TITLE: Dexmedetomidine for Sedation in the ICU or PICU: A Review of Cost-Effectiveness and Guidelines

DATE: 17 December 2014

CONTEXT AND POLICY ISSUES

Sedation of ICU patients is often essential for ICU patients to maximize survival, reduce ICU and hospital stay, and facilitate mechanical ventilation.[1] The standard of care for sedation includes benzodiazepine sedatives and propofol.[1] These sedatives (notably benzodiazepines) are associated with an increased risk of agitation and delirium.[1] It has been hypothesized that dexmedetomidine would be an appropriate alternative to traditional sedatives for maintaining light to moderate sedation. Dexmedetomidine is an alpha$_2$-adrenergic agonist, and it is approved in Canada for intensive care unit sedation and conscious sedation.[2] In January 2014, the Canadian Agency for Drugs and Technologies in Health (CADTH) reviewed the evidence on the clinical effectiveness of using dexmedetomidine for sedation in intensive-care unit.[3] Based on the CADTH review, dexmedetomidine was found to be associated with decreased ICU stay and decreased time on mechanical ventilation. However, it was associated with higher rates of bradycardia than comparators.

Dexmedetomidine is available in 100 mcg/mL in a 2 mL glass vials at $45.21 per vial.[2,3] At the maximum allowed daily dose, dexmedetomidine is more expensive than midazolam, lorazepam, and propofol (Appendix 1). However, it is not clear if the higher cost of dexmedetomidine is offset by its suggested benefits. The objective of this report is to review the cost-effectiveness and the available evidence-based guidelines for using dexmedetomidine for sedation the intensive care unit.

RESEARCH QUESTIONS

1. What is the cost-effectiveness of dexmedetomidine for patients requiring sedation in the intensive care unit (ICU) or pediatric intensive care unit (PICU)?

2. What are the evidence-based guidelines associated with the use of dexmedetomidine for patients requiring sedation in the ICU or PICU?

KEY FINDINGS

Six economic evaluations and two guidelines were included in this review. All except one economic study showed that dexmedetomidine was associated with lower ICU and hospital costs. However, the clinical benefits were marginal and not consistent in the included studies. The included guidelines suggested that the use of dexmedetomidine might be preferred over the benzodiazepine sedatives for better clinical outcomes and lower risk of delirium.

METHODS

Literature Search Strategy

A limited search was conducted on key resources including Medline, The Cochrane Library (2014, Issue11), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2009 and November 19, 2014.

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 1.

Table 1: Selection Criteria

Population	Adult and pediatric patients requiring sedation in the ICU/PICU
Intervention	Dexmedetomidine
Comparator	Traditional sedatives; including but not limited to, midazolam, lorazepam, propofol, ketamine, or narcotics
Outcomes	Cost-effectiveness (e.g., but not limited to, drugs used, less time in ICU, shorter time on ventilator) Guidelines
Study Designs	Health technology assessment, systematic review/meta-analysis, economic evaluations, and evidence-based guidelines

Exclusion Criteria

Studies were excluded if they did not satisfy the selection criteria, if they were duplicate publications, or were published prior to 2009.

Critical Appraisal of Individual Studies

Critical appraisal of the included studies was based on study design.

The methodological quality of the included cost-effectiveness studies were assessed using the guidelines for appraisal of economic studies by Drummond et al.[4] And the Appraisal of Guidelines Research and Evaluation II (AGREE II) instrument was used to evaluate the quality of the included guideline.[5]

For the included studies a numeric score was not calculated. Instead, the strengths and limitations of the study were described.

SUMMARY OF EVIDENCE

Quantity of Research Available

A total of 378 citations were identified in the literature search. Following screening of titles and abstracts, 367 citations were excluded and 11 potentially relevant reports from the electronic search were retrieved for full-text review. Six potentially relevant publications were retrieved from the grey literature search. Of these potentially relevant articles, nine publications were excluded for various reasons, while eight publications (six economic studies and two evidence-based guidelines) met the inclusion criteria and were included in this report. Appendix 2 describes the PRISMA flowchart of the study selection.

Additional references of potential interest that did not meet the selection criteria are provided in Appendix 3.

Summary of Study Characteristics

Appendix 4 summarises the characteristics of the included studies.

Economic evaluation studies

Thomas et al.[6] published a cost-analysis in 2014 comparing dexmedetomidine with propofol when used in the ICU for adult patients who have undergone coronary artery bypass grafts. The analyzed costs included the costs of post-operative ICU room and board, costs of post-ICU telemetry room and board, and the cost of sedation drug therapy. The cost-analysis was based on retrospective cohort of 84 patients, and it consisted of the net financial benefit (or cost) of using propofol or dexmedetomidine in the observed patients.

In 2014, Patanwala et al.[7] conducted a cost analysis comparing dexmedetomidine with propofol when used for adult patients in the ICU. The analysis was conducted from the perspective of a tertiary health care facility in the US. The analysis used data from 3294 patients on the length of ICU stay and total hospital stay. The cost-analysis included the total hospital costs, but the included report did not specify the different cost drivers.

