**Supplemental Table 12. Evidence Summaries and Evidence-to-Decision Profiles for Sedation Group Actionable Questions**

**Question**: Light sedation compared to deep sedation in critically ill intubated adults

| **Quality assessment** | | | | | | | **№ of patients** | | | **Effect** | | | | **Quality** | | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **light sedation** | **deep sedation** | | **Relative (95% CI)** | | | **Absolute (95% CI)** |
| Mortality (90 days) | | | | | | | | | | | | | | | | |
| 2 | randomised trials | not serious | not serious | not serious | serious a | none b | 70/153 (45.8%) | 79/171 (46.2%) | **RR 1.01** (0.80 to 1.27) | | **5 more per 1,000** (from 92 fewer to 125 more) | | | | ⨁⨁⨁◯ MODERATE | CRITICAL |
| Self extubation | | | | | | | | | | | | | | | | |
| 4 | randomised trials | not serious | not serious c | not serious | very serious d | none b | 21/261 (8.0%) | 18/285 (6.3%) | **RR 1.29** (0.58 to 2.88) | | **18 more per 1,000** (from 27 fewer to 119 more) | | | | ⨁⨁◯◯ LOW | CRITICAL |
| Time to extubation (days) | | | | | | | | | | | | | | | | |
| 3 | randomised trials | not serious | serious e | not serious | serious f | none b | 218 | 235 | - | | MD **0.77 days fewer** (2.04 fewer to 0.5 more) | | | | ⨁⨁◯◯ LOW | CRITICAL |
| Shorter time to extubation (Observational studies) | | | | | | | | | | | | | | | | |
| 2 | observational studies | not serious | not serious g | not serious | not serious | none |  |  | **HR 0.91** (0.89 to 0.94) | | | **8 fewer per 100** (from 6 fewer to 11 fewer) h | | | ⨁⨁◯◯ LOW | CRITICAL |
| Delirium | | | | | | | | | | | | | | | | |
| 2 | randomised trials | serious i | not serious | not serious | serious j | none | 49/73 (67.1%) | 48/67 (71.6%) | **RR 1.02** (0.91 to 1.13) | | | **14 more per 1,000** (from 64 fewer to 93 more) | | | ⨁⨁◯◯ LOW | CRITICAL |
| Depression | | | | | | | | | | | | | | | | |
| 2 | randomised trials | not serious | serious k | not serious | very serious l | none | 5/65 (7.7%) | 6/63 (9.5%) | **RR 0.76** (0.10 to 5.58) | | | **23 fewer per 1,000** (from 86 fewer to 436 more) | | | ⨁◯◯◯ VERY LOW | CRITICAL |
| Post-traumatic stress disorder | | | | | | | | | | | | | | | | |
| 2 | randomised trials | not serious | not serious | not serious | very serious m | none | 2/31 (6.5%) | 3/31 (9.7%) | **RR 0.67** (0.12 to 3.79) | | | **32 fewer per 1,000** (from 85 fewer to 270 more) | | | ⨁⨁◯◯ LOW | CRITICAL |
| Tracheostomy | | | | | | | | | | | | | | | | |
| 2 | observational studies | not serious | not serious | not serious | not serious | none | 49/275 (17.8%) | 48/177 (27.1%) | **RR 0.57** (0.41 to 0.80) | | | **117 fewer per 1,000** (from 54 fewer to 160 fewer) | | | ⨁⨁◯◯ LOW | CRITICAL |

**CI:** Confidence interval; **RR:** Risk ratio; **MD:** Mean difference; **HR:** Hazard Ratio

Explanations: a. We downgraded the quality of evidence for imprecision by one level, the CI included significant benefit and harm b. We couldn't assess for publication bias because of small number of eligible studies c. Minimal inconsistency I2=15% d. We downgraded the quality of evidence by two levels for imprecision, the CI included substantial benefit and harm e. We downgraded the quality of evidence by one level for inconsistency, the I2=53% f. We downgraded the quality of evidence by one level for imprecision, the CI included small benefit and harm g. I2= 26%, we did not downgrade for inconsistency h. We manually estimated the absolute difference in percentage as this outcome is originally a continues outcome i. we downgraded the quality of evidence by one level for risk of bias, blinding was unclear in two RCTs j. We downgraded the quality of evidence for imprecision by one level, the number of events was small k. We downgraded the quality of evidence by one level for inconsistency, the I2= 57% l. We downgraded the quality of evidence by two levels for imprecision, the number of events is very low (11 events) and the CI included extreme benefit and extreme harm m. We downgraded the quality of evidence by two levels for imprecision, the number of events was very small (n=5), and the CI included extreme benefit and harm

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| --- | --- | --- | --- | --- |
| Should **light sedation** vs. **deep sedation** be used for **critically ill intubated adults**? | | | | |
| **Population:** | critically ill intubated adults |  | |  | |
| **Intervention:** | light sedation |  |  | | | |
| **Comparison:** | deep sedation |
| **Main outcomes:** | Mortality (90 days); Self extubation; Time to extubation (days); Shorter time to extubation (Observational studies); Delirium; Depression ; Post-traumatic stress disorder ; Tracheostomy; |

**Assessment**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Judgement** | **Research evidence** | **Additional considerations** |
| Problem | **Is the problem a priority?**  ○ No ○ Probably no ○ Probably yes ● Yes | No research evidence was identified. |  |
| Desirable Effects | **How substantial are the desirable anticipated effects?**  ● Trivial | No research evidence was identified. |  |
| Undesirable Effects | **How substantial are the undesirable anticipated effects?** ● Trivial |  |
| Certainty of evidence | **What is the overall certainty of the evidence of effects?**  ● Low | No research evidence was identified. |  |
| Values | **Is there important uncertainty about or variability in how much people value the main outcomes?** ● Possibly important uncertainty or variability | No research evidence was identified. |  |
| Balance of effects | **Does the balance between desirable and undesirable effects favor the intervention or the comparison?** ● Probably favors the intervention | No research evidence was identified. |  |
| Resources required | **How large are the resource requirements (costs)?**  ○ Large costs ○ Moderate costs ● Negligible costs and savings ○ Moderate savings ○ Large savings  ○ Varies ○ Don't know | No research evidence was identified. |  |
| Certainty of evidence of required resources | **What is the certainty of the evidence of resource requirements (costs)?**  ○ Very low ○ Low ○ Moderate ○ High  ○ No included studies | No research evidence was identified. |  |
| Cost  effect-  iveness | **Does the cost-effectiveness of the intervention favor the intervention or the comparison** ● No included studies | No research evidence was identified. |  |
| Acceptability | **Is the intervention acceptable to key stakeholders?**  ● Probably yes | No research evidence was identified. |  |
| Feasibility | **Is the intervention feasible to implement**  ● Yes | No research evidence was identified. |  |

