CI)		**862**		**742**	**100.0%**	**0.83 (0.65 to 1.06)**
Total events	234		209			

Heterogeneity: $\tau^2 = 0.05$; $\chi^2 = 14.95$, df = 6 ($p = 0.02$); $I^2 = 60\%$
Test for overall effect: $z = 1.47$ ($p = 0.14$)

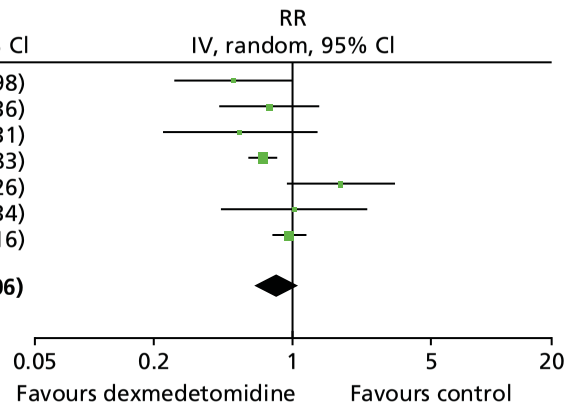

FIGURE 15 Meta-analysis for incidence of delirium. IV, inverse variance; LORAZ, lorazepam compared with dexmedetomidine; MIDAZOLAM, midazolam compared with dexmedetomidine; SC, standard care compared with dexmedetomidine.

Self-extubation

Four trials reported episodes of self-extubation during sedation (*Figure 16*).[70,102,121] Self-extubation occurred in 12 out of 566 (2%) of patients who received dexmedetomidine and 3 out of 564 (< 1%) of those who received an alternative sedative agent. There was no clear evidence of a statistically significant difference between sedative interventions (RR 2.95, 95% CI 0.96 to 9.06, $I^2 = 0\%$; $p = 0.06$).

One trial, which assessed patients after elective surgery,[110] reported one episode of self-extubation among participants who received propofol (1 out of 46) and none among those who received dexmedetomidine (0 out of 43).

Tachycardia

Five trials assessed the incidence of tachycardia among patients receiving sedation (*Figure 17*).[70,71,102,116] There was no evidence of a significant difference (RR 0.93, 95% CI 0.63 to 1.39; $p = 0.73$) between sedative interventions [187 out of 800 (23%) of those who received dexmedetomidine compared with 178 out of 682 (26%) of those who received alternative sedative agents]. Substantial statistical heterogeneity was observed among trials ($I^2 = 82\%$).

Rate of respiratory depression

Rate of respiratory depression was not reported by any of the included trials. However, respiratory rate was reported by two trials.[109,120] In both trials, no significant differences were observed between sedatives. One trial[109] recorded mean breaths per minute of 28 (SD 4 breaths per minute), 28 (SD 3 breaths per minute) and 29 (SD 4 breaths per minute) among patients who received dexmedetomidine and 29 (SD 3 breaths per minute), 30 (SD 3 breaths per minute) and 30 (SD 4 breaths per minute) among those who received propofol at 2 hours, 4 hours and 6 hours after infusion of study drug, respectively. The other trial[120] reported mean respiratory rate per minute pre and post operatively. For patients who received dexmedetomidine, the pre- and post-operative values were 16.53 (SD 3.83) and 17.07 (SD 3.47) breaths per minute, whereas for those who received propofol the values were 17.25 (SD 3.58) and 20 (SD 4.0) breaths per minute, respectively.

Incidence of coma

One trial assessed the incidence of coma during a 12-day evaluation period.[102] Significantly fewer patients who received dexmedetomidine (63%) than those who received lorazepam (92%) experienced coma ($p < 0.001$).

Secondary outcomes and other reported outcomes

It is worth noting that no data were available from the included trials for extubation readiness, discharge readiness and quality of life.

Duration of weaning

Two trials reported duration of weaning.[69,114] Ruokonen and colleagues[69] did not observe any difference ($p = 0.27$) between patients who received dexmedetomidine (median 59.4 hours) and those who received propofol and/or midazolam (median 78 hours). Similarly, Herr and colleagues,[114] who enrolled patients after elective surgery, found that there was no difference between sedative interventions in median times to weaning. Median time to the start of weaning was 259 minutes (25th–75th percentiles 215–410 minutes) for dexmedetomidine and 300 minutes (25th–75th percentiles 210–482 minutes) for propofol.

Time in target sedation range

Three trials provided data on percentage of total time in target sedation range (*Figure 18*).[70,71] There was no evidence of a significant difference between sedative interventions (mean difference 1.94% of total time in target sedation range, 95% CI –1.70 to 5.57% of total time in target sedation range, $I^2 = 0\%$).

Similarly, *Figure 19* shows that no significant differences were evident between dexmedetomidine and alternative sedative agents (mean difference 2.53% of total time in target sedation range, 95% CI –0.82 to 5.87% of total time in target sedation range, $I^2 = 0\%$; $p = 0.14$) when all available data suitable for the analysis (including transformed and imputed data) were considered.

Study or subgroup	Dexmedetomidine Events	Total	Control Events	Total	Weight	RR IV, random, 95% CI
Jakob 2012 PRODEX[70]	1	246	0	247	12.3%	3.01 (0.12 to 73.58)
Jakob 2012 MIDEX[70]	5	247	1	250	27.4%	5.06 (0.60 to 43.01)
Shehabi 2013 SC[121]	2	21	0	16	14.2%	3.86 (0.20 to 75.28)
Pandharipande 2007 LORAZ[102]	4	52	2	51	46.0%	1.96 (0.38 to 10.24)
Total (95% CI)		**566**		**564**	**100.0%**	**2.95 (0.96 to 9.06)**
Total events	12		3			

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.51$, df = 3 ($p = 0.92$); $I^2 = 0\%$
Test for overall effect: $z = 1.89$ ($p = 0.06$)

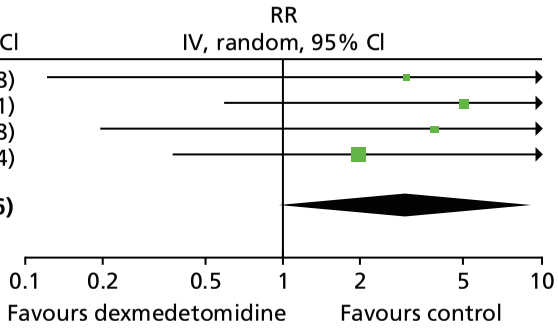

FIGURE 16 Meta-analysis for episodes of self-extubation. IV, inverse variance; LORAZ, lorazepam compared with dexmedetomidine; SC, standard care compared with dexmedetomidine.

Study or subgroup	Dexmedetomidine Events	Total	Control Events	Total	Weight	RR IV, random, 95% CI
Jakob 2012 PRODEX[70]	48	246	28	247	20.0%	1.72 (1.12 to 2.65)
Jakob 2012 MIDEX[70]	34	247	54	250	20.8%	0.64 (0.43 to 0.94)
Maclaren 2013 MIDAZOLAM[116]	7	11	5	12	12.6%	1.53 (0.68 to 3.42)
Riker 2009 MIDAZOLAM[71]	62	244	54	122	22.9%	0.57 (0.43 to 0.77)
Pandharipande 2007 LORAZ[102]	36	52	37	51	23.7%	0.95 (0.74 to 1.22)
Total (95% CI)		**800**		**682**	**100.0%**	**0.93 (0.63 to 1.39)**
Total events	187		178			

Heterogeneity: $\tau^2 = 0.16$; $\chi^2 = 22.12$, df = 4 ($p = 0.0002$); $I^2 = 82\%$
Test for overall effect: $z = 0.34$ ($p = 0.73$)

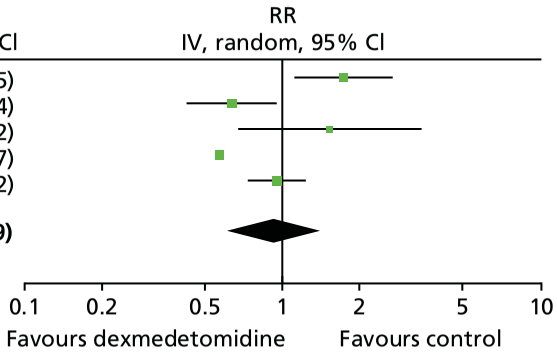

FIGURE 17 Meta-analysis for incidence of tachycardia. IV, inverse variance; LORAZ, lorazepam compared with dexmedetomidine; MIDAZOLAM, midazolam compared with dexmedetomidine.

Study or subgroup	Dexmedetomidine Mean	SD	Total	Control Mean	SD	Total	Weight	Mean difference IV, random, 95% CI
Jakob 2012 PRODEX[70]	64.6	34.666	223	64.7	35.452	214	30.6%	−0.10 (−6.68 to 6.48)
Jakob 2012 MIDEX[70]	60.7	41.125	227	56.6	41.665	233	23.1%	4.10 (−3.47 to 11.67)
Riker 2009 MIDAZOLAM[71]	77.3	24.617	244	75.1	24.617	122	46.3%	2.20 (−3.15 to 7.55)
Total (95% CI)			**694**			**569**	**100.0%**	**1.94 (−1.70 to 5.57)**

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.69$, df = 2 ($p = 0.71$); $I^2 = 0\%$
Test for overall effect: $z = 1.04$ ($p = 0.30$)

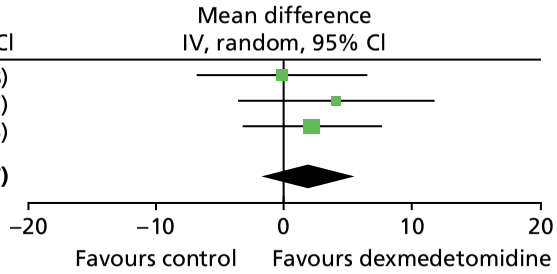

FIGURE 18 Meta-analysis for time in target sedation range. IV, inverse variance; MIDAZOLAM, midazolam compared with dexmedetomidine.

Study or subgroup	Dexmedetomidine Mean	SD	Total	Control Mean	SD	Total	Weight	Mean difference IV, random, 95% CI
Jakob 2012 PRODEX[70]	64.6	34.666	223	64.7	35.452	214	25.9%	−0.10 (−6.68 to 6.48)
Jakob 2012 MIDEX[70]	60.7	41.125	227	56.6	41.665	233	19.6%	4.10 (−3.47 to 11.67)
Riker 2009 MIDAZOLAM[71]	77.3	24.617	244	75.1	24.617	122	39.1%	2.20 (−3.15 to 7.55)
Pandharipande 2007 LORAZ[102]	80	35.003	52	67	35.003	51	6.1%	13.00 (−0.52 to 26.52)
Ruokonen 2009 SC[69]	64	24.75	38	63	25	41	9.3%	1.00 (−9.98 to 11.98)
Total (95% CI)			**784**			**661**	**100.0%**	**2.53 (−0.82 to 5.87)**

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 3.17$, df = 4 ($p = 0.53$); $I^2 = 0\%$
Test for overall effect: $z = 1.48$ ($p = 0.14$)

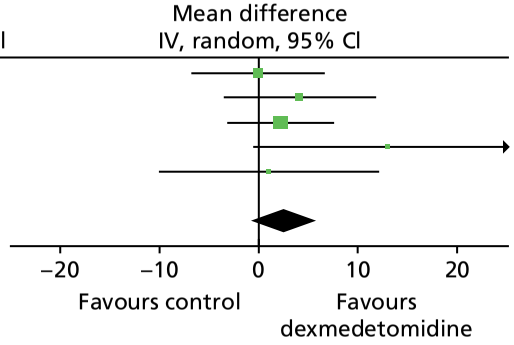

FIGURE 19 Meta-analysis for time in target sedation range: all available data (including transformed and imputed data). IV, inverse variance; LORAZ, lorazepam compared with dexmedetomidine; MIDAZOLAM, midazolam compared with dexmedetomidine; SC, standard care compared with dexmedetomidine.

Two trials, which enrolled patients after elective surgery, assessed time in target sedation range.[111,123] Both trials showed that the proportion of time spent at adequate depth of sedation was similar for sedative interventions (46.3% for dexmedetomidine and 49.1% for propofol in one trial,[123] and 93% for dexmedetomidine and 92% for propofol in the other trial).[111]

Hospital length of stay

Three trials reported overall length of hospital stay and did not find any significant difference between dexmedetomidine and alternative sedative interventions.[70,121] In the MIDEX trial, the median duration of study hospital stay was 35 days (range 14–45 days) for dexmedetomidine and 27 days (range 17–45 days) for midazolam ($p = 0.370$). In the PRODEX trial, the median duration of study hospital stay was 25 days (range 13–45 days) for dexmedetomidine and 28 days (range 14–45 days) for propofol ($p = 0.760$).[70] Shehabi and collegues[121] reported a median of 16.1 days (interquartile range 9.3–33.3 days) for dexmedetomidine and 17 days (interquartile range 4.0–29.0 days) for standard sedative treatments ($p = 0.49$).

Time to extubation

Two trials reported time to extubation (*Figure 20*).[70] Time to extubation was significantly shorter among patients who received dexmedetomidine than among those who received an alternative sedative agent (mean difference –1.83 days, 95% CI –2.70 to –0.95 days, $I^2 = 0\%$; $p < 0.0001$).

Similarly, time to extubation was significantly shorter for patients who received dexmedetomidine than for those who received an alternative sedative agent (*Figure 21*) when all available data suitable for the analysis (including transformed and imputed data) were considered (mean difference –1.85 days, 95% CI –2.61 to –1.09 days, $I^2 = 0\%$; $p < 0.00001$).

Three trials, which enrolled patients after elective surgery, assessed time to extubation.[111,114,123] All three trials showed that times to extubation were similar between sedative interventions. Elbaradie and colleagues[111] reported mean times to extubation of 30 minutes (SD 15 minutes) for dexmedetomidine compared with 35 minutes (SD 12 minutes) for propofol. Herr and colleagues[114] reported median times to extubation of 410 minutes (25th–75th percentiles 310 to 584 minutes) for dexmedetomidine and 462 minutes (25th–75th percentiles 323–808 minutes) for propofol. In the trial by Venn and Grounds,[123] mean extubation times were 29 minutes (range 15–50 minutes) for dexmedetomidine and 28 minutes (range 20–50 minutes) for propofol ($p = 0.63$).

Cost of care

Three trials[71,72,102] reported costs related to sedation. The trial by Pandharipande and colleagues, published in 2007,[102] reported median costs of US$4675 for dexmedetomidine and US$2335 for lorazepam. The median total hospital cost was approximately US$22,500 higher, but not significantly higher, for dexmedetomidine. This difference was attributed to costs that occurred prior to enrolment and randomisation.

The trial by Maldonado and colleagues, published in 2009,[72] reported an average total cost for post-operative care of US$7025 for dexmedetomidine, compared with US$9875 and US$9570 for propofol and midazolam, respectively. There were no significant differences between sedative interventions. For patients who developed delirium, the average cost was US$12,965, compared with an average cost of US$6763 for those who did not ($p = 0.004$).

The SEDCOM trial by Riker and colleagues, published in 2009,[71] reported overall economic costs (expressed in Canadian dollars) of CA$7022 for dexmedetomidine and of CA$7680 for midazolam; medication costs of CA$1929.57 for dexmedetomidine and CA$180.10 for midazolam; costs associated with delirium of CA$2127.49 for dexmedetomidine and CA$3012.30 for midazolam; and MV costs were CA$2938.62 for dexmedetomidine and CA$4447.64 for midazolam.

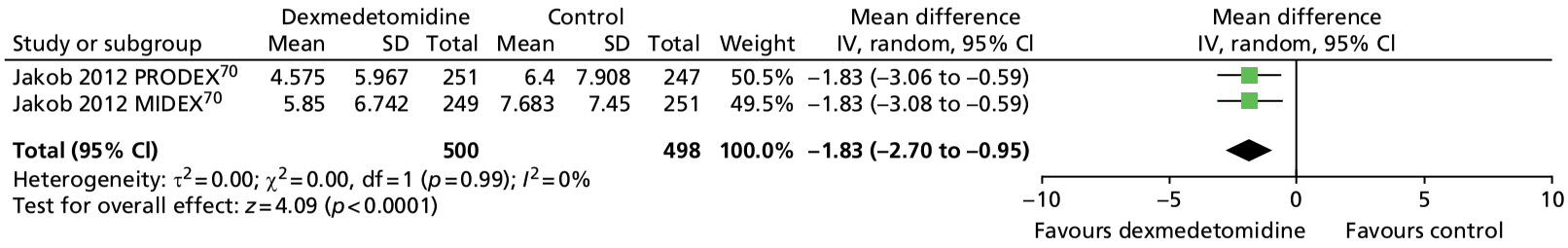

FIGURE 20 Meta-analysis for time to extubation. IV, inverse variance.

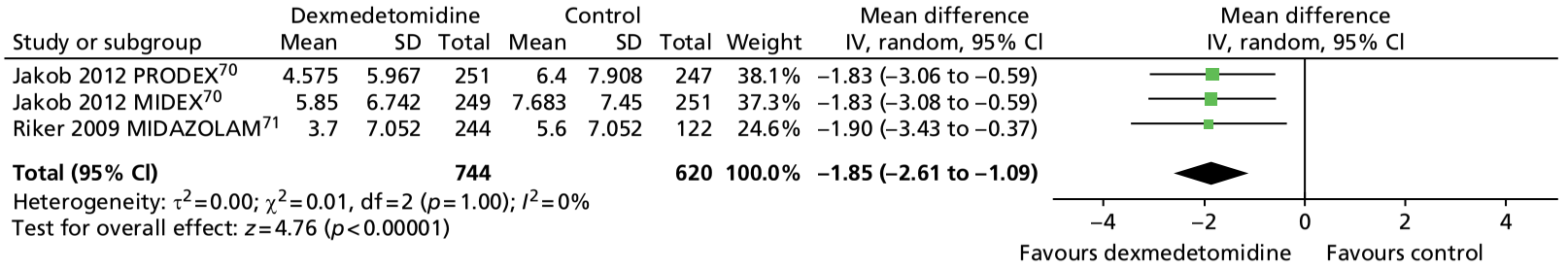

FIGURE 21 Meta-analysis for time to extubation: all available data (including transformed and imputed data). IV, inverse variance; MIDAZOLAM, midazolam compared with dexmedetomidine.

Co-operation and communication

In four multicentre trials with a total of 1461 patients[69–71] that compared dexmedetomidine with midazolam or propofol, secondary efficacy outcomes included nurses' assessment of arousal, co-operation and ability to communicate pain using visual analogue scales. In all four trials,[69–71] patients who received dexmedetomidine were significantly more arousable, more co-operative and better able to communicate their pain than those who received an alternative sedative agent (propofol or midazolam) ($p \leq 0.001$ in all cases).

Neuropsychological testing

In the trial by Pandharipande and colleagues[102] (103 patients in total), neuropsychological tests were administered within 72 hours of discharge from the ICU. A higher proportion of patients who received dexmedetomidine (42%), but not significantly higher, were able to complete the post-ICU neuropsychological testing than those who received lorazepam (31%) ($p = 0.61$). The median Mini-Mental State Examination score, which evaluates global cognitive ability, was 28 for dexmedetomidine and 27 for lorazepam ($p = 0.23$), whereas the median Trails-B scores, which assesses motor speed and attention functions corrected for age and level of education, were 18 for dexmedetomidine and 19 for lorazepam ($p = 0.75$).

Anxiety and depression

The trial by MacLaren and colleagues[116] assessed the rates of post-ICU anxiety, depression and acute stress disorder manifestations among 23 mechanically ventilated patients admitted to ICUs. Validated assessment scales were administered 72 hours after extubation but before hospital discharge. Eight patients in each intervention group (midazolam compared with dexmedetomidine) completed the questionnaires. Manifestations of anxiety and depression were similar between sedative interventions. Five patients (62.5%) who received dexmedetomidine and one patient (12.5%) who received midazolam manifested acute stress disorder ($p = 0.063$).

Memory of intensive care unit experience

Three trials provided information on patients' ICU recall.[110,116,123] MacLaren and colleagues,[116] who assessed a total of 23 patients, reported that the median number of ICU experiences remembered by patients who received dexmedetomidine was significantly higher than that of patients who received midazolam (18.5 compared with 8.5; $p = 0.015$).

Venn and Grounds[123] enrolled a total of 20 patients after elective surgery and assessed recall 48–72 hours after discharge from ICUs. The majority of patients who received dexmedetomidine remembered their length of stay in ICU accurately, compared with those who received propofol (8 out of 10 compared with 2 out of 10 remembered their length of stay in the ICU; $p = 0.023$), but few remembered the duration of MV (3 out of 10 compared with 2 out of 10). Sleeping difficulty and noise were more often reported by patients who received propofol and discomfort on the ventilator by those who received dexmedetomidine. No patient recorded pain.

Corbett and colleagues,[110] who enrolled a total of 89 patients after elective surgery, evaluated patients' perception regarding their ICU experience. A validated questionnaire was administered after ICU discharge [mean time between discharge and administration of 46.5 hours (SD 24.5 hours) for dexmedetomidine and 45.5 hours (SD 20.7 hours) for propofol; $p = 0.847$]. Level of overall awareness as a marker to amnesia was similar between sedative interventions as well as the overall level of discomfort and pain. Participants who received dexmedetomidine perceived a significantly shorter length of intubation than those who received propofol ($p = 0.044$). Perceptions in length of stay were similar between patient groups ($p = 0.767$). Patients who received dexmedetomidine reported greater difficulty in resting or sleeping than those who received propofol ($p = 0.051$).

