Interpretation and Implementation of the 2018 SCCM PADIS Guidelines

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Disclosures

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• NIA
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Consultant/Speaker

• LaJolla Pharmaceuticals
Objectives

• Summarize the methods and key recommendations from the 2018 SCCM PADIS guidelines
• Identify current evidence gaps surrounding PADIS optimization in the ICU
• Formulate an inter-professional plan to apply the ABCDEF bundle to daily ICU patient care
Fear
Delirium
Pain
Agitation
Disrupted Sleep
ICU memories
COMA
Mobilization and Rehab
Chronic Pain
Return to Independence
Persistent Cognitive Defects
Depression
Reduced Functionality
Family stress
Mortality
Increased healthcare costs
Quality of Life
METHODS & INTERPRETATION
Introduction

2018 Pain, Agitation/sedation, Delirium, Immobility, and Sleep disruption (PADIS) guideline

• Updating 2013 PAD guidelines by:
  – Adding 2 new topics: rehab/mobilization & sleep disruption
  – > 70% of questions new from 2013
  – Including patients as collaborators and co-authors
  – Adding experts from Europe & Australia
  – Focus on post-ICU, patient-centric outcomes

• 37 recommendations & 2 ungraded good practice statements
  • 2 of 37 recommendations, rated as “strong”
• 32 ungraded statements (non-actionable descriptive questions)
<table>
<thead>
<tr>
<th>Pain</th>
<th>Agitation/Sedation</th>
<th>Delirium</th>
<th>Immobility (Rehab/Mobility)</th>
<th>Sleep (Disruption)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factors that influence pain</td>
<td>Light vs. deep sedation</td>
<td>Delirium prediction</td>
<td>Rehab or mobilization (performed in or out of bed) vs different rehab/mobilization intervention, placebo or sham</td>
<td>Comparison of sleep in critically ill adults vs: • Healthy adults • Delirium (vs no delirium) • MV (vs. no MV) Prevalence unusual sleep</td>
</tr>
<tr>
<td>Assessment • Patient self-report • Behavioral • Proxy reporters • Physiologic measures</td>
<td>Prevalence, rationale and outcomes of physical restraint use</td>
<td>• Risk factors • Influence of level of arousal on delirium assessment • Outcomes of delirium</td>
<td>Harm associated with rehab/mobilization (either in or out of bed)</td>
<td>Use of physiologic/non-physiologic sleep monitoring</td>
</tr>
<tr>
<td>Protocol-based assessment and management: • Analgesia-first • Analgosedation</td>
<td>Daily sedation interruption vs. nurse-protocolized sedation</td>
<td>Delirium assessment using valid tool (vs. no assessment)</td>
<td>Clinical indicators to safely initiate rehab/mobilization (either in or our of bed)</td>
<td>Risk factors affecting ICU sleep quality: • Prior to critical illness • ICU-acquired Disrupted sleep outcomes: • During ICU admission • After ICU discharge</td>
</tr>
<tr>
<td>Multimodal analgesia to reduce opioid use: • Acetaminophen • Nefopam • Ketamine • Neuropathic analgesia • IV lidocaine • NSAID</td>
<td>MV patients after cardiac surgery: • Propofol vs benzodiazepines</td>
<td>Pharmacologic prevention: • Haloperidol • Atypical antipsychotic • Statin • Dexametomidine • Ketamine</td>
<td>Clinical indicators to stop rehab/mobilization (either in or out of bed)</td>
<td>Pharmacologic treatment: • Melatonin • Dexametomidine • Propofol</td>
</tr>
<tr>
<td>Procedural analgesia • Opioid vs. none • High vs. low dose opioid • Local analgesia • Nitrous oxide • Isoflurane • NSAID (systemic/gel)</td>
<td>MV critically ill adults • Propofol vs benzodiazepines • Dexametomidine vs benzodiazepines • Propofol vs dexametomidine</td>
<td>Pharmacologic treatment: • Haloperidol • Atypical antipsychotic • Statin • Dexametomidine • Ketamine</td>
<td>Clinical indicators to stop rehab/mobilization (either in or out of bed)</td>
<td>Non-pharmacologic treatment: • AV vs PS mode • Adaptive vs PS mode • Aromatherapy • Music • Noise/Light reduction • Multimodal protocol</td>
</tr>
<tr>
<td>Non-pharmacologic analgesic strategies • Cybertherapy/Hypnosis • Massage • Music • Cold therapy • Relaxation techniques</td>
<td>Objective sedation monitoring tools</td>
<td>Non-pharmacologic delirium reduction interventions: • Single: Bright light therapy • Multi-component: ABCDEF bundle</td>
<td>Non-pharmacologic treatment: • AV vs PS mode • Adaptive vs PS mode • Aromatherapy • Music • Noise/Light reduction • Multimodal protocol</td>
<td></td>
</tr>
</tbody>
</table>
PADIS Guideline Authors

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Methods

• Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology

• Chairs, section heads, panel members, ICU survivors, librarian

• Topics selected/prioritized with input from ICU survivors, then:
  – Literature review: 5 electronic data-bases, 1990 to October 2015
  – Evaluation of methodological rigor with GRADE guidance
  – Formulating & then voting on preliminary recommendations
  – In-person discussion among the full panel (SCCM 2017 Congress)
  – Anonymous Voting (>80% agreement with >70% response rate)
    – 100% of panel voted (with reminders/prompts)

• ICU survivors participated in every step

<table>
<thead>
<tr>
<th></th>
<th><strong>Strong</strong></th>
<th><strong>Conditional</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients</strong></td>
<td>Applies to <em>almost all</em> patients</td>
<td>Applies to <em>most</em> patients (significant exceptions based on patient condition, values &amp; preferences)</td>
</tr>
<tr>
<td><strong>Supporting evidence</strong></td>
<td>Moderate to high quality across broad populations</td>
<td>Conflicting, low quality, insufficient, and/or limited populations</td>
</tr>
<tr>
<td><strong>Benefits versus burdens</strong></td>
<td>Benefits clearly outweigh burdens</td>
<td>May be close balance between benefits and burdens</td>
</tr>
<tr>
<td><strong>Influence of future research</strong></td>
<td>Limited potential to change recommendation</td>
<td>Possible/probable potential to change recommendation</td>
</tr>
<tr>
<td><strong>Performance or quality indicators</strong></td>
<td>Can be readily adapted in most health-care systems</td>
<td>Requires significant deliberation at the local level based on practice patterns, patients served, and resource availability</td>
</tr>
</tbody>
</table>

Interpreting and Implementing the 2018 Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption Clinical Practice Guideline

Michele C. Balas, PhD, RN, CCRN-K, FCCM, FAAN; Gerald L. Weinhouse, MD; Linda Denehy, PT, PhD; Gerald Canques, MD, PhD; Bram Rochwerger, MD, MSc; Cheryl J. Misak, DPhil; Yoanna Skrobik, MD, FRCP(c), MSc, FCCM; John W. Devlin, PharmD, FCCM; Gilles L. Fraser, PharmD, MCCM.

three actionable and three descriptive questions. (A prioritized topic list is in Supplemental Table 10 [Supplemental Digital Content 13, http://links.lww.com/CCM/D771], and voting results appear in Supplemental Table 11 [Supplemental Digital Content 14, http://links.lww.com/CCM/D772].) The evidence summaries and evidence-to-decision tables used to develop recommendations for the agitation (sedation) group are available in Supplemental Table 12 (Supplemental Digital Content 15, http://links.lww.com/CCM/D773), and the forest plots for all completed meta-analyses are available in Supplemental Figure 3 (Supplemental Digital Content 16, http://links.lww.com/CCM/D774).

