Dexmedetomidine: The Good, The Bad and The Delirious

By
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Disclosures
I have no actual or potential conflict of interest in relation to this presentation.

Objectives
1. List two negative consequences associated with the occurrence of delirium.
2. Explain the mechanism of action of dexmedetomidine.
3. Summarize the benefits of dexmedetomidine over other medications commonly used for intensive care unit (ICU) sedation.

The Delirious

Definition of Delirium
"A common disorder characterized by a recent onset of fluctuating awareness, impairment of memory, attention, and disorganized thinking."

Characteristics of Delirium
Types of Delirium

- **Hyperactive**
  - Increased psycho-motor activity
  - Agitated behavior

- **Hypoactive**
  - Decreased psycho-motor activity
  - Lethargy
  - Often overlooked

Incidence of Delirium

- Patients age ≥ 65 of age
  - 14% to 24% at hospital admission
  - 6% to 56% of non-ICU hospital patients
  - 70% to 87% of ICU hospital patients
  - 15% to 53% of postoperative patients

Incidence of Delirium

- Delirium in ICU patients < 65 years of age
  - By itself, not a statistically significant risk factor
    - Ouimet and colleagues
      - Age 64.5 for + delirium vs. 62.8 for no delirium (p = 0.069)
    - Eli and colleagues
      - Mean age 54 for + delirium vs. 56 for no delirium (p=0.05)

Delirium Risk Factors

- Advanced age (≥ 65 years old)
- Preexisting dementia
- History of stroke
- Parkinson disease
- Multiple comorbid conditions
- Impaired vision or hearing
- Male gender
- History of alcohol abuse

Adverse Consequences of Delirium

- Increased ICU Length of stay
  - Lat and colleagues: 12.2 days vs. 7.4 days (p <0.01)*
- Increased days on mechanical ventilation
  - Lat and colleagues: 9.1 days vs. 4.9 days (p <0.01)*
- Increased overall hospital length of stay
  - Ely and colleagues showed a median of 10 additional days in length of stay*
- Care of delirious patients ≥ 65 years of age accounts for > 49% of all hospital days.


Adverse Consequences of Delirium

- Increased number of hospital acquired complications
  - Pressure sores and falls
  - Increased likelihood to be discharged to an long-term care facility
- Increased mortality at 6 months and one year post ICU discharge
  - Ely and colleagues showed patients with delirium had a 3x higher risk of 6 month mortality*
    - Every day of delirium in the ICU associated with a 10% higher mortality risk

### Adverse Consequences of Delirium
- Delirious ICU patients 18 months post discharge
  - More cognitive problems
    - Especially names and memory
- Non ICU patients also experienced persistent cognitive impairment
  - Memory
  - “Social blunders”
  - Failed cognitive questionnaire


### Monetary Costs of Delirium
- Estimated increased cost of $2,500 to treat a patient with delirium
  - $6.9 billion additional annual Medicare expenditure (2004 dollars)
- Daily cost of ICU care $3,500*
  - Additional $1,500 per day of mechanical ventilation


### Unique Mechanism of Action
- Benzodiazepines and propofol act on the γ-aminobutyric receptor
- Dexmedetomidine is an α₂- adrenergic receptor agonist
  - Eight times more selective for α₂-adrenoceptors than clonidine
  - Produces sedation and analgesia
    - Attributed to α₂₄-adrenoceptor subtype
    - Opioid sparing analgesic effect
  - No apparent effect on respiratory rate or oxygen saturation


### Incidence of Delirium with Dexmedetomidine vs. Traditional Medications

### Dexmedetomidine: The Good

![Dexmedetomidine molecule](image)

#### Dexmedetomidine: FDA Approved Indications
- Sedation of initially intubated and mechanically ventilated patients during treatment in an intensive care setting, administered by continuous infusion for up to 24 hours
- Sedation of non-intubated patients prior to and/or during surgical and other procedures

*Precede® (dexmedetomidine hydrochloride) prescribing information. Hospira, Inc., Lake Forest, IL 60045 USA*
Effect of Sedation With Dexmedetomidine vs. Lorazepam on Acute Brain Dysfunction in Mechanically Ventilated Patients (MENDS Trial)