Lachaine et al.[8] conducted in 2012 a cost-consequence analysis comparing dexmedetomidine with midazolam when used for ICU patients. The analysis was conducted from the perspective of a public payer in Canada with a 30-day time horizon. The clinical information was based on a published RCT of 375 patients in medical or surgical ICUs for whom mechanical ventilation and sedation for a period of three days or more was anticipated. The analysis considered the costs of additional administration of midazolam, costs of ICU stay with mechanical ventilation, the costs associated with delirium, the costs associated with adverse events, and the cost of the two medications.

The Scottish Medical Consortium and All Wales Therapeutic and Toxicology Centre each reviewed an independent listing submission for dexmedetomidine in 2012.[9,10] The submission included a cost-utility analysis that compared dexmedetomidine with propofol and midazolam when used for adult ICU patients requiring sedation level not deeper than arousal in response to verbal stimulation. The analysis was conducted from the perspective of public payer in Scotland and the region of Wales over a 45-day time-horizon. The analysis considered the time before removing intubation and the length of stay in ICU, high dependency or general wards. Data for the analysis were based on two RCTs of 498 and 501 general ICU patients. The analyzed costs included the drug costs, treatment administration cost, first-line rescue strategy cost, mechanical ventilation costs, ICU costs, hospital stay costs, and the costs for management of adverse events.

Dasta et al.[11] conducted a cost-minimization analysis comparing dexmedetomidine with midazolam when used in ICU patients for sedation. The analysis considered the costs of the two medications, cost of ICU stay, cost of mechanical ventilation, and cost of treating adverse events. Clinical information was based on the same study the was used by Lachine et al.[8]

Evidence-based guidelines

Barr et al.[12] conducted a 2013 update of the "Clinical Practice Guidelines for the Sustained Use of Sedatives and Analgesics in the Critically Ill Adult" that was originally published in 2002. The scope of the guideline included short- and long-term management of pain, agitation, and delirium in both intubated and non-intubated adult ICU patients. Relative to sedative medications, the guideline considered benzodiazepines (i.e., midazolam and lorazepam), propofol, and dexmedetomidine. The guideline committee included 20 participants specializing in the management of patients in the ICU, and one librarian. Guideline committee members participated in the selection of the literature and the evaluation of evidence quality.

Celis-Rodriguez et al.[13] (2013) updated the "Clinical practice guidelines for evidence-based management of sedoanalgesia in critically ill adult patients" that was originally published in 2007. The scope of the guideline included the use of sedation and the management of pain in adult patients admitted to the ICU, with or without tracheal intubation and respiratory support, and/or with certain conditions or diseases. Relative to conscious sedation, the guidelines specified lorazepam, midazolam, propofol, diazepam, dexmedetomidine, thiopental sodium, haloperidol, clozapine, methadone, ketamine, and non-pharmacological strategies. The guideline committee included 21 participants specializing in critical care medicine; three of them also specialized in epidemiology.

Both guidelines followed the GRADE procedure for the development and evaluation of recommendations. GRADE is a method of grading the quality of evidence and the strength of recommendations in guidelines developed by the University of McMaster.[14]

Summary of Critical Appraisal

Appendix 5 summarises the critical appraisal of the included studies

Economic evaluation studies

The study by Thoma et al.[6] adjusted for differences in patients' baseline characteristics. A retrospective design and small patient sample (84 patients) were limitations of this study. Another limitation was that the analysis did not include the cost of adjunctive opioid therapies (which were used more in the dexmedetomidine group than in midazolam group). This could underestimate the costs associated with the use of dexmedetomidine. Another limitation was that the analysis did not account for the uncertainty in the differences between groups in terms of ICU stay and total hospital stay.

Patanwala et al.[7] used a large database which included data for more than three thousand patients, and the analysis was adjusted for baseline differences between groups. A potential limitation of the study was that the retrospective nature of the database used. The analysis adjusted for potential baseline confounders; however, the comprehensiveness of this adjustment could not be verified from the available data.

The study by Lachaine et al.[8] was conducted from the perspective of Canadian public payer, and it was based on direct evidence from an RCT. Potential limitations of the study included lack of transparency on evidence search. The analysis was based on one clinical study and it was not reported whether a systematic review of the literature was conducted to confirm the inclusion of all available evidence. Of note, the reviews by the Scottish Medical Consortium and All Wales Therapeutic and Toxicology Centre included two RCTs which were published before Lachaine's study, and no justification of their exclusion from Lachaine's study was provided. Another limitation of the study was that it did not account for the uncertainty in the differences between groups in terms of ICU stay. This would be reflected as uncertainty in the cost estimation and cost difference between the two groups.

The submissions reviewed by the Scottish Medical Consortium and All Wales Therapeutic and Toxicology Centre were based on direct evidence from two RCTs.[9,10] The economic analysis reported by the Scottish Medical Consortium reported the results as cost minimization instead of cost-utility; this was based on the assumption of equal efficacy and safety between comparators.[9] According to the reported results from these two reviews and the other economic evaluations, this assumption seems to be valid. The All Wales Therapeutic and Toxicology Centre reported that some of the data used in the model could not be verified, and that it was not clear if costs were appropriately estimated.[10] Another limitation identified by the All Wales Therapeutic and Toxicology Centre was that the analysis did not include the cost of rescue medications or the costs of adverse event management.[10]

Dasta et al.[11] based their analysis on direct evidence from one RCTs. The study did not search for additional sources of evidence related to the comparative efficacy and safety between dexmedetomidine and midazolam. The study did not consider the uncertainty in differences between groups in terms of ICU stay which could underestimate the costs associated with dexmedetomidine.