PAIN
## Protocol-Based Pain Assessment/Management

### PICO Question

<table>
<thead>
<tr>
<th>P</th>
<th>Critically ill adult patients in an ICU</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Protocol-based (analgesia/analgosedation) pain assessment and management program</td>
</tr>
<tr>
<td>C</td>
<td>Usual care</td>
</tr>
</tbody>
</table>
| O | • Pain intensity  
   • Medication exposure (opioids and sedatives)  
   • Adverse events  
   • Duration of mechanical ventilation  
   • ICU Length of stay |
Good practice statement:
Management of pain for adult ICU patients should be guided by routine pain assessment and pain should be treated before a sedative agent is considered

• Analgesia-first sedation:
  - An analgesic (usually an opioid) is used before a sedative to reach the sedative goal

• Analgesia-based sedation:
  - An analgesic (usually an opioid) is used instead of a sedative to reach the sedative goal.
Key Concepts with Analgesia-Based Sedation

• **Takes advantage of certain opioid properties**
  – Reduces/eliminates sedative requirements and their associated ADRs
  – Improves sedation-agitation scores
  – Dyspnea & respiratory depressant properties

• **May accentuate opioid-related ADR’s**
  – Gastric dysmotility, delirium, hypotension, myoclonus, chest wall rigidity

• **May not be appropriate for patients with GABA agonist/sedative needs:**
  – Alcohol/drug withdrawal & drug intoxication
  – Neuromuscular blockade
  – Elevated intracranial pressure & status epilepticus
Recommendation:
We **suggest** using an assessment-driven, protocol-based (analgesia/analgosedation), stepwise approach for pain and sedation management in critically ill adults (*Conditional recommendation*, moderate quality of evidence)

Key factors leading to a conditional (versus a strong) recommendation:
- Only 3 of 5 RCTs have consistent results for critical outcomes
- Most RCTs focused ICU subgroups (e.g. medical)
- Behavior pain scales not consistently used
- Safety outcomes not well described
- Choice of opioid varied
- All studies conducted in Europe
- None of the studies blinded
- Control group managed differently across studies
Multimodal Analgesia

• **Definition**
  
  – Combining different analgesics that act by different mechanisms and at different sites in the nervous system, resulting in additive or synergistic analgesia with lowered adverse effects compared to sole administration of individual analgesics

• Also known as “balanced analgesia”

• Established 1993

• Recommended by perioperative practice guidelines

• Limited ICU literature
# Multimodal Analgesia

## PICO Question

<table>
<thead>
<tr>
<th><strong>P</strong></th>
<th>Critically ill adult patients in an ICU</th>
</tr>
</thead>
</table>
| **I** | **Adjunctive:**  
  - Acetaminophen (IV/PO/PR)  
  - Nefopam  
  - Ketamine  
  - Neuropathic analgesia  
  - IV lidocaine  
  - NSAID (IV/PO) |
| **C** | No use of the adjunctive intervention |
| **O** |  
  - VAS score at 24 hours postoperatively (in cm)  
  - Mean BPS pain scores until patient extubated  
  - Pain score at extubation  
  - Time to extubation (minutes)  
  - Rescue opioid doses  
  - Opioid consumption (in morphine equivalents) |
**Adjuvant Treatment - Acetaminophen**

**VAS Pain Score at 24 hours (postoperatively)**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Adjunctive paracetamol Mean [cm]</th>
<th>SD [cm]</th>
<th>Total</th>
<th>Placebo Mean [cm]</th>
<th>SD [cm]</th>
<th>Total</th>
<th>Mean Difference IV, Fixed, 95% CI [cm]</th>
<th>Mean Difference IV, Fixed, 95% CI [cm]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cattabriga 2007</td>
<td>1</td>
<td>0.74</td>
<td>56</td>
<td>2</td>
<td>1.48</td>
<td>57</td>
<td>28.9%</td>
<td>-1.00 [-1.43, -0.57]</td>
</tr>
<tr>
<td>Memis 2010</td>
<td>2.4</td>
<td>0.55</td>
<td>20</td>
<td>2.64</td>
<td>0.3</td>
<td>20</td>
<td>71.1%</td>
<td>-0.24 [-0.51, 0.03]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>76</strong></td>
<td></td>
<td><strong>77</strong></td>
<td></td>
<td></td>
<td><strong>100.0%</strong></td>
<td><strong>Mean Difference IV, Fixed, 95% CI [cm]</strong></td>
<td><strong>Mean Difference IV, Fixed, 95% CI [cm]</strong></td>
</tr>
<tr>
<td>Heterogeneity: Chi² = 8.52, df = 1 (P = 0.004); I² = 88%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Test for overall effect: Z = 3.89 (P &lt; 0.0001)</td>
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</table>

**Adjuvant Treatment - Acetaminophen**

**Opioid Consumption (Morphine Equivalents)**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Adjunctive paracetamol Mean [mg]</th>
<th>SD [mg]</th>
<th>Total</th>
<th>Placebo Mean [mg]</th>
<th>SD [mg]</th>
<th>Total</th>
<th>Mean Difference IV, Fixed, 95% CI [mg]</th>
<th>Mean Difference IV, Fixed, 95% CI [mg]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cattabriga 2007</td>
<td>5</td>
<td>5.9</td>
<td>56</td>
<td>5</td>
<td>7.4</td>
<td>57</td>
<td>70.1%</td>
<td>0.00 [-2.47, 2.47]</td>
</tr>
<tr>
<td>Memis 2010</td>
<td>9.59</td>
<td>2.275</td>
<td>20</td>
<td>24.75</td>
<td>8.3</td>
<td>20</td>
<td>29.3%</td>
<td>-15.16 [-18.93, -11.39]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>76</strong></td>
<td></td>
<td><strong>77</strong></td>
<td></td>
<td></td>
<td><strong>100.0%</strong></td>
<td><strong>Mean Difference IV, Fixed, 95% CI [mg]</strong></td>
<td><strong>Mean Difference IV, Fixed, 95% CI [mg]</strong></td>
</tr>
<tr>
<td>Heterogeneity: Chi² = 43.48, df = 1 (P &lt; 0.00001); I² = 98%</td>
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<tr>
<td>Test for overall effect: Z = 4.31 (P &lt; 0.0001)</td>
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</tbody>
</table>

**Considerations:**
- Data limited to cardiac/abdominal surgery patients only
- Both RCTs single center; one very low quality
- Analgesia side effects not well evaluated
- Risk for hypotension in more unstable ICU patients?
- Availability and cost of IV acetaminophen varies widely around the world
Adjunctive Acetaminophen (IV/PO/PR)

**Recommendation:**
We **suggest** using acetaminophen as an adjunct to an opioid to decrease pain intensity and opioid consumption for pain management in critically ill adults (conditional recommendation, very low quality of evidence)
Adjunctive Low-dose Ketamine in Surgical ICU Patients

Single center, prospective, randomized, double blind trial including 93 patients scheduled to have major abdominal surgery and post-op management and ventilation in the SICU. Patients were randomized to receive morphine PCA with either placebo or ketamine (for 48 hours). Both groups were allowed as needed morphine boluses.

