Identification, Prevention and Treatment of Delirium: The Role of the Health System Pharmacist

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Objectives
- Increase awareness of outcomes associated with delirium
- Identify risk factors for development of delirium
- Describe the pharmacological options available for delirium in critically ill patients
- Compare the current literature on the advantages and disadvantages of these agents
- Discuss how the use of these agents can be applied to your current practice

Disclosure
- I do not have a vested interest in or affiliation with any corporate organization offering financial support or grant monies for this continuing education activity, or any affiliation with an organization whose philosophy could potentially bias my presentation
- Jennifer Cortes- member of the education committee

SCCM PAD Guidelines
- SCCM clinical practice guidelines- 2013
  - Pain
  - Agitation and sedation
  - Delirium
- Goal: to recommend best practices for managing PAD to improve clinical outcomes in adult ICU patient

Defining Delirium
- Acute onset of cerebral dysfunction
- Change in baseline mental status, inattention, and either disorganized thinking or altered level of consciousness
Defining Delirium

- Features
  - Disturbed level of consciousness
  - Change in cognition or development of a perceptual disturbance
  - Patient does not have to be hallucinating or delusional

What Does Delirium Look Like?

- Sleep disturbances
- Abnormal psychomotor activity
- Emotional disturbances
- Agitation-Hyperactive
- Calm or lethargic: Hypoactive

Acute Brain Dysfunction

Incidence of Delirium

| Medical floor admission (non-elderly) | 5% |
| Medical floor admission (elderly)    | 10-30% |
| Hip fracture surgery (elderly)       | 30-42% |
| Cardiac surgery (elderly)            | 50% |
| Medical ICU (intubated; non-elderly) | 30-40% |
| Medical ICU (intubated; elderly)     | 50-70% |

What outcomes are associated with delirium in adult ICU patients?

- Increased mortality (A)
- Prolonged ICU and hospital LOS (A)
- Post-ICU cognitive impairment (B)

Delirium Outcomes

- 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
Risk Factors

- Preexisting dementia
- History of hypertension
- History of alcoholism
- High severity of illness at admission

Risk Factors

- Relationship between opioids, benzodiazepine, propofol, dexmedetomidine and delirium is conflicting
- Benzodiazepine use may be a risk factor (B)
- Unknown whether dexmedetomidine lowers the risk (B)

What risk factors are associated with development of delirium in the ICU?

Four baseline factors positively and significantly associated with delirium (B)

Patient Factors
- Chronic alcohol use
- Severity of illness
- Increased age?

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

Predisposing Disease
- Dementia
- HTN
- Cardiac disease
- Pulmonary disease

Acute Illness
- Length of stay
- Fever
- Medicine service
- Lack of nutrition
- Hypotension
- Sepsis
- Metabolic disorders
- Tubes/catheters
- Medications

Should ICU patients be monitored routinely for delirium with an objective bedside delirium instrument?

Routine monitoring for delirium recommended (+1B)
What We Don’t Know
Can Hurt Us

- Presence of delirium often underestimated
  - Frequently presents as hypoactive
- Detection improved when caregivers use a valid and reliable assessment tool

Which Scale To Use?

- CAM-ICU
  - Confusion Assessment Method for the ICU
- ICDSC
  - Intensive Care Delirium Screening Checklist
- High inter-rater reliability
- High sensitivity and specificity against American Psychiatric Association’s criteria for delirium (A)

Symptoms: Perception vs. Reality

Keys to Boosting Delirium Screening

- Is sedation assessment consistently occurring and are the measurements reliable?
  - If yes, consider tackling delirium screening
- Do nurses and physicians support delirium screening?
  - If yes, develop an implementation team involving key stakeholders
- Develop an educational model:
  - Both didactic (e.g. web) and at bedside
  - Both day and night RNs
  - Pharmacists can play important role

CAM-ICU

Must have 1 AND 2

1. Acute onset or fluctuating mental status
   - Different from baseline or
   - Sedation score fluctuation over 24 hr (RASS) — can only do if not deeply sedated (i.e. RASS is ≤7–8)
2. Inattention (present if score ≤ 7/10)
   - SAFEHART or
   - ASE pictures
   - Command – hold up fingers (score 1 point if able to do with both hands)
   - Present if cumulative score ≤ 3
3. Disorganized thinking
   - Four yes/no questions (score each correct answer one point)
   - OR
   - Present if cumulative score ≤ 3
4. Altered level of consciousness
   - Use sedation score

