**Supplemental Table 19 Evidence Profiles and Evidence to Decision Tables for All Delirium Group Actionable Questions**

**Author(s)**: Mark E. Nunnally

**Question**: Haloperidol compared to no such strategy in critically ill adults WITHOUT delirium

**Setting**: Intensive care units

**Bibliography**: Wang 2012 [(1)](https://paperpile.com/c/z7wvc0/bRbp)

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| **Quality assessment** | **№ of patients** | **Effect** | **Quality** | **Importance** |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **haloperidol** | **no such strategy** | **Relative(95% CI)** | **Absolute(95% CI)** |
| discharge to a nursing home |
|  |  |  |  |  |  |  |  |  | not estimable  |  | -  |  |
| cognitive impairment |
|  |  |  |  |  |  |  |  |  | not estimable  |  | -  |  |
| PTSD incidence |
|  |  |  |  |  |  |  |  |  | not estimable  |  | -  |  |
| incidence of depression |
|  |  |  |  |  |  |  |  |  | not estimable  |  | -  |  |
| functionality |
|  |  |  |  |  |  |  |  |  | not estimable  |  | -  |  |
| distress |
|  |  |  |  |  |  |  |  |  | not estimable  |  | -  |  |
| mortality (at any time point) |
| 1  | randomised trials  | not serious  | not serious  | serious a | very serious b | none  | 0/35 (0.0%)  | 4/53 (7.5%)  | **RR 0.17**(0.01 to 3.00)  | **63 fewer per 1,000**(from 75 fewer to 151 more)  | ⨁◯◯◯VERY LOW  | CRITICAL  |
| delirium duration  |
|  |  |  |  |  |  |  |  |  | not estimable  |  | -  |  |
| delirium severity |
|  |  |  |  |  |  |  |  |  | not estimable  |  | -  |  |
| duration of mechanical ventilation |
|  |  |  |  |  |  |  |  |  | not estimable  |  | -  |  |
| ICU readmission rate |
|  |  |  |  |  |  |  |  |  | not estimable  |  | -  |  |
| intensity of treatment |
|  |  |  |  |  |  |  |  |  | not estimable  |  | -  |  |
| costs |
|  |  |  |  |  |  |  |  |  | not estimable  |  | -  |  |
| Delirium incidence |
| 1  | randomised trials  | not serious  | not serious  | serious a | serious c | none  | 35/229 (15.3%)  | 53/228 (23.2%)  | **RR 0.66**(0.45 to 0.97)  | **79 fewer per 1,000**(from 7 fewer to 128 fewer)  | ⨁⨁◯◯LOW  | IMPORTANT  |
| ICU length of stay (assessed with: hours) |
| 1  | randomised trials  | not serious  | not serious  | serious a | serious d | none  | 229  | 228  | -  | MD **0.07 days lower**(0.07 lower to 0.03 higher)  | ⨁⨁◯◯LOW  | IMPORTANT  |

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

**Explanations**

a. Low APACHE scores in patients suggests less-ill study sample.

b. 4 total events.

c. 88 total events.

d. Precision around an estimate of no substantial benefit or harm.

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| Population:  | critically ill adults WITHOUT delirium  | Background:  |
| Intervention:  | haloperidol  |  |
| Comparison:  | no such strategy  |  |
| Main outcomes:  | * mortality (at any time point)
* Delirium incidence
* ICU length of stay
 |  |
| Setting:  | Intensive care units  |  |
|  | **Criteria**  | **Judgements**  | **Research evidence**  |
| Problem | **Is there a problem priority?**  | ○ No ○ Probably no ○ Uncertain ○ Probably yes ● Yes ○ Varies  | The evidence for this question comes from a single study - Wang et al 2012 [(1)](https://paperpile.com/c/z7wvc0/bRbp) which included 229 receiving a bolus IV injection of haloperidol of 0.5 mg and then 0.1 mg/hr continuous infusion and 228 receiving placebo following surgery. Mortality is reported from 28 day follow-up. Iit includes ONLY patients 65 years and older who were presenting for non-cardiac surgeries and went to the ICU following surgery. Mean APACHE II scores were much lower than among populations of studies in the other PICO questions regarding the use of haloperidol. The Wang study APACHE II scores were  *8.7 (+/-3.0) in the Intervention and 8.6 (+/-2.8) in the placebo.*  This is much lower than in the mixed ICU populations of patients studied in the Al-Qadheeb 2016 [(2)](https://paperpile.com/c/z7wvc0/syze) where APACHE II scores were 19 (17-23) in the Intervention and 20 (17-24) in the placebo (Subsyndromal Question 17); or Page, 2013 where  APACHE II scores were 19.8 (SD 6.2) in the Intervention and 19.7 (S.D. 6.9) in the placebo, or Girard, 2010 [(3)](https://paperpile.com/c/z7wvc0/aYCW) APACHE II scores were 26 (21-31) in the Intervention (haloperidol) and 26 (23-32) in Intervention 2 (ziprasidone) and 26 (21-32) in the placebo. (Treatment of Delirium Question 18).  This suggests that these are a very different group of patients than those studied in the later questions.    |
| Benefits & harms of the options | **What is the overall certainty of this evidence?**  | ○ No included studies ○ Very low ● Low ○ Moderate ○ High  | **Summary of findings**: Haloperidol compared to no such strategy in critically ill adults WITHOUT delirium

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Outcome** | **With no such strategy** | **With haloperidol** | **Difference (95% CI)**  | **Relative effect (RR) (95% CI)**  |
| mortality (at any time point) | 75 per 1,000 | **13 per 1,000**(1 to 226) | **63 fewer per 1,000**(from 75 fewer to 151 more) | **RR 0.17**(0.01 to 3.00) |
| Delirium incidence | 232 per 1,000 | **153 per 1,000**(105 to 225) | **79 fewer per 1,000**(from 7 fewer to 128 fewer) | **RR 0.66**(0.45 to 0.97) |
| ICU length of stay | The mean ICU length of stay was **0** days | The mean ICU length of stay in the intervention group was 0.07 days lower (0.07 lower to 0.03 higher) | MD **0.07 days lower**(0.07 lower to 0.03 higher) | - |

 |
| **Is there important uncertainty about how much people value the main outcomes?**  | ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability ○ No known undesirable outcomes  |
| **Are the desirable anticipated effects large?**  | ○ No ● Probably no ○ Uncertain ○ Probably yes ○ Yes ○ Varies  |
| **Are the undesirable anticipated effects small?**  | ○ No ○ Probably no ● Uncertain ○ Probably yes ○ Yes ○ Varies  |
| **Are the desirable effects large relative to undesirable effects?**  | ○ No ○ Probably no ● Uncertain ○ Probably yes ○ Yes ○ Varies  |
| Resource use | **Are the resources required small?**  | ○ No ○ Probably no ○ Uncertain ● Probably yes ○ Yes ○ Varies  | Haloperidol is a relatively inexpensive antipsychotic agent. |
| **Is the incremental cost small relative to the net benefits?**  | ○ No ○ Probably no ● Uncertain ○ Probably yes ○ Yes ○ Varies  |  |
| Acceptability | **Is the option acceptable to key stakeholders?**  | ○ No ○ Probably no ● Uncertain ○ Probably yes ○ Yes ○ Varies  |  |
| Feasibility | **Is the option feasible to implement?**  | ○ No ○ Probably no ○ Uncertain ○ Probably yes ● Yes ○ Varies  |  |

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| **Recommendation** **Should haloperidol vs. no such strategy be used in critically ill adults WITHOUT delirium?** |
| **Balance of consequences**  | Undesirable consequences *clearly outweigh* desirable consequences in most settings | Undesirable consequences *probably outweigh* desirable consequences in most settings | The balance between desirable and undesirable consequences *is closely balanced or uncertain* | Desirable consequences *probably outweigh* undesirable consequences in most settings | Desirable consequences *clearly outweigh* undesirable consequences in most settings |
|  | ○ | ○ | ● | ○ | ○ |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Type of recommendation**  | We recommend against offering this option | We suggest not offering this option | We suggest offering this option | We recommend offering this option |
|  | ○ | ● | ○ | ○ |
| **Recommendation**  | We do not suggest using haloperidol for subsyndromal delirium in critically ill patients, as there is not enough evidence that it decreases the incidence or ICU length of stay. |
| **Justification**  | The justification for this recommendation is based upon the low overall certainty of evidence based upon a single study of surgical patients who were not very ill with much lower APACHE scores than are common in most mixed ICU settings.  While the use of haloperidol after surgery for patients admitted to the ICU seemed to decrease the incidence of delirium as measured with the CAM-ICU with an estimate of 0.66 favoring the interventional use of haloperidol, the confidence intervals are still very broad (0.45 to 0.97).  Furthermore, although incidence is lower, there is no evidence that this decrease in incidence results in any other meaningful change in outcome - ICU length of stay for either group is not significantly different (Length of stay I=  0.89, SD 0.31 vs P= 0.96, SD 0.67) with both groups leaving the ICU within a day. |
| **Subgroup considerations**  | Patients who experience significant distress secondary to symptoms of an episode of delirium such as anxiety, fearfulness, hallucinations, or delusions or who may be physically threatening to self or others may benefit from the use of lowest effective doses of atypical antipsychotics for symptomatic relief. Atypical antipsychotics should be discontinued following the resolution of the patient's distress.    |
| **Implementation considerations**  |  |
| **Research possibilities**  |  More research is needed on the benefit of haloperidol in treating distress due to delirium symptoms, longterm outcomes  and system innovations to ensure that patients do not remain on antipsychotics indefinitely following symptomatic initiation during a delirium episode. |

**Author(s)**: Mark E. Nunnally **D**

**Question**: An atypical antipsychotic compared to no such strategy in critically ill adults WITHOUT delirium

**Setting**: Intensive care units

**Bibliography**: Prakanrattana 2007 [(4)](https://paperpile.com/c/z7wvc0/ZT3t)

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| --- | --- | --- | --- | --- |
| **Quality assessment** | **№ of patients** | **Effect** | **Quality** | **Importance** |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **an atypical antipsychotic**  | **no such strategy** | **Relative(95% CI)** | **Absolute(95% CI)** |
| discharge to a nursing home |
|  |  |  |  |  |  |  |  |  | not estimable  |  | -  |  |
| cognitive impairment |
|  |  |  |  |  |  |  |  |  | not estimable  |  | -  |  |
| PTSD incidence |
|  |  |  |  |  |  |  |  |  | not estimable  |  | -  |  |
| incidence of depression |
|  |  |  |  |  |  |  |  |  | not estimable  |  | -  |  |
| functionality |
|  |  |  |  |  |  |  |  |  | not estimable  |  | -  |  |
| distress |
|  |  |  |  |  |  |  |  |  | not estimable  |  | -  |  |
| mortality (at any time point) |
|  |  |  |  |  |  |  |  |  | not estimable  |  | -  |  |
| delirium duration  |
|  |  |  |  |  |  |  |  |  | not estimable  |  | -  |  |
| delirium severity |
|  |  |  |  |  |  |  |  |  | not estimable  |  | -  |  |
| duration of mechanical ventilation |
|  |  |  |  |  |  |  |  |  | not estimable  |  | -  |  |
| ICU readmission rate |
|  |  |  |  |  |  |  |  |  | not estimable  |  | -  |  |
| intensity of treatment |
|  |  |  |  |  |  |  |  |  | not estimable  |  | -  |  |
| costs |
|  |  |  |  |  |  |  |  |  | not estimable  |  | -  |  |
| Delirium incidence |
| 1  | randomised trials  | serious a | not serious  | not serious  | serious b | none  | 7/63 (11.1%)  | 20/63 (31.7%)  | **RR 0.35**(0.16 to 0.77)  | **206 fewer per 1,000**(from 73 fewer to 267 fewer)  | ⨁⨁◯◯LOW  | IMPORTANT  |
| ICU length of stay (assessed with: days) |
| 1  | randomised trials  | serious a | not serious  | not serious  | serious c | none  | 63  | 63  | -  | MD **0.1 days higher**(0.64 lower to 0.84 higher)  | ⨁⨁◯◯LOW  | IMPORTANT  |

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

**Explanations**

a. Unblinded study, no intention-to-treat analysis mentioned,

b. 27 total events.

c. 95% CI includes longer and shorter stay.

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| Population:  | critically ill adults WITHOUT delirium  | Background:  |
| Intervention:  | an atypical antipsychotic  |  |
| Comparison:  | no such strategy  |  |
| Main outcomes:  | * Delirium incidence
* ICU length of stay
 |  |
| Setting:  | Intensive care units  |  |
| Perspective:  |  |  |
|  | **Criteria**  | **Judgements**  | **Research evidence**  |
| Problem | **Is there a problem priority?**  | ○ No ○ Probably no ○ Uncertain ○ Probably yes ● Yes ○ Varies  | **Summary –** There is one RCT study using atypical antipsychotics as a preventive strategy in cardiac surgery patients (n = 126) in the ICU; INCLUSION criteria included age of greater than 40 years of age, undergoing CABG as an elective surgery. EXCLUSION criteria: the need for emergency surgery, CAM positive before surgery, and intubation prior to surgery. The CAM-ICU was performed twice daily (by anesthesiologist/and ICU nurses) as a measure of delirium on POD 0-4. The intervention included 1 mg of risperidone sublingually for one dose upon recovery from anesthesia with the comparison treatment a listerine strip under the tongue. Delirium incidence favored the intervention 7/63 vs 20/63 (Risk Ratio =0.35 95%: 0.16, 0.77). The length of ICU stay was no different between the groups (see below). Given the lack of blinding and few events of interest, this study confers low evidence in addressing the PICO question.  |
| Benefits & harms of the options | **What is the overall certainty of this evidence?**  | ○ No included studies ○ Very low ● Low ○ Moderate ○ High  | **The relative importance or values of the main outcomes of interest:**

|  |  |  |
| --- | --- | --- |
| **Outcome** | **Relative importance**  | **Certainty of the evidence (GRADE)**  |
| Delirium incidence | IMPORTANT | ⨁⨁◯◯LOW |
| ICU length of stay | IMPORTANT | ⨁⨁◯◯LOW |

 |
| **Is there important uncertainty about how much people value the main outcomes?**  | ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability ○ No known undesirable outcomes  |
| **Are the desirable anticipated effects large?**  | ○ No ○ Probably no ● Uncertain ○ Probably yes ○ Yes ○ Varies  |
| **Are the undesirable anticipated effects small?**  | ○ No ○ Probably no ● Uncertain ○ Probably yes ○ Yes ○ Varies  |
| **Are the desirable effects large relative to undesirable effects?**  | ○ No ○ Probably no ● Uncertain ○ Probably yes ○ Yes ○ Varies  |
| Resource use | **Are the resources required small?**  | ○ No ○ Probably no ○ Uncertain ● Probably yes ○ Yes ○ Varies  | The price of risperidone is relatively low.  However, the long-term consequences of ongoing therapy could be substantive. |
| **Is the incremental cost small relative to the net benefits?**  | ○ No ○ Probably no ● Uncertain ○ Probably yes ○ Yes ○ Varies  |  |
| Acceptability | **Is the option acceptable to key stakeholders?**  | ○ No ○ Probably no ● Uncertain ○ Probably yes ○ Yes ○ Varies  |  |
| Feasibility | **Is the option feasible to implement?**  | ○ No ○ Probably no ○ Uncertain ○ Probably yes ● Yes ○ Varies  |  |

