Evidence-Based ICU Sedation Guidelines in 2012: Are We There?

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Disclaimer Past 5 Years

• Speaker
  – 2011 Orion x 2, Hospira x 1
  – 2012 KOL to HealthCanada for Hospira

• Research Support
  – Astra Zeneca (multicenter quetiapine study)
  – The Medicines Company (clevidipine ICH)
  – 2011-12 NIH
    • ATACH II - University Minnesota
    • CLEAR III - Johns Hopkins
  – Aspect/Covidien Equipment Support BIS-TH
  – Canyon Pharmaceuticals (Desirudin trial)
Disclaimers Past 25 Years
Evidence-Based ICU Sedation Guidelines in 2012: Are We There?

- **Yes**
  - GRADE-based Guidelines 2006-2013 ACCM
  - 53 statements - recommendations (28 in 2002)
  - PICO questions developed by 4 subgroups
  - Strength recommendations based on strength of evidence and relative risks or benefits

- **Professional librarian assisted with MeSH terms, searches, Refworks database >18,000 references**

- **Anonymous on-line voting by 21 Task Force members - managed by SCCM staff**

- **No**
Hey! Look what Zog do...
Integrated P-A-D Management

Pain Management

Treatment of Agitation

Delirium Prevention, Treatment

OUTCOMES
• We recommend that pain be routinely monitored in all adult ICU patients (+1B) using NRS 0-10 self-report.

• The Behavioral Pain Scale (BPS) and the Critical-Care Pain Observation Tool (CPOT) are the most valid and reliable behavioral pain assessment tools.

• We do not suggest that vital signs (or observational pain scales that include vital signs) be used alone for pain assessment in adult ICU patients (-2C), but as a cue to further assess pain. (+1C).
# Behavioral Pain Scale (BPS) 3-12

<table>
<thead>
<tr>
<th>Item</th>
<th>Description</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Facial expression</td>
<td>Relaxed</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Partially tightened (e.g., brow lowering)</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Fully tightened (e.g., eyelid closing)</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Grimacing</td>
<td>4</td>
</tr>
<tr>
<td>Upper limbs</td>
<td>No movement</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Partially bent</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Fully bent with finger flexion</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Permanently retracted</td>
<td>4</td>
</tr>
<tr>
<td>Compliance with</td>
<td>Tolerating movement</td>
<td>1</td>
</tr>
<tr>
<td>ventilation</td>
<td>Coughing but tolerating ventilation most of the time</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Fighting ventilator</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Unable to control ventilation</td>
<td>4</td>
</tr>
</tbody>
</table>

Payen JF. Crit Care Med 2001; 29:2258-63
## Critical Care Pain Observation Tool

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Description</th>
<th>Score</th>
</tr>
</thead>
</table>
| Facial expression | No muscular tension observed  
Presence of frowning, brow lowering, orbit tightening, and levator contraction  
All of the above facial movements plus eyelid tightly closed | Relaxed, neutral  
Tense  
Grimacing | 0  
1  
2 |
| Body movements | Does not move at all (does not necessarily mean absence of pain)  
Slow, cautious movements, touching or rubbing the pain site, seeking attention through movements  
Pulling tube, attempting to sit up, moving limbs/thrashing, not following commands, striking at staff, trying to climb out of bed | Absence of movements  
Protection  
Restlessness | 0  
1  
2 |
| Muscle tension Evaluation by passive flexion and extension of upper extremities | No resistance to passive movements  
Resistance to passive movements  
Strong resistance to passive movements, inability to complete them | Relaxed  
Tense, rigid  
Very tense or rigid | 0  
1  
2 |
| Compliance with the ventilator (intubated patients) | Alarms not activated, easy ventilation  
Alarms stop spontaneously  
Asynchrony: blocking ventilation, alarms frequently activated | Tolerating ventilator or movement  
Coughing but tolerating  
Fighting ventilator | 0  
1  
2 |
| OR | Talking in normal tone or no sound  
Sighing, moaning  
Crying out, sobbing | Talking in normal tone or no sound  
Sighing, moaning  
Crying out, sobbing | 0  
1  
2 |
## Assessing Pain Associated with Improved Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Day 2 Pain Assessment?</th>
<th>Unadjusted OR</th>
<th>P</th>
<th>Adjusted OR</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICU Mortality</td>
<td>22%</td>
<td>19%</td>
<td>0.91</td>
<td>0.69</td>
<td>1.06</td>
</tr>
<tr>
<td>ICU LOS</td>
<td>18 d</td>
<td>13 d</td>
<td>1.70</td>
<td>&lt; 0.01</td>
<td>1.43</td>
</tr>
<tr>
<td>MV duration</td>
<td>11 d</td>
<td>8 d</td>
<td>1.87</td>
<td>&lt; 0.01</td>
<td>1.40</td>
</tr>
<tr>
<td>Ventilator Acquired Pneumonia</td>
<td>24%</td>
<td>16%</td>
<td>0.61</td>
<td>&lt; 0.01</td>
<td>0.75</td>
</tr>
</tbody>
</table>

