Dexmedetomidine and its Role for the Prevention and Treatment of Delirium in the ICU

Janelle Poyant, PharmD, BCPS
PGY2 Critical Care Pharmacy Resident

Pharmacy Grand Rounds
April 4, 2017
Objectives

• Review the guideline recommendations for treatment and prevention of delirium

• Evaluate the literature describing the potential role of dexmedetomidine for delirium in the ICU

• Identify clinical scenarios warranting the use of dexmedetomidine for delirium in the ICU
Delirium

- Monitoring
  - CAM-ICU
  - ICDSC

Hyperactive
  - Agitated, restless

Hypoactive
  - Lethargy, sedated

Mixed
Delirium is Associated with Poor Outcomes

- Increased mortality
- Prolonged ICU and hospital length of stay
- More days on mechanical ventilation
- Development of post-ICU cognitive impairment

“I have never felt like myself again. I can't think clearly, my memory has suffered…”

“The work I did before seemed foreign and unfamiliar…”

http://icudelirium.org/testimonials.html
### Risk Factors for Delirium

<table>
<thead>
<tr>
<th>Non-Modifiable</th>
<th>Modifiable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preexisting dementia</td>
<td>Alcoholism</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Smoking</td>
</tr>
<tr>
<td>High severity of illness</td>
<td>Metabolic acidosis</td>
</tr>
<tr>
<td>Older age</td>
<td>ICU environment</td>
</tr>
<tr>
<td>Male sex</td>
<td>Immobility</td>
</tr>
<tr>
<td>Respiratory disease</td>
<td>Lines/access</td>
</tr>
<tr>
<td>Vision impairment</td>
<td>Sleep dysregulation</td>
</tr>
<tr>
<td>Hearing impairment</td>
<td>Fever/Pain</td>
</tr>
<tr>
<td></td>
<td>Benzodiazepine/Opioid use</td>
</tr>
<tr>
<td></td>
<td>Anticholinergic use</td>
</tr>
</tbody>
</table>

- Non-Modifiable: Preexisting dementia, Hypertension, High severity of illness, Older age, Male sex, Respiratory disease, Vision impairment, Hearing impairment
- Modifiable: Alcoholism, Smoking, Metabolic acidosis, ICU environment, Immobility, Lines/access, Sleep dysregulation, Fever/Pain, Benzodiazepine/Opioid use, Anticholinergic use

References:
Postoperative Delirium

- Cardiac surgery: prevalence ~20-50%
- Non-cardiac surgery: prevalence: 30%
- Risk factors: anesthesia, prolonged bypass time, postoperative sedative use, advanced age

Fong HK, et al. _Anesth Analg_. 2006; 102:1255-66

Inadequate pain control
Use of analgesics
The following pharmacologic agent(s) is/are recommended by the PAD Guidelines for the prevention of ICU delirium

• Haloperidol
• Seroquel
• Olanzapine
• A and B
• None of the above
Guidelines: Prevention of Delirium

No recommendation for the use of pharmacologic agents

- Timely management of the cause
- Early and aggressive mobilization
- Sleep enhancement
- Visual and hearing aids
- Pain control
- Light sedation

Dexmedetomidine

α-adrenergic synapse on the locus ceruleus

α₁-receptor

α₂-receptor

Norepinephrine

Norepinephrine

Synaptic vessel

Negative feedback

Dexmedetomidine

Dexmedetomidine and Delirium: Theories

- Intrinsic delirium sparing properties
- \( \gamma \)-aminobutyric acid (GABA) receptor sparing activity
- Induction of a natural, sleep-like state
- Lack of significant anticholinergic effects
Light Sedation Confers Less Delirium

- Lends support for less benzodiazepine use
- Dexmedetomidine is effective for targeting light sedation

2007 MENDS

2009 SEDCOM

2012 MIDEX/PRODEX

MENDS: Maximizing Efficacy of Targeted Sedation and Reducing Neurological Dysfunction
SEDCOM: Safety and Efficacy of Dexmedetomidine Compared with Midazolam
MIDEX/PRODEX: Dexmedetomidine vs Midazolam or Propofol