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| **Recommendation** **Should an atypical antipsychotic vs. no such strategy be used in critically ill adults WITHOUT delirium?** |
| **Balance of consequences**  | Undesirable consequences *clearly outweigh* desirable consequences in most settings | Undesirable consequences *probably outweigh* desirable consequences in most settings | The balance between desirable and undesirable consequences *is closely balanced or uncertain* | Desirable consequences *probably outweigh* undesirable consequences in most settings | Desirable consequences *clearly outweigh* undesirable consequences in most settings |
|  | ○ | ○ | ● | ○ | ○ |

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| --- | --- | --- | --- | --- |
| **Type of recommendation**  | We recommend against offering this option | We suggest not offering this option | We suggest offering this option | We recommend offering this option |
|  | ○ | ● | ○ | ○ |
| **Recommendation**  | We do not suggest using atypical antipsychotics for prevention of delirium in critically ill patients. |
| **Justification**  | This recommendation reflects  the uncertainty of the data, given the single study of small size,  small number of outcome events (delirium), and the nonrepresentative nature of the relatively healthy elective cardiac surgery population of study.  While the study demonstrated a reduction of delirium as measured by the CAM-ICU screening tool in the intervention group, other meaningful clinical outcomes such as ICU and hospital length of stay  were not significantly different in the treatment group -  suggesting that this uncertain treatment benefit may not outweigh the risks of exposing patients to the risk of atypical antipsychotics.   |
| **Subgroup considerations**  | Patients who experience significant distress secondary to symptoms of an episode of delirium such as anxiety, fearfulness, hallucinations, or delusions or who may be physically threatening to self or others may benefit from the use of lowest effective doses of atypical antipsychotics for symptomatic relief. Atypical antipsychotics should be discontinued following the resolution of the patient's distress.  |
| **Research possibilities**  | Further research on subsyndromal patients randomized to atypical antipsychotics such as risperidone should be replicated with larger samples and should include not only post-surgical populations, but also critically ill patients with medical illnesses.   More research is needed on the benefit of atypical antipsychotics such as risperidone in treating distress due to delirium symptoms, longterm outcomes and system innovations to ensure that patients do not remain on antipsychotics indefinitely following symptomatic initiation during a delirium episode. |
| **Comments during electronic voting by entire panel** | What is an atypical antipsychotic (other than risperidone)? Important to define, with examples. |

**Author(s)**: Mark E. Nunnally, MD

**Question**: An alpha-2 agonist (e.g., dexmedetomidine) compared to no such strategy for patients WITHOUT delirium

**Setting**: Intensive care unit

**Bibliography**: Su X, Meng Z-T, Wu X-H, et al. Dexmedetomidine for prevention of delirium in elderly patients after non-cardiac surgery: a randomised, double-blind, placebo-controlled trial. Lancet, 2016; published online August 16, 2016. [(5)](https://paperpile.com/c/z7wvc0/zw2U)

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| **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)** | **no such strategy** | **Relative(95% CI)** | **Absolute(95% CI)** |
| Incidence of delirium (follow up: 7 days) |
| 1  | randomised trials  | not serious a | not serious  | serious b | not serious c | none  | 32/350 (9.1%)  | 79/350 (22.6%)  | **OR 0.35**(0.22 to 0.54)  | **133 fewer per 1,000**(from 90 fewer to 165 fewer)  | ⨁⨁⨁◯MODERATE  | IMPORTANT  |
| Length of stay in hospital |
| 1  | randomised trials  | not serious a | not serious  | serious b | serious d | none  | 350  | 350  | -  | HR **1.09 higher**(0.94 higher to 1.27 higher)  | ⨁⨁◯◯LOW  | IMPORTANT  |
| Mortality (follow up: 30 days) |
| 1  | randomised trials  | not serious a | not serious  | serious b | very serious e | none  | 1/350 (0.3%)  | 4/350 (1.1%)  | **OR 0.25**(0.03 to 2.23)  | **9 fewer per 1,000**(from 11 fewer to 14 more)  | ⨁◯◯◯VERY LOW  | CRITICAL  |
| Time to extubation (follow up: 7 days) |
| 1  | randomised trials  | not serious a | not serious  | serious b | serious f | none  | 350  | 350  | -  | HR **1.25 higher**(1.02 higher to 1.53 higher)  | ⨁⨁◯◯LOW  | IMPORTANT  |

**CI:** Confidence interval; **OR:** Odds ratio

**Explanations**

a. Consent process suggested delirium may have been present in patients pre-randomization.

b. Postoperative patients; not studied in first 24 hours.

c. 111 total events; uncertainty as to whether some delirium existed pre-randomization.

d. 95% CI embraces increased and decreased length of stay

e. 95% CI embraces significant benefit and harm. 4 total events.

f. HR values in 95% CI do not embrace clinically meaningful effect.

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| --- | --- | --- |
| Population:  | patients WITHOUT delirium  | Background:  |
| Intervention:  | an alpha-2 agonist (e.g., dexmedetomidine)  |  |
| Comparison:  | no such strategy  |  |
| Main outcomes:  | * Incidence of delirium
* Length of stay in hospital
* Mortality
* Time to extubation
 |  |
| Setting:  | Intensive care unit  |  |
|  | **Criteria**  | **Judgements**  | **Research evidence**  |
| Problem | **Is there a problem priority?**  | ○ No ○ Probably no ○ Uncertain ○ Probably yes ● Yes ○ Varies  | The evidence for this recommendation is based upon a single study [(5)](https://paperpile.com/c/z7wvc0/zw2U): This randomized controlled trial included 700 patients aged 65 years or older who underwent elective non-cardiac surgery under general anaesthesia and were admitted to the ICU after surgery before 2000 h in 2 tertiary care hospitals in Beijing, China. Exclusion criteria: preoperative history of schizophrenia, epilepsy, Parkinsonism, or myasthenia gravis; inability to communicate in the preoperative period (coma, profound dementia, or language barrier); brain injury or neurosurgery; known preoperative left ventricular ejection fraction less than 30%, sick sinus syndrome, severe sinus bradycardia (<50 beats per min [bpm]), or second- degree or greater atrioventricular block without pacemaker; serious hepatic dysfunction (Child-Pugh class C); serious renal dysfunction (undergoing dialysis before surgery); or low likelihood of survival for more than 24 h. Exposure included use of 0.1 micrograms/Kg of dexmedetomidine vs placebo from the time of admission to the ICU following surgery. Patients were followed for 7 days and evaluated for delirium with the CAM-ICU. |
| Benefits & harms of the options | **What is the overall certainty of this evidence?**  | ○ No included studies ○ Very low ○ Low ● Moderate ○ High  | **The relative importance or values of the main outcomes of interest:**

|  |  |  |
| --- | --- | --- |
| **Outcome** | **Relative importance**  | **Certainty of the evidence (GRADE)**  |
| Incidence of delirium | IMPORTANT | ⨁⨁⨁◯MODERATE |
| Length of stay in hospital | IMPORTANT | ⨁⨁⨁◯MODERATE |
| Mortality | CRITICAL | ⨁⨁◯◯LOW |
| Time to extubation | IMPORTANT | ⨁⨁⨁◯MODERATE |

The incidence of delirium in the 7 days following surgery was significantly reduced in the intervention group: I = 32 (9%) of 350 vs P = 79 (23%) of 350 with OR = 0.35 (95%CI: 0.22-0.54). Time to extubation was statistically significantly shorter with the Intervention: 4.6 hours (95% CI: 3.4 - 5.8) vs 6.9 hours (95% CI: 5.2 -8.6) for placebo as was ICU length of stay: 20.9 hours (95% CI: 20.4-21.4) vs 21.5 (95%CI: 20.7 -22.3).  There were no significant harms documented with the intervention compared to placebo. The reason for answering "uncertain" to the question about the desirable anticipated effects is because there is little evidence for significant meaningful clinical benefits in outcome. For example we are uncertain that the length of stay change of 0.6 hours, and decrease in mechanical ventilation by 2.3 hours are clinically meaningful benefits.  Mortality and significant side effects were rare in both groups, making it difficult to understand the true risk of the intervention in this population.  |
| **Is there important uncertainty about how much people value the main outcomes?**  | ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability ○ No known undesirable outcomes  |
| **Are the desirable anticipated effects large?**  | ○ No ○ Probably no ● Uncertain ○ Probably yes ○ Yes ○ Varies  |
| **Are the undesirable anticipated effects small?**  | ○ No ○ Probably no ● Uncertain ○ Probably yes ○ Yes ○ Varies  |
| **Are the desirable effects large relative to undesirable effects?**  | ○ No ○ Probably no ● Uncertain ○ Probably yes ○ Yes ○ Varies  |
| Resource use | **Are the resources required small?**  | ○ No ● Probably no ○ Uncertain ○ Probably yes ○ Yes ○ Varies  | Expense of dexmedatomidine is considerable. |
| **Is the incremental cost small relative to the net benefits?**  | ○ No ○ Probably no ● Uncertain ○ Probably yes ○ Yes ○ Varies  |   |
| Acceptability | **Is the option acceptable to key stakeholders?**  | ○ No ○ Probably no ○ Uncertain ● Probably yes ○ Yes ○ Varies  |  |
| Feasibility | **Is the option feasible to implement?**  | ○ No ○ Probably no ○ Uncertain ● Probably yes ○ Yes ○ Varies  |  |

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| **Recommendation** **Should an alpha-2 agonist (e.g., dexmedetomidine) vs. no such strategy be used for patients WITHOUT delirium?** |
| **Balance of consequences**  | Undesirable consequences *clearly outweigh* desirable consequences in most settings | Undesirable consequences *probably outweigh* desirable consequences in most settings | The balance between desirable and undesirable consequences *is closely balanced or uncertain* | Desirable consequences *probably outweigh* undesirable consequences in most settings | Desirable consequences *clearly outweigh* undesirable consequences in most settings |
|  | ○ | ○ | ● | ○ | ○ |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Type of recommendation**  | We recommend against offering this option | We suggest not offering this option | We suggest offering this option | We recommend offering this option |
|  | ○ | ● | ○ | ○ |
| **Recommendation**  | We make NO RECOMMENDATION for dexmedetomidine in patients without delirium. but it may be helpful in a postoperative population. |
| **Justification**  | Based upon this evidence, routine use of dexmedetomidine in the postoperative recovery period did not result in significantly meaningful clinical improvements in outcome. Given that the risks associated with this intervention are uncertain we do not believe that patients should be exposed to these risks based upon this evidence.  |
| **Subgroup considerations**  | Dexmedetomidine may be helpful in noncardiac surgery postoperative patients.  We suggest dexmedetomidine in this population. |
| **Research possibilities**  | The findings from this single study requires replication, with the inclusion of clinical meaningful outcomes following discharge such as cognitive and physical function or quality of life scales measuring patient or family distress.  |
| **Voting comments** | May be reasonable to state it’s better than other sedatives IF an infusion is necessary for other reasons |

**Author(s)**: Mark E. Nunnally

**Question**: Stains compared to control for delirium prevention

**Setting**: Intensive care unit

**Bibliography**: Vallabhajosyula S, Kanmanthareddy A, Erwin PJ, Esterbrooks DJ, Morrow LE. Role of statins in delirium prevention in critical ill and cardiac surgery patients: A systematic review and meta-analysis [(6)](https://paperpile.com/c/z7wvc0/b5DH)

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| **Quality assessment** | **№ of patients** | **Effect** | **Quality** | **Importance** |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **stains** | **control** | **Relative(95% CI)** | **Absolute(95% CI)** |
| Delirium incidence |
| 6  | observational studies  | not serious  | serious a | not serious  | serious b | none  | 710/22292 (3.2%)  | 3478/267481 (1.3%)  | **RR 1.05**(0.89 to 1.25)  | **1 more per 1,000**(from 1 fewer to 3 more)  | ⨁◯◯◯VERY LOW  | IMPORTANT  |

**CI:** Confidence interval; **RR:** Risk ratio

**Explanations**

a. I-squared 73%. Visual inspection of forest plot reveals heterogeneity.

b. 95% CI embraces harm and benefit.

|  |  |
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| **Question** |  |
| Should stains vs. control be used for delirium prevention?  |
| Population:  | delirium prevention  | Background:  |  |
| Intervention:  | statins  |  |
| Comparison:  | control  |  |
| Main outcomes:  | * Delirium incidence
 |  |
| Setting:  | Intensive care unit  |  |
| **Assessment** |
|  | **Criteria**  | **Judgements**  | **Research evidence**  | **Additional considerations**  |
| Problem | **Is there a problem priority?**  | ○ No ○ Probably no ○ Uncertain ○ Probably yes ○ Yes ○ Varies  | There are no randomized controlled trials upon which to base this recommendation.  The only evidence at this time includes observational studies of critically ill patients taking statins.   |  |
| Benefits & harms of the options | **What is the overall certainty of this evidence?**  | ○ No included studies X Very low ○ Low ○ Moderate ○ High  | **The relative importance or values of the main outcomes of interest:**

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| **Outcome** | **Relative importance**  | **Certainty of the evidence (GRADE)**  |
| Delirium incidence | IMPORTANT | ⨁◯◯◯VERY LOW |