Intensive Care Delirium Screening Checklist (ICDSC)

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 present
- Score of 1-3 = Subsyndromal Delirium
- Score of 2-4 = Delirium

Keys to Boosting Delirium Screening

• Be comfortable with “not being able to evaluate” some patients or symptoms
  – Document and communicate a reason
• Recognize and promote that nurses have been evaluating many of the symptoms of delirium for years without realizing it
• Make sure all clinicians know the delirium screening tool and discuss results on daily rounds

Summary

• Delirium associated with increased mortality, LOS and post-ICU cognitive impairment
• Risk factors include
  – Dementia
  – HTN
  – Alcoholism
  – Severity of illness
• Delirium assessment should be routinely performed in all ICU patients

Delirium? Stop and THINK

Do any meds need to be stopped or lowered?
• Especially consider sedatives
• Is patient on minimal amount necessary?
  – Daily sedation cessation
  – Targeted sedation plan
• Do sedatives need to be changed?

Toxic Situations
  • CHF, shock, dehydration
  • Deliriogenic meds (tight titration)
  • New organ failure (liver/kidney)

Hypoxemia

Infection/sepsis (nosocomial)

Immobilization

Nonpharm interventions
  • Hearing aids, glasses, nonverbal, sleep protocols, music, noise control, ambulation
  • K+ or electrolyte problems

Can we prevent delirium?

Medication-Related Delirium: Minimizing the Risk

Avoid polypharmacy/Ensure medication dosing is appropriate
Consider medication withdrawal
Avoid anticholinergic medications whenever possible
Avoid benzodiazepine medications whenever possible
Minimize use of non-benzodiazepine sleep medications
Use the lowest effective corticosteroid dose
Use the lowest effective opioid dose to control pain/maximize use of non-opioid analgesics
Avoid metoclopramide (Reglan®) when possible
If delirium occurs in a patient receiving famotidine, switch to pantoprazole
If delirium occurs in a patient who is receiving levetiracetam (Keppra®), consider other anticonvulsant options
Reassess need for continued antibiotic therapy
Monitor diuretic therapy for signs of dehydration and/or electrolyte abnormalities
Check a serum drug concentration if a medication is being administered where supratherapeutic concentrations might cause delirium-like symptoms

Non-pharmacological Interventions

• Control stimuli (decrease or augment)
• Presence of familiar objects/ family support
• Use both verbal and nonverbal communication
• Let patient wear glasses/hearing aid if possible
• Avoid restraints
• Restore sleep-wake cycle
Sleep

- Sleep deprivation
  - Few complete sleep cycles
  - Environmental disruptions
  - Infrequent rapid-eye-movement sleep
- Development of delirium and increased physiological stress
  - Affects healing response

Non-pharmacological Interventions

**MOBILITY!!**

- Recommend early mobilization of adult ICU patients be performed whenever feasible to reduce the incidence and duration of delirium (+1b)

Early Mobilization

- Return to independent functional status at d/c
  - Intervention 59% vs. control 35%; *p* = 0.02

Mobility

**PROACTIVE** in developing non-pharmacological delirium protocol that includes **MOBILITY!**

Should haloperidol be used prophylactically to prevent delirium in ICU patients?

Haloperidol not recommended to prevent delirium in ICU patients. (-2C)

Prophylaxis and Post-op Delirium

Haloperidol PO 0.5 mg TID pre-op and post-op X 3 days vs. placebo in patients (age ≥ 70) undergoing elective hip fracture surgery

Incidence of Delirium

![Incidence of Delirium Graph](image1.png)

- Haloperidol
- Placebo

Delirium Duration

![Delirium Duration Graph](image2.png)

- Haloperidol
- Placebo

P < 0.001

Hospital LOS

![Hospital LOS Graph](image3.png)

- Haloperidol
- Placebo

P < 0.001

Haloperidol PO 0.5 mg TID pre-op and post-op X 3 days vs. placebo in patients (age ≥ 70) undergoing elective hip fracture surgery
Prophylaxis and Delirium Incidence