**Summary of judgements**

|  | **Judgement** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Problem** | No | Probably no | Probably yes | **Yes** |  | Varies | Don't know |
| **Desirable Effects** | **Trivial** | Small | Moderate | Large |  | Varies | Don't know |
| **Undesirable Effects** | Large | Moderate | Small | **Trivial** |  | Varies | Don't know |
| **Certainty of evidence** | Very low | **Low** | Moderate | High |  |  | No included studies |
| **Values** | Important uncertainty or variability | **Possibly important uncertainty or variability** | Probably no important uncertainty or variability | No important uncertainty or variability |  |  |  |
| **Balance of effects** | Favors the comparison | Probably favors the comparison | Does not favor either the intervention or the comparison | **Probably favors the intervention** | Favors the intervention | Varies | Don't know |
| **Resources required** | Large costs | Moderate costs | **Negligible costs and savings** | Moderate savings | Large savings | Varies | Don't know |
| **Certainty of evidence of required resources** | Very low | Low | Moderate | High |  |  | No included studies |
| **Cost effectiveness** | Favors the comparison | Probably favors the comparison | Does not favor either the intervention or the comparison | Probably favors the intervention | Favors the intervention | Varies | **No included studies** |
| **Equity** | Reduced | Probably reduced | Probably no impact | Probably increased | Increased | Varies | Don't know |
| **Acceptability** | No | Probably no | **Probably yes** | Yes |  | Varies | Don't know |
| **Feasibility** | No | Probably no | Probably yes | **Yes** |  | Varies | Don't know |

**Should light sedation vs. deep sedation be used in critically ill intubated adults?**

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| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Type of recommendation** | |  |  |  |  |  | | --- | --- | --- | --- | --- | | Strong recommendation against the intervention | Conditional recommendation against the intervention | Conditional recommendation for either the intervention or the comparison | Conditional recommendation for the intervention | Strong recommendation for the intervention | | ○ | ○ | ○ | ● | ○ | |
| **Recommendation** | We suggest using light sedation versus deep sedation in critically ill mechanically ventilated patients (conditional recommendation, low quality evidence). |
| **Justification** | **Defining light sedation**: There are no universally accepted definitions of what constitutes light versus deep sedation in mechanically ventilated critically ill patients. For the purpose of the actionable questions pertaining to this topic, we evaluated studies in which the authors a priori included a definition of what constituted light versus deep sedation in their trial. For example in the studies by Shehabi et al.[1] a RASS of -2 to 1 was considered light sedation; Tregiarri [2] defined light sedation as Ramsay 1-2; and Tanaka [3] defined light sedation as a GCS>=9 which corresponds to a RASS -2 or lighter based on some earlier correlation studies. We did not use surrogates of light sedation such as reported plasma levels or ability to communicate versus not, unless accompanied by sedation scores that showed that patients met the defined criteria for light sedation in that study. Finally, the spirit of the definition was that patients would be targeted to be in the lighter vs deeper group for a substantial portion of the time; thus some studies that evaluated daily wake up trials were not included since they showed a lightening to a lower sedation score at a single time point in the day and not a sustained period.  •Low quality evidence  •Small benefit (reduced DMV, reduced tracheostomy)  •Uncertainty about other outcomes  •Uncertainty about harm outcomes  •Inconsistent V&P- different patients may have different preference with regards to light sedation  •Uncertainty about cost-effectiveness  •Intervention is likely acceptable and feasible to implement |
| **comments during electronic Voting by Entire panel** | discussion should include rationale for "light" sedation& its facilitation of accurate pain& delirium assessments, physical activity, meaningful level of care discussions and MV liberation  delirium is a critical outcome for the sedation group, not critical in the delirium group  The EtoD body of the evidence proflie reports no evidence found - which conflicts with the data in the forest plots and GDT profile. Was the decision is based on the number of trachs? No other outcomes were significantly different. |

**Author(s)**: Alhazzani W, Alshamsi F

**Question**: Propofol compared to benzodiazepines in post cardiac surgery patients

**Setting**: cardiovascular ICU

**Bibliography**:

| **Quality assessment** | | | | | | | **№ of patients** | | **Effect** | | **Quality** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **propofol** | **benzodiazepines** | **Relative (95% CI)** | **Absolute (95% CI)** |
| Time to Extubation-Hours | | | | | | | | | | | | |
| 7 | randomised trials | serious a | serious b | not serious | not serious | none | 207 | 202 | - | MD **1.41 lower** (2.19 lower to 0.64 lower) | ⨁⨁◯◯ LOW | CRITICAL |
| Time to light sedation | | | | | | | | | | | | |
| 2 | randomised trials | serious c | not serious | not serious | serious d | none e | 35 | 35 | - | MD **51.81 lower** (77.42 lower to 26.19 lower) | ⨁⨁◯◯ LOW | IMPORTANT |

**CI:** Confidence interval; **MD:** Mean difference

#### Explanations

a. We downgraded the quality of evidence by one level for risk of bias, none of the studies were judged as low risk of bias, it is not clear if the observed treatment effect is influenced by study design

b. We downgraded the quality of evidence for inconsistency by one level, the I2=93%, however, the variation between studies was not very large and all point estimates were in favour of propofol.

c. We downgraded the quality of evidence by one level for risk of bias, the two trials were judged to be at high risk of bias, therefore, the observed treatment effect can't be confidently attributed to the intervention alone

d. We downgraded the quality of evidence by one level for imprecision, the CI interval was wide and tot al number of patients was small

e. We were not able t assess for publication bias, as only two studies were identified. However, we did not downgrade for publication bias

|  |  |  |  |
| --- | --- | --- | --- |
| Should **propofol** vs. **benzodiazepines** be used for **post cardiac surgery patients**? | | | |
| **Intervention:** | propofol |  |  | |
| **Comparison:** | benzodiazepines |
| **Main outcomes:** | Time to Extubation-Hours; Time to light sedation; |
| **Setting:** | cardiovascular ICU |