Evidence-based guidelines:

Both the guidelines by Barr et al.[12] and Celis-Rodrigeuz et al.[13] were based on a systematic review of the literature and quality evaluation of the available evidence. The systematic reviews were conducted according pre-specified protocols for evidence search and synthesis. The two guidelines followed the GRADE guideline for the development of guidelines. Both guidelines

were limited to adult patients only and did not include paediatric patients. Other limitations of the guidelines were that they did not consider patients preferences and values, and they did not consider the economic impact of their recommendations.

Summary of Findings

Appendix 6 summarises the findings from the included studies

Economic evaluation studies:

Dexmedetomidine versus propofol

Thoma et al.[6] reported that the use of dexmedetomidine was associated with lower total post-operative costs (US $10,111) compared with propofol (US $12,859). A similar relationship between the two comparators was reported when only post-operative ICU room costs were considered (US $4,494 versus US $6,495, respectively). These costs, however, did not account for the cost of adjunctive opioid therapies (which were used more in the dexmedetomidine group than in midazolam group). This could underestimate the costs associated with the use of dexmedetomidine.

Patanwala et al.[7] reported that dexmedetomidine was associated with a total hospital cost (median) of US $46,716 compared with US $31,041 in the propofol group. The main driver of the cost difference was the length of ICU stay (4 days versus 2 days in the dexmedetomidine and propofol groups respectively).

Reviews by the Scottish Medical Consortium and All Wales Therapeutic and Toxicology Centre reported that the total costs associated with dexmedetomidine ranged between £18,828 and £21,897 compared with £20,307 to £23,815 in the propofol group.[9,10] And that dexmedetomidine was associated with 0.058 quality-adjusted life years compared with 0.057 in the propofol group. In this analysis dexmedetomidine was dominant, but the incremental quality-adjusted life years was very low (0.001). The All Wales Therapeutic and Toxicology Centre reported that the probabilistic sensitivity analysis suggested that the probability of dexmedetomidine being cost-effective compared to propofol was 93.1%, based on a cost-effectiveness threshold of £25,000 per quality-adjusted life-year.

Dexmedetomidine versus midazolam

Lachaine et al.[8] reported that dexmedetomidine was associated with total costs that ranged from CAN $6,542 to $7,256 versus $6,886 to $7,918 in the midazolam group. The incremental costs ranged from -$1,376 to $370. These estimates did not consider the uncertainty related to length of ICU stay.

The Scottish Medical Consortium and All Wales Therapeutic and Toxicology Centre reviews showed that the total costs associated with dexmedetomidine ranged between £20,393 and £23,973 compared with £22,536 to £26,602 in the midazolam group,[9,10] and that dexmedetomidine was associated with 0.055 quality-adjusted life years compared with 0.052 in the midazolam group. The All Wales Therapeutic and Toxicology Centre reported that the probabilistic sensitivity analysis suggested that the probability of dexmedetomidine being cost-effective compared to midazolam was 85.5%, based on a cost-effectiveness threshold of £25,000 per quality-adjusted life-year.

Dasta et al.[11] reported that the total cost associated with dexmedetomidine was US $27,694 compared with US $34,122. The costs related to ICU stay were US $20,178 and US $25,618 for the dexmedetomidine and midazolam groups respectively.

Evidence-base guidelines

Both guidelines reported recommendations related to the use of dexmedetomidine in the ICU; these recommendations were based mainly on moderate to weak evidence.

Both guidelines recommended that propofol or dexmedetomidine might be preferred over midazolam or lorazolam to improve clinical outcomes in mechanically ventilated patients; however, these outcomes were not specifically reported. However, the strength of this recommendation was weak in Barr's guideline, and it was a strong recommendation in the guideline by Celis-Rodriguez et al.[9,10] This difference in recommendation strength could not be explained. The two guidelines also agreed that for patients at risk of developing delirium, sedation with dexmedetomidine might be associated with a lower prevalence of delirium compared to benzodiazepine infusions.

For patients with renal failure, Celis-Rodriguez et al.,[10] recommended the use of dexmedetomidine for sedation, but they reported that the loading dose should be reduced and the infusion rate by adjusted according to patient's response.

Limitations

Few limitations of the current review could be identified. Of these, the included economic studies were based on information from RCTs or retrospective databases. The quality of these sources was not evaluated in this review, and the accuracy of this information was not verified. Another limitation of this review was that none of the included economic studies or guidelines was specific to paediatric patients, and findings and recommendations for adult patients might not be generalizable to paediatric patients. Furthermore, the indication for ICU admission was specific in one study only; all other studies included general ICU patients. This might mask differences in the clinical outcomes and costs between alternative sedation drugs. The provision of care as well as drug and healthcare system costs may vary considerably from one jurisdiction to another; therefore, the generalizability of the included studies to the Canadian context might be questionable because only one study by Lachaine et al.[8] was conducted from a Canadian perspective.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

This report aimed to evaluate the cost-effectiveness and the evidence-based guidelines of using dexmedetomidine in the intensive care unit. A total of six economic analyses and two guidelines were retrieved.