Payen JF. Anesthesiology 2009; 111:1308-16
PAD Guidelines: 2013

- We recommend **IV opioids** as first-line drug to treat non-neuropathic pain (+1C). All IV opioids, when titrated to similar pain intensity endpoints, are equally effective (C).
- **RECOMMEND** = enteral *gabapentin or carbamazepine* in addition to IV opioid for neuropathic pain
- **SUGGEST** = *Non-opioid analgesics* [acetaminophen, NSAID, ketamine] - may reduce dose or need for IV opioids
The RASS and SAS are the most valid and reliable sedation assessment tools for measuring quality and depth of sedation in adult ICU patients (B).

We do not recommend objective measures of brain function (AEP, BIS, Narcotrend, PSI, or state entropy) be used as the primary method to monitor depth of sedation in non-comatose, non-paralyzed critically ill adult patients. These monitors are inadequate substitutes for sedation scoring systems (-1B).

These should be used in adult ICU patients who are receiving neuromuscular blocking agents (+2B).
Processed EEG Monitors

- Bispectral Index or BIS most studied
  - Translates raw EEG via Fast Fourier Transformation
  - Power Spectral Analysis
  - Bispectral analysis
  - Numeric value 0-100

- Other monitors-Sedline (PSI), Narcotrend, Entropy, Cerebral State Monitor, ...

- The clinical implications of 0-100 values for these monitors are **NOT** interchangeable
Actual SAS - BIS Agreement

Fraser GL. Pharmacotherapy 2005;25:19S-27S
We suggest that analgesia-first sedation be used in adult ICU patients who are mechanically ventilated (+2B)

Maintaining light levels of sedation is associated with improved clinical outcomes (e.g., shorter mechanical ventilation and a shorter ICU LOS) (B)

We recommend that sedative medications be titrated to maintain a light rather than a deep level of sedation in adult ICU patients, unless clinically contraindicated (+1B)

We recommend either daily sedation interruption or a light target level of sedation be routinely used in mechanically ventilated adult ICU patients (+1B)
Sedation-Agitation Scale  SAS

7 Dangerous agitation
6 Very agitated
5 Agitated
4 Calm and Cooperative
3 Sedated
2 Very Sedated
1 Unarousable

AWAKE
NOT AWAKE

Richmond Agitation Sedation Scale  RASS

+4  Combative
+3  Very agitated
+2  Agitated
+1  Restless
0    Alert and calm
-1   Drowsy
-2   Light sedation
-3   Moderate sedation
-4   Deep sedation
-5   Unarousable

AWAKE
NOT AWAKE

Sessler. AJRCCM 2002; 166:1338
Patients with RASS -3
Awake vs Not Awake, n=38

9 (24%) (10-38%)

29 (76%)
Lighter Level of Sedation

- Protocol vs non-protocol-directed sedation
- Similar rate continuous infusion (40.7% vs 41.5%) but shorter duration (3.5 vs 5.6 days, p=0.003)
- Median duration of MV 55.9 vs 117.0 hrs, p = .008
- ICU LOS (5.7 vs 7.5 days; p = .013)
- Hospital LOS (14.0 vs 19.9; p < .001)
- Lower tracheostomy rate (6.2% vs 13.2%, p = .038)
- Lighter sedation – better outcome

Lighter Level of Sedation

- 128 adults continuous infusion sedation drugs
- Daily wake-up versus standard care
- Daily wake-up shortened:
  - duration ventilation: 4.9 vs 7.3 days, p=0.004
  - median ICU LOS: 6.4 vs 9.9 d, p=0.02
  - diagnostic testing: 9% vs 27%, p=0.02
- % days patients were awake while receiving a sedative infusion 86% vs 9%, p<0.001
- Lighter sedation – better outcome