- Double-blind, randomized, controlled study
- 106 ICU patients randomized to dexmedetomidine or lorazepam infusion for up to 120 hours
- Target RASS determined by patient’s care team
- Dexmedetomidine infusion rate
  - Initial: 0.15 mcg/kg/hr, titratable to 1.5 mcg/kg/hr
- Lorazepam infusion rate
  - Initial: 1 mg/hr, titratable to 10 mg/hr
- Both arms: Intermittent or continuous infusion fentanyl

MENDS Trial Results

- More days alive without delirium or coma
  - Dexmedetomidine median 7 days vs. lorazepam 3 days (p=0.01)
- Less prevalence of coma
  - Dexmedetomidine 63% vs. lorazepam 92% (p<0.001)
- More time within 1 point of desired RASS score
  - Dexmedetomidine 80% vs. lorazepam 67% (p=.04)

Dexmedetomidine vs. Midazolam for Sedation of the Critically ILL Patient (SEDCOM Trial)

- Prospective, double-blind, randomized trial conducted in 68 facilities in five countries
- Randomized 2:1 to receive Dexmedetomidine (n=250) over midazolam (n=125)
- Target Richmond Agitation and Sedation Score (RASS) of -2 to +1
- Dexmedetomidine initiated at 0.8 mcg/kg/hr
  - Optional 1 mcg/kg loading dose
- Midazolam initiated at 0.06 mg/kg/hr
  - Optional 0.05 mg/kg loading dose
- Both arms: prn iv fentanyl and iv haloperidol

SEDCOM Trial Results

- No difference in target RASS score
- Significant difference in delirium
  - Dexmedetomidine 54% vs. midazolam 76.6% (p<0.001)
- Shorter median time to extubation
  - Dexmedetomidine 3.7 days vs. midazolam 5.6 days (p<0.01)
- Increased incidence of bradycardia
  - Dexmedetomidine 42.2% vs. midazolam 18.9% (p<0.001)
  - Non-significant increase in those requiring treatment (p=0.07)
- Significantly less tachycardia (p<0.001) and less hypertension requiring treatment (p=0.02)

Cost Savings Dexmedetomidine vs. Midazolam for Long-term ICU Sedation

- Secondary analysis of SEDCOM study data
  - Decreased total patient ICU cost in dexmedetomidine patients
    - $9679 median cost savings over midazolam
      - (95% CI, -17045 to – 2314, p<0.01)
    - Cost savings
      - Reduced ICU length of stay
        - Median savings $6584
      - Reduced mechanical ventilation
        - Median savings $2558

Dexmedetomidine and the Reduction of Postoperative Delirium after Cardiac Surgery

- 118 elective cardiac valve surgery patients
- Prospective, open-label, randomized trial
  - Three arms
    - Dexmedetomidine n=40
      - 0.4 mcg/kg bolus
      - 0.2 to 0.7 mcg/kg/hr infusion
    - Propofol n=38
      - 25 to 50 mcg/kg/min infusion
    - Midazolam n=40

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Dexmedetomidine and the Reduction of Postoperative Delirium after Cardiac Surgery

- Incidence of delirium:
  - Dexmedetomidine 3%
  - Propofol 50%
  - Midazolam 50%

- Delirious patients:
  - Significantly longer ICU stay (4.1 days vs. 1.9 days, p<0.001)
  - Significantly longer hospital LOS (10 days vs. 7.1 days, p<0.001)


Safety of Dexmedetomidine Use Beyond 24 Hours

- MENDS Trial
  - Dexmedetomidine infused for up to 5 days
  - Similar side adverse events
    - Except bradycardia (HR < 60)
      - Nine dexmedetomidine arm vs. two lorazepam arm (p=0.03)

- SEDCOM Study
  - Dexmedetomidine infused for a median of 3.5 days (range 2 days to 5.2 days)
  - Similar adverse events
    - Except bradycardia (HR< 40)
      - Nonsignificant increase in those requiring treatment (p=0.07)


Guinter and Kristeller
- Reviewed 6 adult studies with > 24hrs of dexmedetomidine use
- Conclusion
  - “Safety and efficacy of dexmedetomidine in adults likely persists for beyond 24 hours, without the emergence of rebound effects after discontinuation.”


