Agitation in the ICU
Have we swung the pendulum too far from benzodiazepines?

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Conflict of Interest
• The author of this presentation has no conflicts of interest to disclose

Objectives
• Provide an overview of ICU delirium and the 2013 Society of Critical Care Medicine (SCCM) Pain, Agitation, Delirium (PAD) Guidelines
• Analyze how the management of agitation has evolved
• Evaluate how sedation affects delirium outcomes
• Assess the role of benzodiazepines in the management of agitation

Patient Case
• SS is a 35 year old male admitted s/p MVC driving reverse on I-35 diagnosed with traumatic brain injury and multiple rib fractures
• Placed on light sedation protocol with fentanyl and propofol
  – Day 5, triglyceride level = 812 mg/dL
  – Switched to dexmedetomidine
• RASS = +2
  A. Midazolam infusion
  B. Lorazepam intermittent bolus
  C. PRN quetiapine
  D. PRN haloperidol

What would you do?

Why We Need Sedation

The Balancing Act

Over sedation
• Hypotension/hypotension
• Prolonged mechanical ventilation
• Increased length of stay
• Complications
• Increased diagnostic testing
• Delirium

Under sedation
• Hypertension/tachycardia
• Wound rethritism
• Agitation/irritability
• Device removal
• Ventilator asynchrony
• Pain/discomfort
Delirium Definition

“A syndrome characterized by the acute onset of cerebral dysfunction with a change or fluctuation of mental status, inattention, and either disorganized thinking or an altered level of consciousness.”

Classifications

- **Hyperactive**
  - More often associated with hallucinations and delusions
- **Mixed**
  - Mixed features of hyper and hypoactive
- **Hypoactive**
  - Calm or lethargic
  - More often associated with decreased alertness, apathy

Overall Impact

- ↑ Re-intubation rate
- ↑ Length of stay
- ↑ Cost of care
- ↑ Mortality
- ↑ Long-term cognitive impact

Delirium Predicts Mortality

- **Objective**
  - Determine if delirium is an independent predictor of clinical outcomes
- **Design**
  - Single-center, prospective cohort study
- **Population**
  - Mechanically ventilated MCU and coronary ICU patients
- **Interventions**
  - Delirium group vs. No-delirium group
- **Outcomes**
  - Primary: 6-month mortality, hospital LOS, overall LOS
  - Secondary: Ventilator-free days, cognitive impairment at discharge

Primary Outcomes

- **6-month mortality**
  - 34% in delirium group died vs. 15% in no delirium group
- **Hospital LOS**
  - Delirium group spent median LOS 10 days longer
- **Overall LOS**
  - Risk of remaining in hospital wards after ICU discharge 60% greater than those with no delirium

Secondary Outcomes

- **Ventilator-free days**
  - Fewer days spent alive and free of ventilator (19 vs. 24) (p<0.001)
- **Cognitive Impairment**
  - Twice as many patients in delirium group with cognitive impairment at discharge (54.9% vs. 26.9%) (p=0.01)
**Overall Impact**

- ↑ Intubation rate
- ↑ Length of stay
- ↑ Cost of care
- ↑ Mortality
- ↑ Long-term cognitive impact

**Long-Term Cognitive Impact**

- [Graph showing changes over time]

**Etiology**

**Disease-induced**
- Shock, trauma, intra-cerebral hemorrhage, myocardial infarction, PE

**Iatrogenic or environmental**
- Drug-induced
- Prolonged physical restraints and immobilization

**Drug and alcohol withdrawal**
- Opiate or prescription drugs patients taking chronically
- Chronic alcohol use

**Risk Factors**

**Paradigm Shift**

- **2002 SCCM PAD Guidelines**
  - Benzodiazepine first-line sedative (midazolam/diazepam/lorazepam) (C)

- **2013 SCCM PAD Guidelines**
  - Avoidance of benzodiazepines (2B)
Connecting the Dots...

BZD = Delirium = ↑ Mortality

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What would you do?

A. Midazolam infusion
B. Lorazepam intermittent bolus
C. PRN quetiapine
D. PRN haloperidol

Rise of Antipsychotics

- Used mostly for acute agitation
- PAD guidelines recommendations
  - Haloperidol (C)
  - Quetiapine (C)
- High variability in prescribing patterns
- Scant evidence-based recommendations regarding appropriate medical management
- Heterogeneity between trials

Limited Antipsychotic Evidence

<table>
<thead>
<tr>
<th>Design</th>
<th>Population</th>
<th>Interventions</th>
<th>Duration</th>
<th>Results</th>
<th>Conclusion</th>
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<tbody>
<tr>
<td>Double-blind, placebo-controlled, randomized, double-blind, randomized, placebo-controlled</td>
<td>Haloperidol 2.5 mg Q12H vs. 0.9% saline placebo</td>
<td>14 days</td>
<td>No difference in duration of delirium symptoms (p=0.25)</td>
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Limited Antipsychotic Evidence