**Assessment**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Judgement** | **Research evidence** | **Additional considerations** |
| Problem | **Is the problem a priority?** ● Yes |  |  |
| Desirable Effects | **How substantial are the desirable anticipated effects?**  ● Moderate |  | In the discussions, the expert group and patient representative agreed that in cardiac surgical patients a shortened time to light sedation of at least 30 minutes and time to extubation of at least 1 hour were clinically significant. |
| Undesirable Effects | **How substantial are the undesirable anticipated effects?** ● Trivial |  |
| Certainty of  evidence | **What is the overall certainty of the evidence of effects**  ● Low | | **Outcomes** | **Importance** | **Quality of the evidence (GRADE)** | | --- | --- | --- | | Time to Extubation-Hours | CRITICAL | ⨁⨁◯◯ LOWa,b,c | | Time to Extubation-Hours Sens analysis | CRITICAL | ⨁⨁◯◯ LOWa,d | | Longterm Cognitive Decline | CRITICAL | ⨁⨁◯◯ LOWe,f,g | | Time to light sedation | IMPORTANT | ⨁⨁◯◯ LOWh,i,j |  1. We downgraded the quality of evidence by one level for risk of bias, none of the studies were judged as low risk of bias, it is not clear if the observed treatment effect is influenced by study design 2. We downgraded the quality of evidence by one level for inconsistency, although I2 = 94% indicated significant statistical inconsistency, all point estimates were in favour of propofol and the variation in the magnitude was not large enough and subgroup analyses failed to explain this heterogeneity, 3. Although the upper end of the CI represented trivial benefit, we did not downgrade the quality of evidence as we already downgraded for other categories 4. We downgraded the quality of evidence for inconsistency by one level, the I2=93%, however, the variation between studies was not very large and all point estimates were in favour of propofol. 5. We downgraded the quality of evidence by one level for risk of bias, this trial was assessed as unclear risk of bias, therefore, the impact of the trial design on the observed effect is uncertain 6. This category does not apply as this is a single trial 7. We downgraded the quality of evidence for imprecision by one level, the CI included very large and small benefit, and the number of events was small (48 events in total) 8. We downgraded the quality of evidence by one level for risk of bias, the two trials were judged to be at high risk of bias, therefore, the observed treatment effect can't be confidently attributed to the intervention alone 9. We downgraded the quality of evidence by one level for imprecision, the CI interval was wide and tot al number of patients was small 10. We were not able t assess for publication bias, as only two studies were identified. However, we did not downgrade for publication bias |  |
| Values | **Is there important uncertainty about or variability in how much people value the main outcomes** ● Probably no important uncertainty or variability |  |  |
| Balance of  effects | **Does the balance between desirable and undesirable effects favor the intervention or the comparison?**  ● Probably favors the intervention |  | intervention is propofol |
| Resources  required | **How large are the resource requirements (costs)?**  ● Negligible costs and savings | There are no recent CEA studies that compare propofol to BZD | While older studies may have shown a reduction in cost using propofol over benzodiazepines, the group felt the cost savings now would be negligible given the effect size on outcomes was moderate and the medications per say are off patent now |
| Certainty of  evidence of  required  resources | **What is the certainty of the evidence of resource requirements (costs)?** ● No included studies |  |  |
| Cost  effect-  iveness | **Does the cost-effectiveness of the intervention favor the intervention or the comparison?** ● Does not favor either the intervention or the comparison |  | See notes above on cost |
| Accept-  ability | **Is the intervention acceptable to key stakeholders?** ● Yes |  |  |
| Feasibility | **Is the intervention feasible to implement?**  ● Yes |  |  |

**Summary of judgements**

|  | **Judgement** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Problem** | No | Probably no | Probably yes | **Yes** |  | Varies | Don't know |
| **Desirable Effects** | Trivial | Small | **Moderate** | Large |  | Varies | Don't know |
| **Undesirable Effects** | Large | Moderate | Small | **Trivial** |  | Varies | Don't know |
| **Certainty of evidence** | Very low | **Low** | Moderate | High |  |  | No included studies |
| **Values** | Important uncertainty or variability | Possibly important uncertainty or variability | **Probably no important uncertainty or variability** | No important uncertainty or variability |  |  | No known undesirable outcomes |
| **Balance of effects** | Favors the comparison | Probably favors the comparison | Does not favor either the intervention or the comparison | **Probably favors the intervention** | Favors the intervention | Varies | Don't know |
| **Resources required** | Large costs | Moderate costs | **Negligible costs and savings** | Moderate savings | Large savings | Varies | Don't know |
| **Certainty of evidence of required resources** | Very low | Low | Moderate | High |  |  | **No included studies** |
| **Cost effectiveness** | Favors the comparison | Probably favors the comparison | **Does not favor either the intervention or the comparison** | Probably favors the intervention | Favors the intervention | Varies | No included studies |
| **Equity** | Reduced | Probably reduced | Probably no impact | Probably increased | Increased | Varies | Don't know |
| **Acceptability** | No | Probably no | Probably yes | **Yes** |  | Varies | Don't know |
| **Feasibility** | No | Probably no | Probably yes | **Yes** |  | Varies | Don't know |

**Conclusions**

**Should propofol vs. benzodiazepines be used in post cardiac surgery patients?**

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| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Type of recommendation** | |  |  |  |  |  | | --- | --- | --- | --- | --- | | Strong recommendation against the intervention | Conditional recommendation against the intervention | Conditional recommendation for either the intervention or the comparison | Conditional recommendation for the intervention | Strong recommendation for the intervention | | ○ | ○ | ○ | ● | ○ | |
| **Recommendation** | We **suggest** using propofol over BZD for sedation in post-cardiac surgery patients (Conditional recommendation, Low QoE) |
| **Justification** | In the discussions, the expert group and patient representative felt that elective cardiac surgical patients are different from critically ill medical and surgical patients who have been mechanically ventilated for a period of time; we therefore addressed the question separately for mechanically ventilated cardiac surgical patients and critically ill MV medical and surgical patients.  For the purpose of this question “post-cardiac surgical patients” were those who were mechanically ventilated after elective cardiac surgery  In cardiac surgical patients a shortened time to light sedation of at least 30 minutes and time to extubation of at least 1 hour were deemed clinically significant by the group.  •Low quality evidence  •Moderate benefit (reduced time to extubation, shorter wake up time- time to light sedation)  •Uncertainty about other outcomes  •Trivial harm  •V&P probably consistent  •Uncertainty about cost-effectiveness  •Intervention is likely acceptable and feasible to implement |