<table>
<thead>
<tr>
<th>Treatment: haloperidol 0.5 mg IV bolus + 0.1 mg/hr infusion x 12 hr</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Haloperidol (n=229)</strong></td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>APACHE-2</td>
</tr>
<tr>
<td>Intubated (%)</td>
</tr>
</tbody>
</table>


Prophylaxis and Delirium Incidence

<table>
<thead>
<tr>
<th>Treatment: haloperidol 0.5 mg IV over 12 hrs (n=229)</th>
<th>Placebo (n=228)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall Incidence</strong></td>
<td>15.3%</td>
<td>23.3%</td>
</tr>
<tr>
<td>Length of stay in intensive care unit, median</td>
<td>21.3 (9.1-33.2)</td>
<td>23.0 (9.9-25.1)</td>
</tr>
<tr>
<td>Time to start of delirium*, mean (95% CI), d</td>
<td>6.2 (5.9-6.4)</td>
<td>5.7 (5.4-6.0)</td>
</tr>
</tbody>
</table>


Prophylaxis in critically ill patients at high risk for delirium

<table>
<thead>
<tr>
<th><strong>PREDILRIC risk (%)</strong></th>
<th>Control Group</th>
<th>Intervention Group</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>73</td>
<td>75</td>
<td>0.58</td>
<td></td>
</tr>
</tbody>
</table>


- Prophylaxis resulted in 20% reduction in 28 day mortality
- High risk patients appear to benefit most from prophylaxis but no significance was found

Should atypical antipsychotics be used prophylactically to prevent delirium in ICU patients? Atypical antipsychotics not recommended to prevent delirium in ICU patients. (-2C)

Ziprasidone & haloperidol for delirium prophylaxis (MIND)

<table>
<thead>
<tr>
<th>Outcomea</th>
<th>Haloperidol, n = 35</th>
<th>Ziprasidone, n = 30</th>
<th>Placebo, n = 36</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delirium/coma-free daysb</td>
<td>14.8 (6.0-18.0)</td>
<td>15.0 (11.1-18.0)</td>
<td>12.5 (12.3-17.2)</td>
<td>0.66</td>
</tr>
<tr>
<td>Delirium days</td>
<td>4 (2-7)</td>
<td>4 (2-8)</td>
<td>4 (2-8)</td>
<td>0.93</td>
</tr>
<tr>
<td>Resolution of delirium on study drug, n (%)</td>
<td>24 (69)</td>
<td>20 (67)</td>
<td>21 (58)</td>
<td>0.28</td>
</tr>
<tr>
<td>Cumulative days</td>
<td>2 (0-4)</td>
<td>2 (0-4)</td>
<td>2 (0-5)</td>
<td>0.90</td>
</tr>
<tr>
<td>% of days accurately labeledb</td>
<td>78 (56-80)</td>
<td>50 (96-94)</td>
<td>71 (52-92)</td>
<td>0.53</td>
</tr>
<tr>
<td>Ventilation-free days</td>
<td>7.5 (6.0-8.9)</td>
<td>12.0 (10.0-13.0)</td>
<td>12.5 (10.0-21.30)</td>
<td>0.25</td>
</tr>
<tr>
<td>Length of stay, days</td>
<td>ICU</td>
<td>11.7 (8.0-15.7)</td>
<td>9.6 (8.0-14.5)</td>
<td>7.3 (4.7-12.3)</td>
</tr>
<tr>
<td>Hospital</td>
<td>11.3 (9.0-30.4)</td>
<td>13.5 (9.0-30.7)</td>
<td>15.4 (9.8-36.3)</td>
<td>0.88</td>
</tr>
<tr>
<td>21-day mortality, n (%)</td>
<td>4 (11)</td>
<td>9 (30)</td>
<td>6 (17)</td>
<td>0.11</td>
</tr>
<tr>
<td>Average extrapyramidal symptoms scorec</td>
<td>0 (0-2)</td>
<td>0 (0-4)</td>
<td>0 (0-4)</td>
<td>0.56</td>
</tr>
</tbody>
</table>

**Girard et al. Crit Care Med; 2010:38;428-37.**

Should dexmedetomidine be used prophylactically to prevent delirium in ICU patients? Provide no recommendation for dexmedetomidine to prevent delirium in adult ICU patients as there is no compelling evidence. (0,C)
Does treatment with haloperidol reduce the duration of delirium in adult ICU patients?

