Preventing Delirium in Critically Ill Geriatric Patients: Pearls from Acute Care Practice

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Objectives

• Recognize risk factors for delirium

• Distinguish high-risk medications considering pharmacokinetic (PK) and pharmacodynamic (PD) changes with aging

• Outline the pharmacists role in delirium prevention

• Discuss strategies to limit indiscriminate prescribing of high-risk medications
What is Delirium?

• “An acute disruption of attention and cognition. It is a common, serious, and potentially preventable source of morbidity and mortality among hospitalized older patients.” – AHRQ*

• Prevalence
  – On admission (14 – 24%)
  – Acute care (6 – 56%)
  – Postoperatively (15 – 53%)
  – Intensive care unit - ICU (70– 87%)
  – Up to 60% in post-acute care settings

*Agency for Healthcare Research and Quality
**Psychomotor Variants**
(Medical ICU Patients ≥ 65 years old)

- **Hyperactive** - 1.6%
- **Mixed** - 54.9%
- **Hypoactive** - 43.5%

Hypoactive delirium is more common in the elderly and often unrecognized.

*Peterson et al. J Am Geriatr Soc. 2006;54:479–484*
The Problem

• Leading cause of preventable injury in the elderly

• Over 50% of ICU days are incurred by adults 65 years and older

• Many cases are missed

• Associated with adverse outcomes
  – ↑ Mortality
  – ↑ ICU and hospital Length of stay
  – ↑ Duration on mechanical ventilation
  – ↑ Long-term cognitive impairment
  – ↑ Dependence or nursing home placement
  – ↑ Healthcare costs (~$143 billion - $152 billion/yr nationally)
Delirium Linked to Long-term Cognitive Impairment (BRAIN-ICU)

- Included 821 patients admitted to a medical or surgical ICU
- Age: 51-71 years
- Results:
  - ~74% developed delirium
  - At 3 months, 40% with global cognition scores (GCS) similar to traumatic brain injury patients, and 26% similar to mild Alzheimer's disease
  - Delirium duration was a risk factor for worse GCS at 3 and 12 months (P=0.001 and P=0.04, respectively)

RBANS = Repeated battery for the assessment of neuropsychological status
MCI = Mild cognitive impairment
TBI = Traumatic brain injury
Longer Delirium Days Predicts Mortality

• Included 304 ICU patients age 60 or older

• Mean age: 74.7 ± 8.5 years

• Results:
  – Median duration of delirium was 3 days
  – 50% mortality during follow-up
  – ICU delirium days was a predictor of mortality
    (HR 1.10; 95% CI: 1.03-1.18)

Kaplan-Meier survival curve for 1-year mortality post-ICU admit. Log-rank chi-square statistic = 28.3; degrees of freedom = 3; P < 0.001
Detection

• Routine monitoring is feasible and recommended in clinical practice

• Validated Tools
  – Confusion Assessment Method for the ICU (CAM-ICU)
  – Intensive Care Delirium Screening Checklist (ICDSC)

1 Acute onset & fluctuating course + 2 Inattention + OR 3 Disorganized thinking + 4 Altered of consciousness = Delirium

Risk Factors

- **Predisposing (vulnerability)**
  - Older age
  - Preexisting dementia*
  - Hypertension*
  - Alcoholism*
  - Visual impairment

- **Precipitating (potentially modifiable)**
  - Psychoactive medications
  - Benzodiazepine / ethanol withdrawal
  - Severity of acute illness*
  - Metabolic abnormalities
  - Infection
  - Immobility
  - Sleep deprivation
  - Untreated pain

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*significantly associated with ICU delirium in 2 or more multivariate analysis

Figure adapted from: Inouye SK. *Clin Geriatr Med*. 1998;14(4):745-64
Psychoactive medications and Delirium

- May account for up to 40% of all delirium cases
- Most evidence with benzodiazepines, anticholinergics and opioids (meperidine) in the elderly

Neurotransmitter hypothesis

- ↓ Acetylcholine
- ↑ Serotonin
- ↑ Cortisol & endorphin
- ↓ GABA
- ↑ Dopamine = ↓ ACH

[References]

Sanders RD. Med Hypotheses 2011; 77(1): 140-143
• Prospective cohort study of medical ICU patients (N=304)
• Mean age was 75 ± 8 years
• No sedation or pain protocols during enrollment
• Results
  – 79% overall incidence of delirium
  – Median duration of delirium was 3 days
  – Benzodiazepine or opioid use was associated with increased delirium duration (RR 1.64, 95% CI: 1.27-2.10)*
  – Subgroup analysis of patients without dementia revealed an increased rate of delirium with benzodiazepines or opioids (RR-2.42, 95% CI 1.65-3.55)§