Dexmedetomidine and Cardiac Surgery
Prevention of Delirium

• 2009 DEXCOM study

Patients (n=306)
• ≥60 years undergoing pump cardiac surgery

Intervention
• Dexmedetomidine (0.1-0.7 mcg/kg/hr)
• Morphine (10-70 mcg/kg/hr)

Primary Endpoint
• Prevalence of delirium via CAM-ICU within 5 days after surgery


DEXCOM: Dexmedetomidine Compared to Morphine
Dexmedetomidine and Cardiac Surgery
Prevention of Delirium

### Dexmedetomidine and Cardiac Surgery
#### Prevention of Delirium

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Dexmedetomidine (n=152)</th>
<th>Morphine (n=147)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with delirium, n(%)</td>
<td>13 (8.6)</td>
<td>22 (15.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Delirium days</td>
<td>2 (1-7)</td>
<td>5 (2-12)</td>
<td>0.031</td>
</tr>
<tr>
<td>Time on study drug, hours</td>
<td>18 (15-20)</td>
<td>17 (15-20)</td>
<td>NS</td>
</tr>
<tr>
<td>Time to extubation, hours</td>
<td>14 (10-18.5)</td>
<td>15 (10-22)</td>
<td>0.036</td>
</tr>
</tbody>
</table>

*Data presented as median (IQR) unless otherwise stated

**Outcome**
- Patients with delirium, n(%)
- Delirium days
- Time on study drug, hours
- Time to extubation, hours

**IQR**: Interquartile Range

Dexmedetomidine and Cardiac Surgery Prevention of Delirium - Applicability

- Study design inherently flawed
- Dexmedetomidine allowed decreased use of deliriogenic medication
- Time to extubation not clinically significant
- Results applicable to a limited population

Dexmedetomidine and Non-Cardiac Surgery
Prevention of Delirium

• 2016, Su and colleagues

Patients (n=700)
- >65 years old admitted to an ICU postoperatively

Intervention (POD 1)
- Dexmedetomidine (0.1 mcg/kg/hr - nocturnal)
- Placebo

Primary Endpoint
- Incidence of delirium in first seven days after surgery


POD: Postoperative Day
Dexmedetomidine and Non-Cardiac Surgery Prevention of Delirium

- Overall incidence: 22.6% vs 9.1% (p<0.0001)

Dexmedetomidine and Non-Cardiac Surgery Prevention of Delirium

<table>
<thead>
<tr>
<th>Outcome*</th>
<th>Placebo (n=350)</th>
<th>Dexmedetomidine (n=350)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to extubation, h</td>
<td>6.9 (5.2-8.6)</td>
<td>4.6 (3.4-5.8)</td>
<td>0.031</td>
</tr>
<tr>
<td>ICU LOS, h</td>
<td>21.5 (20.7-22.3)</td>
<td>20.9 (20.4-21.4)</td>
<td>0.027</td>
</tr>
<tr>
<td>Hospital LOS, d</td>
<td>11 (10.2-11.8)</td>
<td>10 (9.2-10.8)</td>
<td>NS</td>
</tr>
<tr>
<td>All cause 30-d mortality, n(%)</td>
<td>4 (1.1)</td>
<td>1 (0.3)</td>
<td>NS</td>
</tr>
<tr>
<td>Time to onset of delirium, d</td>
<td>5.8 (5.5-6.0)</td>
<td>6.5 (6.4-6.7)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Haloperidol treatment, n(%)</td>
<td>2 (0.6)</td>
<td>1 (0.3)</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Data presented as median (IQR) unless otherwise stated
Dexmedetomidine and Non-Cardiac Surgery Prevention of Delirium - Strengths

- Large, randomized, placebo-controlled trial
- Patients were extubated per-protocol
- Hypothesis generating
  - Administered immediately postoperative
  - Nocturnal administration
  - Sub-sedative dose

