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Dexmedetomidine for Sedation in the Critical Care Setting: An Economic Assessment

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Authors: Anthony Budden, Omar Akhtar, Samer Nuwwareh

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Reviewers

External Reviewers

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Rakesh V. Patel, MD, PharmD, MSc

Authorship

Anthony Budden was involved in reviewing the literature, conceptualizing the economic analysis, collecting cost information, and drafting the report.

Omar Akhtar was involved in review in the literature, assisting with the economic analysis, and reviewing drafts of the report.

Samer Nuwwareh was involved with the clinical review of the evidence.

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Conflicts of Interest

There were no conflicts of interest declared.

Summary

- Findings from a focused clinical review of the comparative effectiveness of dexmedetomidine versus traditional sedatives (propofol, midazolam, or lorazepam) found that the characteristics of the identified clinical studies differed in terms of patient populations, settings, design, and results. Hence, results from individual clinical studies may not be generalizable outside the specific populations and settings in which the studies were undertaken.
- A cost analysis was undertaken to assess dexmedetomidine compared with traditional sedatives (lorazepam, midazolam, or propofol) in specific populations and settings, based on clinical studies selected from the clinical review in consultation with a Canadian clinical expert as most relevant to the Canadian clinical setting.
- The results of the analysis indicate that dexmedetomidine may be cost saving based on the underlying assumptions, which may differ between clinical settings.

Background

In 2014, CADTH undertook two rapid response projects, *Dexmedetomidine for Sedation of Patients in the ICU or PICU: Review of Clinical Effectiveness and Safety*[1] and *Dexmedetomidine for Sedation in the ICU or PICU: A Review of Cost-Effectiveness and Guidelines*.[2]

The CADTH Rapid Response on the cost-effectiveness of dexmedetomidine identified six economic evaluations that were deemed relevant for inclusion and comment.[2] The majority of the economic analyses reported that dexmedetomidine was associated with lower intensive care unit (ICU) and hospital costs and, as a result, with lower total costs compared with traditional sedatives. However, the authors of these economic analyses noted that the clinical benefits were marginal and not consistent among the included studies.

Since 2014, no cost-effectiveness studies of dexmedetomidine have been undertaken in the Canadian setting.

CADTH undertook a focused clinical review to determine the comparative effectiveness of dexmedetomidine versus midazolam, propofol, or lorazepam (Appendix 6) for use in the economic assessment. The results of the clinical review indicated that dexmedetomidine appears to result in a reduced incidence of delirium compared with midazolam and propofol; a reduced time to extubation and duration of mechanical ventilation compared with midazolam; and a higher rate of bradycardia compared with lorazepam, midazolam, and propofol. However, many of the other parameters reported results that were inconclusive or difficult to interpret. The key findings of importance to the economic assessment were the impact of dexmedetomidine on duration of stay in the ICU, duration of mechanical ventilation, and impact on episodes of delirium, with and without agitation.

Context and Policy Issues

Dexmedetomidine is available in a concentration of 100 mcg/mL in a 2 mL glass vial.[3] At the maximum allowed daily dose, dexmedetomidine is more expensive than midazolam, lorazepam, and propofol. However, it is not clear whether the higher cost of dexmedetomidine is offset by its suggested benefits.

CADTH customers have requested information on the comparative cost-effectiveness of dexmedetomidine to assess its use for sedation in a Canadian ICU setting to facilitate invasive or non-invasive ventilation.

Research Question

What is the comparative cost-effectiveness of dexmedetomidine versus conventional sedatives (propofol, lorazepam, and midazolam) for the sedation of patients in a Canadian ICU setting to facilitate invasive or non-invasive ventilation?

Review of Economic Literature

An updated review of the published and grey literature was conducted to identify relevant economic evaluations that assessed dexmedetomidine as a treatment for sedation in hospital ICUs since the publication of the 2014 CADTH review.[2] Therefore, the search was limited to documents published between January 1, 2014, and September 15, 2016.

The updated search identified 294 citations. Two reviewers screened the titles and abstracts to determine potentially relevant articles for retrieval based on the following criteria: economic studies (cost-utility, cost-effectiveness, cost-consequence, or cost–benefit analyses) comparing dexmedetomidine with conventional sedatives (lorazepam, midazolam, and propofol) in patients treated in the ICU.

Two citations fulfilled the inclusion criteria and were retrieved for full-text review: one cost-utility analysis (Bioc et al.)[4] and a cost–benefit analysis (Carrasco et al.).[5] The cost-utility analysis by Bioc et al. considered non-benzodiazepine sedation (e.g., dexmedetomidine or propofol) compared with sedation with benzodiazepines, but did not present the results stratified by individual treatment. The article by Carrasco et al. assessed the cost–benefit profile of dexmedetomidine compared with propofol in critically ill, non-intubated patients who were in an agitated, delirious state and who were refractory to haloperidol treatment at a single site in the UK.[5] The authors found that dexmedetomidine was overall less costly than propofol because it resulted in shorter ICU stays, and that its use had greater intangible or difficult-to-quantify benefits, including a potential decrease in the risk of orotracheal intubation. The applicability of these studies to the research question of this review is limited, given that the focus of the current study is on Canadian costs and practices. Appendix 1 provides further details of these studies.

Three additional studies that undertook cost analyses or cost-minimization analyses were identified.[6-8] Several study limitations were identified that limited the generalizability and applicability of these studies, including the objective of the study (e.g., assessment of the impact of a change in clinical practice); the cost information used (i.e., non-Canadian); and the comparisons assessed (e.g., use of dexmedetomidine after prior sedation with clonidine). Appendix 1 provides further details of these studies.

Based on the review of the literature, no relevant economic evaluations specifically addressing the research question were identified. Therefore, a *de novo* economic evaluation was deemed necessary.

Summary of the Clinical Review

The clinical review, based on a limited literature search of key resources, identified 19 publications describing 19 unique randomized controlled trials. The review found that dexmedetomidine was associated with statistically significantly lower delirium rates and shorter time to extubation than midazolam and propofol. Furthermore, dexmedetomidine was associated with a reduction in duration of mechanical ventilation when compared with midazolam, based on one large study.[9]

One study, reported in two publications, compared lorazepam and dexmedetomidine.[10,11] The results of this study were not conclusive, except for the incidence of bradycardia, which showed statistically significantly higher rates with dexmedetomidine. Likewise, dexmedetomidine was associated with higher rates of bradycardia compared with midazolam and propofol.

Full details on the clinical review are provided in Appendix 6.

Economic Evaluation

Methods

The objective of the study was to evaluate the cost-effectiveness of dexmedetomidine versus conventional sedatives (lorazepam, midazolam, and propofol) for the sedation of patients in a Canadian ICU setting to facilitate invasive or non-invasive ventilation.

The findings from the clinical review indicate there may be some benefit to using dexmedetomidine compared with traditional sedatives. However, because of heterogeneity in the patient populations and outcomes reported, and inconsistency in reporting between the studies, literature was selected to inform the economic evaluation in consultation with a clinical expert to ensure relevance to the Canadian clinical setting.

Type of Analysis

The original intent of the economic exercise was to conduct a cost-effectiveness analysis, although this was subject to the availability and suitability of the clinical findings. Several issues were identified that precluded the feasibility of a modelling exercise, including the lack of comparative data, population heterogeneity within and across studies, different clinical practices within the studies, the capture of different clinical outcomes among the studies, and the use of different methodologies.

Given the complexities of the clinical evidence, a cost analysis, rather than a cost-effectiveness analysis, was conducted. Costs were applied to individual studies, depending on the available information. The clinical studies selected were those in which the populations were deemed relevant to the Canadian setting, based on clinical expert consultation.

The analyses assessed dexmedetomidine with the specific comparator from the study. Evidence gaps exist in several parameters of interest, and these gaps were explored, where possible, in sensitivity analyses.

Target Populations and Settings

The target population for the economic evaluation was patients admitted to Canadian ICUs who required sedation to facilitate invasive or non-invasive ventilation.

The base-case analyses were undertaken in patient populations based on feedback from a clinical expert regarding the three clinical studies that best represented the Canadian population and the use of dexmedetomidine compared with each of the three comparators (Table 1).

Relevant studies were identified by a clinical expert and included regardless of how treatment was dosed and administered — i.e., studies were included even if they did not use Canadian dosage practices.

Table 1: Populations for the Base-Case Analyses

Study	Comparison	Population
Pandharipande et al. 2007[12]	Dexmedetomidine: **Initial dose 0.15 mcg/kg/h; titrate to max 1.5 mcg/kg/h** **Lorazepam:** **Initiate at 1 mg/h, titrate to max 10 mg/h**	**Adult medical and surgical ICU patients (includes sepsis, pulmonary, shock, malignancy, post-surgical) who require MV for longer than 24 h, who have no history of neurological disease, and who can be sedated for up to 5 days**
Riker et al. 2009[13]	Dexmedetomidine: **Optional loading dose. Initial dose 0.8 mcg/kg/h; titrate between 0.2 mcg/kg/h and 1.4 mcg/kg/h** Midazolam: **Optional loading dose. Start at 0.06 mg/kg/h, titrate between 0.02 mg/kg/h and 1.0 mg/kg/h**	**Adult medical and surgical ICU patients (sepsis, shock, pneumonia, post-surgical) who were intubated and receiving MV for < 96 h before start of study drug, and were expected to require ventilation and sedation for at least 3 more days**
Djaiani et al. 2016[14]	Dexmedetomidine: **Bolus loading dose 0.4 mcg/kg (10 min to 20 min); maintenance infusion range 0.2 mcg/kg/h to 0.7 mcg/kg/h** Propofol: **25 mcg/kg/min to 50 mcg/kg/min**	**Patients aged 60 years or older who underwent cardiac surgery or older than 70 years who underwent isolated coronary revascularization or single-valve repair/replacement surgery, and who did not have a history of serious mental illness, delirium, or severe dementia.**

ICU = intensive care unit; max = maximum; MV = mechanical ventilation.

Perspective

The analysis was undertaken from the perspective of a Canadian hospital with an ICU.

Interventions

The intervention of interest, dexmedetomidine, was compared with conventional sedatives used in the ICU, specifically lorazepam, midazolam, and propofol. The dosage schedules reflect the dose used in the clinical studies. Differences in mean or median dose may have been due to the differences in dosage schedules among hospitals, or due to the differences in the patient populations, as sedative doses are titrated to achieve a target level of sedation. Further, sedation targets for individual patients change over the course of their ICU stay; for example, deep sedation may be required on days one and two, while less sedation may be required as patients move toward extubation or cessation of non-invasive ventilation. This further complicates comparisons of doses and dosage strategies. Therefore, no assessment regarding the comparability of the dosage schedules can reliably be undertaken, given the heterogeneity of the studies.

Cost-Analysis Inputs

The cost analysis required information for several parameters, including patient characteristics, clinical outcomes, and resource use and cost

information. The data-input tables are reported in Appendix 2, Appendix 3, and Appendix 4.

The clinical data were obtained from studies included in the CADTH clinical review. The outcomes of clinical importance identified in the CADTH review are reported in Table 29. Feedback was received from Canadian clinical experts and stakeholders regarding the clinical parameters likely to have an impact on the overall cost of treatment with dexmedetomidine compared with conventional sedatives. The following parameters were identified:

- Drug dose and duration (including patient characteristics as required)
- Duration of ICU stay
- Duration of mechanical ventilation
- Incidence of delirium
- Duration of delirium
- Incidence of agitation
- Duration of agitation.

Although initially considered, the incidence of bradycardia and hypotension was not included in the cost analysis, as the cost to treat these events was considered minimal by Canadian clinical experts.

If data for a clinical parameter were not available from the individual studies, the cost component was excluded from the analysis. Assumptions were made regarding patient characteristics as required, given the importance of dosage in the analysis.

If data regarding the incidence and duration of delirium or agitation events were collected in the studies, these were included in the cost analysis. However, if the incidence was available but the duration was not available, resource-use assumptions were made for the treatment of delirium and agitation based on feedback from a Canadian clinical expert. It was assumed that additional nurse time would be required to manage patients with delirium and that delirium was likely to last at least two days. In the base case, a value of three days was used in the analysis, with a lower bound of two days and an upper bound of four days. The expert indicated that agitation without delirium is rare. While delirium without agitation is not uncommon, the driver of management costs is the agitation portion of the delirium, and agitation is typically considered as a component of delirium. Based on this feedback, the assumption was made that any additional costs associated with agitation would be captured within the additional costs attributed to delirium. This assumption is tested in a scenario analysis.

The following cost inputs were considered as part of the economic analysis: drug costs, the cost of a day in the ICU, the cost of mechanical ventilation (assumed exclusive from the ICU cost), and the cost of treating a delirium episode in the ICU (assumed exclusive from the ICU cost).

Drug costs were derived from the QuintilesIMS DeltaPA database.[15] The DeltaPA database presents information from a range of sources, and, as a

consequence, reports a wide range of prices.[15] Due to the large variation in prices, the median cost was used for the base-case analysis, while the minimum and maximum prices were also reported if available. Only two different prices of dexmedetomidine were reported; thus, the value reported most often was used.

Hospital-specific data were obtained primarily from Ontario sources. The range of the cost of a day in ICU was derived from a report on Ontario hospitals (Schedule A, 2016/17 Ontario hospitals, Interprovincial per diem rates for inpatient services),[16] while the nursing cost was derived from the Ontario Nurses Association collective bargaining agreement as a proxy for the assumed cost required for additional nursing requirements when delirium is present in ICU patients.[17] In the Ontario Nurses Association collective agreement, the wage of nurses varies based on years of experience; thus, assumptions were made to identify a base value and the upper and lower bounds. The wage rate was based on the April 2017 values, and additional costs were applied for benefits and vacation pay.[18] The base value for the cost of a day in ICU was derived from a report by the Canadian Institute for Health Information, which reported this cost based on data captured in the Canadian Management Information System database.[19] Thus, the base value for the cost of a day in ICU is not specific to Ontario. The cost of mechanical ventilation was derived from a US publication, which reported that 31.9% of the cost of a stay in ICU can be attributed in to mechanical ventilation.[20]

The base-case analyses are presented as costs derived from each study reported, disaggregated by cost component (Appendix 3).

Assumptions

The following assumptions were made based on the quality and availability of data, as well as on feedback from a Canadian clinical expert:

- The cost of a day in the ICU is the same, regardless of which sedative is used.
- The cost of a day with mechanical ventilation was added to the cost of a day in ICU. This may overestimate the cost of a day in ICU with mechanical ventilation, but a Canadian cost of a day in ICU stratified by mechanical ventilation could not be identified.
- The cost of additional nurse resources to manage patients with delirium and agitation is exclusive from the cost of a day in ICU.
- The duration of an episode of delirium is three days.

Sensitivity Analyses

Sensitivity analyses were conducted to evaluate the degree to which the uncertainty in cost and clinical parameters affected the findings of the cost analysis.

A series of multi-way sensitivity analyses on the parameter values were undertaken to test the robustness of the results. The analyses were

performed on the upper and lower bounds of the clinical and cost-model inputs. When possible, the upper and lower bounds were reported as identified in their respective original sources, and could represent 95% confidence intervals (based on standard deviation), interquartile range, or range. The values for the base-case analyses are reported in Table 2.

Table 2: Measurements of the Clinical Data Used in the Comparisons

Comparison	Base Value	Bounded Values
Dexmedetomidine versus lorazepam	**Median**	**Interquartile range**
Dexmedetomidine versus midazolam	**Median**	**Interquartile range**
Dexmedetomidine versus propofol	**Median**	**Range**

These measurements, used for the rest of the studies, can be seen in the data-table inputs in Appendix 3. A probabilistic sensitivity analysis was not undertaken. If there were no upper and lower values available, the high and low values were based on ± 20% of the parameter's base value for most parameters. The exception to this was the upper and lower dose ranges of the sedatives, which were derived from the Health Canada–approved product monographs for dexmedetomidine, lorazepam, midazolam, and propofol.[3,21-23] Dose ranges in the lorazepam product monograph differed substantially from the dosage protocol used in the included study. Due to the uncertainty associated with an appropriate dosage schedule, the upper and lower dose ranges were determined as ± 20% the base value.

Scenario Analyses

Scenario analyses were conducted to evaluate the impact of the model on different model assumptions. The following scenarios were tested:

- Cost of agitation events were included.
- Costs were applied to five additional studies (identified in the CADTH clinical review). Results were reported with and without the inclusion of agitation events.

Model Results

Base Case

Table 3 presents the results of the cost analysis comparing dexmedetomidine with lorazepam in adult medical and surgical ICU patients, as defined by the 2007 study by Pandharipande et al.[12] The total estimated cost per patient was $27,209 for dexmedetomidine and $32,366 for lorazepam. The cost savings (approximately $5,000) associated with dexmedetomidine were driven primarily by ICU costs based on the clinical findings, which indicated a non-significant reduction in the duration of stay in the ICU for patients sedated with dexmedetomidine compared with lorazepam (7.5 days versus 9 days, $P = 0.92$). Information on the need for and duration of mechanical ventilation were difficult to interpret because of the way these were reported in the study (mechanical ventilation–free days per 28-day period) and thus were not included, and the incidence and duration of delirium were not collected.

Table 3: Base-case Analysis Results: Dexmedetomidine Versus Lorazepam

Comparison:	**Dexmedetomidine versus lorazepam**		
Study:	**Pandharipande et al. 2007[12]**		
Population:	**Adult medical and surgical ICU patients (includes sepsis, pulmonary, shock, malignancy, post-surgical) who require MV for longer than 24 h, who have no history of neurological disease, and who can be sedated for up to 5 days**		
Component	Cost of Treatment With Dexmedetomidine	Cost of Treatment With Lorazepam	Incremental Cost
Drug cost	**$269**	**$38**	**$231**
ICU costs (exclusive of MV)	**$26,940**	**$32,328**	**–$5,388**
Cost of MV	**$0**	**$0**	**$0**
Cost of treating delirium	**$0**	**$0**	**$0**
Total cost	**$27,209**	**$32,366**	**–$5,157**

ICU = intensive care unit; MV = mechanical ventilation.

Table 4 presents the results of the cost analysis comparing dexmedetomidine with midazolam in adult medical and surgical ICU patients, as defined by the 2009 study by Riker et al.[13] The total estimated cost per patient was $26,762 for dexmedetomidine and $34,012 for midazolam; thus, dexmedetomidine was associated with a cost saving of approximately $7,000. The additional drug cost associated with dexmedetomidine was offset by the increased costs associated with the duration of stay in ICU observed in the study (5.7 days versus 7.6 days, *P* = 0.24). Information on the need for and duration of mechanical ventilation, and the incidence and duration of delirium, were not reported in the study.

Table 4: Base-Case Analysis Results: Dexmedetomidine Versus Midazolam

Comparison:	**Dexmedetomidine versus midazolam**		
Study:	**Riker et al. 2009[13]**		
Population:	**Adult medical and surgical ICU patients (sepsis, shock, pneumonia, post-surgical) who were intubated and receiving MV for < 96 h before start of study drug, and were expected to require ventilation and sedation for at least 3 more days**		
Component	Cost of Treatment With Dexmedetomidine	Cost of Treatment With Midazolam	Incremental Cost
Drug cost	**$1,330**	**$296**	**$1,033**
ICU costs (exclusive of MV)	**$21,193**	**$27,299**	**–$6,106**
Cost of MV	**$4,240**	**$6,417**	**–$2,177**
Cost of treating delirium	**$0**	**$0**	**$0**
Total cost	**$26,762**	**$34,012**	**–$7,250**

ICU = intensive care unit; MV = mechanical ventilation.

Table 5 presents the results of the cost analysis comparing dexmedetomidine with propofol in patients aged 60 years or older who underwent elective cardiac surgery, as defined by Djaiani et al. 2016.[14] The total estimated cost per patient was $7,148 for dexmedetomidine and $5,587

for propofol; thus, dexmedetomidine was associated with an incremental cost ($1,561). Dexmedetomidine was associated with a higher drug cost (based on assumed mean doses of dexmedetomidine of 0.8 mcg/kg/h, and of propofol of 1.5 mg/kg/h) and a lower cost associated with treating delirium based on a shorter duration of post-operative delirium in the dexmedetomidine group (two days versus three days, *P* = 0.04), but was also associated with increased costs based on duration of time in ICU observed in the study (43 hours versus 29 hours, no *P* value reported). Information on the duration of mechanical ventilation was not reported in the study.

Table 5: Base-Case Analysis Results: Dexmedetomidine Versus Propofol

Comparison:	**Dexmedetomidine versus propofol**		
Study:	**Djaiani et al. 2016[14]**		
Population:	**Patients aged 60 years or older who underwent cardiac surgery or older than 70 years who underwent isolated coronary revascularization or single-valve repair/replacement surgery, and who did not have a history of serious mental illness, delirium, or severe dementia.**		
Component	Cost of Treatment With Dexmedetomidine	Cost of Treatment With Propofol	Incremental Cost
Drug cost	**$341**	**$149**	**$192**
ICU costs (exclusive of MV)	**$6,430**	**$4,418**	**$2,012**
Cost of MV	**$0**	**$0**	**$0**
Cost of treating delirium	**$378**	**$1,020**	**–$642**
Total cost	**$7,148**	**$5,587**	**$1,561**

ICU = intensive care unit; MV = mechanical ventilation.