No published evidence that treatment with haloperidol reduces the duration of delirium...(No evidence)

Delirium Treatment

Antipsychotic therapy for delirium treatment in ICU’s

Table 5. Medication used by healthcare professionals to treat delirium in the intensive care unit

<table>
<thead>
<tr>
<th>Year</th>
<th>Med</th>
<th>Ns</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>2002</td>
<td>APP</td>
<td>434</td>
<td>70</td>
</tr>
<tr>
<td></td>
<td>Haloperidol</td>
<td>403</td>
<td>66</td>
</tr>
<tr>
<td></td>
<td>IPP</td>
<td>34</td>
<td></td>
</tr>
</tbody>
</table>

Does treatment with atypical antipsychotics reduce the duration of delirium in adult ICU patients?

Atypical Antipsychotics may reduce the duration of delirium in adult ICU patients (C)

Quetiapine in critically ill patients with delirium

- **N = 36**
  - 18 quetiapine & placebo
  - 50 mg PO BID (max 200 mg BID) or placebo
    - Haloperidol IV PRN for agitation allowed in both groups
  - Time to first resolution of delirium
    - 1 day vs. 4.5 days; \( p = 0.001 \)

Quetiapine in critically ill patients with delirium

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Quetiapine (n=18)</th>
<th>Placebo (n=18)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time in delirium (hours)</td>
<td>36 (22-87)</td>
<td>120 (60-195)</td>
<td>0.006</td>
</tr>
<tr>
<td>Time spent agitated (SAS ≥ 5) (hours)</td>
<td>6 (0-38)</td>
<td>36 (11-66)</td>
<td>0.02</td>
</tr>
<tr>
<td>Percent of time spent in delirium after ICU discharge</td>
<td>0 (0-0)</td>
<td>14 (0-47)</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Subject placement after hospital discharge (%)

- Home / rehabilitation center 89         56          0.06
- Chronic care facility / another acute care hospital / death 11         44
Is dexmedetomidine preferred over benzodiazepines to reduce the duration of delirium?

Patients with delirium unrelated to alcohol or benzodiazepine withdrawal dexmedetomidine rather than benzodiazepine infusions be administered for sedation in order to reduce duration of delirium...(+28)

**SEDCOM Trial**

- Baseline CAM-ICU (+)
  - 32.3% reduction
  (95% CI 21% - 43%; p < 0.001)
  - Prevalence: 68.7% vs. 95.5%, p = 0.03
- Delirium free days
  - 2.5 vs. 1.7; p = 0.002

**DEXCOM Trial**

- Interventions
  - Dexmedetomidine 0.1 – 0.7 mcg/kg/hr IV
  - Morphine 10 – 70 mcg/kg/hr IV
  - Propofol boluses/infusion permitted

<table>
<thead>
<tr>
<th>Variable</th>
<th>Dexmedetomidine (n = 152)</th>
<th>Morphine (n = 147)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with delirium %</td>
<td>8.6</td>
<td>15</td>
<td>0.088</td>
</tr>
<tr>
<td>Delirium days, median</td>
<td>2 (1 – 7)</td>
<td>5 (2 – 12)</td>
<td>0.031</td>
</tr>
<tr>
<td>IABP &amp; delirium %</td>
<td>15</td>
<td>36</td>
<td>0.001</td>
</tr>
<tr>
<td>Time to extubation, h</td>
<td>14</td>
<td>15</td>
<td>0.036</td>
</tr>
</tbody>
</table>

No difference in MAAS target, ICU/Hospital LOS or mortality

**In Conclusion...**

- Delirium associated with increased mortality, prolonged ICU and hospital LOS, and post-ICU cognitive impairment
- Must screen for modifiable and non-modifiable risk factors
- Routinely monitor patients for delirium using the CAM-ICU or ICDSC
- Early mobilization reduces incidence and duration of delirium
- Promote sleep in ICU patients
- Suggest not using haloperidol or atypical antipsychotics prophylactically but evolving evidence
- Weak data supports use of antipsychotics on short term basis
- Using dexmedetomidine for sedation versus a benzodiazepine may shorten duration of delirium

**QUESTIONS??**
### References


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### References