Subgroup analyses

We were able to perform subgroup analyses of primary and secondary outcomes according to type of comparator (see *Appendix 7*). Generally, results of subgroup analyses were consistent with those of the overall population. However, subgroups were usually too small to provide reliable conclusions and caution should be applied in their interpretation.

No subgroup analyses were possible for age, severity of disease, different duration of MV, type of clinical setting and nurse/patient ratio because of the paucity of suitable data.

Duration of MV was significantly longer for participants treated with dexmedetomidine than for those treated with propofol, but it was significantly shorter than for those who received standard care. There were no differences between participants who received dexmedetomidine and those who received midazolam. Overall, duration of MV was significantly different across the various subgroups. A high level of heterogeneity was evident in the analyses ($I^2 = 78.1\%$).

Incidence of delirium was significantly lower in participants treated with dexmedetomidine than among those treated with propofol or midazolam. There were no differences between participants treated with dexmedetomidine than for those treated with standard care or lorazepam. Overall, there were significant differences in the incidence of delirium across the comparator subgroups and there was evidence of high heterogeneity ($I^2 = 76.9\%$). The incidence of tachycardia was significantly lower for participants treated with propofol than for those treated with dexmedetomidine. There were no differences between participants who received dexmedetomidine and those who received midazolam or lorazepam. Overall, there were significant differences in the incidence of tachycardia between the comparator subgroups and, again, there was evidence of substantial heterogeneity ($I^2 = 77.6\%$).

Table 3 presents an overview of all meta-analyses results including both main analyses and subgroup analyses.

TABLE 3 Summary of meta-analyses results

Outcome or subgroup	Number of studies	Number of participants	RR (95% CI)
Mortality	9	1692	1.02 (0.85 to 1.24)
Propofol	3	578	0.86 (0.60 to 1.23)
Midazolam	3	889	1.11 (0.82 to 1.50)
Standard care	2	122	1.62 (0.76 to 3.43)
Lorazepam	1	103	0.63 (0.30 to 1.33)
Duration of MV	4	1120	–0.30 (–1.70 to 1.11)
Propofol	2	535	[a]0.84 (0.11 to 1.57)**
Midazolam	1	500	–0.88 (–2.65 to 0.88)**
Standard care	1	85	[a]–2.36 (–4.62 to –0.10)**
Ventilator-free days	2	140	3.28 (0.06 to 6.49)[b]
Lorazepam	1	103	4.00 (0.27 to 7.73)[a]
Standard care	1	37	1.20 (–5.12 to 7.52)
ICU length of stay	8	1662	–1.26 (–1.96 to –0.55)*
Propofol	3	568	–0.40 (–1.41 to 0.61)
Midazolam	3	906	–1.86 (–2.71 to –1.01)
Lorazepam	1	103	–1.50 (–3.97 to 0.97)
Standard care	1	85	–1.00 (–3.44 to 1.44)
Hypotension	5	1464	1.28 (0.93 to 1.75)
Propofol	1	493	0.97 (0.62 to 1.53)
Midazolam	3	886	1.41 (0.90 to 2.22)
Standard care	1	85	2.15 (0.20 to 22.79)

TABLE 3 Summary of meta-analyses results (*continued*)

Outcome or subgroup	Number of studies	Number of participants	RR (95% CI)
Hypertension	3	1356	1.09 (0.89 to 1.33)
Propofol	1	493	1.41 (0.96 to 2.07)
Midazolam	2	863	1.00 (0.82 to 1.22)
Bradycardia	6	1567	1.88 (1.28 to 2.77)*
Propofol	1	493	1.29 (0.79 to 2.10)[a]
Midazolam	3	886	1.94 (1.20 to 3.13)
Standard care	1	85	7.50 (0.40 to 140.91)
Lorazepam	1	103	4.41 (1.00 to 19.44)[c]
Delirium	7	1604	0.83 (0.65 to 1.06)
Propofol	1	493	[a]0.50 (0.26 to 0.98)**
Midazolam	3	886	[a]0.71 (0.61 to 0.82)**
Standard care	2	122	1.44 (0.86 to 2.41)**
Lorazepam	1	103	0.96 (0.79 to 1.16)**
Self-extubation	4	1130	2.95 (0.96 to 9.06)
Propofol	1	493	3.01 (0.12 to 73.58)
Midazolam	1	497	5.06 (0.60 to 43.01)
Standard care	1	37	3.86 (0.20 to 75.28)
Lorazepam	1	103	1.96 (0.38 to 10.24)
Tachycardia	5	1482	0.93 (0.63 to 1.39)
Propofol	1	493	[a]1.72 (1.12 to 2.65)**
Midazolam	3	886	0.71 (0.47 to 1.07)**
Lorazepam	1	103	0.95 (0.74 to 1.22)**
Time in target sedation range	5	1445	2.53 (–0.82 to 5.87)
Propofol	1	437	–0.10 (–6.68 to 6.48)
Midazolam	2	826	2.83 (–1.53 to 7.20)
Lorazepam	1	103	13.00 (–0.52 to 26.52)
Standard care	1	79	1.00 (–9.98 to 11.98)
Time to extubation	3	1364	–1.85 (–2.61 to –1.09)*
Propofol	1	498	–1.83 (–3.06 to –0.59)[a]
Midazolam	2	866	–1.86 (–2.83 to –0.89)[a]

*$p < 0.05$ for overall effect; **$p < 0.05$ for subgroup differences.
a $p < 0.05$ within subgroup.
b $p = 0.05$.
c $p = 0.05$ within subgroup.
Note
Results of continuous outcomes reported using all available data plus data imputed from range plus SD imputed from available information; data from Maldonado and colleagues[72] included in both propofol compared with dexmedetomidine and midazolam compared with dexmedetomidine analyses.

Chapter 4 Discussion

Statement of principal findings

The purpose of this assessment was to systematically review the available evidence of the effects of alpha-2 agonists (dexmedetomidine and clonidine) compared with alternative sedative agents in UK ICU clinical practice. We included evidence from published RCTs comparing (1) dexmedetomidine with clonidine, or (2) dexmedetomidine or clonidine with propofol or benzodiazepines in critically ill adults admitted to ICUs who required MV. Relevant RCTs were identified through comprehensive literature searches. We considered the following primary outcomes: mortality, duration of MV, ventilator-free days, length of ICU stay and adverse events (e.g. hypotension, hypertension, bradycardia, delirium or coma). We also considered the following secondary outcomes: time spent in target sedation range, length of hospital stay, extubation readiness, discharge readiness, duration of weaning, quality of life and economic costs. When possible, outcome data across included trials were statistically combined in a formal meta-analysis.

Clinical effectiveness

This assessment is based on evidence from 18 RCTs with a total of 2489 critically ill mechanically ventilated ICU patients. Only 1 of the 18 identified trials compared dexmedetomidine directly with clonidine, while the remaining trials assessed the effects and safety of dexmedetomidine compared with propofol or compared with benzodiazepines (i.e. midazolam or lorazepam). Not all trials provided data for the assessment of all primary and secondary outcomes under consideration. Clinical heterogeneity among trials was mostly because of type of patient population (e.g. general ICU patients and patients admitted to ICU following elective surgical); type of comparator treatment (i.e. propofol, midazolam or lorazepam); type of outcome measures; and length of follow-up. Overall, trials were at high or unclear risk of bias.

Clonidine compared with dexmedetomidine

Srivastava and colleagues[5] assessed 70 patients on short-term MV in ICUs and showed that target sedation was achieved in a higher number of patients treated with dexmedetomidine with a lesser need for additional sedation. Haemodynamic/cardiovascular parameters appeared to be more stable among patients who received dexmedetomidine than among those who received clonidine.

Clonidine does not currently have a UK marketing authorisation for use as a sedative agent in ICUs and there is no recommendation or consensus on best dose regimen for sedation. Nevertheless, the recent findings of the UK national survey conducted by the ICNARC (Sheila Harvey, ICNARC, 2014) among 235 adult general ICUs have shown that around one-third of the units (32.7%) reported very frequent use of clonidine while 10.3% reported very frequent use of dexmedetomidine. Occasional use of clonidine was reported by 60.3% of the units, with only 3.7% indicating that it was never used.

Clonidine compared with propofol or benzodiazepines (i.e. midazolam or lorazepam)

No trials of clonidine compared with alternative sedative agents were identified in the included studies.

Propofol or benzodiazepines (i.e. midazolam or lorazepam) compared with dexmedetomidine

Seventeen trials compared the effects of dexmedetomidine with an alternative sedative agent other than clonidine. Nine trials (1134 patients) assessed propofol compared with dexmedetomidine, four trials (939 patients) compared midazolam with dexmedetomidine, one trial (118 patients) compared both propofol and midazolam with dexmedetomidine (three treatment arms), two trials (122 patients) compared 'standard care' (i.e. propofol and/or midazolam) with dexmedetomidine (i.e. propofol and/or midazolam) and one trial (106 patients) compared lorazepam with dexmedetomidine.

When all available data were combined in meta-analyses, length of ICU stay and time to extubation were significantly shorter among patients who received dexmedetomidine than among those who received an alternative sedative agent (see *Figures 11* and *21*). In contrast, we did not observe a significant reduction in duration of MV or ventilator-free days with the use of dexmedetomidine. A reduction in ICU length of stay has been reported consistently in recently published systematic reviews,[10,66,73,74,126] while results for other efficacy outcomes have not. Pasin and colleagues,[73] in line with our findings, observed a reduction in time to extubation. Chen and colleagues[74] demonstrated a significant reduction in the duration of MV after dexmedetomidine while Tan and Ho,[66] Xia and colleagues[10] and Zhuo and colleagues[126] did not. It is worth noting that the inclusion/exclusion criteria and number of assessed studies varied considerably among these previous systematic reviews.

In line with the findings of a recent systematic review that has assessed how outcomes are defined in clinical trials of mechanically ventilated adults and children,[127] we found that outcome sets and especially measures of ventilator dependence (e.g. duration of MV, ventilation-free days and time to extubation) differed among included trials. In particular, we observed a considerable variation among trials with regard to outcome definitions, measurement criteria and time of assessment.

The proportion of time spent in adequate sedation range was not different between sedative interventions (see *Figure 19*), indicating that dexmedetomidine was as effective as common sedative agents.

With regard to the incidence of adverse events, the results of our meta-analyses show an increased risk of bradycardia after dexmedetomidine compared with alternative sedative agents (see *Figure 14*), but no evidence of an increased risk of hypotension, hypertension or tachycardia. However, bradycardia did not impact negatively on mortality, which showed no evidence of differences between sedative interventions (see *Figure 5*). In most of the trials that contributed to the meta-analyses, bradycardia required relatively standard intervention and rarely interruption of treatment. Riker and colleagues,[71] for example, stated that bradycardia required titration or interruption in 4.9% of the treated patients. Similarly, Ruokonen and colleagues[69] indicated that 4.8% of the patients discontinued dexmedetomidine because of bradycardia. Moreover, akin to the findings of the meta-analysis by Tan and Ho,[66] bradycardia in our assessment was not observed to be accompanied by an increased risk of hypotension.

We did not observe a reduced risk of delirium among patients treated with dexmedetomidine. However, delirium was not consistently defined in the included studies, different tools were used for its assessment and most trials excluded patients with pre-existing neurological conditions and substance abuse. These inconsistencies across trials may have contributed to the observed level of statistical heterogeneity. In the literature, the systematic reviews by Pasin and colleagues[73] and by Zhuo and colleagues[126] have suggested a lower incidence of delirium for dexmedetomidine. It is worth noting, however, that the meta-analysis conducted by Pasin and colleagues[73] demonstrated a reduced risk for dexmedetomidine compared with other sedative agents when all clinical settings were considered, but not when only trials based on general ICU settings were analysed ($p = 0.05$). Moreover, their analyses were not limited to mechanically ventilated patients but included all patients admitted to ICUs and statistical heterogeneity was evident in all the analyses. In addition, the systematic reviews by Chen and colleagues[74] and by Tan and Ho[66] did not show any clear beneficial effect of dexmedetomidine in reducing the risk of delirium.

We observed more episodes of self-extubation among patients treated with dexmedetomidine; however, we could not find clear evidence of a difference between sedative interventions (see *Figure 16*).

There were not enough data to assess the incidence of coma reliably.

Subgroup analyses according to type of comparator were generally consistent with those of the overall population. However, subgroups were usually too small to provide reliable conclusions.

Only limited data were available for duration of weaning and length of hospital stay, and no data were available for extubation readiness, discharge readiness and quality of life.

Overall, across trials, patients treated with dexmedetomidine were reported to be more arousable, more co-operative and better able to communicate than those who received alternative sedative agents (four trials).

A cost-minimisation analysis conducted by Dasta and colleagues,[128] on the results of the Riker and colleagues' trial,[71] showed that compared with midazolam, sedation with dexmedetomidine resulted in significantly lower total ICU costs, mainly resulting from reduced length of ICU stay and lower MV costs.

Uncertainties from the assessment

This assessment was conducted according to current methodological standards and the methods were specified a priori in a research protocol, which was informed by an advisory group established for the purpose of this assessment. In particular, we performed comprehensive literature searches of the major electronic databases and we contacted experts in the field to identify all existing relevant evidence. We reviewed all potential eligible studies for inclusion and assessed their methodological quality using the best recommended risk-of-bias tool. We developed specific data extraction forms on prespecified outcome parameters and data extraction was performed by one reviewer and chekced by a second reviewer. Despite all these efforts, there is still the possibility that some relevant evidence may have been missed. Furthermore, we need to acknowledge the following limitations:

- This assessment provides mainly evidence on the use of dexmedetomidine as sedative agent in ICUs. The evidence on the effects of clonidine in ICUs was scant (only one trial comparing clonidine with dexmedetomidine was identified in our included studies). Nevertheless, one-third of UK ICUs have reported frequent or very frequent use of clonidine and nearly two-thirds have reported occasional or rare use of clonidine to sedate critically ill adults (Sheila Harvey, ICNARC, 2014). Clonidine appears to be used off-label and evidence regarding its effectiveness and safety profile is clearly needed.
- The included trials were clinically heterogeneous. In particular, patient populations, comparator interventions, dose of sedative agents, length of follow-up assessments, and choice and definitions of outcome measures varied considerably across trials.
- The overall risk of bias was high or unclear in the majority of included trials. Only four trials were judged to be at low risk of bias. In particular, blinding of outcome assessors was reported in only 5 of the 18 included trials.
- Length of follow-up after discharge from ICUs varied among included trials. Apart from one trial in which survivors were followed up for 1 year after discharge from ICUs, none of the remaining trials reported the long-term outcomes of patients receiving dexmedetomidine (generally, length of follow-up ranged from 24 to 72 hours in most trials).
- Units of measurement, especially for continuous data, varied considerably among trials. This required data transformation and imputation, and it hampered our ability to combine data across trials reliably.
- Subgroup analyses according to type of comparator were not very informative as subgroups were too small. There were not enough data to perform subgroup analyses according to type of patient population, which is likely to impact on the effects of sedation (e.g. elective ICU setting compared with general ICU setting).
- There was substantial variation in the choice and definitions of outcome measures among included trials. No trials reported information on extubation readiness, discharge readiness or quality of life.
- A number of trials and, in particular, all the largest included trials excluded patients with bradycardia and hypotension. This may impact on the generalisability of our findings.
- In two large multicentre trials (MIDEX and PRODEX, with a total of 1001 patients), discontinuation because of a lack of efficacy was observed significantly more frequently among patients treated with dexmedetomidine. However, patients in these trials received standard sedation prior to randomisation and this may have potentially masked the benefits of dexmedetomidine because a change of sedative drug (from that received prior to randomisation) might have negatively affected the subsequent efficacy of dexmedetomidine.

Chapter 5 Conclusions

This assessment summarised evidence from 18 RCTs, including data from 2489 patients. Data were available to make summary conclusions about several aspects of the use of dexmedetomidine; however, the methodological quality of identified evidence was variable, with many studies at high or unclear risk of bias. Evidence on the use of clonidine as a sedative agent in ICUs was limited. Dexmedetomidine was observed to be as effective as propofol and commonly used benzodiazepines (i.e. midazolam and lorazepam) in ensuring an adequate light sedation level of critically ill, mechanically ventilated adults admitted to ICUs. Compared with propofol and benzodiazepines, dexmedetomidine was also observed to be effective in reducing the ICU length of stay and time to extubation.

Use of dexmedetomidine, however, was associated with an increased risk of bradycardia but not of overall mortality. There was not enough evidence to assess the risk of coma and not clear evidence of a reduced risk of delirium.

Implications for health care

- Dexmedetomidine was observed to be effective in reducing the ICU length of stay and time to extubation. Use of dexmedetomidine, however, was associated with an increased risk of bradycardia, but not of overall mortality.
- Owing to the observed heterogeneity among included trials with regard to patients' characteristics, clinical setting, doses of sedative agents, outcome measures and length of follow-up, our results need to be interpreted with caution and may not be easily generalisable. Moreover, all included trials enrolled adult patients. Therefore, our findings cannot be generalised to paediatric ICU populations.
- Many trials excluded patients with bradycardia, hypotension, liver disease and neurological conditions and, therefore, we do not know the full effects of dexmedetomidine in these categories of patients.
- Most of the included trials have reported only short-term outcomes and, therefore, the long-term effects of the use of dexmedetomidine for ICU patients are still to be fully established.
- Only a few trials included DSI within their study protocol. It is possible that the effects of dexmedetomidine are different when DSIs are implemented in ICU practice.

Recommendations for research

The main gap in the current evidence is the dearth of RCTs comparing clonidine with dexmedetomidine, as well as clonidine with traditional alternative sedative agents (propofol and midazolam).

Larger well-designed RCTs are needed:

- To assess the use of clonidine as main sedative agent.
- To define which subgroups of ICU patients are more likely to benefit from dexmedetomidine as main sedative agent. The two main subgroups of interest are patients who require short-term sedation after elective surgery and general critically ill patients who require long-term sedation.
- To assess the effects of alpha-2 agonists in children admitted to ICUs. This would need to include dose-ranging trials, as different weight-based doses may be required in this patient population.

Future trials should be multicentre, use proper blinding procedures (in particular blinding of outcome assessors), include a common set of relevant outcome measures, define how outcomes will be measured, use validated instruments to assess the level of sedation and the incidence of events such as delirium and coma, assess long-term effects of alpha-2 agonists and include a full economic evaluation.

With regard to the choice of relevant outcome measures, time to extubation, duration of MV, length of ICU stay and incidence of delirium, bradycardia and hypotension are most relevant from an ICU perspective. On the basis of our observed data, mortality remains important but less so as the primary outcome of interest in future trials. Moreover, future trials should assess patients' ability to communicate with health-care personnel as well as patients' perspective of quality of sedation (e.g. perception of pain and discomfort, anxiety and memories of ICU experience).

Ideally, future trials should consider the core outcome set for ventilation studies that is currently under development as part of the COMET (Core Outcome Measures in Effectiveness Trials) initiative.[129]

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Contributions of authors

Moira Cruickshank (Research Fellow) led the day-to-day running of the assessment, reviewed the evidence on the clinical effectiveness of the sedative interventions under investigation and drafted the first version of this report.

Lorna Henderson (Medical Statistician) contributed to data extraction, interpretation of results and conducted all statistical analyses with supervision from **Graeme MacLennan** (senior statistician).

Cynthia Fraser (Senior Information Officer) was responsible for running the literature searches, obtaining full-text papers and compiling the reference list of the report.

Marion Campbell (Director of the Health Services Research Unit) provided content expertise and guidance, contributed to the interpretation of results and commented on the draft version of this report.

Bronagh Blackwood (Senior Lecturer) and **Anthony Gordon** (Clinical Senior Lecturer and Consultant, Critical Care Medicine) provided expert advice, contributed to the interpretation of results and commented on the draft version of this report.

Miriam Brazzelli (Senior Research Fellow) oversaw and co-ordinated all aspects of the assessment, led and co-ordinated the expert advisory group participation, interpreted data and contributed to draft the first version of this report.

All authors approved the final version of the report.

Data sharing statement

All available data and information have been included within this report or added as appendices.

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Appendix 1 Literature search strategies

Database: EMBASE (1996 to 2014 week 45), MEDLINE without Revisions (1996 to November week 1 2014), MEDLINE In-Process & Other Non-Indexed Citations (12 November 2014)

Ovid Multifile Search URL: https://shibboleth.ovid.com/.

Date of search: 12 November 2014.