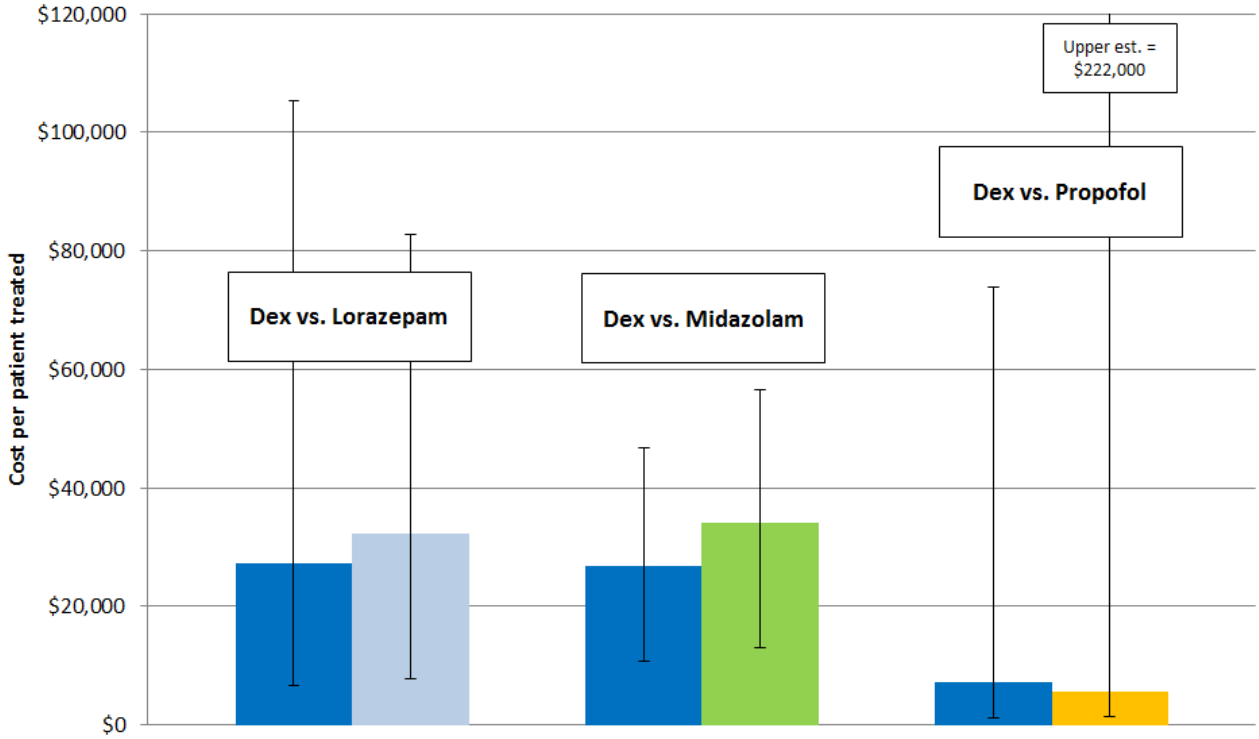
Sensitivity Analysis

Figure 1 reports the results of the multi-way sensitivity analyses and indicates the variability in the results using the upper or lower bound for each of the parameter inputs for the lorazepam, midazolam, or propofol studies.

The upper and lower bounds for the lorazepam and midazolam studies were reported based on interquartile ranges. In the propofol study, a range was reported, which can explain the large differences in the upper bounds for the assessment of dexmedetomidine and propofol compared with the assessments of dexmedetomidine and lorazepam, and the assessments of dexmedetomidine and midazolam.

The analysis comparing dexmedetomidine with lorazepam indicates that, when the upper bound is considered, dexmedetomidine is estimated to be more costly than lorazepam. This is driven by the bounds around the ICU length of stay reported in the study (Table 11).

Figure 1: Multi-way Sensitivity Analysis Results



Dex = dexmedetomidine; est. = estimate; vs. = versus.

Legend: blue = dexmedetomidine; light blue = lorazepam; green = midazolam; yellow = propofol.

Scenario Analysis

The results of the scenario analyses indicate substantial variability, based on the different studies and populations assessed (Appendix 5). The majority of the scenario analyses supported the results of the base-case analysis that dexmedetomidine may be less costly than conventional sedatives, depending on the circumstances and clinical assumptions. There was one outlier scenario: an analysis comparing dexmedetomidine with propofol in patients admitted to the ICU for early septic shock (based on the study by Memis et al.[24]), which indicated that dexmedetomidine was notably more costly than propofol ($7,372). This was driven by a difference in ICU length of stay in the study.

The results of the scenario analyses also indicated that the inclusion of costs associated with agitation did not affect the results of the analysis.

Discussion

The following limitations should be noted in light of the paucity of information:

- The treatment protocols in the included studies may not be reflective of Canadian clinical practice; however, feedback from the clinical expert indicated that the patient populations were likely to be representative.
- The generalizability of the results of the studies is uncertain, as study populations may not be reflective of Canadian populations, and outcome measures may not be used in Canada.
- The lack of disaggregated information on ICU costs raises issues of potential double-counting. For example, it is likely that mechanical ventilation is included in the cost of a day in ICU, although how this cost should be weighted compared with the cost of a day in ICU with no mechanical ventilation is uncertain.
- The main driver of the results is the cost of the ICU stay, which is based on results that were not statistically significant in all studies.
- The impact of delirium with or without agitation is associated with different costs and requires different levels of care. Given the lack of disaggregated cost information available, the assumptions and costs used may differ depending on the geographic location and hospital setting.
- The impact of delirium with or without agitation may not be fully captured in the analysis, as feedback from the clinical expert indicated that nurses may cover multiple patients in the ICU, and any additional resources spent to manage a patient with delirium may have an impact on other patients within the ICU.
- The clinical expert noted that delirium is not a dichotomous variable and has a spectrum of severity. This spectrum influences greatly the intervention(s) needed, health care personnel needed, and duration of such needs. The available data for delirium were presented as a dichotomous variable (i.e., either delirium was present or it was not). This results in some uncertainty as to whether the type of sedation affected the severity of the delirium event.
- Even when the increased nursing requirements are factored into the costs to treat agitation, the impact of agitation events on total ICU costs is likely to be underestimated; however, there are no data to assess this impact.

Conclusions

In the cost analysis comparing the use of dexmedetomidine with traditional sedatives (lorazepam, midazolam, or propofol) in hospital ICUs, dexmedetomidine is associated with greater drug costs than the comparator sedatives but may result in reduced costs associated with length of ICU stay and incidence of delirium. However, this was not always the case, as these findings varied notably depending on the comparator, the population assessed, and underlying assumptions (specifically concerning a reduced length of stay in the ICU).

Appendix 1: Review of Identified Published Economic Literature

Table 6: Summary of Published Economic Literature

First Author	Country, Perspective	Population	Comparators	Modelling Approach	Inputs Modelled	Conclusion
Economic Evaluations						
Carrasco et al. 2016[5]	**UK, TPP**	**Adult admissions to a medical-surgical ICU with a diagnosis of agitated delirium**	**Dex versus propofol**	**Cost–benefit analysis**	**Pharmaceutical costs (total dose, time), direct and indirect cost of care (time in ICU)**	**Dex is cost saving, but also associated with intangible or difficult-to-quantify benefits (e.g., decrease of orotracheal intubation risk).**
Bioc et al. 2014[4]	**US (assumed, based on inputs), TPP**	**Non-cardiac surgery, critically ill adults requiring ≥ 1 day of MV**	**Benzo versus non-benzo–based sedation (Dex/ propofol)**	**Cost-utility, Markov cohort model**	**ICU length of stay, duration of MV, delirium prevalence, and short-term mortality**	**ICER for non-benzo regimen sedation versus benzo regimen sedation to avert a day in the ICU was $3,136. ICER to avert a day on MV was $3,406. No difference between non-benzo treatments.**
Cost Analyses						
Gagnon et al. 2015[7]	**US (assumed), hospital**	**Adults receiving sedation in the ICU (excluding cardiac and cardiothoracic surgery patients)**	**Dex versus clonidine**	**Cost-minimization (drug-acquisition cost only)**	**Drug-acquisition cost**	**Transitioning Dex patients to clonidine was well tolerated and associated with cost savings.**
Schliki et al. 2016[8]	**US (assumed), hospital**	**Patients who received Dex for ICU sedation while on MV (excluding vulnerable populations, fast-track**	**Dex (pre- and post-Dex use guideline change)**	**Cost analysis**	**Drug-acquisition cost, total cost of hospital stay**	**Change in Dex use guidelines decreased aggregate use of Dex and increased cost**

First Author	Country, Perspective	Population	Comparators	Modelling Approach	Inputs Modelled	Conclusion
		cardiothoracic surgery patients, and intraoperative use)				**savings without adversely affecting clinical outcomes.**
Turunen et al. 2015[6]	**Europe, NR**	**Population data based on PRODEX and MIDEX studies**	**Dex versus midazolam, Dex versus propofol**	**Cost-minimization approach**	**Net effect of Dex on total ICU costs**	**Median total ICU costs lower with Dex versus midazolam and propofol alone and when pooled**

Benzo = benzodiazepine; Dex = dexmedetomidine; ICER = incremental cost-effectiveness ratio; ICU = intensive care unit; MV = mechanical ventilation; NR = not reported; TPP = third-party payer.

Appendix 2: Patient Characteristics From the Trials

Table 7: Patient Characteristics: Lorazepam Studies

Source	MENDS – Pandharipande et al. 2007[12]	
Trial population	**Adult medical and surgical ICU patients (includes sepsis, pulmonary, shock, malignancy, post-surgical) who require MV for longer than 24 h, who have no history of neurological disease, and who can be sedated for up to 5 days**	
Treatments	Dexmedetomidine	Lorazepam
Patient age[a]	**60 (49 to 65)**	**59 (45 to 67)**
Patient weight (kg)	**NR**	**NR**
Dosage[a]	**0.74 mcg/kg/h (0.39 mcg/kg/h to 1.04 mcg/kg/h)**	**3.0 mg/h (2.2 mg/h to 6.0 mg/h)**
Duration of dosage (h)	**NR**	**NR**
Dosage protocol	**Initiate at 0.15 mcg/kg/h, titrate to max 1.5 mcg/kg/h**	**Initiate at 1 mg/h, titrate to max 10 mg/h**

ICU = intensive care unit; max = maximum; MV = mechanical ventilation; NR = not reported.
[a] Median (interquartile range).

Table 8: Patient Characteristics: Midazolam Studies

Source	SEDCOM – Riker et al. 2009[13]	
Trial population	**Adult medical and surgical ICU patients (sepsis, shock, pneumonia, post-surgical) who were intubated and receiving MV for < 96 h before start of study drug, and were expected to require ventilation and sedation for at least 3 more days**	
Treatments	Dexmedetomidine	Midazolam
Patient age[a]	**61.5 (14.8)**	**62.9 (16.8)**
Patient weight (kg)[a]	**88.1 (33.9)**	**87.8 (31.5)**
Dosage[a]	**0.83 mcg/kg/h (0.37 mcg/kg/h)**	**0.056 mcg/kg/h (0.028 mg/kg/h)**
Duration of dosage (h)[b]	**84 (48 to 124.8)**	**98.4 (67.2 to 146.4)**
Dosage protocol	**Optional loading dose. Start at 0.8 mcg/kg/h, titrate between 0.2 and 1.4 mcg/kg/h**	**Optional loading dose. Start at 0.06 mg/kg/h, titrate between 0.02 and 1.0 mg/kg/h**
Source	MIDEX – Jakob et al.[9]	
Trial population	**Adult medical, surgical and trauma patients on invasive MV who had been in ICU for up to 72 h (and up to 48 h continuous sedation) with clinical need for light to moderate sedation for at least 24 h post-treatment initiation**	
Treatments	Dexmedetomidine	Midazolam
Patient age[b]	**65 (55 to 74)**	**65 (55 to 74)**
Patient weight	**NR**	**NR**
Dosage[b]	**0.450 mcg/kg/h (0.273 mcg/kg/h to 0.756 mcg/kg/h)**	**0.062 mg/kg/h (0.041 mg/kg/h to 0.098 mg/kg/h)**
Duration of dosage (h)[b]	**42 (23 to 72)**	**43 (24 to 92)**
Dosage protocol	**No loading dose; 0.2 mcg/kg/h to 1.4 mcg/kg/h**	**No loading dose; 0.03 mg/kg/h to 0.2 mg/kg/h**

ICU = intensive care unit; MV = mechanical ventilation; NR = not reported.
[a] Mean (standard deviation).
[b] Median (interquartile range).

Table 9: Patient Characteristics: Propofol Studies

Source	Djaiani et al.[14]	
Trial population	**Patients aged 60 years or older who underwent cardiac surgery or older than 70 years who underwent isolated coronary revascularization or single-valve repair/replacement surgery, and who did not have a history of serious mental illness, delirium, or severe dementia.**	
Treatments	Dexmedetomidine	Propofol
Patient age[a]	**72.7 (6.4)**	**72.4 (6.2)**
Patient weight (kg)[a]	**82.0 (15.3)**	**79.6 (16.9)**
Dosage	**NR**	**NR**
Duration of dosage (h)	**NR**	**NR**
Dosage protocol	**Bolus loading dose 0.4 mcg/kg (10 min to 20 min), maintenance infusion 0.2 mcg/kg/h to 0.7 mcg/kg/h**	**25 mcg/kg/min to 50 mcg/kg/min**
Source	PRODEX – Jakob et al.[9]	
Trial population	**Adult medical, surgical and trauma patients on invasive MV who had been in ICU for up to 72 h (and up to 48 h continuous sedation) with clinical need for light to moderate sedation for at least 24 h post-treatment initiation**	
Treatments	Dexmedetomidine	Propofol
Patient age[b]	**65 (51 to 75)**	**65 (51 to 74)**
Patient weight (kg)	**NR**	**NR**
Dosage[b]	**0.925 mcg/kg/h (0.673 mcg/kg/h to 1.17 mcg/kg/h)**	**1.752 mcg/kg/h (1.211 mcg/kg/h to 2.424 mcg/kg/h)**
Duration of dosage (h)[b]	**42 (22 to 72)**	**47 (25 to 103)**
Dosage protocol	**No loading dose; 0.2 mcg/kg/h to 1.4 mcg/kg/h**	**No loading dose; 0.3 mcg/kg/h to 4 mg/kg/h**
Source	Liu et al. 2016[25]	
Trial population	**Adult patients who underwent elective cardiac valve surgery with cardiopulmonary bypass, who were admitted to the ICU, intubated and ventilated**	
Treatments	Dexmedetomidine	Propofol
Patient age[b]	**55 (48 to 62)**	**53 (48 to 63)**
Patient weight	**NR**	**NR**
Dosage[b]	**0.67 mcg/kg/h (0.38 mcg/kg/h to 0.76 mcg/kg/h)**	**0.90 mcg/kg/h (0.73 mcg/kg/h to 1.19 mcg/kg/h)**
Duration of dosage (h)[b]	**14.4 (11.35 to 17.87)**	**14.2 (11.8 to 16.4)**
Dosage protocol	**No loading dose; 0.2 mcg/kg/h to 1.5 mcg/kg/h**	**No loading dose; 5 mcg/kg/h to 50 mcg/kg/min**
Source	Memis et al. 2009[24]	
Trial population	**Adult patients admitted to the ICU with early septic shock,[c] receiving MV. Only patients with arterial oxygen tension (Pao_2) between 80 and 140 mm Hg and arterial carbon dioxide tension ($Paco_2$) between 35 and 50 mm Hg were included.**	
Treatments	Dexmedetomidine	Propofol
Patient age[d]	**54 (25 to 78)**	**60 (31 to 80)**
Patient weight (kg)	**NR**	**NR**
Dosage[e]	**0.95 mcg/kg/h (0.6 mcg/kg/h to 1.4 mcg/kg/h)**	**1.8 mcg/kg/h (0.8 mcg/kg/h to 2.4 mcg/kg/h)**
Duration of dosage (h)	**NR**	**NR**

Dosage protocol	**Loading dose of 1 mcg/kg over 10 min, then 0.2 mcg/kg/h to 2.5 mcg/kg/h**	**Loading dose 1 mg/kg over 15 min, then 1 mcg/kg/h to 3 mg/kg/h**
Source	Herr et al.[26]	
Trial population	**Adults admitted to the ICU who underwent CABG surgery**	
Treatments	Dexmedetomidine	Propofol
Patient age[a]	**61.9 (9.5)**	**62.4 (8.7)**
Patient weight (kg)[a]	**85.0 (14.4)**	**84.1 (14.4)**
Dosage	**NR**	**NR**
Duration of dosage (h)	**NR**	**NR**
Dosage protocol	**Loading dose of 1 mcg/kg over 20 min, then maintained at 0.4 mcg/kg/h (range: 0.2 mcg/kg/h to 0.7 mcg/kg/h)**	**No dose or rate specified. Investigators instructed to follow usual dosage practice.**

CABG = coronary artery bypass graft; ICU = intensive care unit; MV = mechanical ventilation; NR = not reported.
[a] Mean (standard deviation).
[b] Median (interquartile range).
[c] Patients had to fulfill clinical and laboratory criteria of septic shock (as outlined in the panel recommendations from the 2001 International Sepsis Definitions Conference).
[d] Mean (range).
[e] Median (range).

The following assumptions were made when components were missing from the published report regarding the mean or median dose, duration of dose, or patient weight. The base values were estimated after considering the mean or median inputs from the other included studies for which data were available.

Table 10: Patient Characteristic Assumptions

Parameter	Base Value	Lower Bound	Upper Bound
Patient weight	**70 kg**	**56 kg[a]**	**84 kg[a]**
Duration of dose	**24 h**	**19.2 h[a]**	**28.8 h[a]**
Dosage of dexmedetomidine	**0.80 mcg/kg/h**	**0.2 mcg/kg/h[b]**	**1.10 mcg/kg/h[b]**
Dosage of lorazepam	**3 mg/h**	**2.4 mg/h[a]**	**3.6 mg/h[a]**
Dosage of midazolam	**0.06 mg/kg/h**	**0.01 mg/kg/h[b]**	**0.1 mg/kg/h[b]**
Dosage of propofol	**1.5 mg/kg/h**	**0.5 mg/kg/h[b]**	**2.5 mg/kg/h[b]**

[a] The upper and lower bounds were based on assumption of ± 20% difference from the base value.
[b] The upper and lower bounds were based on the ranges presented in the Health Canada–approved product monograph.

Appendix 3: Clinical Outcomes From Studies

Table 11: Clinical Inputs: Pandharipande et al. 2007

Trial	MENDS Trial (Pandharipande et al. 2007)[12]			
Population description	**Adult medical and surgical ICU patients (includes sepsis, pulmonary, shock, malignancy, post-surgical) who require MV for longer than 24 h, who have no history of neurological disease, and who can be sedated for up to 5 days.**			
Parameter	Dex	Lorazepam	*P* value	Notes
LOS in ICU (days)[a]	**7.5 (5 to 19)**	**9 (6 to 15)**	**0.92**	
Duration of MV (days)	**NR**	**NR**		**MV-free days reported. Median time from onset of MV to enrolment was 22.1 h (Dex) compared with 16.7 h (lorazepam). Not considered appropriate as a proxy**
Incidence of delirium (%)	**NR**	**NR**	**NA**	**Reports prevalence, not incidence. Incidence is not reported because pre-intensive delirium could not be determined. Prevalence is not a suitable proxy for incidence; as a result, these figures were not used.**
Duration of delirium (days)[b]	**NR**	**NR**	**NA**	**Duration was reported based on the prevalence numbers. Reported as delirium-free days (based on assumption of 1 week after 5-day sedation). Not used in analysis**
Incidence of agitation (%)	**NR**	**NR**	**NA**	
Duration of agitation (h)	**NR**	**NR**	**NA**	

Dex = dexmedetomidine; ICU = intensive care unit; LOS = length of stay; MV = mechanical ventilation; NA = not applicable; NR = not reported.
[a] Median (interquartile range).
[b] Delirium assessed as days alive without delirium or coma, and percentage of days spent within 1 point of the sedation goal on the Richmond Agitation–Sedation Scale (RASS). Patients monitored twice daily for delirium using the Confusion Assessment Method for the ICU (CAM-ICU) for as long as they were in hospital (up to 12 days).

Table 12: Clinical Inputs: Riker et al. 2009

Trial	SEDCOM Trial – Riker et al. 2009[13]			
Population description	**Adult medical and surgical ICU patients (sepsis, shock, pneumonia, post-surgical) who were intubated and receiving MV for < 96 h before start of study drug, and were expected to require ventilation and sedation for at least 3 more days**			
Parameter	Dex	Midazolam	*P* value	Notes
LOS in ICU (days)[a]	**5.9 (5.7 to 7.0)**	**7.6 (6.7 to 8.6)**	**0.24**	
Duration of MV (days)	**3.7 (3.1 to 4.0)**	**5.6 (4.6 to 5.9)**	**0.01**	**Time to extubation (start of study drug to successful extubation) was used as a proxy for duration of MV.**
Incidence of delirium (%)	**NR**	**NR**	**NA**	**Reports prevalence, not incidence. Approximately 60% in each group had delirium at baseline.**
Duration of delirium (days)[b]	**NR**	**NR**	**NA**	**Reported delirium-free days, calculated as days alive without delirium while on study drug**
Incidence of agitation (%)	**NR**	**NR**	**NA**	
Duration of agitation (h)	**NR**	**NR**	**NA**	

Dex = dexmedetomidine; ICU = intensive care unit; LOS = length of stay; MV = mechanical ventilation; NA = not applicable; NR = not reported.
[a] Median (interquartile range).
[b] Delirium assessed daily during the arousal assessment with patients in the Richmond Agitation–Sedation Scale (RASS) range of −2 to 1 using the Confusion Assessment Method for the ICU (CAM-ICU).