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<td>Double-blind, placebo-controlled, randomized, double-blind, randomized, placebo-controlled</td>
<td>Quetiapine 50 mg daily vs. 0.9% saline placebo</td>
<td>14 days</td>
<td>No difference in duration of delirium symptoms (p=0.66)</td>
<td>Quetiapine nonsuperior to placebo in the treatment of ICU delirium</td>
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Rise of Antipsychotics

% Respondent Use

Atypical AP

Haloperidol

2007

2001
Consequences

- Cholinesterase inhibitors mentioned as possibly beneficial in American Psychiatric Association guidelines
  - Off label use support by case series
- Maarten M, et al. first multicenter, randomized, placebo-controlled trial
  - Mortality higher in rivastigmine group (n=12 vs. n=4, p=0.07)
  - Study immediately halted!
  - Rivastigmine use also associated with more severe delirium type and longer ICU stay

- Is there risk in using antipsychotics for agitation…?

Off Label Use in Elderly

- Atypical antipsychotics commonly used for off label conditions
  - Agitation, dementia, anxiety
  - Associated with increased mortality
    - Only small improvement in global symptoms
  - Other risks: QT prolongation, hypotension, extrapyramidal symptoms

Have we swung the pendulum too far?

Benzodiazepines

Antipsychotics

Patient Case

- SS is a 35 year old male admitted s/p MVC driving reverse on I-35 diagnosed with traumatic brain injury and multiple rib fractures
- Placed on light sedation protocol with propofol
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  A. Midazolam infusion
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  D. PRN haloperidol

What would you do?

Now what?

Timeline of Benzodiazepine Use

Recommended first-line for acute agitation in 2002 PAD guidelines

2013 guidelines suggest avoiding use as sedative to improve clinical outcomes

Since 2013 guideline release, new studies warrant reconsideration
Sedative Choice ≠ Outcomes

**Objective**
- To assess global cognition and executive function 3 and 12 months after discharge

**Design**
- Multicenter, prospective cohort study

**Population**
- Patients admitted to ICU with respiratory failure or shock

**Interventions**
- Duration of delirium and use of sedative or analgesic medication

**Outcomes**
- Prevalence and severity of long-term cognitive impairment 3 and 12 months after discharge

Pandharipande P, et al. NEJM. 2013; 369;14

Delirium Duration

- Longer duration of delirium independently associated with worse global cognition and executive function ($p = 0.001$) (-6.3 [-10.3 to -2.3])

Medication Use

- No independent association between higher doses of benzodiazepines and worse long-term cognitive scores

Inflammation and Delirium

**Objective**
- To compare biological and drug treatment characteristics in patients with coma and/or delirium while in the ICU

**Design**
- Single-center, prospective cohort study

**Population**
- ICU patients admitted > 24 hours receiving IV fentanyl or IV midazolam

**Interventions**
- Levels of inflammatory mediators present and doses of fentanyl and midazolam

**Outcomes**
- Correlation of clinical variables with delirium and association of inflammatory mediators with coma or delirium


Midazolam correlation with incidence of delirium

- Time to first occurrence of delirium unrelated to administered doses of midazolam ($p = 0.4$)
- Duration of delirium not associated with cumulative midazolam dose ($p = 0.25$)

Inflammatory mediators association with delirium

- 100% delirious patients vs. 33% comatose patients plasma IL-6 conc > 40 pg/mL
- 29% delirious vs. 7% comatose plasma IL-1B concentration above detectable level

Sedation Depth and Mortality

**Objective**
- To evaluate the relationship between early deep sedation, time to extubation, delirium, and long-term mortality

**Design**
- Multicenter, prospective longitudinal cohort study

**Population**
- MICU/SICU patients intubated ≥ 24 hours

**Interventions**
- Deep vs. light sedation level at 48 hours (midazolam, propofol, and dexmedetomidine used)

**Outcomes**
- Time to extubation, subsequent delirium, in-hospital mortality, and 180-day mortality


**Extubation**
- Deeply sedated patients had longer time to extubation ($p = 0.008$)

**Delirium**
- Time to delirium after 48 hours significantly shorter with deep sedation ($p = 0.001$)

**Mortality**
- Higher hospital ($p = 0.004$) and 180-day mortality ($p = 0.001$)
Additional Findings…

- Covariates adjusted for
  - Sedatives used, diagnosis, age, APACHE II score, vasopressors, dialysis
  - Found that cumulative midazolam dose in first 48 hours associated with RASS -3 to -5
- Irrespective of sedative choice, early deep sedation was independently associated with delayed extubation and higher mortality