Kunisawa* - Dexmedetomidine is approved in Japan for a duration up to five days
- No restrictions on long term use in Brazil, Columbia and the Dominican Republic

Venn and colleagues* - Dexmedetomidine well tolerated for up to seven days

Roukonen and colleagues** - Dexmedetomidine infusion
  - Median of 40 hours (range 3-198 hours)

**Intensive Care Med 2003;29:201-207.

Thank You!
**Question 1**

Delirium is associated with?

A. Decreased length of hospital stay  
B. Decreased mortality  
C. Long-term cognitive impairment  
D. Decreased ventilator free days  
E. a and b  

Answer: C

**Question 2**

Dexmedetomidine’s mechanism of action is most similar to?

A. Morphine  
B. Diazepam  
C. Propofol  
D. Clonidine  

Answer: D

**Question 3**

Dexmedetomidine for sedation tends to?

A. Decrease the amount of supplemental narcotics required  
B. Increase the amount of supplemental benzodiazepines required  
C. Increase delirium  
D. Induce coma  
E. b and c  

Answer: A

**Question 4**

Dexmedetomidine use for ICU sedation is associated with?

A. An increased incidence of delirium  
B. Elevated serum triglycerides  
C. Decreased incidence of delirium  
D. Respiratory depression  
E. c and d  

Answer: C

**Question 5**

Studies have shown rebound hypertension from abrupt cessation of dexmedetomidine.

A. True  
B. False  

Answer: B

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Dexmedetomidine: the Good, the Bad, + the Delirious

Simon Lam, PharmD, BCPS  
Cleveland Clinic  
Medical ICU Clinical Specialist
Objectives

• Evaluate the clinical data comparing the use of dexmedetomidine (DEX) with other sedatives

• Discuss the potential role of DEX for ICU sedation in selected patients

Dexmedetomidine Use

Ideal Patient

Wrong Patient

Everyone else

Dexmedetomidine MOA

Dexmedetomidine vs. Haloperidol

• Randomized, open-label pilot trial
• Enrolled patients in whom extubation was not possible solely due to agitation
• Dexmedetomidine 0.2-0.7 mcg/kg/hr vs. haloperidol 0.5-2 mg/hr
• Primary outcome: time to extubation

DEX vs. Haloperidol

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>DEX (n=10)</th>
<th>Haloperidol (n=10)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>APACHE II</td>
<td>13.3 (10-18)</td>
<td>15.5 (11-19)</td>
<td>0.383</td>
</tr>
<tr>
<td>Time intubated prior to randomization, h</td>
<td>45.0 (34.5-75.3)</td>
<td>65.2 (28.0-87.0)</td>
<td>0.496</td>
</tr>
</tbody>
</table>

Outcome

<table>
<thead>
<tr>
<th>Outcome</th>
<th>DEX (n=10)</th>
<th>Haloperidol (n=10)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to extubation, h</td>
<td>19.9 (7.3-24)</td>
<td>42.5 (33.2-117.8)</td>
<td>0.016</td>
</tr>
<tr>
<td>ICU length of stay, d</td>
<td>1.5 (1-3)</td>
<td>6.5 (4-9)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

Longer QTc*, %                   | 30            | 70                 | 0.07 |

*One patient had excessive QT prolongation necessitating haloperidol discontinuation

DEX vs. Propofol/Midazolam

• Pilot randomized trial of dexmedetomidine versus standard care (propofol or midazolam)
  – Stratified for baseline sedative, sedation target (RASS 0 to -3 or RASS -4 to -5) and admission type
  – DEX up to 1.4 mcg/kg/hr vs. propofol up to 4 mg/kg/hr (67 mcg/kg/min) or midazolam
• Daily sedation stops included in study protocol
• Co-primary outcomes
  – Time at target sedation (non-inferiority)
  – Length of ICU stay