Table 13: Clinical Inputs: Jakob et al. 2012 (MIDEX)

Trial	MIDEX Trial – Jakob et al.[9]			
Population description	**Adult medical, surgical, and trauma patients on invasive MV who had been in ICU for up to 72 h (and up to 48 h continuous sedation) with clinical need for light to moderate sedation for at least 24 h post-treatment initiation**			
Parameter	Dex	Midazolam	*P* value	Notes
LOS in ICU (days)[a]	**8.79 (4.79 to 34.63)**	**10.13 (5.83 to 26.25)**	**NS**	
Duration of MV (days)[a]	**5.13 (2.79 to 14.04)**	**6.83 (3.83 to 15.83)**	**NS**	**Time post-randomization; includes non-invasive MV**
Incidence of delirium (%)[b]	**7.7**	**7.6**	**NR**	**Total incidence of delirium. Also reported that 7.3% and 6.8% of Dex and midazolam patients, respectively, required intervention for delirium**
Duration of delirium (days)	**NR**	**NR**	**NA**	
Incidence of agitation (%)	**15**	**14.4**	**NR**	**Total incidence of agitation. Also reported that 13.4% and 11.6% of Dex and midazolam patients, respectively, required intervention for agitation**
Duration of agitation (h)	**NR**	**NR**	**NA**	

Dex = dexmedetomidine; ICU = intensive care unit; LOS = length of stay; MV = mechanical ventilation; NA = not applicable; NR = not reported; NS = not significant (*P* value not reported).
[a] Median (interquartile range).
[b] Delirium assessed by clinician assessment, presence of adverse events, then supplemented using the Confusion Assessment Method for the ICU (CAM-ICU) 48 h after stopping sedative. Uncertain whether incidence of delirium informed by CAM-ICU.

Table 14: Clinical Inputs: Djaiani et al. 2016

Trial	Djaiani et al.[14]			
Population description	**Patients aged 60 years or older who underwent cardiac surgery or older than 70 years who underwent isolated coronary revascularization or single-valve repair/replacement surgery, and who did not have a history of serious mental illness, delirium, or severe dementia.**			
Parameter	Dex	Propofol	*P* value	Notes
LOS in ICU (days)[a]	**1.79 (0.75 to 13.13)**	**1.23 (0.71 to 39.88)**	**0.38**	**Median (range) ICU LOS was longer in the propofol group for patients with delirium: 3.19 days (0.74 to 39.9) compared with 2.83 days (0.83 to 8.92).**
Duration of MV (days)	**NR**	**NR**	**NA**	
Incidence of delirium (%)[b]	**17.5**	**31.5**	**0.028**	**There was 13% versus 26% haloperidol use (Dex versus propofol), and 3.3% versus 5.4% quetiapine use.**
Duration of delirium (days)[a]	**2 (1 to 4)**	**3 (1 to 5)**	**0.04**	**Time to onset of delirium post-surgery was also reported.**
Incidence of agitation (%)	**NR**	**NR**	**NA**	
Duration of agitation (h)	**NR**	**NR**	**NA**	

Dex = dexmedetomidine; ICU = intensive care unit; LOS = length of stay; MV = mechanical ventilation; NA = not applicable; NR = not reported.
[a] Median (range).
[b] Assessment of delirium performed at baseline and at 12-hourly intervals or as needed using the Confusion Assessment Method for the ICU (CAM-ICU), and at discharge using the Confusion Assessment Method (CAM).

Table 15: Clinical Inputs: Jakob et al. 2012 (PRODEX)

Trial	PRODEX Trial – Jakob et al.[9]			
Population description	**Adult medical, surgical, and trauma patients on invasive MV who had been in ICU for up to 72 h (and up to 48 h continuous sedation) with clinical need for light to moderate sedation for at least 24 h post-treatment initiation**			
Parameter	Dex	Propofol	*P* value	Notes
LOS in ICU (days)[a]	**6.83 (3.75 to 20.0)**	**7.71 (3.88 to 21.67)**	**NS**	
Duration of MV (days)[a]	**4.04 (1.88 to 10.71)**	**4.92 (2.0 to 13.63)**	**NS**	**Time post-randomization. Includes non-invasive mechanical ventilation**
Incidence of delirium (%)[b]	**2.8**	**6.9**	**NR**	**Total incidence of delirium. Also reported that 2.5% and 6.5% of Dex and propofol patients, respectively, required intervention for delirium**
Duration of delirium (days)	**NR**	**NR**	**NA**	
Incidence of agitation (%)	**7.3%**	**11.3%**	**NR**	**Total incidence of agitation. Also reported that 6.1% and 9.7% of Dex and propofol patients, respectively, required intervention for agitation**
Duration of agitation (h)	**NR**	**NR**	**NA**	

Dex = dexmedetomidine; ICU = intensive care unit; LOS = length of stay; MV = mechanical ventilation; NA = not applicable; NR = not reported; NS = not significant (*P* value not reported).
[a] Median (interquartile range).
[b] Delirium assessed by clinician assessment, presence of adverse events, then supplemented using the Confusion Assessment Method for the ICU (CAM-ICU) 48 h after stopping sedative; uncertain whether incidence of delirium was informed by CAM-ICU.

Table 16: Clinical Inputs: Liu et al. 2016

Trial	Liu et al.[25]			
Population description	**Adult patients who underwent elective cardiac valve surgery with cardiopulmonary bypass, who were admitted to the ICU, intubated, and ventilated**			
Parameter	Dex	Propofol	*P* value	Notes
LOS in ICU (days)	**NR**	**NR**	**NA**	
Duration of MV (days)[a]	**0.79 (0.74 to 0.92)**	**0.88 (0.73 to 0.94)**	**0.784**	**Derived from time intubated post-randomization**
Incidence of delirium (%)	**NR**	**NR**	**NA**	
Duration of delirium (days)	**NR**	**NR**	**NA**	**Delirium reported as AE during ICU say though there is uncertainty as to whether this was pre- or post-sedation. More patients in the propofol arm were reported to experience delirium.**
Incidence of agitation (%)	**NR**	**NR**	**NA**	
Duration of agitation (h)	**NR**	**NR**	**NA**	

AE = adverse event; Dex = dexmedetomidine; ICU = intensive care unit; LOS = length of stay; MV = mechanical ventilation; NA = not applicable; NR = not reported.
[a] Median (interquartile range).
[b] Delirium assessed using the Confusion Assessment Method for the ICU (CAM-ICU). Timing of assessment not reported.

Table 17: Clinical Inputs: Memis et al. 2009

Trial	Memis et al. 2009[24]			
Population description	**Adult patients admitted to the ICU with early septic shock,[a] receiving MV. Only patients with arterial oxygen tension (Pao_2) between 80 and 140 mm Hg and arterial carbon dioxide tension ($Paco_2$) between 35 and 50 mm Hg were included.**			
Parameter	Dex	Propofol	*P* value	Notes
LOS in ICU (days)[b]	**14 (10.26 to 17.74)**	**12 (8.72 to 15.28)**	**> 0.05**	**After treatment initiation**
Duration of MV (days)	**NR**	**NR**	**NA**	
Incidence of delirium (%)[c]	**NR**	**NR**	**NA**	
Duration of delirium (days)	**NR**	**NR**	**NA**	
Incidence of agitation (%)	**NR**	**NR**	**NA**	
Duration of agitation (h)	**NR**	**NR**	**NA**	

Dex = dexmedetomidine; ICU = intensive care unit; LOS = length of stay; MV = mechanical ventilation; NA = not applicable; NR = not reported.
[a] Patients had to fulfill clinical and laboratory criteria of septic shock (as outlined in the panel recommendations from the 2001 International Sepsis Definitions Conference)
[b] Median (interquartile range).
[c] Delirium not assessed.

Table 18: Clinical Inputs: Herr et al. 2013

Trial	Herr et al.[26]			
Population description	**Adults admitted to the ICU who underwent CABG surgery**			
Parameter	Dex	Propofol	*P* value	Notes
LOS in ICU (days)	**NR**	**NR**	**NA**	
Duration of MV (days)[a]	**NR**	**NR**	**NA**	**Data on time to extubation post-sternal closure, from time patients started Dex but before arriving in the ICU. Determined not appropriate to use as a proxy for duration of MV.**
Incidence of delirium (%)[b]	**NR**	**NR**	**NA**	
Duration of delirium (days)	**NR**	**NR**	**NA**	
Incidence of agitation (%)[c]	**3**	**0.68**	**0.214**	
Duration of agitation (h)	**NR**	**NR**	**NA**	

CABG = coronary artery bypass graft; Dex = dexmedetomidine; ICU = intensive care unit; LOS = length of stay; MV = mechanical ventilation; NA = not applicable; NR = not reported.
[a] Median (interquartile range).
[b] Delirium not assessed.
[c] Not specified how agitation is assessed.

Appendix 4: Resource Use and Cost Inputs

Table 19: Resource Use Assumptions

Parameter	Input/Value	Sensitivity Analysis	Source
Delirium	**Nurse time for 72 h**	**Range: 48 h to 96 h**	**Feedback from clinical expert**
Agitation	**No impact**	**Test in scenario analysis, applying same inputs as delirium**	**Feedback from clinical expert**
Proportion of ICU cost attributed to MV (used to derive MV cost per day)	**32%**	**No values tested**	**Lachaine et al.[27]**

ICU = intensive care unit; MV = mechanical ventilation.

Table 20: Cost Inputs

Cost parameter	Unit	Unit Value	Range Tested	Source
Dexmedetomidine	**mcg**	**$0.2165**	**$0.1732 to $0.2597**	**DeltaPA[15]**
Lorazepam	**mg**	**$0. 5300**	**$0.4935 to $1.0600**	**DeltaPA[15]**
Midazolam	**mg**	**$0.6120**	**$0.2448 to $1.3600**	**DeltaPA[15]**
Propofol	**mg**	**$0.0520**	**$0.0375 to $0.0650**	**DeltaPA[15]**
ICU	**day**	**$3,592**	**$1,298 to $5,512[a]**	**Schedule A: 2016/17 Ontario hospital interprovincial per diem rates for inpatient services; Care in Canadian ICUs[16,19]**
Mechanical ventilation	**day**	**$1,146**	**$917 to $1,375**	**Lachaine et al.[27]**
Delirium[b]	**hour**	**$44.99**	**$38.76 to $53.38**	**Collective agreement between "the Hospital" and Ontario Nurses' Association "the Union"[17]**
Agitation events[b,c]	**hour**	**$44.99**	**$38.76 to $53.38**	**Collective agreement between "the Hospital" and Ontario Nurses' Association "the Union"[17]**

ICU = intensive care unit.

[a] Range based on available data from Ontario hospitals in Schedule A.

[b] Cost based on assumed additional nurse time, from the hourly wages for a registered nurse on April 1, 2017, reported using a range based on years of experience, and includes benefits and vacation pay. Base value used 5 years' experience, with the upper and lower bounds using 2 years and 8 years.

[c] If included.

Appendix 5: Scenario Analyses

Table 21: Scenario Analysis Results: Pandharipande et al. 2007 (Dexmedetomidine Versus Lorazepam)

Comparison:	**Dexmedetomidine versus lorazepam**		
Study:	**Pandharipande et al. 2007[12]**		
Population:	**Adult medical and surgical ICU patients (includes sepsis, pulmonary, shock, malignancy, post-surgical) who require MV for longer than 24 h, who have no history of neurological disease, and who can be sedated for up to 5 days**		
Component	Cost of Treatment With Dexmedetomidine	Cost of Treatment With Lorazepam	Incremental Cost[a] (Dexmedetomidine Versus Lorazepam)
Drug cost	**$269**	**$38**	**$231**
ICU costs (exclusive of MV)	**$26,940**	**$32,328**	**–$5,388**
Cost of MV	**$0**	**$0**	**$0**
Cost of treating delirium	**$0**	**$0**	**$0**
Cost of treating agitation	**$0**	**$0**	**$0**
Total cost	**$27,209**	**$32,366**	**–$5,157**
Total cost (excl. agitation)	**$27,209**	**$32,366**	**–$5,157**

Excl. = excluding; ICU = intensive care unit; MV = mechanical ventilation.
[a] Results may not add up due to rounding of the values in the report.

Table 22: Scenario Analysis Results: Riker et al. 2009 (Dexmedetomidine Versus Midazolam)

Comparison:	**Dexmedetomidine versus midazolam**		
Study:	**Riker et al. 2009[13]**		
Population:	**Adult medical and surgical ICU patients (sepsis, shock, pneumonia, post-surgical) who were intubated and receiving MV for < 96 h before start of study drug, and were expected to require ventilation and sedation for at least 3 more days**		
Component	Cost of Treatment With Dexmedetomidine	Cost of Treatment With Midazolam	Incremental Cost[a] (Dexmedetomidine Versus Midazolam)
Drug cost	**$1,330**	**$296**	**$1,033**
ICU costs (exclusive of MV)	**$21,193**	**$27,299**	**–$6,106**
Cost of MV	**$4,240**	**$6,417**	**–$2,177**
Cost of treating delirium	**$0**	**$0**	**$0**
Cost of treating agitation	**$0**	**$0**	**$0**
Total cost	**$26,762**	**$34,012**	**–$7,250**
Total cost (excl. agitation)	**$26,762**	**$34,012**	**–$7,250**

Excl. = excluding; ICU = intensive care unit; MV = mechanical ventilation.
[a] Results may not add up due to rounding of the values in the report.

Table 23: Scenario Analysis Results: Djaiani et al. 2016 (Dexmedetomidine Versus Propofol)

Comparison:	Dexmedetomidine versus propofol		
Study:	Djaiani et al. 2016[14]		
Population:	Patients aged 60 years or older who underwent cardiac surgery or older than 70 years who underwent isolated coronary revascularization or single-valve repair/replacement surgery, and who did not have a history of serious mental illness, delirium, or severe dementia.		
Component	Cost of Treatment With Dexmedetomidine	Cost of Treatment With Propofol	Incremental Cost[a] (Dexmedetomidine Versus Propofol)
Drug cost	$341	$149	$192
ICU costs (exclusive of MV)	$6,430	$4,418	$2,012
Cost of MV	$0	$0	$0
Cost of treating delirium	$378	$1,020	–$642
Cost of treating agitation	$0	$0	$0
Total cost	$7,148	$5,587	$1,561
Total cost (excl. agitation)	$7,148	$5,587	$1,561

Excl. = excluding; ICU = intensive care unit; MV = mechanical ventilation.
[a] Results may not add up due to rounding of the values in the report.

Table 24: Scenario Analysis Results: Jakob et al. 2012 (MIDEX)

Comparison:	Dexmedetomidine versus midazolam		
Study:	Jakob et al. 2012 (MIDEX)[9]		
Population:	Adult medical, surgical, and trauma patients on invasive MV who had been in ICU for up to 72 h (and up to 48 h continuous sedation) with clinical need for light to moderate sedation for at least 24 h post-treatment initiation		
Component	Cost of Treatment With Dexmedetomidine	Cost of Treatment With Midazolam	Incremental Cost[a] (Dexmedetomidine Versus Midazolam)
Drug cost	$286	$114	$172
ICU costs (exclusive of MV)	$31,574	$36,387	–$4,813
Cost of MV	$5,878	$7,826	–$1,948
Cost of treating delirium	$249	$246	$3
Cost of treating agitation	$492	$531	–$39
Total cost	$38,480	$45,105	–$6,625
Total cost (excl. agitation)	$37,988	$44,573	–$6,586

Excl. = excluding; ICU = intensive care unit; MV = mechanical ventilation.
[a] Results may not add up due to rounding of the values in the report.

Table 25: Scenario Analysis Results: Jakob et al. 2012 (PRODEX)

Comparison:	Dexmedetomidine versus propofol		
Study:	Jakob et al. 2012 (PRODEX)[9]		
Population:	Adult medical, surgical, and trauma patients on invasive MV who had been in ICU for up to 72 h (and up to 48 h continuous sedation) with clinical need for light to moderate sedation for at least 24 h post-treatment initiation		
Component	Cost of Treatment With Dexmedetomidine	Cost of Treatment With Propofol	Incremental Cost[a] (Dexmedetomidine Versus Propofol)
Drug cost	**$589**	**$300**	**$289**
ICU costs (exclusive of MV)	**$24,533**	**$27,694**	**–$3,161**
Cost of MV	**$4,629**	**$5,637**	**–$1,008**
Cost of treating delirium	**$91**	**$224**	**–$133**
Cost of treating agitation	**$249**	**$379**	**–$130**
Total cost	**$30,091**	**$34,234**	**–$4,143**
Total cost (excl. agitation)	**$29,841**	**$33,855**	**–$4,013**

Excl. = excluding; ICU = intensive care unit; MV = mechanical ventilation.
[a] Results may not add up due to rounding of the values in the report.

Table 26: Scenario Analysis Results: Liu et al. 2016

Comparison:	Dexmedetomidine versus propofol		
Study:	Liu et al. 2016[25]		
Population:	Adult patients who underwent elective cardiac valve surgery with cardiopulmonary bypass, who were admitted to the ICU, intubated, and ventilated		
Component	Cost of Treatment With Dexmedetomidine	Cost of Treatment With Propofol	Incremental Cost[a] (Dexmedetomidine Versus Propofol)
Drug cost	**$146**	**$47**	**$100**
ICU costs (exclusive of MV)	**$0**	**$0**	**$0**
Cost of MV	**$902**	**$1,002**	**–$100**
Cost of treating delirium	**$0**	**$0**	**$0**
Cost of treating agitation	**$0**	**$0**	**$0**
Total cost	**$1,049**	**$1,049**	**–$1**
Total cost (excl. agitation)	**$1,049**	**$1,049**	**–$1**

Excl. = excluding; ICU = intensive care unit; MV = mechanical ventilation.
[a] Results may not add up due to rounding of the values in the report.

Table 27: Scenario Analysis Results: Memis et al. 2009

Comparison:	Dexmedetomidine versus propofol		
Study:	Memis et al. 2009[24]		
Population:	Adult patients admitted to the ICU with early septic shock, receiving MV. Only patients with arterial oxygen tension (Pao_2) between 80 and 140 mm Hg and arterial carbon dioxide tension ($Paco_2$) between 35 and 50 mm Hg were included.		
Component	Cost of Treatment With Dexmedetomidine	Cost of Treatment With Propofol	Incremental Cost[a] (Dexmedetomidine Versus Propofol)
Drug cost	**$345**	**$157**	**$188**
ICU costs (exclusive of MV)	**$50,288**	**$43,104**	**$7,184**
Cost of MV	**$0**	**$0**	**$0**
Cost of treating delirium	**$0**	**$0**	**$0**
Cost of treating agitation	**$0**	**$0**	**$0**
Total cost	**$50,633**	**$43,261**	**$7,372**
Total cost (excl. agitation)	**$50,633**	**$43,261**	**$7,372**

Excl. = excluding; ICU = intensive care unit; MV = mechanical ventilation.
[a] Results may not add up due to rounding of the values in the report.

Table 28: Scenario Analysis Results: Herr et al. 2003

Comparison:	Dexmedetomidine versus propofol		
Study:	Herr et al. 2003[26]		
Population:	Adults admitted to the ICU who underwent CABG surgery		
Component	Cost of Treatment With Dexmedetomidine	Cost of Treatment With Propofol	Incremental Cost[a] (Dexmedetomidine Versus Propofol)
Drug cost	**$353**	**$157**	**$196**
ICU costs (exclusive of MV)	**$0**	**$0**	**$0**
Cost of MV	**$0**	**$0**	**$0**
Cost of treating delirium	**$0**	**$0**	**$0**
Cost of treating agitation	**$97**	**$22**	**$75**
Total cost	**$450**	**$179**	**$271**
Total cost (excl. agitation)	**$353**	**$157**	**$196**

CABG = coronary artery bypass graft; Excl. = excluding; ICU = intensive care unit; MV = mechanical ventilation.
[a] Results may not add up due to rounding of the values in the report.

Appendix 6: Clinical Review

Context and Policy Issues

Delirium and agitation are common in critically ill patients; an 87% prevalence rate of delirium has been reported in patients in intensive care units (ICUs).[28] Several reports have linked delirium in ICU with higher mortality rates[29,30] and longer duration of mechanical ventilation.[29,30] These adverse events have an impact on hospital resources, with an estimated annual financial impact of $4 billion to $16 billion.[31]

Zaal et al.[32] conducted a meta-analysis of studies that reported on the potential risk factors for delirium in the ICU. Among other factors, the authors reported that mechanical ventilation and the use of benzodiazepine sedatives were strongly associated with an increased risk of delirium, while the use dexmedetomidine sedation was strongly associated with reduced risk. In 2015, Chen et al.[33] published a Cochrane review that compared dexmedetomidine with traditional sedatives, including propofol, midazolam, and lorazepam when used for long-term sedation (more than 24 h) during mechanical ventilation in critically ill patients. The authors concluded that dexmedetomidine reduced the duration of mechanical ventilation and ICU length of stay. However, the evidence was not conclusive regarding the comparative efficacy of these drugs in reducing the risk of delirium or coma.