Search strategy

1. Conscious Sedation/
2. exp Respiration, Artificial/ use medf
3. exp artificial ventilation/ use emef
4. exp Critical Care/ use medf
5. Intensive Care/ use emef
6. Critical Illness/
7. (sedation or sedate?).tw.
8. ((mechanical$ or artificial$) adj5 ventilat$).tw.
9. or/1-8
10. Dexmedetomidine/
11. (dexmedetomidine or dexdor or precedex or primadex or dexdomitor or mpv1440 or mpv 1440).tw,rn.
12. Clonidine/
13. (clonidine or clofenil or klofenil or m5041t or m 5041t or catapres$ or st155 or st 155).tw,rn.
14. or/10-13
15. exp clinical trial/ use emef
16. randomized controlled trial.pt.
17. controlled clinical trial.pt
18. randomization/ use emef
19. randomi?ed.ab.
20. placebo.ab.
21. drug therapy.fs.
22. randomly.ab.
23. trial.ab.
24. groups.ab.
25. or/15-24
26. exp animals/ not humans/
27. nonhuman/ not human/
28. exp child/ not exp adult/
29. (conference abstract or letter).pt.
30. 25 not (26 or 27 or 28 or 29)
31. 9 and 14 and 30
32. limit 30 to yr="1999 -Current"
33. remove duplicates from 31

Science Citation Index (1999 to 13 November 2014)

Bioscience Information Service (1999 to 13 November 2014).

ISI Web of Knowledge URL: http://wok.mimas.ac.uk/.

Date of search: 13 November 2014.

Search strategy

1. (TS=critical illness) AND DOCUMENT TYPES: (Article)
2. (TS=critical care) AND DOCUMENT TYPES: (Article)
3. (TS=intensive care) AND DOCUMENT TYPES: (Article)
4. (TS=(sedation or sedate*)) AND DOCUMENT TYPES: (Article)
5. (TS=((mechanical* or artificial*) NEAR/3 ventilat*)) AND DOCUMENT TYPES: (Article)
6. #5 OR #4 OR #3 OR #2 OR #1
7. (TS=(dexmedetomidine or dexdor or precedex or primadex or dexdomitor or mpv1440 or "mpv1440")) AND DOCUMENT TYPES: (Article)
8. (TS=(clonidine or clofenil or klofenil or m5041t or "m 5041t" or catapres$ or st155 or "st 155")) AND DOCUMENT TYPES: (Article)
9. #8 OR #7
10. #9 AND #6
11. (TS=trial*) AND DOCUMENT TYPES: (Article)
12. (TS=randomized) AND DOCUMENT TYPES: (Article)
13. (TS=randomised) AND DOCUMENT TYPES: (Article)
14. (TS=randomly) AND DOCUMENT TYPES: (Article)
15. #14 OR #13 OR #12 OR #11
16. #15 AND #10 Refined by: [excluding] WEB OF SCIENCE CATEGORIES: (PEDIATRICS)

Scopus (14 November 2014)

URL: www.scopus.com/home.url.

Date of search: 14 November 2014.

Search strategy

#1 (Dexmedetomidine or Clonidine).ti [In press articles].

The Cochrane Library [Cochrane Central Register of Controlled Trials (Issue 10 October 2014), Cochrane Database of Systematic Reviews (Issue 11 November 2014)]

URL: www3.interscience.wiley.com/.

Date of search: 13 November 2014.

Search strategy

1. MeSH descriptor: [Conscious Sedation] explode all tree
2. MeSH descriptor: [Respiration, Artificial] explode all trees
3. MeSH descriptor: [Critical Care] explode all trees
4. MeSH descriptor: [Critical Illness] explode all trees
5. (sedation or sedate*):ti,ab,kw (Word variations have been searched)
6. ((mechanical* or artificial*) near/5 ventilat*):ti,ab,kw (Word variations have been searched)
7. #1 or #2 or #3 or #4 or #5 or #6
8. MeSH descriptor: [Dexmedetomidine] explode all trees
9. MeSH descriptor: [Clonidine] explode all trees
10. dexmedetomidine or dexdor or precedex or primadex or dexdomitor or mpv1440 or "mpv1440":ti,ab,kw (Word variations have been searched)
11. clonidine or clofenil or klofenil or m5041t or "m 5041t" or catapres$ or st155 or "st 155":ti,ab,kw (Word variations have been searched)
12. #8 or #9 or #10 or #11
13. #7 and #12
14. MeSH descriptor: [Child] explode all trees
15. MeSH descriptor: [Adult] explode all trees
16. #14 not #15
17. #13 not #16

Health Technology Assessment Database/Database of Abstracts of Reviews of Effects

Centre for Reviews and Dissemination URL: http://nhscrd.york.ac.uk/welcome.htm.

Date of search: 12 November 2014.

Search strategy

1. MeSH DESCRIPTOR Conscious Sedation
2. MeSH DESCRIPTOR Respiration, Artificial EXPLODE ALL TREES
3. MeSH DESCRIPTOR Critical Illness
4. MeSH DESCRIPTOR Critical Care EXPLODE ALL TREES
5. #1 OR #2 OR #3 OR #4
6. MeSH DESCRIPTOR Clonidine EXPLODE ALL TREES
7. MeSH DESCRIPTOR D exmedetomidineEXPLODE ALL TREES
8. #6 OR #7
9. #5 AND #8

Clinical Trials.gov

URL: http://clinicaltrials.gov/ct/gui/c/r.

Date of search: 15 November 2014.

Search strategy

Interventions=Dexmedetomidine or Clonidine

International Clinical Trials Registry Platform

World Health Organization URL: www.who.int/ictrp/en/.

Date of search: 15 November 2014.

Search strategy

Intervention= Dexmedetomidine or Clonidine

Appendix 2 Full-text screening form

Sedation in intensive care: Full text screening form

Assessor initials:
Date:

Study ID (Surname of first author + year of publication)

Type of study

Q1. Is the study either:

- ☐ An RCT in which people are randomised to receive either dexmedetomidine or clonidine (as intervention and comparator) OR
- ☐ An RCT in which people are randomised to receive either dexmedetomidine or clonidine (as intervention) and propofol or benzodiazepines (as comparator)

Yes / Unclear → Go to next section; No → Exclude

Participants in the study

Q2. Are the participants all of the following:

- ☐ Adults AND
- ☐ In ICU AND
- ☐ Mechanically ventilated/require mechanical ventilation

Yes / Unclear → Go to next section; No → Exclude

Outcomes reported

Q3. Does the study report any of the following:

- ☐ Mortality
- ☐ Duration of mechanical ventilation
- ☐ Ventilator free days
- ☐ Length of ICU stay
- ☐ Adverse events (incl. rate of hypotension/hypertension/bradycardia/respiratory depression/delirium/coma/unplanned or accidental removal of lines or catheters)
- ☐ Unpleasant side effects (e.g. unpleasant memories, diarrhea, constipation)
- ☐ Duration of weaning
- ☐ Time in target sedation range
- ☐ Proportion of patients in target sedation range
- ☐ Discharge readiness
- ☐ Extubation readiness
- ☐ Length of hospital stay
- ☐ QoL
- ☐ Costs

Yes / Unclear → Go to next section; No → Exclude

Reasons for decision

Include **Unclear** **Exclude**

Appendix 3 List of included studies (including secondary publications)

Abdulatif 2004

Abdulatif M, Hamed HM, el-Borolossy K, Teima DO. A comparative study of the use of dexmedetomidine and propofol as sedatives for mechanically ventilated patients in ICU. *Egypt J Anaesthes* 2004;**20**:437–42.

Corbett 2005

Corbett SM, Rebuck JA, Greene CM, Callas PW, Neale BW, Healey MA, *et al.* Dexmedetomidine does not improve patient satisfaction when compared with propofol during mechanical ventilation. *Crit Care Med* 2005;**33**:940–5.

Elbaradie 2004

Elbaradie S, El Mahalawy FH, Solyman AH. Dexmedetomidine vs. propofol for short-term sedation of postoperative mechanically ventilated patients. *J Egypt Nat Cancer Inst* 2004;**16**:153–8.

Esmaoglu 2009

Esmaoglu A, Ulgey A, Akin A, Boyaci A. Comparison between dexmedetomidine and midazolam for sedation of eclampsia patients in the intensive care unit. *J Crit Care* 2009;**24**:551–5.

Herr 2003

Herr DL, Sum-Ping ST, England M. ICU sedation after coronary artery bypass graft surgery: dexmedetomidine-based versus propofol-based sedation regimens. *J Cardiothorac Vasc Anesthes* 2003;**17**:576–84.

Jakob 2012

Jakob SM, Ruokonen E, Grounds RM, Sarapohja T, Garratt C, Pocock SJ, *et al.* Dexmedetomidine vs midazolam or propofol for sedation during prolonged mechanical ventilation: two randomized controlled trials. *JAMA* 2012;**307**:1151–60.

MacLaren 2013

MacLaren R, Preslaski CR, Mueller SW, Kiser TH, Fish DN, Lavelle JC, *et al.* A randomized, double-blind pilot study of dexmedetomidine versus midazolam for intensive care unit sedation: patient recall of their experiences and short-term psychological outcomes. *J Intensive Care Med* 2013;**30**:167–75.

Maldonado 2009

Maldonado JR, Wysong A, van der Starre PJ, Block T, Miller C, Reitz BA. Dexmedetomidine and the reduction of postoperative delirium after cardiac surgery. *Psychosomatics* 2009;**50**:206–17.

Memis 2009

Memis D, Kargi M, Sut N. Effects of propofol and dexmedetomidine on indocyanine green elimination assessed with LIMON to patients with early septic shock: a pilot study. *J Crit Care* 2009;**24**:603–8.

Pandharipande 2007

Pandharipande PP, Pun BT, Herr DL, Maze M, Girard TD, Miller RR, *et al.* Effect of sedation with dexmedetomidine vs lorazepam on acute brain dysfunction in mechanically ventilated patients: the MENDS randomized controlled trial. *JAMA* 2007;**298**:2644–53.

Secondary reports

Pandharipande PP, Sanders RD, Girard TD, McGrane S, Thompson JL, Shintani AK, *et al.* Effect of dexmedetomidine versus lorazepam on outcome in patients with sepsis: an a priori-designed analysis of the MENDS randomized controlled trial. *Crit Care* 2010;**14**:R38.

Fine PG. Sedation in mechanically ventilated patients. *J Pain Palliat Care Pharmacother* 2008;**22**:15.

Riker 2009

Riker RR, Shehabi Y, Bokesch PM, Ceraso D, Wisemandle W, Koura F, *et al.* Dexmedetomidine vs midazolam for sedation of critically ill patients: a randomized trial. *JAMA* 2009;**301**:489–99.

Secondary reports

Lachaine J, Beauchemin C. Economic evaluation of dexmedetomidine relative to midazolam for sedation in the intensive care unit. *Can J Hosp Pharm* 2012;**65**:103–10.

Shehabi Y, Riker RR, Bokesch PM, Wisemandle W, Shintani A, Ely EW, *et al.* Delirium duration and mortality in lightly sedated, mechanically ventilated intensive care patients. *Crit Care Med* 2010;**38**:2311–18.

Riker R, Shehabi Y, Wisemandle W, Bokesch PM, Rocha MG, Bradt J. Dexmedetomidine improves outcomes for long term ICU sedation when compared to midazolam: the Sedcom study. *Chest* 2008;**134**:34003s.

Ruokonen 2009

Ruokonen E, Parviainen I, Jakob SM, Nunes S, Kaukonen M, Shepherd ST, *et al.* Dexmedetomidine versus propofol/midazolam for long-term sedation during mechanical ventilation. *Intensive Care Med* 2009;**35**:282–90.

Secondary report

Takala J, Nunes S, Parviainen I, Jakob S, Kaukonen M, Shepherd S. Comparison of dexmedetomidine with propofol/midazolam in sedation of long-stay intensive care patients: a prospective randomized, controlled, multicenter trial. *Crit Care* 2007;**11**:P423.

Shah 2014

Shah PN, Dongre V, Patil V, Pandya S, Mungantiwar A, Choulwar A. Comparison of post-operative ICU sedation between dexmedetomidine and propofol in Indian population. *Ind J Crit Care Med* 2014;**18**:291–6.

Shehabi 2013

Shehabi Y, Bellomo R, Reade MC, Bailey M, Bass F, Howe B, *et al.* Early goal-directed sedation versus standard sedation in mechanically ventilated critically ill patients: a pilot study. *Crit Care Med* 2013;**41**:1983–91.

Srivastava 2014

Srivastava U, Sarkar ME, Kumar A, Gupta A, Agarwal A, Singh TK, *et al.* Comparison of clonidine and dexmedetomidine for short-term sedation of intensive care unit patients. *Ind J Crit Care Med* 2014;**18**:431–6.

Tasdogan 2009

Tasdogan M, Memis D, Sut N, Yuksel M. Results of a pilot study on the effects of propofol and dexmedetomidine on inflammatory responses and intraabdominal pressure in severe sepsis. *J Clin Anesth* 2009;**21**:394–400.

Venn 2001

Venn RM, Grounds RM. Comparison between dexmedetomidine and propofol for sedation in the intensive care unit: patient and clinician perceptions. *Br J Anaesth* 2001;**87**:684–90.

Secondary report

Venn RM, Bryant A, Hall GM, Grounds RM. Effects of dexmedetomidine on adrenocortical function, and the cardiovascular, endocrine and inflammatory responses in post-operative patients needing sedation in the intensive care unit. *Br J Anaesth* 2001;**86**:650–6.

Appendix 4 Excluded studies grouped according to the rationale for exclusion

Study not a randomised controlled trial (*n* = 30)

Abd Aziz N, Chue MC, Yong CY, Hassan Y, Awaisu A, Hassan J, *et al.* Efficacy and safety of dexmedetomidine versus morphine in post-operative cardiac surgery patients. *Int J Clin Pharm* 2011;**33**:150–4.

Ahmed S, Murugan R. Dexmedetomidine use in the ICU: are we there yet? *Crit Care* 2013;**17**:320.

Akin S, Aribogan A, Arslan G. Dexmedetomidine as an adjunct to epidural analgesia after abdominal surgery in elderly intensive care patients: a prospective, double-blind, clinical trial. *Curr Ther Res Clin Exp* 2008;**69**:16–28.

Anger KE, Szumita PM, Baroletti SA, Labreche MJ, Fanikos J. Evaluation of dexmedetomidine versus propofol-based sedation therapy in mechanically ventilated cardiac surgery patients at a tertiary academic medical center. *Crit Pathway Cardiol* 2010;**9**:221–6.

Barletta JF, Miedema SL, Wiseman D, Heiser JC, McAllen KJ. Impact of dexmedetomidine on analgesic requirements in patients after cardiac surgery in a fast-track recovery room setting. *Pharmacotherapy* 2009;**29**:1427–32.

Bliesener B, Kleinschmidt S. [Incidence and duration of postoperative delirium after cardiac surgery: comparison between dexmedetomidine and morphine for postoperative sedation and analgesia.] *Anaesthesist* 2010;**59**:256–7.

Brar NK. Dexmedetomidine takes on propofol and midazolam. *Clin Pulm Med* 2012;**19**:237.

Cox CE, Govert JA. Assessing the comparative value of sedatives in the intensive care unit. *Crit Care Med* 2010;**38**:709–11.

Curtis JA, Hollinger MK, Jain HB. Propofol-based versus dexmedetomidine-based sedation in cardiac surgery patients. *J Cardiothorac Vasc Anesthes* 2013;**27**:1289–94.

Devabhakthuni S, Pajoumand M, Williams C, Kufera JA, Watson K, Stein DM. Evaluation of dexmedetomidine: safety and clinical outcomes in critically ill trauma patients. *J Trauma Injury Infect Crit Care* 2011;**71**:1164–71.

Devlin JW, Al-Qadheeb NS, Chi A, Roberts RJ, Qawi I, Garpestad E, *et al.* Efficacy and safety of early dexmedetomidine during noninvasive ventilation for patients with acute respiratory failure: a randomized, double-blind, placebo-controlled pilot study. *Chest* 2014;**145**:1204–12.

Kopel L, Carvalho RT, Araujo H-BN, Fagundes AA, Ribeiro M, Bastos J. Dexmedetomidine for sedation following cardiovascular surgery: a two different loading doses. *Crit Care* 2005;**9**:P120.

Liatsi D, Tsapas B, Pampori S, Tsagourias M, Pneumatikos I, Matamis D. Respiratory, metabolic and hemodynamic effects of clonidine in ventilated patients presenting with withdrawal syndrome. *Intens Care Med* 2009;**35**:275–81.

Martin E, Ramsay G, Mantz J, Sum-Ping ST. The role of the alpha2-adrenoceptor agonist dexmedetomidine in postsurgical sedation in the intensive care unit. *J Intens Care Med* 2003;**18**:29–41.

Mehta S, Burry L, Cook D, Fergusson D, Steinberg M, Granton J, *et al.* Daily sedation interruption in mechanically ventilated critically ill patients cared for with a sedation protocol: a randomized controlled trial. *JAMA* 2012;**308**:1985–92.

Moritz RD, Machado FO, Pinto EP, Cardoso GS, Nassar SM. [Evaluate the clonidine use for sedoanalgesia in intensive care unit patients under prolonged mechanical ventilation.] *Rev Brasil Terap Inten* 2008;**20**:24–30.

Nader ND, Li CM, Dosluoglu HH, Ignatowski TA, Spengler RN. Adjuvant therapy with intrathecal clonidine improves postoperative pain in patients undergoing coronary artery bypass graft. *Clin J Pain* 2009;**25**:101–6.

Nour El-Din BM. Clinical evaluation of dexmedetomidine following ultra-fast track off-pump coronary artery bypass grafting. *Egypt J Anaesthes* 2004;**20**:253–9.

Ozaki M, Takeda J, Tanaka K, Shiokawa Y, Nishi S, Matsuda K, *et al.* Safety and efficacy of dexmedetomidine for long-term sedation in critically ill patients. *J Anesthes* 2014;**28**:38–50.

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

Perez-Rada FJ, Franco-Calderon JL, Torres CM. Comparison of cerebral hemodynamic variables in hemorrhagic stroke using dexmedetomidine-propofol versus dexmedetomidine-midazolam. *Crit Care* 2009;**13**(Suppl. 1):P402.

Prause A, Wappler F, Scholz J, Bause H, Schulte am EJ. Respiratory depression under long-term sedation with sufentanil, midazolam and clonidine has no clinical significance. *Intens Care Med* 2000;**26**:1454–61.

Shehabi Y, Grant P, Wolfenden H, Hammond N, Bass F, Campbell M, *et al.* Prevalence of delirium with dexmedetomidine compared with morphine based therapy after cardiac surgery: a randomized controlled trial (DEXmedetomidine COmpared to Morphine – DEXCOM Study). *Anesthesiology* 2009;**111**:1075–84.

Shehabi Y, Chan L, Kadiman S, Alias A, Ismail WN, Tan MATI, *et al.* Sedation depth and long-term mortality in mechanically ventilated critically ill adults: a prospective longitudinal multicentre cohort study. *Intens Care Med* 2013;**39**:910–18.

Short J. Use of dexmedetomidine for primary sedation in a general intensive care unit. *Crit Care Nurse* 2010;**30**:29–38.

Spiegler P. It is time to wake up in the intensive care unit. *Clin Pulmon Med* 2008;**15**:232–3.

Tanaka LMS, Azevedo LCP, Park M, Schettino G, Nassar AP, Rea-Neto A, *et al.* Early sedation and clinical outcomes of mechanically ventilated patients: a prospective multicenter cohort study. *Crit Care* 2014;**18**:R156.

Triltsch AE, Welte M, von HP, Grosse J, Genahr A, Moshirzadeh M, *et al.* Bispectral index-guided sedation with dexmedetomidine in intensive care: a prospective, randomized, double blind, placebo-controlled phase II study. *Crit Care Med* 2002;**30**:1007–14.

Venn RM, Bradshaw CJ, Spencer R, Brealey D, Caudwell E, Naughton C, *et al.* Preliminary UK experience of dexmedetomidine, a novel agent for postoperative sedation in the intensive care unit. *Anaesthesia* 1999;**54**:1136–42.

Wajida G, Kelly JS. Sedation in the Intensive Care Setting. In Urman RD, Kaye AD, editors. *Moderate and Deep Sedation in Clinical Practice.* Cambridge: Cambridge University Press; 2012. pp. 218–29.

Participants outwith scope of review (*n* = 10)

Chen J, Zhou JQ, Chen ZF, Huang Y, Jiang H. Efficacy and safety of dexmedetomidine versus propofol for the sedation of tube-retention after oral maxillofacial surgery. *J Oral Maxillofacial Surg* 2014;**72**:285–7.

Coull JT, Jones ME, Egan TD, Frith CD, Maze M. Attentional effects of noradrenaline vary with arousal level: selective activation of thalamic pulvinar in humans. *Neuroimage* 2004;**22**:315–22.

Goodwin HE, Gill RS, Murakami PN, Thompson CB, Lewin JJ, III, Mirski MA. Dexmedetomidine preserves attention/calculation when used for cooperative and short-term intensive care unit sedation. *J Crit Care* 2013;**28**:1113.

Huang Z, Chen YS, Yang ZL, Liu JY. Dexmedetomidine versus midazolam for the sedation of patients with non-invasive ventilation failure. *Intern Med* 2012;**51**:2299–305.

Memis-D, Lu S, Vatan I, Yandim T, Yüksel M, Süt N. Effects of midazolam and dexmedetomidine on inflammatory responses and gastric intramucosal pH to sepsis, in critically ill patients. *Br J Anaesth* 2007;**98**:550–2.

Mirski MA, Lewin JJ, III, Ledroux S, Thompson C, Murakami P, Zink EK, *et al.* Cognitive improvement during continuous sedation in critically ill, awake and responsive patients: the Acute Neurological ICU Sedation Trial (ANIST). *Intens Care Med* 2010;**36**:1505–13.