Sedation Depth and Mortality

PAD guidelines
"Greatest difference in time to awakening seen when deep sedation was the goal of therapy"

Shehabi, et al.
"Early deep sedation predicts outcomes irrespective of sedative choice"

2002
2013

PK/PD Sedatives

<table>
<thead>
<tr>
<th>Drug</th>
<th>MOA</th>
<th>T½ (hr)</th>
<th>Active-Metabolites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midazolam</td>
<td>GABAa agonist</td>
<td>3-11</td>
<td>Yes*</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>GABAa agonist</td>
<td>8-15</td>
<td>No</td>
</tr>
<tr>
<td>Diazepam</td>
<td>GABAa agonist</td>
<td>20-120</td>
<td>No</td>
</tr>
<tr>
<td>Propofol</td>
<td>GABAa agonist</td>
<td>30-60</td>
<td>No</td>
</tr>
<tr>
<td>Dexmedetomidine</td>
<td>Alpha₂ agonist</td>
<td>2 hr</td>
<td>No</td>
</tr>
</tbody>
</table>

*Active metabolites prolong sedation, especially in renal failure

PK/PD Implications

<table>
<thead>
<tr>
<th>PK/PD Implications</th>
<th>Delirium Prevalence</th>
<th>All-cause Short-Term Mortality</th>
</tr>
</thead>
</table>

If *sedation depth* rather than *sedative choice* predicts outcomes…

Why were benzodiazepines shown to be less favorable than other sedative agents?
Continuous Infusion Sedation

<table>
<thead>
<tr>
<th>Study</th>
<th>Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jakob 2012</td>
<td>Dexmedetomidine CI vs. Propofol CI or Midazolam CI</td>
</tr>
<tr>
<td>Pandharipande 2007</td>
<td>Dexmedetomidine CI vs. Lorazepam CI</td>
</tr>
<tr>
<td>Riker 2009</td>
<td>Dexmedetomidine CI vs. Midazolam CI</td>
</tr>
<tr>
<td>Rouknen 2009</td>
<td>Dexmedetomidine CI vs. Midazolam CI vs. Propofol CI</td>
</tr>
<tr>
<td>Weinbroun 1997</td>
<td>Propofol CI vs. Midazolam CI</td>
</tr>
</tbody>
</table>

CI = continuous infusion

Importance of Timing

- Methodological inconsistency in timing of delirium assessments regarding sedative administration
  - Medication not always completely stopped prior to assessment
  - Different sedatives = different half-lives
    - Benzodiazepines take longer to clear

![Graph showing the timing of sedation stopped](image)

CAM-ICU Assessment

- **Feature 1**
  - Is patient different than his/her baseline mental status?
  - OR has patient had fluctuation in mental status in past 24 hours

- **Feature 2**
  - SAVEAHAART

- **Feature 3**
  - Present if RASS anything other than 0 (alert and calm)

- **Feature 4**
  - Ability to answer yes/no questions

CAM-ICU Positive (delirium present)

Looking more closely...

Lorazepam is an Independent Risk Factor for Transitioning to Delirium in Intensive Care Unit Patients – Anesthesiology. 2006.

- Lack of delirium assessments
- Lack of power


- Propofol group had more rapid awakening, leading to better performance of spontaneous breathing trials and earlier extubation
- Lorazepam group had earlier resumption of sedation
Is Delirium Dichotomous?

Yes vs. No

Heterogenous

Sedation-Related Delirium

<table>
<thead>
<tr>
<th></th>
<th>ND</th>
<th>RRD</th>
<th>Mixed</th>
<th>PD</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days MV</td>
<td>2.4 (1.3-3.1)</td>
<td>2.5 (1.6-2.8)</td>
<td>1.1 (2.2-12.0)</td>
<td>6.2 (3.7-12.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ICU LOS</td>
<td>4.0 (2.4-8.1)</td>
<td>4.5 (2.2-7.2)</td>
<td>9.7 (6.0-17.7)</td>
<td>13.1 (8.8-19.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hospital LOS</td>
<td>8.1 (7.7-16.9)</td>
<td>8.7 (3.8-16.4)</td>
<td>26.8 (9.6-50.0)</td>
<td>25.4 (13.6-29.6)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Sedation-Related Delirium

- Rapidly reversible delirium ≠ persistent delirium
- Sedative-induced delirium ≠ sepsis-related delirium

Persistent | Rapidly-reversible

Sicker group, higher ages, more sepsis, likely more encephalopathy, ↑ 1-year mortality (p<0.001)

No difference in discharge disposition or mortality risk from patients with no delirium

Future Considerations

- Benzodiazepines when administered intermittently may still have a role to play in the treatment of agitation
  - PRN use in previous large randomized-controlled studies (PRODEX/MIDEX/Sedcom)
  - Shown to be effective in achieving goal sedation