A systematic review and meta analysis of observational studies reports that exposure to statins was not associated with decreased delirium incidence (Vallabhajosyula et al.) [(6)](https://paperpile.com/c/z7wvc0/b5DH)From Abstract: *"Results: Of a total 57 identiﬁed studies, 6 were included. The studies showed high heterogeneity (I2 = 73%) for all and moderate for cardiac surgery studies (I2 = 55%). Of 289,773 patients, statins were used in 22,292 (7.7%). Cardiac surgery was performed in 4,382 (1.5%) patients and 2,321 (53.0%) used statins. Delirium was noted in 710 (3.2%) and 3,478 (1.3%) of the patients in the statin and nonstatin groups, respectively, with no difference between groups in the total cohort (RR, 1.05 [95% CI, 0.85-1.29]; P = .56) or in cardiac surgery patients (RR, 1.03 [95% CI, 0.68-1.56]; P = .89)."* |  |
| **Is there important uncertainty about how much people value the main outcomes?**  | ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability ○ No known undesirable outcomes  |
| **Are the desirable anticipated effects large?**  | ○ No ● Probably no ○ Uncertain ○ Probably yes ○ Yes ○ Varies  |
| **Are the undesirable anticipated effects small?**  | ○ No ○ Probably no ● Uncertain ○ Probably yes ○ Yes ○ Varies  |
| **Are the desirable effects large relative to undesirable effects?**  | ○ No ○ Probably no ● Uncertain ○ Probably yes ○ Yes ○ Varies  |
| Resource use | **Are the resources required small?**  | ○ No ○ Probably no ○ Uncertain ● Probably yes ○ Yes ○ Varies  |  |  |
| **Is the incremental cost small relative to the net benefits?**  | ○ No ○ Probably no ● Uncertain ○ Probably yes ○ Yes ○ Varies  |  |  |
| Acceptability | **Is the option acceptable to key stakeholders?**  | ○ No ○ Probably no ○ Uncertain ● Probably yes ○ Yes ○ Varies  |  |  |
| Feasibility | **Is the option feasible to implement?**  | ○ No ○ Probably no ○ Uncertain ● Probably yes ○ Yes ○ Varies  |  |  |

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| **Recommendation** **Should statins vs. control be used for delirium prevention?** |
| **Balance of consequences**  | Undesirable consequences *clearly outweigh* desirable consequences in most settings | Undesirable consequences *probably outweigh* desirable consequences in most settings | The balance between desirable and undesirable consequences *is closely balanced or uncertain* | Desirable consequences *probably outweigh* undesirable consequences in most settings | Desirable consequences *clearly outweigh* undesirable consequences in most settings |
|  | ○ | ○ | ● | ○ | ○ |

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| **Type of recommendation**  | We recommend against offering this option | We suggest not offering this option | We suggest offering this option | We recommend offering this option |
|  | ○ | ● | ○ | ○ |
| **Recommendation**  |

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| We do not suggest using a statin to prevent delirium in critically ill adults.   (Conditional recommendation, Very low quality of evidence) |

 |
| **Comments during electronic voting by entire panel** | Wording should be stronger; no benefit/ lots of potential harm... vs. haloperidol (ubiquitous use) 'GRADE' should guide but not dictate. Would favour 'We suggest not using statins....' |

**Author(s)**: Mark E. Nunnally

**Question**: Haloperidol compared to no such strategy in critically ill adults WITH subsyndromal delirium

**Setting**: Intensive care units

**Bibliography**: Al-Quadheeb 2016 [(2)](https://paperpile.com/c/z7wvc0/syze)

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| **Quality assessment** | **№ of patients** | **Effect** | **Quality** | **Importance** |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **haloperidol** | **no such strategy** | **Relative(95% CI)** | **Absolute(95% CI)** |
| discharge to a nursing home |
|  |  |  |  |  |  |  |  |  | not estimable  |  | -  |  |
| cognitive impairment |
|  |  |  |  |  |  |  |  |  | not estimable  |  | -  |  |
| PTSD incidence |
|  |  |  |  |  |  |  |  |  | not estimable  |  | -  |  |
| incidence of depression |
|  |  |  |  |  |  |  |  |  | not estimable  |  | -  |  |
| functionality |
|  |  |  |  |  |  |  |  |  | not estimable  |  | -  |  |
| distress |
|  |  |  |  |  |  |  |  |  | not estimable  |  | -  |  |
| Mortality (at any time point) |
| 1  | randomised trials  | not serious  | not serious  | not serious  | very serious a | none  | 9/34 (26.5%)  | 7/34 (20.6%)  | **RR 1.29**(0.54 to 3.06)  | **60 more per 1,000**(from 95 fewer to 424 more)  | ⨁⨁◯◯LOW  | CRITICAL  |
| Delirium duration  |
| 1  | randomised trials  | not serious  | not serious  | not serious  | serious b | none  | 34  | 34  | -  | MD **0 days** (0.56 lower to 0.56 higher)  | ⨁⨁⨁◯MODERATE  | IMPORTANT  |
| delirium severity |
|  |  |  |  |  |  |  |  |  | not estimable  |  | -  |  |
| Duration of mechanical ventilation (assessed with: days) |
| 1  | randomised trials  | not serious  | not serious  | not serious  | serious b | none  | 34  | 34  | -  | MD **0.5 days fewer**(2.09 fewer to 1.09 more)  | ⨁⨁⨁◯MODERATE  | IMPORTANT  |
| ICU readmission rate |
|  |  |  |  |  |  |  |  |  | not estimable  |  | -  |  |
| intensity of treatment |
|  |  |  |  |  |  |  |  |  | not estimable  |  | -  |  |
| costs |
|  |  |  |  |  |  |  |  |  | not estimable  |  | -  |  |
| Delirium incidence |
| 1  | randomised trials  | not serious  | not serious  | not serious  | serious c | none  | 12/34 (35.3%)  | 8/34 (23.5%)  | **RR 1.5**(0.7 to 3.2)  | **118 more per 1,000**(from 71 fewer to 518 more)  | ⨁⨁⨁◯MODERATE  | IMPORTANT  |
| ICU length of stay (assessed with: days) |
| 1  | randomised trials  | not serious  | not serious  | not serious  | serious b | none  | 34  | 34  | -  | MD **0.5 days fewer**(2.09 fewer to 1.09 more)  | ⨁⨁⨁◯MODERATE  | IMPORTANT  |

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

**Explanations**

a. 16 total events. 95% CI embraces large effect for harm and benefit.

b. 95% CI embraces longer and shorter duration.

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| **Question** |  |
| Should haloperidol vs. no such strategy be used in critically ill adults WITH subsyndromal delirium?  |
| Population:  | critically ill adults WITH subsyndromal delirium  | Background:  |  |
| Intervention:  | haloperidol  |  |
| Comparison:  | no such strategy  |  |
| Main outcomes:  | * Mortality (at any time point)
* Delirium duration
* Duration of mechanical ventilation
* Delirium incidence
* ICU length of stay
 |  |
| Setting:  | Intensive care units  |  |
| **Assessment** |
|  | **Criteria**  | **Judgements**  | **Research evidence**  | **Additional considerations**  |
| Problem | **Is there a problem priority?**  | ○ No ○ Probably no ○ Uncertain ○ Probably yes ● Yes ○ Varies  | The evidence used to answer this question comes from  1 RCT: Al-Quadheeb 2016 [(2)](https://paperpile.com/c/z7wvc0/syze). This evidence revealed no statistically significant effect of haloperidol compared to placebo treatment with regard to incidence, duration, days of mechanical ventilation, ICU length of stay,  or delirium duration.   | Although no open label haloperidol was used in this study, the numbers of participants was small and included 34 in both the haloperidol and placebo arms.  |
| Benefits & harms of the options | **What is the overall certainty of this evidence?**  | ○ No included studies ○ Very low ● Low ○ Moderate ○ High  | **The relative importance or values of the main outcomes of interest:**

|  |  |  |
| --- | --- | --- |
| **Outcome** | **Relative importance**  | **Certainty of the evidence (GRADE)**  |
| Mortality (at any time point) | CRITICAL | ⨁⨁◯◯LOW |
| Delirium duration  | IMPORTANT | ⨁⨁⨁◯MODERATE |
| Duration of mechanical ventilation | IMPORTANT | ⨁⨁⨁◯MODERATE |
| Delirium incidence | IMPORTANT | ⨁⨁⨁◯MODERATE |
| ICU length of stay | IMPORTANT | ⨁⨁⨁◯MODERATE |

The benefits were assessed as being "probably no important uncertainty or variability" because reducing the incidence of full syndrome delirium is an important outcome for patients, families of patients and care providers.  The desirable anticipated effects were assessed as being "probably no" because of the consistency in estimates for all of the outcomes between the Al-Qadheeb study [(2)](https://paperpile.com/c/z7wvc0/syze) and the results of the 3 RCTs used to answer question 18. The undesirable anticipated effects of haloperidol were rated as "uncertain" given the small sample size and that much larger numbers are required to demonstrate the absence of harm.  As highlighted in question 18, patients who are started on an antipsychotic for delirium in the ICU often remain on these medications after discharge from the ICU and even after hospital discharge [(7)](https://paperpile.com/c/z7wvc0/HLWW).  These are additional harms that are not addressed by this current literature.   | The overall certainty of evidence  was rated as low due to the small number of participants and the single study underlying the evidence.  |
| **Is there important uncertainty about how much people value the main outcomes?**  | ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability ○ No known undesirable outcomes  |
| **Are the desirable anticipated effects large?**  | ○ No ● Probably no ○ Uncertain ○ Probably yes ○ Yes ○ Varies  |
| **Are the undesirable anticipated effects small?**  | ○ No ○ Probably no ● Uncertain ○ Probably yes ○ Yes ○ Varies  |
| **Are the desirable effects large relative to undesirable effects?**  | ○ No ● Probably no  |
| Resource use | **Are the resources required small?**  | ○ No ○ Probably no ○ Uncertain ● Probably yes  | Haloperidol is a relatively inexpensive medication.  |  |
| **Is the incremental cost small relative to the net benefits?**  | ○ No ○ Probably no ● Uncertain  |  |  |
| Acceptability | **Is the option acceptable to key stakeholders?**  | ○ No ○ Probably no ● Uncertain  | If haloperidol has effects such as decreasing distress during a delirium (an outcome that could not be evaluated using this existing evidence) key stakeholders, including patients and  family members would likely opt to use such a medication.   |  |
| Feasibility | **Is the option feasible to implement?**  | ● Yes  |  |  |

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| **Recommendation** **Should haloperidol vs. no such strategy be used in critically ill adults WITH subsyndromal delirium?** |
| **Balance of consequences**  | Undesirable consequences *clearly outweigh* desirable consequences in most settings | Undesirable consequences *probably outweigh* desirable consequences in most settings | The balance between desirable and undesirable consequences *is closely balanced or uncertain* | Desirable consequences *probably outweigh* undesirable consequences in most settings | Desirable consequences *clearly outweigh* undesirable consequences in most settings |
|  | ○ | ● | ○ | ○ | ○ |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Type of recommendation**  | We recommend against offering this option | We suggest not offering this option | We suggest offering this option | We recommend offering this option |
|  | ○ | ● | ○ | ○ |
| **Recommendation**  | We do not suggest using haloperidol for sub-syndromal delirium in critically ill patients as there is little evidence that it decreases incidence of full syndrome delirium,  ICU length of stay, days of mechanical ventilation, delirium duration, or mortality.  |
| **Justification**  | We are moderately certain that haloperidol use is not associated with decreased duration of delirium or ICU length of stay. We have low certainty about the effect of haloperidol on mortality. Given the lack of clear benefit patients should not be routinely exposed to potential harms associated with this medication.    |
| **Subgroup considerations**  | Patients who experience significant distress secondary to symptoms of a delirium such as anxiety, fearfulness, hallucinations, or delusions or who may be physically threatening to self or others may benefit from the use of lowest effective doses of haloperidol for symptomatic relief. Haloperidol should be discontinued following the resolution of the patient's distress.   |
| **Research possibilities**  | More research is needed on the benefit of haloperidol in treating distress due to delirium symptoms and system innovations to ensure that patients do not remain on antipsychotics indefinitely following symptomatic initiation during a delirium episode. |
| **Comments during electronic voting by entire panel** | Can we say haloperidol should never be used in sub-syndromal delirium? What if pt. is subsyndromal & agitated, belligerent, etc. without enteral access? |

**Author(s)**: Mark E. Nunnally

**Question**: An atypical antipsychotic compared to no such strategy in critically ill adults WITH subsyndromal delirium

**Setting**: intensive Care Units

**Bibliography**: Hakim 2012 [(8)](https://paperpile.com/c/z7wvc0/0Ayf)

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| --- | --- | --- | --- | --- |
| **Quality assessment** | **№ of patients** | **Effect** | **Quality** | **Importance** |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **an atypical antipsychotic**  | **no such strategy** | **Relative(95% CI)** | **Absolute(95% CI)** |
| discharge to a nursing home |
|  |  |  |  |  |  |  |  |  | not estimable  |  | -  |  |
| cognitive impairment |
|  |  |  |  |  |  |  |  |  | not estimable  |  | -  |  |
| PTSD incidence |
|  |  |  |  |  |  |  |  |  | not estimable  |  | -  |  |
| incidence of depression |
|  |  |  |  |  |  |  |  |  | not estimable  |  | -  |  |
| functionality |
|  |  |  |  |  |  |  |  |  | not estimable  |  | -  |  |
| distress |
|  |  |  |  |  |  |  |  |  | not estimable  |  | -  |  |
| Mortality (at any time point) |
| 1  | randomised trials  | not serious  | not serious  | serious a | very serious b | none  | 2/51 (3.9%)  | 1/50 (2.0%)  | **RR 1.96**(0.18 to 20.94)  | **19 more per 1,000**(from 16 fewer to 399 more)  | ⨁◯◯◯VERY LOW  | CRITICAL  |
| Delirium duration  |
| 1  | randomised trials  | not serious  | not serious  | serious a | very serious c | none  | 7  | 17  | -  | MD **0 days** (1.15 lower to 1.15 higher)  | ⨁◯◯◯VERY LOW  | IMPORTANT  |
| delirium severity |
|  |  |  |  |  |  |  |  |  | not estimable  |  | -  |  |
| duration of mechanical ventilation |
|  |  |  |  |  |  |  |  |  | not estimable  |  | -  |  |
| ICU readmission rate |
|  |  |  |  |  |  |  |  |  | not estimable  |  | -  |  |
| intensity of treatment |
|  |  |  |  |  |  |  |  |  | not estimable  |  | -  |  |
| costs |
|  |  |  |  |  |  |  |  |  | not estimable  |  | -  |  |
| Delirium incidence |
| 1  | randomised trials  | not serious  | not serious  | serious a | serious d | none  | 8/51 (15.7%)  | 19/50 (38.0%)  | **RR 0.41**(0.20 to 0.86)  | **224 fewer per 1,000**(from 53 fewer to 304 fewer)  | ⨁⨁◯◯LOW  | IMPORTANT  |
| ICU length of stay (assessed with: days) |
| 1  | randomised trials  | not serious  | not serious  | serious a | not serious e | none  | 51  | 50  | -  | MD **1 day fewer**(1.29 fewer to 0.71 fewer)  | ⨁⨁⨁◯MODERATE  | IMPORTANT  |

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

**Explanations**

a. Patients selected in PACU after cardiac surgery.

b. 3 total events.

c. 95% CI embraces lengthening and shortening of delirium duration.

d. 27 total events.

e. 101 participants. 95% CI goes to less than 1 day difference. Not downgraded.