At the maximum allowed daily dose, dexmedetomidine is more expensive than midazolam, lorazepam, and propofol. However, it is not clear whether the higher cost of dexmedetomidine is offset by its suggested benefits.

The objective of this review is to evaluate the comparative effectiveness of dexmedetomidine versus the conventional sedative agents when used in ICU for mechanically ventilated patients, to inform the economic assessment of dexmedetomidine in this setting.

Research Question

What is the comparative effectiveness of dexmedetomidine versus traditional sedatives (lorazepam, midazolam, and propofol) for the sedation of adult patients in the ICU setting to facilitate invasive or non-invasive ventilation?

Key Findings

A total of 19 studies were included in this review. Dexmedetomidine was associated with lower delirium rates and time to extubation than midazolam and propofol. It was also associated with a shorter duration of mechanical ventilation than midazolam; however, this potential benefit was not observed when compared with propofol or lorazepam. This did not appear to result in a shorter ICU stay. There were insufficient data on the rate of re-intubation to draw firm conclusions. Dexmedetomidine was associated with higher rates of bradycardia than lorazepam, midazolam, or propofol.

Methods

Literature Search Strategy

A limited literature search was conducted on key resources including Medline, PubMed, the Cochrane Library, University of York Centre for Reviews and Dissemination databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. The search was limited to English-language documents. No date limits were applied to the clinical search. Regular alerts updated the search until project completion.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed, and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 29.

Table 29: Selection Criteria

Population	Adults admitted to either the medical, surgical, or post-cardiac surgery ICU and requiring sedation to facilitate invasive or non-invasive ventilation Notes: • Non-invasive ventilation is limited to CPAP or IPAP/EPAP modes of ventilation.
Intervention	Dexmedetomidine continuous infusion
Comparator	Lorazepam, midazolam, or propofol
Outcomes	**Key outcomes:** • Duration of invasive or non-invasive ventilation • Rate of re-intubation within first 24 h following extubation **Other outcomes:** • Incidence of agitation • Days spent in delirium • Duration of ICU stay • Time to extubation and extubation time[a] • Incidence of bradycardia and hypotension.
Study Designs	Randomized controlled trials

CPAP = continuous positive airway pressure; ICU = intensive care unit; IPAP/EPAP = inspiratory positive airway pressure /expiratory positive airway pressure.
[a] The definition used for time to extubation and extubation time is as the following except otherwise highlighted: Extubation time: time from discontinuation of sedative infusion to extubation; Time to extubation: time from start of the sedative infusion until extubation.

Exclusion Criteria

Trials that evaluated usage of dexmedetomidine other than that specified in Table 29 were not included in this review. Studies evaluating pediatric populations were also excluded. Studies that compared dexmedetomidine with more than one sedative without reporting the results for each comparator separately were also excluded.

Data Analysis

Head-to-head trials between dexmedetomidine and any of the three comparators (lorazepam, midazolam, or propofol) were eligible for this review. If more than one trial comparing dexmedetomidine with any of the comparators was included, meta-analyses were performed, and results were pooled, if appropriate. If meta-analysis was deemed inappropriate because of heterogeneity of the clinical trials and methodological characteristics of included studies, a narrative synthesis and summary of the included study findings was completed instead.

If meta-analysis was deemed appropriate, meta-analyses were carried out using Cochrane Review Manager software to derive pooled estimates of interest. A random-effects model was used. Analyses of dichotomous outcomes were summarized using relative risks (RRs) and 95% confidence intervals (CIs), and analyses of continuous outcomes were summarized using mean differences and 95% CIs. Findings were reported as "inconclusive" if the CI of the overall estimate included the null value (i.e., 1 for dichotomous and 0 for continuous outcomes). The chi-square test was used to assess effect size variance, with $P < 0.05$ indicating statistically significant heterogeneity across trials. When significant heterogeneity was identified and sufficient data were available, subgroup analyses were made to identify the primary sources of heterogeneity, such as patient characteristics.

Critical Appraisal of Individual Studies

The quality of the included randomized controlled trials (RCTs) was evaluated using the SIGN50 checklist for the controlled studies.

Summary of Evidence

Quantity of Research Available

A total of 657 potential studies were identified by searching the bibliographic database, and 579 were excluded based on screening the title and abstract because they were not relevant to the question of interest. The full-text documents of the remaining 78 articles were retrieved. Thirty-two additional articles were identified from the grey literature and by hand searching. Of the 110 articles, 91 did not meet the inclusion criteria and were excluded, leaving 19 articles that reported 19 unique RCTs. As well, two articles reported one trial, and one article reported on two separate trials.

A PRISMA diagram demonstrating the study selection process is presented in Clinical Appendix 1..

Summary of Study Characteristics

Study characteristics are summarized in Clinical Appendix 2.

Dexmedetomidine Versus Lorazepam

Pandharipande et al.[11,12] published the results of a double-blind RCT that compared the efficacy of dexmedetomidine versus lorazepam in reducing the duration of delirium and coma while providing adequate sedation in mechanically ventilated patients in the ICU. The study included 106 adult mechanically ventilated medical and surgical patients in the ICU. Patients were sedated for up to 120 hours with either dexmedetomidine (0.15 mcg/kg/mL) or lorazepam (1 mg/mL). The primary outcome was days alive without delirium or coma.

Dexmedetomidine Versus Midazolam

Six studies compared dexmedetomidine versus midazolam and included from 23[34] to 500[9] adult patients in the ICU. The reported reasons for ICU admission were medical,[35] abdominal surgery,[36] cardiac surgery,[37] or combination of medical and surgical reasons.[9,13,34] In two studies, Gupta et al.[36] and Yapici et al.,[37] patients had failed a first attempt of weaning from mechanical ventilation using midazolam sedation.

Included patients were sedated with dexmedetomidine dosages that ranged from 0.2 to 1.4 mcg/kg/h. Midazolam doses ranged from 0.02 mg/kg/h to 0.2 mg/kg/h; one study, MacLaren et al.,[34] did not base midazolam dose on patient's weight and used a median trial dose of 3.7 mg/h (maximum of 10 mg/h per individual patient). Titration of the study drugs was based on achieving a Richmond Agitation–Sedation Scale (RASS) score between 0 and 3. The duration of sedation varied from one day[36] to more than three days (exact duration not reported);[13,34] two studies did not report the sedation duration.[35,37]

The primary outcomes of the included studies were rates of post-ICU anxiety,[34] level of sedation as assessed by Ramsay Sedation Scale (RSS),[34] time at target sedation level,[9] time to extubation,[37] and percentage of time within target RASS range.[13] Esmaoglu et al. did not specify a primary outcome; the authors reported on heart rate reduction, mean arterial blood pressure, and duration of ICU stay.[35]

Dexmedetomidine Versus Propofol

Ten studies compared dexmedetomidine with propofol and included from 20[38] to 498[9] adult patients in the ICU. Admission to ICU was for medical reasons in one study,[24] general surgery in two studies,[39,40] cardiac surgery in four,[14,25,26,41] and a mixture of medical and surgical reasons in three studies.[9,38,42]

Dosages of study drugs ranged from 0.2 mcg/kg/h to 1.4 mcg/kg/h for dexmedetomidine, and from 0.3 mg/kg/h to 4 mg/kg/h for propofol. Two studies specified a maximum of 24 hours of sedation;[14,26] however, the remaining studies did not report the length of this duration.

The primary outcomes of the included studies were sublingual blood flow,[25] respiratory asynchrony index,[38] incidence of post-operative delirium,[14] and time in target sedation.[9,26] Jakob et al. used RASS scores to determine the time in target sedation,[9] while Herr et al. allowed the staff of each participating centre to use the scale that they were familiar with.[26] In five studies, the primary outcome was not explicitly reported;[24,39-42] one of these studies reported that the statistical power estimation was based on a 30% reduction in heart rate.[42] Another study reported that the power calculation was based on a 5% difference in the proportion of patients who had adequate sedation based on analgesic requirements.[40]

Dexmedetomidine Versus Midazolam and Propofol

Two studies included three treatment groups in order to compare dexmedetomidine with midazolam or propofol in the same trial.[43,44] One study included 90 elective neurosurgery patients,[43] while the other study included 118 patients who had elective cardiac valve operations.[44]

Dexmedetomidine dosages ranged from 0.2 mcg/kg/h to 0.7 mcg/kg/h, propofol dosages ranged from 1 mg/kg/h to 3 mg/kg/h, and midazolam dosages ranged from 0.5 mg/h to 2 mg/h in one study,[44] and were a constant rate of 0.08 mg/kg/h in the other.[43]

The primary outcomes were the incidence of delirium on one study,[44] while Srivastava et al. reported on sedation adequacy (RSS-based), analgesic requirements, and change in heart rate, without explicitly reporting what the main end point was.

Summary of Critical Appraisal

Critical appraisal of the included studies is provided in Clinical Appendix 3.

Dexmedetomidine Versus Lorazepam

Patients in Pandharipande et al. were randomized using computer-generated, permuted blocks. Blinding was assured by keeping patients and study personnel unaware of the allocated drug; only the investigational pharmacist was aware of the allocated treatment but did not interfere with the study evaluation. However, the ICU nurses titrated study drugs, and the titration rate differed between dexmedetomidine and lorazepam. It was not clear how the nurse could be blinded from the administered drug, or whether they were blinded to the study hypothesis and outcomes.

The study size was based on statistical power estimation to detect a 30% increase in delirium-free and coma-free days.

Dexmedetomidine Versus Midazolam

Random patient allocation was achieved using computerized systems in four studies.[9,13,34,36] Esmaoglu et al. used a coin toss to randomly allocate patients to the treatment groups; however, it was not clear how allocation was concealed.[35] Yapici et al. did not report their method of randomization.[37]

Three studies adopted a double-blind study design;[9,13,34] in one study, blinding was maintained by giving 0.9% sodium chloride as dummy treatment for both groups.[9] Another study used an equal adjusted infusion rate for the two groups,[34] while the third study did not report how treatment blinding was maintained. Gupta et al. used an open-label trial design,[36] while Yapici et al.[37] and Esmaoglu et al.[35] did not report treatment blinding.

Yapici et al.[37] and Gupta et al.[36] enrolled patients who had sedation failure using midazolam, which might have biased the study in favour of dexmedetomidine by explicitly selecting patients who had failed midazolam. However, a clinical expert consulted for this review emphasized that this is probably how dexmedetomidine is used in the ICU because of its relatively higher cost.

MacLaren et al.[34] and Riker et al.[13] provided open-label midazolam for randomized patients to control agitation. However, it was not clear how these rescue treatments were factored in the comparison between dexmedetomidine and midazolam; without proper adjustments, the rescue treatment with midazolam might bias the results against dexmedetomidine.

Four studies reported that the trial size was based on statistical power estimation.[9,13,34,35] Jakob et al. [9] based the power estimation on a 15% non-inferiority margin of time in target sedation between dexmedetomidine and midazolam, while Riker et al. relied on a 7.4% difference in time in target sedation between dexmedetomidine and midazolam.[13] MacLaren et al.[34] reported that they used a statistical power estimation to determine the sample size; however, they reported that they concluded the trial without enrolling the pre-determined number of patients. Gupta et al.[36] and Yapici et al.[37] enrolled a convenience sample of patients rather than using power estimation.

Dexmedetomidine Versus Propofol

In three studies, patients were randomized to the treatment groups using computerized methods,[9,14,24] and the sealed envelope method was used in three other studies.[26,39,40] The remaining studies did not report the method of randomization.[25,38,41,42]

Jakob et al.[9] used a double-blind design that was enforced by a double-dummy treatment. Liu et al.[25] employed a single-blinded design in which the investigator who assessed the primary end point (sublingual microcirculation) was blinded to the allocated treatment; however, all other end points were evaluated by unblinded staff. Seven studies reported that they used an open-label design;[14,24,26,38,39,41,42] open-label designs might introduce bias in the assessment of subjective outcomes such as agitation and delirium. Venn et al.[40] did not report treatment blinding.

Herr et al.[26] administered open-label propofol for patients who were inadequately sedated with the study medications; however, this rescue treatment might bias the study against dexmedetomidine if the analyses were not adjusted properly for this open-label use. Such bias was avoided in three studies by using rescue treatment other than the study drugs.[9,38,39] Djaiani et al.[14] switched patients from dexmedetomidine to propofol if

patients required sedation beyond 24 hours; it was not clear from the reported results how the investigators considered this treatment switch during the results analyses. The remaining studies did not report about the use of rescue medications.

In three studies — Memis et al.,[24] Elbaradie et al.,[41] and Venn et al.[40] — the sample size was based on convenience rather than on statistical power estimation. All other studies used statistical power estimation to calculate the sample size.

Dexmedetomidine Versus Midazolam and Propofol

Srivastava et al. used a computer-generated table of random numbers to randomize patients to treatment groups,[43] while Maldonado et al.[44] reported that they used a random drawing, but they did not provide details on how this drawing was conducted and whether they took measures to conceal the allocation. In both studies, investigators were not blinded to the allocated treatment; this might have introduced bias in the evaluation of subjective end points such as agitation and delirium. Sample size was determined by statistical power estimation based on a 30% reduction in the mean heart rate[14] or a 30% difference in incidence of delirium.[44]

Summary of Findings

Findings of individual studies are summarized in Clinical Appendix 4. Findings are presented by outcome.

1. Duration of Mechanical Ventilation

Four studies reported results on duration of mechanical ventilation;[9,12,34] results are summarized in Table 30.

Compared with lorazepam, dexmedetomidine was associated with numerically fewer days (four fewer days) of mechanical ventilation; however, the difference was not statistically significant.

MacLaren et al.[34] and Jakob et al.[9] reported inconsistent comparisons between dexmedetomidine and midazolam. MacLaren et al. reported that dexmedetomidine was associated with shorter duration (2.7 days) of total mechanical ventilation than midazolam; however, when the authors considered the duration of mechanical ventilation after the administration of study drugs only, dexmedetomidine was associated with numerically (not statistically significant) longer duration (0.5 day) of mechanical ventilation.[34] Jakob et al. reported that dexmedetomidine was associated with a statistically significantly shorter total duration (1.7 days difference) of mechanical ventilation than midazolam. Results from the two studies were not pooled in a meta-analysis because the authors elected to report results as medians and interquartile ranges rather than means and standard deviations. Nevertheless, the interpretation of these results should include the strengths and limitations of both studies. For example, it was noted that MacLaren et al. administered open-label midazolam to control agitated patients, and a clinical expert confirmed that this might introduce a bias against dexmedetomidine.[34] Furthermore, MacLaren's study did not include

enough patients (N = 23 patients) to reach the desired statistical power. On the contrary, the MIDEX study by Jakob et al.[9] was well conducted and sufficiently powered with relatively high number of patients (N = 500 patients).

Jakob et al.[9] reported that dexmedetomidine was associated with numerically shorter duration (0.9 day) of mechanical ventilation than propofol, but the difference was not statistically significant.

Table 30: Duration of Mechanical Ventilation

Study	Outcome Measure	Dexmedetomidine	Comparator	Difference (95% CI) *P* value	Included in the Meta-Analysis
		Effect Size, N	Effect Size, N		
Dexmedetomidine Versus Lorazepam					
Pandharipande et al. 2007,[12] 2010[11]	MV-free days; median (range)	22 (0 to 24) N = 52	18 (0 to 23) N = 51	0.22	Not applicable
Dexmedetomidine Versus Midazolam					
MacLaren et al. 2015[34]	Days, median of total duration (IQR)	8.2 (5.7 to 15.5) N = 11	10.9 (4.4 to 12.6) N = 12	Not reported	No
	Days after study drug median (IQR)	3.4 (2.6 to 14.2) N = 7	2.9 (2 to 4.4) N = 8	Not significant	No
Jakob et al. 2012[9] MIDEX	Hours after study drug median (IQR)	123 (67 to 337) N = 249	164 (92 to 380) N = 251	0.03	No
Dexmedetomidine Versus Propofol					
Jakob et al. 2012[9] PRODEX	Hours, median of total duration (IQR)	97 (45 to 257) N = 251	118 (48 to 327) N = 247	0.24	No

CI = confidence interval; IQR = interquartile range; MV = mechanical ventilation.

2. *Rate of Re-Intubation Within First 24 Hours Following Discontinuation of Sedation*

A total of four studies reported the number of re-intubation events (Table 31). However, none of these studies included this end point as a main outcome; rather, it was reported as an adverse event.[34,38,40,43] There was one re-intubation event reported in dexmedetomidine group; however, no conclusion can be made about the effect of the compared drugs on these events.

Table 31: Rate of Re-Intubation

Study	Outcome Measure	Dexmedetomidine	Comparator	Difference (95% CI) *P* value	Included in the Meta-Analysis
		Effect Size, N	Effect Size, N		
Dexmedetomidine Versus Lorazepam					
No results reported					
Dexmedetomidine Versus Midazolam					
MacLaren et al. 2015[34]	Re-intubations within 72 h, n (%)	1/7	0/8	Not reported	Yes
Srivastava et al. 2014[43]	Total re-intubations, n (%)	0/30	0/30		Yes

Study	Outcome Measure	Dexmedetomidine Effect Size, N	Comparator Effect Size, N	Difference (95% CI) *P* value	Included in the Meta-Analysis
Pooled results		1/37	0/38	RR: 3.38 (0.16 to 71.67) Heterogeneity: Not applicable Test for overall effect: Z = 0.78 (*P* = 0.44)	
Dexmedetomidine Versus propofol					
Conti et al. 2016[38]	Re-intubation, n (%)	0/10	0/10	Not reported	Yes
Srivastava et al. 2014[43]	Re-intubation, n (%)	0/30	0/30	Not reported	Yes
Venn et al. 2001[40]	Re-intubation, n (%)	0/10	0/10	Not reported	Yes
Pooled results		0/50	0/50	Not estimable	

CI = confidence interval; RR = risk ratio.

3. *Episodes of Agitation*

One study[9] reported the incidence of agitation in the use of dexmedetomidine and midazolam. This study found no difference in the incidence of agitation between the two drugs. Four studies reported the incidence of agitation episodes in the use of dexmedetomidine and propofol (Table 32),[9,26,38,39] one of which reported the agitation as a compound end point of agitation, coma, or anxiety.[38] In total, there were numerically fewer agitation events associated with dexmedetomidine (6.3%) than with propofol (7.8%). The risk ratio was not statistically significant.

Table 32: Episodes of Agitation

Study	Outcome Measure	Dexmedetomidine Effect Size, N	Comparator Effect Size, N	Difference (95% CI) *P* value	Included in the Meta-Analysis
Dexmedetomidine Versus Lorazepam					
No results reported					
Dexmedetomidine Versus Midazolam					
Jakob et al. 2012[9] **MIDEX**	Incidence, n (%)	39 (15.2%) N = 247	41 (16.4%) N = 250	0.903	Not applicable
Dexmedetomidine Versus Propofol					
Conti et al. 2016[38]	Incidence of coma, **agitation**, or anxiety; n (%)	2 (20%) N = 10	3 (30%) N = 10	Not reported	No
Jakob et al. 2012[9] **PRODEX**	Incidence, n (%)	19 (7.7%) N = 246	29 (11.7%) N = 247	0.171	Yes
Terao et al. 2012[39]	Incidence, n (%)	2 (12.5%) N = 16	2 (12.5%) N = 16	0.99	Yes
Herr et al. 2003[26]	Incidence, n (%)	5 (3%); N = 148	1 (< 1%); N = 147	0.214	Yes
Pooled results		26/410 (6.3%)	32/410 (7.8%)	RR: 1.03 (0.37 to 2.92) Heterogeneity: chi-square = 3.38, (*P* = 0.18); I^2 = 41% Test for overall effect: Z = 0.06 (*P* = 0.95)	

CI = confidence interval; RR = risk ratio.

4. *Incidence of Delirium*

Table 33 provides a summary results of the occurrence of delirium.[12-14,34,37,44] Some studies reported the prevalence of delirium, which included patients who had delirium at baseline, while other studies reported the incidence of new delirium cases. Several studies reported both the incidence and prevalence of delirium. The incidence of delirium provides a better representation of the effect of sedation on the occurrence of delirium.

Pandharipande et al. reported that the prevalence of delirium was 79% for patients treated with dexmedetomidine versus 82% for patients treated with lorazepam; the risk ratio was not statistically significant.[11,12] Prevalence was used to describe the rates of brain organ dysfunction instead of incidence because pre-intensive care unit delirium or coma status could not be determined. Therefore, the prevalence represented the occurrence of brain organ dysfunction at any time during the assessment period.[11,12]

The pooled results from MacLaren et al.[34] and Maldonado et al.[44] showed that dexmedetomidine was associated with a statistically significantly lower incidence of delirium than midazolam (10.4% versus 46.8%); the risk ratio was 0.22 (95% CI, 0.09 to 0.53).

The comparison between dexmedetomidine and propofol showed that dexmedetomidine was associated with a lower incidence of delirium (15.3% versus 35.2%). The pooled incidence provided a statistically significant risk ratio of 0.39 (95% CI, 0.16 to 0.94), favouring dexmedetomidine.