*Adjusted for dementia, haloperidol use and APACHE II score
§Adjusted for haloperidol use and APACHE II score
Prospective cohort study of general medicine patients (N=426)
• Included patients ≥ 70 years of age

Adjusted odds ratio for the risk of cognitive decline in the diphenhydramine-exposed group was 2.3 (95% CI, 1.4-3.6)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Diphenhydramine Exposed (N=114)</th>
<th>Diphenhydramine Nonexposed (N=312)</th>
<th>RR, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delirium symptoms*</td>
<td>47 (42)</td>
<td>75 (24)</td>
<td>1.7 (1.3-2.3)</td>
</tr>
<tr>
<td>CAM delirium criteria or</td>
<td>16 (14)</td>
<td>25 (8)</td>
<td>1.8 (1.0-3.2)</td>
</tr>
<tr>
<td>MMSE decline ≥ 3 points</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inattention</td>
<td>13 (13)</td>
<td>14 (5)</td>
<td>3.0 (1.5-5.9)</td>
</tr>
<tr>
<td>Disorganized speech</td>
<td>4 (4)</td>
<td>2 (1)</td>
<td>5.5 (1.0-29.8)</td>
</tr>
<tr>
<td>Altered consciousness</td>
<td>17 (15)</td>
<td>15 (5)</td>
<td>3.1 (1.6-6.0)</td>
</tr>
<tr>
<td>New urinary catheters</td>
<td>9 (8)</td>
<td>10 (3)</td>
<td>2.5 (1.0-6.0)</td>
</tr>
<tr>
<td>Length of stay &gt; 7 days</td>
<td>55 (48)</td>
<td>117 (38)</td>
<td>1.3 (1.0-1.6)</td>
</tr>
</tbody>
</table>

Data represents number (%); *Any 1 of 9 commonly accepted delirium symptoms; MMSE = Mini-Mental State Examination

Why are elderly patients vulnerable to adverse drug reactions?
## PK/PD Changes with Aging

<table>
<thead>
<tr>
<th>Physiologic changes</th>
<th>Clinical implications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Absorption</strong></td>
<td>↓ gastric acid  ↓ surface area  ↓ splanchnic blood flow  ↓ intestinal motility</td>
</tr>
<tr>
<td><strong>Distribution</strong></td>
<td>↓ total body water  ↑ total body fat  ↓ serum albumin  ↓ lean body mass</td>
</tr>
<tr>
<td><strong>Metabolism</strong></td>
<td>↓ hepatic blood flow  ↓ hepatic mass</td>
</tr>
<tr>
<td><strong>Elimination</strong></td>
<td>↓ renal blood flow  ↓ renal mass  ↓ GFR &amp; tubular function</td>
</tr>
</tbody>
</table>

| **Clinical implications** | | |
|---------------------------|------------------------|
| ↓ Vd hydrophilic drugs e.g. lithium |
| ↑ Vd lipophilic drugs e.g. diazepam |
| ↑ bioavailability active drug e.g. phenytoin, warfarin |
| ↓ metabolic drug clearance  ↑ risk of accumulation (enzyme activity unpredictable) |
| ↓ renal clearance of parent compounds & metabolites e.g. meperidine, morphine |

↑↑↑ Sensitivity to psychoactive drugs and risk for adverse drug reactions

DELIRIUM PREVENTION

An ounce of prevention is worth a pound of cure
- Benjamin Franklin
The ABCDE Bundle

- **Awakening & Breathing coordination**
- **Choice of sedatives & analgesics**
- **Daily delirium Monitoring**
- **Early mobility Exercise**

↑ Liberation from ventilator
↑ Earlier ICU & hospital discharge
↑ Return to normal brain function
↑ Independent functional status
↑ Survival

Girard TD et al. Lancet. 2008;371(9607):126-34
ICU Sedation

• Minimize Sedation!

• Choice of sedative
  – Benzdiazepines (midazolam, lorazepam, dazepam)
    • May increase risk for delirium
    • Avoid when possible
  – Propofol
    • Insufficient evidence to determine association with delirium
  – Dexmedetomidine
    • May be associated with less delirium compared to lorazepam (MENDS trial) and midazolam (SEDCOM trial)

Dexmedetomidine vs. Lorazepam ≤ 120 hours (MENDS Trial)

• Included 106 mechanically ventilated medical / surgical ICU patients
• Results: ↓ delirium days and more time within goal RASS with dexmedetomidine

Pandharipande PP et al. JAMA 2007;298:2644-2653
Riker RR et al. JAMA. 2009;301(5):489-499

RASS = Richmond Agitation Sedation Scale
Hospital Elder Life Program (HELP)

