Recognizing, Preventing and Treating Delirium in the Critically Ill

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Case Study

• PN is 58- yo male admitted with COPD/ pneumonia
• Currently receiving midazolam 2 mg/hr + frequent boluses and fentanyl 100 mcg/hr + occasional boluses
• RASS "sedation" score overnight ranges between -3 (moderate sedation) to +2 (agitated)
• Intermittently responsive to commands, oriented only to person despite frequent reminders, thought nurse was his wife

DELIRIUM: EPIDEMIOLOGY AND RISK FACTORS

Prevalence of ICU Delirium

• Adults: 60-80% of MICU/SICU/TICU mechanically ventilated patients develop delirium
• Children: 13.2%
• 20-50% of lower severity ICU patients develop delirium
• Hypoactive more common than hyperactive
• Most delirium goes undiagnosed in ICU if a validated delirium screening tool is not implemented

Sequelea of Delirium

- Increased mortality
- 3x greater re-intubation rate
- Average 10 additional days in hospital
- Higher costs of care

- Increased mortality
- Development of dementia
- Long-term cognitive impairment
- Requirement for care in chronic care facility
- Decreased functional status at 6 months

Paradigm Shift in the Outcomes Being Evaluated in Clinical Research

Outcomes During ICU Stay

- Time spent within sedation goal
- Episodes of agitation
- Episodes of agitated-related events
- Delirium
  - Prevalence of delirium
  - Days spent with delirium
  - Duration of mechanical ventilation
  - Duration of ICU stay
  - ICU mortality

Outcomes After ICU Stay

- Disposition and functionality
- Cognition/Dementia
- Sleep quality
- ICU memories/PTSD
- Quality of life
- Depression
- Executive function

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### Patient Factors
- Alcoholism
- Increased age
- Male gender
- Living alone
- Smoking

### Less Modifiable

### Environment
- Use of physical restraints
- Isolation
- No clock
- No daylight
- No visitors
- Noise

### More Modifiable

### Pre-existing Disease
- Dementia
- Hypertension
- Pulmonary disease
- Renal disease

### Acute Illness
- Severity of illness
- Development of coma
- Length of stay
- Fever
- Medicine service
- Lack of nutrition
- Septic/hypotension
- Metabolic disorders
- Tubes/catheters

### Medications:
- Benzodiazepines
- Opioids
- Anticholinergics
- Corticosteroids


### Ouimert S et al. ICM. 2007; 33:66-73.


### More Modifiable


### DELIRIUM MONITORING

### Survey: Symptoms Most Associated with Delirium

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Frequency (%)</th>
<th>Frequency in Pharmacist Survey (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hallucinations</td>
<td>42</td>
<td>N/A</td>
</tr>
<tr>
<td>Psychomotor slowing</td>
<td>36</td>
<td>N/A</td>
</tr>
<tr>
<td>Altered LOC</td>
<td>85</td>
<td>6</td>
</tr>
<tr>
<td>Disorganized thinking</td>
<td>89</td>
<td>17</td>
</tr>
<tr>
<td>Agitation</td>
<td>86</td>
<td>49</td>
</tr>
<tr>
<td>Inattention</td>
<td>95</td>
<td>8</td>
</tr>
</tbody>
</table>


### Confusion Assessment Method (CAM-ICU)

1. Acute onset of mental status changes or a fluctuating course
2. Inattention
3. Altered level of consciousness
4. Disorganized thinking

= Delirium


### Pediatric CAM-ICU

- 146 paired assessments
- Age = 12.2 years old
- 2 critical care clinicians vs. pediatric psychiatrists
- Sensitivity = 83% (95% CI, 66-93%)
- Specificity = 96% (95% CI, 95-100%)
- Inter-rater reliability = K=0.96

### Intensive Care Delirium Screening Checklist

1. Altered level of consciousness
2. Inattention
3. Disorientation
4. Hallucinations
5. Psychomotor agitation or retardation
6. Inappropriate speech
7. Sleep/wake cycle disturbances
8. Symptom fluctuation