Considerations:
- Only one RCT available (with a very high risk of bias)
- Data limited to abdominal surgery patients only
- Safety (particularly delirium) not reported
- Role of sedation on effect unclear
- Builds on considerable observational data in non-ICU post operative populations

Adjunctive Low-dose Ketamine

**Recommendation:**
We *suggest* using low-dose ketamine (0.5 mg/kg IVP x 1; 1 -2 mcg/kg/min) as an adjunct to opioid therapy when seeking to reduce opioid consumption in *post-surgical adults* admitted to the ICU (Conditional recommendation, Very low quality of evidence)
Adjunctive Neuropathic Pain Medications

Adjuvant Treatment – Neuropathic medication

Opioid Consumption in first 24 hours

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Neurpathic Pain Agent Mean [mg]</th>
<th>SD [mg]</th>
<th>Total</th>
<th>Control Mean [mg]</th>
<th>SD [mg]</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference IV, Fixed, 95% CI [mg]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joshi 2013</td>
<td>5.08</td>
<td>4.52</td>
<td>20</td>
<td>12.53</td>
<td>3.91</td>
<td>20</td>
<td>15.6%</td>
<td>-7.45 [-10.07, -4.83]</td>
</tr>
<tr>
<td>Pandey 2002</td>
<td>21.11</td>
<td>2.138</td>
<td>18</td>
<td>31.944</td>
<td>2.508</td>
<td>18</td>
<td>46.3%</td>
<td>-10.83 [-12.36, -9.31]</td>
</tr>
<tr>
<td>Pandey 2005</td>
<td>34.75</td>
<td>3.8</td>
<td>12</td>
<td>59.04</td>
<td>3.5</td>
<td>12</td>
<td>12.6%</td>
<td>-24.29 [-27.21, -21.37]</td>
</tr>
<tr>
<td>Pandey 2005</td>
<td>34.01</td>
<td>3.43</td>
<td>12</td>
<td>59.04</td>
<td>3.5</td>
<td>12</td>
<td>14.0%</td>
<td>-25.63 [-27.80, -22.26]</td>
</tr>
<tr>
<td>Pesonen 2011</td>
<td>9</td>
<td>6</td>
<td>35</td>
<td>16</td>
<td>7</td>
<td>35</td>
<td>11.5%</td>
<td>-7.00 [-10.05, -3.95]</td>
</tr>
</tbody>
</table>

Total (95% CI) 97 97 100.0% -13.54 [-14.57, -12.50]

Heterogeneity: Chi² = 168.44, df = 4 (P < 0.00001); I² = 98%
Test for overall effect: Z = 25.61 (P < 0.00001)

Significantly reduced in favor of neuropathic medication

Adjuvant Treatment – Neuropathic medication

Time to Extubation (hours)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Neurpathic Pain Agent Mean [hours]</th>
<th>SD [hours]</th>
<th>Total</th>
<th>Control Mean [hours]</th>
<th>SD [hours]</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference IV, Fixed, 95% CI [hours]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joshi 2013</td>
<td>7.45</td>
<td>1.95</td>
<td>20</td>
<td>7.68</td>
<td>1.98</td>
<td>20</td>
<td>76.6%</td>
<td>-0.23 [-1.45, 0.99]</td>
</tr>
<tr>
<td>Pesonen 2011</td>
<td>10.63</td>
<td>4.75</td>
<td>29</td>
<td>8.33</td>
<td>3.88</td>
<td>31</td>
<td>23.4%</td>
<td>2.30 [0.10, 4.50]</td>
</tr>
</tbody>
</table>

Total (95% CI) 49 51 100.0% 0.36 [-0.70, 1.43]

Heterogeneity: Chi² = 3.88, df = 1 (P = 0.05); I² = 74%
Test for overall effect: Z = 0.67 (P = 0.51)

No difference

Adjuvant Treatment – Neuropathic medication

ICU Length of Stay (Days)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Neurpathic Pain Agent Mean [days]</th>
<th>SD [days]</th>
<th>Total</th>
<th>Control Mean [days]</th>
<th>SD [days]</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference IV, Fixed, 95% CI [days]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joshi 2013</td>
<td>3.05</td>
<td>0.68</td>
<td>20</td>
<td>3.2</td>
<td>1.77</td>
<td>20</td>
<td>25.4%</td>
<td>-0.15 [-0.98, 0.88]</td>
</tr>
<tr>
<td>Pesonen 2011</td>
<td>1.5</td>
<td>0.8</td>
<td>29</td>
<td>1.5</td>
<td>1.1</td>
<td>31</td>
<td>74.6%</td>
<td>0.00 [-0.48, 0.48]</td>
</tr>
</tbody>
</table>

Total (95% CI) 49 51 100.0% -0.04 [-0.46, 0.38]

Heterogeneity: Chi² = 0.09, df = 1 (P = 0.76); I² = 0%
Test for overall effect: Z = 0.18 (P = 0.86)

No difference
Recommendations:

We **suggest** using a neuropathic pain medication (e.g., gabapentin, carbamazepine, and pregabalin) with opioids for pain management in ICU adults **after cardiovascular surgery** (Conditional recommendation, Low quality of evidence)
Multimodal Analgesia

Evidence Gaps:

- Each adjunctive non-opioid analgesic requires larger studies in critically ill adults to clearly evaluate their opioid-sparing properties and their ability to reduce opioid-associated adverse effects.
- Little data in medical ICU patients.
- Safety concerns related to specific non-opioid analgesics need to be evaluated in critically ill adults.
- Optimal dose and route of administration unclear.
- Efficacy and safety data of combination non-opioid analgesics required.
**PADIS Algorithm for Use of Adjuvant Analgesics in Critically Ill Adults**

**Recommendation:**
We suggest offering massage for pain management in critically ill adults (Conditional recommendation, Low quality of evidence).

**Recommendation:**
We suggest offering music therapy to relieve both non-procedural and procedural pain in critically ill adults (Conditional recommendation, Low quality of evidence).