Dexmedetomidine and Non-Cardiac Surgery
Prevention of Delirium - Limitations

• Statistical significance ≠ clinical significance
• D7 endpoint with a D1 intervention
• Consent was obtained postoperatively
• Perioperative delirium is a small fraction of ICU delirium
  • Patients may not warrant an ICU stay
  • Limited to the surgical-ICU population

Dexmedetomidine and Delirium Prevention

- Dexmedetomidine ≠ delirium prevention
- Use light sedation when indicated
- Focus on modifiable risk factors
  - Limit benzodiazepine use
  - Timely management of the cause
  - Early and aggressive mobilization
  - Sleep enhancement
  - Visual and hearing aids
  - Pain control

A 70 year old male with hypertension and preexisting dementia is admitted to the ICU after cardiac surgery. He is intubated and requiring pressors. What is your sedative of choice?

- Propofol infusion
- Dexmedetomidine infusion
- Propofol and dexmedetomidine concomitantly
- Lorazepam infusion
- Analgesedation with morphine infusion
Guidelines: Treatment of Delirium

- Mechanically ventilated: prevalence ~80%
- Antipsychotics have limited data
- Dexmedetomididine > benzodiazepines
- Ideal agent?
  - Intravenous administration
  - Relieve symptoms without excess sedation
  - Less adverse effects than antipsychotics
  - Easily titrated

Dexmedetomidine Added to Standard Care Treatment of Delirium

• 2016, DahLIA study

Patients (n=74)
• Adults on MV unable to extubate due to agitation and delirium

Intervention
• Dexmedetomidine (0.5-1.5 mcg/kg/hr)
• Placebo

Primary Endpoint
• Ventilator-free hours in the 7 days following randomization
# Dexmedetomidine Added to Standard Care Treatment of Delirium

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Dexmedetomidine (n=39)</th>
<th>Placebo (n=32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (IQR), y</td>
<td>48 (47-65)</td>
<td>56.5 (46-69.5)</td>
</tr>
<tr>
<td><strong>APACHE II, median (IQR)</strong></td>
<td>14 (10-22)</td>
<td>14 (11-20)</td>
</tr>
<tr>
<td>Mechanical restraint*</td>
<td>13 (33.3)</td>
<td>11 (33.4)</td>
</tr>
<tr>
<td>Midazolam*</td>
<td>4 (10.5)</td>
<td>5 (15.6)</td>
</tr>
<tr>
<td><strong>Propofol</strong></td>
<td>38 (100)</td>
<td>29 (90.6)</td>
</tr>
<tr>
<td>Morphine*</td>
<td>9 (23.7)</td>
<td>9 (28.1)</td>
</tr>
<tr>
<td>Fentanyl*</td>
<td>14 (36.8)</td>
<td>11 (34.4)</td>
</tr>
<tr>
<td><strong>Antipsychotic</strong></td>
<td>9 (23.7)</td>
<td>6 (18.8)</td>
</tr>
<tr>
<td>Duration of intubation prior to enrollment, median (IQR), h</td>
<td>63 (26-96)</td>
<td>43.5 (23-72)</td>
</tr>
</tbody>
</table>

aData shown as n(%) unless otherwise indicated
*During the 24 hours prior to randomization

Dexmedetomidine Added to Standard Care Treatment of Delirium

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Dexmedetomidine (n=39)</th>
<th>Placebo (n=32)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total duration of infusion, h*</td>
<td>23.5 (19.5-35.0)</td>
<td>35 (24.8-71.5)</td>
<td>0.004</td>
</tr>
<tr>
<td>Continued after extubation, n(%)</td>
<td>4 (10.3)</td>
<td>4 (12.5)</td>
<td>NS</td>
</tr>
<tr>
<td>Study days any antipsychotic was administered, median (95%CI), %</td>
<td>26.3 (21.3-39.0)</td>
<td>40.0 (20.6-49.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Ventilator-free during first 7 days, median (IQR), h</td>
<td>144.8 (114.0-156.0)</td>
<td>127.5 (92-142.8)</td>
<td>0.01</td>
</tr>
<tr>
<td>Time to extubation, h*</td>
<td>21.9 (18.3-27.7)</td>
<td>44.3 (25.3-94.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time to first results indicating absence of delirium, h*</td>
<td>23.3 (13.0-54.0)</td>
<td>40.0 (25.3-76.0)</td>
<td>0.01</td>
</tr>
<tr>
<td>Proportion of days spent with delirium*</td>
<td>47 (30-76)</td>
<td>62 (46-86)</td>
<td>0.05</td>
</tr>
</tbody>
</table>