Table 33: Incidence and Duration of Delirium

Study	Outcome Measure	Dexmedetomidine	Comparator	Difference (95% CI) *P* value	Included in Meta-Analysis
		Effect Size, N	Effect Size, N		
Dexmedetomidine Versus Lorazepam					
Pandharipande et al. 2007,[12] 2010[11]	Prevalence, n (%)	41 (79%)	42 (82%)	0.65	Not applicable
Dexmedetomidine Versus Midazolam					
MacLaren et al. 2015[34]	All cases, n (%)	4 (36.4) N = 11	8 (66.7) N = 12	> 0.1	Yes
	Incidence, n (%)	**1/8 (12.5%)**	**5/7 (71.2%)**	**0.07**	**Yes**
Yapici et al. 2011[37]	Prevalence at baseline 36 h post-operative, n (%)	38 (100) N = 38	34 (100) N = 34	0.05	No
	Prevalence after 24 h 60 h post-operative, n (%)	1 (2.7%) N = 38	7 (21%) N = 34	< 0.05	Yes
Maldonado et al. 2009[44]	Mean length of delirium, days (%)	2.0 (0)	5.4 (6.6)	0.63	No
	Incidence, n (%)	**4/40 (10%)**	**17/40 (44%)**	**0.002**	**Yes**
Riker et al. 2009[13]	Prevalence, n (%)	132 (54) N = 244	93 (76.6) N = 122	< 0.001	Yes
Pooled results	Prevalence	137/293	108/168	RR: 0.59 (0.34 to 1.03)	
	Incidence	5/48	22/47	RR: 0.22 (0.09 to 0.53) Heterogeneity: chi-square =	

Study	Outcome Measure	Dexmedetomidine Effect Size, N	Comparator Effect Size, N	Difference (95% CI) *P* value	Included in Meta-Analysis
				0.07 (*P* = 0.79); I^2 = 0% Test for overall effect: Z = 3.36 (*P* = 0.0008)	
Dexmedetomidine Versus propofol					
Djaiani et al. 2016[14]	**Incidence, n (%)**	**16 (17.5); N = 91**	**29 (31.5); N = 92**	**0.028**	**Yes**
Maldonado et al. 2009[44]	Mean length of delirium, days (%)	2.0 (0)	3.0 (3.1)	0.93	No
	Incidence, n (%)	**4/40 (10%)**	**16/36 (44%)**	**0.001**	**Yes**
Pooled results	Incidence	20/131	45/128	RR: 0.39 (0.16 to 0.94) Heterogeneity: chi-square = 2.50, (*P* = 0.11); I^2 = 60% Test for overall effect: Z = 2.10 (*P* = 0.04)	

CI = confidence interval; RR = risk ratio.

5. Duration of ICU Stay

Results of duration of ICU stay are provided in Table 34.

Pandharipande et al. reported that dexmedetomidine was associated with numerically shorter duration of ICU stay than lorazepam (7.5 versus 9 days), but the difference between the two treatments was not statistically significant.[12]

Comparison between dexmedetomidine and midazolam showed that patients sedated with dexmedetomidine had consistently shorter duration of extubation, ranging from 1.1 day to 1.8 days less than in patients sedated with midazolam.[9,13,34,35,44] However, the difference between the two treatments was statistically significant in one study only.[35] Pooling of the individual studies was not feasible because the majority of these studies (four of five) reported the results in terms of median and not mean duration.

Six studies provided inconsistent findings between dexmedetomidine and propofol for duration of ICU stay.[9,14,24,38,39,44] In four studies, dexmedetomidine was associated with a shorter ICU stay than propofol, with a difference ranging from one day to four days; none of these differences reached a statistical significance.[9,38,39,44] Djaiani et al.[14] and Memis et al.[24] reported that dexmedetomidine was associated with longer ICU stay than propofol by 0.5 to two days; similarly, these differences were not statistically significant. Meta-analysis of these results was not feasible because the results were reported in terms of medians.

Table 34: Duration of ICU Stay

Study	Outcome Measure	Dexmedetomidine Effect Size, N	Comparator Effect Size, N	Difference (95% CI) *P* value	Included in the Meta-Analysis
Dexmedetomidine Versus Lorazepam					
Pandharipande et al. 2007,[12] 2010[11]	Days, **median** (IQR)	7.5 (5 to 19)	9 (6 to 15)	0.92	Not applicable

Study	Outcome Measure	Dexmedetomidine Effect Size, N	Comparator Effect Size, N	Difference (95% CI) *P* value	Included in the Meta-Analysis
Dexmedetomidine Versus Midazolam					
MacLaren et al. 2015[34]	Days, **median** of total duration (IQR)	18.4 (11.5 to 33.9), n = 11	16.1 (6.5 to 28.1), n = 12	Not reported	No
	Days after study drug initiation; **median** (IQR)	10.2 (6.8 to 25.2) n = 11	12 (4.8 to 14.8) n = 12	> 0.1	No
Jakob et al. 2012[9] **MIDEX**	From randomization until fit to discharge; **median** (IQR), h	211 (115 to 831) N = 251	243 (140 to 630) N = 249	Not significant	No
Maldonado et al. 2009[44]	Randomization to discharge, **mean (SD), days**	1.9 (0.9) N = 40	3.0 (3.0) N = 40	0.14	No
Esmaoglu et al. 2009[35]	Total time, **median** (range) (h)	45.5 (15 to 118)	83 (15 to 312)	0.021	No
	Stop sedation to discharge from ICU, **median (range)** (h)	21 (1 to 150) N = 20	52 (6 to 288) N = 20	0.000	No
Riker et al. 2009[13]	**Median** (95% CI), days	1.9 (5.7 to 7.0) N = 244	7.6 (6.7 to 8.6) N = 122	0.24	No
Pooled results				Not enough studies to pool	
Dexmedetomidine Versus Propofol					
Conti et al. 2016[38]	**Total duration (range)**, days	6.02 (2.2to 8.5) N = 10	10.06 (5.0 to 24.8) N = 10	**HR: 0.84 (0.31, 2.33) *P* = 0.742**	No
Djaiani et al. 2016[14]	**Median (range)**, h	43 (18 to 315) N = 91	29.4 (17 to 957) N = 92	Not reported	No
Terao et al. 2012[39]	**Median** (IQR), days	2 (2 to 4) N = 16	3 (3 to 7) N = 16	0.06	No
Jakob et al. 2012[9] **PRODEX**	From randomization until fit to discharge; **median (IQR),** h	164 (90 to 480) N = 251	185 (93 to 520) N = 247	Not significant	No
Memis et al. 2009[24]	Total ICU stay, days (SD)	14 (8) N = 20	12 (7) N = 20	> 0.05	Yes
Maldonado et al. 2009[44]	Days randomization to discharge, **mean (SD)**	1.9 (0.9) N = 40	3.0 (2.0) N = 38	0.14	Yes
Pooled results	Days randomization to discharge			Mean difference: –0.044 (–2.93 to 2.04) Heterogeneity: chi-square = 1.66 (*P* = 0.20); I^2 = 40% Test for overall effect: Z = 0.35 (*P* = 0.73)	

CI = confidence interval; HR = hazard ratio; ICU = intensive care unit; IQR = interquartile range; SD = standard deviation.

6. *Time to Extubation and Extubation Time*

Twelve studies reported either time to extubation or extubation time (Table 35); none of these studies compared dexmedetomidine with lorazepam.

Comparison between dexmedetomidine and midazolam showed that dexmedetomidine was associated with statistically significantly shorter extubation time in four studies;[9,13,36,37] the differences in time ranged from 7.1 hours[36] to 46 hours.[9] MacLaren et al. reported that dexmedetomidine was associated with a 12-hour longer time to extubation than midazolam;[34] the authors did not report the results of statistical testing of this outcome. Furthermore, the contradictory result from MacLaren's study should be interpreted with caution because of the limitations of this study and its relatively small size. Srivastava et al.[43] reported that dexmedetomidine was associated with an almost 13-hour shorter extubation time than midazolam, and the difference was statistically significant.

Dexmedetomidine was also associated with shorter time to extubation compared with propofol;[9,14,38] the time difference ranged from 0.5 hours[38] to 32 hours.[38] However, these differences were statistically significant in one large study (N = 498),[9] not significant in a small one (N = 20),[38] while the third study did not report the results of statistical testing.[14]

Differences in extubation times between dexmedetomidine and propofol were not consistent.[26,40,41,43] Two studies reported that dexmedetomidine was associated with one minute[40] to nine minutes[43] longer extubation time than propofol; Srivastava et al.[43] reported that this difference was statistically significant, while Venn et al.[40] reported a non-statistically significant difference. Elbaradie et al.[41] and Herr et al.[26] reported non-statistically significant shorter extubation times with dexmedetomidine than propofol that ranged from 5 minutes[41] to 52 minutes.[26] Pooling of the two studies provided a non-statistically significant difference of 2.4 minutes.

Table 35: Time to Extubation and Extubation Time

Study	Outcome Measure	Dexmedetomidine	Comparator	Difference (95% CI) *P* value	Included in the Meta-Analysis
		Effect Size, N	Effect Size, N		
Dexmedetomidine Versus Lorazepam					
No results reported					
Dexmedetomidine Versus Midazolam					
MacLaren et al. 2015[34]	Time (days) to extubation[a]; median (IQR)	3.4 (2.6 to 14.2) N = 11	2.9 (2 to 4.4) N = 12	Not reported	No
Gupta et al. 2015[36]	Time (h) to extubation[a]; mean (SD)	24.21 (1.6651) N = 20	31.35 (3.3447) N = 20	0.0260	Yes
Srivastava et al. 2014[43]	**Extubation time**[b] (min); mean (SD)	35.28 (5.92) N = 30	48.21 (7.23) N = 30	< 0.001	No
Jakob et al. 2012[9] MIDEX	Time (h) to extubation[a]; median (IQR)	101 (65 to 313) N = 249	147 (81 to 325) N = 251	0.01	No

Study	Outcome Measure	Dexmedetomidine	Comparator	Difference (95% CI) *P* value	Included in the Meta-Analysis
		Effect Size, N	Effect Size, N		
Yapici et al. 2011[37]	Time (h) to extubation[a]; mean (SD)	46.62 (6.96) N = 38	58.389 (3.958) N = 34	< 0.0001	Yes
Riker et al. 2009[13]	Time (days) to extubation[a]; median (95% CI)	3.7 (3.1 to 4.0) N = 244	5.6 (4.6 to 5.9) N = 122	1.9 days; 0.01	No
Pooled results	Mean difference in time to extubation (95% CI), h	N = 58	N = 54	–9.34 (–13.87 to –4.81) chi-square (*P* = 0.003); I² = 89% Z = 4.04 (*P* < 0.0001)	
Dexmedetomidine Versus propofol					
Conti et al. 2016[38]	Time (h) to extubation[a]; median (range)	25.2 (24.5 to 118.7) N = 10	57.3 (24.7 to 113.0) N = 10	HR: 0.97 (0.37 to 2.54) *P* = 0.958	No
Djaiani et al. 2016[14]	Time (h) to extubation[a]; median (range)	5.4 (2 to 142) N = 91	5.9 (1 to 202) N = 92	Not reported	No
Srivastava et al. 2014[43]	**Extubation time**[b]; mean (SD), min	35.28 (5.92) N = 30	26.13 (5.32) N = 30	< 0.001	Yes
Terao et al. 2012[39]	Delayed extubation, n (%)	2 (12.5%) N = 16	6 (37.5%) N = 16	0.22	No
	Intubation duration, median (range), min	877 (565 to 13,000)	1,003 (770 to 7,050)	0.27	No
Jakob et al. 2012[9] **PRODEX**	Times (h) to extubation[a]; median (IQR)	69 (39 to 184) N = 251	93 (45 to 286) N = 247	0.04	No
Elbaradie et al. 2004[41]	**Extubation time**[b]; mean (SD), min	30 (15) N = 30	35 (12) N = 30	0.32	Yes
Herr et al. 2003[26]	**Extubation time**[c]; median (range), min	410 (310 to 584) N = 148	462 (323 to 808) N = 147	Not reported	No
Venn et al. 2001[40]	**Extubation time**[b] mean (range), min	29 (15 to 50) N = 10	28 (20 to 50) N = 10	0.63	No
Pool results	Mean difference in extubation time, min (95% CI)	N = 60	N = 60	2.44 (–11.41 to 16.28) chi-square (*P* = 0.0002); I² = 93% Z = 0.34 (*P* = 0.73)	

CI = confidence interval. HR = hazard ratio; SD = standard deviation.
[a] Time to extubation is defined as the time from the start of sedative infusion to extubation.
[b] Extubation time was defined as the time from discontinuation of sedative infusion to extubation.
[c] Extubation time was defined as the interval between sternal closure and when the patient was considered ready for extubation.

7. *Bradycardia*

Eight studies reported the incidence of bradycardia;[9,12,13,25,26,34,38,42] the majority of studies reported bradycardia as part of the adverse events, and they did not indicate how bradycardia was defined (Table 36).

Pandharipande et al.[12] reported a statistically significantly higher incidence of bradycardia with dexmedetomidine compared with lorazepam (17% versus 4%).

Three studies consistently showed that dexmedetomidine was associated with a higher incidence of bradycardia than midazolam.[9,13,34] The pooled risk ratio was 1.94 (95% CI, 1.18 to 3.17). Riker et al.[13] also reported the incidence of bradycardia cases that required additional medical attention or intervention, and they showed that dexmedetomidine had higher incidence than midazolam (4.9% versus 0.8%), but the risk ratio was not statistically significant.

In four studies comparing dexmedetomidine with propofol,[25,26,38,42] dexmedetomidine was associated with higher incidence rates of bradycardia than propofol. The pooled risk ratio was 2.93 (95% CI, 1.0 to 8.5).

Table 36: Incidence of Bradycardia

Study	Outcome Measure	Dexmedetomidine	Comparator	Difference (95% CI) *P* value	Included in the Meta-Analysis
		Effect Size, N	Effect Size, N		
Dexmedetomidine Versus Lorazepam					
Pandharipande et al. 2007,[12] 2010[11]	< 60 beats/min, n (%)	9 (17) N (52)	2 (4) N = (51)	0.03	Not applicable
Dexmedetomidine Versus Midazolam					
MacLaren et al. 2015[34]	n (%)	7 (63.6) N = 11	7 (58.3) N = 12	> 0.1	Yes
Jakob et al. 2012[9] MIDEX	n (%)	35 (14.2) N = 249	13 (5.2) N = 251	< 0.001	Yes
Riker et al. 2009[13]	As AE, n (%)	103 (42.2) N = 244	23 (18.9) N = 122	< 0.001	Yes
	Requiring intervention, n (%)	12 (4.9) N = 244	1 (0.8) N = 122	0.07	Not enough studies to pool
Pooled results	Incidence of all cases; risk ratio (95% CI)	145/504	43/385	1.94 (1.18 to 3.17 Heterogeneity: chi-square = 4.90 (*P* = 0.09); I^2 = 59% Test for overall effect: Z = 2.62 (*P* = 0.009)	
	Incidence of cases requiring intervention			Not enough studies to pool	
Dexmedetomidine Versus Propofol					
Liu et al. 2016[25]	Incidence, n (%)	5 (17) N = 29	1 (3) N = 32	0.093	Yes
Conti et al. 2016[38]	n (%)	1/16 (6.3) N = 10	0 N = 10	Not reported	Yes
Paliwal et al. 2015[42]	Incidence, n (%)	4 (13.3) N = 30	0 N = 30		Yes
Herr et al. 2003[26]	Incidence, n (%)	5 (3%) N = 148	2 (1%) N = 147	0.448	Yes
	Incidence of tachycardia, n (%)	5 (3%) N = 148	5 (3%) N = 147	> 0.999	No
	Ventricular	0	7 (5%)	0.007	No

Study	Outcome Measure	Dexmedetomidine	Comparator	Difference (95% CI) *P* value	Included in the Meta-Analysis
		Effect Size, N	Effect Size, N		
	tachycardia, n (%)	N = 148	N = 147		
Pooled results	Incidence	15/223	4/219	2.93 (1.00 to 8.54) Heterogeneity: chi-square = 2.33 (*P* = 0.51); I^2 = 0% Test for overall effect: Z = 1.96 (*P* = 0.05)	

AE = adverse event; CI = confidence interval.

8. Hypotension

The incidence of hypotension was reported in six studies.[9,13,25,26,34,43] Similar to bradycardia, hypotension was reported as an adverse event without explicit definition in each study (Table 37).

Four studies reported higher rates of hypotension in patients sedated with dexmedetomidine than in patients sedated with midazolam;[9,13,34,43] however, the pooled risk ratio was not statistically significant. A similar trend was observed in studies that compared dexmedetomidine with propofol.[25,26,43]

Table 37: Incidence of Hypotension

Study	Outcome Measure	Dexmedetomidine	Comparator	Difference (95% CI) *P* value	Included in the Meta-Analysis
		Effect Size, N	Effect Size, N		
Dexmedetomidine Versus Lorazepam					
No results reported					
Dexmedetomidine Versus Midazolam					
MacLaren et al. 2015[34]	Incidence, n (%)	10 (90.9) N = 11	6 (50) N = 12	0.069	Yes
Srivastava et al. 2014[43]	Requiring intervention N (%)	2 (6.66%) N = 30	0 N = 30	Not reported	Yes
Jakob et al. 2012[9] MIDEX	Incidence, n (%)	51 (20.6) N = 249	29 (11.6) N = 251	0.007	Yes
Riker et al. 2009[13]	As AE, n (%)	137 (56.1) N = 244	68 (55.7) N = 122	> 0.99	Yes
	With intervention, n (%)	69 (28.3) N = 244	33 (27) N = 122	0.90	Yes
Pooled results	Relative risk; all cases	198/504 (39.3%)	103/385 (26.7%)	1.41 (0.89 to 2.24) Heterogeneity: chi-square = 8.54 (*P* = 0.01); I^2 = 77% Test for overall effect: Z = 1.46 (*P* = 0.14)	
	Relative risk; cases requiring intervention	71/274 (25.9%)	33/152 (21.7%)	1.11 (0.62 to 1.96) Heterogeneity: chi-square = 1.05 (*P* = 0.31); I^2 = 4% Test for overall effect: Z = 0.34 (*P* = 0.73)	
Dexmedetomidine Versus Propofol					
Liu et al. 2016[25]	Incidence, n (%)	9 (31) N = 29	11 (34) N = 32	0.793	Yes

Study	Outcome Measure	Dexmedetomidine	Comparator	Difference (95% CI) *P* value	Included in the Meta-Analysis
		Effect Size, N	Effect Size, N		
Srivastava et al. 2014[43]	Requiring intervention N (%)	2 (6.66%) N = 30	0; N = 30	Not reported	Yes
Herr et al. 2003[26]	Incidence, n (%)	36 (24%) N = 148	24 (16%) N = 147	0.111	Yes
	Incidence of hypertension, n (%)	18 (12%) N = 148	6 (4%) N = 147	0.018	No
Pooled results	Relative risk; all cases	45/177 (25.4%)	35/179 (19.6%)	1.26 (0.79 to 2.00) Heterogeneity: chi-square = 1.3 (*P* = 0.25); I^2 = 24% Test for overall effect: Z = 0.96 (*P* = 0.34)	
	Relative risk; cases requiring intervention			Not enough studies to pool	

AE = adverse effect; CI = confidence interval.

Limitations

A main limitation of the current review was the heterogeneity of the included population. In some studies, only surgical ICU patients were included, while other studies included only medical ICU patients; a third category of studies included a mixture of surgical and medical patients. The evaluation of sedatives in general can be complicated by a patient's medical condition as well as previous and concurrent medications. For example, surgical ICU patients are most likely to receive sedatives as part of their anesthetic regimen during surgery; this might introduce bias in the included studies, especially when the same sedatives received during surgery were used as comparators to dexmedetomidine. There were not enough studies to evaluate the comparative effects in each patient category.

Another limitation of this review was the variations in surgical and ICU protocols from one hospital to another. This might affect the type of concurrent interventions administered to ICU patients as well as the definition of clinical end points. These differences could not be evaluated in this review because such details were not usually reported in published clinical trial articles. Furthermore, only one study by Djaiani et al.[14] was conducted at a Canadian hospital.

The majority of the included studies reported outcomes as medians; therefore, a meta-analysis of some outcomes was not feasible.

Conclusions

The objective of this review was to evaluate the comparative effectiveness of dexmedetomidine versus traditional sedatives (lorazepam, midazolam, and propofol) for the sedation of adult patients in the ICU setting to facilitate mechanical ventilation, to inform the relevant information to be included in an economic assessment of dexmedetomidine for use in the ICU. A total of 19 studies were included in this review.