---

**Is my patient at risk of opioid side-effects?**
(e.g. respiratory depression, coma, lower GI tract paralysis/ileus, hyperalgesia, immunosuppression)?

If YES: Pharmacological strategy to decrease opioid dose/opioid side-effects by the addition of “adjunctive” non-opioid analgesics

**Nociceptive pain**

Choice of adjunctive non-opioids depends on patient’s medical history and clinical status. Medications can be administered together to maximize opioid-sparing effect.

**Acetaminophen**
Avoid or stop if: ↑ liver enzymes
Comment: No data for oral route in ICU patients but to be considered

**Nefopam**
Avoid or stop if:  - risk of ↑ heart rate,  - anticholinergic “like effects” (glaucoma, urinary retention, delirium, seizure)
Comment: Consider to administer alone as an alternative to opioids Unavailable in North America

**Low-dose ketamine**
Avoid or stop if: hallucination, dissociation
Comment: Data and CPG restricted to surgical ICU patients

**Neuropathic pain**

**Neuropathic agents**
- gabapentin
- pregabalin
- carbamazepine

Avoid or stop if: ↓ level of consciousness
Comment: Data and CPG restricted to cardiovascular surgical ICU patients

Avoid or stop if:
- level of consciousness

Avoid or stop if:
- cardiac and neurotoxicity

**Role of nerve blocks not evaluated in PADIS but likely important**

---

**Non recommended adjunctive analgesics for routine practice (negative studies ± harms)**

| IV Lidocaïne | Lack of data regarding cardiac and neurotoxicity in ICU patients |
| Non Steroidal | Risk of gastric ulcer, bleeding, renal injury, immunosuppression |
| Anti Inflammatory Drugs > 1 dose |  |
AGITATION/SEDATION
Agitation/Sedation

- Sedatives may predispose pts to increased morbidity
  - Must determine specific indication for use (is pain present?)
  - Assess sedation status frequently using valid/reliable scales
  - Critically ill patients are prone to ↑ adverse events given:
    - reduced drug clearance; unpredictable response, baseline hemodynamic instability

2013 Guidelines

- Improving pts short-term outcome by:
  - Targeting light levels of sedation OR daily awakening trials
  - Minimizing benzodiazepines

2018 Guidelines

- Improving post-ICU outcomes by:
  - Sedation delivery paradigm & specific sedative medication choice

- 3 actionable (PICO) questions + 3 descriptive questions
**Light vs. Deep Sedation**

<table>
<thead>
<tr>
<th></th>
<th>PICO Question</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>P</strong></td>
<td>Critically ill adults</td>
</tr>
<tr>
<td><strong>I</strong></td>
<td>Lightly sedated <em>(RASS = -2 to +1 or equivalent)</em> (<em>DSI/SAT studies not included</em>)</td>
</tr>
<tr>
<td><strong>C</strong></td>
<td>Deeply sedated</td>
</tr>
</tbody>
</table>
| **O** | • 90-day mortality  
    • Tracheostomy  
    • Depression |
|   | • Time to extubation  
    • Cognitive & physical function decline*  
    • Delirium  
    • Post-traumatic stress disorder (PTSD) |

- **Rationale:** 8 RCTs, 3 observational studies
  
  *No RCTs evaluated post-ICU cognitive or physical functioning*
Light vs. Deep Sedation

- **Time to extubation** (3 RCTs, 453 pts; low quality)
  - Associated w/ shorter time, MD -0.77 days (95% CI, -2.04 to 0.50)

  ![Graph showing mean difference and 95% CI for RCTs]

- **Time to extubation** (3 observational, 1524 pts; low quality)
  - Associated w/ shorter time, MD -3.46 days (95% CI, -5.70 to -1.23)

  ![Graph showing mean difference and 95% CI for observational studies]
Light vs. Deep Sedation

- **Tracheostomy rate** (1 RCT & 1 observational, 452 pts)
  - Reduced, RR 0.57 (95% CI, 0.41 to 0.80)

- Light sedation was **NOT associated** with reduction in:
  - Delirium (2 RCTs, 140 pts), RR 0.96 (95% CI, 0.80 to 1.16)
  - PTSD (2 RCTs, 62 pts), RR 0.67 (95% CI, 0.12 to 3.79)
  - Depression (2 RCTs, 128 pts), RR 0.76 (95% CI, 0.10 to 5.58)
Light vs. Deep Sedation

- **90 days mortality** (2 RCTs, 324 pts)
  - NOT significant, RR 1.01 (95% CI, 0.80 to 1.27; low quality)

- **Self-extubation** (4 RCT, 546 pts)
  - Not significant, RR 1.29 (95% CI, 0.58 to 2.88; low quality)
Light vs. Deep Sedation

Recommendation:
We *suggest* using light (vs. deep) sedation in critically ill, mech-ventilated adults (*conditional recommendation*, low quality of evidence).

Evidence gaps:
- No consensus on definition of light, moderate & deep sedation
- Relationship between changing sedation levels over time & clinical outcomes remain unclear
- The effect of light sedation on post-ICU, patient-specific factors need to be evaluated in RCTs
- Dearth of info re: interactions between sedative choice, depth & patient-specific factors
Daily Sedative Interruption/Nurse Protocolized Sedation

- **Data:** 5 unblinded RCTs compared DSI to either usual or NP care (739 pts, usually benzodiazepine + opioid)
  - While differences exist between individual RCTs re: the ability of DSI (vs. its comparator) to maintain light sedation, the overall ability for DSI and NP to achieve light sedation is similar
  - Both DSI & NP are safe

**Ungraded statement:**
Daily sedative interruption protocols and nursing protocolized targeted sedation can achieve & maintain a light level of sedation

**Evidence gaps:**
- Variability in nursing sedation assessment frequency & reporting
- Variability in sedative administrative routes among institutions
- Pt & family preference/education should be considered
Recommendation:
We *suggest* using **either** propofol or dexmedetomidine over benzodiazepines for sedation in critically ill, mechanically ventilated adults (*conditional recommendation*, low quality of evidence).