**Question**: Propofol compared to a benzodiazepine in critically ill ventilated adults (both intubated and non-intubated)

| **Quality assessment** | | | | | | | **№ of patients** | | **Effect** | | | **Quality** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **propofol** | **a benzodiazepine** | **Relative (95% CI)** | | **Absolute (95% CI)** |
| Mortality 90 day | | | | | | | | | | | | | |
| 10 | randomised trials | not serious | not serious | not serious | serious a | none | 95/432 (22.0%) | 94/426 (22.1%) | **RR 1.01** (0.79 to 1.29) | | **2 more per 1,000** (from 46 fewer to 64 more) | ⨁⨁⨁◯ MODERATE | CRITICAL |
| Time to Extubation-Hours (assessed with: hours) | | | | | | | | | | | | | |
| 16 | randomised trials | serious b | very serious c | not serious | not serious | none | 366 | 364 | - | | MD **13.71 hours lower** (20.01 lower to 7.4 lower) | ⨁◯◯◯ VERY LOW | CRITICAL |
| Time to Extubation-Hours Sens analysis | | | | | | | | | | | | | |
| 10 | randomised trials | not serious d | very serious e | not serious | not serious | none | 211 | 212 | - | | MD **11.6 lower** (15.62 lower to 7.58 lower) | ⨁⨁◯◯ LOW | CRITICAL |
| Time to light sedation | | | | | | | | | | | | | |
| 7 | randomised trials | not serious | serious f | not serious | serious g | none | 185 | 172 | - | MD **7.23 hours lower** (8.91 lower to 5.54 lower) | | ⨁⨁◯◯ LOW | CRITICAL |
| Delirium | | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious | not serious | very serious h | none | 4/14 (28.6%) | 5/14 (35.7%) | **RR 0.80** (0.27 to 2.37) | | **71 fewer per 1,000** (from 261 fewer to 489 more) | ⨁⨁◯◯ LOW | CRITICAL |
| Self Extubations | | | | | | | | | | | | | |
| 2 | randomised trials | not serious | not serious | not serious | very serious i | none j | 3/103 (2.9%) | 1/101 (1.0%) | **RR 2.82** (0.30 to 26.45) | | **18 more per 1,000** (from 7 fewer to 252 more) | ⨁⨁◯◯ LOW | CRITICAL |
| Neuropsychological Dysfunction | | | | | | | | | | | | | |
| 2 | randomised trials | not serious | very serious k | not serious | serious l | none | 34/58 (58.6%) | 41/56 (73.2%) | **RR 0.93** (0.69 to 1.24) m | | **51 fewer per 1,000** (from 176 more to 227 fewer) | ⨁◯◯◯ VERY LOW | CRITICAL |

**CI:** Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

#### Explanations

a. We downgraded the quality of evidence by one level for imprecision, the CI included both significant benefit and harm

b. We downgraded the quality of evidence by one level for risk of bias, majority of studies were judged to be at high risk of bias

c. We downgraded the quality of evidence by two levels for inconsistency, the I2=100%

d. Although non of the studies were at low risk of bias, we did not downgrade the quality of evidence as we downgraded by two levels for other categories

e. We downgraded the quality of evidence by two levels for very serious inconsistency, the I2=99%, and subgroup analyses failed to explain the observed heterogeneity

f. We downgraded the quality of evidence by two levels for serious inconsistency, the I2=98%

g. We downgraded the quality of evidence for imprecision by one level,

h. We downgraded the quality of evidence by two levels for serious imprecision, the number of events was very low and the CI was extremely wide

i. We downgraded the quality of evidence by two levels for serious imprecision, the number of events is 4 in totoal

j. We couldn't reliably assess for publication bias

k. We downgraded the quality of evidence by two levels for serious imprecision, the I2=91%

l. We downgraded the quality of evidence by one level for imprecision, the CI is wide including significant benefit and harm

m. Fixed effect model used

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| --- | --- | --- | --- |
| **Question** | | | |
| Should **propofol** vs. **a benzodiazepine** be used for **critically ill ventilated adults (both intubated and non-intubated)**? | | | |
| **Population:** | critically ill ventilated adults (both intubated and non-intubated) | **Background:** |  |
| **Intervention:** | propofol |
| **Comparison:** | a benzodiazepine |
| **Main outcomes:** | Mortality 90 day; Time to Extubation-Hours; Time to Extubation-Hours Sens analysis; Time to light sedation; Delirium; Self Extubations; Neuropsychological Dysfunction; |

**Assessment**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Judgement** | **Research evidence** | **Additional considerations** |
| Problem | **Is the problem a priority?**  ● Yes | No research evidence was identified. | text |
| Desirable  Effects | **How substantial are the desirable anticipated effects?**  ● Moderate | No research evidence was identified. | For the general medical and surgical ICU patients who have been on sedation for a while (excluding the fast track surgical and cardiac surgical patients discussed earlier), the group, including the patient representative, felt that shortened time to light sedation of at least 4 hours and time to extubation of approximately 8-12 hours (a shift or so) were clinically significant  One study looked at functional decline but had a large effect size and was a small study reducing the confidence in that study. While those outcomes would be a large effect, there was a tempered enthusiasm due to the quality of the study |
| Undesirable Effects | **How substantial are the undesirable anticipated effects?**  ● Trivial | Undesirable effects includes S/E, extubation .. etc. While there was a numerical increase in the self extubations in the propofol arm, the Ci were wide precluding any firm conclusion. Addiitonally it was not clear if the self extubations actually caused any harm (this was important for the physician group), though the patient representative did feel from a family perpective, a self extubation would be viewed as a undesirable effect. In the end thought to be a trivial undesirable anticipated effect given small numbers  Delirium and neuropsychological outcomes were not addressed in many of these earlier studies making it difficult to comment on those undesirable effects. |
| Certainty  of evidence | **What is the overall certainty of the evidence of effects?**  ● Low | No research evidence was identified. |  |
| Values | **Is there important uncertainty about or variability in how much people value the main outcomes?** ● Probably no important uncertainty or variability | No research evidence was identified. |  |
| Balance  of effects | **Does the balance between desirable and undesirable effects favor the intervention or the comparison?**  ● Probably favors the intervention | No research evidence was identified. |  |
| Resources  required | **How large are the resource requirements (costs)?**  ● Negligible costs and savings | older studies showed that propofol was more costly, but these data do not apply now, and | The moderate effect on outcomes precludes any major effects on costs especially now that propofol is off patent. |
| Certainty of  evidence of  required resources | **What is the certainty of the evidence of resource requirements (costs)?**  ● No included studies | No research evidence was identified. |  |
| Cost  effectiveness | **Does the cost-effectiveness of the intervention favor the intervention or the comparison?**  ● Does not favor either the intervention or the comparison | No research evidence was identified. |  |
| Acceptability | **Is the intervention acceptable to key stakeholders?**  ● Yes | No research evidence was identified. |  |
| Feasibility | **Is the intervention feasible to implement?**  ● Yes | No research evidence was identified. |  |