Score 1 point for each component present during shift.
- Score of 1-3 = Subsyndromal Delirium
- Score of ≥4 = Delirium

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### Current Delirium Screening Practices of Critical Care Pharmacists

- Delirium status frequently or always discussed: 50%
- Delirium status screened ≥50% of the time: 18%
- Pharmacist screened for delirium ≥1 patient: 32%
- 64% screen for delirium in ≤10% of patients

Barriers to delirium screening per pharmacists:
- Lack of time = 34%
- Is a nursing role = 24%
- Do not feel comfortable using screening tool = 13%

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### Strategies to Boost Delirium Screening

- Ensure sedation assessment is occurring regularly and reliably
- Obtain strong buy-in from both RN and MD ICU managers
- Education:
  - Didactic (e.g., web) and at bedside
  - Delivered to both day and night nurses
  - Ensure that education is repeated on a continuous basis
- Ability to recognize delirium may be compromised in routine practice (e.g., sensitivity of CAM-ICU = 47% in 10 Dutch ICUs)
- Should include all physicians
- Nurses have been evaluating many delirium symptoms for years.....they just do not realize it!
- Incorporate in any DA-SBT protocol and daily rounds checklist

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### Which symptom does indicates “delirium” in PN?

A. Fluctuating symptoms
   - varying RASS score and intermittently attentive

B. Agitation
   - RASS score of +2 requiring sedation boluses

C. Inattention
   - only intermittently following commands

D. Disorganized thinking
   - not oriented to place and thought the nurse was his wife

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Early Mobilization

<table>
<thead>
<tr>
<th></th>
<th>Mobilization (N = 49)</th>
<th>Control (N = 55)</th>
<th>P - Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICU/hospital days with delirium (days)</td>
<td>2</td>
<td>4</td>
<td>0.03</td>
</tr>
<tr>
<td>% time in ICU with delirium</td>
<td>33%</td>
<td>57%</td>
<td>0.02</td>
</tr>
<tr>
<td>% time in Hospital with Delirium</td>
<td>28%</td>
<td>41%</td>
<td>0.01</td>
</tr>
</tbody>
</table>


Daily Awakening – Spontaneous Breathing Trial

<table>
<thead>
<tr>
<th></th>
<th>DA-SBT (N = 49)</th>
<th>SBT only (N = 55)</th>
<th>P - Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coma (days)</td>
<td>2</td>
<td>3</td>
<td>0.03</td>
</tr>
<tr>
<td>Delirium (days)</td>
<td>2</td>
<td>2</td>
<td>0.55</td>
</tr>
</tbody>
</table>

*Median days


SEDCOM: Reduced Delirium with Dexmedetomidine vs Midazolam

<table>
<thead>
<tr>
<th></th>
<th>Patients, With Delirium</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Day 1</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Day 2</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Day 3</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Day 4</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Day 5</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Day 6</td>
<td>100</td>
<td></td>
</tr>
</tbody>
</table>


MENDS: Dexmedetomidine vs Lorazepam

P = 0.011

P = 0.001

P = 0.025

Dexmedetomidine (n = 52)

Lorazepam (n = 51)

*No daily sedation awakening


Impact of an Analgesia-First Strategy

P = 0.04

P = 0.02


Canadian ICU Sedation Protocol Decreased Subsyndromal Delirium but Not Delirium Incidence When Coma and Benzodiazepine Use Was Avoided


Mechanically Ventilated Patients with Sub-syndromal Delirium [ICDSC 1-3]

Haloperidol 1mg IVP q6h

Placebo

- No antipsychotic rescue medication or dexmedetomidine allowed
- Sedation titrated to maintain SAS ≥ 3

Outcomes:

Primary: % of patients progressing to full delirium

Secondary:

1. Hours spent agitated
2. Hours spent mechanically ventilated
3. Safety
4. 1 week, psychologic and cognitive evaluation
5. 6 month sleep, psychologic, cognitive and functional evaluation

DELIRIUM TREATMENT

Mechanisms for Delirium in the Critically Ill are Numerous and Still Not Clearly Understood

- Neurotransmitter imbalance
- Neuroinflammation
- Blood brain barrier permeability
- Impaired oxidative metabolism
- Microglial activation
- Abnormal levels of large neutral amino acids (e.g., tryptophan) and its metabolism (e.g., kynurenine pathway)

Adoptions: Crit Care Clin 2008; 24:789

What is the first-line pharmacologic treatment option for ICU patients with delirium at your institution?