With respect to the cost-effectiveness, dexmedetomidine was compared with propofol and midazolam in the included studies. All except one study showed that dexmedetomidine reduced the total hospital costs and the ICU costs. However, when the benefits were evaluated in terms of length of ICU stay or total hospital stay, the results were not consistent. This was reflected with very limited gain in terms of quality adjusted life-years.

The included guidelines suggested that the use of dexmedetomidine might be preferred over the benzodiazepine sedatives for better clinical outcomes and lower risk of delirium. However, the reported recommendations did not declare a preference for dexmedetomidine over propofol.

PREPARED BY:
Canadian Agency for Drugs and Technologies in Health
Tel: 1-866-898-8439
www.cadth.ca

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10. AWMSG Secretariat assessment report (full submission): advice no. 2312: dexmedetomidine (Dexdor®) 100 micrograms/ml concentrate foe solution for infusion. Penarth, Wales, UK: All Wales Therapeutics and Toxicology Centre; 2014 May 4.

11. Dasta JF, Kane-Gill SL, Pencina M, Shehabi Y, Bokesch PM, Wisemandle W, et al. A cost-minimization analysis of dexmedetomidine compared with midazolam for long-term sedation in the intensive care unit. Crit Care Med. 2010 Feb;38(2):497-503.

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APPENDIX 1: COST COMPARISON OF ICU SEDATIVES

Table 2. Cost comparison of ICU sedatives[a]

Group	Drug / Comparator	Strength	Dosage Form	Price ($)	Recommended Dose[b]	Average Daily Drug Cost ($)[c]
Selective α2 adrenergic agonist	Dexmedetomidine HCL	100 mcg / mL	2 mL vial for Injection	$45.2 / vial	77 mcg / hr	$452.0
Benzodiazepines	Midazolam	1 mg / mL 5 mg / mL	10 mL vials for Injection 50 mL vials for injection	$5.8 / vial $126.3 / vial	10.5 mg / hr	$126.3
	Lorazepam	4 mg / mL	1 mL vials for injection	$12.42 / vial	IM: 4 mg IV: 2 mg	IM: $49.68 IV: $24.84
	Propofol	10 mg / mL	20mL glass infusion vials 50 mL glass infusion vials 100 mL glass infusion vials	$9.2 / vial $23.0 / vial $46.0/ vial	21 mg / hr	$230.0

hr=hour, IM = intramuscular; IV = intravenous

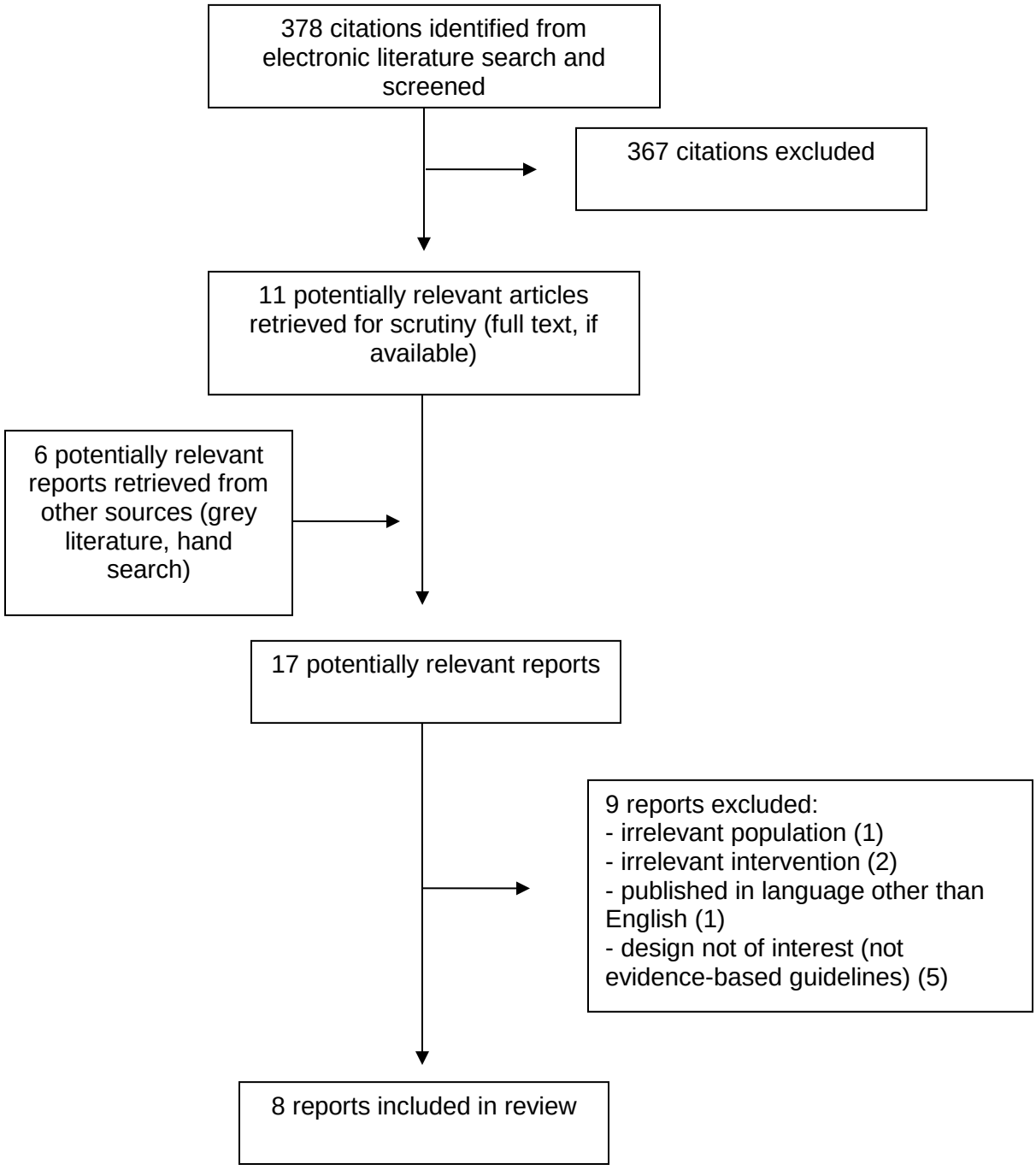
Source: McKesson (December 2014)[3]