**Summary of judgements**

|  | **Judgement** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Problem** | No | Probably no | Probably yes | **Yes** |  | Varies | Don't know |
| **Desirable Effects** | Trivial | Small | **Moderate** | Large |  | Varies | Don't know |
| **Undesirable Effects** | Large | Moderate | Small | **Trivial** |  | Varies | Don't know |
| **Certainty of evidence** | Very low | **Low** | Moderate | High |  |  | No included studies |
| **Values** | Important uncertainty or variability | Possibly important uncertainty or variability | **Probably no important uncertainty or variability** | No important uncertainty or variability |  |  |  |
| **Balance of effects** | Favors the comparison | Probably favors the comparison | Does not favor either the intervention or the comparison | **Probably favors the intervention** | Favors the intervention | Varies | Don't know |
| **Resources required** | Large costs | Moderate costs | **Negligible costs and savings** | Moderate savings | Large savings | Varies | Don't know |
| **Certainty of evidence of required resources** | Very low | Low | Moderate | High |  |  | **No included studies** |
| **Cost effectiveness** | Favors the comparison | Probably favors the comparison | **Does not favor either the intervention or the comparison** | Probably favors the intervention | Favors the intervention | Varies | No included studies |
| **Equity** | Reduced | Probably reduced | Probably no impact | Probably increased | Increased | Varies | Don't know |
| **Acceptability** | No | Probably no | Probably yes | **Yes** |  | Varies | Don't know |
| **Feasibility** | No | Probably no | Probably yes | **Yes** |  | Varies | Don't know |

**Conclusions**

**Should propofol vs. a benzodiazepine be used in critically ill ventilated adults (both intubated and non-intubated)?**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Type of recommendation** | |  |  |  |  |  | | --- | --- | --- | --- | --- | | Strong recommendation against the intervention | Conditional recommendation against the intervention | Conditional recommendation for either the intervention or the comparison | Conditional recommendation for the intervention | Strong recommendation for the intervention | | ○ | ○ | ○ | ● | ○ | |
| **Recommendation** | We **suggest** using propofol over BZD for sedation in critically ill ventilated patients (conditional reccomendation, low quality of evidence) |
| **Justification** | For the general medical and surgical ICU patients who have been on sedation for a while (excluding the fast track surgical and cardiac surgical patients discussed earlier), the group, including the patient representative, felt that shortened time to light sedation of at least 4 hours and time to extubation of approximately 8-12 hours (a shift or so) were clinically significant.  While there was a numerical increase in the self extubations in the propofol arm, the CI were wide precluding any firm conclusion. Additionally it was not clear if the self extubations actually caused any harm (this was important for the physician group), though the patient representative did feel from a family perspective, a self extubation would be viewed as an undesirable effect. In the end thought to be a trivial undesirable anticipated effect given small numbers  Delirium and neuropsychological outcomes were not addressed in many of these earlier studies making it difficult to comment on those undesirable effects.  •Low quality evidence  •Moderate benefit (reduced time to extubation, shorter wake up time)  •Uncertainty about other outcomes  •Trivial harm  •V&P probably will not largely vary between patients  •Uncertainty about cost-effectiveness  •Intervention is likely acceptable and feasible to implement |
| **comments during electronic Voting by Entire panel** | In some circumstances benzos are fine... deep sedation, gaba agonist withdrawal.  administration of drugs...propofol (continuous infusion) vs benzo (whatever way, not just infusion?) wording of the question should be related to recommendation outcomes  specify which benzos were in studies; was delirium diagnosis made by a clinician (gold standard) or screened with a scale confounded (or not) by sedation?  little evaluation of propofol infusion syndrome with potential risk of a large-scale change to much greater propofol use. Given modest benefits of propofol in meta-analysis and their questionable clinical significance, a small increase in PRIS would reverse potential propofol benefit.  Will more propofol infusion result in less bolus dosing of sedation before starting any infusion? With unintended consequences when the field is moving to minimize infusions.  wording of recommendation should clarify if the benzo comparison group is benzo infusion, rather than influsion and/or bolus dosing. A bolus-only benzo approach (if present in any study) should not be grouped with a benzo infusion control group.  most of the studies are old and likely had different sedation practices than current practice and the associated sensitivity analysis showed weaker evidence benefit when only the more modern studies were included? validity of these data - and of recommendation - to current practice.Also,the only 2 outcomes that had benefit not patient-centered; the size of the difference was larger than the expert group's impression of the MID for these 2 outcomes, but those MID are, I believe, only based on expert opinion. Ppfol infusion syndrome could be a real issue if there is much larger scale use as a result of this SCCM recommendation with more liberal use, higher doses and longer durations, and less careful selection/screening of patients for use of this drug |

**Question**: Should dexmedetomidine compared to a benzodiazepine in critically ill ventilated adults (both intubated and non-intubated)

| **Quality assessment** | | | | | | | **№ of patients** | | **Effect** | | | | **Quality** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **an alpha-2 agonist (e.g. dexmedetomidine)** | **a benzodiazepine** | **Relative (95% CI)** | | | **Absolute (95% CI)** |
| 28 Day Mortality | | | | | | | | | | | | | | |
| 3 | randomised trials | not serious | not serious a | not serious | serious b | none c | 127/543 (23.4%) | 95/424 (22.4%) | **RR 0.98** (0.68 to 1.41) | | | **4 fewer per 1,000** (from 72 fewer to 92 more) | ⨁⨁⨁◯ MODERATE | CRITICAL |
| Duration of Mechanical Ventilation (days) | | | | | | | | | | | | | | |
| 5 | randomised trials | not serious d | serious e | not serious | serious f | none c | 586 | 466 | - | | | MD **0.71 lower** (1.87 lower to 0.45 higher) | ⨁⨁◯◯ LOW | CRITICAL |
| ICU length of stay in days | | | | | | | | | | | | | | |
| 3 | randomised trials | not serious | serious g | not serious | serious h | none c | 545 | 424 | - | | | MD **0.23 lower** (0.57 lower to 0.11 higher) | ⨁⨁◯◯ LOW | CRITICAL |
| Delirium | | | | | | | | | | | | | | |
| 4 | randomised trials | not serious | serious i | not serious | serious j | none c | 193/563 (34.3%) | 164/444 (36.9%) | | **RR 0.81** (0.60 to 1.08) | | **70 fewer per 1,000** (from 30 more to 148 fewer) | ⨁⨁◯◯ LOW | CRITICAL |
| Bradycardia | | | | | | | | | | | | | | |
| 6 | randomised trials | not serious | not serious | not serious | serious k | none c | 151/583 (25.9%) | 39/464 (8.4%) | | **RR 2.44** (1.77 to 3.36) | | **121 more per 1,000** (from 65 more to 198 more) | ⨁⨁⨁◯ MODERATE | IMPORTANT |
| Hypotension | | | | | | | | | | | | | | |
| 4 | randomised trials | not serious | serious l | not serious | serious m | none c | 192/531 (36.2%) | 98/413 (23.7%) | | **RR 1.38** (0.79 to 2.41) | **90 more per 1,000** (from 50 fewer to 335 more) | | ⨁⨁◯◯ LOW | IMPORTANT |