|  |  |
| --- | --- |
| **Question** |  |
| Should an atypical antipsychotic vs. no such strategy be used in critically ill adults WITH subsyndromal delirium?  |
| Population:  | critically ill adults WITH subsyndromal delirium  | Background:  |  |
| Intervention:  | an atypical antipsychotic  |  |
| Comparison:  | no such strategy  |  |
| Main outcomes:  | * Mortality (at any time point)
* Delirium duration
* Delirium incidence
* ICU length of stay
 |  |
| Setting:  | intensive Care Units  |  |
| Perspective:  |  |  |
| **Assessment** |
|  | **Criteria**  | **Judgements**  | **Research evidence**  | **Additional considerations**  |
| Problem | **Is there a problem priority?**  | ○ No ○ Probably no ○ Uncertain ○ Probably yes ● Yes  | The evidence for this question comes from one RCT: Hakim 2012 [(8)](https://paperpile.com/c/z7wvc0/0Ayf), which included 101 patients with subsyndromal delirium (ICDSC <4) following surgery who were randomized to receive risperidone 0.5 mg every 12 hours (n=51), or placebo (D5W IV) after on-pump cardiac surgery.    |  |
| Benefits & harms of the options | **What is the overall certainty of this evidence?**  | ○ No included studies ○ Very low ● Low  | **The relative importance or values of the main outcomes of interest:**

|  |  |  |
| --- | --- | --- |
| **Outcome** | **Relative importance**  | **Certainty of the evidence (GRADE)**  |
| Mortality (at any time point) | CRITICAL | ⨁⨁◯◯LOW |
| Delirium duration  | IMPORTANT | ⨁⨁◯◯LOW |
| Delirium incidence | IMPORTANT | ⨁⨁⨁◯MODERATE |
| ICU length of stay | IMPORTANT | ⨁⨁⨁⨁HIGH |

The overall certainty of the evidence for this question was rated as low due to there being only one study upon which the evidence was based. However use of this one study suggests moderate certainty regarding delirium incidence with evidence favoring the intervention group  and risk ratio of 0.41 (0.02, 0.86 95 % CI). Length of stay in the ICU has high certainty and favors neither intervention or control (mean difference -1.00; 95% CI -1.29, -0.71)Additionally, patients who are started on an antipsychotic for delirium in the ICU often remain on these medications after discharge from the ICU and even after hospital discharge [(7)](https://paperpile.com/c/z7wvc0/HLWW). These are additional harms that cannot be addressed by this current literature.    |  |
| **Is there important uncertainty about how much people value the main outcomes?**  | ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability  |
| **Are the desirable anticipated effects large?**  | ○ No ○ Probably no ● Uncertain  |
| **Are the undesirable anticipated effects small?**  | ○ No ○ Probably no ● Uncertain  |
| **Are the desirable effects large relative to undesirable effects?**  | ○ No ○ Probably no ● Uncertain  |
| Resource use | **Are the resources required small?**  | ○ No ○ Probably no ○ Uncertain ● Probably yes  | Expense of risperidone is intermediate.   |  |
| **Is the incremental cost small relative to the net benefits?**  | ○ No ○ Probably no ● Uncertain  |  |  |
| Acceptability | **Is the option acceptable to key stakeholders?**  | ○ No ○ Probably no ● Uncertain  |  |  |
| Feasibility | **Is the option feasible to implement?**  | ○ No ○ Probably no ○ Uncertain ○ Probably yes ● Yes  |  |  |

|  |
| --- |
| **Recommendation** **Should an atypical antipsychotic vs. no such strategy be used in critically ill adults WITH subsyndromal delirium?** |
| **Balance of consequences**  | Undesirable consequences *clearly outweigh* desirable consequences in most settings | Undesirable consequences *probably outweigh* desirable consequences in most settings | The balance between desirable and undesirable consequences *is closely balanced or uncertain* | Desirable consequences *probably outweigh* undesirable consequences in most settings | Desirable consequences *clearly outweigh* undesirable consequences in most settings |
|  | ○ | ○ | ● | ○ | ○ |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Type of recommendation**  | We recommend against offering this option | We suggest not offering this option | We suggest offering this option | We recommend offering this option |
|  | ○ | ● | ○ | ○ |
| **Recommendation**  | We make no recommendation about the use of atypical antipsychotics for subsyndromal delirium, but suggest their use (riseridone only?)  for patients recovering from cardiac surgery with cardiopulmonary bypass, based on low certainty evidence from one study (2C). |
| **Justification**  | The recommendation is based upon the overall certainty of the evidence for this question - rated as low due to there being only one study upon which the evidence was based (actually low for the reasons on the Evidence Profile: imprecision). However use of this one study suggests moderate certainty regarding delirium incidence with evidence favoring the intervention group and risk ratio of 0.41 (0.02, 0.86 95 % CI). Length of stay in the ICU has high certainty and favors neither intervention nor control (mean difference -1.00; 95% CI -1.29, -0.71). Even if this intervention does decrease the incidence of delirium in select patients (i.e. subsyndromal postoperative patients) this evidence does not demonstrate other change in outcomes related to delirium such as delirium duration, ICU length of stay or mortality. Given the lack of demonstrated benefit patients should not routinely be exposed to potential harms associated with these medications.     as there is not enough evidence that it decreases the incidence (there is, albeit of moderate certainty/fragile evidence), duration, days of mechanical ventilation or ICU length of stay.   |
| **Subgroup considerations**  | Patients who experience significant distress secondary to symptoms of an episode of delirium such as anxiety, fearfulness, hallucinations, or delusions or who may be physically threatening to self or others may benefit from the use of lowest effective doses of atypical antipsychotics for symptomatic relief. Atypical antipsychotics should be discontinued following the resolution of the patient's distress.   We suggest using risperidone for patients recovering from cardiac surgery with cardiopulmonary bypass, based on low certainty evidence from one study (2C). |
| **Research possibilities**  | Further research on subsyndromal patients randomized to atypical antipsychotics such as risperidone should be replicated with larger samples and should include not only post surgical populations, but also critically ill patients with medical illnesses.   More research is needed on the benefit of atypical antipsychotics such as risperidone in treating distress due to delirium symptoms, longterm outcomes  and system innovations to ensure that patients do not remain on antipsychotics indefinitely following symptomatic initiation during a delirium episode. |
| **Comments during electronic voting by entire panel** | Should specify when screened with ICDSC; the recommendation suggests it’s never appropriate to give these drugs; would explaining when it’s appropriate be useful? |

**Author(s)**: Mark E. Nunnally

**Question**: Haloperidol compared to no such strategy in critically ill adults WITH delirium

**Setting**: Intensive care units

**Bibliography**: Atalan 2013, Girard 2010, Page 2013 [(3, 9, 10)](https://paperpile.com/c/z7wvc0/aYCW%2BHojb%2Borje)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Quality assessment** | **№ of patients** | **Effect** | **Quality** | **Importance** |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **haloperidol** | **no such strategy** | **Relative(95% CI)** | **Absolute(95% CI)** |
| discharge to a nursing home |
|  |  |  |  |  |  |  |  |  | not estimable  |  | -  |  |
| cognitive impairment |
|  |  |  |  |  |  |  |  |  | not estimable  |  | -  |  |
| PTSD incidence |
|  |  |  |  |  |  |  |  |  | not estimable  |  | -  |  |
| incidence of depression |
|  |  |  |  |  |  |  |  |  | not estimable  |  | -  |  |
| functionality |
|  |  |  |  |  |  |  |  |  | not estimable  |  | -  |  |
| distress |
|  |  |  |  |  |  |  |  |  | not estimable  |  | -  |  |
| Mortality (at any time point) |
| 3  | randomised trials  | not serious a | not serious  | serious b | serious c | none  | 26/132 (19.7%)  | 26/133 (19.5%)  | **RR 1.00**(0.62 to 1.61)  | **0 fewer per 1,000**(from 74 fewer to 119 more)  | ⨁⨁◯◯LOW  | CRITICAL  |
| Delirium duration (assessed with: days) |
| 3  | randomised trials  | not serious a | not serious  | serious b | serious d | none  | 132  | 133  | -  | MD **0.29 days more**(1.49 fewer to 2.07 more)  | ⨁⨁◯◯LOW  | IMPORTANT  |
| delirium severity |
|  |  |  |  |  |  |  |  |  | not estimable  |  | -  |  |
| Duration of mechanical ventilation (assessed with: days) |
| 2  | randomised trials  | serious e | serious f | serious b | serious d | none  | 61  | 63  | -  | MD **1.12 days fewer**(4.85 fewer to 2.61 more)  | ⨁◯◯◯VERY LOW  | IMPORTANT  |
| ICU readmission rate |
|  |  |  |  |  |  |  |  |  | not estimable  |  | -  |  |
| intensity of treatment |
|  |  |  |  |  |  |  |  |  | not estimable  |  | -  |  |
| costs |
|  |  |  |  |  |  |  |  |  | not estimable  |  | -  |  |
| ICU length of stay (assessed with: days) |
| 3  | randomised trials  | not serious a | serious g | serious b | serious d | none  | 132  | 133  | -  | MD **1.4 days more**(0.67 fewer to 3.48 more)  | ⨁◯◯◯VERY LOW  | IMPORTANT  |

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

**Explanations**

a. 1 of three studies, contributing 53/265 patients, judged to be at high risk. Not downGRADEd.

b. 1 Study used morphine as control. Studies included patients with subsyndromal and no delirium.

c. 95% CI embraces benefit and harm.

d. 95% CI embraces longer and shorter duration.

e. 1 of 2 studies, contributing 53/124 patients, judged to be at high risk of bias.

f. I-squared 44%. Visual inspection of Forest plot suggests heterogeneity.

g. I-squared 60%. Visual inspection of Forest plot suggests heterogeneity.

|  |  |
| --- | --- |
| **Question** |  |
| Should haloperidol vs. no such strategy be used in critically ill adults WITH delirium?  |
| Population:  | critically ill adults WITH delirium  | Background:  |  |
| Intervention:  | haloperidol  |  |
| Comparison:  | no such strategy  |  |
| Main outcomes:  | * Mortality (at any time point)
* Delirium duration
* Duration of mechanical ventilation
* ICU length of stay
 |  |
| Setting:  | Intensive care units  |  |
| Perspective:  |  |  |
| **Assessment** |
|  | **Criteria**  | **Judgements**  | **Research evidence**  | **Additional considerations**  |
| Problem | **Is there a problem priority?**  | ○ No ○ Probably no ○ Uncertain ○ Probably yes ● Yes ○ Varies  | The evidence used to answer this question comes from  3 RCT's: 1) Page 2013 [(9)](https://paperpile.com/c/z7wvc0/Hojb); 2) Girard 2010 [(3)](https://paperpile.com/c/z7wvc0/aYCW) (haloperidol arm); 3) Atalan 2013 [(10)](https://paperpile.com/c/z7wvc0/orje). This evidence revealed no statistically significant effect of haloperidol compared to placebo/comparison treatment with regard to ICU length of stay, days of mechanical ventilation, delirium duration, or mortality.  It is important to note that the patients in both of these studies included those with prevalent delirium, as well as subsyndromal  and no delirium at entry into the trial. These estimates are not as specific to the populations as the questions specify. Implications are that the estimates are biased to the null hypothesis.  | These are small studies (total patients in meta-analysis include 132, and 133 patients in haloperidol and comparator arms respectively.  These trials also  include haloperidol open label rescue administration and so it is possible that larger trials without rescue medication might demonstrate a difference employing such a strategy.  |
| Benefits & harms of the options | **What is the overall certainty of this evidence?**  | ○ No included studies ○ Very low ● Low ○ Moderate ○ High  | **The relative importance or values of the main outcomes of interest:**

|  |  |  |
| --- | --- | --- |
| **Outcome** | **Relative importance**  | **Certainty of the evidence (GRADE)**  |
| Mortality (at any time point) | CRITICAL | ⨁⨁⨁◯MODERATE |
| Delirium duration  | IMPORTANT | ⨁⨁⨁◯MODERATE |
| Duration of mechanical ventilation | IMPORTANT | ⨁◯◯◯VERY LOW |
| ICU length of stay | IMPORTANT | ⨁⨁◯◯LOW |

The benefits were assessed as being "probably no" because of the consistency in estimates in all three studies, despite the small size of the trials and heterogeneity of design and use of open label haloperidol.  The undesirable effects of haloperidol were rated as "uncertain" given the small sample size and that much larger numbers are required to demonstrate the absence of harm.  Additionally, patients who are started on an antipsychotic for delirium in the ICU often remain on these medications after discharge from the ICU and even after hospital discharge [(7)](https://paperpile.com/c/z7wvc0/HLWW).  These are additional harms that cannot be addressed by this current literature.   |  |
| **Is there important uncertainty about how much people value the main outcomes?**  | ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability ○ No known undesirable outcomes  |
| **Are the desirable anticipated effects large?**  | ○ No ● Probably no ○ Uncertain ○ Probably yes ○ Yes ○ Varies  |
| **Are the undesirable anticipated effects small?**  | ○ No ○ Probably no ● Uncertain ○ Probably yes ○ Yes ○ Varies  |
| **Are the desirable effects large relative to undesirable effects?**  | ○ No ● Probably no ○ Uncertain ○ Probably yes ○ Yes ○ Varies  |
| Resource use | **Are the resources required small?**  | ○ No ○ Probably no ○ Uncertain ● Probably yes ○ Yes ○ Varies  | Haloperidol is an inexpensive antipsychotic medication.  |  |
| **Is the incremental cost small relative to the net benefits?**  | ○ No ○ Probably no ● Uncertain ○ Probably yes ○ Yes ○ Varies  | The relative net benefits are uncertain based upon this evidence.  |  |
| Acceptability | **Is the option acceptable to key stakeholders?**  | ○ No ○ Probably no ● Uncertain ○ Probably yes ○ Yes ○ Varies  | If haloperidol has effects such as decreasing distress during a delirium (an outcome that could not be evaluated using this existing evidence) key stakeholders, including patients and  family members would likely opt to use such a medication.   |  |
| Feasibility | **Is the option feasible to implement?**  | ○ No ○ Probably no ○ Uncertain ○ Probably yes ● Yes ○ Varies  |  |  |

|  |
| --- |
| **Recommendation** **Should haloperidol vs. no such strategy be used in critically ill adults WITH delirium?** |
| **Balance of consequences**  | Undesirable consequences *clearly outweigh* desirable consequences in most settings | Undesirable consequences *probably outweigh* desirable consequences in most settings | The balance between desirable and undesirable consequences *is closely balanced or uncertain* | Desirable consequences *probably outweigh* undesirable consequences in most settings | Desirable consequences *clearly outweigh* undesirable consequences in most settings |
|  | ○ | ○ | ● | ○ | ○ |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Type of recommendation**  | We recommend against offering this option | We suggest not offering this option | We suggest offering this option | We recommend offering this option |
|  | ○ | ● | ○ | ○ |
| **Recommendation**  | We do not suggest using haloperidol for delirium in critically ill patients as there is little evidence that it decreases ICU length of stay, days of mechanical ventilation, delirium duration, or mortality.  |
| **Justification**  | We are moderately certain that haloperidol use is not associated with decreased duration of delirium or ICU length of stay. We have low certainty about the effect of haloperidol on duration of ventilation or mortality. Given the lack of clear benefit patients should not be routinely exposed to potential harms associated with this medication.    |
| **Subgroup considerations**  | Patients who experience significant distress secondary to symptoms of a delirium such as anxiety, fearfulness, hallucinations, or delusions or who may be physically threatening to self or others may benefit from the use of lowest effective doses of haloperidol for symptomatic relief. Haloperidol should be discontinued following the resolution of the patient's distress.    |
| **Research possibilities**  | More research is needed on the benefit of haloperidol in treating distress due to delirium symptoms and system innovations to ensure that patients do not remain on antipsychotics indefinitely following symptomatic initiation during a delirium episode. |
| **Comments during electronic voting by entire panel** | The group evaluated the evidence & considered it; yet I can't see haloperidol not being used in this situation.Prefer "no recommendation" for this as opposed to suggest against.The question implies it is never indicated. Could it be worded like Q11 where it’s acknowledged it may sometimes be necessary? |