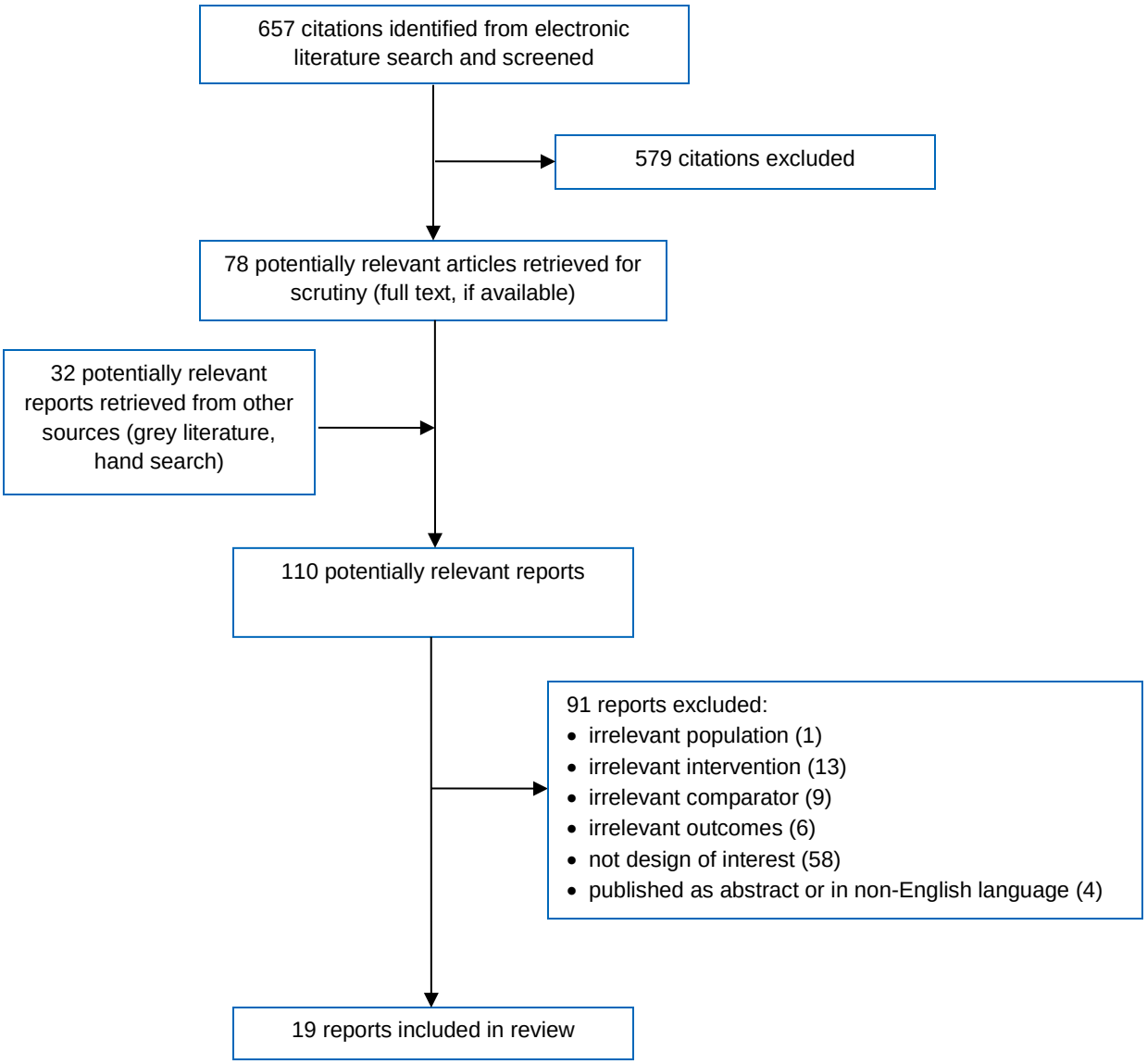
Dexmedetomidine was associated with statistically significantly lower delirium rates and shorter time to extubation than midazolam and propofol. Furthermore, dexmedetomidine was associated with a statistically significant reduction in duration of mechanical ventilation when compared with midazolam.

Only one included study compared lorazepam with dexmedetomidine, and the results of this study were not conclusive except for the incidence of bradycardia, which showed statistically significantly higher rates with dexmedetomidine. Likewise, dexmedetomidine was associated with higher rates of bradycardia than midazolam and propofol.

A previous systematic review by Chen et al. reported that long-term dexmedetomidine, compared with traditional sedatives, was associated with reduced duration of mechanical ventilation and ICU length of stay.[33] However, there was no evidence that it reduced the risk of delirium.[33] In contrast to Chen's review, the current review showed a beneficial effect of dexmedetomidine in reducing the risk of delirium, but the evidence did not show any benefit in reducing ICU stay. These discrepancies could be explained by the differences in inclusion criteria in both reviews. Chen et al.[33] included studies that reported on longer-term use of sedation (more than 24 hours); in the current review, however, all studies that included mechanically ventilated ICU patients were included, regardless the duration of sedation. Another recent meta-analysis[45] had similar findings to the current review with regard to the risk of delirium and bradycardia.

Clinical

Appendix 1: Selection of Included Studies



APPENDIX 2: Characteristics of the Included Studies

Table 38: Lorazepam as Comparator

Main Reason(s) For ICU Admission Inclusion Criteria	Intervention and Comparator(s)
Pandharipande et al. 2007,[12] 2010[11]	
• **Reason for ICU admission:** medical (30%) and surgical (70%) • **Inclusion:** adult medical and surgical patients in the ICU requiring mechanical ventilation for longer than 24 h • **Exclusion:** 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 ischemia, second- or third-degree heart block, severe dementia, benzodiazepine dependency, pregnancy or lactation, and severe hearing disabilities	• Dexmedetomidine (0.15 mcg/kg/mL): Dosage ranged from 1 mL/h (0.15 mcg/kg/h) to 10 mL/h (1.5 mcg/kg/h). • Lorazepam (1 mg/mL): Dosage ranged from 1 mg/h to 10 mg/h. • Study drug was titrated by bedside nurse to achieve the sedation goal set by the patient's medical team using the Richmond Agitation–Sedation Scale. Infusion was started at 1 mL/h to a maximum of 10 mL/h. • Drug was infused as needed until extubation or for the maximum time allowed by the FDA (120 h), and infusions could be discontinued at any time if patient was at sedation target. • Patients who were mechanically ventilated beyond the 120-hour study drug period were then sedated according to the standard practice of the particular ICU. • Pain was treated with intermittent doses of fentanyl. • 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 mg to 50 mg was allowed, while the study drug or fentanyl infusions were titrated upward.

ICU = intensive care unit.

Table 39: Midazolam as Comparator

Main Reason(s) For ICU Admission Inclusion Criteria	Intervention and Comparator(s)
MacLaren et al. 2015[34]	
• **Reason for ICU admission:** medical (87%) and surgical (13%) • **Inclusion:** the trial included critically ill patients requiring mechanical ventilation and receiving a *continuous* benzodiazepine infusion with an anticipated need of at least 12 additional hours of sedation at a Riker sedation agitation score of 3 to 4. • **Exclusion:** age less than 18 or greater than 85 years; administration of benzodiazepines for purposes other than sedation (e.g., seizure control); administration of neuromuscular blockers for more than 12 h; administration of epidural medications; active myocardial ischemia; second- or third-degree heart block; hemodynamic 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	• Dexmedetomidine (0.075 mcg/kg/mL): Dosage started from 0.15 mcg/kg/h to 1.5 mcg/kg per hour. Median dosage was 0.61 mcg/kg/h for 3.5 days • Midazolam (0.5 mg/mL): Dosage started from 1 mg/h and titrated up to a maximum of 10 mg/h. Median dosage 3.7 mg/h for 3 days • Study drug was titrated by bedside nurse to achieve a Riker score of 3 to 4. • Open-label midazolam or fentanyl were permitted according to the sedation and analgesia protocol if agitation or pain were present or if the maximum study drug dose was reached.
Gupta et al. 2015[36]	
• **Main reason for ICU admission:** post-abdominal surgery • **Inclusion:** patients had been mechanically ventilated for < 96 h before start of study drug infusion, were anticipated to be weaned off mechanical ventilation in next 24 h, and had failed spontaneous breathing trial before randomization • **Exclusion:** significant liver (Child–Pugh class C) or kidney disease, severe neurological disorders, acute myocardial infarction, heart block, heart rate < 50 beats/min, systolic blood pressure < 90 mm Hg despite continuous infusions of vasopressors, receiving other sedatives and anticonvulsant drugs, pregnancy/lactation, and allergy to midazolam or dexmedetomidine	• Before the start of trial, patients were receiving morphine or fentanyl for analgesia and midazolam or lorazepam for sedation per choice of treating intensivist • Patients received IV infusion of dexmedetomidine at a rate of 0.2 mcg/kg/h to 0.7 mcg/kg/h (adjusted as needed for the desired level of sedation i.e., RSS score 2 to 4) (N = 20). • Patient received IV infusion of midazolam at the rate of 0.04 mg/kg/h to 0.2 mg/kg/h (adjusted as needed for the desired level of sedation i.e., RSS score 2 to 4) (N = 20). • Study drug infusion was given up to a maximum period of 24 h. • Analgesia was provided, consisting of regular paracetamol infusion to all patients.

Main Reason(s) For ICU Admission Inclusion Criteria	Intervention and Comparator(s)
Jakob et al. 2012[9] MIDEX trial	
• **Main reason for ICU admission**: medical (65.6%), surgical (22.6%), and trauma (7.2%) • **Inclusion:** age 18 years or older, invasive mechanical ventilation, clinical need for light to moderate sedation (target sedation RASS score was from 0, alert and calm, to −3, responds to verbal stimulation by movement or eye opening to voice but no eye contact) using midazolam or propofol infusion expected to last for 24 h or longer after randomization, and randomization within 72 h of ICU admission and within 48 h of starting continuous sedation • **Exclusion:** acute severe neurological disorder, mean arterial pressure less than 55 mm Hg despite appropriate intravenous volume replacement and vasopressors, heart rate less than 50/min, atrioventricular-conduction block grade II or III (unless pacemaker installed), and use of 2 agonists or antagonists within 24 h before randomization	• Dexmedetomidine: 0.2 mcg/kg/h to 1.4 mcg/kg/h • Midazolam: 0.03 mg/kg/h to 0.2 mg/kg/h • Study treatments were infused without loading dose at a dose matching the pre-randomization dose of midazolam for 1 h. • Study drugs were titrated by the patient's nurse stepwise to maintain the target RASS score.
Yapici et al. 2011[37]	
• **Main reason for ICU admission:** cardiac surgery • **Inclusion:** patients who underwent elective coronary artery bypass grafting, valve replacement, or both, and who had failed the first attempt at weaning • **Exclusion:** unstable or uncontrolled diabetes; extreme obesity; an ejection fraction < 30% and hemodynamic instability (e.g., requirement for dobutamine or dopamine at > 10 mcg/kg/min, requirement for epinephrine at > 0.1 mcg/kg/min, or a cardiac index of < 2.0 L/min/m^2); prolonged duration of operation (> 6 h), cardiopulmonary bypass (> 3 h), or aortic cross-clamping (> 150 min); a preoperative history of neurologic events or a psychiatric disorder, as evidenced by preoperative medical records; intraoperative episodes of hypotension, as indicated in the anesthesia chart; post-operative coma; or death	• Surgical anesthesia protocol: Fentanyl (20 mcg/kg to 50 mcg/kg) and midazolam (0.05 mg/kg to 0.1 mg/kg) were used for induction, and fentanyl (20 mcg/kg/h to 50 mcg/kg/h) and propofol (4 mg/kg/h to 8 mg/kg/h) were infused for maintenance. • None of the patients received any sedative agent after admission to the ICU, and, for purposes of analgesia, only opioids (fentanyl 0.7 mcg/kg/h to 10 mcg/kg/h) were administered during the first 8 h in the ICU. • Patients who failed first attempt of extubation and were in agitated state after the first 12 h to 18 h in ICU were given midazolam (0.05 mg/kg/h to 0.2 mg/kg/h) and fentanyl (0.7 mcg/kg/h to 10 mcg/kg/h). If patients were still agitated at 36 h in the ICU, they were randomized. • Infusion of dexmedetomidine hydrochloride at a dosage of 0.3 mcg/kg/h to 0.7 mcg/kg/h (N = 38) • Midazolam (0.05 mg/kg/h to 0.2 mg/kg/h), (N = 34)

Main Reason(s) For ICU Admission Inclusion Criteria	Intervention and Comparator(s)
Esmaoglu et al. 2009[35]	
• **Main reason for ICU admission:** pregnancy termination due to eclampsia • **Inclusion:** patients whose pregnancies were terminated via Caesarean delivery because of eclampsia and who needed ventilatory support • **Exclusion:** chronic hypertension; cardiac, neurological, hepatic, renal, or endocrinal disease; allergic reactions to the medicine used during the treatment; or hemolysis, elevated liver enzymes and platelets (HELLP) syndrome	• Dexmedetomidine: loading dose 1 mcg/kg per 20 min, followed by a continuous infusion at 0.7 mcg/kg/h (400 mcg dexmedetomidine is put in 100 mL physiological saline solution) • Midazolam: loading dose of 100 mg in 100 mL 0.9% saline solution at 0.05 mg/kg, continued at 0.1 mg/kg/h • When sedation became inadequate (Ramsay sedation score < 2), propofol was given as a bolus (0.5 mg/kg) in both groups. • When visual analogue scale greater than 4, fentanyl (1 mcg/kg) was administered.
Riker et al. 2009[13]	
• **Inclusion:** 18 years or older surgical (13.5%) or medical (85%) patients in the ICU, who were intubated and mechanically ventilated for less than 96 h before start of study drug, and who had an anticipated ventilation and sedation duration of at least 3 more days • **Exclusion:** trauma or burns as admitting diagnoses; dialysis of all types; pregnancy or lactation; neuromuscular blockade other than for intubation, epidural or spinal analgesia; general anesthesia 24 h before 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 less than 30%; heart rate less than 50/min; second- or third-degree heart block; or systolic blood pressure less than 90 mm Hg despite continuous infusions of 2 vasopressors before the start of study drug infusion	• Dexmedetomidine (0.2 mcg/kg/h to 1.4 mcg/kg/h [n = 244]) • Midazolam (0.02 mg/kg/h to 0.1 mg/kg/h [n = 122]) • Study drugs were titrated to achieve light sedation (RASS scores between −2 and 1) from enrolment until extubation or 30 days. • Dosage of study drug was adjusted by the managing clinical team based on sedation assessment performed with the RASS a minimum of every 4 h. • Patients in either group not adequately sedated by study drug titration could receive open-label midazolam bolus doses of 0.01 to 0.05 mg/kg at 10- to 15-min intervals until adequate sedation (RASS score range −2 to 1) was achieved, with a maximum dose of 4 mg in 8 h. • Analgesia with fentanyl bolus doses (0.5 mcg/kg to 1.0 mcg/kg) could be administered as needed every 15 min. • Intravenous haloperidol was permitted for treatment of agitation or delirium in increments of 1 mg to 5 mg, repeated every 10 to 20 min as needed.

ICU = intensive care unit; RASS = Richmond Agitation–Sedation Scale; RSS = Ramsay Sedation Scale.

Table 40: Propofol as Comparator

Main Reason(s) For ICU Admission Inclusion Criteria	Intervention and Comparator(s)
Liu et al. 2016[25]	
• **Main reason for ICU admission:** cardiac bypass surgery • **Inclusion:** patients aged 18 years or older, undergoing elective cardiac valve surgery with cardiopulmonary bypass, admitted to the ICU intubated and ventilated, and expected to require **sedation for more than 4 h** • **Exclusion**: acute severe neurologic disorder, mean arterial pressure less than 55 mm Hg (despite administration of appropriate intravenous volume replacement and vasopressors), heart rate less than 50 beats/min, grade II or III atrioventricular-conduction block (unless pacemaker installed), propofol or dexmedetomidine allergy or other contraindications, insulin-dependent diabetes, or body mass index ≥ 30 kg/m^2. In addition, patients who underwent reoperation, received 2 or more sedatives after randomization, and had a **sedation time of < 4 h or ≥ 24 h** also were excluded.	• Dexmedetomidine: The maximum intravenous infusion speed of dexmedetomidine was not greater than1.5 mcg/kg/h. • Propofol: The maximum intravenous infusion speed of propofol was not greater than 50 mcg/kg/min. • Dexmedetomidine or propofol was infused continuously without a loading dose. The sedation level was assessed using the RASS, which ranged from –5 (unarousable) to 4 (combative). The RASS score was assessed every 2 h or more often if required (e.g., patient's condition changed). The sedative was titrated to maintain the RASS score between 0 and –3. • The infusion of sedative was stopped before extubation at the discretion of the attending physicians.
Conti et al. 2016[38]	
• **Main reason for ICU admission:** medical (50%), surgical (35%), and trauma (15%). The main medical reason for admission to the ICU was cardiac disorders (10 patients). • **Inclusion:** adult ICU patients who had failed one weaning trial, who were intubated and mechanically ventilated in the ICU for > 24 h, and who had received propofol as the sole agent for continuous sedation (minimum 12 h) with a target sedation level of +1 to − 2 on the RASS • **Exclusion:** acute severe intracranial or spinal neurological disorder, uncompensated acute circulatory failure, or severe bradycardia	• Dexmedetomidine (0.2 mcg/kg/h to 1.4 mcg/kg/h) and median duration was **31.5 h** (18 h to 174 h) • Propofol (0.3 mg/kg/h to 4 mg/kg/h) and median duration was 47.9 h (22 h to 113 h) • Study drugs were given to maintain the RASS score within the range of +1 to −2. • The assigned study treatment was continued until extubation was successful, but for no longer than 14 days • Rescue midazolam was used if needed; however, because it had the potential to interfere with the study measurements, participants were advised that it should be used as sparingly as possible.

Main Reason(s) For ICU Admission Inclusion Criteria	Intervention and Comparator(s)
Djaiani et al. 2016[14]	
• **Main reason for ICU admission:** Post-cardiac surgery • **Inclusion:** patients **older than 60** years undergoing elective complex cardiac surgery and older than 70 years undergoing either isolated coronary revascularization or single-valve repair/replacement surgery with the use of cardiopulmonary bypass • **Exclusion:** patients with a history of serious mental illness, delirium, or severe dementia, as well as patients undergoing emergency procedures	• Dexmedetomidine: a bolus of 0.4 mcg/kg (over a period of 10 to 20 min) followed by an infusion of 0.2 to 0.7 mcg/kg/h. • Dexmedetomidine was continued for a maximum period of 24 h. Dexmedetomidine infusion was not discontinued before extubation. • Propofol: infusion 25 to 50 mcg/kg/min until readiness for tracheal extubation • If mechanical ventilation was required beyond the 24-h period, patients in the dexmedetomidine group were converted to propofol sedation. • Study drugs were titrated to achieve light sedation, resulting in a calm and co-operative patient (RASS score of 4).
Paliwal et al. 2015[42]	
• **Main reason for ICU admission:** COPD, abdominal surgery, poisoning, and septicemia • **Inclusion:** hemodynamically stable ICU patients, aged between 18 to 80, requiring sedation and mechanical ventilation • **Exclusion:** pregnancy; excessive obesity (body weight more than 50% above ideal body weight); severe hepatic, renal, or CNS involvement; significant arrhythmias or high degree of atrioventricular nodal block; and allergies to drugs	• Dexmedetomidine loading dose (1 mcg/kg) over 10 min followed by maintenance infusion of 0.5 mcg/kg/h (0.2 mcg/kg/h to 0.7 mcg/kg/h) • Propofol loading dose (1 mg/kg) over 5 min followed by infusion of 2 mg/kg/h (1 mg/kg/h to 3 mg/kg/h) • All patients received fentanyl 1 mcg/kg before the study drugs. • Sedation target was RSS score of 4 or 5. If the aimed RSS score was not achieved or maintained by the study drug alone (dexmedetomidine at its maximum dose of 0.7 mcg/kg/h for 1 h and propofol at its maximum dose of 3 mg/kg/h for 1 h), then it was supplemented with 0.2 mg/kg propofol bolus for maximum three successive boluses at an interval of 3 to 5 min.

Main Reason(s) For ICU Admission Inclusion Criteria	Intervention and Comparator(s)
Terao et al. 2012[39]	
• **Main reason for ICU admission:** extensive cervical spine surgery • **Inclusion:** consecutive patients who required post-operative endotracheal intubation and mechanical ventilation under sedation overnight • **Exclusion:** preoperative endotracheal intubation and patients younger than 18 years of age	• Dexmedetomidine at 0.1 mcg/kg/min for 10 min as a loading dose, followed by a continuous infusion at 0.4 mcg/kg/h (N = 16) • Propofol at 0.1 mg/kg/min for 10 min as a loading dose, followed by a continuous infusion at 1 mg/kg/h (N = 16) • All patients received analgesia with bolus of buprenorphine 4 mcg/kg at the end of anesthesia, followed by a continuous infusion at a fixed dose of 0.3 mcg/kg/h • Doses were adjusted to maintain the desired sedation at RSS score of 2, 3, or 4 • If adequate sedation was not achieved at maximum infusion rate (1 mcg/kg/min in group D and 3 mg/kg/h in group P), another sedative, as additional use, was administered at initial continuous infusion rate.
Jakob et al. 2012[9] PRODEX trial	
• **Main reason for ICU admission**: medical (56.2%), surgical (33.9%), and trauma (9.8%) • **Inclusion:** age 18 years or older, invasive mechanical ventilation, clinical need for light to moderate sedation (target sedation RASS score was from 0, alert and calm, to −3, responds to verbal stimulation by movement or eye opening to voice but no eye contact[19]) using midazolam or propofol infusion expected to last for 24 h or longer after randomization, and randomization within 72 h of ICU admission and within 48 h of starting continuous sedation • **Exclusion:** acute severe neurological disorder, mean arterial pressure less than 55 mm Hg despite appropriate intravenous volume replacement and vasopressors, heart rate less than 50/min, atrioventricular-conduction block grade II or III (unless pacemaker installed), and use of 2 agonists or antagonists within 24 h before randomization	• Dexmedetomidine: 0.2 mcg/kg/h to 1.4 mcg/kg/h • Propofol: 0.3 mg/kg/h to 4.0 mg/kg/h • Study treatments were infused without loading dose at a dose matching the pre-randomization dose of propofol for 1 h. • Study drugs were titrated by the patient's nurse stepwise to maintain the target RASS score.