Evidence Gaps:
- Effect of sedative choice on *longer-term, patient-centered, outcomes* needs to be investigated; a reliance on evaluating faster extubation no longer suffices
- Patient perceptions, including their ability to communicate, while on different sedatives, needs to be evaluated
- Pharmacology of sedatives and their delivery methods needs to be considered
- Cost considerations are important and often vary between different countries
- Sedative choice in the context of *analgesedation* requires further evaluation
- Choice of sedative in certain patient subgroups needs further evaluation
  - Neurologically injured, hemodynamically unstable, needing deep sedation
IMMOBILTY
## Use of Rehabilitation/Mobility

<table>
<thead>
<tr>
<th><strong>P</strong></th>
<th>Critically ill adults</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>I</strong></td>
<td>Rehab or mobilization (performed in-bed or out-of-bed)</td>
</tr>
<tr>
<td><strong>C</strong></td>
<td>Usual care, different rehab/mobility intervention, or placebo,</td>
</tr>
<tr>
<td><strong>O</strong></td>
<td>Patient, family, or health system outcomes</td>
</tr>
</tbody>
</table>
Efficacy and Benefit

1. Muscle strength at ICU discharge (6 RCTs, 304 pt)
   - Improved by 6.2 points (95% CI, 1.7 to 10.8; scale is 0 to 60)
     - low quality (statistical heterogeneity, CI includes MCID)

* At hospital discharge
** At ICU awakening
Efficacy and Benefit

2. Duration of mech. ventilation (11 RCTs, 1128 pt)
   - Reduced by 1.3 days (95% CI, 2.4 to 0.2 days)
   - low quality (2 large RCT high ROB, competing risk, heterogeneity)
**Efficacy and Benefit**

4. **Hospital mortality** (13 RCTs, 1421 pt)
   - No effect, RR=0.93 (95% CI, 0.74 to 1.18) – moderate quality (CI includes harm)
Efficacy and Benefit

5. **Physical func:** small N d/t heterogeneity in measures; NOT significant
   - Timed Up & Go test, mean dif 2.22 (95% CI, -4.99 to 9.43; 3 RCT, 172 pt)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Mean Difference IV, Random, 95% CI</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Denehy 2013</td>
<td>5.90 [-0.58, 12.38]</td>
<td>2013</td>
</tr>
<tr>
<td>Brummel 2014</td>
<td>-17.00 [-44.86, 10.86]</td>
<td>2014</td>
</tr>
<tr>
<td>Moss 2015</td>
<td>0.40 [-7.99, 8.79]</td>
<td>2015</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>2.22 [-4.99, 9.43]</td>
<td></td>
</tr>
</tbody>
</table>

   - Phys Func. in ICU (PFIT) test, mean dif -0.19 (95% CI, -0.69 to 0.31; 3 RCT, 209 pt)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Mean Difference IV, Random, 95% CI</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Denehy 2013</td>
<td>-0.30 [-0.88, 0.28]</td>
<td>2013</td>
</tr>
<tr>
<td>Kayambu 2015</td>
<td>0.20 [-0.97, 1.37]</td>
<td>2015</td>
</tr>
<tr>
<td>Hodgson 2016</td>
<td>0.00 [-2.02, 2.02]</td>
<td>2016</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>-0.19 [-0.69, 0.31]</td>
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</tbody>
</table>
Recommendation …

- Given a small benefit and the low overall quality of evidence, panel members agreed:
  - desirable consequences *probably* outweigh undesirable consequences

**Formal Recommendation:**
We *suggest* performing rehabilitation or mobilization in critically ill adults (*conditional recommendation*, low quality evidence).

- supports performing rehab/mobility over usual care or similar interventions with a reduced duration, frequency, or later onset

- Implementation influenced by feasibility, staffing & resources across ICUs
Table 1. Safety criteria for start/stop rehab/mobilization (in-bed or out-of-bed)

<table>
<thead>
<tr>
<th>Safety criteria</th>
<th>Starting a Rehab/Mobility session</th>
<th>Stopping a Rehab/Mobility session</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>System</strong></td>
<td><strong>Start when ALL of the following are present:</strong></td>
<td><strong>Stop when ANY of the following are present:</strong></td>
</tr>
</tbody>
</table>
| Cardiovascular  | ● Heart rate between 60 - 130 bpm  
● Systolic B/P between 90 - 180 mmHg, or  
● Mean arterial pressure between 60-100 | ● Heart rate decreases <60 or increases >130  
● Systolic decreases <90 or increases >180  
● MAP decreases <60 or increases >100 |
| Respiratory     | ● Respiratory rate between 5 - 40 bpm  
● SpO₂ ≥88%  
● FiO₂ <0.6 & PEEP <10 cmH₂O  
● Airway (ETT or trach) adequately secured | ● Resp. rate decreases <5 or increases >40  
● SpO₂ decreases <88%  
● Concerns re: securement of ETT or trach |
| Neurologic      | ● Able to open eyes to voice | ● Change in LOC |
| **Other**       | The following should be **absent:**  
● New or symptomatic arrhythmia  
● Chest pain with concern for ischemia  
● Unstable spinal injury or lesion  
● Unstable fracture  
● Active or uncontrolled GI bleed | If following develop & clinically relevant:  
● New/symptomatic arrhythmia  
● Chest pain with concern for ischemia  
● Ventilator asynchrony  
● Fall  
● Bleeding  
● Medical device removal or malfunction  
● Distress reported by patient or clinician |
| **Mobility may be performed with** | ● Femoral VAD, except sheath, in which hip mobilization is generally avoided  
● Continuous renal replacement therapy  
● Vasoactive medication infusion |  |
Sleep
# Non-Pharmacologic Interventions to Improve Sleep

## PICO Question

<table>
<thead>
<tr>
<th>P</th>
<th>Critically ill adult patients in an ICU</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>- Assist control mode at night</td>
</tr>
<tr>
<td></td>
<td>- Adaptive ventilation at night</td>
</tr>
<tr>
<td></td>
<td>- NIV-specific ventilator</td>
</tr>
<tr>
<td></td>
<td>- Aromatherapy</td>
</tr>
<tr>
<td>C</td>
<td>No use of the intervention</td>
</tr>
<tr>
<td>O</td>
<td>- Time spent at each sleep stage</td>
</tr>
<tr>
<td></td>
<td>- Sleep duration</td>
</tr>
<tr>
<td></td>
<td>- Sleep fragmentation</td>
</tr>
<tr>
<td></td>
<td>- Circadian rhythm</td>
</tr>
<tr>
<td></td>
<td>- Delirium occurrence</td>
</tr>
<tr>
<td></td>
<td>- Duration of mechanical-ventilation</td>
</tr>
<tr>
<td></td>
<td>- ICU mortality</td>
</tr>
<tr>
<td></td>
<td>- Patient experience</td>
</tr>
</tbody>
</table>
Assist Control (vs. PS) ventilator mode at night

- **Sleep Efficiency** (3 RCTs, 61 pts)
  - Increased by mean difference of 18.33% (95% CI, 7.89-28.76)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Control Ventilation</th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference</th>
<th>IV, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andrejak 2013</td>
<td>61</td>
<td>25</td>
<td>26</td>
<td>39</td>
<td>29</td>
<td>26</td>
<td>50.3%</td>
<td>22.00</td>
<td>[7.28, 36.72]</td>
<td></td>
</tr>
<tr>
<td>Cabello 2008</td>
<td>58</td>
<td>28.2</td>
<td>15</td>
<td>44</td>
<td>37.8</td>
<td>15</td>
<td>19.1%</td>
<td>14.00</td>
<td>[-9.87, 37.87]</td>
<td></td>
</tr>
<tr>
<td>Toublanc 2007</td>
<td>65</td>
<td>25</td>
<td>20</td>
<td>50</td>
<td>35</td>
<td>20</td>
<td>30.6%</td>
<td>15.00</td>
<td>[-3.85, 33.85]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td></td>
<td>61</td>
<td>100.0%</td>
<td>18.33</td>
<td>[7.89, 28.76]</td>
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</tr>
</tbody>
</table>