[a] This is not a comprehensive list, other sedatives may be used in the context of the ICU

[b] Recommended doses are reflective of maximum maintenance doses for ICU sedation in the product monograph for 70 kg patients.

[c] calculated for 70 kg patients

APPENDIX 2: SELECTION OF INCLUDED STUDIES



APPENDIX 3: EXCLUDED STUDIES OF POTENTIAL INTEREST

The following citations include clinical practice guidelines or reviews of the literature with some clinical recommendations:

1. MacLaren R, Krisl JC, Cochrane RE, Mueller SW. A case-based approach to the practical application of dexmedetomidine in critically ill adults. Pharmacotherapy. 2013 Feb;33(2):165-86.

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APPENDIX 4: CHARACTERISTICS OF THE INCLUDED STUDIES

Table 3. Characteristics of the included economic analyses

Target population and perspective	Intervention and comparators	Type of analysis	Time horizon	Clinical data used in the analysis	Costs included in the analysis	Utility values used in the analysis
Thoma et al. 20146 - USA						
Patients undergoing coronary artery bypass graft (CABG). The perspective of the analysis was not specified, but the ICU costs were based on US estimates	Dexmedetomidine was compared with propofol	Cost analysis	Not reported	Post-operative ICU stay, total post-operative hospital stay, and the need for adjunctive opioid therapy. Data for these outcomes were obtained from a retrospective cohort study of 84 patients.	Cost of ICU stay and cost of total hospital stay	Not applicable
Patanwala et al. 2014[7] – USA						
Adult patients admitted to the ICU who received either dexmedetomidine or propofol for sedation. The analysis was conducted from the perspectives a tertiary health care facility in the US	Dexmedetomidine was compared with propofol	Cost analysis	Not reported	Length of ICU stay and length of hospital stay. Data for these outcomes were obtained, retrospectively, from the hospital database. Data were obtained for 3294 patients admitted to ICU for trauma, general medicine, general surgery, cardiac surgery, neurosurgery, and thoracic surgery.	Total hospital costs that included labour, over-head costs, supplies, and medications.	Not applicable

Target population and perspective	Intervention and comparators	Type of analysis	Time horizon	Clinical data used in the analysis	Costs included in the analysis	Utility values used in the analysis
Lachaine et al. 2012[8] – Canada						
Patients in ICU settings requiring sedation. The analysis was adapted to the perspective of public payer in Canada	Dexmedetomidine was compared with midazolam	Cost consequence analysis	30 days	Duration of mechanical ventilation, length of stay in ICU, and adverse events were considered. Data for these outcomes were obtained from an RCT of 375 patients in medical or surgical ICUs for whom mechanical ventilation and sedation for a period of three days or more is anticipated.	Costs of additional administration of midazolam, costs of ICU stay with mechanical ventilation, the costs associated with delirium, and the cost of the evaluated medications	Not applicable
Scottish Medical Consortium 2012[9] – Scotland						
Adult ICU patients requiring sedation level not deeper than arousal in response to verbal stimulation. The analysis was adapted to the perspective of public payer in Scotland	Dexmedetomidine was compared with propofol and midazolam	Appraisal of a cost-utility analysis submitted by the sponsor of dexmedetomidine.	45 days	Length of stay in ICU, high dependency, and general ward. Time before removing intubation. Mortality was assumed equal with the three comparators. Data were based on two RCTs of 498 and 501 general ICU patients.	Medicines, preparation and administration, management of adverse events, and co-prescribed medicines	Utility data with or without intubation were retrieved from the literature
All Wales Therapeutic and Toxicology Centre 2012[10] – Region of Wales						
Adult ICU patients requiring sedation level not deeper than arousal in	Dexmedetomidine was compared with propofol and midazolam	Appraisal of a cost-utility analysis submitted by the	45 days	Length of stay in ICU, high dependency, and general ward. Time before removing	Medicines, preparation and administration, management of	Utility data with or without intubation were retrieved from the literature