**Author(s)**: Mark E. Nunnally

**Question**: An atypical antipsychotic compared to no such strategy in critically ill adults WITH delirium

**Setting**: Intensive care units

**Bibliography**: Devlin 2010, Girard 2010 [(3, 11)](https://paperpile.com/c/z7wvc0/S7NP%2BaYCW)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Quality assessment** | **№ of patients** | **Effect** | **Quality** | **Importance** |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **an atypical antipsychotic**  | **no such strategy** | **Relative(95% CI)** | **Absolute(95% CI)** |
| discharge to a nursing home |
|  |  |  |  |  |  |  |  |  | not estimable  |  | -  |  |
| cognitive impairment |
|  |  |  |  |  |  |  |  |  | not estimable  |  | -  |  |
| PTSD incidence |
|  |  |  |  |  |  |  |  |  | not estimable  |  | -  |  |
| incidence of depression |
|  |  |  |  |  |  |  |  |  | not estimable  |  | -  |  |
| functionality |
|  |  |  |  |  |  |  |  |  | not estimable  |  | -  |  |
| distress |
|  |  |  |  |  |  |  |  |  | not estimable  |  | -  |  |
| Mortality (at any time point) |
| 2  | randomised trials  | not serious a | not serious  | not serious  | very serious b | none  | 6/48 (12.5%)  | 9/54 (16.7%)  | **RR 0.75**(0.29 to 1.96)  | **42 fewer per 1,000**(from 118 fewer to 160 more)  | ⨁⨁◯◯LOW  | CRITICAL  |
| Delirium duration (assessed with: days) |
| 2  | randomised trials  | not serious a | serious c | not serious  | serious d | none  | 48  | 54  | -  | MD **0.87 days fewer**(6.7 fewer to 4.97 more)  | ⨁⨁◯◯LOW  | IMPORTANT  |
| delirium severity |
|  |  |  |  |  |  |  |  |  | not estimable  |  | -  |  |
| Duration of mechanical ventilation (assessed with: days) |
| 2  | randomised trials  | not serious a | not serious  | not serious  | very serious d | none  | 41  | 54  | -  | MD **0.34 days fewer**(6.54 fewer to 5.86 more)  | ⨁⨁◯◯LOW  | IMPORTANT  |
| ICU readmission rate |
|  |  |  |  |  |  |  |  |  | not estimable  |  | -  |  |
| intensity of treatment |
|  |  |  |  |  |  |  |  |  | not estimable  |  | -  |  |
| costs |
|  |  |  |  |  |  |  |  |  | not estimable  |  | -  |  |
| ICU length of stay (assessed with: days) |
| 2  | randomised trials  | not serious a | not serious  | not serious  | serious d | none  | 48  | 54  | -  | MD **1.93 days more**(1.17 fewer to 5.02 more)  | ⨁⨁⨁◯MODERATE  | IMPORTANT  |

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

**Explanations**

a. 1 study at unclear risk of bias. Open-label haloperidol used in both studies.

b. 15 total events. 95% CI embraces substantial benefit and harm.

c. I-squared 83%. Forest plot shows visible difference in effects.

d. 95% CI embraces significant shortened and lengthened duration.

|  |  |  |
| --- | --- | --- |
| Population:  | critically ill adults WITH delirium  | Background:  |
| Intervention:  | an atypical antipsychotic  |  |
| Comparison:  | no such strategy  |  |
| Main outcomes:  | * Mortality (at any time point)
* Delirium duration
* Duration of mechanical ventilation
* ICU length of stay
 |  |
| Setting:  | Intensive care units  |  |
| Perspective:  |  |  |
|  | **Criteria**  | **Judgements**  | **Research evidence**  |
| Problem | **Is there a problem priority?**  | ○ No ○ Probably no ○ Uncertain ○ Probably yes ● Yes ○ Varies  | The evidence for this recommendation comes from 2 RCT's: Devlin 2010 [(11)](https://paperpile.com/c/z7wvc0/S7NP) (quetiapine)  and Girard 2010[(3)](https://paperpile.com/c/z7wvc0/aYCW) (ziprasidone), including a total of 48 patients in the intervention groups and 54 in the placebo comparator group. Open label haloperidol was used in both of these studies.   |
| Benefits & harms of the options | **What is the overall certainty of this evidence?**  | ○ No included studies ○ Very low ● Low ○ Moderate ○ High  | **The relative importance or values of the main outcomes of interest:**

|  |  |  |
| --- | --- | --- |
| **Outcome** | **Relative importance**  | **Certainty of the evidence (GRADE)**  |
| Mortality (at any time point) | CRITICAL | ⨁⨁⨁◯MODERATE |
| Delirium duration  | IMPORTANT | ⨁⨁◯◯LOW |
| Duration of mechanical ventilation | IMPORTANT | ⨁⨁◯◯LOW |
| ICU length of stay | IMPORTANT | ⨁⨁⨁◯MODERATE |

The evidence was rated as very low since there are only 2 studies with very small numbers of participants and open label haloperidol administered during the study. The desirable anticipated effects are not obvious based on these two studies.  *(Please note - it could be rated as "probably no" if we want to keep consistent with the haloperidol recommendation.)* |
| **Is there important uncertainty about how much people value the main outcomes?**  | ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability ○ No known undesirable outcomes  |
| **Are the desirable anticipated effects large?**  | ○ No ○ Probably no ● Uncertain ○ Probably yes ○ Yes ○ Varies  |
| **Are the undesirable anticipated effects small?**  | ○ No ○ Probably no ● Uncertain ○ Probably yes ○ Yes ○ Varies  |
| **Are the desirable effects large relative to undesirable effects?**  | ○ No ○ Probably no ● Uncertain ○ Probably yes ○ Yes ○ Varies  |
| Resource use | **Are the resources required small?**  | ○ No ○ Probably no ● Uncertain ○ Probably yes ○ Yes ○ Varies  | These particular antipsychotics are more expensive than haloperidol and other typicals that have been on the market for many years.  |
| **Is the incremental cost small relative to the net benefits?**  | ○ No ○ Probably no ● Uncertain ○ Probably yes ○ Yes ○ Varies  |  |
| Acceptability | **Is the option acceptable to key stakeholders?**  | ○ No ○ Probably no ● Uncertain ○ Probably yes ○ Yes ○ Varies  | If atypical antipsychotics have effects such as decreasing distress during an episode of delirium (an outcome that could not be evaluated using this existing evidence) key stakeholders, including patients and  family members would likely opt to use such a medication.   |
| Feasibility | **Is the option feasible to implement?**  | ○ No ○ Probably no ○ Uncertain ○ Probably yes ● Yes ○ Varies  |  |

|  |
| --- |
| **Recommendation** **Should an atypical antipsychotic vs. no such strategy be used in critically ill adults WITH delirium?** |
| **Balance of consequences**  | Undesirable consequences *clearly outweigh* desirable consequences in most settings | Undesirable consequences *probably outweigh* desirable consequences in most settings | The balance between desirable and undesirable consequences *is closely balanced or uncertain* | Desirable consequences *probably outweigh* undesirable consequences in most settings | Desirable consequences *clearly outweigh* undesirable consequences in most settings |
|  | ○ | ○ | ● | ○ | ○ |
| **Type of recommendation**  | We recommend against offering this option | We suggest not offering this option | We suggest offering this option | We recommend offering this option |
|  | ○ | ● | ○ | ○ |
| **Recommendation**  | We do not suggest using atypical antipsychotics for delirium in critically ill patients. |
| **Justification**  | We have moderate evidence that atypical antipsychotic use is not associated with a decreased ICU length of stay. We have low certainty about the effect of atypical antipsychotics on delirium duration or duration of ventilation or mortality, but given the lack of demonstrated benefit patients should not routinely be exposed to potential harms associated with these medications.    |
| **Subgroup considerations**  | Patients who experience significant distress secondary to symptoms of an episode of delirium such as anxiety, fearfulness, hallucinations, or delusions or who may be physically threatening to self or others may benefit from the use of lowest effective doses of atypical antipsychotics for symptomatic relief. Atypical antipsychotics should be discontinued following the resolution of the patient's distress.   |
| **Research possibilities**  | More research is needed on the benefit of atypical antipsychotics in treating distress due to delirium symptoms, longer term outcomes after critical illness and system innovations to ensure that patients do not remain on antipsychotics indefinitely following symptomatic initiation during a delirium episode. |
| **Comments during electronic voting by entire panel** | Clinically atypicals reduce delirium in some patients, perhaps at the cost of ↑sedation & risk of AEs and complications. perhaps “no recommendation". Maybe part of the problem is that not all delirium is the same. "Routine" use of these drugs may not be indicated but considered if agitation, hallucinations, etc. |

**Author(s)**: Mark E. Nunnally, Karin Neufeld

**Date**:

**Question**: An an alpha-2 agonist (e.g., dexmedetomidine) compared to no such strategy in critically ill adults WITH delirium

**Setting**: Intensive care unit

**Bibliography**: Reade MC, et. al. JAMA 2016, PMID: 26975647 [(12)](https://paperpile.com/c/z7wvc0/Ldrn)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Quality assessment** | **№ of patients** | **Effect** | **Quality** | **Importance** |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **an an alpha-2 agonist (e.g., dexmedetomidine)** | **no such strategy** | **Relative(95% CI)** | **Absolute(95% CI)** |
| In-hospital mortality |
| 1  | randomised trials  | serious a | not serious  | serious b | very serious  | none  | 2/39 (5.1%)  | 0/32 (0.0%)  | **% Difference 5.1**(-1.8 to 12.1)  | **-- per 1,000**(from -- to --)  | ⨁◯◯◯VERY LOW  | CRITICAL  |
| Hospital length of stay |
| 1  | randomised trials  | serious a | not serious  | serious b | serious c | none  | 39  | 32  | -  | median **0 days** (3 lower to 3 higher)  | ⨁◯◯◯VERY LOW  | IMPORTANT  |
| ICU length of stay |
| 1  | randomised trials  | serious a | not serious  | serious b | serious c | none  | 39  | 32  | -  | median **1 days fewer**(2.1 fewer to 0.1 more)  | ⨁◯◯◯VERY LOW  | IMPORTANT  |
| Duration of CAM positive delirium |
| 1  | randomised trials  | serious a | not serious  | serious b | not serious  | none  | 39  | 32  | -  | median **24 hours lower**(41 lower to 6 lower)  | ⨁⨁◯◯LOW  | IMPORTANT  |
| Ventilator-free days (follow up: 7 days) |
| 1  | randomised trials  | serious a | not serious  | serious b | not serious  | none  | 39  | 32  | -  | median **17 days higher**(4 higher to 33.2 higher)  | ⨁⨁◯◯LOW  | IMPORTANT  |
| Required mechanical restraint |
| 1  | randomised trials  | serious a | not serious  | serious b | serious d | none  | 10/39 (25.6%)  | 15/32 (46.9%)  | **% Difference -20.6**(-42.8 to 1.7)  | **-- per 1,000**(from -- to --)  | ⨁◯◯◯VERY LOW  | NOT IMPORTANT  |

**CI:** Confidence interval

**Explanations**

a. Trial stopped early by sponsor.

b. Single study looked at agitated patients who were reintubated.

c. 71 patients.

d. 25 total events. 95% confidence interval embraces harm and benefit.

|  |  |  |
| --- | --- | --- |
| Population:  | critically ill adults WITH delirium  | Background:  |
| Intervention:  | an an alpha-2 agonist (e.g., dexmedetomidine)  |  |
| Comparison:  | no such strategy  |  |
| Main outcomes:  | * In-hospital mortality
* Hospital length of stay
* ICU length of stay
* Duration of CAM positive delirium
* Ventilator-free days
 |  |
| Setting:  | Intensive care unit  |  |
|  | **Criteria**  | **Judgements**  | **Research evidence**  |
| Problem | **Is there a problem priority?**  | ○ No ○ Probably no ○ Uncertain ○ Probably yes ● Yes ○ Varies  | The evidence for this recommendation comes from a single study (Reade et al, 2016) [(12)](https://paperpile.com/c/z7wvc0/Ldrn): 77 patients >18 yo who only required MV due to the degree of agitation (need for restraint, antipsychotic or sedative + CAM-ICU positive + MAAS score of 5 or greater) were recruited from 15 ICU's in Aus. and NZ and randomized to dexmedetomidine (n=39) or placebo (n= 32). Note is made that 21,500 intubated patients were screened to recruit the patients in this study; also the sponsor stopped the study before recruitment was completed.   |
| Benefits & harms of the options | **What is the overall certainty of this evidence?**  | ○ No included studies ○ Very low ● Low ○ Moderate ○ High  | **The relative importance or values of the main outcomes of interest:**

|  |  |  |
| --- | --- | --- |
| **Outcome** | **Relative importance**  | **Certainty of the evidence (GRADE)**  |
| In-hospital mortality | CRITICAL | ⨁◯◯◯VERY LOW |
| Hospital length of stay | IMPORTANT | ⨁⨁◯◯LOW |
| ICU length of stay | IMPORTANT | ⨁⨁◯◯LOW |
| Duration of CAM positive delirium | IMPORTANT | ⨁⨁⨁◯MODERATE |
| Ventilator-free days | IMPORTANT | ⨁⨁⨁◯MODERATE |