Senoglu N, Oksuz H, Dogan Z, Yildiz H, Demirkiran H, Ekerbicer H. Sedation during noninvasive mechanical ventilation with dexmedetomidine or midazolam: a randomized, double-blind, prospective study. *Curr Ther Res Clin Exp* 2010;**71**:141–53.

Srivastava VK, Agrawal S, Kumar S, Mishra A, Sharma S, Kumar R. Comparison of dexmedetomidine, propofol and midazolam for short-term sedation in postoperatively mechanically ventilated neurosurgical patients. *J Clin Diag Res* 2014;**8**:GC04–7.

Terao Y, Ichinomiya T, Higashijima U, Tanise T, Miura K, Fukusaki M, *et al.* Comparison between propofol and dexmedetomidine in postoperative sedation after extensive cervical spine surgery. *J Anesth* 2012;**26**:179–86.

Yu T, Huang Y, Guo F, Yang Y, Teboul JL, Qiu H. The effects of propofol and dexmedetomidine infusion on fluid responsiveness in critically ill patients. *J Surg Res* 2013;**185**:763–73.

No relevant outcomes (*n* = 5)

Kadoi Y, Saito S, Kawauchi C, Hinohara H, Kunimoto F. Comparative effects of propofol vs dexmedetomidine on cerebrovascular carbon dioxide reactivity in patients with septic shock. *Br J Anaesth* 2008;**100**:224–9.

Memis D, Dokmeci D, Karamanlioglu B, Turan A, Ture M. A comparison of the effect on gastric emptying of propofol or dexmedetomidine in critically ill patients: preliminary study. *Eur J Anaesthesiol* 2006;**23**:700–4.

Pandharipande P, Girard TD, Sanders RD, Thompson JL. Comparison of sedation with dexmedetomidine versus lorazepam in septic ICU patients. *Crit Care* 2008;**12**(Suppl. 2):P275.

Sahin N, Kabukou H, Ozkan N, Tirtiz TA. The effects of postoperative dexmedetomidine and midazolam infusion on haemodynamics and sedation in patients after coronary artery bypass grafting. *Eur J Anaesthesiol* 2005;**22**(Suppl. 35):40.

Singh A, Ambike D, Thatte WS, Das B. Dexmedetomidine versus midazolam infusion for sedation in mechanically ventilated patients in critical care setting: A randomized controlled trial. *Indian J Crit Care Med* 2013;**17**(Suppl. 1):4.

Published as abstract only (*n* = 2)

Gupta R, Mehta Y, Ali T, Joby GV. A randomized controlled study to compare the efficacy and safety of prolonged sedation with dexmedetomidine vs midazolam for mechanically ventilated patients in the intensive care. *Intens Care Med* 2013;**39**.

Riker RR, Ramsay MA, Prielipp RC, Jorden V. Long-term dexmedetomidine for ICU sedation: a pilot study. *Anesthesiology* 2001;**95**.

Foreign-language article requiring translation (*n* = 11)

Aoki M, Nishimura Y, Baba H, Okawa Y. [Effects of dexmedetomidine hydrochloride on postoperative sedation in cardiovascular surgery.] *Kyobu Geka* 2006;**59**:1181–5.

Cerny V, Samek J, Cichy D. [Postoperative sedation with dexmedetomidine in patients after off pump coronary artery bypass.] *Anesteziol Inten Med* 2004;**15**:21–7.

Eremenko AA, Chernova EV. [Dexmedetomidine use for intravenous sedation and delirium treatment during early postoperative period in cardio-surgical patients.] *Anesteziol Reanimatol* 2013;**5**:4–8.

Eremenko AA, Chemova EV. [Comparison of dexmedetomidine and propofol for short-term sedation in early postoperative period after cardiac surgery.] *Anesteziol Reanimatol* 2014;**2**:37–41.

Fang S, Zhu Y, Xu H, Jiang H. [Dexmedetomidine for sedation during intubation period in postoperative patients receiving orthognathic surgery in intensive care unit.] *Zhongguo Xinyao Yu Linchuang Zazhi* 2012;**31**:454–7.

Iwasaki Y, Nakamura T, Hamakawa T. [Retrospective evaluation of dexmedetomidine for postoperative sedation in patients for cerebral aneurysm surgery.] *Masui* 2010;**59**:1396–9.

Kaneko T. [Postoperative management of carotid endarterectomy with dexmedetomidine – a comparison with propofol.] *Masui* 2008;**57**:696–703.

Karabulut S, Tuncel Z, Kudsioglu T, Coskun FI, Yapici N, Altuntas Y, *et al.* [Sedation and analgesia after cardiac surgery: comparison of dexmedetomidine, midazolam/fentanyl and midazolam/dexketoprofen trometamol.] *Gogus-Kalp-Damar Anestezi ve Yogun Bakim Dernegi Dergisi* 2014;**20**.

Moritz RD, Machado FO, Pinto EP, Cardoso GS, Nassar SM. [Evaluate the clonidine use for sedoanalgesia in intensive care unit patients under prolonged mechanical ventilation.] *Revista Brasi Terap Inten* 2008;**20**:24–30.

Wan LJ, Huang QQ, Yue JX, Lin L, Li SH. [Comparison of sedative effect of dexmedetomidine and midazolam for post-operative patients undergoing mechanical ventilation in surgical intensive care unit.] *Zhongguo Wei Zhong Bing Ji Jiu Yi Xue* 2011;**23**:543–6.

Yao L, Zhou XM, Zhao JJ. [The role of dexmedetomidine in treatment of serious patients in intensive care unit.] *Zhongguo Wei Zhong Bing Ji Jiu Yi Xue* 2010;**22**:632–4.

Unable to locate full text (*n* = 1)

Assad Farhat OM, Abdel-Raouf S, Hussien GZ, Labib D. Comparative study between the effects of dexmedetomidine versus propofol infusion on human neutrophil functions in cardiac surgical patients in ICU. *Egypt J Anaesth* 2010;**26**:113–22.

Appendix 5 Characteristics of included studies

TABLE 4 Characteristics of included studies

Study details	Participant characteristics	Intervention characteristics	Summary of outcomes
First author, year: Abdulatif, 2004[109] Secondary reports: none Language: English Publication type: full text Number of centres: NR Country: Egypt Start/end dates: NR Prospective/retrospective data collection: prospective Study design: randomised comparative study Randomisation method: NR Length of follow-up: 6 hours Source of funding: NR	Type of participants: patients had established respiratory failure requiring MV using pressure support ventilation with or without continuous positive airway pressure Enrolled: NR Randomised: • A: 20 • B: 20 Analysed: • A: 20 • B: 20 Age (years), mean (SD): • A: 43 (3.7) • B: 40 (5.2) Sex, *n* (%): • A: male 10 (50), female 8 (40), NR 2 (10) • B: male 9 (45), female 10 (50), NR 1 (5) Inclusion criteria: patients had established respiratory failure requiring MV using pressure support ventilation with or without continuous positive airway pressure Exclusion criteria: exclusion criteria included significant renal or hepatic dysfunction, cardiovascular instability, concurrent use of inotropes or vasoactive drugs, CNS or psychological disorders, use of muscle relaxants to facilitate ventilation, pregnancy or morbid obesity	ICU setting: NR Sedative agents: • A: dexmedetomidine • B: propofol Route/dose/frequency: • A: initial i.v. loading dose (1 µg/kg) over 10 minutes, followed by continuous i.v. infusion (5 µg/ml) at a rate of 0.5 µg/kg/hour (0.1 ml/kg/hour) to be increased to a maximum of 1 µg/kg/hour • B: i.v. infusion (10 mg/ml) starting with a dose of 1 mg/kg/hour (0.1 ml/hour) and increasing up to 2 mg/kg/hour Length of infusion of study drug: 6 hours Target sedation level: RSS score of 2 or 3 Rescue medication: 1-mg bolus of midazolam Pain control: NR Daily interruption: NR	Physiological parameters, clinical adverse respiratory effects

Study details	Participant characteristics	Intervention characteristics	Summary of outcomes
First author, year: Corbett, 2005[110] Secondary reports: none Language: English Publication type: full text Number of centres: 1 Country: USA Start/end dates: October 2002–April 2004 Prospective/retrospective data collection: prospective Study design: RCT Randomisation method: via a random-number table, occurred in the operating room before sternal closure, and the drug was initiated after bypass Length of follow-up: at least 24 hours after extubation	Type of participants: after non-emergent CABG surgery Enrolled: NR Randomised: NR Analysed: • A: 43 • B: 46 Age (years), mean (SD): • A: 63.5 (10.1) • B: 62.4 (10.7) Sex, *n* (%): • A: male, 35 (81); female, 8 (19) • B: male, 38 (83); female, 8 (17) Inclusion criteria: ≥ 18 years of age and requiring non-emergent CABG surgery with an expected MV length of 24 hours	ICU setting: NR Sedative agents: • A: dexmedetomidine • B: propofol Route/dose/frequency: • A: 1 µg/kg (actual body weight) loading dose intravenously administered over 15 minutes, followed by a 0.4 µg/kg/hour i.v. infusion • B: 5 µg/kg/minute i.v. infusion titrated within the range of 0.2–0.7 µg/kg/hour or 5–75 µg/kg/minute Length of infusion of study drug: • A: up to 1 hour post extubation • B: discontinued before extubation Target sedation level: RSS score of 5 for the first 2 hours post-operatively, followed by a score of 3 or 4 for the length of intubation	Patient satisfaction, length of MV and ICU stay, vital signs, adverse events

continued

TABLE 4 Characteristics of included studies (*continued*)

Study details	Participant characteristics	Intervention characteristics	Summary of outcomes
Source of funding: NR	Exclusion criteria: 1. inability to obtain informed consent 2. documented hypersensitivity to either drug or any component of the drugs 3. severe hypotension, defined as systolic blood pressure of 90 mmHg immediately before initiation of study drug 4. heart rate of 40 beats per minute immediately before initiation of the study drug 5. renal insufficiency, defined as a creatinine clearance of 30 ml/minute per Cockcroft–Gault 6. hepatic dysfunction, defined as liver function tests greater than four times the upper limit of normal (alanine transaminase of 288 units/l or aspartate transaminase of 184 units/l) 7. requirement for continued neuromuscular blocking agents post operatively 8. requirement for epidural or spinal anaesthesia 9. gross obesity defined as 100% over ideal body weight 10. known history of alcohol or drug abuse 11. any neurological impairment or recent severe central nervous system trauma that could potentially alter the patient's ability to reasonably complete a post-operative questionnaire	Rescue medication: midazolam was allowed for breakthrough anxiety, administered at 1–2 mg every hour in the propofol arm and every 2 hours in the dexmedetomidine arm Pain control: morphine was available as needed for pain every hour in a 1- to 4-mg dose for propofol patients and in a 1- to 2-mg dose for dexmedetomidine patients Daily interruption: NR	

Study details	Participant characteristics	Intervention characteristics	Summary of outcomes
First author, year: Elbaradie, 2004[111] Secondary reports: none Language: English Publication type: full text Number of centres: 1 Country: Egypt Start/end dates: NR Prospective/retrospective data collection: prospective Study design: randomised controlled, patient-blinded study Randomisation method: at the end of surgery, patients were selected randomly using a toss into two equal group Length of follow-up: NR Source of funding: NR	Type of participants: after major thoracic, abdominal or pelvic cancer surgeries Enrolled: NR Randomised: 30 Analysed: NR Age (years), mean (SD): • A: 65 (6.5) • B: 67 (5.7) Sex, *n* (%): NR Inclusion criteria: adult patients who were expected to require a minimum of 6-hour post-operative sedation and ventilation after major thoracic, abdominal or pelvic cancer surgeries Exclusion criteria: neurosurgical procedures, known allergy to propofol or dexmedetomidine, known or suspected pregnancy, gross obesity (over 50% above ideal bodyweight), severe hepatic or renal disease where the neurological condition was difficult to evaluate, spinal or epidural anaesthesia, history of corticosteroid therapy within the last 3 months, or uncontrolled diabetes	ICU setting: surgical ICU Sedative agents: • A: dexmedetomidine • B: propofol Route/dose/frequency: • A: loading infusion dose of dexmedetomidine 2.5 µg/kg/hour over 10 minutes followed by maintenance infusion at a rate of 0.2–0.5 µg/kg/hour into a peripheral vein, with the dosage adjusted to achieve the desired level of sedation • B: undiluted as a bolus dose of 1 mg/kg initially, followed by an infusion of 0.5–1 mg/kg/hour, with the dosage adjusted to achieve the desired level of sedation Length of infusion of study drug: discontinued in preparation for extubation Target sedation level: recorded hourly using the RSS score and continuously using the bispectral index. Three levels of sedation were considered: adequate (sedation level was grade 2, 3, 4 or 5), insufficient (sedation level was 1) and excessive (sedation level was grade 6) Rescue medication: the dose of both drugs was adjusted by varying the dose by 10% increase or decrease in infusion rate in order to maintain the level of sedation within the range previously considered adequate Pain control: all patients received short-acting fentanyl infusion 0.25–0.5 µg/kg/hour Daily interruption: NR	Sedation, time in adequate sedation under ventilator, extubation times, blood pressure, heart rates, serum levels of cortisol and IL-6, respiratory adverse events

continued

TABLE 4 Characteristics of included studies (*continued*)

Study details	Participant characteristics	Intervention characteristics	Summary of outcomes
First author, year: Esmaoglu, 2009[112] Secondary reports: none Language: English Publication type: full text Number of centres: 1 Country: Turkey Start/end dates: NR Prospective/retrospective data collection: prospective Study design: RCT Randomisation method: patients were randomly divided into two groups using coin toss Length of follow-up: NR Source of funding: NR	Type of participants: patients whose pregnancies were terminated via caesarean delivery because of eclampsia Enrolled: NR Randomised: • A: 20 • B: 20 Analysed: • A: 20 • B: 20 Age (years), mean (SD): • A: 25.1 (4.8) • B: 26.8 (7.1) Sex, *n* (%): • A: female, 20 (100) • B: female, 20 (100) Inclusion criteria: patients whose pregnancies were terminated via caesarean delivery because of eclampsia and who needed ventilatory support Exclusion criteria: chronic hypertension; cardiac, neurological, hepatic, renal, or endocrinal disease; or allergic reactions to the medicine used during the treatment or developed haemolysis, elevated liver enzymes and platelets	ICU setting: NR Sedative agents: • A: dexmedetomidine • B: midazolam Route/dose/frequency: A: loading dose administered at 1 µg/kg per 20 minutes, followed by a continuous infusion at 0.7 µg/kg/hour B: loading dose of 100 mg in 100 ml 0.9% NaCl at 0.05 mg/kg and continued at 0.1 mg/kg/hour Length of infusion of study drug: NR Target sedation level: RSS score 2 or 3 criteria Rescue medication: propofol was given as a bolus (0.5 mg/kg) in both groups Pain control: fentanyl was administered in the dose of 1 µg/kg Daily interruption: NR	Patients requiring antihypertensive, arterial pressure, ICU length of stay

Study details	Participant characteristics	Intervention characteristics	Summary of outcomes
First author, year: Herr, 2003[114] Secondary reports: none Language: English Publication type: full text Number of centres: 25 Country: USA, Canada Start/end dates: NR Prospective/retrospective data collection: prospective Study design: multicentre, open-label, randomised study	Type of participants: after CABG surgery Enrolled: NR Randomised: NR Analysed: • A: 148 • B: 147 Age (years), mean (SD): • A: 61.9 (9.5) • B: 62.4 (8.7) Sex, *n* (%): • A: male, 137 (93); female, 11 (7%) • B: male, 128 (87); female, 19 (13) Inclusion criteria: adults who were scheduled for CABG surgery	ICU setting: NR Sedative agents: • A: dexmedetomidine • B: propofol Route/dose/frequency: • A: 1.0 µg/kg dexmedetomidine over 20 minutes as the loading dose, followed by a maintenance infusion of 0.4 µg/kg/hour. After transfer to the ICU, the infusion rate was titrated in the range of 0.2–0.7 µg/kg/hour as necessary to maintain a RSS score of ≥ 3 before extubation, ≥ 2 after extubation • B: no dose or rate of propofol was specified by the protocol. Investigators were told to follow their usual practice with regard to propofol-based sedation Length of infusion of study drug: 24 hours	Efficacy of sedation of dexmedetomidine compared with propofol-based ICU sedation, total dose of morphine administered for pain by time period; time to weaning; time to extubation, adverse events

continued

TABLE 4 Characteristics of included studies (*continued*)

Study details	Participant characteristics	Intervention characteristics	Summary of outcomes
Randomisation method: randomised before surgery by sealed envelopes provided by the statistician. Investigators did not know the randomisation block size Length of follow-up: 24 hours after discharge from ICU Source of funding: NR	Exclusion criteria: women who were pregnant or lactating; patients whose neurological condition or responses could be difficult to evaluate; patients who had unstable or uncontrolled diabetes, were grossly obese, had an ejection fraction of 30% or were hospitalised for a drug overdose	Target sedation level: • A: RSS score of ≥ 3 before extubation, score of ≥ 2 after extubation • B: not specified. Investigators were told to follow their usual practice with regard to propofol-based sedation Rescue medication: • A: patients who received dexmedetomidine could be given propofol if the investigator believed that they should be more heavily sedated and the infusion rate was already at the recommended maximum of 0.7 µg/kg/hour • B: not specified. Investigators were told to follow their usual practice with regard to propofol-based sedation Pain control: only morphine or non-steroidal anti-inflammatory drugs were allowed for pain relief in both groups Daily interruption: NR	

Study details	Participant characteristics	Intervention characteristics	Summary of outcomes
First author, year: Jakob, 2012; MIDEX[70] Secondary reports: none Language: English Publication type: full text Number of centres: 44 Country: nine European countries Start/end dates: 2007–10 Prospective/retrospective data collection: prospective Study design: Phase 3 multicentre, randomised, double-blind trial Randomisation method: by central interactive voice response system funded by the sponsor and stratified for study centre in blocks of four Length of follow-up: 45 days Source of funding: Orion Pharma, Espoo, Finland	Type of participants: general ICU Enrolled: NR Randomised: • A: 249 • B: 252 Analysed: • A: 249 • B: 251 Age (years), median (IQR): • A: 65 (55–74) • B: 65 (55–74) Sex, *n* (%): • A: male, 153 (61); female, 96 (39) • B: male, 175 (70); female, 76 (30) Inclusion criteria: age ≥ 18 years, invasive MV, clinical need for light to moderate sedation using midazolam or propofol infusion expected to last for 24 hours or longer after randomisation, and randomisation within 72 hours of ICU admission and within 48 hours of starting continuous sedation Exclusion criteria: acute severe neurological disorder, mean arterial pressure < 55 mmHg despite appropriate i.v. volume replacement and vasopressors, heart rate < 50 beats per minute, atrioventricular conduction grade II or III (unless pacemaker installed) and use of alpha-2 agonists or antagonists within 24 hours prior to randomisation	ICU setting: NR Sedative agents: • A: dexmedetomidine • B: midazolam Route/dose/frequency: six dose levels of each study drug covered the full dose range (dexmedetomidine 0.2–1.4 µg/kg per hour; midazolam, 0.03–0.2 mg/kg per hour). Study treatments were infused without loading dose at a dose matching the prerandomisation dose of midazolam for 1 hour. Thereafter, study drugs were titrated by the patient's nurse stepwise to maintain the target RASS score Length of infusion of study drug: maximum 14 days from randomisation Target sedation level: target RASS score was determined before starting study treatment and at daily sedation stops. Assessment of RASS score was performed every 2 hours and prior to any dose of rescue therapy Rescue medication: propofol Pain control: fentanyl boluses Daily interruption: need for re-sedation and continued ventilation was assessed after a daily sedation stop and spontaneous breathing trial	Proportion of time in the target sedation range (RASS score 0 to –3) without use of rescue therapy of the total duration of study drug infusion; duration of MV from randomisation until free from MV (including non-invasive) without reinstitution for the following 48 hours; length of ICU stay from randomisation until medically fit for discharge; nurses' assessment of arousal, ability to co-operate with care and ability to communicate pain using VAS; adverse events and serious adverse events with incidence of > 2% in any treatment group

continued

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TABLE 4 Characteristics of included studies (*continued*)