Target population and perspective	Intervention and comparators	Type of analysis	Time horizon	Clinical data used in the analysis	Costs included in the analysis	Utility values used in the analysis
response to verbal stimulation The analysis was adapted to the perspective of public payer in the region of Wales		sponsor of dexmedetomidine.		intubation. Mortality was assumed equal with the three comparators. two RCTs of 498 and 501 general ICU patients.	adverse events, and co-prescribed medicines	
Dasta et al. 2010[11] – USA						
Patients in ICU settings requiring sedation. The analysis was supported by Hospira (manufacturer of dexmedetomidine) The perspective of the analysis was not specified, but the ICU costs were based on US estimates	Dexmedetomidine was compared with midazolam	Cost minimization analysis	Not reported	Duration of mechanical ventilation, length of stay in ICU, and adverse events were considered. Data for these outcomes were obtained from one RCT of 375 patients in medical or surgical ICUs for whom mechanical ventilation and sedation for a period of three days or more is anticipated. .	Costs of the evaluated medications, cost of ICU stay, cost of mechanical ventilation, and cost of treating adverse events.	Not applicable

Table 4. Characteristics of the included evidence-based guidelines

	Barr et al. 2013[12] – USA and Canada	Celis-Rodriguez et al. 2013[13] – multi national
Scope		
Disease/ condition	Sedation in ICU	Management of adult ICU patients
Intended users	Clinicians caring for ICU patients	Physicians, nurses, and physiotherapists involved in the management of critically ill adult patients.
Objectives	To recommend best practices for managing pain, agitation, and delirium (PAD); and to improve clinical outcomes in adult ICU patients.	To provide recommendations on the use of sedation and the management of pain in adult patients admitted to the ICU, with or without tracheal intubation and respiratory support, and/or with certain conditions or diseases.
Target population	Intubated and nonintubated adult medical, surgical, and trauma ICU patients.	1. Patients requiring conscious or cooperative sedation 2. Patients with delirium and withdrawal symptoms 3. Patients without endotracheal intubation and mechanical ventilation 4. Patients undergoing withdrawal or the endotracheal tube and mechanical ventilation 5. Special populations: trauma patients, elderly subjects, pregnant patients and burn patients 6. Neurological and neuro-critical patients 7. Patients with kidney or liver failure 8. Patients requiring special procedures (tracheostomy, thoracic catheters or tubes, peritoneal lavage, wound or burn lavage and debridement)
Intervention and comparators	Relative to sedation, the guidelines specified benzodiazepines (e.i., midazolam and lorazepam), propofol, and dexmedetomidine.	Relative to conscious sedation, the guidelines specified lorazepam, midazolam, propofol, diazepam, dexmedetomidine, thiopental sodium, haloperidol, clozapine, methadone, ketamine, and non-pharmacological strategies.
Methodology		
Evidence search and selection	Systematic literature search was conducted using eight electronic	Systematic literature search was conducted for each question in the

	databases. Members of the guideline committee conducted the literature selection.	guideline using seven databases. Three members of the guideline committee participated in the literature selection.
Quality evaluation of evidence	Two groups of the guideline committee conducted quality evaluation of the included studies using the GRADE system.	Three members of the guideline committee evaluated the quality of the included studies using the GRADE system.
Strength of evidence evaluation	The two quality control groups graded the evidence from “A” (high evidence) to “C” (low evidence)	The three members who evaluated the quality of studies graded the evidence from “A” (high evidence) to “C” (low evidence)
Synthesis of evidence	Narrative summaries of the included studies were prepared. Meta-analyses were conducted if multiple studies related to a particular outcome demonstrated disparate results.	Narrative summaries of the included studies were reported. The guideline did not conduct any meta-analysis
Economic evaluation	Not included	Not included
Recommendations development	Based on collective review of the evidence profile for each question, and using nominal group technique	Based on consensus of 21 experts in critical care medicine from different countries.
Strength of recommendations evaluation	The guideline committee evaluated the strength of recommendations based on the quality of evidence and the risk and benefits across all critical outcomes. The strength of recommendation was defined as strong (1), or weak (2); and either for (+) or against (-) an intervention.	The guideline committee defined the strength of recommendation was defined as strong (1), or weak (2). This was based on the risk and benefit profile, and the quality of evidence.
Guideline validation	The guideline report did not specify any validation method.	The guideline report did not specify any validation method.

APPENDIX 5: APPRAISAL OF THE INCLUDED STUDIES

Study	Strength	Limitations
Economic evaluations		
Thoma et al. 2014[6]	The analyses were adjusted for several baseline differences between the observed groups.	The analysis was based on a retrospective study of a relatively small patient sample (84 patients). The study reported that the cost of adjunctive opioid therapies would be included in the analysis, but the reported results did not confirm this. Of note, dexmedetomidine patients required higher midazolam dose equivalent (1.1 mg) than propofol group (0.1 mg), and the p-value was 0.008. The study reported that post-operative ICU stay and total hospital stay were not statistically significantly different between dexmedetomidine and propofol (p-value = 0.055 and 0.62 respectively). The cost analysis did not account for this uncertainty. However when the authors arbitrarily classified patients according to their ICU stay (≤48hours), data showed statistically significantly higher proportion of dexmedetomidine patients (81%) required ICU stay ≤48 hours the propofol patients (57.1); the p-value was 0.018.
Patanwala et al. 2014[7]	The analyses were based on large database that contained more than three thousand patients. The analyses were adjusted for several baseline differences between the observed groups.	The analysis was based on a retrospective database; however, the analyses were adjusted for baseline differences.