The primary outcome of this study, time spent ventilator free during the first 7 days after randomization -  was significantly in favor of the intervention: I= 144.8 hours (IQR: 114-156) vs P= 127.5 (IQR:92-142.8). Secondary outcomes included significantly less delirium in intervention group compared to the placebo group measured in multiple ways.  However there was no difference in 1) length of stay in the ICU, 2) overall hospital length of stay, or 3) location of discharge (rehab. vs home) between groups.  There were 3 in- hospital deaths among the intervention group and 0 in the placebo group.  KJN 1/08/16: Changed the assessment of desirable effects from probably yes to uncertain because of the non-representativeness of the sample.  MN: this should be factored in with directness.  However, you can question the effects.  I've left as Uncertain. |
| **Is there important uncertainty about how much people value the main outcomes?**  | ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability ○ No known undesirable outcomes  |
| **Are the desirable anticipated effects large?**  | ○ No ○ Probably no ● Uncertain ○ Probably yes ○ Yes ○ Varies  |
| **Are the undesirable anticipated effects small?**  | ○ No ○ Probably no ● Uncertain ○ Probably yes ○ Yes ○ Varies  |
| **Are the desirable effects large relative to undesirable effects?**  | ○ No ○ Probably no ● Uncertain ○ Probably yes ○ Yes ○ Varies  |
| Resource use | **Are the resources required small?**  | ○ No ● Probably no ○ Uncertain ○ Probably yes ○ Yes ○ Varies  | Cost of this agent is still relatively expensive compared to other agents used in the ICU for sedation.  |
| **Is the incremental cost small relative to the net benefits?**  | ○ No ○ Probably no ● Uncertain ○ Probably yes ○ Yes ○ Varies  |  |
| Acceptability | **Is the option acceptable to key stakeholders?**  | ○ No ○ Probably no ○ Uncertain ● Probably yes ○ Yes ○ Varies  |  |
| Feasibility | **Is the option feasible to implement?**  | ○ No ○ Probably no ○ Uncertain ● Probably yes ○ Yes ○ Varies  |  |

|  |
| --- |
| **Recommendation** **Should an an alpha-2 agonist (e.g., dexmedetomidine) vs. no such strategy be used in critically ill adults WITH delirium?** |
| **Balance of consequences**  | Undesirable consequences *clearly outweigh* desirable consequences in most settings | Undesirable consequences *probably outweigh* desirable consequences in most settings | The balance between desirable and undesirable consequences *is closely balanced or uncertain* | Desirable consequences *probably outweigh* undesirable consequences in most settings | Desirable consequences *clearly outweigh* undesirable consequences in most settings |
|  | ○ | ○ | ● | ○ | ○ |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Type of recommendation**  | We recommend against offering this option | We suggest not offering this option | We suggest offering this option | We recommend offering this option |
|  | ○ | ○ | ● | ○ |
| **Recommendation**  | We suggest using dexmedetomidine for delirium in mechanically ventilated patients where patients where agitation is precluding extubation/mechanical ventilation liberation.    |
| **Justification**  |  |
| **Subgroup considerations**  | The use of Dexmedetomidine should be considered in agitated patients who are difficult to wean from the ventilator.  |
| **Research possibilities**  | We need more RCT's in Medical Intensive Care Unit patient populations that are powered appropriately and completed as designed.   |

**Author(s)**: Mark E. Nunnally, Karin Neufeld

**Date**:

**Question**: Statins compared to placebo for patients with delirium

**Setting**: Intensive care unit

**Bibliography**: Needham, D. M., Colantuoni, E., Dinglas, V. D., Hough, C. L., Wozniak, A. W., Jackson, J. C., . . . Hopkins, R. O. (2016). Rosuvastatin versus placebo for delirium in intensive care and subsequent cognitive impairment in patients with sepsis-associated acute respiratory distress syndrome: An ancillary study to a randomised controlled trial. The Lancet.Respiratory Medicine, doi:S2213-2600(16)00005-9 [pii] [(13)](https://paperpile.com/c/z7wvc0/tx5i)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Quality assessment** | **№ of patients** | **Effect** | **Quality** | **Importance** |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **statins** | **placebo** | **Relative(95% CI)** | **Absolute(95% CI)** |
| Hospital Mortality |
| 1  | randomised trials  | not serious  | not serious  | not serious  | serious a | none  | 22/137 (16.1%)  | 14/135 (10.4%)  | **RR 1.55**(0.83 to 2.90)  | **57 more per 1,000**(from 18 fewer to 197 more)  | ⨁⨁⨁◯MODERATE  | CRITICAL  |
| Duration of mechanical ventilation (Days) |
| 1  | randomised trials  | not serious  | not serious  | not serious  | serious a | none  | 137  | 135  | -  | MD **0** (2.63 lower to 2.63 higher)  | ⨁⨁⨁◯MODERATE  | IMPORTANT  |
| ICU length of stay |
| 1  | randomised trials  | not serious  | not serious  | not serious  | serious a | none  | 137  | 135  | -  | MD **1 higher**(1.26 lower to 3.26 higher)  | ⨁⨁⨁◯MODERATE  | IMPORTANT  |
| Proportion of days with delirium |
| 1  | randomised trials  | not serious  | not serious  | not serious  | serious a | none  | 137  | 135  | -  | MD **3 higher**(4.01 lower to 10.01 higher)  | ⨁⨁⨁◯MODERATE  | IMPORTANT  |

**CI:** Confidence interval; **RR:** Risk ratio; **MD:** Mean difference a. 95% CI embraces benefit and harm.

|  |  |  |
| --- | --- | --- |
| Population:  | patients with delirium  | Background:  |
| Intervention:  | statins  |  |
| Comparison:  | placebo  |  |
| Main outcomes:  | * Hospital Mortality
* Duration of mechanical ventilation (Days)
* ICU length of stay
* Proportion of days with delirium
 |  |
| Setting:  | Intensive care unit  |  |
|  | **Criteria**  | **Judgements**  | **Research evidence**  |
| Problem | **Is there a problem priority?**  | ○ No ○ Probably no ○ Uncertain ○ Probably yes ● Yes  | The evidence for this recommendation comes from one study (Needham et al 2016) [(13)](https://paperpile.com/c/z7wvc0/tx5i): a randomized double blind, placebo controlled trial of 272 patients in Medical ICUs at 35 US hospitals randomized to rosuvastatin (40 mg loading dose and 20 mg daily until 3 days after discharge from the ICU) or placebo -Inclusion CRITERIA: patients with ARDS; receiving Mechanical Ventilation through an endotracheal tube; meeting SIRS criteria with a known or suspected infection; EXCLUSION CRITERIA: ARDS > 48 hours, Pre-Existing condition adversely affecting survival or weaning from Mech Vent; receiving statins within 48 hours of randomization; > 5X's CK, AST, ALT; SPECIFIC to COGNITIVE OUTCOMES ADDITIONAL EXCLUSIONS WERE< 18 years of age; non-English speakers; Homeless; pre-existing cognitive impairment.   |
| Benefits & harms of the options | **What is the overall certainty of this evidence?**  | ○ No included studies ○ Very low ○ Low ● Moderate ○ High  | **The relative importance or values of the main outcomes of interest:**

|  |  |  |
| --- | --- | --- |
| **Outcome** | **Relative importance**  | **Certainty of the evidence (GRADE)**  |
| Hospital Mortality | CRITICAL | ⨁⨁⨁◯MODERATE |
| Duration of mechanical ventilation (Days) | IMPORTANT | ⨁⨁⨁◯MODERATE |
| ICU length of stay | IMPORTANT | ⨁⨁⨁◯MODERATE |
| Proportion of days with delirium | IMPORTANT | ⨁⨁⨁◯MODERATE |

This trial suggests that exposure to rosuvastatin among critically ill patients with ARDS is not associated with a decrease in delirium duration (as measured as a proportion of days with delirium: Intervention = 34% [s.d. 30] and Placebo = 31% [s.d. 29]); mechanical ventilation duration, ICU length of stay, and hospital mortality were not statistically significantly different between the two groups. The question: **Are the undesirable anticipated effects small?** was answered "Uncertain" as it is unclear from this relatively small single trial what the true risks of the exposure to rosuvastatin are.   |
| **Is there important uncertainty about how much people value the main outcomes?**  | ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability ○ No known undesirable outcomes  |
| **Are the desirable anticipated effects large?**  | ● No ○ Probably no ○ Uncertain ○ Probably yes ○ Yes ○ Varies  |
| **Are the undesirable anticipated effects small?**  | ○ No ○ Probably no ● Uncertain ○ Probably yes ○ Yes ○ Varies  |
| **Are the desirable effects large relative to undesirable effects?**  | ● No ○ Probably no ○ Uncertain ○ Probably yes ○ Yes ○ Varies  |
| Resource use | **Are the resources required small?**  | ○ No ○ Probably no ○ Uncertain ● Probably yes ○ Yes ○ Varies  |  |
| **Is the incremental cost small relative to the net benefits?**  | ○ No ● Probably no ○ Uncertain ○ Probably yes ○ Yes ○ Varies  | This was answered "no" as this study did not demonstrate any net benefit to the intervention and any increased costs are significant.  |
| Acceptability | **Is the option acceptable to key stakeholders?**  | ○ No ○ Probably no ○ Uncertain ● Probably yes ○ Yes ○ Varies  |  |
| Feasibility | **Is the option feasible to implement?**  | ○ No ○ Probably no ○ Uncertain ○ Probably yes ● Yes ○ Varies  |  |

|  |
| --- |
| **Recommendation** **Should statins vs. placebo be used for patients with delirium?** |
| **Balance of consequences**  | Undesirable consequences *clearly outweigh* desirable consequences in most settings | Undesirable consequences *probably outweigh* desirable consequences in most settings | The balance between desirable and undesirable consequences *is closely balanced or uncertain* | Desirable consequences *probably outweigh* undesirable consequences in most settings | Desirable consequences *clearly outweigh* undesirable consequences in most settings |
|  | ○ | ● | ○ | ○ | ○ |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Type of recommendation**  | We recommend against offering this option | We suggest not offering this option | We suggest offering this option | We recommend offering this option |
|  | ○ | ● | ○ | ○ |
| **Recommendation**  | We do not suggest using rosuvastatin for delirium in critically ill patients. |
| **Justification**  | We are moderately certain that routine rosuvastatin use among patients with ARDS is not associated with decreased duration of delirium, days of mechanical ventilation, ICU length of stay or mortality. Given the lack of clear benefit patients should not be routinely exposed to potential harms associated with this medication.    |
| **Research possibilities**  | Replication of this single study is warranted in addition to the testing of other statins, such as simvastatin.  Differences in biologic activity within this class of agents may result in different anti-inflammatory activity and delirium prevention or reduction. Also pharmacokinetics and dynamics differ between agents, including the ability to cross the blood-brain barrier.  |
| **Comments during electronic voting by entire panel** | would prefer stronger wording against |

**Question**: A single-component non-pharmacologic strategy that is not focused on sleep improvement or early mobilization, reduce delirium (incidence/prevalence, LOS-ICU, hospital mortality or other outcomes) compared to no such intervention in critically ill adults