Study details	Participant characteristics	Intervention characteristics	Summary of outcomes
First author, year: Jakob, 2012; PRODEX[70] Secondary reports: none Language: English Publication type: full text Number of centres: 33 Country: six European countries and Russia Start/end dates: 2007–10 Prospective/retrospective data collection: prospective Study design: Phase 3 multicentre, randomised, double-blind trial Randomisation method: by central interactive voice response system funded by the sponsor and stratified for study centre in blocks of four Length of follow-up: 45 days Source of funding: Orion Pharma, Espoo, Finland	Type of participants: general ICU Enrolled: NR Randomised: • A: 251 • B: 249 Analysed: • A: 251 • B: 247 Age (years), median (IQR): • A: 65 (51–75) • B: 65 (51–74) Sex, *n* (%): • A: male, 160 (64); female, 91 (36) • B: male, 166 (67); female, 81 (33) Inclusion criteria: ≥ 18 years, invasive MV, clinical need for light to moderate sedation using midazolam or propofol infusion expected to last for 24 hours or longer after randomisation, and randomisation within 72 hours of ICU admission and within 48 hours of starting continuous sedation Exclusion criteria: acute severe neurological disorder, mean arterial pressure < 55 mmHg despite appropriate i.v. volume replacement and vasopressors, heart rate < 50 beats per minute, atrioventricular-conduction grade II or III (unless pacemaker installed), and use of alpha-2 agonists or antagonists within 24 hours prior to randomisation	ICU setting: NR Sedative agents: • A: dexmedetomidine • B: propofol Route/dose/frequency: six dose levels of each study drug covered the full dose range (dexmedetomidine 0.2–1.4 µg/kg/hour; propofol 0.3–4.0 mg/kg/hour). Study treatments were infused without loading dose at a dose matching the prerandomisation dose of propofol for 1 hour. Thereafter, study drugs were titrated by the patient's nurse stepwise to maintain the target RASS score Length of infusion of study drug: maximum 14 days from randomisation Target sedation level: target RASS score was determined before starting study treatment and at daily sedation stops. Assessment of RASS score was performed every 2 hours and prior to any dose of rescue therapy Rescue medication: midazolam Pain control: fentanyl boluses Daily interruption: need for resedation and continued ventilation was assessed after a daily sedation stop and spontaneous breathing trial	Proportion of time in the target sedation range (RASS score 0 to –3) without use of rescue therapy of the total duration of study drug infusion; duration of MV from randomisation until free from MV (including non-invasive) without reinstitution for the following 48 hours; length of ICU stay from randomisation until medically fit for discharge; nurses' assessment of arousal, ability to co-operate with care and ability to communicate pain using VAS; adverse events and serious adverse events with incidence > 2% in any treatment group

Study details	Participant characteristics	Intervention characteristics	Summary of outcomes
First author, year: MacLaren, 2013[116] Secondary reports: none Language: English Publication type: full text Number of centres: 1 Country: USA Start/end dates: September 2009–May 2012 Prospective/retrospective data collection: prospective Study design: prospective, randomised, double-blind pilot study Randomisation method: within 24 hours of qualifying for daily awakenings, patients were randomised by a computer-generated random numbers table Length of follow-up: at least 72 hours after extubation or tracheostomy but before hospital discharge	Type of participants: medical or surgical ICU patients Enrolled: NR Randomised: • A: 11 • B: 12 Analysed: • A: 11 • B: 12 Age (years), mean (SD): • A: 58.3 (15.3) • B: 57.8 (9.3) Sex, *n* (%): • A: male, 6 (55); female, 5 (45) • B: male, 7 (58); female, 5 (42) Inclusion criteria: critically ill patients requiring MV and receiving a benzodiazepine infusion with an anticipated need of at least 12 additional hours of sedation at a Riker SAS score of 3 or 4 were recruited once they qualified for daily awakenings	ICU setting: medical and surgical ICUs Sedative agents: • A: dexmedetomidine • B: midazolam Route/dose/frequency: • A: dexmedetomidine was started at 0.15 µg/kg/hour and adjusted by 0.15 µg/kg/hour to a maximum of 1.5 µg/kg/hour • B: midazolam was started at 1 mg/hour and adjusted by 1 mg/hour to a maximum of 10 mg/hour. All infusions were adjusted by increments of 2 ml/hour to maintain blinding Length of infusion of study drug: at least 12 hours Target sedation level: Riker SAS score 3 or 4 Rescue medication: open-label midazolam Pain control: open-label fentanyl	Post-ICU anxiety, depression and acute stress disorder manifestations; recall, anxiety, depression and acute stress disorder; successful ventilator liberation (i.e. at least 72 hours of tracheal extubation); hourly and cumulative doses of conventional sedatives and analgesics; percentage of Riker scores at various sedation levels; percentage of PABS scores indicating minimal pain (≤ 3); delirium during each 12-hour nursing shift; ICU and hospital lengths of stay; hypotension, bradycardia, or tachycardia

continued

TABLE 4 Characteristics of included studies (*continued*)

Study details	Participant characteristics	Intervention characteristics	Summary of outcomes
Source of funding: Hospira	Exclusion criteria: aged < 18 years or > 85 years; administration of benzodiazepines for purposes other than sedation (e.g. seizure control); administration of neuromuscular blockers for > 12 hours; administration of epidural medications; active myocardial ischaemia; second- or third-degree heart block; haemodynamic instability; active neuromuscular disease; Child–Pugh class C liver disease; alcohol abuse within 6 months of study eligibility; baseline dementia; solid organ transplant; pregnancy; moribund state with planned withdrawal of life support; enrolment in another therapeutic study; or known or suspected severe adverse reactions to any benzodiazepines, dexmedetomidine, or clonidine	Daily interruption: daily awakenings performed when the following conditions met: patient haemodynamically stable, patient not receiving neuromuscular blockade, and patient on 70% for fraction of inspired oxygen and 14 cmH_2O for positive end-expiratory pressure	

Study details	Participant characteristics	Intervention characteristics	Summary of outcomes
First author, year: Maldonado, 2009[72] Secondary reports: none Language: English Publication type: full text Number of centres: 1 Country: USA Start/end dates: NR Prospective/retrospective data collection: prospective Study design: open-label RCT Randomisation method: randomisation was performed the evening before surgery by random drawing Length of follow-up: 3 days post-operatively	Type of participants: following cardiac valve surgery Enrolled: 179 eligible Randomised: • A: 40 • B: 38 • C: 40 Analysed: • A: 30 • B: 30 • C: 30 Age (years), mean (SD): • A: 55 (16) • B: 58 (18) • C: 60 (16) Sex, *n* (%): • A: male, 26 (65); female, 14 (35) • B: male, 22 (58); female, 16 (42) • C: male, 27 (68); female, 13 (32)	ICU setting: NR Sedative agents: • A: dexmedetomidine • B: propofol • C: midazolam Route/dose/frequency: • A: loading dose: 0.4 µg/kg, followed by a maintenance drip of 0.2–0.7 µg/kg/hour • B: propofol drip (25–50 µg/kg/minute) • C: midazolam drip (0.5–2 mg/hour) Length of infusion of study drug: patients were weaned off propofol or midazolam infusions before extubation, whereas patients receiving dexmedetomidine were extubated while still on the medication and were kept on the maintenance infusion as deemed clinically necessary for a maximum of 24 hours Target sedation level: RSS score of 3 before extubation and of 2 after extubation	Proportion of patients in each treatment group who received a diagnosis of post-operative delirium, length of stay in ICU, length of stay in hospital, use of post-operative rescue medications, delirium

continued

TABLE 4 Characteristics of included studies (*continued*)

Study details	Participant characteristics	Intervention characteristics	Summary of outcomes
Source of funding: NR	Inclusion criteria: all patients meeting inclusion and exclusion criteria admitted to a large, tertiary-care university medical centre scheduled for elective cardiac valve operations were eligible for this prospective, randomised clinical trial Exclusion criteria: pre-existing diagnosis of dementia or schizophrenia, the preoperative use of psychotropic medications, active or recent substance abuse or dependence, aged less than 18 years or older than 90 years, documented stroke within the last 6 months, evidence of advanced heart block, pregnancy or anticipated intraoperative deep hypothermic circulatory arrest	Rescue medication: for additional sedation while intubated, patients received increased doses of the drug they had been randomly assigned to Pain control: fentanyl 25–50 µg every hour as needed for pain was the only opiate used in the first 24 hours; ketorolac, hydrocodone and oxycodone were allowed for pain management after the first 24 hours Daily interruption: NR	

Study details	Participant characteristics	Intervention characteristics	Summary of outcomes
First author, year: Memis, 2009[117] Secondary reports: none Language: English Publication type: full text Number of centres: 1 Country: Turkey Start/end dates: NR Prospective/retrospective data collection: prospective Study design: RCT (pilot) Randomisation method: an independent nurse prepared sealed envelopes from a computer-generated table before the study started Length of follow-up: NR Source of funding: NR	Type of participants: all patients fulfilled clinical and laboratory criteria of septic shock Enrolled: NR Randomised: • A: 20 • B: 20 Analysed: • A: 20 • B: 20 Age (years), mean (range): • A: 60 (31–80) • B: 54 (25–78) Sex, *n* (%): • A: male, 14 (70); female, 6 (30) • B: male, 13 (65); female, 7 (35) Inclusion criteria: all patients fulfilled clinical and laboratory criteria of septic shock Exclusion criteria: known allergy to propofol or dexmedetomidine, patients with known or suspected brain death, unstable haemoglobin levels (change in haemoglobin level of > 0.5 g/dl), significant arrhythmias, acute myocardial ischaemia (continuous ST segment analysis), patients requiring continuous renal replacement therapy, pregnancy and aged < 18 years	ICU setting: NR Sedative agents: • A: dexmedetomidine • B: propofol Route/dose/frequency: • A: loading dose at 1 µg/kg over 10 minutes, followed by a maintenance dose of 0.2–2.5 µg/kg per hour into a peripheral or central vein over a 24-hour infusion • B: loading dose of 1 mg/kg over 15 minutes, followed by a maintenance of 1 to 3 mg/kg per hour over a 24-hour infusion Length of infusion of study drug: 24 hours Target sedation level: RSS score of below 2 Rescue medication: NR Pain control: alfentanil was infused at 0.25–1.0 µg/kg/minute Daily interruption: NR	Indocyanine green plasma disappearance rate, mortality, haemodynamic parameters, adverse events

continued

TABLE 4 Characteristics of included studies (*continued*)

Study details	Participant characteristics	Intervention characteristics	Summary of outcomes
First author, year: Pandharipande, 2007[102] Secondary reports: Fine, 2008;[113] and Pandharipande, 2010[118] Language: English Publication type: full text Number of centres: 2 Country: USA Start/end dates: August 2004–April 2006 Prospective/retrospective data collection: prospective Study design: double-blind RCT Randomisation method: participants were randomised using computer-generated, permuted block randomisation (known only to investigational pharmacists) and stratified by site Length of follow-up: until discharge from hospital or death, and survivors were observed for vital status until 1 year after enrolment Source of funding: Hospira	Type of participants: medical and surgical ICU patients Enrolled: NR Randomised: • A: 54 • B: 52 Analysed: • A: 52 • B: 51 Age (years), median (IQR): • A: 60 (49–65) • B: 59 (45–67) Sex, *n* (%): • A: male, 30 (58); female, 22 (42) • B: male, 23 (45); female, 28 (55) Inclusion criteria: adult medical and surgical ICU patients requiring MV for longer than 24 hours Exclusion criteria: neurological disease that would confound the diagnosis of delirium, active seizures, Child–Pugh class B or C liver disease, moribund state with planned withdrawal of life support, family or physician refusal, alcohol abuse, active myocardial ischaemia, second- or third-degree heart block, severe dementia, benzodiazepine dependency, pregnancy or lactation, and severe hearing disabilities or inability to understand English to allow delirium evaluations	ICU setting: medical and surgical ICUs Sedative agents: • A: dexmedetomidine • B: lorazepam Route/dose/frequency: the study drug infusion was started at 1 ml/hour (0.15 µg/kg/hour dexmedetomidine or 1 mg/hour lorazepam) and titrated by the bedside nurse to a maximum of 10 ml/hour (1.5 µg/kg/hour dexmedetomidine or 10 mg/hour lorazepam) Length of infusion of study drug: maximum 120 hours Target sedation level: sedation level was assessed using the RASS. Both the physician goal RASS scores and the nurse goal RASS scores were recorded twice daily at the time of the study assessments. No specific RASS score were reported Rescue medication: if 10 ml/hour of the study drug did not result in adequate sedation or if patients required frequent intermittent doses of fentanyl for pain, a continuous infusion of fentanyl was permitted. If a patient experienced sudden and urgent levels of agitation that had the potential to cause harm to the patient or staff, a propofol bolus of 25–50 mg was allowed, while the study drug or fentanyl infusions were titrated upwards Pain control: intermittent doses of fentanyl Daily interruption: the decision to perform daily cessation of sedatives and spontaneous breathing trials was considered part of the managing teams' protocol and not mandated as part of the study protocol	Delirium-free and coma-free days, efficacy of the two sedation regimens in achieving clinically individualised target sedation goals, lengths of stay with ventilation, in the ICU, and in the hospital, along with neuropsychological testing after ICU discharge, 28-day mortality and 12-month survival from enrolment

Study details	Participant characteristics	Intervention characteristics	Summary of outcomes
First author, year: Riker, 2009[71] Secondary reports: Riker, 2008;[119] Shehabi, 2010;[52] and Lachaine, 2012[115] Language: English Publication type: full text Number of centres: 68 Country: Argentina, Australia, Brazil, the USA and New Zealand Start/end dates: March 2005–August 2007 Prospective/retrospective data collection: prospective Study design: double-blind RCT Randomisation method: central randomisation using an interactive voice-response system and computer-generated schedule Length of follow-up: 48 hours after cessation of study drug	Type of participants: general ICU Enrolled: • A + B: 420 Randomised: • A: 250 • B: 125 Analysed: • A: 244 • B: 122 Age (years), mean (SD): • A: 61.5 (14.8) • B: 62.9 (62.8) Sex, *n* (%): • A: male, 125 (51); female, 119 (49) • B: male, 57 (47); female, 65 (53) Inclusion criteria: aged ≥ 18 years, intubated and mechanically ventilated for < 96 hours prior to start of study drug, and an anticipated ventilation and sedation duration of ≥ 3 days	ICU setting: NR Sedative agents: • A: dexmedetomidine • B: midazolam Route/dose/frequency: 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/hour for dexmedetomidine and 0.06 mg/kg/hour for midazolam, corresponding to the mid-point of the allowable infusion dose range Length of infusion of study drug: until extubation or to a maximum of 30 days Target sedation level: RASS score target range of −2 to 1	Percentage of time within the target sedation range (RASS score −2 to 1) during the double-blind treatment period, prevalence and duration of delirium, use of fentanyl and open-label midazolam, nursing shift assessments, adverse events

continued

TABLE 4 Characteristics of included studies (*continued*)

Study details	Participant characteristics	Intervention characteristics	Summary of outcomes
Source of funding: Hospira	Exclusion criteria: trauma or burns as admitting diagnoses, dialysis of all types, pregnancy or lactation, neuromuscular blockade other than for intubation, epidural or spinal analgesia, general anaesthesia 24 hours prior to or planned after the start of study drug infusion, serious central nervous system pathology (acute stroke, uncontrolled seizures, severe dementia), acute hepatitis or severe liver disease (Child–Pugh class C), unstable angina or acute myocardial infarction, left ventricular ejection fraction < 30%, heart rate < 50 beats per minute, second- or third-degree heart block, or systolic blood pressure < 90 mmHg despite continuous infusions of two vasopressors before the start of study drug infusion	Rescue medication: patients in either group not adequately sedated by study drug titration could receive open-label midazolam bolus doses of 0.01–0.05 mg/kg at 10- to 15-minute intervals until adequate sedation (RASS score of range −2 to 1) was achieved with a maximum dose of 4 mg in 8 hours Pain control: fentanyl bolus doses (0.5–1.0 µg/kg) could be administered as needed every 15 minutes Daily interruption: a daily arousal assessment was performed throughout the treatment period, during which patients within the RASS score range of −2 to 1 were asked to perform four tasks. Patients were considered awake with successful completion of the assessment when they could perform three of four tasks. If the patient's RASS score was > 1 at the time of a scheduled assessment, study medication was titrated until a RASS score of −2 to 1 was achieved and then the arousal assessment was performed. If patients were oversedated to a RASS value of −3 to −5, study drug was interrupted until a RASS score of −2 to 0 was achieved and then the arousal assessment was performed	

Study details	Participant characteristics	Intervention characteristics	Summary of outcomes
First author, year: Ruokonen, 2009[69] Secondary reports: Takala, 2007[125] Language: English Publication type: full text Number of centres: 2 Country: Finland and Switzerland Start/end dates: NR Prospective/retrospective data collection: prospective Study design: multicentre, prospective, randomised, double-blind, double dummy, active comparator study Randomisation method: NR Length of follow-up: 45 days Source of funding: Orion Pharma, Helsinki, Finland	Type of participants: general ICU Enrolled: • A + B + C: 95 Randomised: • A: 41 • B: 28 • C: 16 Analysed: • A: 41 • B: 28 • C: 16 Age (years), median (range): • A: 64 (18–83) • B + C: 68 (18–83) Sex, *n* (%): • A: male, 32 (78); female, 9 (22) • B + C: male, 39 (86); female, 6 (14) Inclusion criteria: aged ≥ 18 years, MV, need for sedation for ≥ 24 hours after randomisation and an expected ICU stay ≥ 48 hours	ICU setting: NR Sedative agents: • A: dexmedetomidine • B: propofol • C: midazolam Route/dose/frequency: • A: dexmedetomidine was infused without a loading dose at 0.8 µg/kg/hour for 1 hour and then adjusted stepwise at 0.25, 0.5, 0.8, 1.1 and 1.4 µg/kg/hour • B: propofol was infused at 2.4 mg/kg/hour for 1 hour and then adjusted stepwise at 0.8, 1.6, 2.4, 3.2 and 4.0 mg/kg/hour • C: depending on standard care at time of randomisation, midazolam was given either as i.v. boluses (1–2 mg), starting at three boluses per hour for 1 hour and thereafter one to four boluses per hour, and if not sufficient as continuous infusion of 0.2 mg/kg/hour, or as a continuous infusion at 0.12 mg/kg/hour for 1 hour, followed by adjustments at 0.04, 0.08, 0.12, 0.16 and 0.20 mg/kg/hour. The initial dose could be reduced, if considered necessary by the treating clinician Length of infusion of study drug: maximum 14 days	Time at target sedation, length of ICU stay, probability of remaining on MV, adverse events

continued

TABLE 4 Characteristics of included studies (*continued*)

Study details	Participant characteristics	Intervention characteristics	Summary of outcomes
	Exclusion criteria: acute severe neurological disorder, mean arterial pressure < 55 mmHg despite volume and vasopressors, heart rate < 50 beats per minute; atrioventricular conduction block II or III (unless pacemaker installed), hepatic Sequential Organ Failure Assessment score > 2, bilirubin > 101 µmol/l, lactation or positive pregnancy test, muscle relaxation, loss of hearing or vision, any other condition interfering with RASS assessment, use of alpha-2 agonists or antagonists at the time of randomisation	Target sedation level: RASS score of 0 to –3 or RASS score of –4 Rescue medication: first-line rescue propofol for patients receiving midazolam, midazolam for those receiving propofol before randomisation; further rescue medication decided by clinician in charge Pain control: fentanyl boluses Daily interruption: need for sedation was assessed at a daily sedation stop (used routinely in all centres before the study) conducted at the same time each day. The first sedation stop was 12–36 hours after randomisation, depending on the time of randomisation	

Study details	Participant characteristics	Intervention characteristics	Summary of outcomes
First author, year: Shah, 2014[120] Secondary reports: none Language: English Publication type: full text Number of centres: 1 Country: India Start/end dates: NR Prospective/retrospective data collection: prospective Study design: phase III, prospective, open, randomised, comparative Randomisation method: NR Length of follow-up: 24 hours Source of funding: Macleods Pharmaceuticals Ltd	Type of participants: surgical patients Enrolled: NR Randomised: • A: 15 • B: 15 Analysed: • A: 15 • B: 15 Age (years), mean (SD): • A: 49.5 (14.15) • B: 49.09 (17.17) Sex, *n* (%): • A: male, 6 (40); female, 9 (60) • B: male, 10 (67); female, 5 (33) Inclusion criteria: patients undergoing surgery on an inpatient basis, required the post-operative MV or post-operative sedation, aged 18–70 years of both gender and willing to give consent Exclusion criteria: patients currently being treated or were treated within the last 30 days with alpha-2 agonist and blockers, with central nervous system, cardiovascular system, liver, renal problems, history of obstructive sleep apnoea, pregnant or lactating females, in whom propofol would be given for anaesthesia	ICU setting: NR Sedative agents: • A: dexmedetomidine • B: propofol Route/dose/frequency: • A: dexmedetomidine was administrated by a loading dose of injection with 1 µg/kg over 10 minutes, followed by a maintenance infusion of 0.2–0.7 µg/kg/hour. The rate of the maintenance infusion was adjusted to achieve the desired level of sedation • B: propofol was started at 5 µg/kg/minutes (0.3 mg/kg/hour). The infusion rate was increased by increments of 5–10 µg/kg/minutes (0.3–0.6 mg/kg/hour) until the desired level of sedation was achieved. A minimum period of 5 minutes between adjustments was allowed for the onset of peak drug effect Length of infusion of study drug: 8–24 hours Target sedation level: RSS score of 2 or 3 Rescue medication: NR Pain control: if VAS score of > 4, analgesia (fentanyl) was given Daily interruption: NR	Cardio respiratory parameters, laboratory parameters, adverse events

continued

TABLE 4 Characteristics of included studies (*continued*)