Light vs Deep Sedation

- 129 adult mechanical ventilation pts - single center
- Randomized, semi-open label trial (blinded outcome)

- **Light** (n=65): Modified Ramsay 1 (awake but tranquil and cooperative) or 2 (asleep - can open eyes to surroundings)

- **Deep** (n=64): Modified Ramsay 3 (asleep - can open eyes to name) or 4 (asleep - can open eyes to physical stimulus)

- Morphine for analgesia in both
- Midazolam for sedation to target
Light vs Deep Sedation

- At 4-wk follow-up, deep sedation had:
  - inability to complete questionnaire 6% vs 0%, p=0.04
  - Higher PTSD scores 56 vs 46, p=0.07
  - trouble remembering ICU 37% vs 14%; p=0.01
  - disturbing ICU memories 18% vs 4%; p=0.05

- At ICU Discharge, Deep sedation had:
  - longer ventilation 5.5 vs 2.9 days, p=0.02
  - longer ICU LOS 5.5 vs 4.0, p=0.03
  - more depression 19% vs 5%, p=0.02

- Lighter sedation – Better Outcome

SLEAP

- RCT 430 ventilated adults: protocol sedation (Brook) (n=209) vs protocol + DSI (Kress) (n=214)
- Benzos/Opioids titrated to SAS 3-4 or RASS -3 to 0
- DSI nurses resumed infusions at half previous dose
- T2Ext 7 d, ICU LOS 10 d, Hosp LOS 20 d in both
- DSI higher daily doses midazolam (102 vs 82 mg/d; P=.04) and fentanyl (550 vs 260; P=0.001)
- More daily benzo boluses (0.25 vs 0.18; P=0.007) and opiates (2.18 vs 1.79; P=0.001).

Mehta. JAMA 2012; 308 (in press)
PAD Guidelines: 2013

- We suggest sedation using non-benzodiazepine sedatives (propofol or dexmedetomidine) over benzodiazepines (midazolam/lorazepam) to improve clinical outcomes in mechanically ventilated ICU patients (+2B)

- Delirium is associated with increased mortality in adult ICU patients (A), prolonged ICU and hospital lengths of stay in adult ICU patients (A), and development of post-ICU cognitive impairment in adult ICU patients (B)
PAD Guidelines: 2013

- We recommend routine monitoring for delirium with the CAM-ICU or the Intensive Care Delirium Screening Checklist (ICDSC) - the most valid and reliable delirium monitoring tools in adult ICU patients (A).

- Coma is an independent risk factor for delirium in ICU patients. Benzodiazepines may be a risk factor for the development of delirium in adult ICU patients (B). There are insufficient data to determine the relationship between propofol and the development of delirium in adult ICU patients (C).
<table>
<thead>
<tr>
<th>Symptom</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Altered LOC</td>
<td>1</td>
</tr>
<tr>
<td>Inattention</td>
<td>1</td>
</tr>
<tr>
<td>Disorientation</td>
<td>0</td>
</tr>
<tr>
<td>Hallucination, delusion, psychosis</td>
<td>0</td>
</tr>
<tr>
<td>Agitation or psychomotor retardation</td>
<td>1</td>
</tr>
<tr>
<td>Inappropriate speech or mood</td>
<td>0</td>
</tr>
<tr>
<td>Sleep/wake cycle disturbance</td>
<td>0</td>
</tr>
<tr>
<td>Symptom fluctuation</td>
<td>1</td>
</tr>
</tbody>
</table>

**Total score (0 – 8)** 4/8
<table>
<thead>
<tr>
<th></th>
<th>No Delirium (ND)</th>
<th>Subsyndromal (SD)</th>
<th>Delirium (D)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICU Mort</td>
<td>2.4%</td>
<td>10.6%</td>
<td>15.9%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>ICU LOS</td>
<td>2.5 d</td>
<td>5.2 d</td>
<td>10.8 d</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Hosp LOS</td>
<td>31.7 d</td>
<td>40.9 d</td>
<td>36.4 d</td>
<td>ND vs SD, = 0.002 ND vs D, &lt; 0.001 SD vs D, = 0.14</td>
</tr>
<tr>
<td>Severity of illness</td>
<td>12.9</td>
<td>16.7</td>
<td>18.6</td>
<td>ND vs SD, &lt; 0.001 ND vs D, &lt; 0.001 SD vs D, &lt; 0.016</td>
</tr>
</tbody>
</table>

Feature 1
Acute Onset of Changes or Fluctuations in the Course of Mental Status

AND

Feature 2
Inattention

AND EITHER

Feature 3
Disorganized Thinking

OR

Feature 4
Altered Level of Consciousness

Delirium
• In mechanically ventilated ICU patients, dexmedetomidine may be associated with a lower prevalence of delirium compared to benzodiazepine infusions (B).