**ALL SINGLE INTERVENTION STUDIES NON PHARM**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Quality assessment** | **№ of patients** | **Effect** | **Quality** | **Importance** |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **a single-component non-pharmacologic strategy that is not focused on sleep improvement or early mobilization, reduce delirium (incidence/prevalence, LOS-ICU, hospital mortality or other outcomes)**  | **no such intervention**  | **Relative(95% CI)** | **Absolute(95% CI)** |
| Delirium incidence/prevalence (Taguchi 2007) [(14)](https://paperpile.com/c/z7wvc0/uVTk) |
| 1  | randomised trials  | serious a | not serious  | not serious  | very serious b | none  | 2/5 (40.0%)  | 1/6 (16.7%)  | **RR 0.31**(-- to --)  | **115 fewer per 1,000**(from -- to --)  | ⨁◯◯◯VERY LOW  | IMPORTANT  |
| Delirium incidence/prevalence (Lee, 2013) [(15)](https://paperpile.com/c/z7wvc0/MsMj) |
| 1  | observational studies  | serious  | not serious  | serious  | very serious c | none  | 6/49 (12.2%)  | 16/46 (34.8%)  | **RR 0.35**(0.15 to 0.82)  | **226 fewer per 1,000**(from 63 fewer to 296 fewer)  | ⨁◯◯◯VERY LOW  | IMPORTANT  |
| Delirium incidence/prevalence (Black, 2011)[(16)](https://paperpile.com/c/z7wvc0/W9NX) |
| 1  | observational studies  | serious  | not serious  | serious  | serious d | none  | 23/79 (29.1%)  | 54/70 (77.1%)  | **RR 0.38**(0.26 to 0.54)  | **478 fewer per 1,000**(from 355 fewer to 571 fewer)  | ⨁◯◯◯VERY LOW  | IMPORTANT  |
| Delirium incidence (Simons, 2016) [(17)](https://paperpile.com/c/z7wvc0/CS7k) |
| 1  | randomised trials  | not serious  | not serious  | not serious  | not serious e | none  | 137/361 (38.0%)  | 123/373 (33.0%)  | **RR 1.15**(0.95 to 1.40)  | **49 more per 1,000**(from 16 fewer to 132 more)  | ⨁⨁⨁⨁HIGH  | IMPORTANT  |
| Delirium incidence/prevalence (Ono, 2011) [(18)](https://paperpile.com/c/z7wvc0/oolo) |
| 1  | randomised trials  | very serious  | serious  | serious  | very serious  | none  | 1/10 (10.0%)  | 5/12 (41.7%)  | not estimable  |  | ⨁◯◯◯VERY LOW  |  |
| Delirium incidence/prevalence (Colombo, 2012) [(19)](https://paperpile.com/c/z7wvc0/7Vmm) |
| 1  | observational studies  | serious  | not serious  | serious  | serious  | strong association  | 32/144 (22.2%)  | 60/170 (35.3%)  | **HR 0.50**(0.31 to 0.89)  | **157 fewer per 1,000**(from 32 fewer to 227 fewer)  | ⨁◯◯◯VERY LOW  |  |
| Delirium incidence/prevalence (Foster, 2013) [(20)](https://paperpile.com/c/z7wvc0/q3LD) |
| 1  | observational studies  | serious  | not serious  | serious  | serious  | none  | 26/84 (31.0%)  | 46/164 (28.0%)  | not estimable  |  | ⨁◯◯◯VERY LOW  |  |
| Delirium incidence/prevalence (Moon, 2015) [(21)](https://paperpile.com/c/z7wvc0/UggW) |
| 1  | randomised trials  | serious  | not serious  | not serious  | not serious  | none  | 12/60 (20.0%)  | 21/63 (33.3%)  | **OR 0.50**(0.22 to 1.14)  | **133 fewer per 1,000**(from 30 more to 234 fewer)  | ⨁⨁⨁◯MODERATE  |  |
| Delirium incidence/prevalence (Hanison, 2015) [(22)](https://paperpile.com/c/z7wvc0/gRno) |
| 1  | observational studies  | very serious  | serious  | serious  | serious  | none  | 50/127 (39.4%)  | 16/23 (69.6%)  | not estimable  |  | ⨁◯◯◯VERY LOW  |  |
| Delirium incidence (Rivosecchi, 2016) [(23)](https://paperpile.com/c/z7wvc0/Kxxl) |
| 1  | observational studies  | serious  | not serious  | serious  | serious  | none  | 24/253 (9.5%)  | 36/230 (15.7%)  | not estimable  |  | ⨁◯◯◯VERY LOW  |  |
| Delirium incidence/prevalence (Balas, 2014) [(24)](https://paperpile.com/c/z7wvc0/rNvF) |
| 1  | observational studies  | serious  | not serious  | serious  | not serious  | strong association  | 73/150 (48.7%)  | 91/146 (62.3%)  | **OR 0.55**(0.33 to 0.93)  | **147 fewer per 1,000**(from 17 fewer to 270 fewer)  | ⨁◯◯◯VERY LOW  |  |
| Delirium (Barnes-Daly, 2017) [(25)](https://paperpile.com/c/z7wvc0/J4e2) |
| 1  | observational studies  | serious  | not serious  | serious  | serious  | none  | -/6064  |  | **RR 1.02**(0.92 to 1.13)  | **1 fewer per 1,000**(from 1 fewer to 1 fewer)  | ⨁◯◯◯VERY LOW  |  |
| Delirium incidence (DiSabatino Smith, 2017) |
| 1  | randomised trials  | serious  | not serious  | serious  | serious  | strong association  | -/149  | -/298  | **OR 0.22**(0.08 to 0.56)  | **0 fewer per 1,000**(from 0 fewer to 0 fewer)  | ⨁⨁◯◯LOW  |  |
| Delirium duration (Lee, 2013) [(26)](https://paperpile.com/c/z7wvc0/E3yt) |
| 1  | observational studies  | serious  | not serious  | serious  | very serious  | none  | 49  | 46  | -  | **0 days** (0 to 0 )  | ⨁◯◯◯VERY LOW  |  |
| Delirium duration (Simons, 2016) [(17)](https://paperpile.com/c/z7wvc0/CS7k) |
| 1  | randomised trials  | not serious  | not serious  | not serious  | not serious  | none  | 361  | 373  | -  | **0 days** (0 to 0 )  | ⨁⨁⨁⨁HIGH  |  |
| Delirium duration in ICU (Rivosecchi, 2016) [(23)](https://paperpile.com/c/z7wvc0/Kxxl) |
| 1  | observational studies  | serious  | not serious  | serious  | serious  | strong association  | 253  | 230  | -  | **0 days** (0 to 0 )  | ⨁◯◯◯VERY LOW  |  |
| Delirium duration (Balas, 2014) [(24)](https://paperpile.com/c/z7wvc0/rNvF) |
| 1  | observational studies  | serious  | not serious  | serious  | serious  | none  | 150  | 146  | -  | **0 days** (0 to 0 )  | ⨁◯◯◯VERY LOW  |  |
| LOS-ICU (Black, 2011) [(16)](https://paperpile.com/c/z7wvc0/W9NX) |
| 1  | observational studies  | serious  | not serious  | serious  | serious  | none  | 69  | 69  | -  | **0 days** (0 to 0 )  | ⨁◯◯◯VERY LOW  |  |
| LOS-ICU (Simons, 2016) [(17)](https://paperpile.com/c/z7wvc0/CS7k) |
| 1  | randomised trials  | not serious  | not serious  | not serious  | not serious  | none  | 361  | 373  | -  | **0 days** (0 to 0 )  | ⨁⨁⨁⨁HIGH  |  |
| LOS-ICU (Colombo, 2012) [(19)](https://paperpile.com/c/z7wvc0/7Vmm) |
| 1  | observational studies  | serious  | not serious  | serious  | serious  | strong association  | 144  | 170  | -  | **0 days** (0 to 0 )  | ⨁◯◯◯VERY LOW  |  |
| LOS-ICU (Moon, 2015) [(21)](https://paperpile.com/c/z7wvc0/UggW) |
| 1  | randomised trials  | serious  | not serious  | not serious  | not serious  | none  | 60  | 63  | -  | **0 days** (0 to 0 )  | ⨁⨁⨁◯MODERATE  |  |
| LOS-ICU (Rivosecchi, 2016) [(23)](https://paperpile.com/c/z7wvc0/Kxxl) |
| 1  | observational studies  | serious  | not serious  | serious  | serious  | none  | 253  | 230  | -  | **0 days** (0 to 0 )  | ⨁◯◯◯VERY LOW  |  |
| LOS-ICU (Balas, 2014) [(24)](https://paperpile.com/c/z7wvc0/rNvF) |
| 1  | observational studies  | serious  | not serious  | serious  | serious  | none  | 150  | 146  | -  | **0 days** (0 to 0 )  | ⨁◯◯◯VERY LOW  |  |
| LOS-ICU (Barnes-Daly, 2017) [(25)](https://paperpile.com/c/z7wvc0/J4e2) |
| 1  | observational studies  | serious  | not serious  | serious  | serious  | very strong association  | 6064  |  | -  | **0** (0 to 0 )  | ⨁◯◯◯VERY LOW  |  |
| LOS-ICU (Ono, 2011) [(18)](https://paperpile.com/c/z7wvc0/oolo) |
| 1  | randomised trials  | very serious  | serious  | serious  | very serious  | none  | 10  | 12  | -  | **0 days** (0 to 0 )  | ⨁◯◯◯VERY LOW  |  |
| Hospital mortality (Simons, 2016) [(17)](https://paperpile.com/c/z7wvc0/CS7k) |
| 1  | randomised trials  | not serious  | not serious  | not serious  | not serious  | none  | 66/361 (18.3%)  | 73/373 (19.6%)  | not estimable  |  | ⨁⨁⨁⨁HIGH  |  |
| Hospital mortality (Moon, 2015) [(21)](https://paperpile.com/c/z7wvc0/UggW) |
| 1  | randomised trials  | serious  | not serious  | not serious  | not serious  | strong association  | 4/60 (6.7%)  | 13/63 (20.6%)  | not estimable  |  | ⨁⨁⨁⨁HIGH  |  |
| Hospital motality (Balas, 2014) [(24)](https://paperpile.com/c/z7wvc0/rNvF) |
| 1  | observational studies  | serious  | not serious  | serious  | serious  | strong association  | 17/150 (11.3%)  | 29/146 (19.9%)  | not estimable  |  | ⨁◯◯◯VERY LOW  |  |
| Hospital mortality (Barnes-Daly, 2017) [(25)](https://paperpile.com/c/z7wvc0/J4e2) |
| 1  | observational studies  | serious  | not serious  | serious  | serious  | very strong association  | -/6064  |  | **OR 0.37**(0.28 to 0.49)  | **0 fewer per 1,000**(from 0 fewer to 0 fewer)  | ⨁◯◯◯VERY LOW  |  |

**CI:** Confidence interval; **RR:** Risk ratio; **HR:** Hazard Ratio; **OR:** Odds ratio

**Explanations**

a. Unblinded

b. 9 total events

c. 22 total events

d. 77 total events

e. 95% confidence interval embraces harm and benefit, tendency to harm.

**Question**: Bright light compared to no bright light for critically ill adults (non pharm delirium single)

**Bibliography**: 1. Ono H, Taguchi T, Kido Y, et al. The usefulness of bright light therapy for patients after oesophagectomy. Intensive & critical care nursing: the official journal of the British Association of Critical Care Nurses 2011;27(3):158-166. 2. Taguchi T, Yano M, Kido Y. Influence of bright light therapy on postoperative patients: a pilot study. Intensive & critical care nursing : the official journal of the British Association of Critical Care Nurses 2007;23(5):289-297. 3. Simons KS, Laheij RJ, van den Boogaard M, et al. Dynamic light application therapy to reduce the incidence and duration of delirium in intensive-care patients: a randomised controlled trial. The lancet Respiratory medicine 2016;4(3):194-202. [(14, 17, 18)](https://paperpile.com/c/z7wvc0/oolo%2BuVTk%2BCS7k)

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| --- | --- | --- | --- | --- |
| **Quality assessment** | **№ of patients** | **Effect** | **Quality** | **Importance** |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Bright light** | **no bright light** | **Relative(95% CI)** | **Absolute(95% CI)** |
| Delirium incidence |
| 3  | randomised trials  | serious a | serious b | not serious  | not serious c | none  | 139/377 (36.9%)  | 130/390 (33.3%)  | **OR 1.18**(0.88 to 1.60)  | **38 more per 1,000**(from 28 fewer to 111 more)  | ⨁⨁◯◯LOW  | IMPORTANT  |
| In-hospital mortality |
| 1  | randomised trials  | not serious  | not serious  | not serious  | serious c | none  | 66/361 (18.3%)  | 73/373 (19.6%)  | **OR 0.92**(0.64 to 1.33)  | **13 fewer per 1,000**(from 49 more to 61 fewer)  | ⨁⨁⨁◯MODERATE  | CRITICAL  |
| Delirium duration (days) |
| 1  | randomised trials  | not serious  | not serious  | not serious  | not serious c | none  | 137  | 123  | -  | MD **0** (0.64 lower to 0.64 higher)  | ⨁⨁⨁⨁HIGH  | IMPORTANT  |
| Length of stay, ICU |
| 2  | randomised trials  | not serious  | not serious d | not serious  | serious c | none  | 371  | 385  | -  | MD **0.19 higher**(0.43 lower to 0.81 higher)  | ⨁⨁⨁◯MODERATE  | IMPORTANT  |
| Length of stay, hospital |
| 1  | randomised trials  | not serious  | not serious  | not serious  | serious c | none  | 361  | 373  | -  | MD **1 lower**(3.04 lower to 1.04 higher)  | ⨁⨁⨁◯MODERATE  | IMPORTANT  |

**CI:** Confidence interval; **OR:** Odds ratio; **MD:** Mean difference

**Explanations**

a. Outcome assessment unblinded in two studies and stopped early.

b. I-squared 48%. visual inspection of forest plot suggests heterogeneity.

c. 95% confidence interval suggests harm and benefit.

d. I-squared 26%. No downGRADED for imprecision, as overlap on forest plot.

|  |  |
| --- | --- |
| **Question** |  |
| Should Bright light vs. no bright light be used for critically ill adults.?  |
| Population:  | critically ill adults.  | Background:  |  |
| Intervention:  | Bright light  |  |
| Comparison:  | no bright light  |  |
| Main outcomes:  | * Delirium incidence
* In-hospital mortality
* Delirium duration (days)
* Length of stay, ICU
* Length of stay, hospital
 |  |
| Setting:  | ICU  |  |
| **Assessment** |
|  | **Criteria**  | **Judgements**  | **Research evidence**  | **Additional considerations**  |
| Problem | **Is there a problem priority?**  | ○ No ○ Probably no ○ Uncertain ○ Probably yes ● Yes ○ Varies  | There are 3 RCTs performed, 2 small [(14, 18)](https://paperpile.com/c/z7wvc0/uVTk%2Boolo)with 11 and 22 patients included, respectively, both with high ROB.both negative. The third is a large, well performed RCT [(17)](https://paperpile.com/c/z7wvc0/CS7k) showing also no beneficial effect on all outcome measures of bright light therapy.Results of Simons study (intervention vs control) - Delirium: 38% vs. 33%; *p=0.16* (using CAM-ICU)-28-days delirium-coma-free days: 26days vs. 27days; *p=0.29*- Duration of delirium: 2days vs. 2days; *p=0.87*-Time to onset delirium: 3days vs. 2days; *p=0.61*- LOS-ICU: 4days vs 4days;*p=0.82*- LOS-Hospital: 15days vs 16days; *p=0.84**-* Hospital mortality: 18% vs 20%; *p=0.66* |  |
| Benefits & harms of the options | **What is the overall certainty of this evidence?**  | ○ No included studies ○ Very low ● Low ○ Moderate ○ High  | **The relative importance or values of the main outcomes of interest:**

|  |  |  |
| --- | --- | --- |
| **Uitkomst** | **Relative importance**  | **Certainty of the evidence (GRADE)**  |
| Delirium incidence | IMPORTANT | ⨁⨁◯◯LAAG |
| In-hospital mortality | CRITICAL | ⨁⨁⨁◯REDELIJK |
| Delirium duration (days) | IMPORTANT | ⨁⨁⨁⨁HOOG |
| Length of stay, ICU | IMPORTANT | ⨁⨁⨁◯REDELIJK |
| Length of stay, hospital | IMPORTANT | ⨁⨁⨁◯REDELIJK |

**Summary of findings**:

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Uitkomst** | **With no bright light** | **With Bright light** | **Difference (95% BI)**  | **Relative effect (RR) (95% BI)**  |
| Delirium incidence | 333 per 1.000 | **371 per 1.000**(306 tot 444) | **38 meer per 1.000**(from 28 minder tot 111 meer) | **OR 1.18**(0.88 tot 1.60) |
| In-hospital mortality | 196 per 1.000 | **183 per 1.000**(135 tot 245) | **13 minder per 1.000**(from 49 meer tot 61 minder) | **OR 0.92**(0.64 tot 1.33) |
| Delirium duration (days) | The mean delirium duration (days) was **0** | The mean delirium duration (days) in the intervention group was 0 undefined (0,64 lager tot 0,64 hoger) | MD **0** (0.64 lager tot 0.64 hoger) | - |
| Length of stay, ICU | The mean length of stay, ICU was **0** | The mean length of stay, ICU in the intervention group was 0,19 undefined hoger (0,43 lager tot 0,81 hoger) | MD **0.19 hoger**(0.43 lager tot 0.81 hoger) | - |
| Length of stay, hospital | The mean length of stay, hospital was **0** | The mean length of stay, hospital in the intervention group was 1 undefined lager (3,04 lager tot 1,04 hoger) | MD **1 lager**(3.04 lager tot 1.04 hoger) | - |

 |  |
| **Is there important uncertainty about how much people value the main outcomes?**  | ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability ○ No known undesirable outcomes  |
| **Are the desirable anticipated effects large?**  | ● No ○ Probably no ○ Uncertain ○ Probably yes ○ Yes ○ Varies  |
| **Are the undesirable anticipated effects small?**  | ● No ○ Probably no ○ Uncertain ○ Probably yes ○ Yes ○ Varies  |
| **Are the desirable effects large relative to undesirable effects?**  | ● No ○ Probably no ○ Uncertain ○ Probably yes ○ Yes ○ Varies  |
| Resource use | **Are the resources required small?**  | ○ No ○ Probably no ● Uncertain  |  |  |
| **Is the incremental cost small relative to the net benefits?**  | ○ No ○ Probably no ● Uncertain  |  |  |
| Acceptability | **Is the option acceptable to key stakeholders?**  | ○ No ● Probably no ○ Uncertain ○ Probably yes ○ Yes ○ Varies  |  |  |
| Feasibility | **Is the option feasible to implement?**  | ○ No ○ Probably no ● Uncertain ○ Probably yes ○ Yes ○ Varies  |  |  |