**CI:** Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

#### Explanations

a. We did not downgraded the quality of evidence for inconsistency, the I2=49%

b. We downgraded the quality of evidence by one level for imprecision, the CI included both significant benefit and harm

c. We were not able to reliably assess for publication bias

d. Although none of the included studies were at low risk of bias, we did not downgrade for risk of bias as its unlikely that the study design biased the results to no difference

e. We downgraded the quality of evidence by one level for inconsistency, the I2=91% and not explained by excluding studies with shorter DMV

f. We downgraded the quality of evidence for imprecision by one level, the CI included both benefit and harm

g. We downgraded the quality of evidence for inconsistency by one level, the I2=52%

h. We downgraded the quality of evidence by two levels for imprecision, the number of patients was small and the CI included significant benefit and harm

i. We downgraded the quality of evidence by one level for inconsistency, the I2=70% not explained by risk of bias

j. We downgraded the quality of evidence by one level for imprecision, the CI included significant benefit and small harm

k. We downgraded the quality of evidence for imprecision by one level, the CI included both extreme and large harm and

l. We downgraded the quality of evidence by one level for inconsistency, the I2=73%

m. We downgraded the quality of evidence by one level for imprecision, the CI included both large benefit and harm

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Question** | | | | |
| Should **an alpha-2 agonist (e.g. dexmedetomidine)** vs. **a benzodiazepine** be used for **critically ill ventilated adults (both intubated and non-intubated)**? | | | | |
| **Population:** | critically ill ventilated adults (both intubated and non-intubated) |  | |  | |
| **Intervention:** | an alpha-2 agonist (e.g. dexmedetomidine) |  |  | |
| **Comparison:** | a benzodiazepine |
| **Main outcomes:** | 28 Day Mortality; Duration of Mechanical Ventilation (days); ICU length of stay in days; Delirium; Bradycardia; Hypotension; |

**Assessment**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Judgement** | **Research evidence** | **Additional considerations** |
| Problem | **Is the problem a priority?**  ● Yes |  |  |
| Desirable  Effects | **How substantial are the desirable anticipated effects?**  ● Moderate |  | While there was no difference in outcomes with regards to morality, there were important trends with regards to delirium, duration of MV and ICU LOS. There was discussion of whether the Jacob study really evaluated delirium like all other studies since they did it once 48 hours after stopping sedation. Importantly the study with the lowest risk of bias (Riker 2009) had the greatest impact on Mv and delirium and therefore should guide reccs and the previous guideline reccs should also inform our decision. The way we will show these is all studies first and then sensitivity excluding Jacob. A note was also made that the Jacob MIDEX study had some non invasive ventilation. Doing a subgroup analysis of the low risk of bias studies may be considered |
| Undesirable  Effects | **How substantial are the undesirable anticipated effects?**  ● Small | While bradycardia were greater in dex group, it is not clear if these are undesirable. In both Pandharipande and Riker the bradycardia did not require intervention to a greater extent than the benzo group. In some patients bradycardia may be helpful when they are running tachycardic. This guided the recc to say the undesirable impact was small |
| Certainty of evidence | **What is the overall certainty of the evidence of effects?**  ● Low | | **Outcomes** | **Importance** | **Quality of the evidence (GRADE)** | | --- | --- | --- | | 28 Day Mortality | CRITICAL | ⨁⨁⨁◯ MODERATEa,b,c | | Duration of Mechanical Ventilation (days) | CRITICAL | ⨁⨁◯◯ LOWc,d,e,f | | ICU length of stay in days | CRITICAL | ⨁⨁◯◯ LOWc,g,h | | Delirium incidence | CRITICAL | ⨁⨁◯◯ LOWc,i,j | | Bradycardia | IMPORTANT | ⨁⨁⨁◯ MODERATEc,k | | Hypotension | IMPORTANT | ⨁⨁◯◯ LOWc,l,m |  1. We did not downgraded the quality of evidence for inconsistency, the I2=49% 2. We downgraded the quality of evidence by one level for imprecision, the CI included both significant benefit and harm 3. We were not able to reliably assess for publication bias 4. Although none of the included studies were at low risk of bias, we did not downgrade for risk of bias as its unlikely that the study design biased the results to no difference 5. We downgraded the quality of evidence by one level for inconsistency, the I2=91% and not explained by excluding studies with shorter DMV 6. We downgraded the quality of evidence for imprecision by one level, the CI included both benefit and harm 7. We downgraded the quality of evidence by two levels for imprecision, the number of patients was small and the CI included significant benefit and harm 8. We downgraded the quality of evidence for inconsistency by one level, the I2=52% 9. We downgraded the quality of evidence by one level for inconsistency, the I2=70% not explained by risk of bias 10. We downgraded the quality of evidence by one level for imprecision, the CI included significant benefit and small harm 11. We downgraded the quality of evidence for imprecision by one level, the CI included both extreme and large harm and 12. We downgraded the quality of evidence by one level for inconsistency, the I2=73% 13. We downgraded the quality of evidence by one level for imprecision, the CI included both large benefit and harm |  |
| Values | **Is there important uncertainty about or variability in how much people value the main outcomes?**  ● Probably no important uncertainty or variability |  | In discussion with patient representative it was felt that patients would value shorter time on MV, and delirium than the concern for bradycardia given the HR was not determined to greater than a small undesirable effect |
| Balanc  e of effects | **Does the balance between desirable and undesirable effects favor the intervention or the comparison?**  ● Probably favors the intervention |  | As above- patient rep felt this still favors intervention since bradycardia impact is small |
| Resources  required | **How large are the resource requirements (costs)?**  ○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings  ○ Varies ○ Don't know | 1. Can J Hosp Pharm 2012;65(2):103–110. [4]  The average cost of the medication DEX Vs. midazolam ($1929.57 Vs. $180.10 per patient).  Average costs associated with mechanical ventilation ($2939 Vs. $4448) and management of delirium ($2127 Vs. $3012). The overall cost per patient was ($7022 V. $7680). | Cost effectiveness favors alpha2 agonists (dex) but costs are varied since off patent but still many countries have different costs for dex which makes this challenging |
| Certainty of  evidence of  required  resources | **What is the certainty of the evidence of resource requirements (costs)?**  x Low |  |  |
| Cost  effectiveness | **Does the cost-effectiveness of the intervention favor the intervention or the comparison?** ● Probably favors the intervention |  |  |
| Acceptability | **Is the intervention acceptable to key stakeholders?**  ● Probably yes |  |  |
| Feasibility | **Is the intervention feasible to implement?**  ● Yes |  |  |