• We provide no recommendation for:
  – the use of dexmedetomidine to prevent delirium.
  – pharmacological or non-pharmacological delirium prevention.

• We do not suggest that haloperidol or atypical antipsychotics be administered to prevent delirium in ICU patients (-2C).

• We recommend that early mobilization be performed to reduce the incidence and duration of delirium (+1B).
There is no published evidence that treatment with haloperidol reduces delirium in adult ICU patients.

Atypical antipsychotics may reduce the duration of delirium in adult ICU patients (C). We do not suggest using antipsychotics in patients at risk for torsades de pointes:
- baseline prolongation of QT interval
- concomitant medications known to prolong QT interval
- history of this arrhythmia.

We do not recommend rivastigmine (-1B).

For delirium not related to alcohol or benzodiazepine withdrawal, we suggest dexmedetomidine rather than benzodiazepine infusions in order to reduce the duration of delirium (+2B).
Unblinded Study: Delirium After Cardiac Surgery

- Randomized open-label study
- Valve replacement surgery
- Dex vs Propofol vs Midazolam
- Trend for cost savings with dex (7.0k vs 9.9k (0.12) vs 9.6k (0.07))
- Dex reduced duration delirium (1% vs 16% vs 29% (all <0.001))
- Delirium increased LOS, cost
- OR for delirium 28.6 and 29.6 (all <.001)

Maldonado JR. Psychosomatics 2009; 50:206
### Sedative-Analgesics

**Risk for Transitioning to Delirium**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Transitioning to Delirium Only Odds Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lorazepam</td>
<td>1.2 (1.1-1.4)</td>
<td>.003</td>
</tr>
<tr>
<td>Midazolam</td>
<td>1.7 (0.9-3.2)</td>
<td>.09</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>1.2 (1.0-1.5)</td>
<td>.09</td>
</tr>
<tr>
<td>Morphine</td>
<td>1.1 (0.9-1.2)</td>
<td>.24</td>
</tr>
<tr>
<td>Propofol</td>
<td>1.2 (0.9-1.7)</td>
<td>.18</td>
</tr>
</tbody>
</table>

![Graph showing the probability of transitioning to delirium with varying lorazepam doses.](image)

Panharipande. Anesthesiology 2006; 104:21
MENDS

Pandharipande. JAMA 2007; 298:2644
Figure 2. Daily Prevalence of Delirium Among Intubated Intensive Care Unit Patients Treated With Dexmedetomidine vs Midazolam

54% DEX vs 76.6% MDZ  p<0.001

Riker. JAMA 2009; 301: 489-99
Early Mobilization

Schweickert. Lancet 2009; 373:1874

<table>
<thead>
<tr>
<th></th>
<th>EM</th>
<th>Control</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time ICU Delirium</td>
<td>33%</td>
<td>57%</td>
<td>0.03</td>
</tr>
<tr>
<td>Time Hosp Delirium</td>
<td>28%</td>
<td>41%</td>
<td>0.01</td>
</tr>
</tbody>
</table>
Early Mobilization