A. Atypical antipsychotic (e.g., quetiapine)
B. Benzodiazepine (e.g., lorazepam)
C. Dexmedetomidine
D. Haloperidol

Survey: First-Choice Delirium Treatment Options

- Delirium should always be managed with a medication: 85%
- Use ≥2 medications to treat delirium: 68%

Characteristics of Haloperidol Use (always or frequently)

- Oral: 23%; IV 93%
- As needed: 93%; Scheduled: 61%; Infusion: 0%
- ≤4mg/day: 47%; 5-10mg/d: 56%; 11-20mg/d: 38%; ≥21mg/d: 9%
- ≤4mg/day: 47%; 5-10mg/d: 56%; 11-20mg/d: 38%; ≥21mg/d: 9%
- Length of stay, days
  - ICU: 11.7, 9.6, 7.3
  - Hospital: 13.8, 13.5, 15.4
- 21-day mortality, n (%)
  - Haloperidol, n = 35
  - Ziprasidone, n = 30
  - Placebo, n = 36

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>0.88</td>
</tr>
<tr>
<td>Resolution of delirium on study drug, n (%)</td>
<td>24 (89)</td>
<td>22 (77)</td>
<td>21 (68)</td>
<td>0.28</td>
</tr>
<tr>
<td>Cona days</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>0.90</td>
</tr>
<tr>
<td>% of days accurately sedated</td>
<td>70</td>
<td>64</td>
<td>71</td>
<td>0.91</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>ICU</td>
<td>11.7</td>
<td>9.6</td>
<td>7.3</td>
</tr>
<tr>
<td></td>
<td>Hospital</td>
<td>13.8</td>
<td>13.5</td>
<td>15.4</td>
</tr>
<tr>
<td>21-day mortality, n (%)</td>
<td>4 (11)</td>
<td>4 (14)</td>
<td>5 (17)</td>
<td>0.81</td>
</tr>
<tr>
<td>Average extrapyramidal symptoms score</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.55</td>
</tr>
</tbody>
</table>


John M. Devlin, PharmD, Nnessa J. Roberts, PharmD, Jeffrey J. Feng, PharmD, Yeonaseo Seo, MD, Richard R. Hiler, MD, Nicholas S. Hill, MD, Tracye Robakowski, RN, Erik Garpestad, MD

- Design: Double-blind, placebo-controlled, randomized trial
- Setting: 3 academic medical centers
- Intervention:
  - Quetiapine 50mg PO/NGT twice daily titrated to a maximum of 200mg twice daily vs Placebo
  - PRN IV haloperidol protocelized and encouraged in each group
  - Oversedation: hold study drug when SAS ≤ 2 (after holding sedation therapy)
- Primary outcome:
  - Time to first resolution of delirium (i.e., first 12 hour period when ICDSC ≤ 3)

Impact of Quetiapine on the Resolution of Individual Delirium Symptoms

Median ICDSC and individual delirium symptoms similar at study baseline

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Quetiapine</th>
<th>Placebo</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inattention</td>
<td>3 hrs</td>
<td>6 hrs</td>
<td>0.10</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>2 hrs</td>
<td>15 hrs</td>
<td>0.10</td>
</tr>
<tr>
<td>Agitation</td>
<td>3 hrs</td>
<td>1 hrs</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Clinical Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Quetiapine (n=18)</th>
<th>Placebo (n=18)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time of study drug administration (hours)</td>
<td>102 (96-109)</td>
<td>106 (100-205)</td>
<td>0.04</td>
</tr>
<tr>
<td>Time in delirium (hours)</td>
<td>36 (12-87)</td>
<td>32 (7-159)</td>
<td>0.006</td>
</tr>
<tr>
<td>Time spent agitated (SAS ≤ 5) (hours)</td>
<td>0 (0-50)</td>
<td>0 (0-50)</td>
<td>0.73</td>
</tr>
<tr>
<td>Percent of time spent in delirium after ICU</td>
<td>0 (0-14)</td>
<td>14 (0-47)</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Subject placement after hospital discharge (%)