Study	Strength	Limitations
Lachaine et al. 2012[8]	The analysis was based on a Canadian context, and included interventions cost from representative Canadian hospitals. Analysis was based on direct evidence (head-to-head clinical study)	The analysis was based on one clinical study, and it was not clear if a comprehensive literature search was conducted to ensure a compressive inclusion of the available evidence. According to the reported efficacy data, the duration of ICU stay was not statistically significantly different between the dexmedetomidine and midazolam (p-value = 0.24). This uncertainty was considered in the sensitivity analysis of time to extubation, but its impact on the other costs was not considered in the analysis.
Scottish Medical Consortium 2012[9]	Analysis was based on direct evidence (head-to-head clinical study) A sensitivity analysis was conducted	The analysis was based on two clinical studies, and it was not clear if a comprehensive literature search was conducted to ensure a compressive inclusion of the available evidence. The type of economic analysis was declared to be cost-utility, but the drug sponsor presented the results as cost minimization. This was done with the assumption of no difference in quality-adjusted life-years. The analysis was adapted to the Scottish health care context, and the findings from this model my not generalizable to the Canadian context.

Study	Strength	Limitations
All Wales Therapeutic and Toxicology Centre (AWTTC) 2012[10]	**Strengths according to AWTTC:** • Appropriate patient pathway in the model • Sensitivity analysis was conducted • The analysis was based on direct evidence (head-to-head trials)	The analysis was based on two clinical studies, and it was not clear if a comprehensive literature search was conducted to ensure a comprehensive inclusion of the available evidence. The analysis was adapted to the Welsh health care context, and the findings from this model might not be generalizable to the Canadian context. **Limitations according to AWTTC:** • AWTTC could not verify some data used in the model • It was not clear that costs were appropriately considered in the model: • Time required for drug administration was based on assumptions, and cost for rescue therapy administration was not considered in the model (in the included clinical studies, rescue therapy was required more frequently by dexmedetomidine recipients than propofol recipients. Utility values were based on a single published study, and these values could not confirmed by other sources
Dasta et al. 2010[11]	Analysis was based on direct evidence (head-to-head clinical study)	The analysis was based on two clinical studies, and it was not clear if a comprehensive literature search was conducted to ensure a comprehensive inclusion of the available evidence. The perspective of the analysis was not clearly specified According to the reported efficacy data in Lachaine et al. 2012,[8] the duration of ICU stay was not statistically significantly different between the dexmedetomidine and midazolam (p-value = 0.24). This was not reflected in the reported resulted for the total cost nor for the costs specific for ICU stay. This raised doubts on the used analyses

Study	Strength	Limitations
		and reported results
ICU = intensive care unit		
Evidence-based guidelines		
Barr et al. 2013[12]	Recommendations were based on systematic review of the literature and quality evaluation of the evidence. Development and evaluation of recommendations followed the GRADE guideline Recommendations were developed by group of experts in the field with the participation of specialist in epidemiology.	Guidelines were specific for adults, and they did not include paediatric patients. The guidelines did not include input from patients groups, and patients' values and preferences were not considered in these guidelines. The economic aspect was not considered.
Celis-Rodriguez et al. 2013[13]		

APPENDIX 6: MAIN FINDINGS IN THE INCLUDED STUDIES

Study	Findings
Economic evaluations	
Thoma et al. 2014[6]	**Dexmedetomidine versus propofol:**[a] Total post-operative cost: $10,111 versus $12,859, and the incremental cost was -$2,748 Post-operative ICU cost: $4,494 versus $6,495, and the incremental cost was -$2,001
Patanwala et al. 2014[7]	**Dexmedetomidine versus propofol:** [a] The median hospital cost (interquartile range): $46,716 ($31,247 to $85,490) versus $31,041 ($17,963 to $57,826)
Lachaine et al. 2012[8]	**Dexmedetomidine versus midazolam:** [a] **Total cost:** Base-case: $7,022 versus $7,680, and the incremental cost was -$658 Sensitivity analysis of time to extubation: $6,542 to 7,256 versus $6,886 to $7,918, and the incremental cost ranged from -$1,376 to $370
Scottish Medical Consortium 2012[9]	**Dexmedetomidine versus propofol:** [a] Cost: £18,828 versus £20,307, and the incremental cost was -£1,479 Quality-adjusted life-year: the incremental utility was 0,001 **Dexmedetomidine versus midazolam:** [a] Cost: £20,393 versus £22,536, and the incremental cost was -£2,143 Quality-adjusted life-year: the incremental utility was 0,002
All Wales Therapeutic and Toxicology Centre 2012[10]	**Dexmedetomidine versus propofol:** [a] Cost: £21,897 versus £23,815, and the incremental cost was -£1,918 Quality-adjusted life-year: 0.058 versus 0.57, the incremental utility was 0,001 Incremental cost per QALY: Dexmedetomidine was dominant **Dexmedetomidine versus midazolam:** [a] Cost: £23,973 versus £26,602, and the incremental cost was -£2,629 Quality-adjusted life-year: 0.055 versus 0.052, the incremental utility was 0,002 Incremental cost per QALY: Dexmedetomidine was dominant
Dasta et al. 2010[11]	**Dexmedetomidine versus midazolam:** [a] **Total cost:** Total costs (unadjusted dataset): $27,694 versus $34,122, and the incremental cost was -$6,428 ICU component cost: $20,178 versus $25,618, and the incremental cost was -$5,440
[a] costs are reported as they were published in the included studies without adjusting for inflation or differences in currency ICU = intensive care unit; QALY = quality-adjusted life-year	