Main Reason(s) For ICU Admission Inclusion Criteria	Intervention and Comparator(s)
Memis et al. 2009[24]	
• **Main reason for ICU admission:** septic shock • **Inclusion:** patients conventionally resuscitated and hemodynamically stable • **Exclusion:** known allergy to propofol or dexmedetomidine, patients with known or suspected brain death, unstable hemoglobin levels (change in hemoglobin > 0.5 g/dL), significant arrhythmias, acute myocardial ischemia (continuous ST-segment analysis), continuous renal replacement therapy, pregnancy, and age below 18 years	• Dexmedetomidine: loading at 1 mcg/kg over 10 min, followed by a maintenance 0.2 mcg/kg/h to 2.5 mcg/kg/h (n = 20) • Propofol: 1 mg/kg over 15 min, followed by a maintenance of 1 mg/kg/h to 3 mg/kg/h over a 24-h infusion (n = 20) • Alfentanil was infused at 0.25 mcg/kg/min to 1.0 mcg/kg/min if analgesia was required. • The level of sedation was measured and recorded hourly using the RSS, and patients were maintained at an RSS score below 2 by adjustment to the sedative regimen. • No other sedative or analgesic agents were given.
Elbaradie et al. 2004[41]	
• **Main reason for ICU admission:** cancer surgery • **Inclusion:** adult patients who are expected to require a minimum of 6 h post-operative sedation and ventilation after major thoracic, abdominal, or pelvic cancer surgery • **Exclusion:** neurosurgical procedures, known allergy to study drugs, pregnancy, gross obesity, severe hepatic or renal disease where neurologic condition was difficult to evaluate, spinal or epidural anesthesia, history of corticosteroid therapy within the last 3 months, or uncontrolled diabetes	• Dexmedetomidine: loading dose 2.5 mcg/kg/h over 10 min followed by maintenance infusion at a rate of 0.2 mcg/kg/h to 0.5 mcg/kg/h • Propofol: 1 mg/kg followed by an infusion of 0.5 mcg/kg/h to 1.0 mg/kg/h • Study drugs were titrated to achieve RSS score of 2 to 5. • All patients received fentanyl infusion 0.25 mcg/kg/h to 0.5 mcg/kg/h.
Herr et al. 2003[26]	
• **Main reason for ICU admission:** coronary artery bypass graft surgery • **Inclusion:** adult patients who were scheduled for coronary artery bypass graft surgery • **Exclusion:** pregnancy or lactation; neurologic condition or responses that were difficult to evaluate (e.g., serious CNS trauma or intracranial surgery); unstable or uncontrolled diabetes; gross obesity; ejection fraction of 30%; or hospitalization for a drug overdose. Patients who received neuromuscular block in the post-operative period or epidural or spinal analgesia during their ICU stay were discontinued from the study**.**	• **Dexmedetomidine**: 1.0 g/kg for more than 20 min and then 0.2 to 0.7 g/kg/h. Infusions were continued for a minimum of 6 h after extubation, up to 24 h. • **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. • Study drugs were titrated to maintain an RSS score > 3 during assisted ventilation and > 2 after extubation. • Patients could be given propofol for additional sedation if necessary. • Morphine or nonsteroidal anti-inflammatory drugs were allowed for pain relief in both groups.

Main Reason(s) For ICU Admission Inclusion Criteria	Intervention and Comparator(s)
Venn et al. 2001[40]	
• **Main reason for ICU admission:** major abdominal or pelvic surgery • **Inclusion:** patients who were expected to require a minimum of 8 h artificial ventilation after complex major abdominal or pelvic surgery • **Exclusion:** not reported	• Dexmedetomidine at 2.5 mcg/kg/h for 10 min as a loading dose, followed by a continuous infusion of 0.2 mcg/kg/h to 2.5 mcg/kg/h (N = 10) • Propofol: up to 1 mg/kg/h for 10 min as a loading dose, followed by a continuous infusion at 1 mg/kg/h to 3 mg/kg/h (N = 10) • Sedation was titrated to maintain an RSS score > 2. • Patients were given alfentanil at 0.25 mcg/kg/min to 1.0 mcg/kg/min infusion to relieve pain. No other sedatives or analgesics were given.

CNS = central nervous system; COPD = chronic obstructive pulmonary disease; ICU = intensive care unit; RASS = Richmond Agitation–Sedation Scale; RSS = Ramsay Sedation Scale.

Table 41: Propofol/Midazolam as Comparators

Main Reason(s) For ICU Admission Inclusion Criteria	Intervention and Comparator(s)
Srivastava et al. 2014[43]	
• **Main reason for ICU admission**: elective neurosurgery • **Inclusion:** adult patients, 20 to 65 years of age, American Society of Anesthesiologists (ASA) grade I to III, undergoing elective neurosurgical procedure, and expected to require post-operative ventilator support • **Exclusion**: Significant hepatic, renal, or neurologic impairment, second or third-degree heart block, history of use of long-term benzodiazepines, use of opioids, known allergy to any of the study drug, gross obesity (more than 50% above ideal body weight), or known or suspected pregnancy.	• Dexmedetomidine loading dose 1 mcg/kg over 15 min, followed by maintenance infusion at a rate of 0.4 mcg/kg/h to 0.7 mcg/kg/h (N = 30) • Propofol loading dose 1 mg/kg over 15 min, followed by maintenance infusion at a rate of 1 mg/kg/h to 3 mg/kg/h (N = 30) • Midazolam loading dose 0.04 mg/kg over 15 min, followed by maintenance infusion at a rate of 0.08 mg/kg/h (N = 30) • All patients received short-acting fentanyl infusions (5 mcg/mL). • The dosages were adjusted to achieve an RSS score of 2 to 4.

Main Reason(s) For ICU Admission Inclusion Criteria	Intervention and Comparator(s)
Maldonado et al. 2009[44]	
• **Main reason for ICU admission:** elective cardiac valve operations • **Inclusion criteria:** adult patients • **Exclusion:** pre-existing diagnosis of dementia or schizophrenia, preoperative use of psychotropic medications, active or recent substance abuse or dependence, age less than 18 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	• Dexmedetomidine: loading dose: 0.4 g/kg, followed by a maintenance drip of 0.2 mcg/kg/h to 0.7 mcg /kg/h. Average amount received 0.35 g/kg/h for 13 h • Propofol: 1.5 mcg/kg/h to 3 mcg/kg/h. Average amount received 26.3 mcg/kg/min for 11 h • Midazolam: 0.5 mg/h to 2 mg/h; average amount received 1.5 mg/h for 10 h • Infusion rates for all sedative protocols were titrated in order to achieve and maintain an RSS score of 3 before extubation and 2 after extubation. • For additional sedation while intubated, subjects received increased doses of the drug they had been randomly assigned to; fentanyl 25 g to 50 g every hour as needed for pain was the only opiate used in the first 24 h; ketorolac, hydrocodone, and oxycodone were allowed for pain management after the first 24 h.

ICU = intensive care unit; RSS = Ramsay Sedation Scale.

Appendix 3: Critical Appraisal of the Included Studies

Table 42: Lorazepam as Comparator

Strengths	Limitations
Pandharipande et al. 2007,[12] 2010[11]	
• Randomization was done using computer-generated, permuted block randomization (known only to the investigational pharmacists) and patients were stratified by site to receive sedation with either dexmedetomidine or lorazepam. • All patients and study personnel, except for the investigational pharmacist, were blinded to study drug assignment. • Sample size was estimated in order to achieve 80% statistical power to detect a 30% increase delirium-free and coma-free days due to the intervention.	• Study drug was titrated by bedside nurse; titration rate differed between dexmedetomidine and lorazepam. It is not clear how the nurse could be blinded from the administered drug.

Table 43: Midazolam as Comparator

Strengths	Limitations
MacLaren et al. 2015[34]	
• Randomization was done using computer-generated random-numbers table for patients to receive dexmedetomidine or midazolam continuous sedation. • Double-blind design: All infusions were adjusted by increments of 2 mL/h to maintain blinding.	• In case of agitation, patients were given open-label midazolam or fentanyl according to the ICU sedation and analgesia protocol. It is not clear how the effect of dexmedetomidine was evaluated when patients received midazolam as a rescue medication. • Sample size calculation was based on statistical power estimation; however, the trial did not include the required number of patients to achieve the desired power.
Gupta et al. 2015[36]	
• Randomization was done using computer-generated random numbers; however, it is not reported how this randomization was concealed.	• Sample size was based on convenience rather than statistical power estimation. • Treatment allocation was not blinded, and this could affect the evaluation of subjective outcomes. • The study included patients who had sedation failure with midazolam. Therefore, the study design might have been biased by selecting patients who failed midazolam.
Jakob et al. 2012[9] MIDEX trial	
• Randomization was done by a central interactive voice-response system. • All patients and study personnel were masked to treatment allocation. Treatments were administered in a double-dummy design, with 0.9% saline solution as dummy for all treatments. • Rescue medication was different than the study drugs. • Sample size was estimated based on an overall	• No major limitations

Strengths	Limitations
64% of time in target range of sedation without using rescue medication. The trial had 90% power to reject a 15% inferiority of dexmedetomidine to standard sedation, using a 2-sided 95% confidence interval for the estimated ratio of dexmedetomidine to standard care.	
Yapici et al. 2011[37]	
• No major strengths	• Randomization method and allocation concealment were not reported. • Before randomization, patients were administered midazolam (study drug) to control agitation; failure to control agitation was an inclusion criteria. Therefore, the study design might have been biased by selecting patients who failed midazolam.
Esmaoglu et al. 2009[35]	
• Sample size was based on a statistical power of 0.88 to detect differences in antihypertensive medications. However, the authors did not report the estimated difference.	• Patients were randomly divided into 2 groups using coin toss. It was not clear how investigators assured that patients were allocated to the resulting toss. • Allocation concealment method was not reported.
Riker et al. 2009[13]	
• Randomization was achieved using an interactive voice-response system and a computer-generated schedule. • Study was double-blind; however, it was not obvious how blinding was concealed though out the study. • Sample size was estimated based on 96% power at an alpha of 0.05 to detect a 7.4% difference in efficacy for the primary outcome (mean percentage of time within target sedation range).	• In case of insufficient sedation, patients were given an open-label midazolam. It is not clear how the effect of dexmedetomidine was evaluated when patients received midazolam as a rescue medication.

ICU = intensive care unit.

Table 44: Propofol as Comparator

Strengths	Limitations
Liu et al. 2016[25]	
• Sample size was estimated to achieve a power of 0.8 and 2-sided alpha level of 0.05 to detect a 10% difference of perfused small-vessel density between interventions.	• Single-blinded design; patients and the researchers who analyzed sublingual microcirculatory images were blinded to the group allocation. However, unblinded medical staff assessed other outcomes (such as hypotension and heart rate). • It was not specified whether patients were given additional or rescue sedatives or analgesia in case of insufficient sedation with the study drugs. • Method of randomization was not reported. • The authors excluded patients who needed to be sedated for ≥ 24 h. Although this is the approved duration for dexmedetomidine in Canada, excluding these patients would mask potential differences between the study drugs in reducing the sedation period before extubation.

Strengths	Limitations
Conti et al. 2016[38]	
• Sample size was estimated to achieve a power of 0.8 and 2-sided alpha level of 0.05 to detect a 8.3% difference in asynchrony index. • When needed, patients were given midazolam as a rescue or additional sedative.	• This was an open-label study. Awareness of the allocated drugs might affect the evaluation of subjective outcomes. • Method of randomization was not reported.
Djaiani et al. 2016[14]	
• Randomization was done through computer-generated code in blocks of four. • Allocation was concealed using opaque sealed envelopes generated according to the randomization schedule and opened by a study coordinator before surgery. • Sample size was based on 14% reduction in delirium prevalence, with an alpha of 0.05 and power of 80%.	• There were three patients in the dexmedetomidine group and six patients in the propofol group who required mechanical ventilation and sedation beyond the 24-h period; after this period, both groups received propofol. The authors reported that none of these patients in dexmedetomidine group developed delirium, whereas three patients in the propofol group were delirious. However, other outcomes were not reported for those patients. • This was an open-label study. Awareness of the allocated drugs might affect the evaluation of subjective outcomes.
Paliwal et al. 2015[42]	
• Sample size was based on the assumption that there would be a 30% reduction in the mean heart rate following therapy, with an alpha of 0.05 and power of 80%.	• Randomization method was not reported. • This was an open-label study. Awareness of the allocated drugs might affect the evaluation of subjective outcomes.
Terao et al. 2012[39]	
• Randomization was done using sealed envelope. • Sample size calculation was based on a clinically important difference of ≥5% different proportion in adequate sedation level between two sedation agents, with a standard deviation of 5%, power minimum of 80%, and alpha of 0.05. • If adequate sedation was not achieved with study drugs, another sedative agent was used. That would minimize confounding when using one of the study drugs as a rescue medication.	• This was an open-label study. Awareness of the allocated drugs might affect the evaluation of subjective outcomes.
Jakob et al. 2012[9] PRODEX	
• Randomization was done by a central interactive voice-response system. • All patients and study personnel were masked to treatment allocation. Treatments were administered in a double-dummy design, with 0.9% saline solution as dummy for all treatments. • Rescue medication was different than the study drugs. • Sample size was estimated based on an overall 64% of time in target range of sedation without using rescue medication. The trial had 90% power to reject a 15% inferiority of dexmedetomidine to standard sedation, using a 2-sided 95% confidence interval for the	• No major limitations

Strengths	Limitations
estimated ratio of dexmedetomidine to standard care.	
Memis et al. 2009[24]	
• Randomization was done using computer-generated table and sealed envelopes.	• This was an open-label study. Awareness of the allocated drugs might affect the evaluation of subjective outcomes. • Sample size was based on convenience rather than statistical power estimation.
Elbaradie et al. 2004[41]	
• No major strengths	• Randomization was done by coin toss; there were no assurances that patients were allocated as tossed. • This was an open-label study. Awareness of the allocated drugs might affect the evaluation of subjective outcomes. • Sample size was based on convenience rather than statistical power estimation.
Herr et al. 2003[26]	
• Sample size estimation was based on the assumption that the smallest difference in mean Ramsay score that would be clinically significant is 0.5 and the pooled standard deviation of mean Ramsay score would be 1.2.	• This was an open-label study. Awareness of the allocated drugs might affect the evaluation of subjective outcomes. • In case of insufficient sedation, patients were given an open-label propofol. It is not clear how the effect of dexmedetomidine was evaluated when patients received propofol as a rescue medication.
Venn et al. 2001[40]	
• Randomization was done with sealed envelopes.	• Exclusion criteria were not reported.

Table 45: Propofol/Midazolam as Comparators

Strengths	Limitations
Srivastava et al. 2014[43]	
• Randomization was done using computer-generated table of random numbers • Drug infusions were prepared by personnel not involved in the study or the patient's care. • Sample size was calculated based on the assumption that there would be a 30% reduction in the mean heart rate following therapy (with alpha of 0.05 and power of 80%).	• This was single-blinded study; patients were blinded, while investigators were not.
Maldonado et al. 2009[44]	
• Randomization was performed the evening before surgery by random drawing. • Sample size estimation was based on a difference in proportions of 30% for incidence of delirium (power of 80%; a two-sided alpha level of 0.05).	• This was open-label study; awareness of the allocated drugs might affect the evaluation of subjective outcomes.

Appendix 4: Results of the Included Studies

Table 46: Dexmedetomidine Versus Lorazepam

Main Study Findings				Conclusions
Pandharipande et al. 2007[12]				
	Dexmedetomidine (N = 52)	**Lorazepam (N = 51)**	**Difference (*P* value)**	"*Dexmedetomidine was more effective than lorazepam for achieving sustained sedation of mechanically ventilated medical and surgical ICU patients.* *Dexmedetomidine treated ICU patients had 4 more days alive and without delirium or coma, significantly higher accuracy at meeting the stated sedation goals, and no added cost of care*." Page 2652
• Age, mean (SD)	60	59	0.97	
• Men: n (%)	30 (58)	23 (45)	0.20	
• Duration of pre-trial MV	22 h	17 h	0.18	
• Other medications	575 mcg/d fentanyl 0.25 mg lorazepam	150 mcg/d fentanyl 0 mg lorazepam	0.006 0.69	
Outcomes				
Duration of Mechanical Ventilation				
• MV-free, median (range), days	22 (0 to 24)	18 (0 to 23)	0.22	
Days Spent in Delirium				
• Median (range), days	2.5 (1 to 5)	4 (1 to 5)	0.71	
• Incidence, n (%)	41 (79)	42 (82)	0.65	
Duration of ICU Stay				
• Days, median (IQR)	7.5 (5 to 19)	9 (6 to 15)	0.92	
Bradycardia				
• < 60/min, n (%)	9 (17)	2 (4)	0.03	
Hypotension				
• Days	0 (0 to 0.2)	0 (0 to 0)	0.51	

ICU = intensive care unit; IQR = interquartile range; MV = mechanical ventilation; SD = standard deviation.

Table 47: Dexmedetomidine Versus Midazolam

Main Study Findings				Conclusions
MacLaren et al. 2015[34]				
	Dexmedetomidine (N = 11)	**Midazolam (N = 12)**	**Difference (*P* value)**	"*Dexmedetomidine did not expedite ventilator liberation, but its use was* ***associated with less midazolam administration****, more hypotension, less delirium, and greater recall of ICU experiences. Patients receiving dexmedetomidine were no more likely to develop symptoms of anxiety or depression, but they were more likely to manifest traits of ASD [acute stress disorder] before hospital discharge*." Page 174 **Reviewer's comment:** Results showed that dexmedetomidine was associated with numerically higher open-label usage of midazolam.
• Age, mean (SD)	58.3 (15.3)	57.8 (9.3)	Not reported	
• Men: n (%)	6 (54.6)	7 (58.3)	Not reported	
• Duration of pre-trial MV	Not reported	Not reported		
• Rescue treatment	Midazolam 65.3 mg	Midazolam 29.0 mg	> 0.1	
Outcomes				
Duration of mechanical ventilation				
• Days median of total duration (IQR)	8.2 (5.7 to 15.5)	10.9 (4.4 to 12.6)	Not reported	
• Days after study drug initiation median (IQR)	3.4 (2.6 to 14.2), n = 7	2.9 (2 to 4.4), n = 8	Not significant	
Rate of re-intubation within first 24 h				
• Re-intubation within 72 h; n (%)	1/7	0/8	Not reported	
Days spent in delirium				
• Days	Not reported	Not reported		
• Prevalence, n (%)	4 (36.4)	8 (66.7)	> 0.1	
• Incidence, n	1	5	0.07	
Duration of ICU stay				
• Days median of total duration (IQR)	18.4 (11.5 to 33.9)	16.1 (6.5 to 28.1)	Not reported	
• Days after study drug initiation median (IQR)	10.2 (6.8 to 25.2)	12 (4.8 to 14.8)	> 0.1	
Time to extubation				
• Days from study drug initiation to extubation median (IQR)	3.4 (2.6 to 14.2)	2.9 (2 to 4.4)	Not reported	
Bradycardia				
• N (%)	7 (63.6)	7 (58.3)	> 0.1	
Hypotension				
• N (%)	10 (90.9)	6 (50)	0.069	
Gupta et al. 2015[36]				
	Dexmedetomidine (N = 20)	**Midazolam (N = 20)**	**Difference (*P* value)**	"*Dexmedetomidine has clinically relevant benefits compared to midazolam in facilitating extubation because of its shorter time to extubation, more hemodynamic stability, easy arousability and lack of respiratory depression; hence, it can be used as an*
• Age, mean (SD)	43.35 (11.60)	39.00 (14.13)	0.294	
• Sex, male: n (%)	12 (60%)	13 (65%)	0.744	
• Duration of pre-trial MV	92 h 36 min	94 h 15 min	Not reported	
• Rescue treatment	Not reported	Not reported	Not reported	

Main Study Findings				Conclusions
Outcomes				*effective, and safe sedative agent to facilitate extubation in ICUs.*" Page 6/14
Time to extubation				
• Mean (SD); h	24.21 (1.6651)	31.35 (3.3447)	0.0260	
Bradycardia				
• Mean HR 0 h to 12 h of drug infusion	Not reported	Not reported	Not significant	
• Mean HR at 16, 20, 24 h of drug infusion	Not reported	Not reported	Not reported	
• Mean HR after 12 h of extubation (SD)	84.85 (9.949)	108.95 (5.671)	0.024	
Jakob et al. 2012[9] MIDEX				
	Dexmedetomidine (N = 249)	**Midazolam (N = 251)**	**Difference (*P* value)**	"*Dexmedetomidine is feasible for long-term sedation in intensive care patients and may provide clinically relevant benefits by reducing the duration of invasive ventilation and improving comfort.*" Page 1158
• Age, mean (SD)	65 (55 to 74)	65 (55 to 74)	0.98	
• Men: n (%)	153 (61.4)	175 (69.7)	0.06	
• Duration of pre-trial MV	Not reported	Not reported	Not reported	
• Rescue treatment	Not reported	Not reported	Not reported	
Outcomes				
Duration of Mechanical Ventilation				
• Median (IQR) of total duration h	123 (67 to 337)	164 (92 to 380)	0.03	
Duration of ICU Stay				
• From randomization until fit to discharge; Median (IQR), h	211 (115 to 831)	243 (140 to 630)	Not significant	
Time to Extubation				
• Median (IQR), h	101 (65 to 313)	147 (81 to 325)	0.01	
Agitation				
• n (%)	39 (15.8)	41 (16.4)	0.903	
Bradycardia				
• n (%)	35 (14.2)	13 (5.2)	< 0.001	
Hypotension				
• n (%)	51 (20.6)	29 (11.6)	0.007	
Yapici et al. 2011[37]				
	Dexmedetomidine (N = 38)	**Midazolam (N = 34)**	**Difference (*P* value)**	*"Dexmedetomidine can be a good choice for the management of the delirium state associated with prolonged mechanical ventilation after cardiac surgery. Initiation of dexmedetomidine treatment when the first signs of delirium appear in patients who could not be switched*
• Age, mean (SD)	58.905 (10.492)	61.167 (9.154)	0.063	
• Sex, male: n (%)	13 (34.21)	14 (41.17)		
• Duration of pre-trial MV	37.095 (6.745)	39.833 (5.833)	0.91	
• ICU sedation regimen	Not reported	Not reported	Not reported	
• Rescue treatment	Not reported	Not reported	Not reported	