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>Pre-QI Period (n=27 Patients with 312 MICU Patient Days)</th>
<th>QI Period (n=30 Patients With 482 MICU Patient Days)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzodiazepines</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients ever receiving benzodiazepines</td>
<td>26 (96)</td>
<td>22 (73)</td>
<td>.030</td>
</tr>
<tr>
<td>MICU days with any benzodiazepine use†</td>
<td>150 (50)</td>
<td>118 (26)</td>
<td>.002</td>
</tr>
<tr>
<td>Daily midazolam-equivalent dose, units (median [IQR] units)</td>
<td>47 (21–114)</td>
<td>15 (3–59)</td>
<td>.090</td>
</tr>
<tr>
<td>Narcotics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients ever receiving narcotics</td>
<td>26 (96)</td>
<td>23 (77)</td>
<td>.050</td>
</tr>
<tr>
<td>MICU days with any narcotic use†</td>
<td>188 (62)</td>
<td>299 (66)</td>
<td>.650</td>
</tr>
<tr>
<td>Daily morphine-equivalent dose (median [IQR] units)</td>
<td>71 (30–180)</td>
<td>24 (3–120)</td>
<td>.010</td>
</tr>
<tr>
<td>Pain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily scores (range, 0–10) (mean ± SD)‡</td>
<td>0.6±1.9</td>
<td>0.6±1.7</td>
<td>.790</td>
</tr>
<tr>
<td>Sedation status (daily RASS23) of MICU days§</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deeply sedated (RASS –4 to –5)</td>
<td>129 (43)</td>
<td>86 (18)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Moderately sedated (RASS –2 to –3)</td>
<td>72 (24)</td>
<td>65 (14)</td>
<td></td>
</tr>
<tr>
<td>Alert (RASS –1 to +1)</td>
<td>88 (30)</td>
<td>311 (67)</td>
<td></td>
</tr>
<tr>
<td>Agitated (RASS +2 to +4)</td>
<td>8 (3)</td>
<td>6 (1)</td>
<td></td>
</tr>
<tr>
<td>Delirium status (daily CAM-ICU27) of MICU days‖</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delirious</td>
<td>107 (36)</td>
<td>125 (28)</td>
<td>.003</td>
</tr>
<tr>
<td>Not delirious</td>
<td>61 (21)</td>
<td>243 (53)</td>
<td></td>
</tr>
<tr>
<td>Unable to assess because of deep sedation</td>
<td>129 (43)</td>
<td>86 (19)</td>
<td></td>
</tr>
</tbody>
</table>

# MIND Trial Results

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Haloperidol, n = 35</th>
<th>Ziprasidone, n = 30</th>
<th>Placebo, n = 36</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delirium/coma-free days</td>
<td>14.0</td>
<td>15.0</td>
<td>12.5</td>
<td>0.66</td>
</tr>
<tr>
<td>Delirium days</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>0.93</td>
</tr>
<tr>
<td>Delirium resolution on drug, n(%)</td>
<td>24 (69)</td>
<td>23 (77)</td>
<td>21 (58)</td>
<td>0.28</td>
</tr>
<tr>
<td>Coma days</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>0.90</td>
</tr>
<tr>
<td>Ventilator-free days</td>
<td>7.8</td>
<td>12.0</td>
<td>12.5</td>
<td>0.25</td>
</tr>
<tr>
<td>Length of stay, days</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICU</td>
<td>11.7</td>
<td>9.6</td>
<td>7.3</td>
<td>0.70</td>
</tr>
<tr>
<td>Hospital</td>
<td>13.8</td>
<td>13.5</td>
<td>15.4</td>
<td>0.68</td>
</tr>
<tr>
<td>21-day mortality, n (%)</td>
<td>4 (11)</td>
<td>4 (13)</td>
<td>6 (17)</td>
<td>0.81</td>
</tr>
<tr>
<td>Brain dysfunction 1st day, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coma</td>
<td>12 (35)</td>
<td>9 (32)</td>
<td>14 (40)</td>
<td></td>
</tr>
<tr>
<td>Delirium</td>
<td>16 (47)</td>
<td>15 (54)</td>
<td>17 (49)</td>
<td></td>
</tr>
</tbody>
</table>

Girard TD. Crit Care Med 2010; 38:428
Haloperidol prophylaxis decreases delirium incidence in elderly patients after noncardiac surgery: A randomized controlled trial

Wei Wang, MD; Hong-Liang Li, MD; Dong-Xin Wang, MD, PhD; Xi Zhu, MD; Shuang-Ling Li, MD; Gai-Qi Yao, MD; Kai-Sheng Chen, MD; Xiu-E Gu, RN, BSN; Sai-Nan Zhu, MS