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| --- |
| **Recommendation** **Should Bright light vs. no bright light be used for critically ill adults.?** |
| **Balance of consequences**  | Undesirable consequences *clearly outweigh* desirable consequences in most settings | Undesirable consequences *probably outweigh* desirable consequences in most settings | The balance between desirable and undesirable consequences *is closely balanced or uncertain* | Desirable consequences *probably outweigh* undesirable consequences in most settings | Desirable consequences *clearly outweigh* undesirable consequences in most settings |
|  | ○ | ○ | ○ | ● | ○ |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Type of recommendation**  | We recommend against offering this option | We suggest not offering this option | We suggest offering this option | We recommend offering this option |
|  | ○ | ● | ○ | ○ |
| **Recommendation**  | We do not suggest the using bright light therapy as a single non-pharmacological intervention alone to reduce delirium in critically ill adults. |
| **Justification**  | The evidence for this recommendation is coming from one large, well performed study [(17)](https://paperpile.com/c/z7wvc0/CS7k) showing no effect on all delirium relevant endpoint (incidence, delirium-and-coma-free days, delirium duration, LOS-ICU/Hospital and mortality).  |
| **Subgroup considerations**  | Subgroup analysis performed in the Simons study also did not show an effect. |
| **Implementation considerations**  | no |
| **Monitoring and evaluation**  | no |
| **Research possibilities**  | no, except for studying the BLT effect as part of a multicomponent intervention study. |
| **Comments during electronic voting by entire panel** | This question has '...improve outcomes...' absent in other statements - is it purposeful?Perhaps specify what single-component is? if it’s bright light therapy, then say that. Delirium incidence should be a critical; question unclear and tangential recommendation Wording awkward. Can the question read "Should Bright light vs. no bright light be used to reduce delirium in critically ill adults?”That question is so hard to read...but I am quite certain it won't end up in any print, right? The research question is not clear - includes both non-pharmacologic strategy or early mobilization. The EtoD profile includes English and non-English text. |

**Table XX**

**Author(s)**: Mark E. Nunnally, Mark vanden Boogaard

**Date**:

**Question**: A multi-component non-pharmacologic strategy not solely focused on sleep improvement or early mobilization compared to no such strategy for critically ill adults

**Setting**: ICU

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| --- | --- | --- | --- | --- |
| **Quality assessment** | **№ of patients** | **Effect** | **Quality** | **Importance** |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **a multi-component non-pharmacologic strategy not solely focused on sleep improvement or early mobilization**  | **no such strategy** | **Relative(95% CI)** | **Absolute(95% CI)** |
| Delirium incidence & prevalence |
| 5  | observational studies  | not serious  | serious a | not serious  | serious  | none  | 144/668 (21.6%)  | 179/650 (27.5%)  | **OR 0.59**(0.39 to 0.88)  | **92 fewer per 1,000**(from 25 fewer to 146 fewer)  | ⨁◯◯◯VERY LOW  | IMPORTANT  |
| In-hospital mortality |
| 1  | randomised trials  | not serious  | not serious  | not serious  | very serious b | none  | 4/60 (6.7%)  | 13/63 (20.6%)  | **OR 0.27**(0.08 to 0.90)  | **141 fewer per 1,000**(from 17 fewer to 186 fewer)  | ⨁⨁◯◯LOW  | CRITICAL  |
| Delirium duration in ICU |
| 1  | observational studies  | not serious  | not serious  | not serious  | serious c | none  | 24  | 36  | -  | MD **0.16 lower**(0.5 lower to 0.18 higher)  | ⨁◯◯◯VERY LOW  | IMPORTANT  |
| ICU LOS |
| 3  | observational studies  | not serious  | serious d | not serious  | serious  | none  | 457  | 463  | -  | MD **0.88 higher**(0.03 lower to 1.78 higher)  | ⨁◯◯◯VERY LOW  | IMPORTANT  |
| ICU readmission |
| 1  | observational studies  | not serious  | not serious  | not serious  | serious c | none  | 3/60 (5.0%)  | 10/63 (15.9%)  | **OR 0.28**(0.07 to 1.07)  | **109 fewer per 1,000**(from 9 more to 146 fewer)  | ⨁◯◯◯VERY LOW  | IMPORTANT  |

**CI:** Confidence interval; **OR:** Odds ratio; **MD:** Mean difference

**Explanations**

a. I-squared 49%. Visual inspection of forest plots suggests heterogeneity.

b. 17 total events. c. 95% confidence interval includes benefit and harm. d. I-squared 62%. Visual inspection of forest plot suggests heterogeneity.

|  |  |
| --- | --- |
| **Question** |  |
| Should a multi-component non-pharmacologic strategy not solely focused on sleep improvement or early mobilization vs. no such strategy be used for critically ill adults?  |
| Population:  | critically ill adults  | Background:  |  |
| Intervention:  | a multi-component non-pharmacologic strategy not solely focused on sleep improvement or early mobilization  |  |
| Comparison:  | no such strategy  |  |
| Main outcomes:  | * Delirium incidence & prevalence
* In-hospital mortality
* Delirium duration
* ICU LOS
* ICU readmission
 |  |
| Setting:  | ICU  |  |
| **Assessment** |
|  | **Criteria**  | **Judgements**  | **Research evidence**  | **Additional considerations**  |
| Problem | **Is there a problem priority?**  | ○ No ○ Probably no ● Uncertain ○ Probably yes ○ Yes ○ Varies  | Five studies are included, one RCT (Moon, 2015) and four before-after studies. Moon [(21)](https://paperpile.com/c/z7wvc0/UggW) (N=123) used delirium risk monitoring, cognition and orientation, environment, early therapeutic intervention as MCI program. - Delirium: 20% vs. 33.3%; *OR 0.50 (95%CI 0.22-1.14),p=0.10* (using CAM-ICU)*-* LOS-ICU: 10.8days vs. 10.0days; *p=0.68*- In-hospital mortality: 6.7% vs. 20.6%; *OR 0.28 (95%CI 0.08-0.90), p=0.02*- 30-days in-hospital mortality: 6.7% vs. 17.5%; *OR 0.34 (95%CI 0.10-1.13), p=0.07*Study of Colombo [(19)](https://paperpile.com/c/z7wvc0/7Vmm) (MCI program Reorientation strategy, and environmental, acoustic and visual stimulation (including music, book reading) included 314 patients and found decrease in delirium (22% vs 35%) and increase in LOS-ICU of 1.5 day; both significant. Studies of Foster [(20)](https://paperpile.com/c/z7wvc0/q3LD) (N=228) and Hanison [(22)](https://paperpile.com/c/z7wvc0/gRno) (N=150) showed no effect on delirium (31% vs 28% and 44% vs 65%; respectively).Rivosecchi [(23)](https://paperpile.com/c/z7wvc0/Kxxl) (MCI program consist of music, opening blinds, reorientation and cognitive stimulation, eye/ear protocol) included N=483 patiens and found a significant decrease on delirium (9.4% vs. 15.7%) and time spent delirious in the ICU (16hrs vs 20hrs). ICU mortality:  11.1% vs 7.5% but was not significant.  | MA showed a 41% reduction on delirium incidence/prevalence, but no effect on LOS-ICU. |
| Benefits & harms of the options | **What is the overall certainty of this evidence?**  | ○ No included studies ○ Very low ● Low ○ Moderate ○ High  | **The relative importance or values of the main outcomes of interest:**

|  |  |  |
| --- | --- | --- |
| **Outcome** | **Relative importance**  | **Certainty of the evidence (GRADE)**  |

**The relative importance or values of the main outcomes of interest:**

|  |  |  |
| --- | --- | --- |
| **Uitkomst** | **Relative importance**  | **Certainty of the evidence (GRADE)**  |
| Delirium incidence & prevalence | BELANGRIJK | ⨁◯◯◯ZEER LAAG |
| In-hospital mortality | CRITICAL | ⨁⨁⨁◯REDELIJK |
| Delirium duration | IMPORTANT | ⨁◯◯◯ZEER LAAG |
| ICU LOS | IMPORTANT | ⨁◯◯◯ZEER LAAG |
| ICU readmission | IMPORTANT | ⨁◯◯◯ZEER LAAG |

**Summary of findings**:

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| --- | --- | --- | --- | --- |
| **Uitkomst** | **With no such strategy** | **With a multi-component non-pharmacologic strategy not solely focused on sleep improvement or early mobilization**  | **Difference (95% BI)**  | **Relative effect (RR) (95% BI)**  |
| Delirium incidence & prevalence | 275 per 1.000 | **183 per 1.000**(129 tot 251) | **92 minder per 1.000**(from 25 minder tot 146 minder) | **OR 0.59**(0.39 tot 0.88) |
| In-hospital mortality | 206 per 1.000 | **66 per 1.000**(20 tot 190) | **141 minder per 1.000**(from 17 minder tot 186 minder) | **OR 0.27**(0.08 tot 0.90) |
| Delirium duration | The mean delirium duration was **0** | The mean delirium duration in the intervention group was 0,16 undefined lager (0,5 lager tot 0,18 hoger) | MD **0.16 lager**(0.5 lager tot 0.18 hoger) | - |
| ICU LOS | The mean ICU LOS was **0** | The mean ICU LOS in the intervention group was 0,88 undefined hoger (0,03 lager tot 1,78 hoger) | MD **0.88 hoger**(0.03 lager tot 1.78 hoger) | - |
| ICU readmission | 159 per 1.000 | **50 per 1.000**(13 tot 168) | **109 minder per 1.000**(from 9 meer tot 146 minder) | **OR 0.28**(0.07 tot 1.07) |

 |  |
| **Is there important uncertainty about how much people value the main outcomes?**  | ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability ● No known undesirable outcomes  |
| **Are the desirable anticipated effects large?**  | ○ No ○ Probably no ○ Uncertain ● Probably yes ○ Yes ○ Varies  |
| **Are the undesirable anticipated effects small?**  | ○ No ○ Probably no ○ Uncertain ○ Probably yes ● Yes ○ Varies  |
| **Are the desirable effects large relative to undesirable effects?**  | ○ No ○ Probably no ○ Uncertain ● Probably yes ○ Yes ○ Varies  |
| Resource use | **Are the resources required small?**  | ○ No ○ Probably no ● Uncertain ○ Probably yes ○ Yes ○ Varies  |  |  |
| **Is the incremental cost small relative to the net benefits?**  | ○ No ○ Probably no ○ Uncertain ● Probably yes ○ Yes ○ Varies  |  |  |
| Acceptability | **Is the option acceptable to key stakeholders?**  | ○ No ○ Probably no ○ Uncertain ○ Probably yes ● Yes ○ Varies  |  |  |
| Feasibility | **Is the option feasible to implement?**  | ○ No ○ Probably no ○ Uncertain ○ Probably yes ● Yes ○ Varies  |  |  |

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| --- |
| **Recommendation** **Should a multi-component non-pharmacologic strategy not solely focused on sleep improvement or early mobilization vs. no such strategy be used for critically ill adults?** |
| **Balance of consequences**  | Undesirable consequences *clearly outweigh* desirable consequences in most settings | Undesirable consequences *probably outweigh* desirable consequences in most settings | The balance between desirable and undesirable consequences *is closely balanced or uncertain* | Desirable consequences *probably outweigh* undesirable consequences in most settings | Desirable consequences *clearly outweigh* undesirable consequences in most settings |
|  | ○ | ○ | ○ | ● | ○ |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Type of recommendation**  | We recommend against offering this option | We suggest not offering this option | We suggest offering this option | We recommend offering this option |
|  | ○ | ○ | ● | ○ |
| **Recommendation**  | We suggest using a multicomponent\* non-pharmacological intervention that is focused  on reducing modifiable risk factors for delirium, improving cognition and optimizing sleep, immobility, hearing and vision in critically ill adults. Discussion: - as part of the recommendation we described the different modifiable risk factors of which the interventions are focusing on, including sleep and immobility. Sleep and immobility are typical part of multicomponent interventions (study of Foster, Moon) [(20, 21)](https://paperpile.com/c/z7wvc0/q3LD%2BUggW)  and therefore we stated this in the recommendation. If feels incorrect to not mention this in the recommendation. - we added a footnote describing the modifiable risk factors combined with some examples of the interventions  - except for the Rivosecchi [(23)](https://paperpile.com/c/z7wvc0/Kxxl) study all other studies did not report that'delirium present at time of ICU admission' was an exclusion criterion. Therefore it is uncertain if these are 'true prevention' studies. *\* Footnote*Examples of multicomponent interventions: cognition (as re-orientation, cognitive stimulation, music, use of clocks), sleep/sedation (as reducing sedation, minimizing light and noise), immobility (early mobilization), hearing and visual impairment (as stimulation of use of hearing aid, glasses). |
| **Justification**  | Although the overall quality of the five studies is rather low, except for one RCT, the evidence is all directed towards a beneficial effect. therefore, and based on the meta-analysis we therefore recommend using a MCI.These multicomponent studies use a bundle of interventions. Pilot studies suggested that it is feasible and safe to combine cognitive and physical therapy early during critical illness [(27)](https://paperpile.com/c/z7wvc0/K9eO), and it is feasible to use non-pharmacologic multicomponent interventions in ICU patients [(20)](https://paperpile.com/c/z7wvc0/q3LD). Studies of multicomponent interventions focus on cognitive impairment (as re-orientation, cognitive stimulation, music, use of clocks), sedation/sleep impairment (as reducing sedation, minimizing light and noise), immobility (early mobilization), hearing and visual impairment (as stimulation of use of hearing aid, glasses).  Overall the use of a such strategies reduced delirium significantly by 41% (OR 0.59; 95%CI 0.39-0.88) Hanisor, 2015; [(19–23)](https://paperpile.com/c/z7wvc0/UggW%2B7Vmm%2Bq3LD%2BgRno%2BKxxl). Furthermore, it significantly decreased time of delirium in the ICU (16hrs vs. 20hrs) [(23)](https://paperpile.com/c/z7wvc0/Kxxl), stay in the ICU [(19)](https://paperpile.com/c/z7wvc0/7Vmm) and improved hospital survival  |
| **Research possibilities**  | More research is needed in a large group of mixed ICU patients with a RCT study design. Preferably measuring the effect of the seperate interventions. Furthermore future studies should also include measuring cost-effectiveness of the MCI programme. |
| **Comments during electronic voting by entire panel** | for consistency, the text at the \* should state ".... reduce immobility (e.g., early rehabilitation / mobilization) draft recommendation very wordy; why can’t it mirror the question?unsure how this will be reconciled / combined with sleep group recommendation on similar intervention, and presented in the MS. |

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