Reade et al. Crit Care 2009;13:R75

Reade et al. Crit Care 2009;13:R75

**DEX vs. Propofol/Midazolam**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>DEX (n=41)</th>
<th>Propofol/Midazolam (n=44)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time at target sedation, %</td>
<td>64 (0-99)</td>
<td>63 (0-100)</td>
<td>ns</td>
</tr>
<tr>
<td>RASS target 0 to -3, %</td>
<td>74 (0-99)</td>
<td>64 (9-100)</td>
<td>ns</td>
</tr>
<tr>
<td>RASS target -4 to -5, %</td>
<td>42 (0-64)</td>
<td>62 (0-85)</td>
<td>0.006</td>
</tr>
<tr>
<td>Duration of mechanical ventilation, h</td>
<td>77.2 (17.5-338.8)</td>
<td>119.6 (20.1-475.0)</td>
<td>0.109*</td>
</tr>
<tr>
<td>Delirium incidence, %</td>
<td>43.9</td>
<td>25.0</td>
<td>0.035</td>
</tr>
<tr>
<td>Positive CAM-ICU assessments, n (%)</td>
<td>17.0</td>
<td>17.9</td>
<td>ns</td>
</tr>
</tbody>
</table>

Data presented as median (range) unless otherwise indicated
* p < 0.05 after adjustment for baseline stratification on multivariate analysis

**Dexmedetomidine Use**

- Ideal patient
- Wrong patient
- Agitation precludes weaning
- Require heavy sedation; hypotension, bradycardia

**Debate Question**

- Should DEX be **routinely used over other medications** as the sedative of choice for critically ill patients?

**DEX Superiority?**

- Associated with better clinical outcomes / surrogate markers
- Favorable safety profile
- Patients already receiving "best care"

**DEX vs. Midazolam: Clinical Outcomes**

Riker R et al. JAMA 2009; 301:489-499. (SEDCOM)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>DEX (n=249)</th>
<th>Midazolam (n=251)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to extubation, d</td>
<td>3.7 (1.1-4.0)</td>
<td>5.6 (4.6-5.9)</td>
<td>0.01</td>
</tr>
<tr>
<td>ICU LOS, d</td>
<td>5.9 (5.7-7.0)</td>
<td>7.6 (6.7-8.3)</td>
<td>0.24</td>
</tr>
<tr>
<td>30 day mortality, n (%)</td>
<td>51 (21.4)</td>
<td>51 (21.4)</td>
<td>0.60</td>
</tr>
</tbody>
</table>

Jakob SM et al. JAMA 2012; 307:1151-1160. (MIDEX)

<table>
<thead>
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<th>Midazolam (n=251)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of mechanical ventilation, h</td>
<td>123 (67-337)</td>
<td>164 (92-380)</td>
<td>0.03</td>
</tr>
<tr>
<td>ICU LOS, h</td>
<td>231 (115-835)</td>
<td>243 (140-630)</td>
<td>0.27</td>
</tr>
<tr>
<td>45 day mortality, n (%)</td>
<td>68 (27.3)</td>
<td>53 (21.1)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Data in median (IQR), unless otherwise noted

**DEX vs. Lorazepam: Clinical Outcomes**


<table>
<thead>
<tr>
<th>Outcome</th>
<th>DEX (n=53)</th>
<th>Lorazepam (n=51)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanical ventilation-free days, d</td>
<td>22 (0-24)</td>
<td>18 (0-23)</td>
<td>0.22</td>
</tr>
<tr>
<td>ICU LOS, d</td>
<td>7 (5)-29</td>
<td>9 (6-13)</td>
<td>0.92</td>
</tr>
<tr>
<td>28 day mortality, n (%)</td>
<td>9 (17)</td>
<td>14 (27)</td>
<td>0.18</td>
</tr>
</tbody>
</table>