<table>
<thead>
<tr>
<th>Sedcom trial</th>
<th>% PRN benzodiazepine use</th>
</tr>
</thead>
<tbody>
<tr>
<td>63% Dexmedetomidine vs. 49% Midazolam (p=0.02)</td>
<td></td>
</tr>
</tbody>
</table>
Timeline of Benzodiazepine Use

- Recommended first-line for acute agitation in 2002 PAP guidelines
- 2013 guidelines suggest avoiding use as sedative to improve clinical outcomes
- Since 2013 guideline release, new studies use of PRN benzodiazepines warrant reconsideration

Patient Case
- SS is a 76 year old male admitted for acute respiratory failure requiring intubation
- Placed on light sedation protocol with fentanyl and propofol
  - Day 5, TG level = 812 mg/dL
  - Switched to dexmedetomidine
    - RASS = +2, unable to achieve RASS -1 to -2

Solution...PRN benzodiazepines!

Conclusions
- ICU Delirium has significant impact on outcomes in critically ill patients
- Major shift in prescribing patterns when literature identified BZD routine use to be an independent risk factor of increased mortality
- Minimal evidence to support routine use of antipsychotics to treat ICU delirium
- Studies after release of new SCCM guidelines suggest ICU delirium not linked to sedative choice but rather to sedation depth
- ICU delirium is not dichotomous, meaning treatment efficacy may be impacted by delirium classification
- Intermittent BZD use is still a valid option for management of agitation in the ICU and warrants future studies

Acknowledgements
- Dr. Mitchell J. Daley, PharmD, BCPS
- Dr. Manasa S. Murthy, PharmD, BCPS

THANK YOU!!!
### Appendix

**STEP 1**

**Level of Consciousness Assessment**

<table>
<thead>
<tr>
<th>Scale</th>
<th>Label</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>+4</td>
<td>COMBATIVE</td>
<td>Combative, violent, immediate danger to staff</td>
</tr>
<tr>
<td>+3</td>
<td>VERY AGITATED</td>
<td>Pulls to remove tubes or catheters; aggressive</td>
</tr>
<tr>
<td>+2</td>
<td>AGITATED</td>
<td>Frequent non-purposeful movement, fights ventilator</td>
</tr>
<tr>
<td>+1</td>
<td>RESTLESS</td>
<td>Anxious, apprehensive, movements not aggressive</td>
</tr>
<tr>
<td>0</td>
<td>ALERT &amp; CALM</td>
<td>Spontaneously pays attention to caregiver</td>
</tr>
<tr>
<td>-1</td>
<td>DROWSY</td>
<td>Not fully alert, but has sustained awakening to voice (eye opening &amp; contact &gt;10 sec)</td>
</tr>
<tr>
<td>-2</td>
<td>LIGHT SEDATION</td>
<td>Briefly awakens to voice (eyes open &amp; contact &lt;10 sec)</td>
</tr>
<tr>
<td>-3</td>
<td>MODERATE SEDATION</td>
<td>Movement or eye opening to voice (no eye contact)</td>
</tr>
<tr>
<td>-4</td>
<td>DEEP SEDATION</td>
<td>No response to voice, but movement or eye opening to physical stimulation</td>
</tr>
<tr>
<td>-5</td>
<td>UNAROUSABLE</td>
<td>No response to voice or physical stimulation</td>
</tr>
</tbody>
</table>

If RASS is ≥ -3 proceed to CAM-ICU (Is patient CAM-ICU positive or negative?)

If RASS is -4 or -5 → STOP (patient unconscious), RECHECK later

---

Ely, et al., JAMA 2003; 286, 2983-2991
### CAM-ICU Worksheet

#### Feature 1: Acute Onset or Fluctuating Course

<table>
<thead>
<tr>
<th>Score</th>
<th>Check here if Present</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
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</table>

**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?**

**Score**

**Check here**

**Either question Yes →**

#### Feature 2: Inattention

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

**Directions:** 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.

SAVE HA ART or CASABL ANCA or ABDABADAAY

Errors are counted when patient fails to squeeze on the letter “A” and when the patient squeezes on any letter other than “A.”

**Number of Errors >2 →**

#### Feature 3: Altered Level of Consciousness

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

**RASS anything other than zero →**

#### Feature 4: Disorganized Thinking

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

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?

**Errors are counted when the patient incorrectly answers a question.**

**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 2nd part of command ask patient to “Add one more finger”

**An error is counted if patient is unable to complete the entire command.**

**Combined number of errors >1 →**

#### Overall CAM-ICU

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

**Criteria Met →**

**△ CAM-ICU Positive (Delirium Present)**

**Criteria Not Met →**

**△ CAM-ICU Negative (No Delirium)**

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