Main Study Findings				Conclusions
Outcomes				*to CPAP [continuous positive airway pressure] after cardiac surgery may help to eliminate the emergence of agitation during sedation tapering and therefore may help to facilitate earlier extubation."* Page E98
Days Spent in Delirium				
• Prevalence 36 h post-operative, n (%)	38 (100)	34 (100)	*P* value > 0.05	
• Prevalence 60 h post-operative, n (%)	1 (2.7%)	7 (21%)	< 0.05	
Time to Extubation				
• Mean (SD); h	46.62 (6.96)	58.389 (3.958)	< 0.0001	
Bradycardia				
• Mean HR after 6 h of randomization	92.81 (15.53)	94.56 (16.33)	0.6417	
• Mean HR after 12 h of randomization	84.29 (14.74)	98.5 (10.08)	0.0017	
• Mean HR after 24 h of randomization	77.71 (9.42)	95.33 (7.07)	< 0.0001	
Esmaoglu et al. 2009[35]				
	Dexmedetomidine (N = 20)	**Midazolam (N = 20)**	**Difference (*P* value)**	"*Dexmedetomidine infusion in eclampsia patients reduces the amount of antihypertensive use and shortens the duration of the ICU stay*" Page 554
• Age, mean (SD)	25.1 (4.8)	26.8 (7.1)	0.370	
• Sex, male: n (%)	Not reported	Not reported	Not reported	
• Duration of pre-trial MV	Not reported	Not reported	Not reported	
• ICU sedation regimen	Not reported	Not reported	Not reported	
• Rescue treatment	9	12	0.527	
Outcomes				
Duration of ICU Stay				
• Total time, median (range) (h)	45.5 (15 to 118)	83 (15 to 312)	0.021	
• Stop sedation, discharge from ICU, median (range) (h)	21 (1 to 150)	52 (6 to 288)	0.000	
Riker et al. 2009[13]				
	Dexmedetomidine (N = 244)	**Midazolam (N = 122)**	**Difference (*P* value)**	"*The study showed no difference in the time patients spent within the sedation target range with dexmedetomidine or midazolam… dexmedetomidine shortened time to removal from mechanical ventilation and reduced the prevalence of delirium.*" Reviewer's comment: The authors did not consider the
• Age, mean (SD)	61.5 (14.8)	62.9 (16.8)	0.26	
• Sex, male: n (%)	125 (51.2)	57 (46.7)	0.44	
• Duration of pre-trial MV	40.6h (22.2 to 64.9)	39.3h (24.5 to 72.8)	0.76	
• ICU sedation regimen	Not reported	Not reported	Not reported	
• Rescue treatment	Mida n: 153 (63) Fent n: 180 (73.8)	Mida n: 60 (49) Fent n: 97 (79.5)	**Mida : 0.02** Fent 0.25	

Main Study Findings				Conclusions
Outcomes				amount of rescue medication (specially midazolam) given to dexmedetomidine group.
Days Spent in Delirium				
• Prevalence	132 (54)	93 (76.6)	< 0.001	
• Mean delirium-free days	2.5	1.7	0.002	
Duration of ICU Stay				
• Median (95% CI), days	5.9 (5.7 to 7.0)	7.6 (6.7 to 8.6)	0.24	
Time to Extubation				
• Median (95% CI), days	3.7 (3.1 to 4.0)	5.6 (4.6 to 5.9)	1.9 days; 0.01	
Bradycardia				
• As AE, n (%)	103 (42.2)	23 (18.9)	< 0.001	
• With intervention, n (%)	12 (4.9)	1 (0.8)	0.07	
Hypotension				
• As AE, n (%)	137 (56.1)	68 (55.7)	> 0.99	
• With intervention, n (%)	69 (28.3)	33 (27)	0.90	

AE = adverse event; CI = confidence interval; Fent = fentanyl; HR = hazard ratio; ICU = intensive care unit; IQR = interquartile range; Mida = midazolam; MV = mechanical ventilation; SD = standard deviation.

Table 48: Dexmedetomidine Versus Propofol

Main Study Findings				Conclusions
Liu et al. 2016[25]				
	Dexmedetomidine (N = 29)	**Propofol (N = 32)**	**Difference (*P* value)**	The authors concluded that dexmedetomidine may accelerate the recovery of sublingual microcirculatory perfusion in patients after valve surgery compared with propofol.
• Age, mean (SD)	53 (48 to 63)	55 (48 to 62)	0.737	
• Sex, male: n (%)	10 (34)	15 (47)	0.435	
• Duration of pre-trial MV	Not reported	Not reported	Not reported	
• Rescue treatment	Not reported	Not reported	Not reported	
Outcomes				
Bradycardia				
• Incidence, n (%)	5 (17)	1 (3)	0.093	
Hypotension				
• Incidence, n (%)	9 (31)	11 (34)	0.793	
Conti et al. 2016[38]				
	Dexmedetomidine (N = 10)	**Propofol (N = 10)**	**Difference (*P* value)**	"*When sedation with propofol or dexmedetomidine was compared at similar Richmond Agitation–Sedation Scale scores in patients for whom the first weaning trial had failed, the asynchrony index was lower with dexmedetomidine, and*
• Age, mean (SD)	68.8 (15.7)		Not reported	
• Sex, male: n (%)	11 (55)		Not reported	
• Duration of pre-trial MV	Not reported	Not reported	Not reported	
• ICU sedation regimen	Not reported	Not reported	Not reported	

Main Study Findings				Conclusions
• Rescue treatment	Mida: 2 patients Fentanyl: 2 patients	Mida: 1 patient Fentanyl: 3 patients	Not reported	*this difference was statistically significant at 12 h*." Page 7
Outcomes				
Rate of Re-Intubation				
• Number of patients	0	0		
Episodes of Agitation				
• Reported as compound AE (coma, agitation, or anxiety)	2	3		
Duration of ICU Stay				
• Total duration (range), days	6.02 (2.2 to 8.5)	10.06 (5.0 to24.8)	HR (96% CI) 0.84 (0.31 to 2.33) *P* = 0.742	
Time to Extubation				
• Median (range), h	25.2 (24.5 to 118.7)	57.3 (24.7 to 113.0)	HR (96% CI) 0.97 (0.37 to 2.54) *P* = 0.958	
Bradycardia				
• N (%)	1/16 (6.3)	0		
Djaiani et al. 2016[14]				
	Dexmedetomidine (N = 91)	**Propofol (N = 92)**	**Difference (*P* value)**	"*Post-operative administration of dexmedetomidine-based sedation regimen resulted in the reduced incidence, delayed onset, and shortened duration of POD [postoperative delirium] when compared with propofol-based sedation in elderly patients after cardiac surgery*." page 367
• Age, mean (SD)	72.7 (6.4)	72.4 (6.2)		
• Sex, male: n (%)	68 (74.7)	70 (76.0)		
• Duration of pre-trial MV	Not reported	Not reported	Not reported	
• ICU sedation regimen	Not reported	Not reported	Not reported	
• Rescue treatment	Haloperidol: 12 (13) Quetiapine: 3 (3.3)	24 (26) 5 (5.4)	0.04 0.72	
Outcomes				
Days Spent in Delirium				
• Incidence, n (%)	16 (17.5)	29 (31.5)	0.028	
Duration of ICU Stay				
• Median (range), h	43 (18 to 315)	29.4 (17 to 957)	Not reported	
Time to Extubation				
• Median (range), h	5.4 (2 to 142)	5.9 (1 to 202)	Not reported	

Main Study Findings				Conclusions
Paliwal et al. 2015[42]				
	Dexmedetomidine (N = 30)	**Propofol (N = 30)**	**Difference (*P* value)**	"*Adequate level of sedation can be achieved by both dexmedetomidine and propofol. While dexmedetomidine- treated patients are easily arousable, the only notable adverse effect is bradycardia.*" Page 4
• Age, mean (SD)	43.3 (20.25)	49.26 (16.74)	> 0.3	
• Sex, male: n (%)	Not reported			
• Duration of pre-trial MV	Not reported			
• Rescue treatment	**Propofol: 18**	**Propofol: 6**	**0.0398**	
Outcomes				
Bradycardia				
• Incidence, N (%)	4 (13.3)	0		
• Baseline; mean HR (SD)	105.8 (26.12)	110.5 (19.13)	> 0.5	
• After load	86.83 (26.28)	105.6 (19.51)	< 0.01	
• 30 min	82.03 (21.29)	103.43 (17.57)	< 0.001	
• 60 min	85.53 (22.31)	102.66 (18.72)	< 0.01	
• 4 h	86.9 (23.09)	102.43 (16.88)	< 0.01	
• 8 h	90.33 (24.00)	100.73 (15.28)	< 0.05	
• 12 h	87.56 (23.92)	99.53 (16.24)	< 0.05	
Hypotension				
• After load; mean blood pressure (SD)	95.10 (12.51)	94.53 (15.32)	Not reported	
• 30 min	89.93 (12.59)	86.16 (14.99)		
• 60 min	88.66 (13.20)	86.46 (15.73)		
• 4 h	89.53 (12.14)	87.46 (15.73)		
• 8 h	89.40 (13.82)	88.53 (15.07)		
• 12 h	86.90 (12.03)	87.23 (15.07)		
Terao et al. 2012[39]				
	Dexmedetomidine (N = 16)	**Propofol (N = 16)**	**Difference (*P* value)**	"*Dexmedetomidine and propofol are both efficacious for sedation after extensive cervical spine surgery; however, dexmedetomidine decreased heart rate and required higher doses of dopamine compared with propofol*."
• Age, mean (SD)	65 (34 to 79)	60 (44 to 86)	0.35	
• Sex, male: n (%)	9 (56)	11 (69)	0.72	
• Duration of pre-trial MV	Not reported	Not reported	Not reported	
• Rescue treatment	1 Atropine: 5 Dopamine: 12	0 0 8	 0.04 0.27	
Outcomes				
Episodes of Agitation				
• Number of patients	2	2	0.99	
Duration of ICU Stay				
• Media (IQR), days	2 (2 to 4)	3 (3 to 7)	0.06	

Main Study Findings				Conclusions
Time to Extubation				
• Delayed extubation, n (%)	2	6	0.22	
• Intubation duration, median (range), min	877 (565 to 13,000)	1,003 (770 to 7,050)	0.27	
Jakob et al. 2012[9] PRODEX				
	Dexmedetomidine (N = 251)	**Midazolam (N = 247)**	**Difference (*P* value)**	"*Dexmedetomidine is feasible for long-term sedation in intensive care patients and may provide clinically relevant benefits by reducing the duration of invasive ventilation and improving comfort.*" Page 1158
• Age, mean (SD)	65 (51 to 75)	65 (51 to 74)	0.93	
• Men: n (%)	160 (63.7)	166 (67.2)	0.45	
• Duration of pre-trial MV	Not reported	Not reported	Not reported	
• Rescue treatment	Not reported	Not reported	Not reported	
Outcomes				
Duration of MV				
• Median (IQR) of total duration, h	97 (45 to 257)	118 (48 to 327)	0.24	
Duration of ICU Stay				
• From randomization until fit to discharge; Median (IQR), h	164 (90 to 480)	185 (93 to 520)	Not significant	
Time to Extubation				
• Median (IQR), h	69 (39 to 184)	93 (45 to 286)	0.04	
Agitation				
• n (%)	19 (7.7)	29 (11.7)	0.171	
Bradycardia				
• N (%)	Not reported	Not reported	Not significant	
Hypotension				
• N (%)	Not reported	Not reported	Not significant	
Memis et al. 2009[24]				
	Dexmedetomidine (N = 20)	**Propofol (N = 20)**	**Difference (*P* value)**	The authors concluded that that neither propofol nor dexmedetomidine change hepatic blood flow in early septic shock patients during sedation.
• Age, mean (SD)	60 (31 to 80)	54 (25 to 78)		
• Sex, male: n (%)	14 (70%)	13 (65%)		
• Duration of pre-trial MV				
• Rescue treatment	Alfentanil: 2.8 mg	3.4 mg	> 0.05	

Main Study Findings				Conclusions
Outcomes				
Duration of ICU stay				
• Days (SD)	14 (8)	12 (7)	> 0.05	
Bradycardia				
• Baseline, mean (SD)	85 (17)	88 (14)		
• After 24 h	72 (13)	79 (14)		
Hypotension				
• Baseline, mean (SD)	74 (8)	75 (6)		
• After 24 h	71 (14)	73 (13)		
Elbaradie et al. 2004[41]				
	Dexmedetomidine (N = 30)	**Propofol (N = 30)**	**Difference (*P* value)**	"*Dexmedetomidine is a safe sedative agent with patients easily aroused to co-operate without showing irritation. Dexmedetomidine significantly reduced the requirement for fentanyl analgesia.*" Page 157 Reviewer's comment: the authors did not report the required amounts of fentanyl analgesia.
• Age, mean (SD)	65 (6.5)	67 (5.7)	0.37	
• Sex, male: n (%)	Not reported		Not reported	
• Duration of pre-trial MV	Not reported	Not reported	Not reported	
• Rescue treatment	Not reported		Not reported	
Outcomes				
Time to extubation				
• Mean extubation time (SD), min	30 (15)	35 (12)	0.32	
Bradycardia				
• Mean heart rate	Dexmedetomidine < propofol		0.041	
Hypotension				
• Mean arterial pressure	Not reported		0.45	
Herr et al. 2003[26]				
	Dexmedetomidine (N = 148)	**Propofol (N = 147)**	**Difference (*P value*)**	"*Dexmedetomidine is safe and effective for the post-surgical sedation of CABG [coronary artery bypass graft] patients when compared with propofol-based sedation as it is currently practiced in the United States and Canada*." Page 583
• Age, mean (SD)	61.9 (9.5)	62.4 (8.7)		
• Sex, male: n (%)	137 (93%)	128 (87%)		
• Duration of pre-trial MV	Not reported	Not reported	Not reported	
• Rescue treatment	Not reported	Not reported	Not reported	
Outcomes				
Episodes of Agitation				
• Incidence, n (%)	5 (3%)	1 (< 1%)	0.214	
Time to Extubation				
• Median (range), min	410 (310 to 584)	462 (323 to 808)		

Main Study Findings				Conclusions
Bradycardia				
• Incidence, n (%)	5 (3%)	2 (1%)	0.448	
• Incidence of tachycardia, n (%)	5 (3%)	5 (3%)	> 0.999	
• Ventricular tachycardia, n (%)	0	7 (5%)	0.007	
Hypotension				
• Incidence	36 (24%)	24 (16%)	0.111	
• Incidence of hypertension, n (%)	18 (12%)	6 (4%)	0.018	
Venn et al. 2001[40]				
	Dexmedetomidine (N = 10)	**Propofol (N = 10)**	**Difference (*P* value)**	"*Dexmedetomidine appears to be a safe and acceptable ICU agent when both the clinician's and patient perspectives are considered*." Page 689
• Age, mean (SD)	65 (60 to 77)	67 (64 to 74)	Not reported	
• Sex, male: n (%)	Not reported	Not reported	Not reported	
• Duration of pre-trial MV	Not reported	Not reported	Not reported	
• Rescue treatment	Alfentanil: 0.8 mg/h	2.5 mg/h	0.004	
Outcomes				
Rate of Re-Intubation				
• N (%)	0	0	Not reported	
Time to Extubation				
• Mean (range) extubation time, min	29 (15 to 50)	28 (20 to 50)	0.63	
Bradycardia				
• Mean HR during intubation	Not reported	Not reported	0.034	
• During sedation infusion	Not reported	Not reported	0.15	
Hypotension				
• Mean blood pressure	Not reported	Not reported	0.60	

AE = adverse event; ICU = intensive care unit; IQR = interquartile range; HR = hazard ratio; Mida = midazolam; MV = mechanical ventilation; SD = standard deviation.

Table 49: Dexmedetomidine Versus Propofol or Midazolam

Main Study Findings						Conclusions
Srivastava et al. 2014[43]						
	Dexmedetomidine (N = 30)	**Midazolam (N = 30)**	**Propofol (N = 30)**	**Difference Versus Midazolam (*P* value)**	**Difference Versus Propofol (*P* value)**	"*Dexmedetomidine is safer and equally effective agent compared to propofol and midazolam for sedation of neurosurgical mechanically ventilated patients with good hemodynamic stability and extubation time as rapid as propofol. Dexmedetomidine also reduced post-operative fentanyl requirements*." Page 7
• Age, mean (SD)	50.5 (7.44)	51.3 (8.04)	52.1 (8.48)	Not reported	Not reported	
• Men: n (%)	25 (83.3)	22 (73.3)	23 (76.7)	Not reported	Not reported	
• Duration of pre-trial MV	12.03 (3.13)	12.72 (3.20)	12.86 (3.52)	Not reported	Not reported	
• Rescue treatment, mcg/kg/h	Fent: 0.26 (0.13)	0.50 (0.14)	0.42 (0.14)	< 0.001	< 0.001	
Outcomes						
Rate of Re-Intubation						
• N (%)	0	0	0	Not reported	Not reported	
Time to Extubation						
• Extubation time, mean (SD)	35.28 (5.92)	48.21 (7.23)	26.13 (5.32)	0.001	Not reported	
Bradycardia						
• N(%)						
• Baseline, mean arterial pressure (SD)	89.25 (7.28)	89.03 (6.38)	86.31 (6.69)	0.905	0.118	
• After 1 h	76.67 (6.64)	84.20 (5.23)	82.10 (6.31)	< 0.001	< 0.01	
• After 4 h	66.89 (4.01)	82.13 (7.60)	80.24 (6.59)	< 0.001	< 0.001	
• After 8 h	68.03 (3.48)	84.27 (6.40)	79.65 (7.04)	< 0.001	< 0.001	
• Post extubation, 1 h	74.36 (4.27)	86.07 (4.61)	86.17 (5.38)	< 0.001	< 0.001	
• Post extubation, 2 h	77.71 (5.20)	87.86 (5.38)	90.41 (6.13)	< 0.001	< 0.001	
Hypotension						
• Requiring intervention n (%)	2 (6.66%)	0	0			
• Baseline, mean arterial pressure (SD)	104.89 (7.51)	105.10 (7.88)	103.17 (7.41)	0.918	0.388	
• After 1 h	95.93 (6.21)	98.28 (6.68)	90.10 (8.26)	0.175	< 0.01	
• After 4 h	95.85 (9.14)	98.38 (5.80)	92.62 (5.26)	0.217	0.105	

Main Study Findings						Conclusions
• After 8 h	98.14 (6.55)	98.28 (6.19)	92.21 (4.19)	0.937	< 0.001	
• Post extubation, 1 h	103.64 (5.21)	107.59 (5.43)	99.34 (5.11)	< 0.05	< 0.01	
• Post extubation, 2 h	105.00 (5.21)	108.41 (4.82)	101.00 (5.13)	< 0.05	< 0.05	
Maldonado et al. 2009[44]						
	Dexmedetomidine (N = 40)	**Midazolam (N = 40)**	**Propofol (N = 38)**	**Difference Versus Midazolam (*P* value)**	**Difference Versus Propofol (*P* value)**	"*Dexmedetomidine administered as a post-operative sedative agent was associated with significantly lower rates of post-operative delirium*." Page 215
• Age, mean (SD)	55 (16)	60 (16)	58 (18)	Not reported	Not reported	
• Men: n (%)	26 (65%)	27 (68%)	22 (58%)	Not reported	Not reported	
• Duration of pre-trial MV	Not reported	Not reported	Not reported	Not reported	Not reported	
• Rescue treatment	Fent: 320 (355) mg Morph eq: 50.3 (38) mg	1,088 (832) mg 122.5 (84)	364 (320) mg 51.6 (36)	< 0.001 < 0.001	0.93 0.99	
Outcomes						
Days Spent in Delirium						
• Days (%)	2/216 (1%)	75/259 (29%)	45/276 (16%)	< 0.001	< 0.001	
• Mean length of delirium, days (%)	2.0 (0)	5.4 (6.6)	3.0 (3.1)	0.63	0.93	
• Incidence, n (%)	4/40 (10%)	17/40 (44%)	16/36 (44%)	0.002	0.001	
Duration of ICU Stay						
• Days, mean (SD)	1.9 (0.9)	3.0 (3.0)	3.0 (2.0)	0.14	0.14	

Fent = fentanyl; ICU = intensive care unit; Morph eq = morphine equivalent; MV = mechanical ventilation; SD = standard deviation.

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