**Summary of judgements**

|  | **Judgement** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Problem** | No | Probably no | Probably yes | **Yes** |  | Varies | Don't know |
| **Desirable Effects** | Trivial | Small | **Moderate** | Large |  | Varies | Don't know |
| **Undesirable Effects** | Large | Moderate | **Small** | Trivial |  | Varies | Don't know |
| **Certainty of evidence** | Very low | **Low** | Moderate | High |  |  | No included studies |
| **Values** | Important uncertainty or variability | Possibly important uncertainty or variability | **Probably no important uncertainty or variability** | No important uncertainty or variability |  |  | No known undesirable outcomes |
| **Balance of effects** | Favors the comparison | Probably favors the comparison | Does not favor either the intervention or the comparison | **Probably favors the intervention** | Favors the intervention | Varies | Don't know |
| **Resources required** | Large costs | Moderate costs | Negligible costs and savings | Moderate savings | Large savings | Varies | Don't know |
| **Certainty of evidence of required resources** | Very low | Low | Moderate | High |  |  | No included studies |
| **Cost effectiveness** | Favors the comparison | Probably favors the comparison | Does not favor either the intervention or the comparison | **Probably favors the intervention** | Favors the intervention | Varies | No included studies |
| **Equity** | Reduced | Probably reduced | Probably no impact | Probably increased | Increased | Varies | Don't know |
| **Acceptability** | No | Probably no | **Probably yes** | Yes |  | Varies | Don't know |
| **Feasibility** | No | Probably no | Probably yes | **Yes** |  | Varies | Don't know |

**Conclusions: Should an alpha-2 agonist (e.g. dexmedetomidine) vs. a benzodiazepine be used in critically ill ventilated adults (both intubated and non-intubated)?**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Type of recommendation** | |  |  |  |  |  | | --- | --- | --- | --- | --- | | Strong recommendation against the intervention | Conditional recommendation against the intervention | Conditional recommendation for either the intervention or the comparison | Conditional recommendation for the intervention | Strong recommendation for the intervention | | ○ | ○ | ○ | ● | ○ | |
| **Recommendation** | We **suggest** using an alpha-2 agonist (e.g. dexmedetomidine) over BZD for sedation in critically ill ventilated patients (conditional recommendation, low QOE) |
| **Justification** | While there was no difference in outcomes with regards to morality, there were important trends with regards to delirium, duration of MV and ICU LOS.  For the general medical and surgical ICU patients who have been on sedation for a while (excluding the fast track surgical and cardiac surgical patients discussed earlier), the group, including the patient representative, felt that shortened time to light sedation of at least 4 hours and time to extubation of approximately 8-12 hours (a shift or so) were clinically significant.  Important to note that the Jacob study evaluated delirium differently than the other studies since they did it once 48 hours after stopping sedation.  The study with the lowest risk of bias (Riker 2009)[5] had the greatest impact on MV and delirium and therefore guided recommendations.  •Low quality evidence  •Moderate benefit with regards to DMV, delirium and ICU LOS, uncertainty about other outcomes  •Small harm possibly with bradycardia. Important to note that bradycardia may be considered beneficial in some circumstances in the ICU, therefore cannot always be considered as a harmful effect. The Riker and Pandharipande studies both demonstrated higher bradycardia in the dex group but there were no differences in the patients that were deemed to require treatment for the bradycardia  •Values and preferences probably will not vary between patients  •DEX is cost-effectiveness  •Intervention is likely acceptable and feasible to implement Low risk of bias study has outcomes favoring intervention supporting recommendations |
| **comments during electronic Voting by Entire panel** | suitability of benzos under certain circumstances? Knowledge gap how to sedate hemodynamically unstable patients very helpful to have the risk of bias chart on the forest plot as it is shown here.  A reader of this recommendation will not know if we are recommending Dexmed infusion rather than attempting prn bolus dosing of benzo, or Dexmed vs. benzo infusion.  no statistically significant differences in the meta-analyses to support this recommendation. subgroup analysis of the RCT(s) with low risk of bias first.  Similar to last set of guidelines and we may not want to contradict, but I no current strength of evidence supporting a conditional recommendation without further analyses to discount the higher ROB; No significant out-come difference across RCTs |

**Question**: An alpha-2 agonist (e.g., dexmedetomidine) compared to propofol in critially ill ventilated adults (both intubated and non-intubated)

| **Quality assessment** | | | | | | | **№ of patients** | | **Effect** | | **Quality** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **an alpha-2 agonist (e.g., dexmedetomidine)** | **propofol** | **Relative (95% CI)** | **Absolute (95% CI)** |
| 28 Day Mortality | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious | not serious | serious a | none b | 37/246 (15.0%) | 46/249 (18.5%) | **RR 0.81** (0.55 to 1.21) | **35 fewer per 1,000** (from 39 more to 83 fewer) | ⨁⨁⨁◯ MODERATE | CRITICAL |
| Delirium | | | | | | | | | | | | |
| 1 | randomised trials | serious c | not serious | not serious | serious d | none b | 7/246 (2.8%) | 19/249 (7.6%) | **RR 0.37** (0.16 to 0.87) | **48 fewer per 1,000** (from 10 fewer to 64 fewer) | ⨁⨁◯◯ LOW | CRITICAL |
| Duration of Mechanical Ventilation in hours | | | | | | | | | | | | |
| 3 | randomised trials | serious e | not serious | not serious | serious f | none b | 427 | 423 | - | MD **0.04 hours lower** (0.08 lower to 0.01 lower) | ⨁⨁◯◯ LOW | CRITICAL |
| ICU Length of stay in days | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious | not serious | very serious g | none b | 251 | 247 | - | MD **2.83 days fewer** (8.13 fewer to 2.47 more) | ⨁⨁◯◯ LOW | CRITICAL |
| Bradycardia | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious | not serious | serious h | none b | 32/246 (13.0%) | 27/249 (10.8%) | **RR 1.20** (0.74 to 1.94) | **22 more per 1,000** (from 28 fewer to 102 more) | ⨁⨁⨁◯ MODERATE | IMPORTANT |
| Hypotension | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious | not serious | serious i | none b | 32/246 (13.0%) | 33/249 (13.3%) | **RR 0.98** (0.62 to 1.54) | **3 fewer per 1,000** (from 50 fewer to 72 more) | ⨁⨁⨁◯ MODERATE | IMPORTANT |