Study details	Participant characteristics	Intervention characteristics	Summary of outcomes
First author, year: Shehabi, 2013[121] Secondary reports: none Language: English Publication type: full text Number of centres: 6 Country: Australia and New Zealand Start/end dates: July 2011–December 2011 Prospective/retrospective data collection: prospective Study design: pilot prospective, multicentre, RCT Randomisation method: block randomisation was undertaken with concealed envelopes Length of follow-up: 90 days after randomisation Source of funding: Hospira	Type of participants: medical, operative elective and operative emergency Enrolled: 154 Randomised: • A: 16 • B: 21 Analysed: • A: 16 • B: 21 Age (years), mean (SD): • A: 61.6 (17) • B: 65 (15) Sex, *n* (%):A: male, 9 (56); female, 7 (44) B: male, 11 (52); female, 10 (48) Inclusion criteria: patients were included if they had been intubated within the previous 12 hours, were expected to need MV for longer than 24 hours, and required immediate and ongoing sedation	ICU setting: NR Sedative agents: • A: dexmedetomidine • B: standard care Route/dose/frequency: • A: dexmedetomidine infusion at a starting dose of 1 µg/kg/hour without a loading dose. Bolus administration of dexmedetomidine was strictly prohibited owing to the risk of severe bradycardia and sinus arrest • B: the primary sedative agent in this group was at the discretion of the treating clinician. This could be midazolam and/or propofol or other agents deemed necessary but not dexmedetomidine. Selected agents could be given by infusion or boluses and titrated by bedside nurses, including cessation when necessary, to achieve the default light sedation or the level of sedation deemed clinically appropriate and specified by the treating clinician Length of infusion of study drug: until sedation/analgesia was no longer required or up to 28 days of therapy	Time to randomisation, time in light sedation range (RASS score of –2 to 1) in 48 hours after randomisation, proportion of patients treated with dexmedetomidine, propofol and midazolam, incidence of delirium and delirium-free days, ventilator-free days at 28 days, mortality at discharge from hospital and 90 days after randomisation

Study details	Participant characteristics	Intervention characteristics	Summary of outcomes
	Exclusion criteria: aged < 18 years; pregnancy proven or suspected primary neurological injury; a 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; a mean blood pressure of < 55 mmHg; a heart rate of < 55 beats per minute; or a high-grade atrioventricular block in the absence of a functioning pacemaker	Target sedation level: RASS score range of –2 to 1 unless otherwise clinically indicated Rescue medication: • A: propofol • B: NR Pain control: by infusion or boluses of an opioid (fentanyl or morphine) or other agents such as ketamine, as determined by the treating physician Daily interruption: no	

continued

TABLE 4 Characteristics of included studies (*continued*)

Study details	Participant characteristics	Intervention characteristics	Summary of outcomes
First author, year: Srivastava, 2014[55] Secondary reports: none Language: English Publication type: full text Number of centres: NR Country: India Start/end dates: NR Prospective/retrospective data collection: prospective Study design: prospective, randomised controlled open-label study Length of randomisation method: NR Length of follow-up: 24 hours Source of funding: none	Type of participants: general ICU Enrolled: • A + B: 70 Randomised: • A: 35 • B: 35 Analysed: • A: 35 • B: 35 Age (years), median (IQR): • A: 49 (45–63) • B: 46 (43–59) Sex, *n* (%): • A: male, 20 (57); female, 15 (43) • B: male, 18 (51); female, 17 (49) Inclusion criteria: aged > 18 years, MV with endotracheal intubation, requiring a minimum of 12 hours of MV with concomitant sedation and a maximum 24 hours of light to moderate sedation Exclusion criteria: pregnant females, patients with a neurological condition, central nervous system trauma, asthma or chronic obstructive pulmonary disease, haemodynamically unstable patients, known cases of conduction defects, cardiac failure, those patients with a creatinine clearance rate of < 30 ml/minute, and those requiring neuromuscular blockade and prior use of alpha-2 agonists	ICU setting: NR Sedative agents: • A: dexmedetomidine • B: clonidine Route/dose/frequency: • A: dexmedetomidine as a loading dose of 0.7 µg/kg over a period of 10 minutes followed by maintenance of 0.2 µg/kg/hour with dosage increments titrated up to 0.7 µg/kg/hour • B: i.v. infusion of clonidine 1 µg/kg/hour and titration was achieved with dosage increments up to 2 µg/kg/hour Length of infusion of study drug: until extubation or for maximum allowable time Target sedation level: RSS score of 3 or 4 Rescue medication: i.v. diazepam bolus of 0.1 mg/kg Pain control: i.v. bolus of 20 µg of fentanyl or infusion Daily interruption: NR	Additional sedation with diazepam, proportion of patients in target sedation range, mean maintenance infusion dose, systolic and diastolic blood pressure, adverse events

Study details	Participant characteristics	Intervention characteristics	Summary of outcomes
First author, year: Tasdogan, 2009[122] Secondary reports: none Language: English Publication type: full text Number of centres: 1 Country: Turkey Start/end dates: NR Prospective/retrospective data collection: prospective Study design: RCT (pilot) Randomisation method: an independent nurse prepared sealed envelopes from a computer-generated table before the study started Length of follow-up: NR Source of funding: NR	Type of participants: patients with sepsis after ileus surgery Enrolled: NR Randomised: • A: 20 • B: 20 Analysed: • A: 20 • B: 20 Age (years), mean (SD): • A: 58 (21–78) • B: 50 (19–74) Sex, *n* (%): • A: male, 14 (70); female, 6 (30) • B: male, 11 (55); female, 9 (45)	ICU setting: NR Sedative agents: • A: dexmedetomidine • B: propofol Route/dose/frequency: • A: loading dose at 1 µg/kg over 10 minutes, followed by a maintenance 0.2–2.5 µg/kg/hour into a peripheral or central vein over a 24-hour infusion • B: loading dose of 1 mg/kg over 15 minutes, followed by a maintenance of 1–3 mg/kg/hour over a 24-hour infusion Length of infusion of study drug: 24 hours Target sedation level: RSS score of < 2 Rescue medication: NR Pain control: alfentanil was infused at 0.25–1.0 µg/kg/minutes	Physiological parameters, mortality, duration of MV, length of stay in ICU, adverse events

continued

TABLE 4 Characteristics of included studies (*continued*)

Study details	Participant characteristics	Intervention characteristics	Summary of outcomes
	Inclusion criteria: adult patients admitted to the ICU after ileus surgery and who were expected to require post-operative sedation and ventilation. Critically ill patients were included in the study as soon as they met at least two of the criteria of sepsis, as defined by the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference Committee Exclusion criteria: known allergy to propofol or dexmedetomidine, possible or confirmed pregnancy, presence of one of the following conditions at randomisation: haemodynamic instability (defined as a systolic blood pressure of < 100 mmHg), heart failure (class III or IV of the New York Heart Association), renal failure (RIFLE classification), liver failure (manifested by a serum total protein concentration of < 3 g/dl, and total bilirubin level of > 5 mg/dl), and known or suspected brain death	Daily interruption: NR	

Study details	Participant characteristics	Intervention characteristics	Summary of outcomes
First author, year: Venn, 2001[123] Secondary reports: Venn, 2001[124] Language: English Publication type: full text Number of centres: 1 Country: UK Start/end dates: NR Prospective/retrospective data collection: prospective Study design: RCT Randomisation method: on arrival in the ICU, patients were allocated randomly, using sealed envelopes Length of follow-up: 48–72 hours after discharge from ICU Source of funding: Abbott Laboratories	Type of participants: after surgery Enrolled: NR Randomised: • A: 20 • B: 20 Analysed: NR Age (years), median (IQR): • A: 65 (60–77) • B: 67 (64–74) Sex, *n* (%): NR Inclusion criteria: adult patients (aged 18 years or older) admitted to the ICU after complex major abdominal or pelvic surgery and expected to require 8-hour post-operative sedation and ventilation Exclusion criteria: allergy to any of the trial drugs, pregnancy, severe hepatic disease, requirement for haemodialysis or haemofiltration, spinal or epidural anaesthesia, use of etomidate in the preceding 24 hours or a history of corticosteroid treatment in the last 3 months	ICU setting: NR Sedative agents: • A: dexmedetomidine • B: propofol Route/dose/frequency: • A: loading dose of dexmedetomidine was 2.5 µg/kg/hour over 10 minutes followed by a maintenance infusion of 0.2–2.5 µg/kg/hour into a peripheral or central vein • B: propofol was given undiluted as an infusion of 1–3 mg/kg/hour after a loading dose infusion of up to 1 mg/kg over 10 minutes, if required Length of infusion of study drug: discontinued in preparation for extubation Target sedation level: RSS score of > 2 Rescue medication: no other sedative or analgesic agents were given Pain control: alfentanil was infused at 0.25–1.0 µg/kg/minutes Daily interruption: NR	Sedation, patient experiences, haemodynamic and physiological parameters

CABG, coronary artery bypass graft; CNS, central nervous system; IQR, interquartile range; IL-6, interleukin 6; i.v., intravenous; NR, not reported; PABS, Pain Assessment Behavioural Score; RIFLE, risk, injury, failure, loss of function, end-stage renal disease; VAS, visual analogue scale.

Appendix 6 Dosage and administration of sedative agents

TABLE 5 Dosage and administration of sedative agents

Study	Dose and frequency of study drugs	
	Dexmedetomidine	Comparator
Abdulatif *et al.*, 2004[109]	Loading dose (1 µg/kg) i.v. over 10 minutes, followed by continuous i.v. infusion (5 µg/ml) at a rate of 0.5 µg/kg/hour (0.1 ml/kg/hour) to be increased to a maximum of 1 µg/kg/hour	Propofol: i.v. infusion (10 mg/ml) starting with a dose of 1 mg/kg/hour (0.1 ml/hour) and increasing up to 2 mg/kg/hour
Corbett *et al.*, 2005[110]	Loading dose 1 µg/kg (actual body weight) intravenously administered over 15 minutes, followed by a 0.4 µg/kg/hour i.v. infusion	Propofol: 5 µg/kg/minute i.v. infusion titrated within the range of 0.2–0.7 µg/kg/hour or 5–75 µg/kg/minute
Elbaradie *et al.*, 2004[111]	Loading infusion dose of dexmedetomidine 2.5 µg/kg/hour over 10 minutes followed by maintenance infusion at a rate of 0.2–0.5 µg/kg/hour into a peripheral vein, with the dosage adjusted to achieve the desired level of sedation	Propofol: undiluted as a bolus dose of 1 mg/kg initially, followed by an infusion of 0.5–1 mg/kg/hour, with the dosage adjusted to achieve the desired level of sedation varying the dose by 10% increase or decrease in infusion rate in order to maintain the level of sedation within the range previously considered adequate
Esmaoglu *et al.*, 2009[112]	Loading dose 1 µg/kg per 20 minutes, followed by a continuous infusion at 0.7 µg/kg/hour	Midazolam: loading dose of 100 mg in 100 ml of 0.9% NaCl at 0.05 mg/kg and continued at 0.1 mg/kg/hour
Herr *et al.*, 2003[114]	Loading dose of 1.0 µg/kg over 20 minutes, followed by a maintenance infusion of 0.4 µg/kg/hour. After transfer to the ICU, the infusion rate was titrated in the range of 0.2 µg/kg/hour to 0.7 µg/kg/hour as necessary to maintain a RSS score of ≥ 3 before extubation, ≥ 2 after extubation	Propofol: no dose or rate of propofol was specified by the protocol. Investigators were told to follow their usual practice with regard to propofol-based sedation
Jakob *et al.*, 2012[70]; MIDEX	Six dose levels of each study drug covered the full dose range (dexmedetomidine, 0.2–1.4 µg/kg/hour; midazolam, 0.03–0.2 mg/kg/hour). Study treatments were infused without loading dose at a dose matching the pre-randomisation dose of midazolam for 1 hour. Thereafter, study drugs were titrated by the patient's nurse stepwise to maintain the target RASS score	Midazolam: six dose levels of each study drug covered the full dose range (dexmedetomidine, 0.2–1.4 µg/kg per hour; midazolam, 0.03–0.2 mg/kg/hour). Study treatments were infused without loading dose at a dose matching the pre-randomisation dose of midazolam for 1 hour. Thereafter, study drugs were titrated by the patient's nurse stepwise to maintain the target RASS score
Jakob *et al.*, 2012[70]; PRODEX	Six dose levels of each study drug covered the full dose range (dexmedetomidine, 0.2–1.4 µg/kg per hour; propofol, 0.3–4.0 mg/kg per hour). Study treatments were infused without loading dose at a dose matching the pre-randomisation dose of propofol for 1 hour. Thereafter, study drugs were titrated by the patient's nurse stepwise to maintain the target RASS score	Propofol: six dose levels of each study drug covered the full dose range (dexmedetomidine 0.2–1.4 µg/kg per hour; propofol 0.3–4.0 mg/kg per hour). Study treatments were infused without loading dose at a dose matching the pre-randomisation dose of propofol for 1 hour. Thereafter, study drugs were titrated by the patient's nurse stepwise to maintain the target RASS score
MacLaren *et al.*, 2013[116]	Dexmedetomidine was started at 0.15 µg/kg/hour and adjusted by 0.15 µg/kg/hour to a maximum of 1.5 µg/kg/hour	Midazolam: midazolam was started at 1 mg/hour and adjusted by 1 mg/hour to a maximum of 10 mg/hour. All infusions were adjusted by increments of 2 ml/hour to maintain blinding

continued

TABLE 5 Dosage and administration of sedative agents (*continued*)

Study	Dose and frequency of study drugs	
	Dexmedetomidine	Comparator
Maldonado *et al.*, 2009[72]	Loading dose of 0.4 µg/kg, followed by a maintenance drip of 0.2–0.7 µg/kg/hour	Propofol: propofol drip (25 µg/kg/minute–50 µg/kg/minute) Midazolam: midazolam drip (0.5 mg/hour–2 mg/hour)
Memis *et al.*, 2009[117]	Loading dose at 1 µg/kg over 10 minutes, followed by a maintenance dose of 0.2–2.5 µg/kg per hour into a peripheral or central vein over a 24-hour infusion	Propofol: loading dose of 1 mg/kg over 15 minutes, followed by a maintenance dose of 1–3 mg/kg per hour over a 24-hour infusion
Pandharipande *et al.*, 2007[102]	Started at 1 ml/hour (0.15 µg/kg per hour dexmedetomidine) and titrated by the bedside nurse to a maximum of 10 ml/hour (1.5 µg/kg/hour dexmedetomidine)	Lorazepam: started at 1 ml/hour (1 mg/hour lorazepam) and titrated by the bedside nurse to a maximum of 10 ml/hour (10 mg/hour lorazepam)
Riker *et al.*, 2009[71]	Optional blinded loading doses (up to 1 µg/kg dexmedetomidine) could be administered at the investigator's discretion. The starting maintenance infusion dose of the blinded study drug was 0.8 µg/kg/hour per hour for dexmedetomidine or responding to the mid-point of the allowable infusion dose range of 4 mg in 8 hours	Midazolam: optional blinded loading doses (0.05 mg/kg midazolam) could be administered at the investigator's discretion. The starting maintenance infusion dose of blinded study drug was 0.06 mg/kg/hour for midazolam, corresponding to the mid-point of the allowable infusion dose range of 4 mg in 8 hours
Ruokonen *et al.*, 2009[69]	Infused without a loading dose at 0.8 µg/kg/hour for 1 hour and then adjusted stepwise at 0.25, 0.5, 0.8, 1.1 and 1.4 µg/kg/hour	Propofol: infused at 2.4 mg/kg/hour for 1 hour and then adjusted stepwise at 0.8, 1.6, 2.4, 3.2 and 4.0 mg/kg/hour Midazolam: depending on standard care at time of randomisation, midazolam was given either as i.v. boluses (1–2 mg), starting at three boluses per hour for 1 hour, and thereafter one to four boluses per hour and, if not sufficient, as continuous infusion of 0.2 mg/kg/hour, or as a continuous infusion at 0.12 mg/kg/hour for 1 hour, followed by adjustments at 0.04, 0.08, 0.12, 0.16 and 0.20 mg/kg/hour. The initial dose could be reduced, if considered necessary by the treating clinician
Shah *et al.*, 2014[120]	Loading dose of injection with 1 µg/kg over 10 minutes, followed by a maintenance infusion of 0.2–0.7 µg/kg/hour. The rate of the maintenance infusion was adjusted to achieve the desired level of sedation	Propofol: started at 5 µg/kg/minute (0.3 mg/kg/hour). The infusion rate was increased by increments of 5–10 µg/kg/minute (0.3–0.6 mg/kg/hour) until the desired level of sedation was achieved. A minimum period of 5 minutes between adjustments was allowed for the onset of peak drug effect
Shehabi *et al.*, 2013[121]	Infusion at a starting dose of 1 µg/kg/hour without a loading dose. Bolus administration of dexmedetomidine was strictly prohibited owing to the risk of severe bradycardia and sinus arrest. If required, sedation could be supplemented with propofol. Dexmedetomidine infusion was administered between a minimum of 0 µg/kg/hour and maximum of 1.5 µg/kg/hour specified by the treating clinician and titrated to achieve the desired level of sedation	Midazolam and/or propofol: the primary sedative agent was at the discretion of the treating clinician and could be midazolam and/or propofol or other agents deemed necessary but not dexmedetomidine. Clonidine and remifentanil could not be administered. Selected agents could be given by infusion or boluses and titrated by bedside nurses, including cessation when necessary, to achieve the default light sedation or level of sedation deemed clinically appropriate and specified by treating clinician
Srivastava *et al.*, 2014[55]	Loading dose of 0.7 µg/kg over a period of 10 minutes followed by maintenance of 0.2 µg/kg/hour, with dosage increments titrated up to 0.7 µg/kg/hour	Clonidine: i.v. infusion of clonidine 1 µg/kg/hour and titration was achieved with dosage increments up to 2 µg/kg/hour

TABLE 5 Dosage and administration of sedative agents (*continued*)

Study	Dose and frequency of study drugs	
	Dexmedetomidine	Comparator
Tasdogan *et al.*, 2009[122]	Loading dose at 1 µg/kg over 10 minutes, followed by a maintenance 0.2 to 2.5 µg/kg per hour into a peripheral or central vein over a 24-hour infusion	Propofol: loading dose of 1 mg/kg over 15 minutes, followed by a maintenance of 1 mg/kg to 3 mg/kg per hour over a 24-hour infusion
Venn and Grounds, 2001[123]	Loading dose of dexmedetomidine was 2.5 µg/kg/hour over 10 minutes, followed by a maintenance infusion of 0.2–2.5 µg/kg/hour into a peripheral or central vein	Propofol: propofol was given undiluted as an infusion of 1–3 mg/kg/hour after a loading dose infusion of up to 1 mg/kg over 10 minutes, if required

i.v., intravenous.

Appendix 7 Subgroup analyses: primary and secondary outcomes

Study or subgroup	Dexmedetomidine Events	Total	Control Events	Total	Weight	RR IV, random, 95% CI
Propofol						
Jakob 2012 PRODEX[70]	43	251	48	247	25.1%	0.88 (0.61 to 1.28)
Memis 2009 PROPOFOL[117]	3	20	4	20	1.9%	0.75 (0.19 to 2.93)
Tasdogan 2009 PROPOFOL[122]	1	20	2	20	0.6%	0.50 (0.05 to 5.08)
Subtotal (95% CI)		**291**		**287**	**27.7%**	**0.86 (0.60 to 1.23)**
Total events	47		54			
Heterogeneity: $\tau^2=0.00$; $\chi^2=0.27$, df=2 ($p=0.88$); $I^2=0\%$						
Test for overall effect: $z=0.83$ ($p=0.41$)						
Midazolam						
Jakob 2012 MIDEX[70]	68	249	53	251	35.4%	1.29 (0.95 to 1.77)
Maclaren 2013 MIDAZOLAM[116]	2	11	1	12	0.7%	2.18 (0.23 to 20.84)
Riker 2009 MIDAZOLAM[71]	55	244	31	122	23.8%	0.89 (0.60 to 1.30)
Subtotal (95% CI)		**504**		**385**	**59.9%**	**1.11 (0.82 to 1.50)**
Total events	125		85			
Heterogeneity: $\tau^2=0.02$; $\chi^2=2.57$, df=2 ($p=0.28$); $I^2=22\%$						
Test for overall effect: $z=0.68$ ($p=0.50$)						
Standard care						
Ruokonen 2009 SC[69]	10	41	7	44	4.6%	1.53 (0.64 to 3.65)
Shehabi 2013 SC[121]	5	21	2	16	1.5%	1.90 (0.42 to 8.58)
Subtotal (95% CI)		**62**		**60**	**6.2%**	**1.62 (0.76 to 3.43)**
Total events	15		9			
Heterogeneity: $\tau^2=0.00$; $\chi^2=0.06$, df=1 ($p=0.81$); $I^2=00\%$						
Test for overall effect: $z=1.26$ ($p=0.21$)						
Lorazepam						
Pandharipande 2007 LORAZ[102]	9	52	14	51	6.3%	0.63 (0.30 to 1.33)
Subtotal (95% CI)		**52**		**51**	**6.3%**	**0.63 (0.30 to 1.33)**
Total events	9		14			
Heterogeneity: not applicable						
Test for overall effect: $z=1.22$ ($p=0.22$)						
Total (95% CI)		**909**		**783**	**100.0%**	**1.03 (0.85 to 1.24)**
Total events	196		162			
Heterogeneity: $\tau^2=0.00$; $\chi^2=7.41$, df=8 ($p=0.49$); $I^2=0\%$						
Test for overall effect: $z=0.28$ ($p=0.78$)						
Test for subgroup differences: $\chi^2=4.21$, df=3 ($p=0.24$); $I^2=28.7\%$						

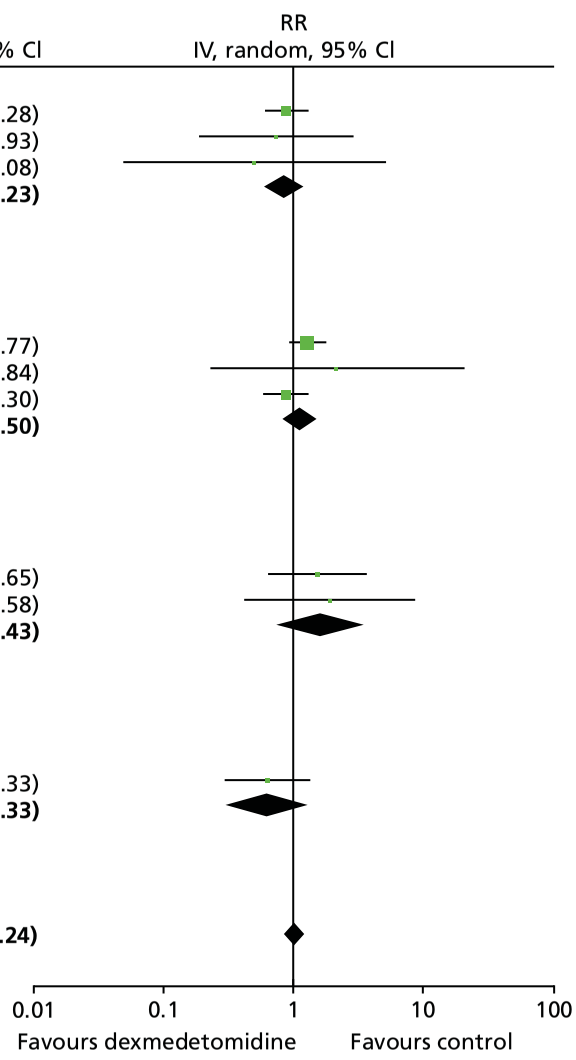

FIGURE 22 Meta-analysis for mortality according to type of comparator. Please note that the totals in the forest plot may be subject to minor rounding errors. IV, inverse variance; LORAZ, lorazepam compared with dexmedetomidine; MIDAZOLAM, midazolam compared with dexmedetomidine; PROPOFOL, propofol compared with dexmedetomidine; SC, standard care compared with dexmedetomidine.