  Heterogeneity: Chi² = 0.49, df = 2 (P = 0.78); I² = 0%

  Test for overall effect: Z = 3.44 (P = 0.0006)

- **% of sleep time spent in REM sleep** (2 RCTs, 42 pts)
  - Increased by mean difference of 2.79% (95% CI, 0.53-5.05)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Control Mode</th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference</th>
<th>IV, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andrejak 2013</td>
<td>35</td>
<td>23</td>
<td>26</td>
<td>20</td>
<td>21</td>
<td>26</td>
<td>65.3%</td>
<td>15.00</td>
<td>[3.03, 26.97]</td>
<td></td>
</tr>
<tr>
<td>Cabello 2008</td>
<td>54</td>
<td>23.7</td>
<td>15</td>
<td>67</td>
<td>22.2</td>
<td>15</td>
<td>34.7%</td>
<td>-13.00</td>
<td>[-29.43, 3.43]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td></td>
<td>41</td>
<td>100.0%</td>
<td>5.29</td>
<td>[-4.38, 14.97]</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

  Heterogeneity: Chi² = 7.29, df = 1 (P = 0.007); I² = 86%

  Test for overall effect: Z = 1.07 (P = 0.28)

- **% of sleep time in Stage 1 sleep** (2 RCTs, 42 pts)
  - NOT significant, increased by 0.31% (95% CI, -5.17 to 5.79)

- **% of sleep time in Stage 2 sleep** (2 RCTs, 42 pts)
  - NOT significant, increased by 5.29% (95% CI, -4.38 to 14.97)
Rationale (cont’d):

- Other critical outcomes
  - Neither delirium, duration of MV, ICU LOS or patient preference evaluated in the 3 RCTs
- Although evidence quality low, risk of change to AC is low and all ventilators have an AC mode.
- For patients who are dyssynchronous on an AC mode (at night), particularly if sedation (with a BZ or Propofol) is required, a switch back to a PS mode may be required

Recommendation:
We suggest using assist control ventilation at night (vs. pressure support ventilation) to improve sleep in critically ill adults (conditional recommendation, low quality of evidence)
Use of Noise and Light Reduction Strategies to Improve Sleep

Rationale:
- Two RCTs and two observational studies evaluated the night time use of earplugs (with/without eye shades) in non-sedated ICU pts
  - Improved patient-reported sleep quality
  - Reduced delirium
  - Pooled analysis from 2 observational studies associated earplug use with a 20% increased chance of achieving 4 hrs sleep
- Studies not blinded, some patients refused earplugs and sicker patients not evaluated.
- Earplugs/eyeshades little risk and low cost

Recommendation:
We suggest using noise and light reduction strategies to improve sleep in critically ill adults (conditional recommendation, low quality of evidence).
Melatonin to improve sleep

Rationale:
• 3 small RCT (n=60), 3-10 mg HS
• Only lower, acuity patients with chronic respiratory failure evaluated
• Each RCT reported different outcomes; pooling not possible
• Variable methods used to evaluate sleep (ie. BIS, RN observation, actigraphy)
• No clear improvements in sleep
• While relatively safe and low cost, not FDA regulated.

Recommendation:
We make no recommendation regarding the use of melatonin to improve sleep in critically ill adults (no recommendation, very low quality of evidence).
Dexmedetomidine to improve sleep

Rationale:
- 2 RCTs (n=74)
  - 1 RCT evaluated MV adults requiring sedation
  - 1 RCT in non-MV adults
- Significant increase in Stage 2 sleep
  - Mean difference = + 47.85% min (95% CI, 24.05-71.64)
- Significant decrease in Stage 1 sleep
  - Mean difference = - 30.37% min (95% CI, -50.01 to -10.73)
- No effect on sleep fragmentation or % time spent in REM sleep
- Neither delirium, duration of MV, ICU LOS or patient preference evaluated in either RCT
- Concerns about generalizability to all ICU adults, hemodynamic effects, and cost in terms of using dexmedetomidine to ONLY improve sleep (vs. when an IV sedative is needed)

Recommendation:
We make no recommendation regarding the use of dexmedetomidine to improve sleep in critically ill adults (no recommendation, very low quality of evidence).
Low-dose Nocturnal Dexmedetomidine Prevents ICU Delirium: A Randomized, Placebo-Controlled Trial

[Graph showing the cumulative proportion of patients without delirium over follow-up days, with Log-rank p=0.0063.]

Skrobik Y, Duprey M, Hill NS, Devlin JW. AJRCCM 2018
# Sleep Promoting Protocol

## PICO Question

<table>
<thead>
<tr>
<th>P</th>
<th>Critically ill adult patients in an ICU</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Multicomponent sleep-promoting protocol</td>
</tr>
<tr>
<td>C</td>
<td>No use of a protocol</td>
</tr>
<tr>
<td>O</td>
<td>• Time spent at each sleep stage</td>
</tr>
<tr>
<td></td>
<td>• Sleep duration</td>
</tr>
<tr>
<td></td>
<td>• Sleep fragmentation</td>
</tr>
<tr>
<td></td>
<td>• Circadian rhythm</td>
</tr>
</tbody>
</table>
### Evidence: Sleep

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Population</th>
<th>Components</th>
<th>Patient-reported Sleep Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hu RF 2010</td>
<td>RCT</td>
<td>Cardiac Surgery</td>
<td>Earplugs, eye shades, music</td>
<td>Better with protocol</td>
</tr>
<tr>
<td>Kamdar B 2013</td>
<td>Before-after</td>
<td>Medical</td>
<td>Ear plugs/eye shades/music Clustering of care, mobilization, Zolpidem (no delirium); Antipsychotic (delirium)</td>
<td>No difference with protocol</td>
</tr>
<tr>
<td>Li SJ 2014</td>
<td>Before-after</td>
<td>Medical</td>
<td>Earplugs, eye shades, music</td>
<td>No difference with protocol</td>
</tr>
<tr>
<td>Patel J 2014</td>
<td>Before-after</td>
<td>Mixed</td>
<td>Ear plugs/eye shades Removal of meds known to worsen sleep</td>
<td>Better with protocol</td>
</tr>
</tbody>
</table>

**Delirium prevalence:** RR: 0.62; 95% CI, 0.42 to 0.91 (for n=3 before-after studies)

**Recommendation:**

We suggest using a sleep-promoting, multicomponent protocol in critically ill adults (conditional recommendation, low quality evidence).
Sleep Evidence Gaps

• The influence of critical illness, delirium and mechanical ventilation on sleep quality remains poorly defined.
• A reliance on patient sleep quality reporting excludes many patients having the most disrupted sleep (delirium, sedated).
• The best method to sleep measurement, classification and how to measure individual sleep-related factors remain unclear.
• Non-pharmacologic sleep improvement strategies need to be rigorously evaluated in large RCTs and involve higher acuity patients.
• Rigorous RCTs of medication(s) solely administered to improve sleep (vs. reduce agitation) need to be conducted.
• The best interventions/combination of interventions to include in a sleep protocol remain uncertain.
Delirium
Delirium Pharmacological Prevention

Question: Should a pharmacologic agent (versus no use of this agent) be used to prevent delirium in all critically ill adults?