Study	Findings
Evidence-based guidelines	
Barr et al. 2013[12]	Recommendations related to dexmedetomidine: 1. The guideline suggested that sedation strategies using non-benzodiazepine sedatives (propofol or dexmedetomidine) might be preferred over sedation with benzodiazepines (midazolam or lorazolam) to improve clinical outcomes in mechanically ventilated adult ICU patients. (Moderate quality evidence, weak recommendation) 2. In mechanically ventilated adult ICU patients at risk of developing delirium, dexmedetomidine infusions administered for sedation might be associated with a lower prevalence of delirium compared to benzodiazepine infusions. (moderate quality evidence_ strength of recommendation was not reported). 3. The guidelines suggested that in adult ICU patients with delirium unrelated to alcohol or benzodiazepine withdrawal, continuous IV infusions of dexmedetomidine rather than benzodiazepine infusions be administered for sedation to reduce the duration of delirium in these patients. (moderate quality evidence, weak recommendation).
Celis-Rodriguez et al. 2013[13]	1. Patients requiring conscious or cooperative sedation: • The use of dexmedetomidine, fentanyl, remifentanill, propofol, or midazolam in doses titrated according to response is recommended for conscious sedation in minor therapeutic, diagnostic or surgical situations in ICU. (Moderate quality of evidence, strong recommendation) 2. Patients with delirium and withdrawal syndrome: • Antipsychotics and/or dexmedetomidine are recommended for the drug treatment of delirium. (Moderate quality of evidence, strong recommendation) • Dexmedetomidine is recommended as an ulternative in the management of delirium. (Moderate quality of evidence, strong recommendation) 3. Withdrawal syndrome in the intensive care unit: • The use of dexmedetomidine or clonidine is suggested to facilitate the withdrawal of sedatives and opioids and to treat withdrawal syndrome. (Moderate quality of evidence, weak recommendation) 4. Withdrawal syndrome due to alcohol: • The use of dexmedetomidine is suggested as a coadjuvant to treatment with benzodiazepines in the management of withdrawal syndrome due to alcohol. 5. Patients without tracheal intubation or ventilatory support • it is advisable to use drugs with a low risk of producing respiratory depression and severe hemodynamic adverse effects, such as haloperidol and dexmedetomidine. (Low quality of evidence, strong recommendation) 6. Patients with mechanical ventilation: • Whenever possible, it is advisable to use conscious or cooperative sedation with titrated doses of a continuous infusion of propofol or dexmedetomidine. (Moderate quality of evidence, strong recommendation). • The use of a sedative with a shorter half-life, such as dexmedetomidine, is recommended for reducing the duration of

Study	Findings
	MV and the incidence of delirium in patients that can tolerate mild sedation levels (RASS 1 to −3 or Ramsay 2---3). (Moderate quality of evidence, strong recommendation). • Dexmedetomidine is recommended as a useful drug for postoperative sedation and analgesia in patients requiring MV for short periods of time, and particularly in septic patients. (Moderate quality of evidence, strong recommendation). 7. Patients undergoing withdrawal of the endotracheal tube and mechanical ventilation: • Dexmedetomidine is recommended in postsurgical patients. (Low quality of evidence, strong recommendation). • Dexmedetomidine is recommended in patients with mechanical ventilation weaning difficulties and in patients with withdrawal syndrome. (Low quality of evidence, strong recommendation). • Dexmedetomidine is recommended in patients with failed previous attempts of weaning from MV secondary to agitation and delirium. (Low quality of evidence, strong recommendation). 8. Special procedures (burn victims): • It is advisable not to use ketamine alone. The drug should be accompanied by midazolam, propofol or dexmedetomidine. (Moderate quality of evidence, strong recommendation). 9. Sedoanalgesia in the immediate postoperative period of cardiovascular surgery: • The use of dexmedetomidine, remifentanil or their combination, the combination of low-dose propofol and midazolam, or the combination of propofol and fentanyl are recommended for postoperative sedation and analgesia. (Moderate quality of evidence, strong recommendation). • Dexmedetomidine is recommended among patients in the postoperative period of cardiovascular surgery, either as single drug or combined with opioid analgesics. (Moderate quality of evidence, strong recommendation). 10. Neurological and neurocritical patients: • It is advisable to use drugs with a short half-life and scant accumulation (propofol, dexmedetomidine and remifentanil), allowing frequent neurological evaluations. (Moderate quality of evidence, strong recommendation). 11. Patients with renal failure: • The use of dexmedetomidine is recommended, reducing the loading dose and adjusting the infusion according to the clinical response obtained. (Low quality of evidence, strong recommendation). 12. Patients with liver failure: • Dexmedetomidine is suggested as coadjuvant treatment in cirrhotic patients with alcohol withdrawal syndrome, when conventional management fails. The dose should be lowered. (Moderate quality of evidence, weak recommendation).