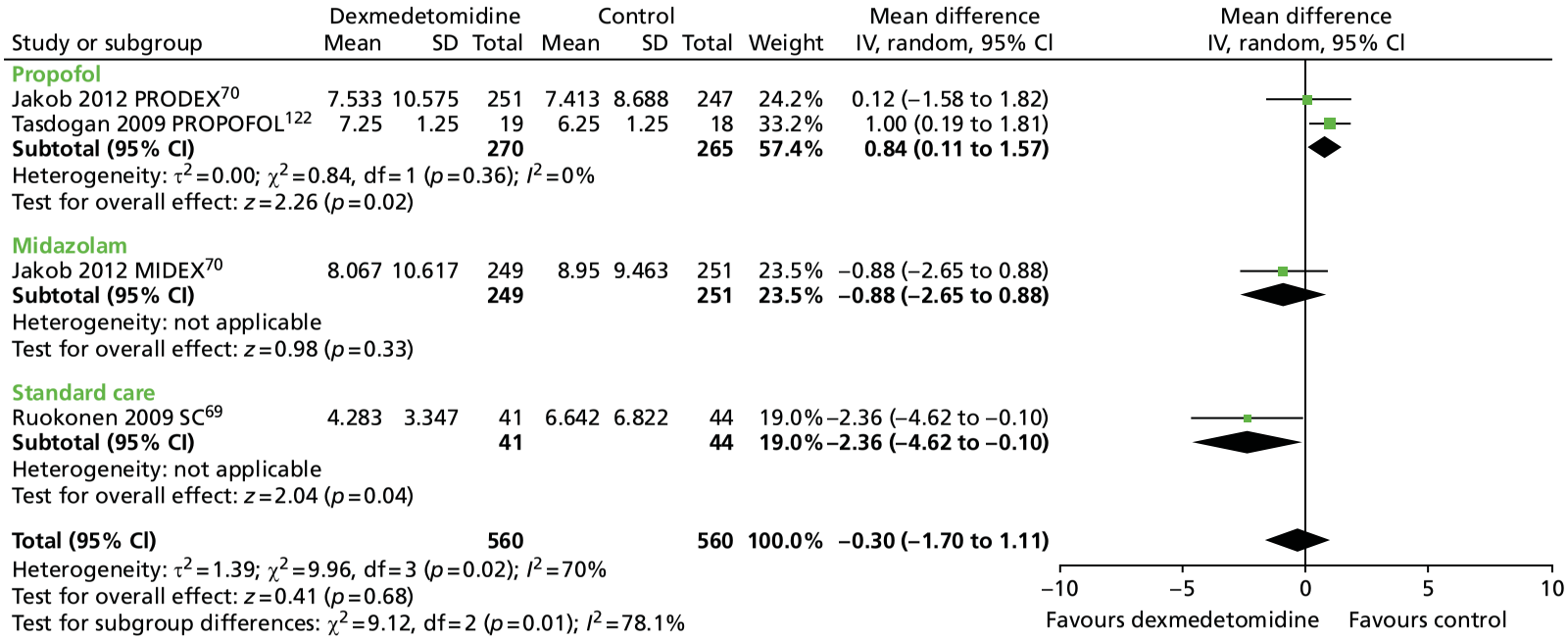

FIGURE 23 Meta-analysis for duration of MV according to type of comparator. IV, inverse variance; PROPOFOL, propofol compared with dexmedetomidine; SC, standard care compared with dexmedetomidine.

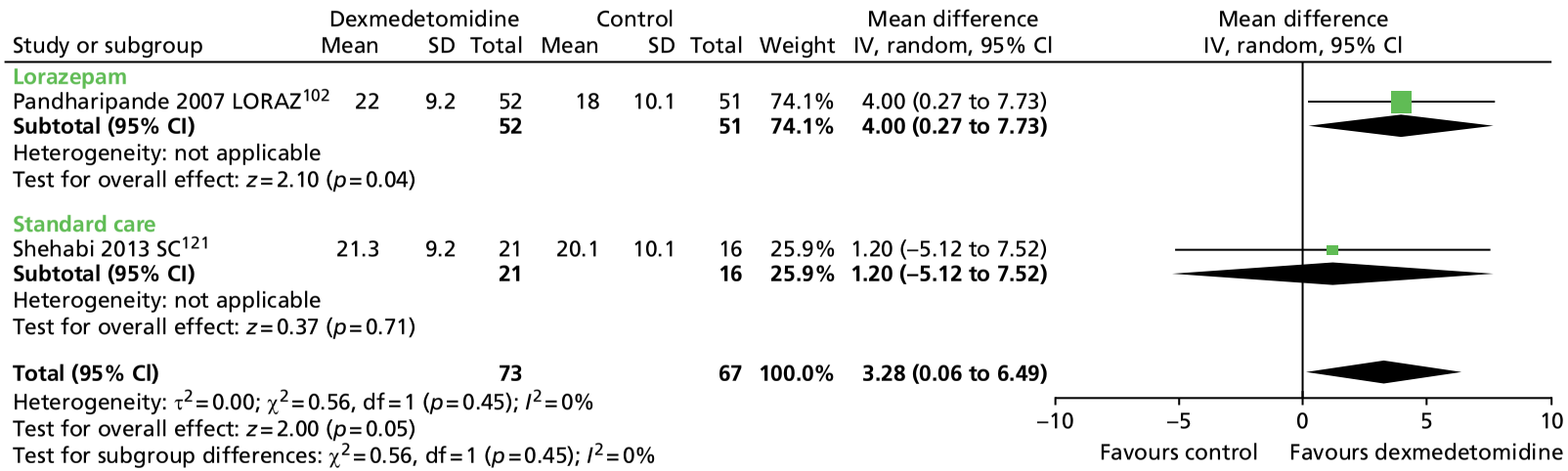

FIGURE 24 Meta-analysis for ventilator-free days according to type of comparator. IV, inverse variance; LORAZ, lorazepam compared with dexmedetomidine; SC, standard care compared with dexmedetomidine.

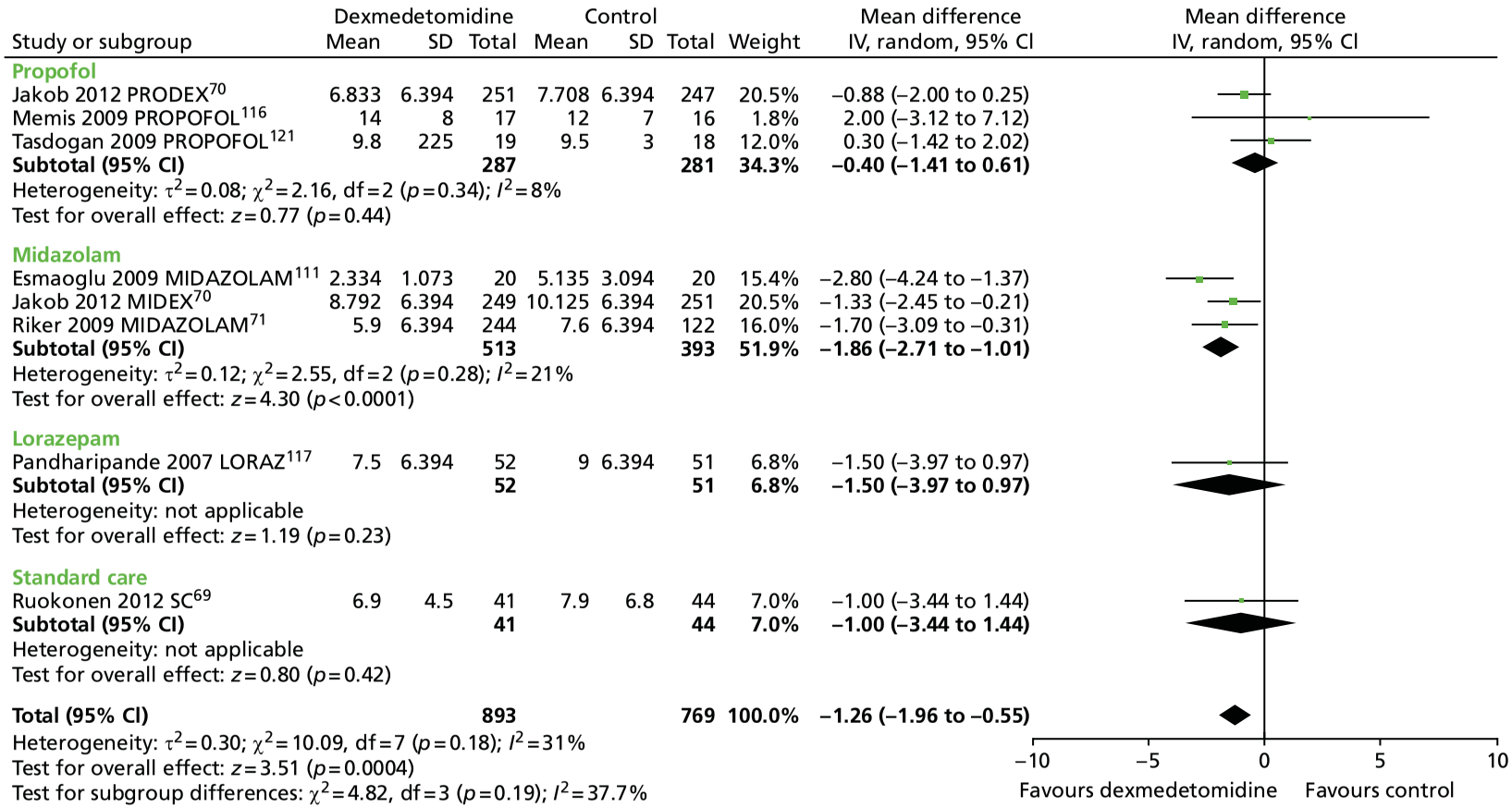

FIGURE 25 Meta-analysis for length of ICU stay according to type of comparator. IV, inverse variance; LORAZ, lorazepam compared with dexmedetomidine; MIDAZOLAM, midazolam compared with dexmedetomidine; PROPOFOL, propofol compared with dexmedetomidine; SC, standard care compared with dexmedetomidine.

Study or subgroup	Dexmedetomidine Events	Total	Control Events	Total	Weight	RR IV, random, 95% CI
Propofol						
Jakob 2012 PRODEX[70]	32	246	33	247	22.2%	0.97 (0.62 to 1.53)
Subtotal (95% CI)		**246**		**247**	**22.2%**	**0.97 (0.62 to 1.53)**
Total events	32		33			
Heterogeneity: not applicable						
Test for overall effect: $z = 0.12$ ($p = 0.91$)						
Midazolam						
Jakob 2012 MIDEX[70]	51	247	29	250	23.7%	1.78 (1.17 to 2.71)
Maclaren 2013 MIDAZOLAM[116]	10	11	6	12	16.6%	1.82 (1.00 to 3.30)
Riker 2009 MIDAZOLAM[71]	137	244	68	122	35.8%	1.01 (0.83 to 1.22)
Subtotal (95% CI)		**502**		**384**	**76.1%**	**1.41 (0.90 to 2.22)**
Total events	198		103			
Heterogeneity: $\tau^2 = 0.12$; $\chi^2 = 8.22$, df = 2 ($p = 0.02$); $I^2 = 76\%$						
Test for overall effect: $z = 1.49$ ($p = 0.14$)						
Standard care						
Ruokonen 2009 SC[69]	2	41	1	44	1.7%	2.15 (0.20 to 22.79)
Subtotal (95% CI)		**41**		**44**	**1.7%**	**2.15 (0.20 to 22.79)**
Total events	2		1			
Heterogeneity: not applicable						
Test for overall effect: $z = 0.63$ ($p = 0.53$)						
Total (95% CI)		**789**		**675**	**100.0%**	**1.28 (0.93 to 1.75)**
Total events	232		137			
Heterogeneity: $\tau^2 = 0.06$; $\chi^2 = 8.99$, df = 4 ($p = 0.06$); $I^2 = 55\%$						
Test for overall effect: $z = 1.53$ ($p = 0.12$)						
Test for subgroup differences: $\chi^2 = 1.53$, df = 2 ($p = 0.47$); $I^2 = 0\%$						

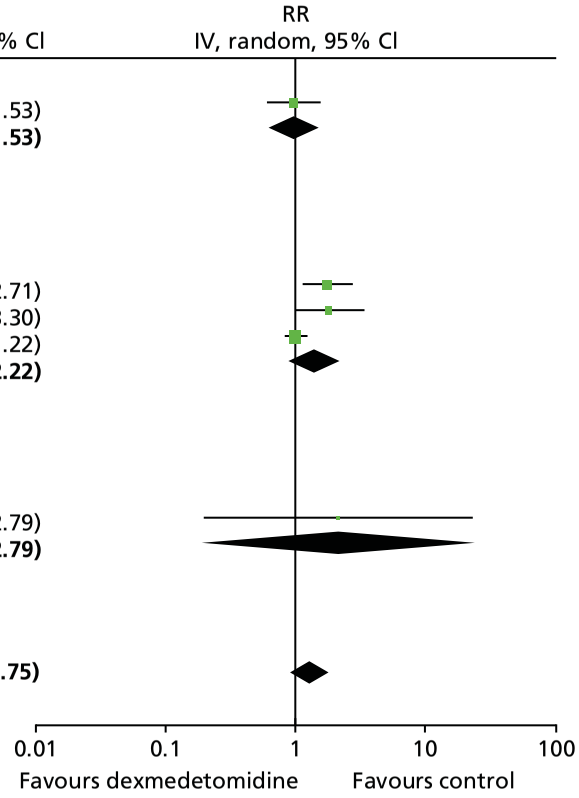

FIGURE 26 Meta-analysis for incidence of hypotension according to type of comparator. IV, inverse variance; LORAZ, lorazepam compared with dexmedetomidine; MIDAZOLAM, midazolam compared with dexmedetomidine; SC, standard care compared with dexmedetomidine.

Study or subgroup	Dexmedetomidine Events	Total	Control Events	Total	Weight	RR IV, random, 95% CI
Propofol						
Jakob 2012 PRODEX[70]	52	246	37	247	23.7%	1.14 (0.96 to 2.07)
Subtotal (95% CI)		**246**		**247**	**23.7%**	**1.14 (0.96 to 2.07)**
Total events	52		37			
Heterogeneity: not applicable						
Test for overall effect: $z = 1.76$ ($p = 0.08$)						
Midazolam						
Jakob 2012 MIDEX[70]	53	247	52	250	28.9%	1.03 (0.73 to 1.45)
Riker 2009 MIDAZOLAM[71]	106	244	54	122	47.3%	0.98 (0.77 to 1.25)
Subtotal (95% CI)		**491**		**372**	**76.3%**	**1.00 (0.82 to 1.22)**
Total events	159		106			
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.05$, df = 1 ($p = 0.82$); $I^2 = 0\%$						
Test for overall effect: $z = 0.02$ ($p = 0.99$)						
Total (95% CI)		**737**		**619**	**100.0%**	**1.09 (0.89 to 1.33)**
Total events	211		143			
Heterogeneity: $\tau^2 = 0.01$; $\chi^2 = 2.53$, df = 2 ($p = 0.28$); $I^2 = 21\%$						
Test for overall effect: $z = 0.79$ ($p = 0.43$)						
Test for subgroup differences: $\chi^2 = 2.47$, df = 1 ($p = 0.12$); $I^2 = 59.5\%$						

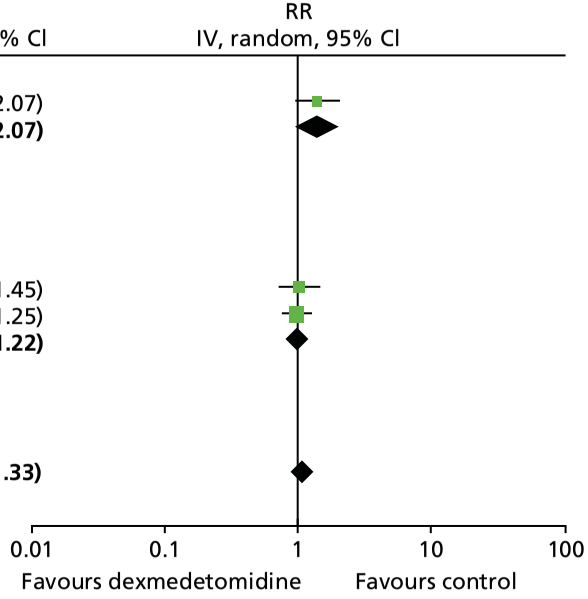

FIGURE 27 Meta-analysis for incidence of hypertension according to type of comparator. Please note that the totals in the forest plot may be subject to minor rounding errors. IV, inverse variance; LORAZ, lorazepam compared with dexmedetomidine; MIDAZOLAM, midazolam compared with dexmedetomidine; PROPOFOL, propofol compared with dexmedetomidine; SC, standard care compared with dexmedetomidine.

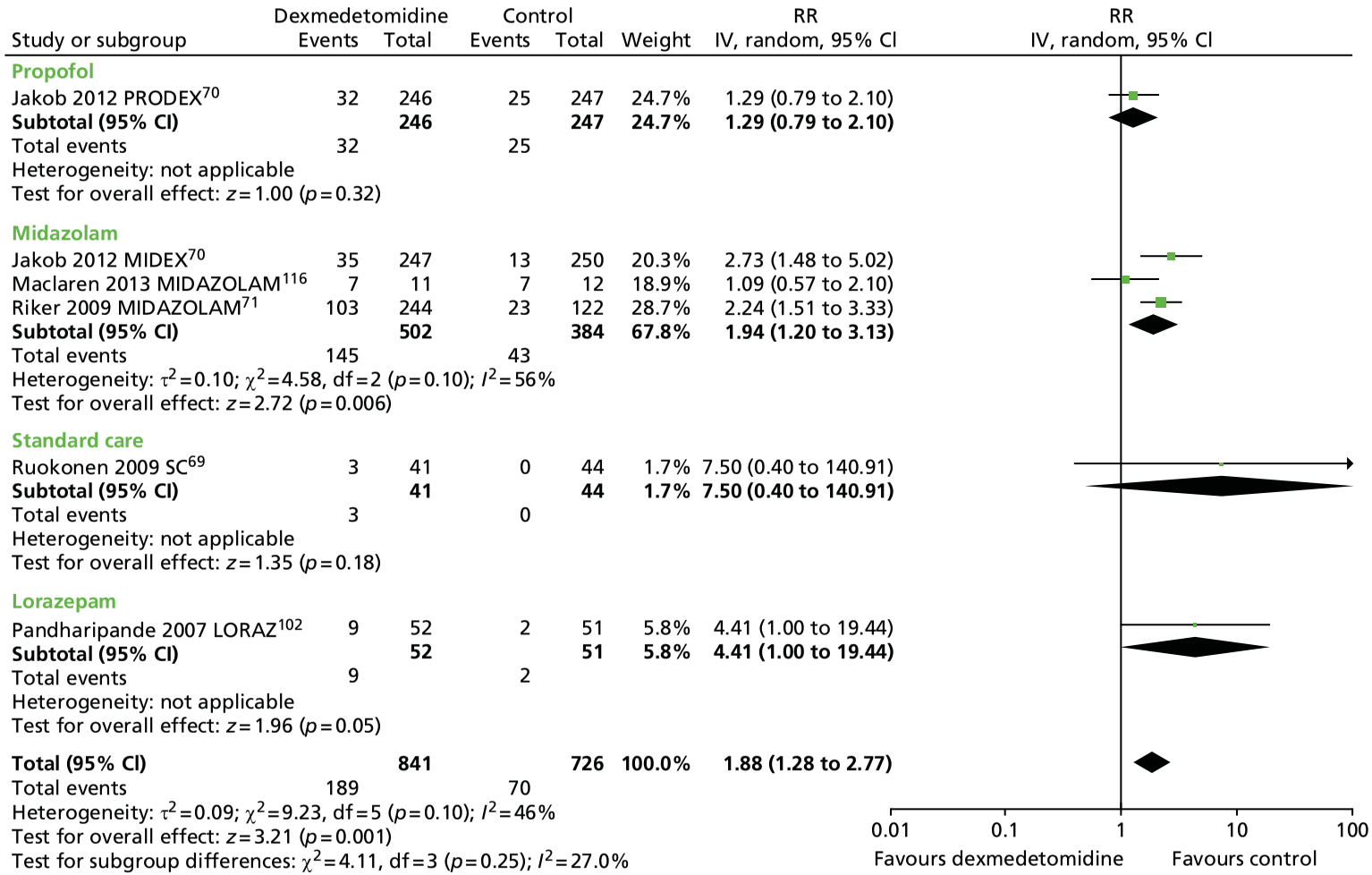

FIGURE 28 Meta-analysis for incidence of bradycardia according to type of comparator. Please note that the totals in the forest plot may be subject to minor rounding errors. IV, inverse variance; LORAZ, lorazepam compared with dexmedetomidine; MIDAZOLAM, midazolam compared with dexmedetomidine; PROPOFOL, propofol compared with dexmedetomidine; SC, standard care compared with dexmedetomidine.