- Included 852 general medicine patients ≥ 70 years of age

- Multicomponent targeted interventions
  - Cognitive re-orientation
  - Non-pharmacologic protocol
  - Vision / Hearing aids
  - Early mobilization
  - Dehydration protocol

- Results favored intervention group
  - ↓ delirium occurrence (9.9% vs. 15%, OR 0.60, 95% CI 0.39-0.92)
  - ↓ delirium days (105 days vs. 161 days, p=0.02)
  - ↓ delirium episodes (62 vs. 90, OR 0.60, p=0.03)

- No significant effect on delirium severity or recurrence rates in the intervention group

Local Prevention Strategies

• Target population: acute care patients ≥ 70 years old

• Interdisciplinary collaboration:
  – Nurse driven screening & safety interventions
  – Physician education and order-set implementation
  – Team Clarity Volunteers interacting with at-risk patients
  – Care Navigator and Team Clarity Aide follow-up post-discharge
  – Pharmacy initiatives
    • Real-time electronic monitoring of high-risk medication orders
    • Systematic order-set modifications & formulary augmentation
    • Incorporation of medical logic modules
    • Provision of clinical & educational support
HELP OUR PATIENTS AVOID DELIRIUM

Medications are common and preventable causes of delirium in the elderly. Please consider these alternatives.

**Recommendations for age > 70 years old:**

**INSOMNIA**

**Instead of:**
- Diazepam
- Zolpidem
- Diphenhydramine
- Lorazepam

**Try:**
- Ramelteon 8mg qHS prn
- Doxepin 3mg qHS prn

**ITCHING**

**Instead of:**
- Diphenhydramine
- Hydroxyzine

**Try:**
- Fexofenadine 60mg daily prn*
- Cetirizine 5mg daily prn*
- Sarna lotion, topical steroids
- If one of the drugs to avoid is necessary, initiate lowest dose:
  - Diphenhydramine (12.5mg)
  - Hydroxyzine (12.5mg)

*Avoid if CrCl <10 or hemodialysis

**MUSCLE SPASMS**

**Instead of:**
- Methocarbamol
- Cyclobenzaprine
- Diazepam
- Carisoprodol

**Try:**
- Optimize pain regimen FIRST
- Local anesthetics/lidocaine
- Heat packs, massage, stretches

**NAUSEA**

**Instead of:**
- Metoclopramide
- Prochlorperazine
- Promethazine

**Try:**
- Ondansetron 4mg q8h prn
- If one of the drugs to avoid is necessary, initiate lowest dose:
  - metoclopramide (5mg IV/PO)
  - prochlorperazine (2.5 IV, 5mg IM)
  - promethazine (12.5mg PO/IV)

Nursing is screening patients age 70 or greater for delirium on all acute care units and pharmacy is actively screening for medications that may contribute to delirium. Anticipate calls regarding delirium detection and prevention. An order set titled "Delirium Elderly Initial Management TM CPOETM is available in MethOD for the evaluation and treatment of newly suspected delirium.

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Local Prevention Strategies (preliminary findings)

Other outcomes for grant initiatives (pending)
- Impact on falls
- Impact on delirium
- Length of stay & discharge disposition
- Mortality
- Costs

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What can you do?

• Suspect delirium

• Remember Dr DRE\(^1\)
  – Diseases: sepsis, withdrawal etc.
  – Drug Removal
  – Environment: immobility, sleep, hearing/visual aids etc.

• Optimize medications:
  – TREAT pain
  – Develop targeted sedation protocol
  – Review standard ordersets for high-risk medications & implement changes
  – Take advantage of technology
  – Educate healthcare providers and patients

1. www.icudelirium.org
Guiding Principles for Geriatric Pharmacotherapy

- Consider risk versus benefit of therapy
- Start low and go slow
- Adjust doses for renal and hepatic impairment
- Limit polypharmacy
- **Common drugs to avoid when possible**
  - Sedative hypnotics e.g. zolpidem, benzodiazepines
  - First generation antihistamines e.g. diphenhydramine
  - Muscle Relaxants e.g. cyclobenzaprine, carisoprodol
  - Meperidine
Summary

• Delirium is a frequent and detrimental complication in critically ill geriatric patients

• Prevention is key and likely requires a multimodal approach

• Pharmacists play a pivotal role in optimizing pharmacotherapy and limiting high-risk medication use in critically ill geriatric patients
“The subject of delirium is generally looked upon by the practical physician as one of the most obscure in the chain of morbid phenomena he has to deal with; whilst the frequency of its occurrence under various conditions of the system renders the affection not a little familiar to his eye”

Gallway MD (1838)
Recommended Resources

• www.ICUdelirium.org


• Clinical Practice Guidelines for the Management of Pain, Agitation, and Delirium in Adult Patients in the Intensive Care Unit (2013)