*Data shown as median (IQR)
Dexmedetomidine Added to Standard Care Treatment of Delirium – Limitations

• Unclear if dexmedetomidine needed

• Extubation issues
  • Extubation failure rate of 1.4%
  • “Extubated” when tracheostomy performed
  • Subjective assessment

• Limited to intubated patients with agitation and delirium

• Not applicable to patients early in their critical illness

A patient is admitted following a methamphetamine OD. She is intubated for airway protection and is sedated with propofol. Upon spontaneous awakening, the patient is extremely agitated but following commands. The team wishes to extubate. What is the best approach?

- Resume propofol and try again tomorrow
- Stop propofol and extubate; treat agitation as needed
- Switch to a dexmedetomidine infusion and reattempt an SBT
- Give haloperidol and reattempt an SBT
Intubated for Agitation, Agitated from Intubation

- Ongoing intubation
- Decrease sedation
- Agitated and tachypneic
- SBT

SBT: Spontaneous Breathing Trial
Dexmedetomidine for Patients Refractory to Haloperidol Infusion
Treatment of Delirium

- 2016, Carrasco and colleagues

**Patients** (n=132)
- Non-intubated with agitated delirium (PRE-DELIRIC), failed haloperidol

**Intervention**
- Haloperidol non-responders: dexmedetomidine (0.2-0.7 mcg/kg/hr)

**Primary Endpoint**
- Percentage of time in RASS 0 to -2

PRE-DELIRIC: Prediction of Delirium in ICU Patients Scale

Dexmedetomidine for Patients Refractory to Haloperidol Infusion
Treatment of Delirium

Initial haloperidol titration (n=132)

- RASS +1 to +4 (Non-Responders)
  - Rescue with dexmedetomidine up to RASS 0 (n=46)
  - Analyzed at ICU discharge (n=46)
  - Analyzed at hospital discharge (n=42)

- RASS 0 to -3 (Responders)
  - Maintenance of haloperidol infusion to RASS 0 (n=86)
  - Analyzed at ICU discharge (n=72)
  - Analyzed at hospital discharge (n=65)
Dexmedetomidine for Patients Refractory to Haloperidol Infusion  
Treatment of Delirium

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Dexmedetomidine (n=46)</th>
<th>Haloperidol (n=86)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time RASS 0 to 2</td>
<td>92.7 (84.5-99.8)</td>
<td>59.3 (49.1-78)</td>
<td>0.001</td>
</tr>
<tr>
<td>Time ICDSC &lt;4</td>
<td>52 (37.5-66.4)</td>
<td>29.5 (13-42.3)</td>
<td>0.005</td>
</tr>
</tbody>
</table>

*Data shown as % (95% CI)

- Non-randomized study design
- Limited clinical applicability due to practice differences
- Limited to hyperactive delirium
Dexmedetomidine and Delirium Treatment

- Trials have significant limitations that need to be considered
- Limited to hyperactive delirium
- Mechanism of effect remains unclear
- Reasons for agitation need to be assessed
## Ongoing Trials