Data in median (IQR), unless otherwise noted

**Data Summary**

- **DEX vs. Propofol/Midazolam**
  - Outcome measures include time to target sedation, RASS, duration of mechanical ventilation, delirium incidence, and positive CAM-ICU assessments.
  - NS indicates not significant.
- **Dexmedetomidine Use**
- **Debate Question**
- **DEX Superiority?**
- **DEX vs. Midazolam: Clinical Outcomes**
  - Includes time to extubation, ICU LOS, and 30 day mortality.
  - SEDCOM is a study by Riker et al. in 2009.
  - MIDEX is a study by Jakob et al. in 2012.
- **DEX vs. Lorazepam: Clinical Outcomes**
  - Measures include mechanical ventilation-free days and ICU LOS.
  - MENDS is a study by Pandharipande et al. in 2007.
DEX vs. Lorazepam: Surrogate Outcomes

- Pandharipande P et al. JAMA 2007; 298:2644-2653

DEX vs. Midazolam: Surrogate Outcomes

- SEDCOM MIDEX
- Agitation • Anxiety • Delirium

Benzodiazepines and Delirium

<table>
<thead>
<tr>
<th>Medication</th>
<th>Delirium OR</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lorazepam</td>
<td>1.2 (1.1-1.4)</td>
<td>0.003</td>
</tr>
<tr>
<td>Midazolam</td>
<td>1.9 (0.9-3.5)</td>
<td>0.09</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>1.2 (0.5-2.9)</td>
<td>0.09</td>
</tr>
<tr>
<td>Morphine</td>
<td>1.1 (0.5-2.2)</td>
<td>0.24</td>
</tr>
<tr>
<td>Propofol</td>
<td>1.2 (0.9-1.7)</td>
<td>0.18</td>
</tr>
</tbody>
</table>

Dex vs. BZD: Outcomes

- Likely earlier extubation with DEX
- No other significant clinical outcome differences
- Likely less delirium
- Methodological issues with MENDS
- Inconsistent effect with midazolam
- BZDs known to be associated with delirium
- Treatment of delirium may not be associated with clinical outcomes

Use of Sedatives in US


DEX vs. Propofol: Outcomes

<table>
<thead>
<tr>
<th>Clinical Outcome</th>
<th>DEX (n=249)</th>
<th>Propofol (n=247)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to extubation, h</td>
<td>69 (39-184)</td>
<td>93 (45-286)</td>
<td>0.04</td>
</tr>
<tr>
<td>Duration of mechanical ventilation, h</td>
<td>97 (45-257)</td>
<td>118 (48-327)</td>
<td>0.24</td>
</tr>
<tr>
<td>ICU LOS, h</td>
<td>164 (90-480)</td>
<td>185 (93-520)</td>
<td>0.54</td>
</tr>
<tr>
<td>45-day mortality, n(%):</td>
<td>43 (17.3)</td>
<td>48 (19.4)</td>
<td>N.S.</td>
</tr>
<tr>
<td>Surrogate Outcome</td>
<td>DEX (n=249)</td>
<td>Propofol (n=247)</td>
<td>p value</td>
</tr>
<tr>
<td>Neurocognitive AE, n(%)</td>
<td>45 (18.3)</td>
<td>71 (28.7)</td>
<td>0.008</td>
</tr>
<tr>
<td>Delirium, n(%)</td>
<td>7 (2.8)</td>
<td>17 (6.9)</td>
<td>N.A.</td>
</tr>
<tr>
<td>CAM-IU positive (48h post sedation), n(%)</td>
<td>22 (9.6)</td>
<td>31 (13.7)</td>
<td>0.231</td>
</tr>
</tbody>
</table>

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- Pandharipande P et al. Anesthesiology 2006; 104:21-26
- Jakob SM et al. JAMA 2012; 307:1151-1160
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- Jakob SM et al. JAMA 2012; 307:1151-1160
Question 1

• When compared to midazolam, dexmedetomidine is more effective at maintaining patients within their target sedation goals.
  A. True
  B. False

  • Answer: B

Question 2

• ICU patients sedated with dexmedetomidine have a shorter duration of mechanical ventilation when compared to propofol.
  A. True
  B. False

  • Answer: B
Question 3

• Compared to sedation with benzodiazepines, dexmedetomidine use has been associated with all of the following except?
  A. Decrease delirium
  B. Decrease incidence of bradycardia
  C. Increase time at target sedation goals
  D. Increase ability to achieve deep sedation

• Answer: B