**CI:** Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

#### Explanations

a. We downgraded the quality of evidence for imprecision by one level, the CI included both benefit and harm

b. We were not able to reliably assess for publication bias

c. We downgraded the quality of evidence by one level for risk of bias, the trial was judged to be at high risk of bias

d. We downgraded the quality of evidence by one level for imprecision, the CI is very wide and the total number of events is low (26 events in total)

e. We downgraded the quality of evidence by one level for risk of bias, the studies were all at high risk of bias, and we can't exclude the possibility of bias

f. We downgraded the quality of evidence by one level for imprecision, the CI included both trivial and significant benefit

g. We downgraded the quality of evidence by two levels for serious imprecision, the CI included very large benefit and harm

h. We downgraded the quality of evidence by one level for imprecision, the CI included large harm and benefit

i. We downgraded the quality of evidence for imprecision by one level, the CI included both significant benefit and harm

|  |  |  |  |
| --- | --- | --- | --- |
| **Question** | | | |
| Should **an alpha-2 agonist (e.g., dexmedetomidine)** vs. **propofol** be used for **critially ill ventilated adults (both intubated and non-intubated)**? | | | |
| **Population:** | critially ill ventilated adults (both intubated and non-intubated) | **Background:** |  |
| **Intervention:** | an alpha-2 agonist (e.g., dexmedetomidine) |
| **Comparison:** | propofol |
| **Main outcomes:** | 28 Day Mortality; Delirium; Duration of Mechanical Ventilation in hours; ICU Length of stay in days; Bradycardia; Hypotension; |

**Assessment**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Judgement** | **Research evidence** | **Additional considerations** |
| Problem | **Is the problem a priority?**  ● Yes |  |  |
| Desirable  Effects | **How substantial are the desirable anticipated effects?**  ● Small |  | There was a consistent message with about a day shorter on mechanical ventilation but no difference in most other outcomes. Similar to the alpha2 vs benzo comparisons the Jakob PRODEX [6] study's eval of delirium was considered difficult to interpret because of its distant measurement. With regards to ICU LOS wide CI. So really only difference was small diff in MV |
| Undesirabl  e Effects | **How substantial are the undesirable anticipated effects?**  ● Trivial | Bradycardia was not different and the hypotension was not diffferent so no real undersirable effect differences |
| Certainty  of evidence | **What is the overall certainty of the evidence of effects?**  ● Low |  |  |
| Values | **Is there important uncertainty about or variability in how much people value the main outcomes?** ● Probably no important uncertainty or |  | With a small difference in MV and no difference in undersiable effects effects the patient rep felt most would not have any uncertainty on what they would prefer |
| Balance  of effects | **Does the balance between desirable and undesirable effects favor the intervention or the comparison?** ● Probably favors the intervention |  |  |
| Resources  required | **How large are the resource requirements (costs)?** ● Don't know |  | no cost data comparing propofol and dex |
| Certainty of  evidence of  required  resources | **What is the certainty of the evidence of resource requirements (costs)?**  ● No included studies |  |  |
| Cost  effecti-  veness | **Does the cost-effectiveness of the intervention favor the intervention or the comparison?**  ● No included studies |  |  |
| Accept  -ability | **Is the intervention acceptable to key stakeholders?** ● Probably yes |  |  |
| Feasibility | **Is the intervention feasible to implement?**  ● Yes |  |  |

**Summary of judgements**

|  | **Judgement** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Problem** | No | Probably no | Probably yes | **Yes** |  | Varies | Don't know |
| **Desirable Effects** | Trivial | **Small** | Moderate | Large |  | Varies | Don't know |
| **Undesirable Effects** | Large | Moderate | Small | **Trivial** |  | Varies | Don't know |
| **Certainty of evidence** | Very low | **Low** | Moderate | High |  |  | No included studies |
| **Values** | Important uncertainty or variability | Possibly important uncertainty or variability | **Probably no important uncertainty or variability** | No important uncertainty or variability |  |  | No known undesirable outcomes |
| **Balance of effects** | Favors the comparison | Probably favors the comparison | Does not favor either the intervention or the comparison | **Probably favors the intervention** | Favors the intervention | Varies | Don't know |
| **Resources required** | Large costs | Moderate costs | Negligible costs and savings | Moderate savings | Large savings | Varies | **Don't know** |
| **Certainty of evidence of required resources** | Very low | Low | Moderate | High |  |  | **No included studies** |
| **Cost effectiveness** | Favors the comparison | Probably favors the comparison | Does not favor either the intervention or the comparison | Probably favors the intervention | Favors the intervention | Varies | **No included studies** |
| **Equity** | Reduced | Probably reduced | Probably no impact | Probably increased | Increased | Varies | Don't know |
| **Acceptability** | No | Probably no | **Probably yes** | Yes |  | Varies | Don't know |
| **Feasibility** | No | Probably no | Probably yes | **Yes** |  | Varies | Don't know |

**Conclusions**

**Should an alpha-2 agonist (e.g., dexmedetomidine) vs. propofol be used in critially ill ventilated adults (both intubated and non-intubated)?**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Type of recommendation** | |  |  |  |  |  | | --- | --- | --- | --- | --- | | Strong recommendation against the intervention | Conditional recommendation against the intervention | Conditional recommendation for either the intervention or the comparison | Conditional recommendation for the intervention | Strong recommendation for the intervention | | ○ | ○ | ● | ○ | ○ | |
| **Recommendation** | We **suggest** using either dexmedetomidine or propofol for sedation in critically ill patients (conditional reccomendation, low QOE) |
| **Justification** | For the general medical and surgical ICU patients who have been on sedation for a while (excluding the fast track surgical and cardiac surgical patients discussed earlier), the group, including the patient representative, felt that shortened time to light sedation of at least 4 hours and time to extubation of approximately 8-12 hours (a shift or so) were clinically significant. There was a consistent message with about shorter time on mechanical ventilation with dexmedetomidine but no difference in most other outcomes. Similar to the alpha2 vs benzo comparisons the Jakob PRODEX [6] study's evaluation of delirium was considered difficult to interpret because of its distant measurement. With regards to ICU LOS there were wide CI, hence the only difference was small diff in MV There was furthermore, no new evidence since the 2013 guidelines which would warrant a change in the interpretation of the data and thus the recommendations  •Low quality evidence  •Small benefit  •Uncertainty about other outcomes  •Trivial harm  •V&P probably will not vary between patients  •Uncertain effect on cost  •Intervention is likely acceptable and feasible to implement |
| **comments during electronic Voting by Entire panel** | Is dex preferable in patients at highest risk of delirium or peri-extubation? These are not equivalent.  Recommendation wording not specific enough when compared to the question.  Challenged by text vs. the meta-analysis. In the meta-analysis, the difference in MV duration was very small, but the text suggests a 1 day difference.  In a recommendation stating "we suggest using either dexmed or ppfol..." the comparator is not clear. The recommendation infers it compares other sedative agents (i.e. benzos), when this was really a comparison of only these 2 drugs. Can we give a more direct recommendation based on the question as originally posed? |

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