Rationale: 3 RCTs, 1283 pts

Significant reduction in delirium incidence favoring the pharmacologic agent:

- **Haloperidol** (457 pts), RR 0.66; 95% CI, 0.45 to 0.97; low quality
  - *Update: REDUCE RCT (1789 pts): No effect on delirium or survival*
- **Risperidone** (126 pts), RR 0.35; 95% CI, 0.16 to 0.77; low quality
- **Dexmed** (700 pts), OR 0.35; 95% CI, 0.22 to 0.54; low quality

**Su et al** Dexmed for prevention of delirium in elderly patients after non-cardiac surgery. *Lancet* 2016

low severity of illness; only surgical pts, assessing short-term outcomes; cost & side effects
Delirium Pharmacological Prevention

Recommendation:
We suggest NOT using haloperidol, an atypical antipsychotic, dexmedetomidine, statin, or ketamine to prevent delirium in all critically ill adults (Conditional recommendation, very low to low quality of evidence)
N=1789 patients randomized!

Baseline Characteristics Not Different

<table>
<thead>
<tr>
<th></th>
<th>Haloperidol 1mg IV q6h (n=350)</th>
<th>Haloperidol 2mg IV q6h (n=732)</th>
<th>Placebo (n=707)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>66.1</td>
<td>66.7</td>
<td>67.0</td>
</tr>
<tr>
<td>Mechanically Ventilated (%)</td>
<td>48.9</td>
<td>49.9</td>
<td>50.5</td>
</tr>
<tr>
<td>APACHE II score</td>
<td>20.1</td>
<td>19.2</td>
<td>19.0</td>
</tr>
<tr>
<td>Sepsis (%)</td>
<td>30.6</td>
<td>37.4</td>
<td>33.1</td>
</tr>
<tr>
<td>PRE-DELIRIC risk for delirium (%)</td>
<td>26.3</td>
<td>26.1</td>
<td>24.6</td>
</tr>
<tr>
<td>QTc, ms</td>
<td>440</td>
<td>447</td>
<td>443</td>
</tr>
</tbody>
</table>

Effect of Haloperidol on Survival Among Critically Ill Adults With a High Risk of Delirium
The REDUCE Randomized Clinical Trial

Mark vanden Boogaard, PhD; Arjen J. C. Slooter, MD, PhD; Roger J. M. Brüggemann, PharmD, PhD; Lisette Schoooven, PhD; Albertus Beishuizen, MD, PhD; J. Wytske Vermeijden, MD, PhD; Dane Pretorius, MD; Jan de Koning, MD; Koen S. Simons, MD; Paul J. W. Dennen, MD, PhD; Peter H. J. Van der Voort, MD, PhD; Saskia Houterman, PhD; J. G. van der Hoeven, MD, PhD; Peter Pickkers, MD, PhD; and the REDUCE Study Investigators

Figure 2. Survival Analysis at 28 and 90 Days

For the 28-day end point, follow-up for the 1-mg haloperidol group was a median of 28 days (interquartile range [IQR], 28-28 days); for the 2-mg group, 28 days (IQR, 28-28 days); and for the placebo group, 28 days (IQR, 28-28 days). For the 90-day end point, follow-up for the 1-mg haloperidol group was 90 days (IQR, 90-90 days), for the 2-mg haloperidol group, 90 days (IQR, 90-90 days); and for the placebo group, 90 days (IQR, 90-90 days).
# Delirium Pharmacological Treatment

<table>
<thead>
<tr>
<th><strong>PICO Question</strong></th>
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<td><strong>P</strong></td>
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<td><strong>C</strong></td>
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<td><strong>O</strong></td>
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</tbody>
</table>
Rationale, includes:
• Unnecessary continuation causes significant morbidity & cost

Recommendation:
We suggest NOT *routinely* using haloperidol and atypical antipsychotic to treat delirium (conditional recommendation, low quality of evidence).

Although this recommendation discourages the “routine” use of antipsychotic agents in the treatment of delirium, patients who experience significant distress secondary to symptoms of a delirium such as anxiety, fearfulness, hallucinations, or delusions, or who are agitated and may be physically harmful to themselves or others, may benefit from short-term use of haloperidol or an atypical antipsychotic until these distressing symptoms resolve based on the panel’s clinical experience. Patients who start with an antipsychotic for delirium in the ICU often remain on these medications unnecessarily after discharge (305–307).
Haloperidol and Ziprasidone for Treatment of Delirium in Critical Illness


A Days Alive without Delirium or Coma

- Ziprasidone
- Haloperidol
- Placebo

Adjusted Median Days (95% CI)

Figure 3. Effects of Haloperidol, Ziprasidone, and Placebo on 90-Day Survival.

Dexmedetomidine vs. Placebo (Treatment)

Rationale: 1 RCT (71 pts)
- Significant increase in ventilator-free hours
  - Mean Difference 17 hrs (95% CI, 4 to 33 hrs); very low quality
- NO effect on ICU/Hosp LOS or hospital discharge location

Recommendation:
We **suggest** using dexmedetomidine for delirium in mechanically ventilated adults where agitation is precluding weaning/extubation (conditional recommendation, low quality of evidence).
**Rationale:** 5 studies (1 RCT*, 4 Before-after), 1318 pts

- Use of these strategies was associated with:
  - Reduced delirium significantly, OR=0.59 (95% CI, 0.39 to 0.88)
  - Decreased ICU duration of delirium, ICU LOS & Hospital mortality

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Design/Population</th>
<th>Intervention vs control</th>
</tr>
</thead>
</table>
| Colombo (2012)  | Before-after Mixed ICU | **N=144 vs N=170 (Usual care)**
Reorientation strategy, and environmental, acoustic and visual stimulation |
| Foster (2013)   | Before-after Mixed ICU | **N=84 vs N=164 (Usual care)**
MCI protocol (sedation, sleep-wake, sensory stimulation, mobility and music) |
| Moon (2015)     | RCT* Mixed ICU    | **N=60 vs N=63 (Usual care, no prevention program)**
MCI prevention program: delirium risk monitoring, cognition and orientation, environment, early therapeutic intervention |
2 cycle MCI program: 1st cycle: reducing delirogenic drugs, daily sedation breaks, environment changes, more light exposure, use of communication aid, 2nd cycle: natural light, use of clocks |
MCI program: music, opening blinds, reorientation and cognitive stimulation, eye/ear protocol |
Multicomponent Delirium Reduction Bundle: The ABCDEF Bundle
*Generally not focused on improving sleep