<table>
<thead>
<tr>
<th>Population</th>
<th>Intervention</th>
<th>Endpoint</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults with hyperactive/mixed delirium in ICU*</td>
<td>Nocturnal dexmedetomidine VS propofol</td>
<td>Reduction of delirium by ICDSC</td>
<td>Recruiting</td>
</tr>
<tr>
<td>Adult ICU patients on ≥1 sedative</td>
<td>Nocturnal dexmedetomidine VS placebo</td>
<td>Development of delirium by ICDSC</td>
<td>Completed</td>
</tr>
<tr>
<td>≥60 years old undergoing CABG</td>
<td>IV APAP/propofol VS IV APAP/dexmedetomidine VS IV propofol/placebo VS IV dexmedetomidine/ placebo</td>
<td>Incidence of delirium</td>
<td>Recruiting</td>
</tr>
</tbody>
</table>

*Excluded if delirium is due to alcohol withdrawal

CABG: Coronary Artery Bypass Grafting
Conclusion

• Delirium is an independent risk factor for increased morbidity and mortality
• Modifiable risk factors should be assessed and acted upon for both prevention and treatment of delirium
• Dexmedetomidine can provide light sedation levels and avoid deliriogenic medications which may reduce delirium
• Dexmedetomidine cannot be recommended for the treatment of delirium
Questions and Discussion
Poyant.Janelle@mayo.edu
Cost Comparisons

- **Dexmedetomidine (IV) – solution 400 mcg/100mL**: $74.77/100ml
- **Propofol (IV) – solution 1000mg/100mL**: $10.75/100ml
  - In a 100kg patient, dexmedetomidine @ 1mcg/kg/hr, the cost of dexmedetomidine would be $448.62 for 24 hours
  - In a 100kg patient, propofol @ 25 mcg/kg/min, the cost of propofol would be $38.70 for 24 hours
## Motor Activity Assessment Scale (MAAS)

<table>
<thead>
<tr>
<th>Description</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>0</strong> Unresponsive</td>
<td>Does not move to noxious stimulus</td>
</tr>
<tr>
<td><strong>1</strong> Responsive only to noxious stimulus</td>
<td>Opens eyes OR raises eyebrows OR turns head towards stimulus OR moves limbs with noxious stimulus</td>
</tr>
<tr>
<td><strong>2</strong> Responsive to touch or name</td>
<td>Opens eyes OR raises eyebrows OR turns head towards stimulus OR moves limbs when touched or name is loudly spoken</td>
</tr>
<tr>
<td><strong>3</strong> Calm and cooperative</td>
<td>No external stimulus is required to elicit movement AND patient is purposeful and follows commands</td>
</tr>
<tr>
<td><strong>4</strong> Restless and cooperative</td>
<td>No external stimulus is required to elicit movement AND patient is picking at sheets or tubes OR uncovering self AND follows commands</td>
</tr>
<tr>
<td><strong>5</strong> Agitated</td>
<td>No external stimulus is required to elicit movement AND patient attempting to sit up OR moves limbs out of bed AND does not consistently follow commands</td>
</tr>
<tr>
<td><strong>6</strong> Dangerously agitated, uncooperative</td>
<td>No external stimulus is required to elicit movement AND patient is pulling at tubes or catheters OR thrashing side to side or striking at staff OR trying to climb out of bed AND does not calm down when asked</td>
</tr>
</tbody>
</table>
ICDSC

1. **Altered Level of Consciousness**
   - Deep sedation/coma over entire shift [SAS= 1; 2; RASS = -4,-5]
   - Agitation [SAS = 5, 6, or 7; RASS= 1-4] at any point
   - Normal wakefulness [SAS = 4; RASS = 0] over the entire shift
   - Light sedation [SAS = 3; RASS= -1, -2, -3]:
     = Not assessable
     = 1 point
     = 0 points
     = 1 point (if no recent sedatives)
     = 0 points (if recent sedatives)

2. **Inattention**
   - Difficulty following instructions or conversation, patient easily distracted by external stimuli.
   - Will not reliably squeeze hands to spoken letter A: S A V E A H A R T

3. **Disorientation**
   - In addition to name, place, and date, does the patient recognize ICU caregivers?
   - Does patient know what kind of place they are in?
     (list examples: dentist’s office, home, work, hospital)

4. **Hallucination, delusion, or psychosis**
   - Ask the patient if they are having hallucinations or delusions.
     (e.g. trying to catch an object that isn’t there).
   - Are they afraid of the people or things around them?