Study or subgroup	Dexmedetomidine Events	Total	Control Events	Total	Weight	RR IV, random, 95% CI
Propofol						
Jakob 2012 PRODEX[70]	12	246	24	247	9.3%	0.50 (0.26 to 0.98)
Subtotal (95% CI)		**246**		**247**	**9.3%**	**0.50 (0.26 to 0.98)**
Total events	12		24			
Heterogeneity: not applicable						
Test for overall effect: $z = 2.02$ ($p = 0.04$)						
Midazolam						
Jakob 2012 MIDEX[70]	19	247	25	250	11.6%	0.77 (0.44 to 1.36)
Maclaren 2013 MIDAZOLAM[116]	4	11	8	12	6.2%	0.55 (0.23 to 1.31)
Riker 2009 MIDAZOLAM[71]	132	244	93	122	28.7%	0.71 (0.61 to 0.83)
Subtotal (95% CI)		**502**		**384**	**46.5%**	**0.71 (0.61 to 0.82)**
Total events	155		126			
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.42$, df = 2 ($p = 0.81$); $I^2 = 0\%$						
Test for overall effect: $z = 4.66$ ($p < 0.00001$)						
Standard care						
Ruokonen 2009 SC[69]	18	41	11	44	10.5%	1.76 (0.95 to 3.26)
Shehabi 2009 SC[121]	8	21	6	16	6.7%	1.02 (0.44 to 2.34)
Subtotal (95% CI)		**62**		**60**	**17.2%**	**1.44 (0.86 to 2.41)**
Total events	26		17			
Heterogeneity: $\tau^2 = 0.01$; $\chi^2 = 1.07$, df = 1 ($p = 0.30$); $I^2 = 6\%$						
Test for overall effect: $z = 1.39$ ($p = 0.17$)						
Lorazepam						
Pandharipande 2007 LORAZ[102]	41	52	42	51	27.0%	0.96 (0.79 to 1.16)
Subtotal (95% CI)		**52**		**51**	**27.0%**	**0.96 (0.79 to 1.16)**
Total events	41		42			
Heterogeneity: not applicable						
Test for overall effect: $z = 0.45$ ($p = 0.65$)						
Total (95% CI)		**862**		**742**	**100.0%**	**0.83 (0.65 to 1.06)**
Total events	234		209			
Heterogeneity: $\tau^2 = 0.05$; $\chi^2 = 14.95$, df = 6 ($p = 0.02$); $I^2 = 60\%$						
Test for overall effect: $z = 1.47$ ($p = 0.14$)						
Test for subgroup differences: $\chi^2 = 12.99$, df = 3 ($p = 0.005$); $I^2 = 76.9\%$						

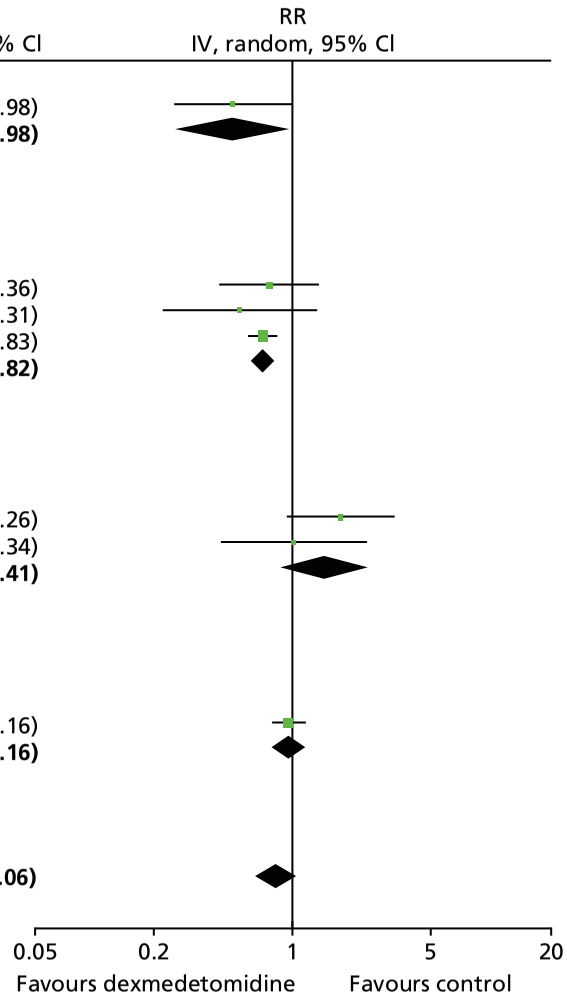

FIGURE 29 Meta-analysis for incidence of delirium according to type of comparator. IV, inverse variance; LORAZ, lorazepam compared with dexmedetomidine; MIDAZOLAM, midazolam compared with dexmedetomidine; PROPOFOL, propofol compared with dexmedetomidine; SC, standard care compared with dexmedetomidine.

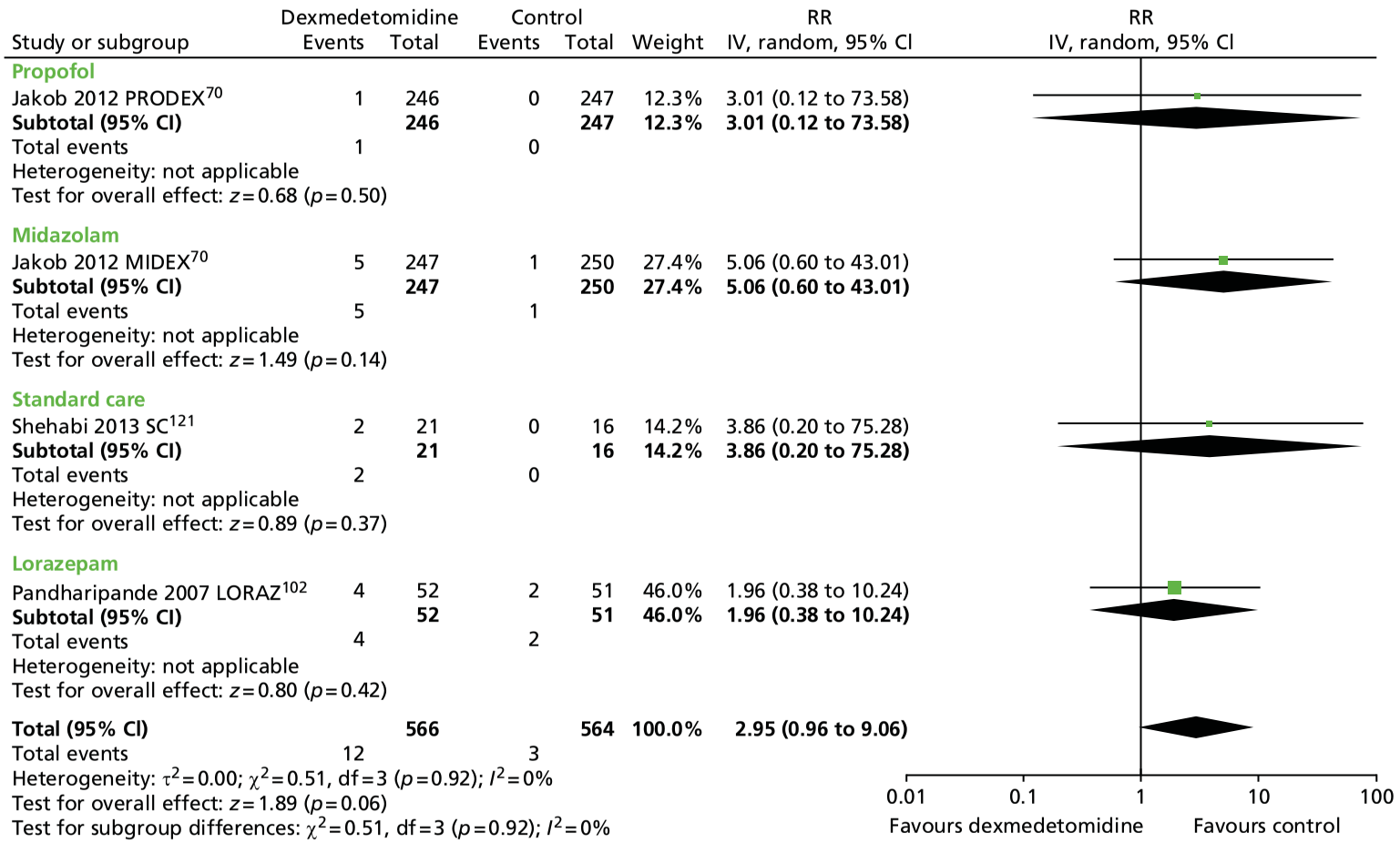

FIGURE 30 Meta-analysis for self-extubation according to type of comparator. IV, inverse variance; LORAZ, lorazepam compared with dexmedetomidine; MIDAZOLAM, midazolam compared with dexmedetomidine; PROPOFOL, propofol compared with dexmedetomidine; SC, standard care compared with dexmedetomidine.

Study or subgroup	Dexmedetomidine Events	Total	Control Events	Total	Weight	RR IV, random, 95% CI
Propofol						
Jakob 2012 PRODEX[70]	48	246	28	247	20.0%	1.72 (1.12 to 2.65)
Subtotal (95% CI)		**246**		**247**	**20.0%**	**1.72 (1.12 to 2.65)**
Total events	48		28			
Heterogeneity: not applicable						
Test for overall effect: $z=2.47$ ($p=0.01$)						
Midazolam						
Jakob 2012 MIDEX[70]	34	247	54	250	20.8%	0.64 (0.43 to 0.94)
Maclaren 2013 MIDAZOLAM[116]	7	11	5	12	12.6%	1.53 (0.68 to 3.42)
Riker 2009 MIDAZOLAM[71]	62	244	54	122	22.9%	0.57 (0.43 to 0.77)
Subtotal (95% CI)		**502**		**384**	**56.3%**	**0.71 (0.47 to 1.07)**
Total events	103		113			
Heterogeneity: $\tau^2=0.07$; $\chi^2=5.02$, df=2 ($p=0.08$); $I^2=60\%$						
Test for overall effect: $z=1.65$ ($p=0.10$)						
Lorazepam						
Pandharipande 2007 LORAZ[102]	36	52	37	51	23.7%	0.95 (0.74 to 1.22)
Subtotal (95% CI)		**52**		**51**	**23.7%**	**0.95 (0.74 to 1.22)**
Total events	36		37			
Heterogeneity: not applicable						
Test for overall effect: $z=0.37$ ($p=0.71$)						
Total (95% CI)		**800**		**682**	**100.0%**	**0.93 (0.63 to 1.39)**
Total events	187		178			
Heterogeneity: $\tau^2=0.16$; $\chi^2=22.12$, df=4 ($p=0.0002$); $I^2=82\%$						
Test for overall effect: $z=0.34$ ($p=0.73$)						
Test for subgroup differences: $\chi^2=8.94$, df=2 ($p=0.01$); $I^2=77.6\%$						

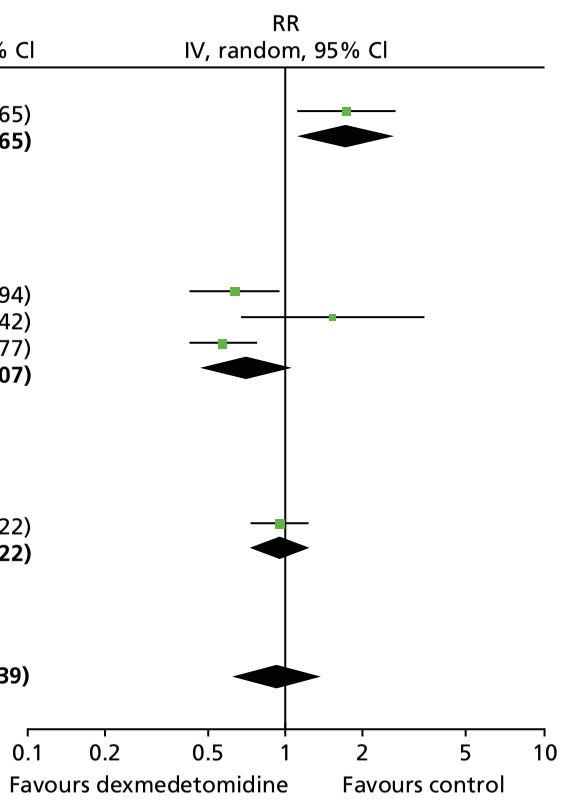

FIGURE 31 Meta-analysis for incidence of tachycardia according to type of comparator. IV, inverse variance; LORAZ, lorazepam compared with dexmedetomidine; MIDAZOLAM, midazolam compared with dexmedetomidine; PROPOFOL, propofol compared with dexmedetomidine; SC, standard care compared with dexmedetomidine.

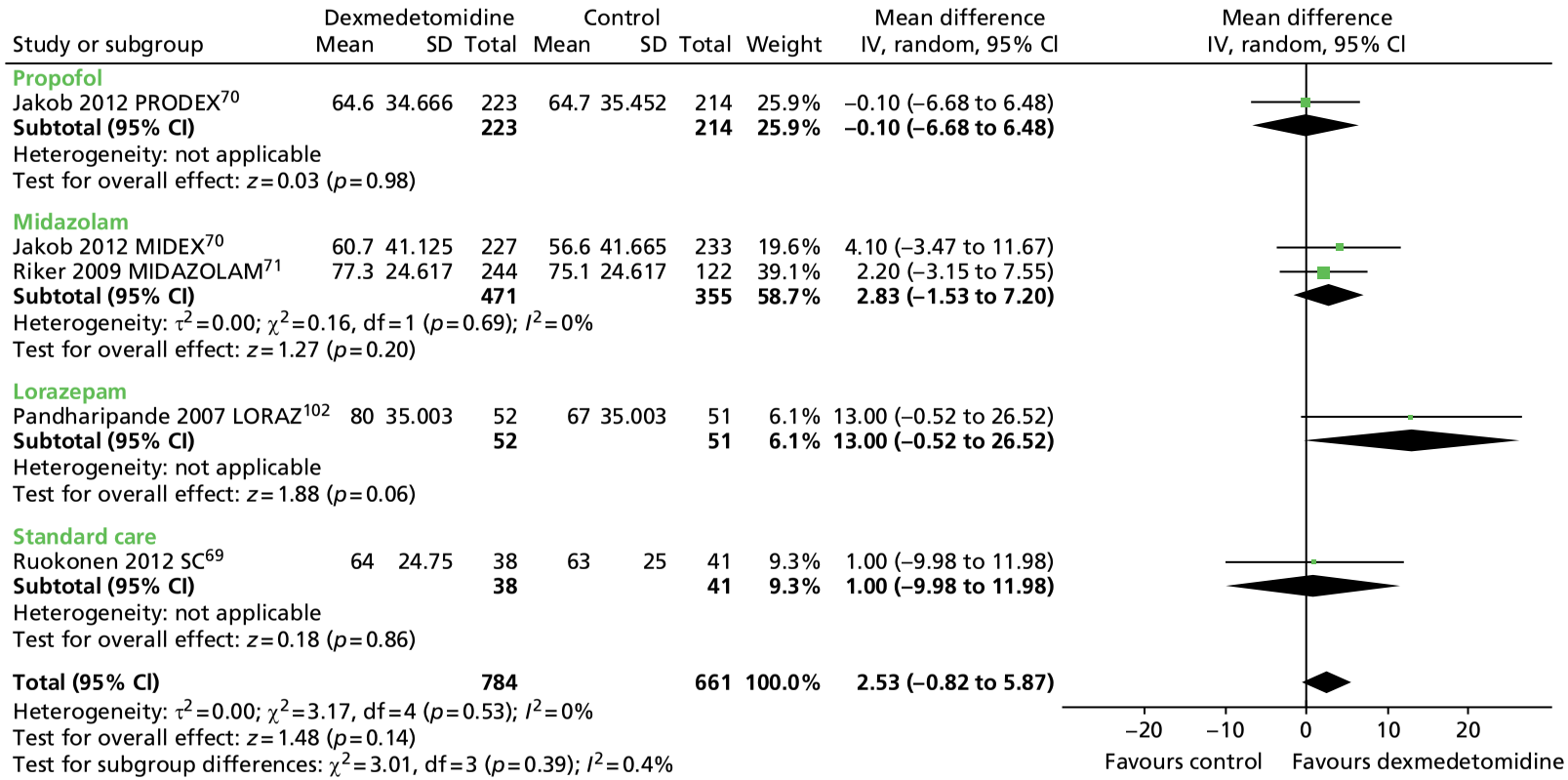

FIGURE 32 Meta-analysis for time in target sedation range according to type of comparator. IV, inverse variance; LORAZ, lorazepam compared with dexmedetomidine; MIDAZOLAM, midazolam compared with dexmedetomidine; PROPOFOL, propofol compared with dexmedetomidine; SC, standard care compared with dexmedetomidine.

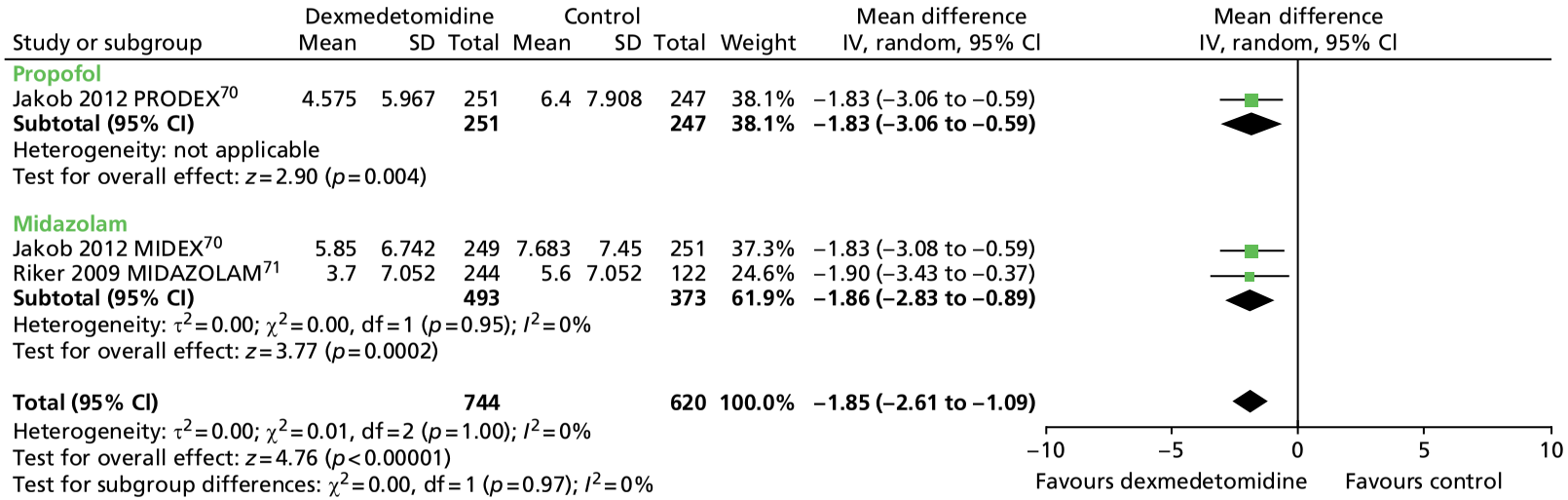

FIGURE 33 Meta-analysis for time to extubation according to type of comparator. IV, inverse variance; MIDAZOLAM, midazolam compared with dexmedetomidine; PROPOFOL, propofol compared with dexmedetomidine; SC, standard care compared with dexmedetomidine.

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