- Home / rehabilitation center: 30 vs. 50, p=0.05
- Chronic care facility / another acute care hospital / death: 11 vs. 44, p=0.05

Methodologic Considerations for Future Studies Investigating Antipsychotic Therapy

For ICU Delirium Prevention or Treatment

- Interventions shown to reduce delirium in the ICU are maximized.
- Use of a placebo arm that does not involve antipsychotic administration.
- Evaluate the response of individual delirium symptoms.
- Antipsychotic dose strategy in study based on formalized dose-response testing.
- Avoidance of excessive levels of sedation
- Adequate sample to standard ICU patient outcomes.
- Evaluation of post-ICU psychologic, sleep and functional outcomes.


- "Antipsychotic medications are often the treatment of choice" (Grade I = recommended with substantial clinical confidence)


- "Haloperidol is the preferred agent for the treatment of delirium in critically ill patients." (Grade C Recommendation)

UK Delirium Guidelines (2010)

- "Low dose and short-term haloperidol or olanzapine therapy if patient remains distressed or agitated that is severe enough to cause arm after identify and manage all possible underlying causes and provide effective communication, reorientation and reassurance" (Grade B)

German Guidelines (2010)

- "May be role for antipsychotic therapy for treatment" - Consider treatment with alpha-2 agonist (not graded)

SCCM Guidelines (2012)

- "Haloperidol is the preferred agent for the treatment of delirium in critically ill patients." (Grade C Recommendation)
Pharmacological Considerations When Treating Delirium

- Pharmacological therapy should be considered **ONLY** after underlying causes for delirium are reversed/treated.
- Pharmacological therapy should be reserved for patients with severe agitation that will affect patient/caregiver safety.
- Wean down any antipsychotic regimen to off if patient no longer agitated.
- Make sure there is a plan to discontinue any antipsychotic regimen at ICU/hospital discharge.

Scheduled Antipsychotic Use in the LTACH Setting

<table>
<thead>
<tr>
<th>Scheduled AP use ≥ 24h</th>
<th>% started on AP at outside ICU</th>
<th>% of LTAC days scheduled AP administered</th>
<th>Name of AP administered</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>-</td>
<td>quetiapine (77%); olanzapine (10%)</td>
</tr>
</tbody>
</table>

% of scheduled AP days the following were administered:
- As needed AP
- Restraints
- Anxiolytic (100% benzodiazepine)

% of scheduled AP days that key delirium words documented:
- Delirium
- Agitation
- Inattention
- Confusion

% of scheduled AP patients ever evaluated by a psychiatrist

% of scheduled AP days ECG conducted (as a % of the AP days)
- ≥ 1 fall
- ≥ 1 episode of a SBP ≤ 90 mmHg
- ≥ 1 extrapyramidal symptom

Conclusions

- Delirium is common in both critically ill adults and children.
- Pharmacists can play a key role in screening for delirium with either the CAM-ICU or ICDSC.
- Education that is substantial, occurs at the bedside, and is repeated on a regular basis should accompany any new delirium screening effort.
- Treat pain and screen for delirium before administering sedation.
- Optimize non-pharmacologic delirium prevention efforts that decrease coma and improve functionality (e.g., DA-SBT, early mobilization).
- Dexmedetomidine may lead to less coma and delirium than benzodiazepine therapy.
- No rigorous evidence to support prophylactic antipsychotic therapy.
- No rigorous evidence that haloperidol improves outcome in any ICU population.
- Antipsychotics should only be used (on a short term basis) for patients having delirium that is accompanied by agitation.
- Pharmacists can play a key role in decreasing the number of ICU and post-ICU patients exposed to antipsychotic therapy.