<table>
<thead>
<tr>
<th>ABCDE(F) multi-intervention approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td><strong>Assessment, Prevention, Management of Pain</strong></td>
</tr>
</tbody>
</table>

**ABCDEF bundle multi-intervention approach (1 Before-after), 296 pts**

- Significantly associated with:
  - Less delirium, 49% vs. 62%, OR=0.55 (95% CI, 0.33 to 0.93)

**ABCDEF bundle approach (1 Cohort study), 6064 pts**

- Included a focus on “F”, Family engagement
- Improvement in bundle compliance significantly associated with:
  - Reduced mortality & more coma/delirium free ICU days
**Recommendation:**
We *suggest* using a multicomponent, non-pharmacologic intervention that is focused on (but not limited to) reducing modifiable risk factors for delirium, improving cognition, and optimizing sleep, mobility, hearing, and vision in critically ill adults (conditional recommendation, low quality of evidence).

*also refer to sleep section recommendation to use a protocol focused solely on improving sleep*

**Evidence gaps:**
- Understanding role of each intervention in a multicomponent intervention plan
- Role of families in reducing patient stress and facilitating non-pharmacologic delirium prevention and management
- Qualitatively evaluate the experience of patients with delirium
- Consistent definition of each intervention
Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adults in the ICU

Overwhelming!
ABCDEF Bundle Elements

A. Assess, Prevent and manage Pain
B. Both SAT and SBT
C. Choice of analgesia and Sedation
D. Delirium: Assess, Prevent and Manage
E. Early Mobility and Exercise
F. Family Engagement and Empowerment

A Framework for Care
Patient (and family)- focused
Applies to Every ICU Patient
Interdisciplinary Team-Focused

- MD Champion
- RN Champion
- RT Champion
- Pharmacy Champion
- Physical Therapy Champion
- Hospital Administrators
- Family
- Patient

Integrated Approach to PAD

Courtesy J Barr, MD
Caring for Critically Ill Patients with the ABCDEF Bundle: Results of the ICU Liberation Collaborative in Over 15,000 Adults

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ICU Liberation Collaborative - Methods

• Collaborative Overview
  – 68 academic, community and VA ICUs
  – 20 months
  – Operationalized the bundle (with flexibility)
  – Operationalized the daily benchmarks for each element
  – Each Site: Interprofessional Executive Team
  – Education and Support Provided:
    • In Person Meetings
    • Coaching Calls
    • Peer Benchmarking
    • Online materials
    • Resource Sharing
Bundle Performance

ABCDEF bundle performance (our main exposure) was evaluated in two ways:

1. Complete performance:
   • patient received every eligible bundle element on any given day

2. Proportional performance
   • percentage of eligible bundle elements performed on any given day
We explored the association between complete and proportional ABCDEF bundle performance and patient, symptom and system outcomes.

*All models were adjusted for a minimum of 18 a priori- determined potential confounders.
<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Complete Bundle Performance</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient-Related Outcomes</strong></td>
<td>AHR (95% CI)</td>
<td></td>
</tr>
<tr>
<td>ICU discharge</td>
<td>1.17 (1.05–1.30)</td>
<td>&lt; 0.004</td>
</tr>
<tr>
<td>Hospital discharge</td>
<td>1.19 (1.01–1.40)</td>
<td>&lt; 0.033</td>
</tr>
<tr>
<td>Death</td>
<td>0.32 (0.17–0.62)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td><strong>Symptom-Related Outcomes</strong></td>
<td>AOR (95%CI)</td>
<td></td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>0.28 (0.22–0.36)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Coma</td>
<td>0.35 (0.22–0.56)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Delirium</td>
<td>0.60 (0.49–0.72)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Significant pain</td>
<td>1.03 (0.88–1.21)</td>
<td>0.7000</td>
</tr>
<tr>
<td>Physical restraints</td>
<td>0.37 (0.30–0.46)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td><strong>System-Related Outcomes</strong></td>
<td>Adjusted OR (95%CI)</td>
<td></td>
</tr>
<tr>
<td>ICU readmission</td>
<td>0.54 (0.37–0.79)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Discharge destination</td>
<td>0.64 (0.51–0.80)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>
Results: Symptom-Related Outcomes

Results:
Symptom-Related Outcomes

Results: Symptom-Related Outcomes

Dose

Results:
System-Related Outcomes

![Graph showing ICU Readmission and Discharge to Facility trends](image)

Assess, Prevent and Manage Pain

Summary
Assessment – Use a valid assessment tool
Prevention – Anticipate pain (risk factors; procedures)
Management of Pain – Treat pain before using a sedative

Metrics
• Every 4 hours
• Self Report:
  • 0–10 Numeric Rating Scale (NRS)
• Unable to Self Report
  • Critical-Care Pain Observation Tool (CPOT)

Role of Pharmacists
• Opioids
• Multimodal analgesia
• Education about range orders
Both SAT and SBT

Summary
Spontaneous Breathing Trial and Extubation Decisions

Metric
• Safety Criteria
• Failure Criteria

Role of Pharmacists
• Maintaining patient wakefulness
• Daily reminders
• Change in sedative/opioid may be required
  • Non-opioid analgesic
  • Dexmedetomidine (vs propofol)
Choice of Analgesia and Sedation

Summary
Assessment – Using a valid tool
Targeted sedation
Making best choice for sedation agent(s)

Metric
• Every 4 hours
• Targets
• Sedation/Agitation Scale
  • RASS
  • SAS

Role of Pharmacists
• Maintain most patients at a light level of sedation
• Reduce use of continuous IV sedatives
• Transition from IV to NGT/PO
• Daily reassessment of all psychoactive medication use
Summary
Assessment – Use a valid tool
Prevention – Non-pharmacologic interventions
  • think sleep improvement and better mobility
Management – Avoid antipsychotics in most patients

Metric
• Once/shift assessment
• Assessment Tools:
  • Confusion Assessment Method for the ICU (CAM-ICU) – when patient maximally awake
  • Intensive Care Delirium Screening Checklist (ICDSC)

Role of Pharmacists
• Educating teams about minimal antipsychotic role
• Daily medication review to remove unnecessary/deliriogenic meds
• Sleep improvement
  • Focus on non-pharm
Early Mobility and Exercise

Summary
Rehabilitation/Mobilization
Regular – early and often

Metric
• Safety Criteria
• Failure Criteria

Role of Pharmacists
• Earlier elements
  • Pain prevention
  • Light sedation level
  • Delirium prevention/management
Family Engagement and Empowerment

Summary
Involving, engaging and empowering patients and families to be active participants in care

Metric
- Every day

Role of Pharmacists
- Availability for education
- Home medication reconciliation
Questions?