- 457 pts non-cardiac surgery (70% cancer surgery, AII 8.7)
- 31% midazolam, 55% propofol, 63% fentanyl, 27% steroids
- Haloperidol (0.5 mg IV + 0.1 mg/h x 12 hrs) vs placebo
- Median ICU LOS 21.3 hrs H vs 23.0 hrs P, p=0.024
- Delirium incidence 1st 7 days 15.3% H vs 23.2% P, p=0.03
- Mean time onset delirium 6.2 days H vs 5.7 days P, p=0.02
- Mean delirium-free days 6.8 days H vs 6.7 days P, p=0.027
- All-cause 28-day mortality 0.9% H vs 2.6% P, p=0.18
- No drug-related side effects were documented

• 1st RCT antipsychotic RX of ICU delirium
• 73 medical - surgical patients
• Oral haloperidol 2.5-5mg q 8 h
• Oral olanzapine 5mg daily with dose titration
• IV haloperidol / benzodiazepines allowed
• No differences except less EPS with olanzapine
Olanzapine ~ Haloperidol for ICU Delirium

Fig. 1 Delirium index scores were performed daily and are shown over time. Overall delirium indices decreased over time (7.08 for all patients on day 1 decreasing to 5.05 on day 5). There are no differences between the two groups.
Quetiapine added to as-needed haloperidol = faster delirium resolution, less agitation, and a greater rate of transfer to home or rehabilitation.

Dexmedetomidine vs Haloperidol

• Randomized, open label, parallel-groups pilot trial
• 20 ventilated patients with agitated delirium
• haloperidol 0.5-2mg/hr
• dexmedetomidine 0.2-0.7 μg/kg/hr
• +/- loading doses (2.5mg haloperidol, 1μg/kg dex)
• Haloperidol increased hours to extubation
  42 (IQR 23.2-117.8) vs 20 (IQR 7.3-24), p=0.016
• Haloperidol increased ICU length of stay
  6.5 (IQR 4-9) vs 1.5 (IQR 1-3) days, p=0.004

Reade MC. Critical Care 2009, 13:R75
Rivastigmine Decreased ICU Survival

p = 0.07

Median duration delirium 5.0 days R vs 3.0 days P, p = 0.06

Van Eijk. Lancet 2010; 376:1829
# Delirium During Study Drug Administration

<table>
<thead>
<tr>
<th></th>
<th><strong>Dexmedetomidine</strong></th>
<th><strong>Midazolam</strong></th>
<th><strong>Diff</strong></th>
<th><strong>P value</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Delirium at baseline</td>
<td>90/130 (68.7%)</td>
<td>63/66 (95.5%)</td>
<td>26.6%</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>No Delirium at baseline</td>
<td>25/76 (32.9%)</td>
<td>22/40 (55.0%)</td>
<td>22.1%</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Riker. *JAMA* 2009; 301: 489-99
PAD Guidelines: 2013

• **NO**
  - Preventive haloperidol or atypical antipsychotics
  - Rivastigmine or haloperidol treatment

• **YES/MAY**
  - Routine monitoring ICDSC or CAMICU
  - Early Mobilization
  - Atypical antipsychotics *(not with torsade risk)*
  - Dexmedetomidine if not WD (benzos-ETOH)
Evidence-Based ICU Sedation Guidelines in 2012: Are We There?

• Yes
  – GRADE-based Guidelines 2006-2013 FCCM
  – 53 statements - recommendations (28 in 2002)
  – PICO questions developed by 4 subgroups
  – Strength recommendations based on strength of evidence and relative risks or benefits

• Professional librarian assisted with MeSH terms, searches, Refworks database >18,000 refs

• Voting Process:
  – anonymous on-line voting by 21 Task Force members - managed by SCCM staff

• No
Evidence-Based ICU Sedation Guidelines in 2012: Are We There?

• No

• Constraints of GRADE and PICO questions asked
  – Specific Populations – mechanical ventilation
  – Medical vs surgical vs trauma vs other
  – Staffing – physicians, nurses, pharm, others
  – Comorbidities not addressed
    • Alcohol and cigarettes
    • Functional status
    • Dementia or psychiatric illness
    • Age
    • Obesity

• Highly variable study designs
Evidence-Based ICU Sedation Guidelines in 2012: Are We There?

- No
- Many assumptions made that are unproven...
  - Is all delirium the same?
  - No confounding of delirium by sedation
  - Prevention vs treatment
  - How to “end” a disease that fluctuates
  - Is there a Gold Standard for ICU assessments
    - Pain
    - Sedation
    - Delirium
- Best primary outcomes
- Intrinsic conflict of interest (non-financial)
Thank You