5. **Psychomotor agitation or retardation**
   - Either: a) Hyperactivity requiring the use of sedative drugs or restraints in order to control potentially dangerous behavior (e.g. pulling IV lines out or hitting staff)
   - OR b) Hypoactive or clinically noticeable psychomotor slowing or retardation

6. **Inappropriate speech or mood**
   - Patient displays: inappropiate emotion; disorganized or incoherent speech; sexual or inappropriate interactions; is either apathetic or overly demanding

7. **Sleep-wake cycle disturbance**
   - Either: frequent awakening/ < 4 hours sleep at night OR sleeping during much of the day

8. **Symptom Fluctuation**
   - Fluctuation of any of the above symptoms over a 24 hr period.

**TOTAL SHIFT SCORE:**

<table>
<thead>
<tr>
<th>Score</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal</td>
</tr>
<tr>
<td>1-3</td>
<td>Subsyndromal Delirium</td>
</tr>
<tr>
<td>4-8</td>
<td>Delirium</td>
</tr>
</tbody>
</table>
# CAM-ICU

## Feature 1: Acute Onset or Fluctuating Course

<table>
<thead>
<tr>
<th>Question</th>
<th>Score</th>
<th>Check here if Present</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is the patient different than his/her baseline mental status? OR Has the patient had any fluctuation in mental status in the past 24 hours as evidenced by fluctuation on a sedation/level of consciousness scale (i.e., RASS/SAS), GCS, or previous delirium assessment?</td>
<td>Either question Yes</td>
<td>□</td>
</tr>
</tbody>
</table>

## Feature 2: Inattention

**Letters Attention Test**  
(See training manual for alternate Pictures)

<table>
<thead>
<tr>
<th>Directions</th>
<th>Score</th>
<th>Check here if Present</th>
</tr>
</thead>
<tbody>
<tr>
<td>Say to the patient, “I am going to read you a series of 10 letters. Whenever you hear the letter “A,” indicate by squeezing my hand.” Read letters from the following letter list in a normal tone 3 seconds apart. <strong>SAVEHAART or CASABLANCA or AABBBAAAAY</strong> Errors are counted when patient fails to squeeze on the letter “A” and when the patient squeezes on any letter other than “A.”</td>
<td>Number of Errors &gt;2</td>
<td>□</td>
</tr>
</tbody>
</table>

## Feature 3: Altered Level of Consciousness

Present if the Actual RASS score is anything other than alert and calm (zero)

<table>
<thead>
<tr>
<th>Score</th>
<th>Check here if Present</th>
</tr>
</thead>
<tbody>
<tr>
<td>RASS anything other than zero</td>
<td>□</td>
</tr>
</tbody>
</table>

## Feature 4: Disorganized Thinking

**Yes/No Questions**  
(See training manual for alternate set of questions)

<table>
<thead>
<tr>
<th>Question</th>
<th>Score</th>
<th>Check here if Present</th>
</tr>
</thead>
</table>
| 1. Will a stone float on water?  
2. Are there fish in the sea?  
3. Does one pound weigh more than two pounds?  
4. Can you use a hammer to pound a nail? | Combined number of errors >1 | □ |

**Command**

Say to patient: “Hold up this many fingers” (Hold 2 fingers in front of patient) “Now do the same thing with the other hand” (Do not repeat number of fingers) “If the patient is unable to move both arms, for 2” part of command ask patient to “Add one more finger”  
An error is counted if patient is unable to complete the entire command.

## Overall CAM-ICU

**Feature 1 plus Feature 2 and either 3 or 4 present = CAM-ICU positive**

<table>
<thead>
<tr>
<th>Criteria Met</th>
<th>CAM-ICU Positive (Delirium Present)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Criteria Not Met</td>
<td>CAM-ICU Negative (No Delirium)</td>
</tr>
</tbody>
</table>

©2017 MFMER | slide-40